AMERICAN SOCIETY OF CLINICAL ONCOLOGY

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"Making a Difference in Cancer Care WITH YOU"

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Letter From the Editor in Chief

On behalf of my Associate Editor, Dr. Nathan Pennell, and Guest Editor, Dr. Hope S. Rugo, I welcome you to the 2017 ASCO Annual Meeting. It is an honor and privilege to present the 37th volume of the NLM-indexed *ASCO Educational Book*. The theme of this year's Meeting is "Making a Difference in Cancer Care ***WITH YOU***," and this theme celebrates the inclusiveness of those that work together to diagnose and care for people with cancer.

With his presidential theme, Dr. Daniel F. Hayes celebrates the inclusive nature of the oncology community. Only when the brightest minds in research, education, and care work together as a community are we able to deliver the highest quality of care to meet the needs of all of our patients. To celebrate the theme of the 2017 Annual Meeting, this volume contains articles coauthored not only by those who diagnose and care for patients with cancer, but also ancillary care specialists, such as nurses and advanced practice providers, and physicians in training. Coauthoring a manuscript takes immense planning and collaboration, and I would like to thank all of the authors for their contributions to the 2017 *ASCO Educational Book*.

We are honored to have Dr. Rugo join us as a Guest Editor for this year's Invited Articles. The Invited Articles allow us to explore critical topics in oncology that are closely related to this year's theme. I would like to thank Dr. Rugo for her dedication and her willingness to oversee this important section. Finally, I would also like to recognize the expert panel who selflessly dedicated their time to perform thorough and thoughtful reviews of the submitted articles. The tremendous work of Dr. Rugo, Dr. Pennell, the expert panel, and all of the authors is especially pertinent to this year's theme of inclusivity and support.

It is my honor to invite you to read the exceptional contributions that comprise this volume. For the first time in several years, the print edition contains the full collection of all of the 2017 articles and is available for purchase on the ASCO University Bookstore. All of the 2017 *ASCO Educational Book* articles, as well as articles from past volumes, are available to view online for free at www.asco.org/edbook.

We welcome your feedback and suggestions on how we can improve the content, so please contact us at edbook@asco.org with your comments.

Sincerely,

Don S. Dizon, MD
Editor in Chief

INVITED ARTICLES

This year's invited articles represent the 2017 ASCO Annual Meeting theme, "Making a Difference in Cancer Care ***WITH YOU***." These important contributions to the 37th volume of the *ASCO Educational Book* celebrate the inclusiveness of those that work together to diagnose and care for people with cancer. The authors represent a diverse, multidisciplinary set of expertise and backgrounds.

Authors were nominated by the *ASCO Educational Book* Editors and 2017 ASCO Annual Meeting leadership, and authors developed their topics under the guidance of Dr. Hope S. Rugo, Guest Editor of the Invited Articles.

ARTICLES

Can Cancer Truths Be Told? Challenges for Medical Journalism
Elaine Schattner, MD

Future Genetic/Genomic Biomarker Testing in Non–Small Cell Lung Cancer
David Planchard, MD, PhD, Jordi Remon, MD, Frédérique Nowak, PhD, and Jean-Charles Soria, MD, PhD

Making the Case for Improving Oncology Workforce Diversity
Karen M. Winkfield, MD, PhD, Christopher R. Flowers, MD, MS, and Edith P. Mitchell, MD, FACP

Minimizing Minimally Invasive Surgery for Endometrial Carcinoma
Melissa K. Frey, MD, Stephanie V. Blank, MD, John P. Curtin, MD

The Road to Addressing Noncommunicable Diseases and Cancer in Global Health Policy
Heath Catoe, MD, PhD, Jordan Jarvis, MSc, Sudeep Gupta, MD, MBBS, Ophira Ginsburg, MD, FRCPC, Gilberto de Lima Lopes Jr., MD, MBA, FAMS

Can Cancer Truths Be Told? Challenges for Medical Journalism

Elaine Schattner, MD

Journalism is a field undergoing rapid transformation. In 2016, nearly two-thirds of U.S. adults received news by social media. The Pew Research Center reported that the proportion and number of men and women seeking news on Reddit, Facebook, Twitter, Instagram, and YouTube has been climbing since 2013.[1] Meanwhile, traditional newspapers contend with falling print circulation, compete for online traffic, and drop staff. The number of U.S. newsroom employees fell steadily after 2006, from 55,000 to fewer than 33,000 jobs.[2]

Medical news presents a unique set of challenges, both for journalists and consumers. On the production side, reporters and editors aim to translate doctors' jargon-loaded updates into digestible, truthful, and appealing bits of information—stories—that resonate with a lay audience. The work is no small task, given the complexity and pace of science and clinical research. On the receiving end, patients or caregivers might read, watch, listen, or skim a feed, consciously or unconsciously taking notes. No matter what the source, an article might influence an individual's thinking about a personal medical decision. On a larger scale, medical journalism can sway policy makers.

The quality and accuracy of news has the potential to alter health outcomes. Put simply, the public depends on reliable news to support everyday medical choices and, occasionally, inform major decisions. When journalists get stories right, they help people to make reasoned choices and ask better questions of their physicians. Conversely, when reporters make errors or editors publish misleading headlines, people with medical conditions and other consumers of news, may be harmed.

This article will explore the capacity and limits of health journalism to inform the public about developments in oncology. We will focus on two issues: one is a perennial concern—balancing hype and reality, with appropriate skepticism—in what might be an era of true progress; second is the changing place of journalism amid a torrent of ungated medical information and stories channeled in blogs, social media posts, and celebrity statements. Finally, we will consider the emerging challenge of distilling valuable and relevant medical news amid a surplus.

BALANCING SKEPTICISM AND HYPE

A 2016 *CBS Evening News* story, "Promising Brain Cancer Trial Given Breakthrough Status by FDA," offers an instructive example[3] of how news can affect patients' thinking, hopefulness, and care. Scott Pelley, said by CBS on its website to be "one of the most experienced reporters in broadcast journalism," anchors the show. He stands upright, against a backdrop of laboratory research images; he speaks with a clear and authoritative voice: "We hope one day to lead the broadcast with a cure for cancer, but tonight, we might have the next best thing" (Fig. 1).

"The treatment is audacious, using poliovirus to kill glioblastoma, a vicious brain cancer that can kill in a matter of months," Pelley states. The program cuts to a young woman who, as told, was the first patient with brain cancer to volunteer in the clinical trial of an experimental treatment at Duke University. The newscaster reviews her case quickly, as a doctor might on rounds. In 2011, a 20-year-old nursing student experienced headaches; doctors found a brain tumor "the size of a tennis ball" and removed 98% of it in surgery; in 2012, the patient had recurrent glioblastoma. *60 Minutes* first reported on the experimental brain cancer treatment in March 2015.[4]

"Something unimaginable happened," Pelley says in the 2016 segment. Her tumor "shrank for 21 months, until it was gone." He shows the patient's MRI to television viewers and explains that it no longer reveals a brain tumor. She and at least two other participants in the phase I trial were doing well and in complete remission for over 3 years, Pelley reported.

Critiques of the *60 Minutes* and *CBS Evening News* coverage of the polio-derived brain cancer vaccine appeared at

From Weill Cornell Medicine, New York, NY.

Disclosures of potential conflicts of interest provided by the author are available with the online article at asco.org/edbook.

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FIGURE 1. Scott Pelley, *CBS Evening News*, May 12, 2016

Related video available here: www.cbsnews.com/news/promising-duke-university-polio-brain-cancer-trial-given-breakthrough-status-60-minutes/. Accessed February 2017.

Forbes.com[5,6] (where I am a contributor) and HealthNewsReview.org, a health journalism watchdog site.[7] Criticisms included failure of Pelley's team to spell out alternative standard and experimental treatments for glioblastoma, no mention of costs, a heavy-weighting of views put forth by those involved with the trial at Duke, a lack of emphasis on the toxicity and deaths experienced by most of the research participants, and the use of the term breakthrough. The harshest piece[8] appeared in *MedPage Today*: "Brain Cancer: Did '60 Minutes' Report Raise False Hope?"

The original *60 Minutes* feature led to a slew of phone calls to the brain cancer team at Duke University, according to the *MedPage* story. A later piece[9] published by *The Hill*, "'60 Minutes': FDA Fast Tracks Cancer Treatment Using Polio Virus," reflects perception that television coverage accelerated the experimental trial and vaccine treatment. As told in the later *CBS Evening News* segment, the investigational agent is being developed by a company based at Duke and involves a scientist interviewed on the program.

The clip illustrates the challenges of discerning cancer progress from hype and news from advertisements. When I rewatched this episode on my personal computer in February 2017, an advertisement for a cancer treatment center kicked in. Yet I found the story compelling and valuable, overall; I wanted to know more about the brain cancer vaccine being tested at Duke University, a major academic medical center. Moreover, if I knew an otherwise healthy person with recurrent glioblastoma, I would want them to be aware of this promising treatment, in case they were seeking experimental options. A possible downside of this kind of story is that patients might have their hopes raised about entering the trial, only to find out that they are ineligible. On the plus side, for journalists to provide well-researched stories like this about the vaccine for glioblastoma, hearing of progress, however preliminary and carefully worded, might be comforting to people who have lost loved ones to the condition.

One reason the CBS story drew some flak may be that it begins with the term promising in the headline. That word—like breakthrough or miracle in a story having to do with cancer—causes journalists, and doctors, to bristle. Some teachers of health care journalism advise these hopeful words be avoided,[10] for similar reasons that oncologists instruct younger doctors not to tell a cancer patient they have been cured, but rather to say they are in remission. The problem with using such optimistic terms is they fail to prime the reader, or patient, for disappointment.

A research letter[11] published in *JAMA Oncology*, "The Use of Superlatives in Cancer Research," suggests that excessively positive language appears with undue frequency in journalism about cancer. The article, based on a Google search of terms in news published over 5 days in late June 2015, generated a blitz of coverage in late October 2015, when the paper appeared online. The story resonated, at least among journalists. "Half of the cancer drugs journalists called 'miracles' and 'cures' were not approved by the FDA," said Vox.com.[12] In a syndicated piece Reuters stated that "Glowing terms are often used for new cancer drugs in health news."[13] "If A New Cancer Drug Is Hailed As A Breakthrough, Odds Are It's Not," stated *NPR Health*.[14] "'Revolutionary.' 'Game changer.' 'Miracle.' How much are we hyping unproven cancer drugs?" asked *The Washington Post*.[15] A March 2017 *STAT News* opinion[16] by two oncology physicians, one of whom is the corresponding author of the original piece, reviews the *JAMA Oncology* report on superlative language. That column, titled "Few People Actually Benefit From 'Breakthrough' Cancer Immunotherapy," refers to "an ocean of hype" and links to another negative report.[17]

The message is clear: do not believe promising headlines about oncology drugs. But what if scientific and clinical advances have led to considerable gains for people with cancer? If progress against disease is real, as it may or may not be, a question for journalists is whether skepticism might be flipped: perhaps the current truth is not so bleak.

FAILING TO REPORT PROGRESS THAT IS SLOW, INCREMENTAL, AND IMPERFECT

Between 1991 and 2014, the death rate from cancer fell by 25% in the United States. This impressive figure headlined a report by the American Cancer Society (ACS), "Cancer Statistics, 2017," published on January 5, 2017.[18] In compiling this update, epidemiologists and statisticians drew on mortality data gathered by the National Center for Health Statistics. They also reviewed cancer incidence and survival data from the Surveillance, Epidemiology, and End Results (SEER) Program, the National Program of Cancer Registries, and the North American Association of Central Cancer Registries.

Yet a casual survey of my acquaintances who are not oncologists confirmed that some educated people, individuals who read print newspapers and listen to National Public Radio, for instance, remained completely unaware of this favorable trend. A recent search of the *New York Times* website using terms like "cancer deaths" and "American Cancer Society" finds no mention of the January 2017 ACS report on the 25% decline in U.S. cancer mortality. The *Wall Street Journal* also appears to have passed on covering this story.

Several national news outlets did pick up the ACS report. TIME.com published a short piece,[19] "Here's Why the Cancer Death Rate Has Plummeted." CNN.com ran a story,[20] "US Cancer Deaths Down 25% Since 1991, Report States," but did not produce searchable video or television coverage. Like CNN, NBC News posted an article[21] on its website, but does not appear to have supported it with video or television footage. *USA TODAY* did not cover the analysis directly, but posted a 47-second video,[22] "2017 Is Looking Healthier: Cancer Death Rate Drops a Fourth Since '91." A caption at USAToday.com attributes the video to Newsy NewsLook, a company[23] that provides a "premium video solution that increases views and revenue for Publishers and Creators." In other words, the *USA TODAY* story on the cancer decline was produced by a commercial video manufacturer.

SPINNING STATISTICS

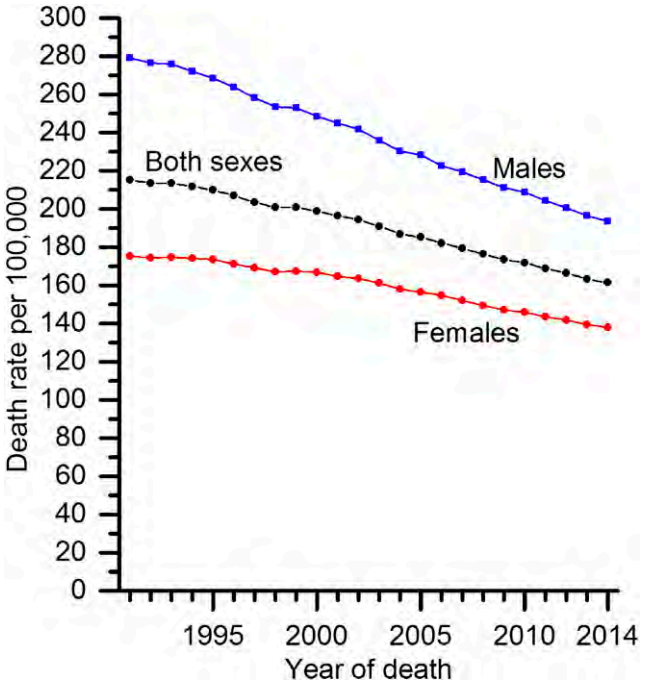
The 25% statistic raises questions (Fig. 2). A critical reader or journalist might ask if the reported reduction in deaths from cancer was observed only in people already known to have cancer (disease-specific mortality) or if the trend was observed in the larger U.S. population. For this ACS analysis, cancer deaths were tallied in the general population. Specifically, deaths from cancer peaked at 215.1 per 100,000 population in 1991 before falling to 161.2, also per 100,000 population, in 2014. That detail means that the lower reported death rate from cancer cannot be attributed to overdiagnosis. Overdiagnosis would affect the number of reported cancer cases (incidence) and might lower the apparent rate of cancer-specific deaths, but it would not affect mortality from cancer in the general population.

The figure persuades because the mortality curve falls steadily between 1991 and 2014; it is not a statistical fluke. U.S. cancer death rates fell for both men and women, although in the past decade, the decline was proportionately greater in men. The ACS authors attributed the trend to reduced smoking, which over time led to fewer lung cancers, and to early detection and treatment of several common cancer forms. The biggest declines were observed in mortality from lung, breast, prostate, and colorectal cancers.

Yet the drop is imperfect. Cancer remains the second-leading cause of death in U.S. men and women. Disparities in cancer incidence and deaths persist, based on race, insurance access, and geography. The ACS reported that death rates from cancer among U.S. blacks exceed those among whites by 15% overall.

A detail worth considering, because it confounds health statistics and public understanding of those, is the expanding and dynamic U.S. population. Although the cancer death rate fell, the Centers for Disease Control and Prevention reported a rising annual number of cancer deaths, from 514,657 deaths in 1991 to 591,699 deaths in 2014.[24] There is no discrepancy in these figures; the absolute increase in cancer deaths can be explained by growth of the population. Based on U.S. Census Bureau estimates,[25,26] the population expanded from 252,131 million in 1991 to approximately 318,700 million in 2014; these figures demonstrate

FIGURE 2. U.S. Cancer Mortality Trends (1991-2014)



over 26% growth in the U.S. population during the relevant 23-year interval.

This sort of apparent contradiction, based on two valid representations of U.S. cancer registry and death data, generates confusion and, sometimes, angry public debate. A relevant example comes from the surprisingly controversial subject of breast cancer statistics.[27] A contentious issue that crops up periodically in news, op-eds, on Twitter and advocacy group Facebook pages, is whether or not there has been meaningful progress in reducing breast cancer deaths.[28] The facts, based on SEER data, are these: in 1991, deaths from breast cancer numbered 32.69 per 100,000 women in the U.S. population; in 2013, those numbered 20.72, per 100,000 U.S. women.[29] These numbers demonstrate a 36% decline in the rate of deaths from breast cancer. Yet the absolute number of deaths declined only slightly during those 22 years, by a few thousand. The Centers for Disease Control and Prevention report that in 1991, deaths from breast cancer numbered 43,583; in 2013, 40,860 women and 464 men died of breast cancer.[30,31]

Although some might deem these statistical quibbles, these figures affect how and if journalists and others represent and perceive progress against breast cancer. These numbers influence the distribution of funding for research, screening, and care. The breast cancer death rate has declined by 36% in the U.S. population, but the annual U.S. toll of deaths from breast cancer still hovers over 40,000, causing consternation and frustration among patients, advocates, and others. Further clouding the picture is that invasive breast cancer is the most common cancer form not declining in the United States; the recent ACS report indicates

that among some groups, such as African Americans, the incidence has been rising.

FOCUS ON DISPARITIES (WHERE INFORMATION MIGHT HELP OUTCOMES)

The fact that cancer death rates have been declining, albeit unevenly, surfaced in a January 2017 *JAMA* analysis.[32] That paper confirms the drop in overall U.S. mortality from cancer after 1980 and highlights disparities. Cancer pockets—marked by a high incidence or death rate from malignancy—exist in broad U.S. geographical areas and small communities. Lung cancer disproportionately affects and kills people in Appalachia, for instance. A high death rate from breast cancer occurs along the lower Mississippi and southern belt states. Clusters, or hot spots, of kidney cancer appear in areas along the Mississippi and in North and South Dakota. Stage at diagnosis and cancer death rates vary among counties within states.

These regional differences in U.S. cancer outcomes support the need for improved education and journalism about health. In 2015, *Newsweek* dedicated an entire issue to cancer. In a long-form feature,[33] journalist Jessica Wapner reveals the outlook for patients with cancer in central Appalachia. She visited a region of eastern Kentucky where prevalent poverty and low education levels contribute to cancer's high toll. People in the area suffer health effects from heavy smoking and excess particulate matter in air. "A long history of poverty and disease in the region has led to a sense of resignation, a fatalistic belief about the inevitability of cancer and the death it brings," Wapner wrote. "Many people who are diagnosed refuse treatment because they don't see the point of going through the pain."

In the context of recent data about the declining U.S. cancer death rate, the *Newsweek* story points to the potential role of news to inform people about progress and nudge them toward better outcomes. Careful journalism might disrupt a fatalistic cycle of disbelief in cancer treatment's value that leads to late presentation of patients with cancer to physicians, lesser outcomes, and more deaths. Consider the plight of a woman or man living in rural Kentucky with a persistent cough and weight loss, symptoms of a possible lung cancer, today. Just knowing that cancer deaths in the U.S. population are down, by as much as 25% in recent years, might prompt some individuals to visit the doctor rather than ignore early signs of disease.

DESPITE PROGRESS, A DIM AND CONFUSING PICTURE

The recent 25% decline in U.S. cancer deaths—what might be deemed as evidence-based news about cancer that is not anecdotal—reflects progress. Yet it got little attention. Of course, with so much ongoing political changes in January 2017, including the possible repeal of the Affordable Care Act and the affect of the travel ban on doctors, the omission of cancer news from headlines might be understood. When newsrooms are strapped for reporters and editors need to choose stories that draw clicks, careful reporting about cancer research, drugs, and clinical developments might be put aside (Sidebar 1).

Yet reports about cancer appear constantly and often cast a negative slant. Many recent articles focus on the exorbitant costs of cancer medications. Some stories feed on anger over high drug prices, raise or address economic issues, and mix with political news. Although reports on treatment costs might be set apart from reports on effectiveness, the issues often get conflated, in part because economists and health policy experts discuss pricing models that depend on how well the drugs reportedly work.

Since January 2017, overlapping articles have emphasized the ineffectiveness of oncology treatments. One example, "Dozens of New Cancer Drugs Do Little to Improve Survival, Frustrating Patients,"[34] appeared in *Kaiser Health News* on February 9, 2017 (Fig. 3). The piece, also available in Spanish (*Nuevas drogas contra el cáncer, ¿ayudan a vivir más?*) draws on a lecture on "Unintended Consequences of Expensive Cancer Therapeutics" published in 2014 in *JAMA Otolaryngology–Head & Neck Surgery*[35] and a few recent papers finding marginal, if any, benefit of new oncology drugs. The story leads with the picture of a woman whose breast cancer progressed through multiple treatments, causing pain. It refers to high prices, averaging $171,000 per year, and relies heavily on negative quotes offered by critics of precision oncology. The same article ran in *USA TODAY* with an abbreviated headline,[36] "Dozens of New Cancer Drugs Do Little to Improve Survival," and on CNN.com,[37] "Amid Flurry of New Cancer Drugs, How Many Offer Real Benefits?"

SIDEBAR 1. Pressures on the Quality of Medical Journalism

1. Newsrooms reduce staff for reporting and editing.
2. Many outlets lack fact-checkers.
3. To keep their jobs, reporters need turn out stories quickly.
4. Journalists may lack the time or scientific background to critically evaluate reports of new technology and drug development.
5. Income is often incentivized by internet traffic (clicks).
6. Even for news outlets that do not acknowledge paying journalists based on traffic, a freelancer is more likely to get repeat assignments after stories "fly"; reporters and columnists lose jobs when clicks are insufficient.
7. Editors favor topics that drive traffic: stories with splashy headlines on financial toxicity, greedy pharmaceutical companies, and bad doctors gain disproportionate coverage.
8. Journalists hesitate before covering "breakthroughs," as they should, for not wanting to seem foolish.

In addition to dismissing the value of cancer drugs, recent health news casts doubt on the reliability of medical research. In January 2017, the BBC highlighted the reproducibility crisis with the headline "Most Scientists 'Can't Replicate Studies by Their Peers.'"[38] The journal *Nature* covers the Reproducibility Initiative, a project funded by the Laura and John Arnold Foundation that aims to replicate key findings in basic cancer research.[39] In early March 2017, *NPR Health* ran a related piece,[40] "Reports Of Medical Breakthroughs Often Don't Prove Out."

The triple takeaway might be that new cancer drugs rarely work, cost lots, and that reports of progress cannot be trusted. Yet the well-documented pattern of reduced U.S. cancer mortality supports that modern oncologists are doing something right overall. Perhaps the day-to-day medical news, with a focus on narrative and twists, and only occasional details about treatments, fails to capture the big picture about cancer and incremental progress.

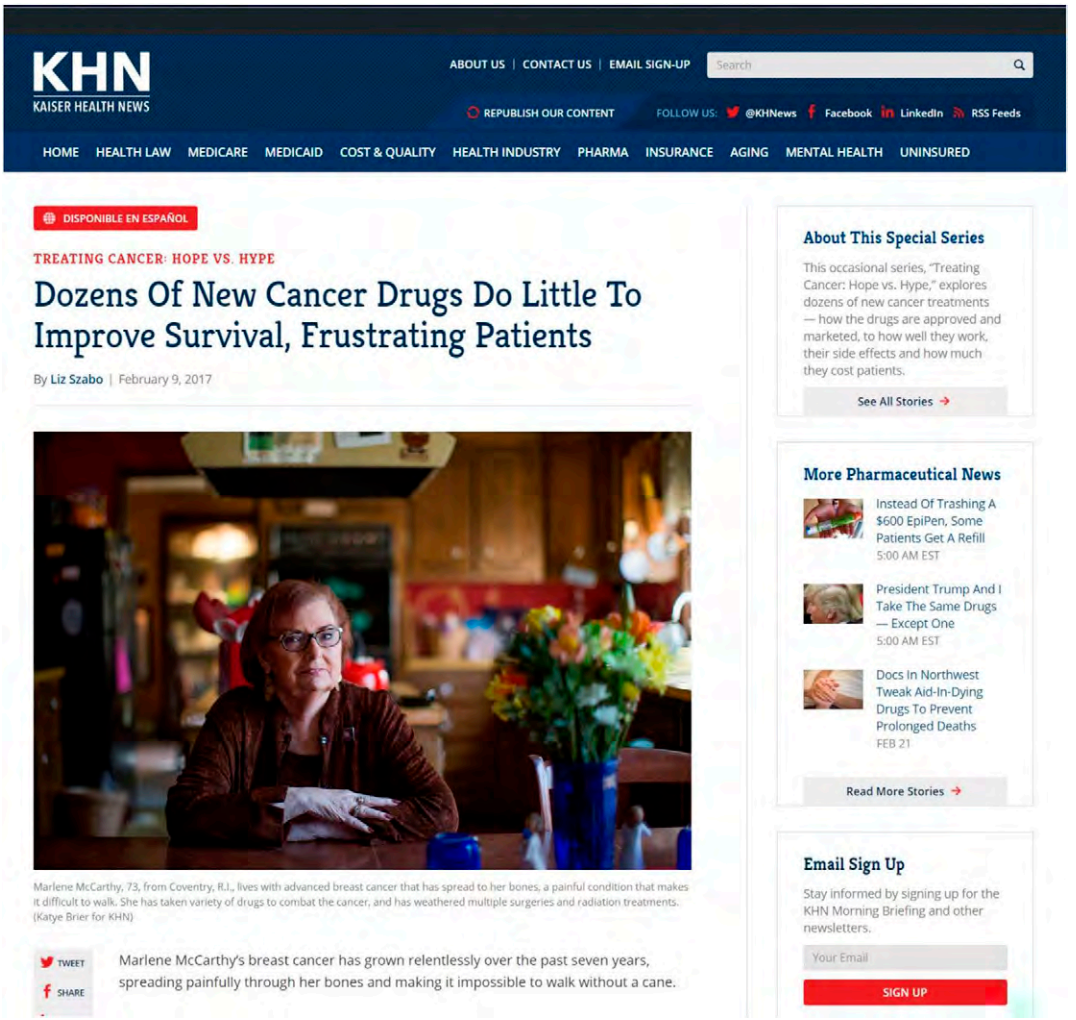
LOSS OF INFORMATION GATEKEEPERS

Thirty years ago, when I graduated from medical school, someone wanting to distribute a factual update, opinion, or analysis generally needed access to a publisher with printing equipment or a company with radio or TV broadcasting equipment. This is no longer the case. Today a doctor, high school student, refugee, patient with cancer, teacher, celebrity—anyone—can write a few lines, take a photo, or film something and post it to the web.

Social media posts, along with other sources of cancer-related information—ranging from direct-to-consumer advertisements sponsored by pharmaceutical companies, to articles put forth by cancer centers on fancy websites, to blog posts authored by individual clinicians—contribute to what might be described as an online free-for-all regarding cancer facts, treatments, and opinion. The expanding volume of stories and data about cancer offers patients and doctors an unprecedented amount of material to sort through. Distilling what is true, relevant, and helpful to an individual patient may be more difficult than ever before.

The disruptive and potentially helpful impact of Twitter, a social media platform, is hard to gauge in terms of clinical care and cancer outcomes. Although the numbers of oncologists, patients with cancer, advocates, researchers, and communications specialists representing pharmaceutical

FIGURE 3. Kaiser Health News: "Treating Cancer: Hope vs. Hype"



companies, hospitals, and pathology laboratories using social media are rising, the consequences of all this activity remain unclear. Preliminary reports about Twitter and health care cannot be generalized, because they draw on data from the platform's users.

Twitter does facilitate rapid transmission of health news. This could be most helpful during a public health emergency. How it might help patients with cancer and their caregivers is by directing those with a condition or interest, like sarcoma, to relevant news such as the U.S. Food and Drug Administration approval of a new drug, clinical trials, conferences, and websites providing vetted information.

POTENTIAL INFLUENCE OF CANCER NEWS ON PUBLIC HEALTH

Although the clinical and public health impact of most health journalism goes unchecked, some well-documented instances demonstrate the alerting function of high-profile stories. Some of the best-studied examples pertain to oncology and cancer screening and date over several decades.[41]

In September 1974, First Lady Betty Ford had a mastectomy for breast cancer. Ford's surgery took place a few weeks before Happy Rockefeller, wife of Vice President Nelson Rockefeller, underwent the same.[42] News surrounding the pair's procedures and their malignant diagnoses generated an uptick in mammography. A 1978 study[43] in *Public Health Reports* found a clear pattern, albeit transient, lasting months, of increased participation in the Health Insurance Plan screening program during that "period of high public attention to breast cancer."[43, p. 320] The authors referred to an "alerting function" of high-profile news; they attributed the term to Earl Ubell, the director of NBC TV News. The newscaster had penned a rare 1976 paper[44] on "Responsibility of the Mass Media in the Control of Sexually Transmitted Diseases."

A decade later, President Ronald Reagan underwent successful surgery to remove a small cancer from his colon in the early summer of 1985. The National Cancer Institute reported a spike in calls to its Cancer Information Service from people with questions about colon and rectal cancers; SmithKline Diagnostics, a large manufacturer of a screening kit to check for blood in stool, reported that its supply ran out.[45] Although Reagan's episode did not have any measured effect on public health, such as reduced deaths from colon cancer, his well-publicized case did influence attitudes about colon and rectal cancer. The *Los Angeles Times* discussed the impact of Reagan's surgery with Irving Rimer of the American Cancer Society: "The taboo against talking about colon and rectal cancer, about the elimination of wastes from the body, and about the bowels in general has been broken," Rimer said in July 1985.[46]

Over time, public cancer disclosures became increasingly frequent. In March 2000, *Today Show* host Katie Couric gained attention by undergoing a live-televised colonoscopy. After her husband's death at age 42 from colon cancer, Couric explicitly aimed to encourage screening. *Time* magazine called it "Katie's Crusade."[47] The strategy worked; in 2003, physicians documented a rise in colonoscopies, particularly among women. Doctors dubbed it "the Couric effect." Those reporting in the *Archives of Internal Medicine*[48] inserted a note of caution: "While celebrity spokespersons have remarkable potential to transmit important medical information, one notable concern is the possibility for well-meaning public figures to use their influence to promote unproven or even dangerous behaviors,"[48, p. 1604] they wrote. "For example, Ms. Couric has advocated colorectal screening at ages younger than recommended by most medical authorities, declaring, 'But all the doctors I know—and I know a lot of them—say they had or will get a colonoscopy by their 40th birthday. That ought to tell you something,'" the journal authors added. "Considering these results, celebrity spokespersons should be advised to deliver carefully targeted, evidence-based recommendations that will ultimately improve public health."

A more recent example comes from the double revelation of Angelina Jolie. In May 2013, the actress informed the world that she carries a *BRCA* mutation in a *New York Times* op-ed.[49] The article emphasized her personal decision to undergo prophylactic, bilateral mastectomy in light of her genetic disposition and strong maternal family history of breast cancer. Her story surely contributed to the increase in *BRCA* genetic evaluations that ensued. In 2015, Jolie followed up with a column about her oophorectomy.[50] Yet a 2016 report in the *British Medical Journal* found no rise in mastectomy after Jolie's revelation.[51] Her case, and the enormous publicity surrounding her decision, generated greater awareness about *BRCA* and, possibly, other hereditary cancer syndromes; it led to more DNA testing, but it appears not to have affected surgery rates.

Two prominent 2016 cases stand out by their possible consequences for men's health. The actor Ben Stiller disclosed that he was treated for prostate cancer found 2 years earlier, at age 48. He wrote a controversial blog post[52] on Medium: "The Prostate Cancer Test That Saved My Life." Stiller gave interviews on TV and radio about his prostate cancer evaluation, surgery, and treatment.[53] However, because the U.S. Preventive Services Task Force and physician groups advise against prostate cancer screening in men, Stiller got into some hot water over his post and remarks on prostate-specific antigen testing.[54,55] Also, in 2016, the Black Eyed Peas musician Jaime Gomez, known as Taboo, announced he had surgery and chemotherapy for testicular cancer.[56,57] The ACS named him a global ambassador. Gomez aims to increase awareness and lessen stigma about cancer in his Mexican and Native American communities.[58]

These cases reveal the potential of cancer news to influence public health. Celebrity health disclosures can help or harm, depending on how effectively, and if, their messages convey medical wisdom. However, most of what people hear about oncology has little to do with celebrities' experiences. The background effect of everyday stories likely has a greater effect on patients' decisions, but it may be impossible to measure.

A PRESCRIPTION FOR CANCER NEWS

One might consider if and why medical journalism matters. Although a physician or patient might enjoy reading a feature on immune therapy or listening to a podcast on ethical or technical aspects of genetic testing, few individuals would make treatment choices based on what they've read in the *Atlantic* or seen on CNN. Yet exposure to news—what journalists are writing in papers and magazines and saying on radio, TV, and social media—can influence a person's background view, so that when they enter a physician's office, they know what questions to ask; a patient might be more wary of an intervention or more willing to accept it. Health news affects whether a person enters a doctor's office in the first place.

I would suggest that good-quality health journalism might be more needed than ever before. As the number of competing online sources of information expands, and patients know their personal doctors less well, the potential consequences of news about oncology, and how that news is steered by editors and social media, will affect cancer patients' decisions, experiences, and outcomes.

Despite progress, negative stories constitute much of what people hear about cancer: patients suffer; many die after treatments fail; medications cost too much and can cause bankruptcy; survivors endure long-term side effects and chronic health problems; researchers fail to reproduce findings; bad oncologists carry out fraudulent billing, etc. News of treatment toxicity, such as recent reports about cardiac effects of oncology drugs,[59-61] might scare a patient, so that they decline treatment that is likely to help. Reports on chemobrain, recently substantiated,[62] could dissuade anyone from taking the medicines an oncologist recommends. Of course, it is every person's right to have this kind of information: the good, the bad, and the mixed results.

News, presented in a balanced way, could help guide patients and caregivers about the risks and benefits of treatment options. Journalism can inform patients' decisions about whether to try medicines, whether and when to accept consultation from a palliative care specialist, or choose hospice care. Although premature reports of groundbreaking findings in mice or breakthroughs in the laboratory can mislead, the public deserves to know about advances. The truth includes progress.

Producing balanced stories that convey information about progress against cancer, without hype, tasks journalists. Transparency will serve them and their audience: physicians and scientists need be upfront about conflicts of interest and funding; recognize and indicate the limits of conclusions from any study; and be open to correction. What journalists can do, although it is not easy, is to seek varied perspectives. Incorporating viewpoints of scientists, physicians, patients, and others, including some who are not directly involved in a story, should add depth and generally improve coverage (Sidebar 2).

As newsrooms shrink and reporters work at a quicker pace, the challenge of producing balanced stories that convey information about real progress against cancer, without hype, may push editors away from the subject. Unless the data for a treatment or experimental results are so extraordinary that they astonish seasoned oncologists, so much that they use terms like breakthrough or possible cure regarding previously hopeless tumors, journalists may think it wise to play it safe, skip coverage, and report on something else. The reality of incremental progress is unfortunately dull, except, of course, to the patients who experience these advances, their loved ones, and providers of care, including physicians who see them do well.

Some journalists might consider, as I have, that detailed information about cancer treatments belongs in doctors' offices and journals and not in the news. However, if people remain uninformed of trends, they may remain ignorant of the big picture. Even doctors who are not specialists may not be aware of some advances that have occurred in the past decade against metastatic lung cancer, melanoma, and a growing list of previously hopeless tumors. There is a need for good-quality news about cancer, especially in communities in which cancer mortality remains disproportionately high.

There is no easy prescription for distilling truth in oncology news. But I am hopeful, as journalists grapple with a changing pace of work and staff and as doctors contend with a changing pace of practice, that better education—of physicians and the public—about cancer, and in basic math, statistics, biology, and other fields relevant to oncology, will prove helpful. For journalists and for doctors, knowing how to interpret, convey, and interpret fluid information, is crucial for public health.

SIDEBAR 2. Possible Solutions for Health Journalism

1. Be transparent at all levels of reporting; reveal funding and other conflicts of interest that may influence physicians and scientists in academics and elsewhere, patients who may have organizational or industry ties, journalists, and publishers of news.
2. Reporters should seek input from varied sources.
3. Educate journalists about math, molecular biology, and statistics.
4. Independent health foundations might support in-depth coverage of advances.
5. Patient-driven "advocacy journalism" could help distribute critical information.
6. Increase public access to real-time and anonymized clinical data; this would enable constant re-evaluation of published work in context of new information.
7. Consider innovative systems of weighted commentary, culled from social media and other sources, to develop post-publication peer review of medical reports.

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Future Genetic/Genomic Biomarker Testing in Non–Small Cell Lung Cancer

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The magnitude of the challenge that cancer poses is increasingly alarming, with a 60% projected increase in the annual incidence, from 12.7 million new cases in 2008 to 22.2 million new cases projected for 2030.[1] However, cancer prognosis has also changed significantly over the past few decades. In the United States, cancer mortality decreased by 32% and 22% in men and women, respectively, between 1990 and 2015,[2] reflecting dramatic improvements in cancer care in the last 25 years. Advances in genomic sequencing and molecular marker identification during the last decade have unequivocally demonstrated that cancer is a heterogeneous disease.[3] Globally, genotype-directed targeted therapies are revolutionizing cancer care, and genetic alterations in genes such as *EGFR, ALK, ROS1, HER2, KIT,* and *BRAF* have been validated as powerful predictive biomarkers in the management of non–small cell lung cancer (NSCLC),[4] along with gastric cancer,[5] gastrointestinal stromal tumors,[6] and melanoma.[7]

In France, eliminating inequalities in access to molecular profiling tests and consequent treatment is a priority.[8] To this end, the French National Cancer Institute (INCa) and the French Ministry of Health established a national network of 28 molecular genetics centers that perform molecular tests for all patients in their region, irrespective of the institution where they are being treated. This program was updated in 2013 introducing next-generation sequencing (NGS) for switching from a gene-by-gene approach to a multiplexed strategy. The economic impact of this strategy has also been evaluated.[9]

CURRENT TECHNOLOGIC APPROACHES

Implementation of personalized medicine requires widely accessible tumor molecular profiling in routine practice, along with molecular centers for performing high-quality tests. Various methods exist for molecular profiling, including conventional Sanger sequencing, amplification refractory mutations systems, restriction fragment length polymorphisms, and, more recently, targeted NGS panels.[10] As it is now standard to test for a high number of mutations to personalize treatment decisions, use of NGS panels that can evaluate tumor biopsies for a wide range of potentially targetable mutations is increasing. Rapid and low-cost sequencing is providing physicians with the necessary tools to translate genomic information into clinically actionable results.

Although the use of NGS is attractive as less DNA is required compared with multiple individual assays, these advancements are not without limitations, and there are substantial improvements to be made in sequencing technologies, data analysis bioinformatics pipelines, and computer resources. Reporting the limitations of an NGS assay along with the result is critical for clinical interpretation, especially in the context of the NGS detection of uncommon molecular alterations for which clinical significance assessment constitutes a real challenge.[10] These elements are increasingly being discussed in molecular tumor boards, which are becoming widespread within the clinical sector. For example, in NSCLC, molecular tumor boards are feasible in daily practice allowing treatment recommendations in a majority of these patients (up to 70%), enrichment of their inclusion in clinical trials (57%) or expanded access programs (23%), and limitation of off-label drug use (9%).[11]

More extensive analysis such as RNA sequencing (RNA-seq), whole-exome sequencing, and whole-genome sequencing are also starting to be used in routine practice (Table 1).[10,12] Compared with the targeted NGS approach, they have the ability to detect rare and novel mutations that occur outside of specific, predefined regions as well as other types of molecular abnormalities such as gene translocations. Whole-exome sequencing and whole-genome sequencing allow detection of germline events involved in cancer susceptibility.[12] However, robust bioinformatics algorithms are needed not only to analyze large volumes of high-throughput data being generated for each patient, but

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TABLE 1. DNA/RNA Sequencing

Technique	Advantages	Disadvantages
Exome sequencing	Detection of genetics variations in all protein-coding regions of the genome	No detection of genetic variations in non–protein coding regions, including gene expression regulatory regions
	Detection of nucleotide variations and small insertions and deletions	Not feasible if limited material samples
	Discovered missense mutations, gene-disrupting mutations, and copy number variants	Slow turnaround time
	Exome size relatively small	
Genome sequencing	Detection of all genetic variations, including protein-coding and regulatory regions	High volume and complex data analysis because of the large size of the human genome
	Detection of nucleotide variations and genome reorganizations such as deletions, duplications, or translocations	High-level bioinformatics and computer resources required
		Greater amounts of DNA needed
		High cost for clinical use
RNA sequencing	Detection of genetic variations in protein-coding regions	Analysis restricted to genes expressed in the tissue or cell analyzed
	RNA expression levels	Genetic variations in untranscribed regions not detected
	Detections of RNA slicing variants and fusion transcripts	Adequate tumor tissue
	Size of the transcriptome smaller than the genome	

also to make predictions on the functional impact for each alteration, to classify drivers and passengers, and to prioritize different targets.

As much as the molecular analyses do themselves, the preanalytical steps of NGS tumor genotyping in routine practice also present practical challenges including sample quality, adequate biopsy specimens, and the need for repeat biopsies after development of drug resistance, emphasizing the importance of quality sample collection and proper processing techniques. It is thus incontestable that there is an unmet need for noninvasive assays that can broadly detect actionable genomic alterations.[13]

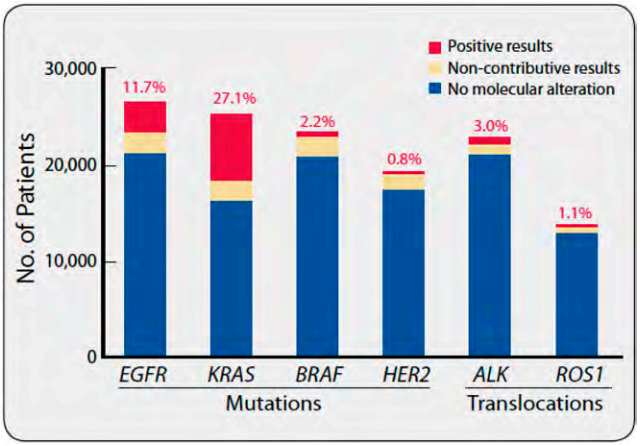
CLINICAL UTILITY OF MOLECULAR TESTING

Lung cancer remains the most common cancer at a global scale, both in terms of new cases (1.8 million cases, 12.9% of all total cancer cases) and deaths (1.6 million deaths, representing 19.4% of total cancer deaths).[14] It is also among the cancers with the highest mutation rates.[15] One of the most important therapeutic advances has been the identification of distinct molecular subsets amenable to targeted therapies, especially among adenocarcinomas, as well as the early success of immune checkpoint inhibitors.[16,17] In this indication, tumor genotyping is an essential routine diagnostic tool in clinical practice,[18] and this strategy correlates with survival improvement for those patients treated with personalized therapies.[4,19]

In lung cancer, the availability of several profiling platforms worldwide has seen impressive progress in molecular testing, breaking through the barrier of unselected treatment in NSCLC and pushing out survival limitations. In 2015, molecular screening (*EGFR, HER2, KRAS, BRAF,* and *PIK3CA* mutations, as well as *ALK* rearrangements) was performed in France at 28 certified centers for about 26,000 patients with NSCLC (Fig. 1). A clinical correlative work with the French Cooperative Thoracic Intergroup highlighted that a genetic driver alteration is recorded in about 50% of the analyses.[4] In addition to the organizational framework set up by the French INCa and the Ministry of Health, other examples of molecular profiling programs at a national level include initiatives from the Network Genomic Medicine in Germany,[20] the LC-SCRUM in Japan,[21] and the Lung Cancer Mutation Consortium in the United States.[19]

Druggable molecular alterations occur in 20% to 25% of adenocarcinomas.[4] The two most common are *EGFR* mutations, which occur in 12% of the Caucasian population (up to

FIGURE 1. Patients With Non–Small Cell Lung Cancer Screened for a Molecular Alteration in 2015



50% in Asian population),[22] and *ALK* rearrangements, which are seen in 5% of the population,[4] independently of the race. These alterations confer sensitivity to specific EGFR tyrosine kinase inhibitors (TKI) such as erlotinib, gefitinib, afatinib, and icotinib (only available in China), and to ALKs such as crizotinib or ceritinib. Up-front personalized treatment with a TKI confers statistically significant and clinically meaningful improvement in progression-free survival and response rate compared with platinum-based chemotherapy in patients with advanced *EGFR*-mutated[23] or *ALK*-rearranged NSCLC.[24,25] However, almost all patients acquire resistance to these therapies, and identifying the mechanisms of resistance becomes critical for the implementation of personalized treatment at progression, especially among *EGFR*-mutant tumors.

The most frequent pathway of resistance to EGFR TKI is the *Thr790Met* mutation in exon 20,[26] which confers sensitivity to third-generation EGFR TKIs such as osimertinib, improving the outcome at progression compared with standard chemotherapy.[27] Other mechanisms of resistance in *EGFR*-mutant tumors include *MET* amplification, *PIK3CA* mutations, *EGFR* amplification, and transformation to a small-cell phenotype.[26] The mechanisms of resistance seen following ALK inhibitor therapy again reflect tumor evolution with secondary *ALK* mutations, *ALK* copy number gain, secondary driver mutations in other genes, and bypass pathways.[28] A number of structurally distinct and more potent second- and third-generation ALK inhibitors are under evaluation for overcoming crizotinib resistance in the case of secondary *ALK* mutations. In this context, personalized treatment according to a molecular profile at progression is clearly the optimal strategy.

Putative oncogenic drivers in squamous cell carcinoma are rare, but several novel molecular abnormalities are being investigated as potentially actionable targets, specifically *FGFR1* amplification and *PIK3CA* and *DDR2* mutations.[29] Screening patients for solitary biomarker-driven studies requires both substantial time investment and adequate tumor tissue, resulting in low rates of enrollment. Because of this, new initiatives for lung treatment are in progress with trials integrating molecular screening and both targeted therapy and immunotherapy arms, such as the Lung Cancer Master Protocol (Lung-MAP; NCT02154490) for squamous cell carcinoma,[30] and the phase II umbrella trials National Lung Matrix Trial (NCT02664935)[31] and SAFIR02 Lung trial (NCT02117167) for squamous and nonsquamous NSCLC (Table 2). In SAFIR02, high throughput molecular analyses (e.g., CGH array, NGS) are used to evaluate the effect of treatment with targeted agents on progression-free survival compared with standard maintenance therapy in patients with metastatic NSCLC.

CHALLENGES AND SOLUTIONS

Beyond the more common nonsquamous NSCLC *EGFR* and *KRAS* mutations and *ALK* rearrangements, an important, albeit smaller, group of patients are found to harbor tumoral *HER2*, *BRAF*,[4] and *MET*[32] mutations or *ROS1*,[33] *NTRK1*,[34] and *RET*[21] gene fusions. The development of TKIs for other oncogene-driven NSCLCs may expand the portfolio of precision therapies as we enter a new paradigm of molecular therapies in oncology. As our understanding of tumor taxonomy and genotypes advances, it seems inevitable that some form of NGS platform will become the clinical standard for gene fusion detection instead of running multiple fluorescence in situ hybridization analyses. Both targeted and extensive RNAseq or whole-exome/whole-genome sequencing have the potential to detect *ALK* and other rearrangements.[10] To be widely used in clinical practice, RNAseq approaches have to be optimized for the clinical grade analysis of formalin-fixed, paraffin-embedded tumor samples. In addition to comprehensively identifying mutations in genes that encode members of RTK-induced signaling cascades, genomics efforts have uncovered mutations in genes involved in other important cellular processes (such as KEAP1-CUL3-NFE2L2, TP63, and SOX2, involved in the oxidative stress response and differentiation pathways).[29] Chromatin-modifying genes are recurrently mutated in lung adenocarcinoma and lung squamous cell carcinoma and also represent potential therapeutic targets in these diseases.[29,35]

The advent of immunotherapy presents additional challenges for molecular testing in NSCLC. To date, a number of potential biomarkers have been identified, but their relevance to clinical practice is still unclear and requires elucidation in prospective studies. Given that the marketing authorization of some checkpoint inhibitors has been restricted to patients with PD-L1–positive disease,[36] immunohistochemical evaluation of PD-L1 expression must be performed in routine practice. Nevertheless, some patients with PD-L1–low or PD-L1–negative tumors respond to these treatments. On a methodologic level, it is essential to harmonize the different detection and scoring methods before the routine use of PD-L1 expression as a predictive marker.[37] Recent whole-exome sequencing studies have shown a significant correlation between the total tumor mutational load and the predicted neoantigen load and clinical benefit with immune checkpoint inhibitors.[38,39] Characterization of neoantigens as a potential biomarker requires sufficient tumor DNA for whole-exome sequencing and carries major expense. But given the cost of these therapies, this initial outlay would be justified if the assay was sufficiently reliably predictive.[40]

Obtaining adequate tissue for diagnosis, tissue subtyping, molecular profiling, and treatment planning are critical for optimal patient management. Added to this, at the time of disease progression, a key challenge is also obtaining a recent sampling of the progressive tissue to determine the selection of second-line therapy. However, lack of tissue biopsy at progression is not uncommon, and furthermore, single site biopsies may not provide a representative profile of the overall predominant resistance mechanisms for a given patient.[41] Liquid biopsies based on circulating cell-free tumor DNA (ctDNA) analysis have been described as surrogate samples for molecular analysis, replacing solid tumor biopsies.[42] This approach offers the potential of real-time

TABLE 2. Molecularly Stratified Ongoing Umbrella Studies in Advanced Stage NSCLC

Study	Phase	No. of Patients	Primary Endpoint	Line	Screening Tests	Molecular Subgroups and Treatment
Lung-MAP[30] U.S.	Multisub-study, randomized phase II/III trial	10,000	PFS, ORR, OS	≥ second-line only SCC	NGS	GDC-0032 (PI3K inhibitor)
					IHC	MEDI4736 (anti-PD-L1)
						Palbociclib (CDK 4/6 inhibitor)
						AZD4547 (FGGFR 1-3 inhibitor)
						Docetaxel
National Lung Matrix Trial[31] U.K.	Multiarm, non-randomized, noncomparative phase II	620	ORR, PFS	≥ second line	NGS	AZD4547 (FGFR inhibitor)
						AZD2014 (MTORC1/2 inhibitor)
						Palbociclib (CDK4/6 inhibitor)
						Crizotinib (ALK/MET/ROS1 inhibitor)
						Selumetinib (MEK inhibitor)
						Docetaxel
						AZD5363 (AKT inhibitor)
						AZD9291 (EGFR and T790M inhibitor)
						MEDI4736 (anti-PDL1)
SAFIR02 Lung Study France	Open-label, multicentric, randomized phase II trial	650	PFS personalized vs. standard maintenance	First-line maintenance after four cycles of CT	NGS	AZD2014 (*m*-TOR inhibitor)
					CGH	AZD4547 (FGFR inhibitor)
						AZD5363 (AKT inhibitor)
						AZD8931 (HER2 and EGFR inhibitor)
						Selumetinib (MEK inhibitor)
						Vandetanib (VEGF, EGFR inhibitor)
						Pemetrexed
						MEDI4736 (anti PD-L1)

Abbreviations: NSCLC, non–small cell lung cancer; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; SCC, squamous cell carcinoma; CT, chemotherapy; NGS, next-generation sequencing; IHC, immunohistochemistry; CGH, comparative genomic hybridization.

sampling of multifocal clonal evolution,[43] as well as potential dynamic markers for monitoring the efficacy of treatment[44,45] and early detection of resistance mutations.[46] Early detection has been reported in patients with EGFR TKIs often prior to radiographic progression[46] and allows therapy to be adapted accordingly.[47] Further studies confirming clinical implications of monitoring the emergence of resistance mutations in plasma are warranted to guide therapeutic strategies. The phase II APPLE trial (NCT02856893) is one example of a strategic trial that is expected to provide some answers in the near future (Fig. 2).

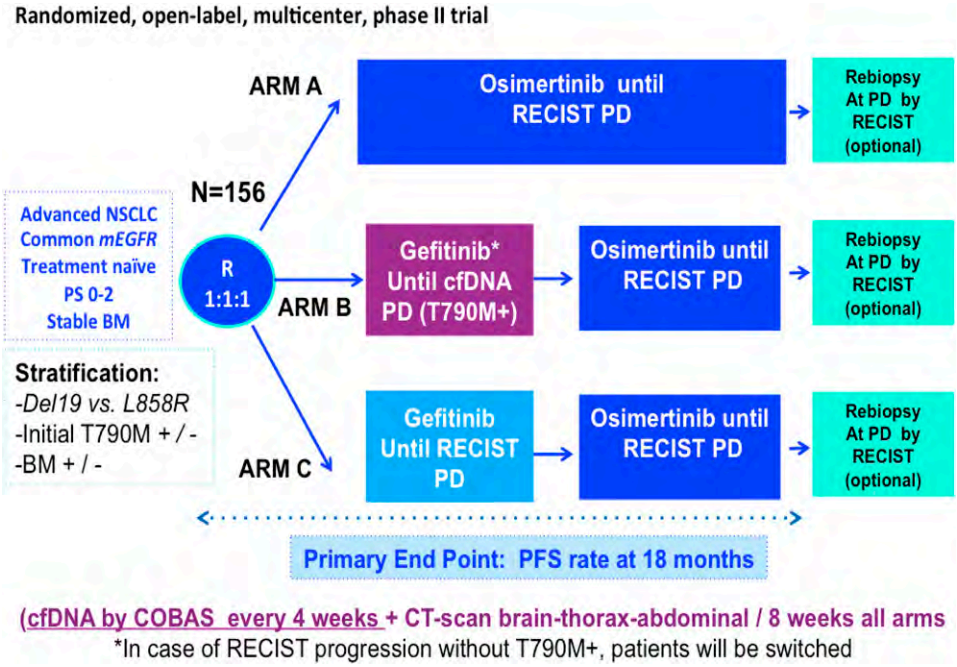
Discrepancies between the tumor biopsy and ctDNA genotyping may result from technologic differences or sampling of different tumor cell populations in a heterogeneous setting.[48] As sensitivity and specificity of ctDNA varies across different technology platforms,[49] the establishment of robust and standardized protocols for blood sampling, processing, storage, DNA extraction, and analysis will support the role of liquid biopsies as standard tests in the near future for tumor genotyping and predictive biomarkers.[49] These recent techniques will ensure that molecular genomic analysis and personalized treatments are soon available to more patients. Finally, circulating tumor cells isolated from the peripheral blood offer a complementary circulating biomarker to ctDNA. Circulating tumor cells permit further immunohistochemistry/fluorescence in situ hybridization characterization, while single-cell DNA sequencing or RNAseq is also possible, as well as the generation of tumor xenografts to assess drug response.[50] However, at present, the technologic complexity of circulating tumor cell isolation and the need to process samples quickly for functional/genomic studies results in greater expense compared with ctDNA analysis.

CONCLUSION

Molecular genotyping in NSCLC is common in the clinic. In the near future, noninvasive biopsies and standardization of NGS with detection of gene fusion alterations will become the new standard in daily clinical practice. With the development of NGS allowing for the detection of multiple genomic alterations, the need to prioritize these gene alterations to drug response is pressing. The immediate challenges in routine practice includes the cost of molecular profiling, limiting social inequalities that affect access to these tests, the widespread molecular tumor boards, and access to clinical trials for patients with uncommon mutations.

Molecular profiling for other thoracic malignancies is another important area currently being addressed. SPECTA-lung (NCT02214134) is a pan-European program aimed at screening patients with thoracic tumors (i.e., lung cancer,

FIGURE 2. APPLE Trial Design



Abbreviations: BM, brain metastases; PFS, progression-free survival; PD, progressive disease; PS, performance status.

malignant pleural mesothelioma, thymoma or thymic carcinoma at any stage) to identify the molecular characteristics of their disease to ensure efficient clinical trial access and personalized treatments in the case of specific mutations. Cross-analysis of mutational data with multiomics data, functional data, and clinicopathologic data in a larger number of samples is an integral part of this. Thus, international collaborative efforts as well as increased integration of technologic aspects of molecular characterization with clinical data are needed to further advance the treatment of patients with NSCLC.

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Making the Case for Improving Oncology Workforce Diversity

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Since its inception in 2008, ASCO's Diversity in Oncology Initiative has engaged in programming designed to support and promote diversity in the oncology workforce.[1] The programs, developed by the ASCO Health Disparities Committee and funded through the Conquer Cancer Foundation, include mentoring and award opportunities for medical students and residents from backgrounds that are traditionally underrepresented in medicine (URM). During a recent evaluation of the Initiative, it was recognized that a more comprehensive plan was needed to ensure it successfully met its intended goal. In response to the organization's goal of increasing diversity and inclusion in oncology professions, the Health Disparities Committee convened a task force in 2015 that ultimately formulated a strategic plan for racial/ethnic workforce diversity, consonant with ASCO's overall Workforce Strategic Plan.[2] In December 2016, the ASCO Board approved the strategic plan, affirming that diversity is central to its mission and strengthens the organization. Although some still question the rationale for efforts around diversity and inclusion, the current state of our nation and our nation's health care system clearly speak to the need for a concerted effort to diversify the oncology workforce.

CANCER DISPARITIES

Cancer is a major health care problem worldwide and the second cause of death in the United States. An estimated 600,920 individuals will succumb to cancer in 2017.[3] The most common cancer-specific causes of death are cancers of the lung and bronchus, colon and rectum, and prostate in men, and the lung and bronchus, colon and rectum, and breast in women. National attention has increasingly shifted to the issue of health disparities based on race/ethnicity and its impact on the health of the nation. African American, American Indian, and Alaskan Native populations have the poorest health status of all racial/ethnic groups in the United States.[4] These communities are plagued by increased incidence of obesity, HIV/AIDS, heart disease, and myriad other conditions. However, African Americans experience the worst cancer outcomes of all races/ethnicities (Fig. 1).[5]

Several metrics have been used to delineate disparate cancer outcomes experienced by medically underserved communities. Disparities in cancer screening, treatment, and outcomes are well documented by socioeconomic status, health care access, insurance status, and race.[4,6,7] For selected cancers, significant differences in incidence and mortality between racial/ethnic groups have been demonstrated. For example, African Americans are more likely to have more advanced-stage disease at the time of cancer diagnosis and to experience lower stage-specific survival rates compared with the white population. Presentation at late stage may be related to access to screening because of lower health insurance coverage rates in African Americans and other minorities compared with non-Hispanic whites. The impact of the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act of 2010 (Affordable Care Act or ACA) on rates of insured cannot be overstated. In 2015, the uninsured rates in the black population dropped to 11% from 21% in 2010. Similarly, for non-Hispanic whites, the uninsured rate declined from 12% in 2010 to 7% in 2015.[3] Although all racial/ethnic groups have seen a steady decline in cancer mortality, the overall cancer death rate in 2014 was 15% higher for African Americans than the white population. The persistent gap in mortality suggests that insurance alone is not enough to level the playing field; more is required to improve access to care along the cancer continuum.

Cancer disparities arise as a result of complex interactions between biologic, clinical, social, and environmental factors at the patient and the population levels (Fig. 2).[8,9] Establishing a comprehensive strategy to meet these needs of patients with cancer requires detailed population-level data on incidence rates and survival disparities that address these factors; an infrastructure to support clinical and basic research to understand how these factors that influence prognosis and survivorship can facilitate strategies and interventions that prevent cancer and improve outcomes; and a well-trained workforce that can use this infrastructure and other resources to examine and address the needs of underserved patient populations.

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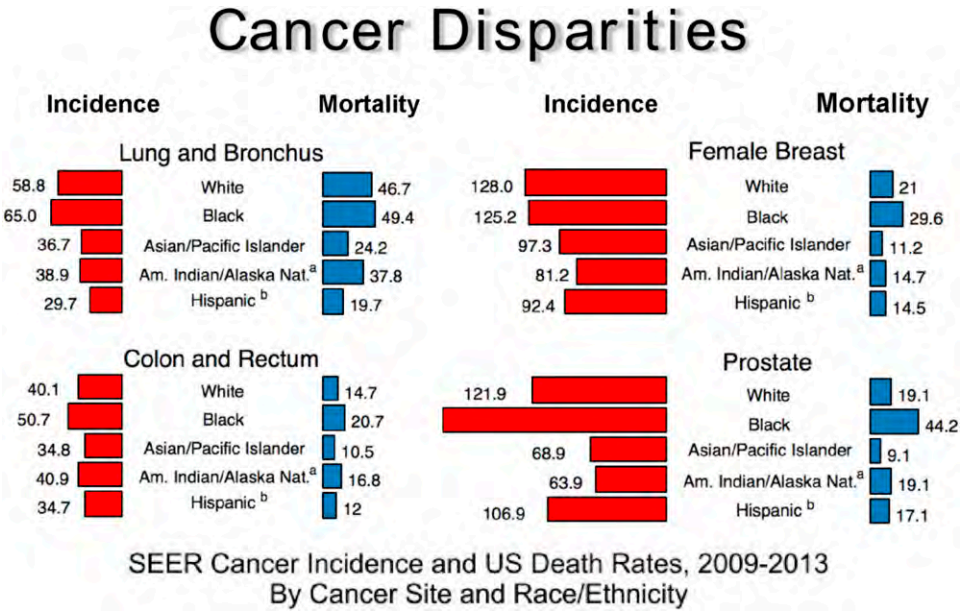
FIGURE 1. Incidence and Cause-Specific Mortality of the Top Four Cancer Sites in the United States by Race/Ethnicity



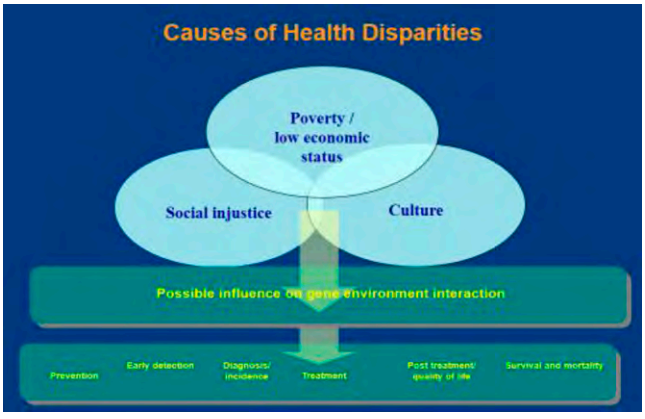
From the Surveillance, Epidemiology, and End Results data from 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, rural Georgia, California excluding San Francisco/San Jose-Monterey/Los Angeles, Kentucky, Louisiana, New Jersey, and Georgia excluding Atlanta/rural Georgia) and U.S. Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention. Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population (19 age groups; Census P25-1103).
(a) Rates for American Indian/Alaska Natives are based on the Contract Health Service Delivery Area counties. (b) Hispanic is not mutually exclusive from the white or black populations, Asian/Pacific Islanders, or American Indians/Alaska Natives. Incidence data for Hispanic numbers are based on North American Association of Central Cancer Registries Hispanic Identification Algorithm and exclude cases from the Alaska Native Registry.

Disparities in health care based on race/ethnicity represent a mutable factor that costs the U.S. government billions of dollars annually. A recent report estimates that from 2009 through 2018, the total cost of these disparities will be approximately $337 billion, with the annual cost estimated to more than double to $50 billion by 2050, attributed in part to the aging black and Hispanic populations.[10] Studies have consistently demonstrated the propensity of URM physicians to provide improved access to health care for underserved populations.[11-14]

ONCOLOGY WORKFORCE

Even the ACA recognized the importance of workforce diversity in stemming health inequities by establishing or renewing funding for several pipeline programs that may impact the racial composition of the workforce.[15,16] However, the U.S. Congress has yet to fund the National Health Care Workforce Commission,[17] an important component of the ACA that could make recommendations to compel institutions to consider workforce diversity in the design and implementation of their clinical practices. Therefore other strategies must be used to address the increasing challenges that will be faced as the diversity of patients with cancer and survivors continues to increase. According to the U.S. Census Bureau, by 2060, minorities (including African Americans, Hispanics, American Indians, and Alaska Natives) will make up 56% of the U.S. population,[18] a major increase from 38% in 2014. Although the lack of workforce diversity has been shown to negatively impact quality and health outcomes for minority patients, a diverse workforce can increase patients' comfort and trust with their providers, thereby improving patient access to and satisfaction with their health care.[12]

FIGURE 2. Causes of Health Disparities



The complex interplay between socioeconomic status, culture, and biology on cancer disparities. In addition to impacting access to care across the entire cancer continuum from prevention through survivorship, health disparities may influence the genetic environment as well.

Lack of diversity is compounded by the growing need for oncologists in general. According to the Association of American Medical Colleges (AAMC), in 1971, there were approximately 3 million cancer survivors in the United States. By 2001, the number of survivors increased to nearly 10 million.[19] Given that the number of cancer survivors likely will continue to increase, there will be a corresponding increase in demand for well-trained clinical oncologists. This is particularly relevant as the current oncology workforce continues to age without a corresponding increase in the number of fellowship positions. As noted above, ASCO had previously articulated a strategic plan focused on general workforce development and has now stepped up to address the need for increased racial/ethnic diversity.

BARRIERS TO ADDRESS

Unfortunately, the field of oncology and its subspecialties reflect and magnify the lack of racial and gender diversity present in the general medical field. In 2007, the AAMC reported that 59% of the oncology workforce from a sample of 4,000 physicians was white.[19] Black, Hispanic, and female physicians are statistically less represented in oncology than white males, perpetuated by a lack of minority and female clinicians entering the oncology workforce and reinforced by a lack of minority and women role models in leadership positions in academic medicine.[20] In 2015, only 3.7% of oncology fellows were black, and 5.3% of fellows were Hispanic.[21] These trends are even more worrisome with respect to the lack of diversity in cancer leadership positions. In 2013, minorities held only 4% of National Institutes of Health Research Project grants despite making up 29% of the U.S. population.[22] It has been long established that faculty diversity not only benefits medical students and trainees but also provides faculty from all backgrounds with an opportunity to enhance their ability to care for an increasingly diverse population.[14] If the oncology workforce continues to lack diversity, the health of the increasingly diverse patient pool will be at stake. Not only is there a need for in-depth training programs to address these disparities, but dissemination of the skills and courses taught to selected individuals who are focused on cultural humility also appears to aid in the dissemination of knowledge to cancer researchers at all levels, including those not in the training program.[23]

To combat these trends, inclusion and diversity have risen to the forefront as desired characteristics of successful organizations that are essential to competition.[24,25] For inclusion to be normalized, it must be integrated into multiple aspects of the entity, including hiring, promotion, and encouraging minority and women leaders to pave the way for those just starting their careers.[24] One evidence-based strategy for encouraging more minorities and women to pursue leadership roles in medicine is accessing programs that provide guidance and support for trainees to pursue clinical research. Dedicated mentorship from and collaboration with women and minorities who have already achieved success in the field is an important component of this strategy.[26] Supporting trainees at multiple levels within the pipeline can provide a career development pathway that is essential to ensuring a well-trained cohort of leaders and care providers in the future. Moreover, facilitating opportunities for minority mentor and minority mentee relationships among seasoned specialists/researchers and trainees has been demonstrated to be important for the career development of minority professionals.[19]

PROGRAMS TO IMPROVE PHYSICIAN WORKFORCE DIVERSITY

Increasing minority participation in science, technology, engineering, and mathematics education at all levels has been recommended as a national priority.[27] Although black and Hispanic individuals make up 11.7% and 14.6% of the U.S. population, respectively, they account for 7.2% and 7.7% of college degree holders and 4.8% and 6.1% of individuals in science and engineering occupations.[27] Having an experienced professional as a mentor can inspire younger mentees to pursue careers in science and clinical care, can provide encouragement for mentees to seek out leadership roles,[19] and is associated with greater career satisfaction.[28] Studies have shown that fostering such relationships benefits the mentors, influencing academic productivity and career advancement.[29,30]

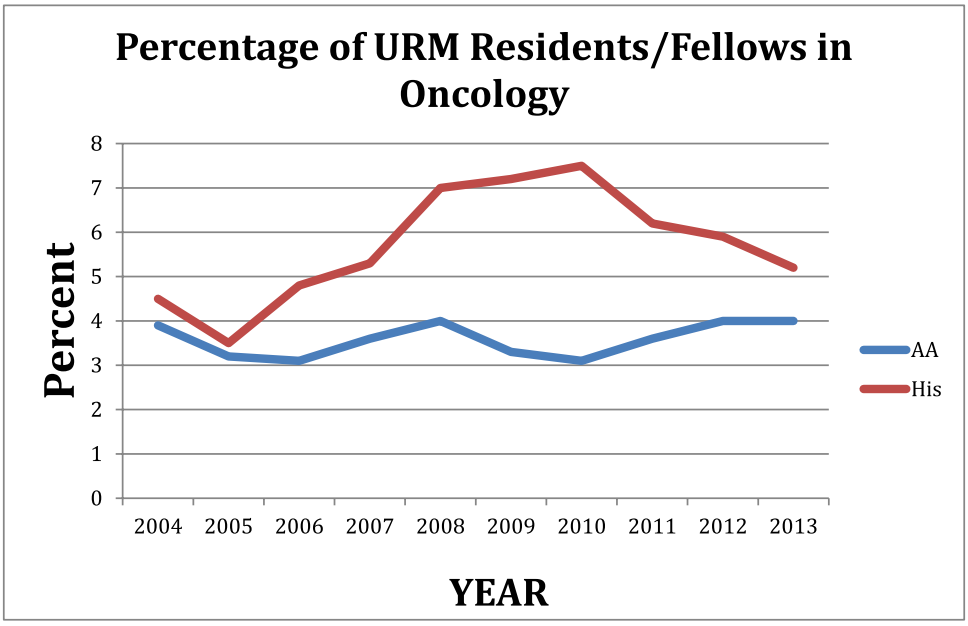
Even when underrepresented minorities enter medical school, several hurdles can restrict the successful recruitment and retention of minorities to careers in cancer clinical care and research. A key barrier is lack of exposure to programs that foster understanding and appreciation of the opportunities available in oncology practice and biomedical research. Prominent societies involved in cancer care, including the American Society of Hematology,[31] the American Society for Radiation Oncology,[32] and the American Association for Cancer Research,[33] among others, have established initiatives designed to provide exposure to research and clinical careers at varying stages of career development. Yet, the fact that some oncologists, even those at prominent academic centers with training programs, do not understand what the acronym "URM" stands for is a bit disconcerting. In 2003, the Association of American Medical Colleges shifted the expansion of "URM" from "underrepresented minority" (black population, Mexican Americans, Native Americans, which includes American Indians, Alaska Natives, and Native Hawaiians) to "underrepresented in medicine."[34] URM has grown to reflect the evolving demographics of the nation, but the sentiment of the acronym has remained consistent: "those racial and ethnic populations that are underrepresented in the medical profession relative to their numbers in the general population." It is imperative that all oncologists—but particularly those who are in a position to influence the character and makeup of training/fellowship programs—acknowledge the lack of diversity in the workforce and understand the importance of reaching out to URM medical students early in their curriculum.

For the past 9 years, ASCO's Diversity in Oncology Initiative program has awarded opportunities for medical students and residents who self-identify as URM. The ASCO Medical Student Rotation Award supports clinical oncology or cancer clinical research rotations and pairs URM medical students with a clinical oncologist who provides ongoing academic and career development advice. The ASCO Resident Travel Award supports residents to attend the ASCO Annual Meeting. Since 2008, the ASCO Diversity in Oncology Initiative has provided over $1 million to fund 137 individuals, and 81 recipients have become ASCO members, providing an early indication of the success of this program amid increasing oncology workforce diversity. However, to ensure sustainability and support the changing needs of the diverse population we serve, ASCO's recently adopted strategic plan for increasing racial and ethnic diversity in the oncology workforce provides a blueprint for a comprehensive approach to diversity and inclusion.

PROGRAM PARTICIPATION IS KEY

Although ASCO plans to set an example by demonstrating what diversity and inclusion looks like within the organization

FIGURE 3. Percentage of URM Residents/Fellows in Oncology Training Programs



Abbreviations: URM, underrepresented in medicine; AA, African American; His, Hispanic.

Adapted from: "The State of Cancer Care in America, 2016: A Report by the American Society of Clinical Oncology."[38] Note: Data represent the total number of fellows (MDs and DOs) in hematology, hematology/oncology, and clinical oncology graduate medical education programs accredited by the Accreditation Council for Graduation Medical Education.

and by continuing to provide opportunities to URM trainees, their efforts alone are not sufficient. Training programs, academic institutions, and individual practices, whether private or hospital-based, must be willing not only to diversify but to create a truly inclusive environment. Medicine has trailed behind in the recognition that diversity breeds innovation and even improves the financial bottom line. Bringing in new talent fromdiverse backgrounds will require an investment of time, thought, and energy. Leadership must set goals and priorities and articulate a vision for inclusivity that others within the organization will value and accept.

Recent reports have demonstrated that while the percentage of Hispanic trainees in oncology is improving, the number of black students graduating from medical school and entering oncology specialties has remained stagnant over the past few decades (Fig. 3).[35,36] Even with the slow increase in the number of Hispanic trainees, a workforce that sufficiently reflects the diversity of the United States will not happen over night. Until the number of URM oncologists increases to adequately address our nation's growing needs, thoughtful strategies related to employment of advanced practice providers from diverse backgrounds, such as nurse practitioners, physician assistants, and clinical nurse specialists, among others,[37] may provide a critical bridge. However, it is just as important for non-URM oncologists and staff to understand their cultural biases and learn the importance of cultural sensitivity and cultural humility. This is particularly important for minority-serving institutions that provide cancer care to a greater percentage of patients from diverse backgrounds. ASCO has thoughtfully created several programs related to cultural competency that can be accessed through ASCO University. There is even a membership category for advanced practice providers to help provide the support needed for these valued members of the oncology care team to develop the knowledge and skills required to fully engage in a diverse oncology practice.

The effective creation of a workforce that is reflective of the patients it serves first requires an institution to embrace diversity and inclusion as its core values. Change will not come quickly or easily, and therefore, the only way to succeed is for organizational leadership to be intentional in the design and implementation of programming.[25] By approving the strategic plan for improving racial/ethnic workforce diversity and sharing it with the world,[39] ASCO has raised the bar by openly setting specific goals and inviting others to hold them accountable. Hopefully, oncology training programs and practices around the country will soon follow the example and work toward creating a more diverse and inclusive environment that will enable us to provide better care for all of our patients.

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Minimizing Minimally Invasive Surgery for Endometrial Carcinoma

Melissa K. Frey, MD, Stephanie V. Blank, MD, and John P. Curtin, MD

Endometrial cancer is the most common gynecologic malignancy, and, in contrast to many other cancer types, the incidence and mortality of endometrial cancer continue to grow. In the United States, there were approximately 40,000 cases of endometrial cancer in 2006; however, in 2017, there will be an estimated 61,380 new cases and 10,920 deaths.[1] The growing obesity epidemic is a considerable contributor to this trend, as more than half of endometrial cancers are attributable to obesity.[2,3] Furthermore, as obesity rates continue to rise, the incidence of endometrial cancer is expected to increase. Models predict an incidence of 42.13 cases per 100,000 women by the year 2030, representing a 55% increase over 2010.[4,5]

Given the substantial increase in the incidence of endometrial cancer, close association with obesity, and the increased prevalence among premenopausal women, management approaches that limit extensive surgical staging will become increasingly important. The Gynecologic Oncology Group LAP2 trial established the oncologic safety of minimally invasive surgery for the treatment of endometrial cancer. This study also demonstrated a reduction in postoperative adverse events and improved quality of life with a minimally invasive approach.[6] The LAP2 results culminated in the American College of Obstetricians and Gynecologists (ACOG) and Society of Gynecologic Oncology (SGO) practice bulletin stating that minimally invasive surgery should be embraced as the standard surgical approach for comprehensive surgical staging in women with endometrial cancer.[7] Minimally invasive surgery is especially important for obese patients, as obesity has been independently associated with increased surgical complications, and surgical morbidity is most profound in open surgery.[8,9] In the LAP2 study, there was a direct relationship between patient body mass index and conversion from laparoscopic approach to laparotomy. In part, this was due to the protocol mandate that all patients have pelvic and para-aortic lymph node sampling performed.

In this review article, we will review two methods that can further minimize minimally invasive surgery for endometrial cancer: (1) assessment of lymph nodes with sentinel lymph node (SLN) mapping, and (2) ovarian preservation at the time of endometrial cancer surgery. We purport that surgical approaches that reduce minimally invasive surgery are essential to the development of safe and cost-effective treatments for patients with endometrial cancer. Additionally, because the majority of women will survive and surpass their endometrial cancer, it is increasingly important to consider the long-term health implications of their treatments and optimize survivorship.

SLN MAPPING

Pelvic and para-aortic lymphadenectomy has been included in the surgical staging criteria for endometrial cancer since 1988.[10] Lymph node status is the most important predictor of survival and provides risk assessment that guides postoperative treatment planning.[11] The SEPAL study suggested a therapeutic effect of lymphadenectomy, with significantly longer overall survival among patients who had pelvic and para-aortic lymphadenectomy in this retrospective analysis.[12] However, two randomized controlled trials have failed to show a survival benefit with pelvic and selective para-aortic lymphadenectomy.[13,14] Lymphadenectomy has been associated with prolonged operating time, additional cost, and increased morbidity including lymphedema, lymphocysts, and neuralgia.[15] Although the therapeutic benefit of lymphadenectomy remains controversial, most agree that lymph node status can help determine which patients should undergo adjuvant therapy and which patients can avoid additional cancer-directed treatment and the associated morbidity. A Surveillance, Epidemiology, and End Results (SEER) database study demonstrated that patients who undergo lymphadenectomy are less likely to receive pelvic radiation.[11]

The SLN is the first node to receive drainage from a primary tumor. This lymph node, therefore, is most likely to

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harbor cancer cells for those cancers that spread via the lymphatic system. SLN mapping and ultrastaging of SLNs have been proposed as a surgical method to reduce the morbidity of surgical staging while maintaining the prognostic information of lymph node status assessment. SLN mapping and ultrastaging are currently considered standard of care for the surgical staging of breast cancer, melanoma, and vulvar cancer.[16,17]

SLN Mapping Technique

Most of the early studies of endometrial cancer SLN mapping used a combination of radioactive tracer with lymphoscintigraphy or single-photon emission CT (SPECT-CT) and colored dye (patent blue, isosulfan blue, and methylene blue) to visualize nodes.[18] Drawbacks of radioactive tracers include difficulty detecting SLN close to the cervix as the gamma-probe detects high activity from the cervical injection site, patient inconvenience of having to undergo preoperative injection and imaging, and costly resources and equipment that are not available to all surgeons.[19] With the current widespread availability of the robotic platform and near-infrared imaging, many surgeons have replaced the dual injections with indocyanine green (ICG) and immunofluorescence detection (Fig. 1). ICG injection seems to negate the higher rates of failed SLN mapping observed in obese patients, possibly because of differences in the molecular weight of the isosulfan blue versus ICG and that ICG is more prominently visualized in the setting of visceral and retroperitoneal fat.[20] Of note, although widely used for endometrial cancer SLN mapping, ICG is not approved by the U.S. Food and Drug Administration for this indication.

In other cancers in which SLN mapping is the standard of care, like breast cancer and melanoma, direct peritumoral injection is straightforward; however, this is not the case for endometrial cancer. Several injection locations have been evaluated, including intracervical, uterine subserosal, fundal, and even peritumoral.[21-23] The SGO Clinical Practice Statement supports cervical injection, stating that it is a reproducible technique that adequately maps the pelvic lymph nodes and occasionally lower aortic nodes; however, they also have noted that there are insufficient data to suggest that the upper aortic lymph nodes (above the inferior mesenteric artery) can be reliably mapped using current cervical injection techniques.[16] López-De la Manzanara Cano et al[24] found that a deeper injection (3 cm) had improved detection of para-aortic SLNs. Many propose restricting the cervical injection to low/intermediate-risk tumors that have a low likelihood of para-aortic involvement,[25] a restriction that would include the majority of endometrial cancers. The SGO Clinical Practice Statement additionally suggests that decisions regarding para-aortic lymphadenectomy should be determined by tumor histology, intraoperative findings, and status of pelvic lymph nodes at surgery.[16]

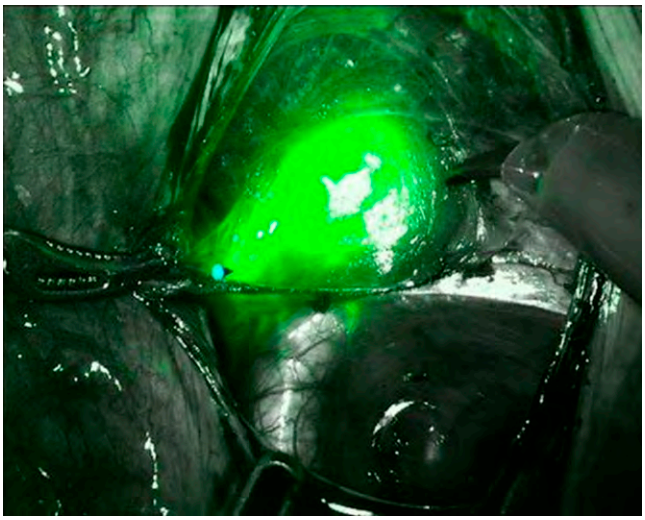
The Memorial Sloan Kettering SLN algorithm mandates that failure to map a SLN results in complete lymphadenectomy on the respective hemipelvis, as well as removal of any suspicious nodes and peritoneal lesions, and meticulous ultrastaging of SLNs. Barlin et al[26] found that applying this mapping algorithm significantly reduced the false-negative rate from 14.9% to 1.9%. A recently published modeling analysis proposed an approach termed SLN-restrictive frozen section strategy, in which patients who did not map SLNs would have intraoperative frozen-section evaluation, and the decision to perform a lymph node dissection would be determined by the identification of high-risk uterine features on frozen-section diagnosis.[27] Whether the ideal management of failed SLN mapping involves either of these approaches remains unknown, but both present reasonable options.

Pathologic ultrastaging of SLN varies among institutions, and clear guidelines have not been established for gynecologic pathologists. The process generally involves examination of multiple deeper level sections of the lymph node using routine staining and keratin immunohistochemical staining. Lymph node metastases are classified according to their size in accordance with the nomenclature used for breast cancer metastases.[28]

1. Macrometastasis: tumor clusters larger than 2 mm.
2. Micrometastasis: tumor clusters between 0.2 to 2 mm in size.
3. Isolated tumor cells: single tumor cells or tumor clusters that are 0.2 mm or smaller in size.
4. Isolated cytokeratin-positive cells.

Kim et al[29] found that SLN mapping detected additional low-volume metastases in 4.5% of patients relative to routine lymph node evaluation. Although most groups consider macrometastasis and micrometastasis to be positive SLN, the prognostic value of isolated tumor cells and isolated cytokeratin-positive cells remains uncertain. Furthermore, appropriate treatment of patients with low-volume metastatic disease is not yet known and varies by institution.

FIGURE 1. SLN Visualized With ICG and Immunofluorescence Detection



Abbreviations: SLN, sentinel lymph node; ICG, indocyanine green.

SLN Mapping Efficacy

Despite more than a decade of studies of SLNs in endometrial cancer, it has yet to be established as a standard of care for patients with this disease, and results in the literature vary. This is likely because of a myriad of currently used SLN mapping techniques combined with the complexity and bilaterality of the nodal basins that drain the uterus.[30-33] The initial results for SLN mapping were promising, including the SENTI-ENDO trial, which found 100% negative predictive value and 100% sensitivity of SLN when considering the hemipelvis as the unit of analysis and 97% negative predictive value and 84% sensitivity when considering the patient as the unit of analysis.[18] However, a meta-analysis of 26 studies found a detection rate of 78% and sensitivity of 93% and cautioned that the demonstrated good diagnostic performance of SLN mapping in endometrial cancer should be interpreted with caution because of the notable small-study effect.[34] A more recent meta-analysis identified a higher pooled detection rate (81%) and sensitivity of 96% for detecting lymphatic metastases, rates that approach those observed in breast cancer and melanoma.[32] The authors suggest that these improvements may reflect gynecologic surgeons' growing experience with SLN mapping and increased use of more innovative dye and detection techniques. To account for the learning curve, the SGO Clinical Practice Statement suggests that surgeons should train by performing SLN dissection and then lymphadenectomy on 20 patients prior to adopting SLN as their standard surgical method.

Benefits of SLN Mapping

The most important advantages of SLN mapping include improved detection of metastatic disease through ultrastaging of lymph nodes and reduction in morbidity by eliminating the complete lymph node dissection. Although finding metastases that would have otherwise been missed seems valuable, some might argue that altering therapy based on this information results in overtreatment, and the use of SLN in endometrial cancer has not been shown to improve oncologic outcomes. The inclusion of lymph node dissection in endometrial cancer staging procedures has been shown to increase operative room time, surgical blood loss, length of hospital stay, and morbidity, including permanent lymphedema. Dowdy et al[15] found that complications in the first 30 days following surgery occurred in 19.3% versus 37.5% of patients in the non–lymph node dissection versus lymph node dissection group. The 30-day cost-of-care was also found to be significantly higher in the lymph node dissection group, correlating directly with increasing severity of adverse events among these patients. There are yet to be prospective evaluations of the morbidity of SLN mapping in endometrial cancer; however, most would agree that these patients should have an experience that more closely emulates the patients without complete lymphadenectomy.

OVARIAN PRESERVATION

Whereas many debate the necessity of nodal assessment as part of the treatment of patients with endometrial cancer, hysterectomy and bilateral salpingo-oophorectomy are standard. The rationale for ovarian removal includes detection and removal of occult metastatic disease as well as synchronous ovarian cancers and diminishment of estrogen production. With an amplified incidence of endometrial cancer along with an increasing proportion of diagnoses occurring in younger women, the number of premenopausal women losing their ovaries to endometrial cancer will grow. Almost one-fourth of U.S. women with endometrial cancer are premenopausal at diagnosis,[35] and other reported incidences are even higher, such as in Korea, with 45% of cases occurring in premenopausal women, 10% in women under 40.[36,37] Removing the ovaries in premenopausal women subjects them to surgical menopause and its attendant symptoms of estrogen deprivation, along with increased risk of cardiovascular disease, osteoporotic fractures, cognitive impairment, and possibly diminished survival, although the most quoted study demonstrating survival benefit to ovarian retention did not include women with cancer.[35,38,39]

Citing these concerns, several groups have considered the safety of ovarian preservation among young women with endometrial cancer. A query of SEER data found that ovarian preservation in women under 45 with low-grade early-stage endometrial cancer had no effect on either cancer-specific or overall survival.[40] A population-based analysis using the National Cancer Database compared the 7% of women with stage I endometrial cancer under the age of 50 with retained ovaries to those who underwent bilateral oophorectomy and also found that ovarian conservation did not adversely affect oncologic outcomes.[41] A nationwide study from tumor registries in Korea evaluated 175 women with endometrial cancer who retained their ovaries. With median follow-up of 55 months, 4% recurrence risk was noted and none in patients with stage I endometrioid tumors. All patients who recurred had risk factors including a nonendometrioid histology, contralateral adnexal involvement, or deep myometrial or cervical stromal invasion. The authors concluded that in selected patients (Table 1), oophorectomy need not be a mandatory component of standard surgical therapy for endometrial cancer.[42] More recently, a follow-up SEER study of ovarian conservation in young women with early-stage low-grade endometrial cancer found the same cause-specific survival for retaining and removing ovaries but improved overall survival with ovarian retention as well as a lower cumulative risk of death from cardiovascular disease.[43]

This finding is not necessarily surprising. Several SEER studies have shown that among women with favorable endometrial cancers, cardiovascular disease is a more probable cause of death than is cancer,[44,45] in part because of the high likelihood of curative cancer treatment[46-52] and the prevalence of cardiovascular disease, especially among patients with endometrial cancer whose risk factors for endometrial cancer are also risk factors for cardiovascular disease. Additionally, when the indication for hysterectomy is not cancer, the case for ovarian retention is compelling. The Nurses' Health Study showed that all-cause mortality, coronary heart disease mortality, and deaths from all cancers

TABLE 1. Proposed Indications for Ovarian Preservation in Patients With Endometrial Cancer[42]

Proposed Indicators
Patients who want to retain ovarian function.
No gross intraoperative extra-uterine tumor spread.
No gross abnormality in bilateral ovaries.
Negative results of frozen biopsy for lymph nodes suspicious for metastasis.
Endometrioid-type histology in preoperative biopsy.
Patients who have no inherited predisposition to breast or ovarian cancer.

were diminished when ovaries were retained at the time of hysterectomy for benign disease versus when ovaries were removed.[39] Several smaller cohort studies similarly confirm this association.[53-56] More recently, a nationwide study in the United Kingdom compared ovarian removal to conservation and found conservation to be associated with lower all-cause mortality as well as lower death rates from heart disease and cancer, causing the authors to conclude that removing ovaries to prevent ovarian cancer comes at the cost of an increased risk of cardiovascular disease and other more prevalent cancers and higher overall mortality.[57]

CONCLUSION

We have explored two methods to additionally minimize minimally invasive surgery for endometrial cancer—SLN mapping and ovarian preservation. The greatest obstacle in adopting SLN mapping as standard of care for endometrial cancer is the lack of large prospective studies that perform complete systematic pelvic and para-aortic lymph node dissection as a true control arm. However, according to a survey of SGO members, 28.6% of respondents performed SLN mapping, 16.7% with the exclusion of pelvic lymphadenectomy, and 54% of institutions performed pathologic ultrastaging of SLN.[16] Furthermore, the National Comprehensive Cancer Network guidelines for endometrial carcinoma now include a SLN algorithm as an option for surgical management of endometrial cancer. The uncertainty surrounding the value of lymph node assessment in endometrial cancer is not likely to be resolved in the near future. However, SLN mapping is emerging as an effective surgical technique to allow tailored adjuvant therapy for high-risk patients while minimizing the risk of harm that occurs with a complete lymphadenectomy. A compelling case also can be made for ovarian retention in women with early-stage, early-grade endometrioid endometrial cancer, particularly in premenopausal women, but potentially in older women as well. Ovarian preservation has been associated with improved overall survival and lower risk of cardiovascular disease in many studies. This is not to say that ovarian preservation should be standard of care in these cases but that ovarian extirpation should not be automatic for all women with endometrial cancer, as a select group may benefit from keeping their ovaries.

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The Road to Addressing Noncommunicable Diseases and Cancer in Global Health Policy

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Premature death and disability from cancer and other noncommunicable diseases (NCDs)—such as diabetes, heart disease, chronic respiratory disease, and others—are on a rapid rise in low- and middle-income countries. Whereas in 1990, 57% of global deaths were attributed to NCDs, they accounted for 70% (38.3 million) in 2013, with 80% of premature deaths reported in low- and middle-income countries.[1,2] Historically viewed as conditions largely affecting rich countries and elderly populations, global NCDs were long neglected as a development and even health priority in resource-limited settings. Now, these countries are experiencing an epidemiologic transition in which more patients are afflicted by NCDs, with longer suffering and death at younger ages than in high-income countries.[3]

Rising global rates of NCDs have enormous economic implications, estimated at a cumulative loss of 47 trillion between 2011 and 2030.[4] Premature NCD death and disability, defined by the World Health Organization (WHO) as those younger than age 70, result in people working fewer years, with lower productivity, and result in higher costs to both the health system and individuals.[5,6] As NCDs are both a cause and a consequence of poverty, they are a threat to sustainable human development on a global scale. Social, economic, and environmental factors, such as globalization, international trade, urbanization, education, labor practices, household income, and food production, all serve as risk factors for NCDs.

This previously under-recognized crisis underlies the importance of global coordinated action to increasingly recognize NCDs as a political issue. In many cases, we have solutions in the form of scientific and technical progress, but these are insufficiently implemented due to a lack of political will. Thus, a movement of stakeholders from across nongovernmental organizations, patient groups, academia, intergovernmental organizations, private sector, and governments have been working to advance global, regional, and national policy and time-bound measurable commitments to reduce the global burden of NCDs.

The inception of global policy to address the growing NCD crisis effectively dates back to the June 1992 United Nations (UN) Conference on Environment and Development in Rio de Janeiro, Brazil. Several key meetings under the auspices of the UN ensued, with a growing consensus and emerging multisector partnerships that would support the path to a set of NCD goals. The 2002 Johannesburg Declaration on Sustainable Development formally addressed the issue of NCDs, and the 2009 Economic and Social Council Ministerial Declaration recognized the burden NCDs placed on countries. These meetings helped lay out frameworks and goals that would eventually lead to the UN High-level Meeting in 2011, a high mark in the global effort to address NCDs.[6]

THE ROLE OF CIVIL SOCIETY

Whereas the HIV/AIDS movement had strong grassroots advocacy with the voices of patients featuring prominently, technical and policy discussions have been more dominant in driving the early stages of the NCD movement. However, an early catalyst for the NCD movement was a group of patients with diabetes in the Caribbean who drew attention to their preventable foot amputations and lack of prioritization of chronic diseases as a human rights concern.[7] They advocated to their governments, leading to the first-ever summit on NCDs involving heads of state in Trinidad and Tobago in September 2007 in which the Port-of-Spain Declaration "Uniting to Stop the Epidemic of Chronic Non-Communicable Diseases" was issued.[8] Leaders of CARICOM, a group of 20 countries within the UN system, raised their concerns about diabetes and other NCDs at the UN, setting the stage for the UN High-level Meeting to take place in 2011.

Strong global-level civil society mobilization on NCDs began in 2009, with the formation of the NCD Alliance

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(https://ncdalliance.org) and other civil society groups, such as the Young Professionals Chronic Disease Network (www.ncdaction.org). As a coalition of disease federations, including the International Diabetes Federation, the World Heart Federation, the Union for International Cancer Control, and the International Union Against Tuberculosis and Lung Disease, the NCD Alliance was established to consolidate funding and influence for policy changes on NCDs as a group and avoid disease silos in global policy for health. Civil society, including academics, pushed for international support and clarification of goals in the form of a political declaration to address NCDs, leading up to the UN High-level Meeting on the Prevention and Control of Non-communicable Diseases in 2011,[9,10] at which international heads of state assembled for the second-ever UN High-level Meeting on a health issue.

UNITED NATIONS HIGH-LEVEL MEETING 2011

As part of its wide-ranging mandate, the UN General Assembly convenes high-level meetings to increase awareness while pressing for common ground and policies on issues of global importance.[11] Participation in the September 2011 meeting included 82 member states, including representation from 35 heads of state, civil society, private sector, and UN agencies. The political declaration on NCDs emerged after controversial negotiations, largely between groups of developed versus developing nations, on access to medicines, food and beverage policies, tobacco control, and financing commitments.[12] Most notably, tensions arose with the addition of intellectual property provisions for the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement. These TRIPS "flexibilities" give countries the right, if criteria are met,[13] to circumvent patents to issue a compulsory license for medicines considered essential for the public health good at an affordable price.[14] Although the HIV/AIDS movement emphasized the right to treatment, this discourse was largely muted at the NCD High-level Meeting. To frame NCDs as a social justice issue and call for action and commitments, students, AIDS activists, and people living with NCDs held the first rally on NCDs outside the UN in New York.[7]

The UN political declaration on the Prevention and Control of Non-communicable Diseases passed, outlining policies to address the four major NCDs defined by WHO, which are cancer, cardiovascular disease, chronic respiratory diseases, and diabetes. Policies responding to current disease treatment revolved around improving health care infrastructure and systems including increased technical resources.[9] The impetus for such shift in policies relates to the goals of sustainable global development based on three pillars defined by economic growth, social equity, and environmental protection.[6] Some of the specific policies implemented soon after the 2011 meeting include those from Gabon with free screening for cancers, Niger aiming to ensure access and affordability of medicines, Spain rethinking health strategies on cancer, Mexico funding evidence-based clinical interventions and new technologies, Trinidad and Tobago starting a Chronic Disease Assistance Program to provide all people with medications, UNASUR (Union of South American Nations) aimed to ensure universal access to medicines, using TRIPS, and India further developing its National Program for Prevention and Control of Cancer to screen for disease.[15]

To provide member states with a clear road map to address NCDs, WHO was tasked to develop a set of targets, which now guide the global NCD response in the form of the NCD global monitoring framework and the NCD Global Action Plan 2013–2020.[16] The targets included advocating and raising awareness, disseminating knowledge and information, encouraging innovation and identifying barriers, advancing multisector action, and advocating for the mobilization of resources. An initial set of nine voluntary targets and 25 indicators for 2025 goals that provided an assessment of NCD mortality and morbidity, risk factors, and national systems response was developed. These targets include: 25% reduction in premature mortality from NCDs, 10% reduction in harmful use of alcohol, 10% reduction in physical inactivity, 30% reduction in tobacco use, 80% coverage of essential NCD medicines and technologies, and 50% coverage of drug therapy and counseling.[17]

ASSESSMENT THUS FAR

The formal process for monitoring progress on the goals is conducted under WHO auspices via country surveys to assess national capacity for the prevention and control of NCD from the 194 member states. These surveys had been ongoing for several years prior, but the questions varied significantly from prior versions, making comparisons problematic, and validation of the data proved challenging.[18] The first survey following the meeting was in 2013 and showed overall progress and improvements, specifically operational national NCD policy with a budget for implementation increased from 32% of countries in 2010 to 50% of countries in 2013, while highlighting the challenges faced by nearly all member states.

The WHO Global Survey was comparable in 2010, 2013, and 2015. Questions include public health infrastructure, partnerships and multisector collaboration for NCDs, the existence of NCD-relevant policies, strategies and action plans, capacity for surveillance to address NCDs and their risk factors at the national level, and capacity for NCD prevention, early detection, treatment, and care within the health system. Comparison of 2010 to 2013 showed increases in designating a unit, branch, or department with responsibility for NCDs from 89% to 94%, with a slight decline to 93% by 2015. Increased funding for NCD prevention and health promotions was shown from 81% to 88% from 2010 to 2015. During this period, 11% versus 6% reported absence of funding for NCDs with the variety in funding sources increasing, the most prevalent being general government revenues. In 2015, the first assessed prevalence of palliative care funding was found in 64% of countries.[18] Although policies were prevalent, operational policies took time to increase from 33% in 2010 to 63% in 2015. Operational plans addressing cancer specifically increased from 50% in 2010 to 71% in

2015. Cancer registries slightly increased from 80% to 81% to 84%, whereas national, population-based cancer registries changed from 39% to 59%.[18]

Monitoring risk factors with surveys increased with each assessment, especially tobacco use surveys. Primary prevention and health promotion increased as well as risk factor detection during this period. Although some form of guidelines for cancer management existed for 73% in 2013, only about half of those had fully implemented them. However, in 2015, evidence-based guidelines were assessed, revealing 60% of countries had them, with approximately 55% having some form of implementation of those guidelines. Prevalence of tests and procedures available increased, such as breast cancer mammogram from 81% to 84% as well as cervical cancer from 65% to 74% from 2010 to 2013. Availability of many essential medicines increased, but, for example, oral morphine went from 48% to 56% to 43% from 2010 to 2015. In 2015, 67% of countries had cancer centers or cancer departments at the tertiary level. However, availability of cancer surgery (69%) and subsidized chemotherapy (63%) were distinctly influenced by country income group.[18,19] One important point to draw from the WHO global surveys is cancer treatment availability is correlated with income of country.

With the 2011 high-level meeting, there may have been hopes to replicate the effect of the high-level meeting for HIV/AIDS in 2001 on funding and donations, which surged afterward, alleviating the treatment-access crisis at that time.[9] However, there remains a dearth of domestic funding information on NCD programs.[10] As was seen in the 2013 survey, there was policy in place for NCD work but less actually working plans in place, suggesting the difficulty of implementation. Funding is an important consideration with enacting domestic policies for prevention and treatment; however, there is a complex network of factors affecting individual countries in implementing domestic policies. A total of 77% to 87% of low- and middle-income countries in 2015 had a major source of funding for NCD programs come from international donors.[19] However, analysis of this funding by the WHO Working Group indicated that donor assistance for health goes mainly to other areas besides NCDs, even though NCDs are more of a health burden.[20] Current funding for NCD policies in low- and middle-income countries could be improved by better allocation of international assistance.

FACTORS IN TREATMENT IMPLEMENTATION

Although policy and goals can be set for prevention and treatment of cancer, implementation of such policies is complex, with barriers that will require creative solutions. The high costs of cancer medications can often be an insurmountable barrier to treatment in poor countries. This is in part due to new medications covered under patent laws that are priced for high-income countries.[14] International patent law is guided by different conventions, partnerships, and agreements, including obligations under the World Trade Organization and TRIPS agreement.[13,21,22] To obtain access to cancer medications, countries can use compulsory licensing to lower the cost of medication through lower domestic production costs and patent fees. Although this is an ongoing point of contention in international patent law, compulsory licensing has had success before with HIV/AIDS medications.[23] Creation of biosimilars, tiered price schemes, public-private partnerships, patent pools, and tax incentives are additional ways in which costs of cancer treatment can be curbed.[24]

Many governments are now considering how to prioritize medicines for cancer care with limited budgets. Guidance on which medications countries can consider as essential while adapting to their needs and public health priorities exists via the WHO Model List of Essential Medicines. In 2015, 16 cancer drugs were added to the existing WHO Model List of Essential Medicines, providing a suite of medications covering basic oncologic diseases, essentially prioritizing access to basic cancer treatments for 26 cancer types.[25] In 2011, the WHO published its Core Medical Equipment guide to further information on essential equipment. Currently the WHO is working on its list of priority medical devices specifically for cancer to guide cost-effective procurement. These guides, expected to be published in summer 2017, will help the lower income, poor resource, and poor infrastructure countries purchase priority medical products with a cost-effective logic in mind.

A COUNTRY EXAMPLE: INDIA IN THE SPOTLIGHT

To more thoroughly understand the whole of challenges faced by countries implementing strategies for cancer prevention and treatment, we will look at India's current state of affairs. India's National Cancer Control Program is a federally coordinated program that was launched in 1975 with the main aims of creating infrastructure for primary prevention, early detection, and treatment of cancers. The main lynchpin of strategy for providing therapeutic care was the creation of so-called Regional Cancer Centres that are so located as to bridge geographic gaps in the availability of public-sector cancer treatment facilities. There are 27 Regional Cancer Centres in India at present. However, infrastructure and human resource for cancer treatment remain inadequate for a country of India's physical size and population. For example, there are less than 1,000 trained medical oncologists and only about 340 radiation therapy centers in India.[26] A considerable fraction of health care capacity, including cancer care, in India is provided by private-sector industry for which services are beyond the reach of a majority of patients. The added complexity is with grossly uneven distribution of health care services in India in which the majority of infrastructure and human resources are located in urban regions, but the majority of the population resides in rural areas. There have been recent proposals to initiate basic cancer care services, including surgery and chemotherapy for common cancers, at the level of district hospitals, of which there are about 600 in India.[26] Several Indian states have initiated programs to deliver cancer care in rural and semi-urban regions along these lines.[27] Recently,

there has been improvement in human resource availability in underserved areas. Several strategies, some incentivized, have been initiated by the federal government to improve rural medical service.[28] There has also been a substantial increase in number of postgraduate training positions in oncology in the past few years. An important recent initiative to link more than 80 public- and private-sector cancer centers in India, called the National Cancer Grid, is also noteworthy in this context.[29] Its main aim is to provide uniform, evidence-based cancer care across different geographic areas in India.

One important aspect of India's cancer-control scenario is a relatively good quality national cancer registration program that has existed under the aegis of the Indian Council of Medical Research since 1981 and currently comprises 23 population-based cancer registries that collect data on cancer incidence from defined geographic regions. Most of these registries are located in urban areas, and very few collect data on mortality. It is estimated that there are about 1.0 to 1.1 million new cancer cases every year with about 0.5 million deaths for a mortality-to-incidence ratio of about 50%, which is much higher than that seen in developed countries.[30] The main contributors to high cancer mortality are advanced stage at diagnosis and inadequate health care infrastructure, especially in rural and semi-urban areas. For example, with a much lower cancer incidence in rural compared with urban areas, the mortality of cancers in males and females is almost equal in rural (95.6–96.6/100,000) and urban (91.2–102.4/100,000) regions of India.[31]

The main strength of Indian cancer-control scenario is widespread availability of inexpensive medications, including anticancer drug generics, biosimilars, and copies,[32] except for a few newer targeted and immunotherapy drugs. The main reason for this has been the development of a robust Indian pharmaceutical industry that has developed considerable expertise in past few decades in making generic versions of most drugs. The generic industry has been helped by legal interpretation of intellectual property rights in India that have generally been against the practice of evergreening of patents.[33] India has also used, somewhat sparingly, the route of compulsory licenses for on-patent drugs in recent years, with mixed results.[14,34] The only case of compulsory licensing by India in the domain of oncology was for sorafenib. This generated strong opposition from the patent holder, Bayer. The Government of India also exercises control over pricing of drugs through periodic Drug Price Control Orders under the Essential Commodities Act enacted in 1955. Again, the use of this legislation has had mixed results, for although it has kept essential drug prices under check, scarcity has been created for some medications that have become unviable to manufacture.[35]

Finally, provision of palliative care for advanced-stage patients has been inadequate, with India faring poorly on the Quality of Death index among various nations.[36] There needs to be urgent multisectoral action to improve availability of opioid analgesics, training of health care professionals, creation and adoption of locally relevant palliative care standards, and development of community models for providing home-based palliative care in India.

CONCLUSION

The ideals for treating NCD as a global health problem have a rich historical route that led to the high-level UN meeting in which the world's countries united around policies enacted to address prevention and treatment. The complexity of implementing those policies, specifically related to cancer, has hindered quickly achieving the WHO global NCD targets. Information on the prevalence and type of cancer in the region, income, and infrastructure is important in making judicious allocations of resources in medication and medical equipment procurement. While considering domestic policies and implementation of cancer prevention and control, one must acknowledge international limitations placed on individual countries through policies and country income. India is a prime example of the interplay between domestic and international factors that must be considered to have an effective system for prevention and treatment of cancer, especially in a low- to middle-income nation.

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POINTS OF VIEW

The section contains articles describing emerging, highly debated, or controversial topics in cancer research, treatment, and care to benefit patients and the field of oncology.

ARTICLES

How Should We Intervene on the Financial Toxicity of Cancer Care?
S. Yousuf Zafar, MD, MHS, Lee N. Newcomer, MD, Justin McCarthy, JD, Shelley Fuld Nasso, Leonard B. Saltz, MD

Practice Model for Advanced Practice Providers in Oncology
Jamie Cairo, DNP, APRN-BC, Mary Ann Muzi, APRN-BC, APCNP, Deanna Ficke, PA-C, Shaunta Ford-Pierce, MSN, NP, FNP-BC, Katrina Goetzke, PA-C, Diane Stumvoll, APGCNP-BC, MSN, Laurie Williams, APNP, MSN, Federico A. Sanchez, MD

How Should We Intervene on the Financial Toxicity of Cancer Care? One Shot, Four Perspectives

S. Yousuf Zafar, MD, MHS, Lee N. Newcomer, MD, Justin McCarthy, JD, Shelley Fuld Nasso, and Leonard B. Saltz, MD

OVERVIEW

The median price of a month of chemotherapy has increased by an order of magnitude during the past 20 years, far exceeding inflation over the same period. Along with rising prices, increases in cost sharing have forced patients to directly shoulder a greater portion of those costs, resulting in undue financial burden and, in some cases, cost-related nonadherence to treatment. What can we do to intervene on treatment-related financial toxicity of patients? No one party can single-handedly solve the problem, and the solution must be multifaceted and creative. A productive discussion of the problem must avoid casting blame and, instead, must look inward for concrete starting points toward improvement in the affordability and value of cancer care. With these points in mind, the authors—representatives from the pharmaceutical industry, insurance providers, oncologists, and patient advocacy—have each been asked to respond with a practical answer to the provocative hypothetical question, "If you could propose one thing, and one thing only, in terms of an action or change by the constituency you represent in this discussion, what would that be?"

Cancer is one of the most expensive diseases to treat in the United States. The median price of a month of chemotherapy has increased by an order of magnitude during the past 20 years, far exceeding inflation over the same period. Some would maintain that prescribing patterns further contribute to higher costs. In the most common models of cancer care delivery, oncologists have little incentive to contain treatment costs when they prescribe chemotherapy, and only recently have considerations of cost and affordability begun to be openly incorporated into guideline development.

Because of increasing deductibles, increasing premiums, cost sharing, coinsurance, and frequent copayments, patients are directly shouldering a greater portion of those costs.[1] One in three American families face health care bills they cannot afford, and 50% of elderly Americans with cancer pay at least 10% of their income toward out-of-pocket treatment-related expenses.[2,3] A growing body of literature has described the treatment-related financial strain experienced by patients with cancer, often called the financial toxicity of cancer treatment. These studies have described how an increasing portion of patients with cancer are at risk for cutting back on groceries, selling their homes, being nonadherent to their prescribed treatment, or—in the most extreme cases—declaring personal bankruptcy to pay for their cancer treatments.[4,5]

What can we do to intervene on treatment-related financial toxicity of patients? Without question, any meaningful steps toward lower costs will involve collaboration among the pharmaceutical industry, insurance providers (government and otherwise), oncologists, and patients; no one party can single-handedly solve the problem. The solution must be multifaceted and creative; prosaic appeals to simply lower drug prices surely will fail. A productive discussion of the problem must avoid casting blame and, instead, must look for common ground, and must look inward for concrete starting points toward improvement in the affordability and value of cancer care.

With these points in mind, the authors of this article—representatives from the pharmaceutical industry, insurance providers, oncologists, and patient advocates—have each been asked to respond with a practical answer to the provocative hypothetical question, "If you could propose one thing, and one thing only, in terms of an action or change by the constituency you represent in this discussion, what would that be?" Note that this exercise is focused on the question of what changes we would make as opposed to the more comfortable and more often answered question of what changes others should make. We undertake this exercise with the full realization of the artificial nature of a limit to one simple answer of what is necessarily a complex, nuanced, and multifaceted problem and the

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awareness that that there is no singular answer that any of us could offer that will be fully inclusive and satisfactory to all voices within each of our stakeholder groups. Rather, we aim here to provide ideas to serve as starting points, both for introspection and to promote discussion.

THE PHARMACEUTICAL INDUSTRY PERSPECTIVE (J. MCCARTHY)

Invest Additional Resources to Identify Patient Populations Most Likely to Benefit From Therapy

The idea of paying for value when it comes to pharmaceuticals is a widely accepted goal. However, there is still no consensus on what this means. Although this concept is still evolving, it relies at its core on biopharmaceutical companies to demonstrate that the products we develop provide meaningful benefits to patient populations, coupled with a reimbursement system that lowers barriers to high-value products. Biopharmaceutical companies should do their part to invest more resources to ensure that the right product is available to the right patient at the right time.

Cancer care is in the midst of an incredible transformation. Many cancers, previously intractable, now can be treated with targeted therapies that greatly boost the chances of better outcomes for patients. Some patients experience long-term benefits from immunotherapies. However, we still know too little about which types of patients are likely to respond best to a particular therapy. The pharmaceutical industry should invest additional resources in studies of a new drug after it has been approved to better understand its utility, whether to identify use at earlier stage of the disease, in a different tumor type, or for an even narrower patient population to avoid patient exposure when the risks are more likely to outweigh the benefits.

For our health care system to truly pay for value, stakeholders also must be willing to develop creative reimbursement mechanisms that incentivize high-value care. Payment reform demonstrations are underway across the health care sector to explore better ways to pay for inpatient and outpatient care. To date, however, little has been done in the prescription drug space. Biopharmaceutical companies and payers—public and private—should collaborate to explore new, high-value reimbursement methods. These methods could include the following:

- Outcomes-based contracts. Biopharmaceutical companies and private payers have experimented recently with contracts in which payment for products is tied to achievement of certain therapeutic goals (e.g., avoiding increased hospitalizations or increasing progression-free survival). These two sectors should work together to advocate removal of regulatory and legal barriers. Doing so would allow robust use of these promising tools to expressly tie payment to value.
- Value-based insurance design. Another nascent concept is value-based insurance design. Although this idea has been used in the context of outpatient and inpatient services, it has not been applied broadly to drugs. For example, an insurer could dramatically reduce cost sharing for high-value drugs or lower cost sharing after a patient experiences disease failure with a lower-cost medication.[6] These types of arrangements are still in their infancy but could help incentivize patients and providers to use and prescribe high-value products.

Transformation of our health care system to one that pays on the basis of value, not volume, will require coordination and cooperation across the sector. Biopharmaceutical companies should do their part to help demonstrate the value of our products to patients, payers, and providers.

KEY POINTS

- **Not only are drug prices rising, but patients also face high cost sharing forcing patients to shoulder a greater portion of costs.**
- **Current reimbursement models provide little incentive to contain costs.**
- **A solution to the problem of financial toxicity must be collaborative and multifaceted.**
- **As a starting point to the discussion, the authors have provided four ideas from each of their stakeholder perspectives as options available to reduce cancer treatment–related financial toxicity, including: high-value reimbursement models; removing coverage mandates for all FDA-approved cancer therapy; ensuring oncologists consider price in treatment decision making; and encouraging patient engagement in decision making to assure treatment truly matches patients' values and preferences.**

THE PAYER'S PERSPECTIVE (L. NEWCOMER)

Remove Coverage Mandates From State and Federal Insurance Law

Insurance regulation forces payers to pay for any U.S. Food and Drug Administration (FDA)–approved cancer therapy in 42 states; Medicare has a similar provision. Such mandatory coverage eliminates any consideration of value. A therapy with mandatory coverage could be curative or could simply add one additional day of life, but the price cannot be negotiated if that therapy has an FDA-approved indication. The laws were well intended originally. As expensive therapies emerged, legislators were concerned that insurers would simply refuse to pay. The unintended consequence of coverage mandates becomes apparent when multiple therapies are available; payers cannot make decisions on the basis of the value of therapy and substitute one therapy for another when it is clinically appropriate. Removal of this legislated requirement would open the marketplace, and pharmaceutical manufacturers would compete on price and outcomes. Payers would compete in the marketplace by offering the best values for therapy within a competitive premium. This competition requires that a transparent and understandable set of criteria for determination of value, partial value, or no value is presented. The market could function normally.

The lung cancer therapy necitumumab is an excellent example of why mandates force prices beyond reason.[7] This

drug was added to cisplatin and gemcitabine and compared with cisplatin and gemcitabine alone in patients with stage IV squamous cell lung cancer. Three percent of the patients who received necitumumab suffered a cardiac arrest. The difference in median progression-free survival was 0.2 months (5.7 vs. 5.5 months), but the overall survival favored the necitumumab group by 1.6 months (11.5 vs. 9.9 months). These results are so meager that the National Comprehensive Cancer Network assigned a category-3 recommendation to the drug—an endorsement that most insurers, including Medicare, do not cover. However, the mandates require coverage at any price, because the drug has an FDA approval. The manufacturer priced this drug at $11,430 per month. The competing regimen, cisplatin and gemcitabine, cost less than $1,000 per month. It is difficult to believe that anyone except the manufacturer would consider this to be a value, but it does not matter. The law mandates coverage; therefore, price is not negotiable.

Necitumumab is not an isolated example. Salas-Vega et al[8] reviewed 62 new cancer molecules approved between 2003 and 2013 in the United States and Europe. The review showed no evidence to suggest that 16 of those drugs (30%) increased overall survival compared with best alternative treatments. If manufacturers knew that these products would not be reimbursed in the market, they would focus their attention on different molecules that offer better results.

Other mandates are emerging. Several states are now considering laws to prohibit step therapy for cancer. Step therapy requires treatment with a preferred regimen before the patient is eligible for a second therapy. This strategy is useful for drugs that have similar clinical response rates, because a payer can obtain competitive bids and then give preference to the lowest-cost regimen. There have been so many drug discoveries in the past decade that many cancer types now have multiple effective agents. Step therapy allows patients to obtain treatment at a lower cost. Prohibition of step therapy eliminates competition, raises costs, and hurts everyone except the pharmaceutical manufacturer.

A free market determines prices on the basis of merit, and mandates prevent free market actions. Removal of mandates presents a win-win proposition for patients and payers.

THE ONCOLOGIST'S PERSPECTIVE (L. SALTZ)

Know the Price

Any one change that doctors could make would only be a first step toward the ultimate goal of provision of lower-cost, higher-value medicines for our patients. To me, that first step would be physician acceptance, practice, and promotion of transparency in price. In simple terms, that means knowing the prices of the drugs prescribed, considering those prices as one of the many factors in decision making, and discussing the prices of the prescribed drugs as openly as we discuss other risks, toxicities, and benefits.

I make a sharp distinction here between the words price and value. A true, constructive consideration of the value of a particular medicine cannot realistically occur unless we know the amount of money that we are being asked to pay for it. That is the definition of price, or cost, that I refer to for this discussion: the amount of money that will be paid for the drug. I am not, for this exercise, getting into who is paying for it, what other costs are or are not involved, what alternatives are available, or any other of a number of important, arguably relevant considerations, and I am not making a judgment about whether the price is too high, too low, or just right. I am simply saying that we must stop putting our heads in the sand and pretending that we do not need to know, think about, or talk freely about, what the price is.

Consider for a moment the inherent ambiguity in the word value. Value can be used as a noun or a verb. The way to define it in a constructive discussion aimed at definitions of high- and low-value care is as a noun; in that respect, the value of a drug would be defined by a ratio of objective positives and negatives of that drug, with price as one of the negatives. Note that price and value move in opposite directions. For any drug with a fixed degree of benefits and adverse effects, the higher the price, the lower the value, and the lower the price, the higher the value. So, we cannot begin to meaningfully determine the value until we know the price, just as we could not meaningfully determine value without knowing the other positive and negative aspects of the drug. Price is not the defining factor in value, but it is one of the components without which the value cannot be defined.

Too often, our consideration of price can be distracted by the shift of the discussion to value and its definition as a verb; we value a response, a defined amount of extended life, or relief from a symptom. The verb definition of value necessarily takes us into subjective, as opposed to objective, criteria, and the very nature of these resist correlation with a price. In fact, such a focus prevents delineation of value and distracts us from a meaningful and constructive discussion of what is high-value care and, just as important, what is not.

Doctors do not have the ability to unilaterally lower the prices of drugs. Doctors do have the ability to be aware of the prices of the drugs, tests, treatments, and recommendations we offer, both directly in terms of out-of-pocket expenses to our patients and more indirectly to society as a whole. Some have argued that it is only the immediate out-of-pocket expense of the individual that should be considered by doctors and that societal costs are not relevant to a patient-physician relationship. I respectfully disagree. Societal costs ultimately are distributed across the population, and all insured patients eventually bear these costs in terms of increased insurance premiums. The price of insurance and the percentage of paychecks that go toward health care costs have been increasing at a substantially more rapid rate than the increases in average worker wages or inflation. The term financial toxicity has gained increasing traction in our understanding of what these costs are doing to our patients on a regular basis. Even when the initial out-of-pocket

expense may appear small, one can realistically expect that these costs will appear in the insurance premiums for all in the years to come.

Even if one were to take the position that the physician focus should be on immediate out-of-pocket expenses of an individual patient (a short-sighted view, as I outlined in the previous paragraph), this would imply a responsibility to understand the coverage and actual out-of-pocket exposure of each patient, as well as, arguably, the ability of each patient to manage those expenses. This often may be beyond provider abilities. It is quite reasonable, however, to assume that vulnerability a patient may have toward the potential cost of even a small part of that therapy increases with more expensive therapy. Physicians see a decrease in simple copayments with fixed nominal costs and an increase in coinsurance charges, whereby the patient will pay a fixed percentage of the price of the drug. In this context, the more expensive drugs create greater out-of-pocket expenses at the same time that they contribute to the aggregate cost of health care and the necessarily compensatory increases in insurance premiums going forward.

Physicians frequently talk to patients about intimate and personal details of their lives. Physicians routinely ask about bowel function, bladder function, sexual function, anxiety, depression, alcohol and illicit drug use, and other intimate and personal details that would be far outside normal social discourse. Within this context, there is a startling inconsistency with any conversational taboo regarding costs. Yet, discussion of the prices of treatments has been a taboo in our doctor-patient relationships, and that requires re-evaluation. Bringing the realistic costs to bear in discussions would make the most involved members of society appropriately informed of the magnitude of the challenges faced in paying for drugs at the current prices. It would also facilitate rational discussions of efforts to use more cost-efficient regimens, use less expensive alternatives, or perhaps forego extremely expensive and toxic options that have little chance to provide meaningful benefit. There are very few things in life that people buy without an awareness of the purchase price. Such an awareness helps people make informed decisions about what goods or services they do or do not wish to purchase and can encourage people to make informed decisions about the consideration of alternatives.

From an academic perspective, discussion of price is warranted both in clinical trial design and in publications. When a trial is designed that increases the length of treatment or increases the dose of a drug to higher than the standard dose, physicians must know and consider what the costs of those changes will be. When a report is published about a regimen for which the prices of the drugs are known, those prices constitute a nontrivial toxicity to which patients will be exposed.

The purpose of academic paper about therapeutic options, and the purpose of open and complete discussions between patients and providers, is to maximize the awareness of the true risks, benefits, and alternatives of the treatment strategy under consideration. It would be wrong to exclude consideration of physical toxicities. It is equally counterproductive to exclude consideration of price, or financial toxicity. The inability to provide full awareness of either of these likely will increase, rather than decrease, the prevalence of and the harm done by these toxicities.

THE PATIENT ADVOCATE'S PERSPECTIVE (S. FULD NASSO)

Engage in Treatment Planning to Better Reflect Patient Values

Patient engagement in treatment decision making can reduce financial toxicity for patients by ensuring that treatments truly match the needs, values, and preferences of patients. A consideration of all clinically meaningful treatment options and their benefits, risks, and out-of-pocket costs should frame the patient decision-making process.

At an individual level, patients can play a role by being active participants in decisions about their care, researching their insurance coverage, initiating discussions about the cost of care with their care team, advocating for coverage of the care that they need, and seeking financial assistance from foundations and company-sponsored assistance programs. Empowered patients and family members know that they must advocate on their own behalf, or on behalf of their loved ones, in all aspects of their care, including financial considerations. Of course, not all patients are prepared and knowledgeable about health insurance, and many patients feel overwhelmed by the amount of information they must process about their diagnosis and treatment options, not to mention the question of how they will pay for their care. Patients need assistance with health insurance literacy; there is evidence that patients do not have a thorough understanding of key insurance constructs, like deductibles, copayments, and coinsurance.[9]

Ideally, patients and caregivers will raise the topic, ask the questions, and seek assistance from their care team and/or a financial counselor. However, a huge barrier for patients is embarrassment about discussions of financial considerations with their care team. It is essential that providers create a welcoming and open environment for patients to express their concerns. Providers should recognize how difficult it is for patients to raise the topic and should open the door to the conversation by asking a question as simple as "Do you have concerns about the cost of your treatment?"

At a practice and policy level, the comprehensive treatment planning process that has been defined by the Institute of Medicine[10]—a definition arrived at with substantial input from oncologists and patients—should be the standard for doctor-patient communication about cancer care. It is important to note that this planning is not about checking a box that a piece of paper was handed to a patient; it is about truly engaging patients in decision making about their care. This plan should include information related to diagnosis, prognosis, treatment goals, expected response to treatment, treatment benefits and harms, out-of-pocket cost of care, and a plan for meeting psychosocial needs. The care planning process also should include consideration of

advance care planning and advance directives and should lead to the development of a survivorship plan after treatment. This cancer care planning process should produce a patient-specific care plan that will guide treatment decisions and facilitate care coordination, including effective symptom management to reduce the burden and cost of adverse effects.

An important component of the planning process is a discussion of the out-of-pocket costs to a patient. We know that some patients do not wish to discuss costs; they might worry about the perception that the oncologist has of them, they might want the best treatment regardless of cost, or they might fear that a discussion of cost will result in inferior treatments.[11] Yet, most patients do want to have this conversation, even if they are reluctant to bring it up. Research shows that having the discussion, even without a change in treatment, can reduce costs for patients.[11]

Patients are concerned about their total financial responsibility across the life of their treatment, not just the cost of one aspect of treatment. Obviously, that is difficult for one provider to share, given the multidimensional aspects of treatment. To the degree that it is possible, knowledge about the total costs will help patients plan and understand the entire picture, not just the cost of a specific drug. Although some of the value frameworks, including those by ASCO, have considered the price of a drug, the out-of-pocket cost is what is most important to an individual to make decisions. In most cases, that distinction will require an understanding of the out-of-pocket maximum. It also is important for patients to understand whether any out-of-network services, which do not contribute to the out-of-pocket maximum, will be required.

CONCLUSION

As a starting point to answer the question (How can we reduce patients' financial toxicity?), we propose four potential solutions from the perspectives of the pharmaceutical industry, payers, physicians, and patients, which we feel are helpful. Of course, we are not the first to propose solutions to the growing financial burden of cancer treatment. The intent of this exercise was to consider solutions from within our own stakeholder groups rather than to pass the responsibility down the road.

As interventions to reduce financial toxicity and improve value are considered, all participants should consider and discuss many long- and short-term interventions. Policy interventions, such as facilitation of value-based contracting or removal of the coverage mandate, all warrant consideration and may be helpful to the long-term process but are unlikely to be realized overnight. In the meantime, short-term interventions, like price awareness and inclusion of cost in treatment and goals of care discussions, are necessary. The discussion cannot stop here. If anything, this exercise demonstrates that all stakeholders—the pharmaceutical industry, payers, providers, and patients—must continue the discussion to ensure the delivery of high-value care.

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Practice Model for Advanced Practice Providers in Oncology

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OVERVIEW

According to ASCO, the number of practicing oncologists has remained stable despite growth demands, leading to an overall shortage in many areas of the country. Nurse practitioners and physician assistants are advanced practice providers (APPs) who can assist in the provision of support and care to patients with cancer, but the role of the APP in the oncology setting has not been well defined. There exists a variety of different practice patterns for APPs who work in oncology, and the lack of role definition and absence of an established practice model are considered leading causes of APP attrition. According to the American Academy of Nurse Practitioners, it has been well demonstrated that, when nurse practitioners are allowed to work to the full scope of their education and preparation, there are notable cost reductions and quality improvements in patient care. The focus of APP education and training is on health promotion, disease prevention, and primary care medical management, but most APPs have limited exposure to management of cancer in patients. With this in mind, Aurora Cancer Care developed a practice model for APPs who work in oncology. The goal of the model is to enhance the quality of care delivered to patients and provide a stimulating work environment that fosters excellent collaborative relationships with oncologist colleagues, supports professional growth, and allows APPs to practice to the full extent of their licensure.

Aurora Health Care is a not-for-profit, large, integrated health care system that provides cancer services in 10 counties, 16 hospitals, and 22 clinics throughout eastern Wisconsin and northern Illinois. A subcommittee of seven APPs who practice in medical oncology was formed with the goals of defining current practice and identifying areas considered problematic or not well defined. The group used the NP Model of Care, designed by Kutzleb et al,[1] to identify five major areas of practice and then developed an action plan and rationale for each of these areas with supporting evidence found in the literature.

Cancer care is becoming increasingly complex, and health care systems are looking for ways to meet patient needs and address issues of cost, quality, and access including shortages of practicing oncologists in many areas of the country.[1,2] APPs can provide high-quality care to patients that not only is cost effective but also can improve outcomes for patients.[3] According to the American Academy of Nurse Practitioners, the best and safest outcomes for patients are produced when health care is provided in coordinated networks that recognize and encourage the unique knowledge base and skills of all practitioners.[4]

Emergency visits and hospital admissions have negative implications for health care systems, payers, and patients. Patients with cancer frequently experience urgent problems related to their cancer and/or its treatment. The majority of hospital admissions are due to uncontrolled symptoms, such as shortness of breath, pain, fever, and nausea, and vomiting, and these admissions tend to correlate with longer hospital stays and result in a higher rate of mortality.[5,6] Patients with cancer who present to the emergency department often experience long wait times and receive costly and fragmented care that does not always meet their needs. APPs can decrease readmission rates and increase the quality of patient care by meeting regularly with patients to manage their treatment plan and treatment-related issues. A model that can lead to improved and more cost-efficient care uses APPs to see patients in urgent care settings. In this model, the APP would perform assessment, triage, and treatment. This approach benefits not only the patient but also the physician, because it allows the physician to keep on track with scheduled appointments without interruptions.[7] There are many documented examples of the successful implementation of this model. For patients with oropharyngeal cancer, a weekly nurse practitioner–led symptom management clinic reduced the rates of both acute care hospitalization and chemotherapy dose deviations in patients receiving intensive chemotherapy and radiation.[8]

The American Cancer Society reports that more than 15.5 million cancer survivors are alive in the United States today, and that number will grow to more than 20 million

From Aurora Cancer Care, Aurora Health Care, Milwaukee, WI.

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by 2026. Cancer survivors have unique physical and psychosocial needs that require specialized care, and APPs have the expertise to provide that care.[9,10] Given appropriate training, APPs also are able to perform select procedures, including bone marrow biopsies and intrathecal chemotherapy administration, independently.[11] Nationally, there is a demand for clinicians with palliative care knowledge. APPs are well suited to integration of palliative care into practice during care of chronically and terminally ill patients.[12]

Use of a collaborative practice model to integrate APPs into oncology practice has been proposed as an ideal solution to the challenge of complex cancer care across multiple settings.[4,13] When APPs work to the full extent of their training and licensure, there are improvements in patient and provider satisfaction as well as an overall positive impact on productivity and revenue.[14] As health care reform continues to be a topic of national conversation, APPs must be at the table and willing to take an active role in designing innovative models of care as members and leaders of interprofessional teams.[14,15] APPs also must take ownership of teaching and mentoring new nurse practitioners and physician assistants. A mentoring program for APPs that is supported and led by APPs can help those new to the field assimilate to their roles. This relationship can provide benefits for the mentee, the mentor, and the organization.[16] A meta-analysis found that job satisfaction and commitment, as well as career outcomes of compensation and promotions, were higher among those who had been mentored.[17]

ROLE OF THE APP IN ONCOLOGY PRACTICE MODEL

Deliver Direct Care and Coordinate the Interdisciplinary Plan of Care for Patients

It is important to introduce the role of the APP to patients as a vital part of the cancer care team. Best practice involves alternating visits between the APP and physician, which allows the APP to have set appointment schedules and an established role in the active care of patients who receive treatment. The following are among the many actions the APP will perform:

- Formulation of diagnosis and treatment plan in collaboration with the oncologist
- Management of chemotherapy in collaboration with the oncologist
- Management of symptoms
- Survivorship care
- Palliative care
- Psychosocial intervention
- Procedures (e.g., bone marrow biopsies, intrathecal chemotherapy)
- Patient education

KEY POINTS

- **APPs enrich the delivery of a comprehensive continuum of care for patients with cancer.**
- **Optimal use of APPs increases opportunities for the physician to focus on appropriately complex and more highly reimbursed patient scenarios, increases appointment opportunities for physicians to see new patients, and decreases wait times for patients. APP visits increase billable services and lead to shorter wait times for patients, which leads to improved clinic workflow.**
- **Optimal APP practice leads to a higher levels of job satisfaction, allows for professional growth and development, and decreases APP attrition.**
- **A collaborative practice of APPs with physician colleagues leads to best practice value-based care.**

Serve As a Consultant to Improve Care According to Expertise in Area of Specialization

Examples of the areas in oncology in which APPs can develop an area of expertise that would help an established oncology practice include the following:

- Establish a survivorship clinic: Survivorship visits allow for dedicated time to thoroughly discuss post-treatment concerns and guidelines for wellness promotion. Follow-up visits with the APP also offer opportunities to monitor chronic post-treatment side effects/signs of recurrence.
- Coordinated hospital consults and daily inpatient rounds: Consultations and rounds by APPs are convenient for physicians and also improves coordination and communication, especially with discharge planning.
- Management of oral chemotherapy: Oral chemotherapy use is increasing. Patients need the same level of monitoring, adherence tracking, and symptom management as those who receive other forms of chemotherapy.
- Specialized visits to focus on palliative and end-of-life care: APPs can provide palliative care visits that focus on goals of care, symptom management, patient and family education and counseling, coordination, and continuity of care.

Identify Learning Needs of Various Populations and Contribute to the Development of Educational Programs and Resources

APPs can provide and coordinate educational resources as outlined below:

- Staff education: APPs can be used as key advisors when educational opportunities are developed for caregivers. APPs hold graduate degrees; on the basis of their experiences and areas of expertise, they are in key positions to provide support and education to other providers within the organization and to serve as role models and provide the leadership needed to implement and expand evidence-based practice.
- Mentoring and training of APPs new to practice and/or oncology: APPs can lead the mentoring and training of new colleagues.
- Leading research: Nurse practitioners and physician assistants have graduate degrees and are well prepared to not only participate in clinical research but also design and lead such activities.

- Community speaking: APPs amass a wealth of knowledge and clinical expertise and are an excellent resource for educating the community at public events. They also spread knowledge by participating in professional associations and speaking/presenting at nursing or other advanced practice conferences and meetings.
- Working with APP colleagues in primary care and other service lines: Serve as a resource to the organization, providing expertise and support to the existing and emerging practices of other service line advance practice providers.

Evaluate the Impact of Changes in Clinical Practice and Formulate Recommendations About Appropriateness and Cost Effectiveness

As a crucial part of an oncology team, APPs can play an important role in the creation and maintenance of workflow processes that make any oncology practice successful. Examples of roles are the following:

- Serve as participant and leader on quality improvement committees
- Serve as consultant in design and implementation of new clinical programs
- Become involved in leadership on the national level with professional organizations and accreditation programs
- Publish articles and make presentations at regional, national, and international conferences

Identify and Build Collaborative Relationships With Physician Care Teams

To guarantee success in the process, it was felt that the APPs and the physicians needed to create outlined relationships. Examples of some relationships are as follows:

- The physician serves as a resource for the APP as part of collaborative relationship. A collaborative practice implies an effective working relationship, in which the APP and physician colleague(s) communicate with one another to provide best practice patient care.
- Physicians support orientation and training. The oncologist functions as an expert resource and support for the APP. Physician-supported orientation can nurture the collaborative relationship and affect the confidence and autonomy of the APP.
- Physicians market collaborative efforts. Physicians can introduce APPs to referring physicians. The networking effect can help facilitate awareness of the APP as a member of the health care team.
- APPs attend local tumor board/multidisciplinary conferences to represent their practice and meet referring surgeons and primary care providers. Attending multidisciplinary conferences and, when possible participating in clinics, can affect APP training and highlight APP knowledge and skills. Participation also offers opportunities for recognition of the APP as a member of the oncology health care team to other health care specialty providers.

FUTURE IMPLEMENTATION PLANS

After the model was formalized by the subcommittee, it was presented to the larger group of APPs who work in medical oncology for discussion and revision. The seasoned and established APPs were encouraged to take the model back to their individual practice sites and evaluate how their current practices fit within the model. There were practice-related issues in some locations, and the new practice model has served as a guide to redefine the scope of APP practice in those areas. In addition, the model has been used successfully as an orientation resource and as a guide for APPs who are new to a practice. Before development of the model, new caregivers often had questions about their defined roles in the clinics. The practice model has helped answer many of those questions and has led to smoother transitions to new practices. It also has guided both new and established APPs to enact performance goals and clarify the scope of professional development.

The model also has benefited physician colleagues. Although many physicians in medical oncology had long worked with APPs and understood the APP scope and practice, others had not and had questions and concerns when a new APP was introduced to their practice areas. This practice model has served as a guide for them and for nursing and clinic supervisors, and it has opened the door for meaningful discussions about collaboration. The model was presented and accepted by the cancer care executive team and now serves as a document to define the role of the APP and the scope of APP practice in the care of patients at the medical oncology practice at Aurora Health Care.

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BREAST CANCER

Breast Cancer in the Central Nervous System: Multidisciplinary Considerations and Management

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OVERVIEW

Breast cancer is the second most common primary tumor associated with central nervous system (CNS) metastases. Patients with metastatic HER2-positive or triple-negative (estrogen receptor (ER)–negative, progesterone receptor (PR)–negative, HER2-negative) breast cancer are at the highest risk of developing parenchymal brain metastases. Leptomeningeal disease is less frequent but is distributed across breast cancer subtypes, including lobular breast cancer. Initial treatment strategies can include surgery, radiation, intravenous or intrathecal chemotherapy, and/or targeted approaches. In this article, we review the epidemiology of breast cancer brain metastases, differences in clinical behavior and natural history by tumor subtype, and important considerations in the multidisciplinary treatment of these patients. We will highlight new findings that impact current standards of care, clinical controversies, and notable investigational approaches in clinical testing.

Spread of cancer to the CNS, either in the form of parenchymal brain metastases or leptomeningeal disease continues to confer a poor prognosis and high symptom burden in many patients, though survival does appear to be improving over time in some patient subsets. Although the area of breast cancer brain metastases has historically been a relatively understudied area, several seminal clinical trials have altered the standard of care over the past few years, and other smaller studies have provided a variety of new treatment options for patients. Furthermore, multiple innovative investigational strategies are being tested in the clinic. For these reasons, more than ever, the management of brain metastases requires a thoughtful, multidisciplinary approach that integrates the anatomic and symptomatic burden of disease, the status of a patient's extracranial disease and systemic therapy needs, prior therapies, and life expectancy.

RISK FACTORS FOR THE DEVELOPMENT OF CNS METASTASES

Breast cancer is the second most common cancer associated with brain metastases in the United States following lung cancer.[1] As patients with advanced breast cancer live longer, the incidence of brain metastases appears to be increasing. In a subset of women, progression in the CNS has become a major life-limiting problem.

The incidence of brain metastases in patients presenting with stage I/II invasive breast cancer, according to subtype, is as follows[2]: luminal A, 0.1%; luminal B, 3.3%; luminal-HER2, 3.2%; HER2, 3.7%; and triple-negative, 7.4%.

Although these numbers are somewhat low, of those patients with distant metastases, approximately 30% to 50% will eventually develop brain metastases.[2-5] Factors associated with an increased likelihood of brain metastases include young age, lymph node positivity, higher grade, hormone receptor negativity and HER2 positivity, and time from diagnosis to first metastasis.[6] The time from the initial diagnosis of primary breast cancer to the development of brain metastases is also influenced by subtype, with the shortest interval observed for patients with triple-negative disease (27 months), and the longest interval observed for those with ER-positive, HER2-positive disease (54 months).[7]

PROGNOSTIC AND PREDICTIVE FACTORS OF SURVIVAL

The predictive factors and the prognosis of patients with brain metastases are now considered to be disease specific (Table 1). One tool that can be used is the Disease-Specific Graded Prognostic Assessment (DS-GPA).[8] The prognostic factors within the breast-specific GPA are presented in Table 2. Note that the time from primary diagnosis to brain metastases was not an independent significant prognostic factor in the breast GPA and is therefore not a part of the index.[7]

The DS-GPA was based on the observed outcome of patients referred for a radiation therapy opinion, and

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TABLE 1. Median Survival Time (Months) by DS-GPA[8]

	Survival Median (Months)	GPA 1 (0–1)	GPA 2 (1.5–2.0)	GPA 3 (2.5–3.0)	GPA 4 (3.5–4)
NSCLC	7	3.02	5.49	9.43	14.78
SCLC	4.9	2.79	4.90	7.67	17.05
Melanoma	6.74	3.38	4.70	8.77	13.23
RCC	9.63	3.27	7.29	11.27	14.77
Breast	13.8	3.35	7.70	15.07	25.3

Abbreviations: DS-GPA, Disease-Specific Graded Prognostic Assessment; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; RCC, renal cell carcinoma.

patients underwent whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), surgery, or a combination of these treatments. Only 6% of patients had a GPA score of 1, with the remaining patients fairly equally distributed between GPA scores of 2, 3, and 4. This retrospective analysis cannot be used to predict the outcomes according to different treatments. Its utility lies in its use as a stratification tool for clinical trials and the comparison of results between clinical trials. It can also aid the oncologist in determining whether the patient might be best served by hospice.

National Comprehensive Cancer Network guidelines as of January 2017 state that CNS imaging of patients with asymptomatic breast cancer is not indicated, based on lack of available evidence of benefit. However, prospective studies to evaluate the risks and benefits of CNS imaging are scant. Given the incidence and relatively short interval to presentation of brain metastases in patients with triple-negative disease, and the high incidence of CNS metastases in patients with HER2-positive breast cancer, further investigation of this issue is highly warranted.

KEY POINTS

- **Risk factors for the development of brain metastases in breast cancer include tumor subtype (HER2-positive, triple-negative, estrogen receptor–negative), young age, higher disease grade, and shorter disease-free interval.**
- **Level I evidence, generated in mixed populations of patients with a variety of solid tumors, supports the role of surgical resection in patients with a single brain metastasis who have good performance status and controlled extracranial disease.**
- **For patients presenting with a limited number of brain metastases, the addition of WBRT to SRS improves intracranial control but does not improve survival and can be associated with neurocognitive deficits. Thus, SRS only is a reasonable approach in such patients. A caveat to these data is that they were generated in all-comers with solid tumors, and patients with breast cancer made up only a minority of patients enrolled.**
- **The use of memantine during and after WBRT is associated with delayed time to cognitive decline, reductions in the rates of decline in memory, executive function, and processing speed.**
- **To date, no systemic therapies have gained regulatory approval for the treatment of breast cancer brain metastases; however, several regimens have demonstrated activity in prospective studies, and multiple new approaches are being tested in ongoing clinical trials.**

LOCAL THERAPY

The Role of Surgery in Patients With Brain Metastases

Among local treatment options, surgery has a clear role in some subgroups of patients. Three phase III trials have compared surgical resection followed by WBRT with WBRT alone for a single brain metastasis (Fig. 1).[9-11] The first two studies have shown a survival benefit for patients receiving the combined treatment (median survival 10 vs. 4–6 months). In the Patchell study, patients who received surgery displayed a lower rate of local relapse (20% vs. 52%) and longer period of functional independence. The third study, which included more patients with active systemic disease (80% vs. 30%–40%) and a low Karnofsky performance status, did not show any benefit with the addition of surgery to WBRT. Therefore, class I evidence shows that the survival benefit of surgical resection in addition to WBRT is limited to the subgroup of patients with controlled systemic disease and good performance status.[12] In properly selected patients with two or three brain metastases, who are in good neurologic condition and have controlled systemic disease, complete surgical resection yields results that are comparable to those obtained in single lesions.[13] One caveat to these and much of the local therapy literature is that patients of multiple primary histologies were included in the trials, with a relatively small fraction of patients with breast cancer (typically 10%–20%), and thus, the recommendations are to some extent extrapolations based on a study population with primarily non–small cell lung cancer.

For the majority of patients, surgical resection allows an immediate relief of symptoms of intracranial hypertension, a reduction of focal neurologic deficits and seizures, and a rapid steroid taper. Gross total resection of a brain metastasis can be achieved with lower morbidity using contemporary image-guided systems, such as preoperative functional MRI, intraoperative neuronavigation, and cortical mapping.[14] An early postoperative MRI can detect residual tumor in up to 20% of patients, and this is associated with an increased risk of local recurrence.[15]

The impact of surgical methodology on the complication rate and functional outcome, as well as on local relapse in

TABLE 2. Prognostic Factors and Assigned Score in Breast Cancer GPA[8]

Prognostic Factor	0	0.5	1	1.5	2.0
KPS	≤ 50	60	70–80	90–100	n/a
Subtype	Basal	n/a	LumA	HER2	LumB
Age, years	≥ 60	< 60	n/a	n/a	n/a

Abbreviations: GPA, Graded Prognostic Assessment; KPS, Karnofksy Performance Status; LumA, luminal A; LumB, luminal B.

patients with a single brain metastasis, has been recently analyzed. Overall, the study suggests that postoperative complication rates are not increased by en bloc resection, as compared with piecemeal resection, for lesions in eloquent brain regions or large tumors.[16] Leptomeningeal dissemination can be a complication, especially for patients with posterior fossa metastases undergoing a piecemeal resection (13.8%) compared with en bloc resection (5%–6%).[17]

Last but not least, surgery is important in providing tissue for molecular analysis to define the molecular profile of the brain metastasis, which can be different from that of the primary cancer. This is critical in the near future for tailoring targeted therapies to the molecular profile of the brain metastases.

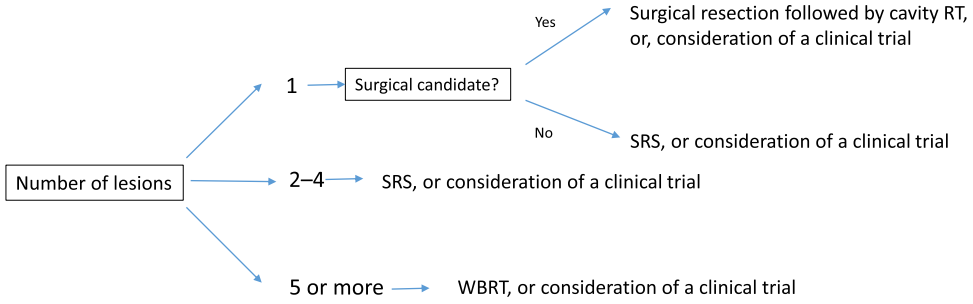
WBRT Compared With SRS Following Surgical Resection

Despite the randomized study by Patchell et al,[18] in which it was found that patients with a single brain metastases who underwent surgical resection and postoperative WBRT had fewer recurrences of cancer in the brain and were less likely to die of neurologic causes as compared with patients treated with surgical resection alone, there has been controversy regarding the role of WBRT in this setting. This led to the N107C/CEC.3 cooperative group study randomly assigning patients with a resected brain metastasis to receive either WBRT or SRS to the cavity. SRS to unresected brain metastases was allowed in both groups. Patients were stratified between primary lung cancer, radio-resistant histologies, or other histologies. This study was presented at the Plenary Session during the 2016 American Society for Radiation Oncology Annual Meeting but is not yet published.[19] Approximately 30% of enrolled patients fell into the other category, although breast cancer is not separated out otherwise. There was no reported difference in overall survival between the two treatment groups (11–12 months), with no difference seen according to age, extracranial disease status, number of brain metastases, histology, or size of resection cavity. However, there was a small but statistically significant difference in the cognitive deterioration–free survival favoring the SRS arm (2.8 months WBRT arm vs. 3.3 months SRS arm; $p < .0001$). Only 5.4% of patients in the WBRT arm were free of cognitive deterioration at 6 months as opposed to 22.9% in the SRS arm.

SRS With or Without WBRT

Several randomized studies have examined the outcome of SRS with or without WBRT.[20-23] One of these was a randomized controlled trial published in 2006 by Aoyama et al[20] (JROSG 99-1), which randomly assigned 132 patients with up to four brain metastases amenable to SRS. The primary endpoint was overall survival, but secondary outcomes included local recurrence, rate of salvage brain treatment, functional preservation, toxic effects, and cause of death. The study was closed earlier than the planned accrual when an interim analysis determined that more than 800 patients would be required to detect a significant difference in the primary endpoint. Breast cancer made up only 7% of enrolled patients, the majority being non–small cell lung cancer. In the SRS-only group, the median survival time and the 1-year actuarial survival rate were not significantly different between the two groups. However, the group receiving SRS and WBRT had a lower intracranial recurrence rate at 1 year (47% vs. 77%; $p < .001$), and required less frequent salvage treatment as opposed to the SRS-only group.

FIGURE 1. Management Algorithm for the Initial Treatment of Patients With Breast Cancer Brain Metastases



This figure provides a broad overview. For details and discussion of nuances of the recommendations, please refer to the text. Treatment recommendations will also depend on performance status, prior therapies, status of extracranial disease, comorbidities, and life expectancy. In most cases, outside of a clinical trial, surgery and/or radiation therapy will be given as initial therapy, and the systemic therapy will be determined by the status of a patient's extracranial disease (i.e., continue prior systemic therapy if systemic disease is stable, and switch if systemic disease is progressive).

Another larger study of 359 patients, of which 12% had breast cancer, randomly assigned patients with up to four brain metastases to receive local therapy (surgery or SRS) with or without WBRT.[23] Overall survival was similar between the two treatment arms (p = .89), although the local control (surgery vs. surgery WBRT: 59% to 27%, p < .001; SRS vs. SRS + WBRT: 31% vs. 19%, p = .04) and need for further salvage therapy (51% vs. 16%, p value not reported) were improved in the WBRT arm.

Lastly, a 2015 meta-analysis by Sahgal et al[24] of these randomized studies found that patients age 50 or younger had a significant survival benefit (p = .04) when SRS alone was used. This analysis found that these results were similar between patients with lung cancer and those with breast cancer, although the authors acknowledged the problems with small sample sizes. The authors concluded that SRS alone is the recommended initial therapy of patients age 50 or younger with one to four brain metastases.

The above findings showing that WBRT is not associated with improved survival, when combined with the data regarding the neurocognitive effects of WBRT, have led to many guidelines recommending SRS only for patients with one to four brain metastases (American Association of Neurological Surgeons, unpublished data, 2017).[22,25]

Quality of Life and Cognitive Dysfunction Following WBRT

Cognitive dysfunction following WBRT represents a topic of increasing importance. Historically, radiation-induced dementia with ataxia and urinary incontinence was described in up to 30% of patients by year 1 who were receiving unconventional, large-size fractions of WBRT (6–8.5 Gy), which are no longer used.[26] The picture on CT/MRI was that of a leukoencephalopathy (diffuse hyperintensity of the periventricular white matter on T2-weighted and fluid attenuation inversion recovery images) with associated hydrocephalus, for which placement of a ventriculoperitoneal shunt could be of some clinical value. When using more conventional size fractions (up to 3 or 4 Gy per fraction), the risk is that of mild cognitive dysfunction, consisting mainly in learning and memory impairment with a variable degree of damage of the white matter and cortical atrophy on MRI.

In recent years, several randomized trials have shed light on the short- and long-term effects of WBRT on neurocognitive function and quality of life. Aoyama et al compared the neurocognitive function of patients who underwent SRS alone or SRS plus WBRT.[27] Similar proportions of patients in both arms (p = .85) achieved a three point or more improvement in their Mini Mental State Examination score shortly after therapy (2–3 months). However, subsequent deterioration of neurocognitive function in long-term survivors (up to 36 months) after WBRT was observed. In a small randomized trial, Chang et al have shown that patients treated with SRS plus WBRT were at greater risk of a decline in learning and memory function at 4 months after treatment compared with those receiving SRS alone.[21] A randomized phase III trial (Alliance trial) has compared SRS alone with SRS plus WBRT in patients with one to three brain metastases using a primary neurocognitive endpoint, defined as decline from baseline in any seven cognitive tests at three months.[28] Neurocognitive decline was significantly more frequent after SRS plus WBRT compared with SRS alone (91.7% vs. 63.5%, p < .001). On individual tests, there was more cognitive deterioration in immediate memory (30.4% vs. 8.8.2%, p = .004), delayed memory (51.1% vs. 19.7%, p < .001), and verbal fluency (18.6% vs. 1.9%, p = .01) in the SRS plusWBRT arm. Finally, a quality-of-life analysis of the EORTC 22952-26001 trial has shown over 1 year of follow-up no significant differences in the global health-related quality of life, but patients undergoing adjuvant WBRT instead of observation had lower transient cognitive functioning, physical functioning, and more fatigue.[22]

Patients with arterial hypertension, diabetes, or other vascular diseases are at a higher risk of developing cognitive dysfunction. The pathogenesis of this radiation damage could consist of an injury of the endothelium of small vessels that leads to an accelerated atherosclerosis and ultimately to a chronic ischemia, resulting in a picture similar to that of the small vessel disease of vascular dementia. For this reason, there is interest in investigating vascular dementia treatments to prevent or reduce radiation-induced cognitive decline. One of these approaches is using memantine in combination with WBRT. Memantine is a noncompetitive, low affinity antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is one of the receptors activated by glutamate, the principal excitatory neurotransmitter. Memantine has the potential to block the excessive NMDA stimulation following ischemia, which ordinarily could lead to excitotoxic damage of the normal brain. In a recently published randomized, double-blind, placebo-controlled phase II trial (RTOG 0614), the use of memantine during and after WBRT resulted in a mild improvement of cognitive function over time, specifically delaying time to cognitive decline and reducing the rates of decline in memory, executive function, and processing speed.[29] The use of another neurotransmitter regulator, such as donepezil, has shown only modest improvements in cognitive function in a controlled trial, especially among patients with greater pretreatment impairment.[30]

Radiation-induced cognitive deficits may result, at least in part, from a radiation injury to the neuronal stem cells in the subgranular zone of the hippocampus.[31] These stem cells are responsible for maintaining neurogenesis, which is critical for preserving memory function, especially in terms of encoding new episodic memories. Low-dose irradiation in rodents results in a blockade of hippocampal neurogenesis and damage of the neurogenic microenvironment, leading to significant short-term memory impairment. Thereby, it has been hypothesized that sparing the hippocampus during WBRT (hippocampal-avoidance WBRT, HA-WBRT) could prevent the damage of the neuronal progenitor cells and better preserve memory functions.[32] The recent single-arm, phase II RTOG 0933 trial has suggested that the conformal avoidance of the hippocampus during WBRT is

associated with some sparing of memory and quality of life; specifically, performance on standardized memory tests declined 7% from baseline to 4 months in patients treated with hippocampal-avoidance WBRT, as compared with 30% in an historical control group.[33] Importantly, 4.5% of patients developing intracranial progression had involvement of the hippocampal-avoidance area by metastatic disease. In this regard, building on results of RTOG 0933 and RTOG 0614, NRG-CC001 is a phase III trial evaluating the potential combined neuroprotective effects of hippocampal avoidance in addition to memantine during WBRT for brain metastases.[34]

Clinical Challenges: Tumor Progression, Radionecrosis, and Pseudoprogression

A critical issue is the distinction between post-treatment effects and true tumor progression in some particular scenarios. Following SRS, changes such as an increase in contrast enhancement, necrosis, edema, and mass effect on MRI are difficult to interpret: in this regard, PET with ^{18}F-fluorodeoxyglucose, amino acids or ^{18}F-fluorodeoxythymidine, MRI perfusion, and magnetic resonance spectroscopy may provide additional information, though are rarely diagnostic.[35-38] In general, careful monitoring with MRI, sometimes for many months, is needed. Radiation necrosis is commonly treated with steroids. Hyperbaric oxygen and/or the anti-VEGF agent bevacizumab, which may allow stabilization/normalization of the vascular permeability, can be useful in patients not responding to steroids,[39] while surgical resection is needed in some patients.

In patients receiving immunotherapy-based treatments, an initial increase in the number and size of metastases can be followed by radiographic stabilization or regression. This pattern might be related to the mechanism of action of immunotherapy, including immune infiltrates and the time to mount an effective immune response. If immune response–related radiographic changes are suspected, the advice is to not interrupt immunotherapy treatment until a short interval scan is obtained.[40,41]

SYSTEMIC THERAPY

Evidence for Efficacy of Available Endocrine Therapies and Cytotoxic Chemotherapies

To date, no systemic agents have gained regulatory approval for the treatment of breast cancer brain metastases. Nevertheless, as summarized in Table 3, CNS activity in case series or in small, prospective studies has been reported across a range of cytotoxic drugs. For example, Rivera and colleagues reported their experience in a phase I trial testing the combination of capecitabine and temozolomide in 24 patients with breast cancer brain metastases (14 newly diagnosed; 10 with progressive brain metastases after prior local therapy). The observed CNS objective response rate was 18%, with median time to progression of 12 weeks.[42] Given the general lack of activity of temozolomide in breast cancer, it would be reasonable to assume that the majority of the activity in this trial can be attributed to the capecitabine. Data from a small series of seven patients treated at Memorial Sloan Kettering Cancer Center corroborate the observation of capecitabine activity in the CNS.[43]

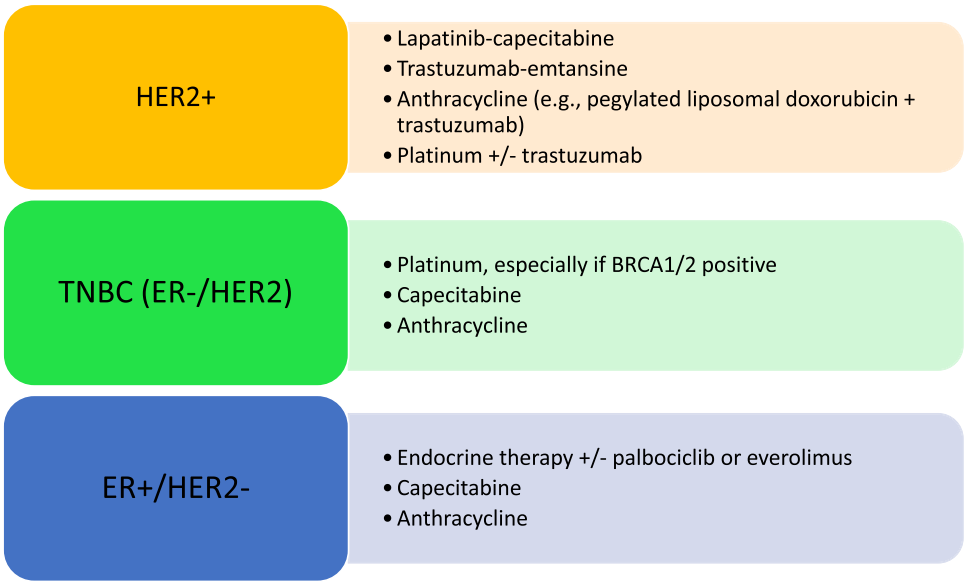
Anthracyclines are also associated with CNS responses in breast cancer, with response rates ranging widely from 17% to 62%, in small experiences. Single-agent temozolomide

TABLE 3. Summary of Case Reports, Case Series, and Prospective Studies Testing Cytotoxic Chemotherapy in Patients With Breast Cancer Brain Metastases

Agent	Details of Regimen	Type of Study	No. of Patients With Breast Cancer Treated With Specified Regimen	CNS ORR in Breast Cancer Subset	Reference
Capecitabine	Capecitabine + temozolomide	Phase I	24	18%	Rivera et al[42]
	Capecitabine	Case series	7	43%	Ekenel at al[43]
Anthracycline	Doxorubicin, cyclophosphamide	Case series	6	17%	Rosner et al[44]
	Pegylated liposomal doxorubicin	Phase II	8	62%	Caraglia et al[45]
	Liposomal doxorubicin + cyclophosphamide	Retrospective	29	41%	Linot et al[46]
Platinum	Cisplatin + etoposide	Prospective	56	38%	Franciosi et al[47]
	Cisplatin + etoposide	Case series	22	55%	Cocconi et al[48]
	Cisplatin + temozolomide	Phase II	15	40%	Christodoulou et al[49]
Irinotecan	Irinotecan + iniparib	Phase II	37	12%	Anders et al[50]
Temozolomide	Temozolomide	Phase II	19	0%	Trudeau et al[51]
	Temozolomide	Phase II	4	0%	Christodoulou et al[52]
	Temozolomide	Phase II	10	0%	Abrey et al[53]
	Temozolomide	Phase II	51	4%	Siena et al[54]
	Temozolomide + vinorelbine	Phase II	11	0%	Iwamoto et al[55]

Abbreviations: CNS, central nervous system; ORR, objective response rate.

FIGURE 2. Options for Systemic Treatment of Breast Cancer Brain Metastases



This figure provides a broad overview. For details and discussion of nuances of the recommendations, please refer to the text. Note that very few prospective trials have been conducted to evaluate the role of systemic therapy for breast cancer brain metastases, and, in many cases, the recommendations above are therefore based on case reports or case series, or extrapolation from systemic therapy trials. See text for details. Of note, there have not been randomized trials directly comparing a local (i.e., surgery, radiation therapy) versus systemic approach for the treatment of breast cancer brain metastases. Treatment recommendations will depend on performance status, prior therapies, status of extracranial disease, comorbidities, and life expectancy.

appears to have minimal activity in breast cancer and does not clearly add to other agents when given in combination.[51,53]

CNS activity for platinum salts has been reported in older case series, including response rates of 38% to 55%, albeit in a patient population less heavily pretreated than a typical patient seen today.[47,48] In this context, recent efforts (not limited to the brain metastasis space) to identify predictive markers of platinum benefit are relevant. The TNT trial evaluated the efficacy of taxanes versus platinums in the first-line treatment of metastatic triple-negative breast cancer. Of note, patients with active brain metastases were excluded. The study demonstrated differential activity according to *BRCA1/2* germline status, with a substantially higher rate of response in extracranial sites to carboplatin compared with docetaxel in *BRCA1/2* carriers.[56] This hypothesis has not been formally tested in the CNS; however, anecdotally, Jennifer Ligibel, MD, and Judy Garber, MD, MPH, have observed durable CNS responses (including one in excess of three years) in some *BRCA1/2* carriers treated with platinum salts (personal communication, January 2017).

Case reports of CNS responses to a variety of endocrine agents, including tamoxifen and aromatase inhibitors, are also present in the literature; however, patients with estrogen receptor–positive tumors typically present with brain metastases late in their disease course, when their disease has become hormone refractory.[57-60]

In general, if considering off-label use of systemic therapy for the treatment of breast cancer brain metastases, the choice of therapy should be in accordance with a patient's tumor subtype, prior therapies, performance status, and comorbidities, in keeping with national and international guidelines for management of metastatic breast cancer (Fig. 2). As with the practice guidelines for use of cytotoxic chemotherapy in patients with extracranial metastases, sequential single-agent chemotherapy is generally preferable to combination chemotherapy.

Investigational Cytotoxic Approaches

In terms of cytotoxic chemotherapy, the trend for the development of compounds focused on the treatment of brain metastases has been to engineer compounds that more effectively penetrate the blood-brain barrier (Table 4). Two of the compounds furthest in development are etirinotecan pegol (NKTR-102) and ANG1005. NKTR-102 is a long-acting topoisomerase-I inhibitor that prolongs exposure to SN38, the active metabolite of irinotecan. CNS activity in breast cancer has been previously observed in the clinic with the parent compound irinotecan.[50] In a mouse model of breast cancer brain metastases (MDA-MB-231Br), NKTR-102 prolonged survival compared with conventional irinotecan.[61] A phase III trial for patients with heavily pretreated breast cancer (either without brain metastases or with stable brain metastases on study entry) was recently reported.[62] Though a negative study overall, a potential signal was observed in the stable brain metastasis subset and a confirmatory study is currently under way. ANG1005 is a novel taxane derivative that is able to penetrate the blood-brain barrier via the low-density lipoprotein receptor–related protein.[63] CNS responses have been observed in early-phase studies, and additional studies are ongoing.[64,65]

HER2-Targeted Therapies

The development of HER2-targeted therapies has dramatically improved overall outcomes for patients with

HER2-positive breast cancer, both in the early and advanced stages. Despite these improvements, up to half of patients with advanced HER2-positive breast cancer will relapse in the CNS.

The small molecule tyrosine kinase inhibitor (TKI) lapatinib has been studied as a single agent and in combination with chemotherapy in multiple prospective clinical trials. As a single agent in pretreated patients, its activity is modest at best, with CNS responses observed in only 6% of patients.[66] Greater activity has been observed in combination with capecitabine, with CNS response rates ranging from 18% to 38% in pretreated patients, and a CNS response rate of 66% in the newly diagnosed setting.[66-70] Responses have been durable in many cases, and overall, the results support the concept of evaluating HER2-targeted TKIs for the treatment of brain metastases.

HER2-targeted TKIs in clinical development include neratinib, afatinib, and tucatinib, among others (Table 4). Neratinib is an irreversible inhibitor of EGFR and HER2 currently in late-stage clinical testing (NALA, neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2-directed regimens in the metastatic setting, NCT01808573). However, the ongoing phase III study excludes patients with active brain metastases. The Translational Breast Cancer Research Consortium is conducting a phase II study evaluating neratinib in patients with progressive brain metastases. Results of the monotherapy neratinib cohort have been published, with an observed CNS objective response rate of 8%.[71] Results of the neratinib/capecitabine combination cohort are anticipated in mid- to late 2017. Like neratinib, afatinib inhibits both EGFR and HER. Although it has gained regulatory approval in lung cancer, clinical development in breast cancer has been terminated based on negative results of the LUX-Breast 1 and LUX-Breast 3 randomized trials.[72,73] In particular, in the LUX-Breast 3 trial, the combination of vinorelbine and afatinib did not afford any additional benefits to patients with HER2-positive breast cancer brain metastases compared with treatment of provider choice.[72]

In contrast to either neratinib or afatinib, tucatinib (ONT-380; ARRY-380) selectively targets HER2 and has minimal activity against EGFR, leading to a more favorable toxicity profile, with less diarrhea and rash. The active metabolite appears to cross the blood-brain barrier, and improvements in survival have been reported in preclinical models of breast cancer brain metastases. In a phase I study of tucatinib with trastuzumab, CNS responses were observed in 7% of patients; approximately one-third of patients achieved stable disease of 16 weeks or longer.[74] The triplet of trastuzumab-capecitabine-tucatinib has been studied in a phase IB study among patients with highly refractory, HER2-positive metastatic breast cancer. Objective responses were observed in 61% of patients, including in 42% of patients who had measurable CNS disease at baseline.[75] The approach is now being tested in an ongoing randomized trial that includes patients with and without brain metastases.

Historically, monoclonal antibodies such as trastuzumab, pertuzumab, or trastuzumab-emtansine were thought to be too large and bulky to penetrate the blood-brain barrier.

TABLE 4. Ongoing Trials of Systemic Therapy for Breast Cancer Brain Metastases

Regimen	Phase	Patients With LMD Included?	Breast Cancer Subtypes	ClinicalTrials.gov ID
Neratinib + capecitabine	II	Yes, if also measurable parenchymal metastasis	HER2+	NCT01494662
Trastuzumab/capecitabine +/− tucatinib (ONT-380)	II	No	HER2+	NCT02614794
“High-dose” trastuzumab + pertuzumab	II	No	HER2+	NCT02536339
Intrathecal trastuzumab + pertuzumab	I	Not specified	HER2+	NCT02598427
“High-dose” lapatinib + capecitabine	I	Yes	HER2+	NCT02650752
Trastuzumab + vinorelbine + everolimus	II	Diffuse LMD excluded	HER2+	NCT01305941
Abemaciclib	II	Yes, separate cohort	ER+	NCT02308020
Palbociclib	II	No	HER2+ or TNBC	NCT02774681
Palbociclib	II	No	Any, but requires evidence of specific pathway alterations in brain metastasis tissue	NCT02896335
Cabozantinib	II	Yes, if also measurable parenchymal metastasis	ER+ or HER2+	NCT02260531
Pembrolizumab	II	Yes, separate cohort	Any	NCT02886585
Durvalumab	II	No	Any	NCT02669914
Etirinotecan pegol	II	No	Any	NCT02312622
Etirinotecan pegol	III	No	Any	NCT02915744
Cabazitaxel	II	No	Any	NCT02166658

Abbreviations: LMD, leptomeningeal disease; ER, estrogen receptor; TNBC, triple-negative breast cancer.

However, studies utilizing ^{89}Zr-labeled trastuzumab as a PET tracer have suggested there is some penetration through a disrupted blood-tumor barrier.[76] Penetration across the blood-tumor barrier is supported by emerging case reports and case series of the CNS activity of trastuzumab-emtansine (TDM1), with response rates qualitatively similar to that reported against extracranial disease.[77-79] A prospective U.S. study is being planned. Another approach under active investigation in the ongoing PATRICIA study is the use of high-dose trastuzumab (6 mg/kg IV weekly) in combination with standard pertuzumab every 3 weeks to drive up concentrations of trastuzumab in brain metastases. Accrual to the study is ongoing.

Clinical Challenges: Is There a Role for Chemoprevention of Brain Metastases?

There is great interest in preventing the emergence of brain metastases (primary prevention) and prolonging the time to subsequent CNS progression in patients who receive initial local therapy (secondary prevention). A common clinical question is whether systemic therapy should be modified following SRS to include a "CNS-active" regimen. At present, there is no direct evidence to support this approach, though the existing data have been sparse and do not perfectly address this question.

In the EMILIA trial, a subset analysis was performed among patients who entered the study with stable brain metastases to determine whether the benefit of trastuzumab-emtansine seen in the overall study (compared with lapatinib-capecitabine) held up in the brain metastasis subset.[80] Patients in the brain metastasis subset appeared to derive similar relative benefits in terms of overall survival prolongation with trastuzumab-emtansine, and there was no obvious signal in favor of lapatinib-capecitabine with respect to CNS progression. In addition, there were no obvious differences in the incidence of new CNS metastases among patients who entered the study without brain metastases at baseline (2% with trastuzumab-emtansine; 0.7% with lapatinib-capecitabine; p = not significant). The analysis had several limitations including that CNS scans were not mandated per protocol and emerging reports supporting CNS activity of trastuzumab-emtansine, making this potentially a comparison between two "CNS-active" regimens.

In general, the consensus approach for treatment of such patients is to continue the prior systemic therapy after SRS, if the systemic disease remains well controlled, but this is an area ripe for clinical trials.[81]

Other Targeted Approaches Under Clinical Investigation

A number of other targets are being explored in the treatment of breast cancer brain metastases, including CDK4/6 inhibitors, PARP inhibitors, and immunomodulatory therapies (Table 4).

When combined with endocrine therapy, the CDK4/6 inhibitors palbociclib and ribociclib prolong progression-free survival compared with endocrine therapy alone.[82-84] Among the CDK4/6 inhibitors, abemaciclib appears to have the best CNS penetration in preclinical models and has been demonstrated to reach therapeutic levels in human "window of opportunity" studies when given prior to planned resection.[85,86] Phase II studies of both palbociclib and abemaciclib for brain metastases are ongoing.

Given the frequency of brain metastases in patients with triple-negative breast cancer, there is interest in developing novel targeted approaches in this patient population. PARP inhibitors have clear activity against extracranial metastases in *BRCA1/2* carriers; however, single-agent activity in sporadic triple-negative breast cancer has been disappointing.[87] Three large randomized phase III trials comparing PARP inhibitors with standard chemotherapy in *BRCA1/2* carriers with metastatic breast cancer are ongoing, but all three studies exclude patients with active brain metastases. There is also ongoing interest in combination approaches to sensitize *BRCA1/2* wild-type breast cancer to PARP inhibitors, including combinations with platinum salts. The U.S. cooperative groups are collaborating on a planned randomized study (S1416) that will examine cisplatin with or without the PARP inhibitor veliparib (ABT-888). Given that veliparib crosses the blood-brain barrier in preclinical models, a CNS-specific cohort will be concurrently enrolled, with a primary endpoint of progression-free survival.[88]

There are accumulating preclinical and clinical evidence suggesting that the immune system is critical for disease outcome in breast cancer, particularly in the triple-negative and HER2-positive subtypes.[89,90] Moreover, PD-L1 expression appears to be common in breast cancer brain metastases.[91] Data in patients with melanoma and lung cancer support potential efficacy of immune checkpoint inhibitors in the CNS.[92] Beyond CTLA-4 and PD-1/PD-L1 inhibitors, there is a wealth of novel immunomodulatory compounds, including STING and GITR agonists, and inhibitors of IDO, TIM3, and LAG3. Unfortunately, the vast majority of ongoing trials of immunotherapy in breast cancer specifically exclude patients with active brain metastases, though there are some studies in this population that have recently opened or are in development (Table 4).

MANAGEMENT OF LEPTOMENINGEAL DISEASE

Estimates of the incidence of leptomeningeal metastases vary widely, ranging from 2% to 40%, either alone or associated with parenchymal brain metastases. In a case series of patients with leptomeningeal disease (1998 to 2013) from Memorial Sloan Kettering Cancer Center, both HER2-positive (26% of cases) and triple-negative (25% of cases) breast cancer subtypes were overrepresented, suggesting they are associated with a propensity toward dissemination in the leptomeninges.[93] Invasive lobular histology also appears to be associated with leptomeningeal spread.[94] The prognosis is poor with median survival of 3.5 to 6 months and 20% survival rate at 1 year.[93,95] Since patients can experience very poor survival, it is critical to consider prognostic factors early in weighing management options, including consideration

of a more palliative/hospice-oriented course, as appropriate. Favorable prognostic factors include HER2-positive subtype, preserved performance status, and CNS-only involvement. Unfavorable prognostic factors include poor performance status, progressive/treatment-refractory extracranial disease, and major neurological deficits.

The most typical management approach is radiation to sites of bulk disease followed by consideration of intra–cerebrospinal fluid (CSF) and/or systemic therapy. Radiation-based approaches, including WBRT, have the potential to provide rapid relief of symptoms, and should be strongly considered, particularly for patients presenting with neurological deficits. Intra-CSF chemotherapy has a role for palliation of neurologic symptoms and should be considered for patients with a large tumor cell load in the CSF.[96] Methotrexate, liposomal cytarabine, and thiotepa are the drugs of choice. At the time of the placement of an Ommaya catheter, and prior to injecting drugs into the CSF, flow studies are recommended to rule out the existence of subarachnoid blocks, as these could preclude optimal distribution of drug and increase the risk of leukoencephalopathy.[97-100] Systemic chemotherapy has been used off-label to treat patients with leptomeningeal disease based on observed efficacy in case reports and small case series. Regimens with reported efficacy (with caveats given the very limited data) include tamoxifen, aromatase inhibitors, high-dose intravenous methotrexate, capecitabine, lapatinib/capecitabine, and platinum salts.

From an investigational standpoint, leptomeningeal disease has frequently been excluded from clinical trials. However, a number of ongoing trials are exploring new therapeutic options (Table 4). Of note, a phase I/II study of intrathecal trastuzumab has recently completed accrual. In this study, trastuzumab was reconstituted in preservative-free sterile water, USP or preservative-free 0.9% sodium chloride, with an induction phase of more frequent administration, followed by tapering of the frequency of administration. The recommended phase II dose has been identified, and efficacy results from the phase II portion are expected later this year.[101] In general, we have not incorporated use of intrathecal trastuzumab into routine clinical practice, pending efficacy results of this study.

CONCLUSION

Increasingly, the management of breast cancer with brain metastases (parenchymal or leptomeningeal disease) requires close multidisciplinary collaboration, balancing the patient's disease burden in the CNS and extracranially, prior therapies, performance status, comorbidities, life expectancy, and preferences, with available treatment options. Surgical resection should be strongly considered in patients presenting with a single brain metastasis, or a large, symptomatic mass, particularly if they have good performance status and controlled extracranial disease. For patients with expected longer survival, the use of up-front SRS and avoidance of WBRT in the setting of a limited number of brain metastases is preferred. Although there are still no systemic therapies approved for the treatment of breast cancer brain metastases, a number of regimens have demonstrated clear activity in prospective experiences and can be considered in the clinic. At present, systemic therapy is an option for patients whose CNS disease has progressed through standard local therapy, and it can even be considered in patients with newly diagnosed disease in lieu of local approaches in some circumstances (e.g., asymptomatic or minimally symptomatic patients). Moving forward, many novel, promising approaches are being tested in the clinic, and results are eagerly awaited.

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Lifestyle Interventions to Improve Cardiorespiratory Fitness and Reduce Breast Cancer Recurrence

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OVERVIEW

As patients are living longer after a cancer diagnosis, survivorship is becoming increasingly important in cancer care. The sequelae of multimodality therapies include weight gain and decreased cardiorespiratory fitness, which increase cardiovascular risk. Evidence suggests that physical activity reduces the risk of breast cancer recurrence and death. Avoidance of weight gain after therapy also improves outcomes after a diagnosis of breast cancer. Prospective randomized trials must be performed to determine the benefits of specific physical activity and dietary habits for survivors of breast cancer. This review outlines the important physiologic changes that occur with antineoplastic therapy and the important role of exercise and diet.

Breast cancer is the most frequently diagnosed cancer among women and the second leading cause of cancer death in the United States.[1] Breast cancer mortality has decreased by nearly 40% during the last 3 decades as a result of advances in prevention, early detection, and treatment.[2] As a result of improved survival and population aging, breast cancer is evolving into a disease of older survivors who face an important new set of health care challenges. Nearly one-third of breast cancer survivors have a peak oxygen uptake (peak VO2)—the gold standard measure of cardiorespiratory fitness—that is below the threshold level required for full and independent living.[3] A consequence of reduced fitness is decreased survival in healthy populations.[4]

In accordance with the multiple-hit hypothesis, unfavorable lifestyle factors (e.g., sedentary lifestyle, sarcopenic obesity) coupled with the adverse effects of anticancer therapy result in reduced physiologic and functional reserve capacity. Interventions that improve cardiovascular health and body composition outcomes (e.g., increased muscle mass, decreased visceral adiposity) may play an important role in improving cardiorespiratory fitness, reduce breast cancer recurrence, and improve mortality.

The aim of this chapter is to briefly review the mechanisms responsible for reduced peak VO2 in survivors of breast cancer and the role of exercise training to improve peak VO2 and the role of diet, weight reduction, and exercise in the moderation of cardiovascular disease sequelae, reduction of breast cancer recurrence, and improvement in mortality.

CARDIORESPIRATORY FITNESS AMONG BREAST CANCER SURVIVORS

Breast cancer survivors with normal resting left ventricular (LV) systolic function have a peak VO2 that is 19% (5.5 mL/kg/min) lower than healthy age-matched noncancer controls.[5-10] The magnitude of the decline in peak VO2 is greatest during the short-term period after completing adjuvant therapy.[3,11] Lower levels of cardiorespiratory fitness, as measured by peak VO2, may also have important prognostic implications and result in shorter survival in women with metastatic disease.[3] Thus, an important goal is to maintain an optimal level of cardiorespiratory fitness across the breast cancer survivorship continuum.

DETERMINANTS OF PEAK VO2: ROLE OF IMPAIRED CARDIOVASCULAR FUNCTION

Given that VO2 is equal to the product of cardiac output and arterial-venous oxygen content difference, the reduced peak VO2 among breast cancer survivors may be due to central (cardiac) or peripheral (skeletal muscle and its microvasculature) factors that result in decreased oxygen delivery to and/or extraction by the active muscles.[5,12]

To date, only one study has examined the acute hemodynamic cardiopulmonary response to maximal aerobic exercise in 47 survivors of breast cancer with normal resting LV systolic function (mean age, 59; mean LV ejection fraction, 64%) and 11 age-matched healthy controls.[6] As shown in Fig. 1, the decreased peak VO2 in survivors of breast cancer was primarily due to a lower stroke volume and cardiac output, as heart rate and arterial-venous oxygen difference

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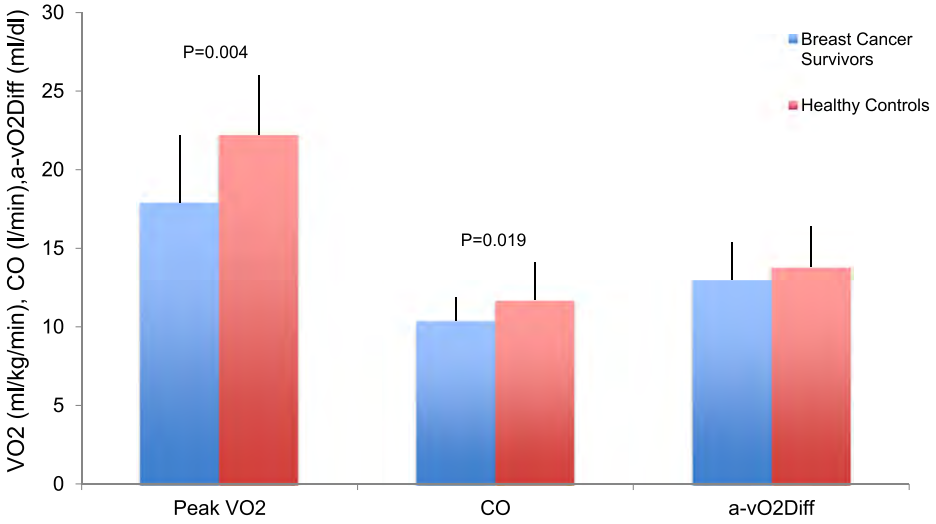
FIGURE 1. Fick Determinants of Impaired Peak VO2 in Breast Cancer Survivors



Abbreviations: Peak VO2, peak oxygen uptake; CO, cardiac output; a-vO2Diff, arterial-venous oxygen difference.

during maximal cycle exercise were not significantly different between groups.[6] The mechanism responsible for the reduced maximal exercise stroke volume was not examined; however, it may be the result of increased LV afterload as maximal systemic vascular resistance was 11% higher in breast cancer survivors compared with controls.[6]

Oxygen extraction is directly related to muscle oxygen diffusive conductance (e.g., transport of O2 from hemoglobin to muscle mitochondria) and inversely related to muscle blood flow.[12] Accordingly, our finding that maximal arterial-venous oxygen difference was not different between survivors of breast cancer and healthy controls despite a lower maximal cardiac output[6] (muscle blood flow) suggests that abnormalities in skeletal muscle microvascular and/or mitochondrial function may play an important role in limiting breast cancer survivors exercise performance.[5] To attenuate the decline (during adjuvant therapy) or increase peak VO2 (post-adjuvant therapy), therapies should focus on improving cardiovascular and skeletal muscle function.

KEY POINTS

- **Breast cancer survivors have reduced cardiorespiratory fitness secondary to impaired cardiovascular reserve.**
- **Exercise training is an effective intervention to improve cardiorespiratory fitness; however, the physiologic mechanisms underpinning this favorable adaptation are unknown.**
- **Concomitant diet and exercise interventions may abrogate breast cancer therapy–induced accelerated CVD sequelae, particularly in overweight/obese women.**
- **Epidemiologic evidence supports the participation in exercise before and after breast cancer diagnosis because it is a contributing factor in decreasing breast cancer recurrence, breast cancer–related mortality, and overall mortality.**

IMPROVEMENT IN PEAK VO2 WITH EXERCISE TRAINING

Exercise training is an effective intervention to improve peak VO2, physical functioning, and quality of life, and reduces symptoms of fatigue in breast cancer survivors.[13] The magnitude of the change in peak VO2 with training appears to be related to the volume of exercise performed, and the threshold workload required to obtain a clinically significant large increase in peak VO2 (effect size > 1) was 600 intensity-minutes in a 10-week supervised exercise training program performed for 90 minutes per week at 70% peak VO2.[14] Although the mechanisms underpinning the exercise-training mediated improvement in peak VO2 have not been studied, they may be due to favorable changes in cardiac, peripheral vascular, or skeletal muscle function.[5]

EFFICACY OF DIET AND EXERCISE INTERVENTIONS TO MODULATE THERAPY-INDUCED CARDIOVASCULAR DISEASE

Breast cancer survivors who are obese have a significantly higher overall, and breast cancer–related, mortality compared with their counterparts who are at a baseline healthy weight within 12 months after diagnosis.[15] There is increasing evidence demonstrating that breast cancer survivors are at a higher risk of morbidity and mortality. Indeed, compared with sex- and age-matched counterparts, patients with breast cancer have an increased incidence of risk factors for cardiovascular disease (CVD; e.g., obesity, hypertension, diabetes, dyslipidemia, exercise intolerance)[16] and CVD-specific morbidity (e.g., coronary artery disease and heart failure). Moreover, in survivors older than age 65, CVD is the leading cause of mortality.[17,18] As prolonged administration of anticancer therapies becomes increasingly common[19] and novel targeted therapies with potentially adverse cardiovascular safety profiles are included in treatment strategies,[20] the incidence of CVD morbidity and mortality among breast cancer survivors will likely continue to rise.

Thus, defining the feasibility and efficacy of innovative interventions that can attenuate CVD sequelae are of primary research and clinical importance.

Exercise, a pleiotropic stimulus leading to physiologic adaptation across multiple organ systems,[21] improves insulin sensitivity, decreases lipids, and lowers blood pressure with concomitant improvements in peak VO2 in noncancer settings.[22-26] Although comparatively less information is available in oncology settings, recent observational data of patients with breast cancer indicate that adherence to national exercise guidelines for adult patients with cancer (i.e., ≥ 9 MET hours/week) was associated with an adjusted 23% reduction in the risk of CVD events compared with not meeting the guidelines (< 9 MET hours/week; p = .0002).[27] The association with exercise did not differ according to age, most CVD risk factors, menopausal status, or anticancer treatment,[27] suggesting that, for many patients with breast cancer, exercise is a potent intervention that can modulate CVD sequelae. However, the protective effects of exercise did not extend to women with a body mass index (BMI) of 35 kg/m^2 or greater.[27] As a result, additional interventions may be required for patients with excess CVD risk associated with obesity.

Based on promising data indicating that weight control, physical activity, and/or diet quality reduce cancer recurrence and improve cancer-specific overall survival, the American Cancer Society issued Guidelines on Nutrition and Physical Activity for Cancer Survivors, which call for maintenance of a healthy body weight, regular physical activity regardless of BMI, and modest weight loss for cancer survivors who are overweight or obese.[28] Importantly, concomitant diet and exercise interventions in nononcology overweight/obese settings have been shown to improve LV function, exercise capacity, glucose, lipid, and blood pressure control, inflammation markers, body composition, and skeletal muscle function.[29] Thus, the synergistic benefits of multicomponent interventions could represent an optimal approach to offset CVD in patients with breast cancer.

CVD SEQUELAE AMONG PATIENTS WITH BREAST CANCER

The incidence of common risk factors for both CVD and cancer such as hypertension (up to 55%),[30] diabetes (up to 10%),[31] hyperlipidemia (up to 20%),[32] obesity (up to 62%),[33] and low exercise tolerance (up to 37%)[3] likely increase the risk of CVD morbidity and mortality[34] For example, Hooning et al examined the long-term causes of mortality among 7,425 women treated for early-stage breast cancer and found that after a median of 13.8 years, survivors diagnosed with one CVD risk factor at any time during the study follow-up had a 1.4- to 3.1-fold higher risk of CVD-related mortality relative to age-matched women among the general population.[16,17] Moreover, Playdon et al reported that a weight gain of more than 5% from diagnosis to post-treatment was associated with a 12% increase in the risk of all-cause mortality compared with weight maintenance in a meta-analysis involving 23,832 patients with early-stage breast cancer.[33] Similarly, among 3,993 women with early-stage disease (5.8 years postdiagnosis), those with a BMI greater than 30 kg/m^2 (classified as obese) had a CVD mortality rate 1.65 times that of women with a normal BMI (18.5–24.9 kg/m^2), and each 5 kg weight gain was associated with a 19% increase in CVD mortality.[35] These findings highlight the importance of identifying women at the greatest risk of accelerated CVD sequalae so targeted interventions can be initiated.

EVIDENCE OF EFFICACY OF COMBINED DIET AND EXERCISE INTERVENTIONS TO MODULATE CVD SEQUELAE

Evidence from nononcology trials indicate that multicomponent interventions may be critical for improving outcomes such as body composition, peak VO2, and biomarkers linked to CVD outcomes. For example, in 107 obese adults (BMI > 30 mg/kg^2) were randomly assigned to one of four groups for 52 weeks: (1) 27 patients in the control group, (2) 26 patients in the diet group, (3) 26 patients in the exercise group, and (4) 28 patients in the diet and exercise group.[36] Peak VO2 improved more in the diet and exercise group than in the diet or exercise alone groups (increases of 17% vs. 10% vs. 8%, respectively; p < .001), whereas body weight decreased by 10% in the diet alone group and by 9% in the diet-exercise group, but did not decrease in the exercise group or the control group (p < .001). Similarly, in 439 postmenopausal women who were overweight/obese and randomly assigned to: (1) a reduced calorie, weight loss diet (diet; 118 patients); (2) moderate-to-vigorous intensity aerobic exercise (exercise; 117 patients); (3) a combination of a reduced calorie, weight loss diet and moderate-to-vigorous intensity aerobic exercise (diet and exercise; 117 patients); or (4) control (87 patients),[37] leptin concentrations, a key regulator of energy homeostasis, metabolism, and adiposity, decreased in all of the intervention groups, but the greatest reduction occurred with diet and exercise (-40%). Taken together, these findings suggest that a combination of weight loss and an exercise program could provide greater improvement in multiple outcomes compared with either intervention alone in overweight/obese populations.

To date, the potential cardioprotective properties of multimodal interventions in patients with breast cancer have received limited attention; however, preliminary observational data indicate that adherence to diet and exercise guidelines improves patient morbidity and mortality. For example, among 938 breast cancer survivors in the Iowa Women's Health Study (mean age, 79; 8.6 years postdiagnosis),[38] adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) prevention guidelines for weight control, physical activity, and diet was associated with lower all-cause mortality (hazard ratio [HR] 0.67; 95% CI, 0.50–0.94), and a 40% reduction in CVD-specific mortality. The majority of trials of patients with breast cancer have examined the efficacy of either exercise alone to improve functional outcomes (e.g., VO2peak) or diet alone to direct weight management or weight loss. As a result, only approximately six trials have investigated

the effect of a combined diet and exercise intervention among patients with breast cancer. For example, 90 postmenopausal patients with breast cancer receiving adjuvant chemotherapy were randomly assigned to (1) a calcium-rich diet intervention (attention control), (2) calcium-rich diet and exercise, or (3) calcium-rich diet with high fruit and vegetable, low-fat diet and exercise. Demark-Wahnefried et al[39] reported that the high fruit and vegetable arm substantially attenuated therapy-induced increases in appendicular body fat. Similarly, Morey et al[40] reported that among 641 older, overweight, long-term survivors of breast (289 patients), prostate (261 patients), and colorectal (91 patients) cancer randomly assigned to either a 12-month home-based program of telephone counseling promoting exercise and diet, or wait-list control, weight loss was significantly greater in counseling groups compared with the wait-list control group (2.06 vs. 0.92 kg, respectively; $p < .001$).

The Life After Cancer Epidemiology (LACE) study examined the impact of dietary adherence in 1,901 women diagnosed with early-stage breast cancer. A prudent dietary pattern was defined by a high intake of fruits, vegetables, whole grains, and poultry, whereas a Western diet was defined by high intake of red and processed meats and refined grains. The prudent diet was associated with a significant decrease in risk of overall death (trend $p = .02$; HR for highest quartile 0.57; 95% CI, 0.36–0.90) and death from non–breast cancer causes (trend $p = .003$; HR for highest quartile 0.35; 95% CI, 0.17–0.73) independent of physical activity, body habitus, or tobacco use. In contrast, a Western diet was related to an increasing risk of overall death (trend $p = .05$) and death from non–breast cancer causes ($p = .02$). Interestingly, both dietary patterns were not associated with reduced risk of breast cancer recurrence or breast cancer–specific mortality.[41]

The Women's Health Initiative Dietary Modification primary breast cancer prevention trial randomly assigned 48,835 postmenopausal women with no prior history of breast cancer and normal mammograms to undergo dietary intervention or to a control group. The dietary intervention reduced dietary fat intake to 20% of calories, increased fruit and vegetable intake (five servings a day), and increased grains to six servings a day. During year 1, intervention group members participated in 18 group sessions and then quarterly maintenance meetings. The control group participants received dietary guidelines. Although the incidence of breast cancer was not significantly decreased among women in the low-fat diet group, women in the intervention group had improved overall survival at 8.5 years (HR 0.65; 95% CI, 0.45–0.94; $p = .02$. At the 16-year mark, breast cancer-specific mortality was still lower than those in the control group (234 vs. 443 deaths, respectively; HR 0.82; 95% CI, 0.70–0.96; $p = .01$). Women with baseline waist circumference of 88 cm or greater and higher baseline levels of dietary fat intake had a stronger interaction in terms of deaths after breast cancer.[42]

The randomized phase III WINS trial evaluated whether dietary fat reduction affected relapse-free survival among 2,437 patients with early-stage breast cancer receiving standard-of-care treatment. Women with a dietary fat intake greater than 20% of calories were randomly assigned to a dietary intervention group or a control group. Women were given a fat-gram goal by centrally trained, registered dietitians implementing a low-fat eating plan. Women in the intervention arm underwent 8 biweekly individual counseling sessions, were subsequently contacted every 3 months, and self-monitored their fat-gram intake using a "keeping score" book. Fat intake was externally monitored by unannounced 24-hour telephone recalls performed annually for 5 years. Women enrolled in the intervention group consumed 9.2% calories from fat and lost nearly 6 pounds. Although there was no survival benefit at 19.4 years, an exploratory subgroup analysis of the group with estrogen negative tumors showed higher median survival of 13.6 years in the intervention group compared with 11.7 years in the control arm (HR 0.46; $p = .006$).[42]

Although these findings are promising for patients with breast cancer with, or at high risk of obesity, the long-term implications of acute multimodal interventions on CVD morbidity and mortality are unknown. To this end, the Look AHEAD (Action for Health in Diabetes) study examined the incidence of a composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalized angina) over 9.6 years in 5,145 overweight or obese individuals with type 2 diabetes randomly assigned to a diet and exercise intervention or control.[43] Although improvements in weight loss, fitness, and CVD risk factors were greater in the intervention group, there was no significant difference between the intervention and control group in CVD morbidity and mortality (403 vs. 418 events, respectively; 1.83/100 person-years vs. 1.92/100 person-years, respectively; HR 0.95; 95% CI, 0.83–1.09; $p = .505$).[43] Thus, the effect of multimodal interventions in patients with breast cancer on outcomes other than weight loss, or in patients with concomitant comorbidities such as hypertension, dyslipidemia, diabetes, or exercise intolerance, are important areas for further research.

In summary, given that patients with breast cancer now live long enough to be at risk for therapy-induced CVD morbidity and mortality, a research agenda that addresses the nature and magnitude of therapy-related CVD could define important targets for interventions. To this end, observational data indicating that exercise-induced modification of CVD events is attenuated in obese breast cancer survivors[27] suggest that, for a subset of patients with breast cancer who are overweight or obese, multimodal interventions may be critical to abrogating accelerated CVD. Prospective trials are needed to define the role of diet and exercise in the management of CVD sequelae in overweight and obese breast cancer survivors.

ROLE OF EXERCISE IN RISK REDUCTION OF BREAST CANCER

The role of exercise in secondary prevention and breast cancer–related mortality is not well-defined. However, the

known physiologic effects of exercise suggest that it may have an important role. Exercise may reduce adverse outcomes associated with fat accumulation such as an altered hormonal environment and adipokine production, which may act to promote tumor development and growth.[44] Randomized, controlled trials of physical activity among postmenopausal women who are overweight demonstrated declines in serum levels of androgen, estrogen, and leptin—hormones important for tumorigenesis.[45-47] For these reasons, exercise may be a modifiable behavior that has the potential to change important breast cancer outcomes. In the next section, we review the salient data on the impact of exercise on breast cancer recurrence and mortality.

Exercise and Risk of Recurrence and Effect on Breast Cancer Mortality: Epidemiologic Data

The majority of studies examining this question have been observational cohort studies based on patient self-reporting, an important limitation. The landmark study is the Nurses' Health Study, a prospective observational study of 2,987 female registered nurses with stage I to III breast cancer between 1983 and 1998.[48] The women were followed every 2 years until 2002 or time of death, and answered questions about their physical activity over the prior year. After adjusting for factors predictive of survival after breast cancer, compared with women who engaged in less than 3 MET-hours/week of physical activity, the relative risk (RR) of death from breast cancer was 0.80 (95% CI, 0.60–1.06) for 3 to 8.9 MET-hours/week; 0.50 (95% CI, 0.31–0.82) for 9 to 14.9 MET-hours/week; 0.56 (95% CI, 0.38–0.84) for 15 to 23.9 MET-hours/week; and 0.60 (95% CI, 0.40–0.89) for 24 or more MET-hours/week (trend p = .004). After multivariable adjustment, the RR of breast cancer recurrence was 0.83 (95% CI, 0.64–1.08) for 3 to 8.9 MET-hours/week; 0.57 (95% CI, 0.38–0.85) 9 to 14.9 MET-hours/week; 0.66 (95% CI, 0.47–0.93) for 15-23.9 MET-hours/week; and 0.74 (95% CI, 0.53–1.04) for 24 or more MET-hours/week as compared with women who engaged in less than 3 MET-hours/week of physical activity (trend p = .05). Interestingly, the RR for each adverse outcome was lowest for the intermediate level of activity, equivalent to walking 3 to 5 hours per week at an average pace. The protective benefit was similar among nonobese and obese women, but the benefit was particularly apparent in women with hormone-responsive tumors. The RR of breast cancer death for women with hormone-responsive tumors who engaged in 9 or more MET-hours/week of activity compared with women with hormone-responsive tumors who engaged in less than 9 MET-hours/week was 0.50 (95% CI, 0.34–0.74). An important limitation of this study is that the participants were mostly non-Hispanic whites and occupationally homogenous.[48]

The Collaborative Women's Longevity Study (CWLS) and the Life After Cancer Epidemiology (LACE) study used the same measure of physical activity as the Nurse's Health Study, but found different results.[49,50] In CWLS, a total of 4,482 eligible women age 20 to 79 diagnosed with invasive breast cancer stages I to III between 1988 and 2001 completed the questionnaire of physical activity a median of 5.6 years after diagnosis. After adjusting for relevant factors, women who engaged in greater levels of activity had a significantly lower risk of dying from breast cancer (HR 0.65; 95% CI, 0.39–1.08 for 2.8 to 7.9 MET hours/week; HR 0.59; 95% CI, 0.35–1.01 for 8.0 to 20.9 MET hours/week; and HR 0.51, 95% CI, 0.29–0.89 for > 21 MET hours/week; trend p = .05). Results were similar for overall survival (HR 0.44; 95% CI, 0.32–0.60 for > 21.0 vs. < 2.8 MET hours/week; trend p < .001) and were similar regardless of a woman's age (although the majority of women were age > 50), stage of disease, and BMI. Similar to the Nurse's Health Study, no benefit was demonstrated for vigorous-intensity activity and most of the participants were Caucasian. [50]

In the LACE study, 1,970 women age 18 to 79 with stage I to III breast cancer from 1997 to 2000 completed the physical activity questionnaire the prior 6 months only. Age-adjusted results suggested that higher levels of physical activity were associated with reduced risk of recurrence and breast cancer mortality (trend p = .05 and .07, respectively, for highest versus lowest level of hours per week of moderate physical activity), but were not significant after adjusting for prognostic factors and other variables. Of note, in multivariable analyses, there remained a significant protective association between physical activity and all-cause mortality (HR 0.66; 95% CI, 0.42–1.03; trend p = .04). A strength and unique characteristic of this study is that it contained 20% minorities. It is hypothesized that the lack of power and healthier nature of the participants led to the null results of this study.[49]

Several studies have looked at exercise in breast cancer at several time points, an advantage over the studies that evaluate a single point in time. The Health, Eating, Activity, and Lifestyle (HEAL) study was a prospective, observational study of 933 women age 18 and older diagnosed with stage I to III cancer between 1995 and 1998 that measured activity levels the year prior to diagnosis and 2 years after diagnosis. Compared with women who were inactive both before and after diagnosis, women who increased physical activity after diagnosis had a 45% lower risk of death (HR 0.55; 95% CI, 0.22–1.38), and women who decreased physical activity after diagnosis had a fourfold greater risk of death (HR 3.95; 95% CI, 1.45–10.50). Although the risk reductions were observed for total deaths, the majority of deaths were from breast cancer.[51] Similarly, the Women's Health Initiative (WHI) study measured activity at diagnosis and 3 or 6 years post diagnosis in 4,643 postmenopausal women. Women participating in at least 9 MET hours/week (approximately 3 hours per week of brisk walking) of physical activity after diagnosis had lower breast cancer mortality (HR 0.61; 95% CI, 0.35–0.99; p = .049) and lower all-cause mortality (HR 0.54; 95% CI, 0.38–0.79); p < .01). Even in women who were inactive prior to diagnosis, those who increased or maintained physical activity of at least 9 MET hours/week after diagnosis had lower all-cause mortality (HR 0.67; 95% CI, 0.46–0.96).[52]

The Women's Healthy Eating and Living Study (WHEL) similarly measured activity at baseline and 1 year in 2,361

women age 18 and older with stage I to III breast cancer. Adherence to activity guidelines was associated with a 35% lower mortality risk (HR 0.65; 95% CI, 0.47–0.91; p < .01). There was no effect seen on breast cancer events, although deaths were mostly secondary to breast cancer. Unlike the WHI study, in WHEL the change in activity during 1 year was not associated with improved outcomes, potentially secondary to shorter interval between reports.[53] The Shanghai Breast Cancer Survival Study (SBCSS) assessed exercise at three time points (6, 18, and 36 months post-diagnosis) in 4,826 Chinese women age 20 to 70 between 2002 and 2006. After adjusting for several covariates, exercise during the first 36 months post-diagnosis was inversely associated with total mortality and recurrence/disease-specific mortality with HRs of 0.70 (95% CI, 0.56–0.88) and 0.60 (95% CI, 0.47–0.76), respectively, regardless of stage and BMI. They observed a dose-response relationship between mortality rates and exercise duration and MET scores, and the mortality association was only among estrogen- and progesterone receptor–negative patients.[54] The clear strength of this study is that it evaluated more than two time points; however it is uncertain if this study can be applied to a Western breast cancer population.

EFFECT OF EXERCISE ON BREAST CANCER RECURRENCE AND MORTALITY: CLINICAL TRIALS

Data from randomized controlled trials are limited. The Supervised Trial of Aerobic versus Resistance Training (START) trial randomly selected 242 patients with breast cancer between 2003 and 2005 to usual care, supervised aerobic, or resistance exercise during chemotherapy.[55] The trial was originally designed to examine the independent effects of aerobic and resistance exercise on quality of life, health-related fitness, and other patient-reported outcomes. As an exploratory analysis, overall survival and disease-free survival was estimated. Eight-year disease-free survival was 82.7% for the exercise groups compared with 75.6% for the control group (HR 0.68; 95% CI, 0.37–1.24; log-rank p = .21). In exploratory subgroup analyses, the strongest effects were among women who were overweight or obese, had stage II/III cancers, estrogen receptor–positive tumors, HER2-positive tumors, and received taxane-based chemotherapies and optimal chemotherapy dosing.[56] This study is limited by its exploratory nature but is certainly hypothesis-generating. Phase III studies comparing exercise to usual care in breast cancer survivors are warranted.

EXERCISE SUMMARY AND RECOMMENDATIONS

Supportive data from randomized controlled trials are lacking, but epidemiologic evidence supports the participation in exercise before and after breast cancer diagnosis to decrease breast cancer recurrence, breast cancer–related mortality, and overall mortality. The American Cancer Society encourages cancer survivors to engage in 150 minutes per week of moderate or 75 minutes per week of vigorous aerobic exercise.[28]

CONCLUSION

Decreased cardiorespiratory fitness, obesity, and a sedentary lifestyle negatively impact the outcomes of breast cancer survivors. Lifestyle interventions to improve survival are of much interest. However, there is a paucity of prospective, randomized clinical trial data to suggest specific exercise and dietary recommendations to improve cardiovascular fitness and reduce breast cancer–specific mortality in this population. Prospective, randomized studies that address interventions are necessary to guide breast cancer survivors.

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Novel Targeted Agents and Immunotherapy in Breast Cancer

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OVERVIEW

The treatment of breast cancer is generally determined according to breast cancer subtype: hormone receptor–positive (luminal), triple-negative (basal-like), and HER2-overexpressing breast cancer. Recent years have seen the development of exciting novel and potent therapeutics based on molecular pathways, immune modulation, and antibody conjugates. In this article, we cover new and emerging therapeutic areas and ongoing clinical trials that may result in further improvements in breast cancer outcomes.

Breast cancer clinicians have been fortunate in the past to have proven efficacious treatment options to offer their patients. Novel therapeutics continue to expand treatment options for patients with early-stage and advanced breast cancer. For estrogen receptor–positive (ER+), HER2-negative, and HER2-amplified disease, novel agents can combine with existing effective therapies to reverse or delay treatment resistance. Determining the optimal combination and best treatment sequence remains a difficult challenge, however. In contrast, triple-negative breast cancer (TNBC) is a heterogeneous disease that has devastating consequences on relapse with limited treatment options, and improvements in outcomes will rely on novel therapies and identifying the subgroups of patients most likely to benefit. We discuss potential further therapeutic directions for the three main breast cancer subtypes in this article.

MECHANISMS OF ENDOCRINE THERAPY RESISTANCE IN ER+ BREAST CANCER

Acquired resistance (defined as recurrence at least 6–12 months after completion of adjuvant therapy or disease progression more than 6 months after endocrine therapy initiated in the metastatic setting) and occasionally primary resistance (recurrence either within adjuvant therapy or within 6–12 months of completion of adjuvant therapy or disease progression more than 6 months after treatment in the metastatic setting) to antiestrogen therapy is inevitable in patients with ER+ metastatic breast cancer (MBC).[1] A variety of mechanisms have been implicated in primary and acquired resistance to endocrine agents (Sidebar 1). Below we review some of the strategies to overcome endocrine therapy resistance.

Cyclin-Dependent Kinases 4 and 6 Inhibitors

Inhibitors of the cyclin-dependent kinases 4 and 6 (CDK4/6) have demonstrated impressive activity in patients with ER+/HER2-negative MBC.[2] Palbociclib is an orally active pyridopyrimidine first-in-class compound that is a potent and highly selective reversible inhibitor of CDK4/6.[3] By inhibiting CDK4/6, palbociclib prevents tumor cell entry into S phase.[4] Consistent with its CDK4/6 specificity, treatment with palbociclib reduces expression of the proliferation marker Ki67 and is completely inactive in Rb-deficient tumor cells.[5] Preclinical data have shown that endocrine-resistant ER+ breast cancer cells are highly sensitive to palbociclib with and without antihormonal therapy.[6]

In previously untreated metastatic ER+/HER2-negative MBC, the phase I/II PALOMA-1 trial found an impressive improvement in progression-free survival (PFS) with palbociclib plus letrozole over letrozole alone.[7] The confirmatory phase III PALOMA-2 study randomized a total of 666 postmenopausal patients with ER+ MBC and no prior systemic therapy to receive letrozole with palbociclib or letrozole with placebo. Median PFS (the primary endpoint) was 24.8 months versus 14.5 months in favor of the palbociclib arm (hazard ratio [HR], 0.58; 95% CI, 0.46–0.72; $p < .000001$).[6] Response rate was also improved in the palbociclib arm (42.1% vs. 34.7%, $p = .031$), and clinical benefit rate was 84.9% versus 70.3% ($p < .0001$). Similar evidence of efficacy was seen in the phase III PALOMA-3 trial with the combination of fulvestrant plus palbociclib, in which the PFS was 9.2 months versus 3.8 months with fulvestrant plus placebo (HR, 0.42; $p < .000001$) in patients with disease progression after at least one line of hormonal therapy and at most one line of chemotherapy but naive to CDK4/6 inhibitors.[2,8] In both phase III trials, the most common grade 3 or 4 adverse

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SIDEBAR 1. Mechanisms of Resistance to Endocrine Agents

Primary Resistance

- Receptor tyrosine kinase/growth factor signaling pathway
- *FGFR* amplification
- *EGFR*/*ERBB2* mutations
- Cell cycle control signaling pathway
- Cyclin D1 amplification or expression
- *MYC* amplification and overexpression
- Hormone signaling pathway
- Loss of ERα
- Post-translational modification of ERα
- Expression of ER coactivation/corepression factors

Acquired Resistance

- PI3K/AKT1/MTOR signaling pathway
- PI3K/AKT/mTOR pathway activation
- Mitogen-activated protein (MAP) kinase pathway
- MAPK/ERK pathway activation
- Hormone signaling pathway
- *ESR1* mutations
- Changes in the tumor microenvironment

event in the palbociclib arms was neutropenia (incidence 62%–65%), but treatment was otherwise well tolerated. Both palbociclib with letrozole for first-line treatment and palbociclib with fulvestrant for second line treatment of patients with ER+/HER2-negative MBC are approved by the U.S. Food and Drug Administration (FDA).

KEY POINTS

- **Breast cancer was the first solid tumor type leading the way with targeted therapy: tamoxifen and, subsequently, trastuzumab.**
- **ER+, HER2-negative disease has lately seen the emergence of highly effective CDK4/6 inhibitors, which likely will represent a major advance for this breast cancer subtype.**
- **HER2+ breast cancer represents the poster child for oncogene addiction and targeted therapy: the advent of trastuzumab has resulted in early-stage HER2+ disease becoming highly curable, and we now understand that these tumors remain addicted to HER2-signaling. Newer HER2-directed therapies, probably in combination with immunotherapies, will result in patients with advanced disease enjoying long periods of time with excellent quality of life.**
- **Triple negative breast cancer remains the major challenge for breast cancer clinicians. It is hoped that newer DNA damage repair inhibitors, immunotherapies, and antibody-drug conjugates will result in improved survival.**

mTOR Inhibitors

The addition of the mTOR inhibitor everolimus to endocrine therapy can reverse endocrine resistance in ER+ MBC, as shown in the BOLERO-2[9] and TAMRAD[10] randomized phase III trials. In both studies, all patients were previously exposed to aromatase inhibitors (AIs), and most of them developed progression after initial response (acquired resistance). This led to the approval of everolimus by the FDA and the European Medicines Agency in combination with endocrine therapy after failure of AIs in 2012. In contrast to these positive results, the phase III HORIZON trial found the addition of the mTOR inhibitor temsirolimus to letrozole did not improve PFS over letrozole alone.[11] This trial was conducted in the first-line setting, and most patients were AI naive, suggesting that mTOR signaling may have a specific role in acquired resistance to endocrine therapy. There are several ongoing trials that will better define the role of everolimus in advanced disease: BOLERO-6 (NCT01783444), a phase II trial comparing exemestane/everolimus to capecitabine in ER+/HER2-negative disease refractory to AI, and BOLERO-4 (NCT01698918), a phase II single-arm study evaluating the role of everolimus as first-line treatment. Everolimus is also being evaluated in the adjuvant setting with two different studies using two different approaches: (1) SWOG1207 (NCT01674140) will randomly assign high-risk premenopausal and postmenopausal patients to add everolimus or placebo to their standard adjuvant endocrine therapy, and (2) NCT01805271 will evaluate the addition of everolimus to adjuvant endocrine therapy in high-risk ER+/HER2-negative patients with breast cancer who remain disease free after at least 1 year of treatment.

PI3K Inhibitors

PI3K inhibitors consist of pan-PI3K targeting all class I isoforms, isoform-specific PI3K inhibitors, and dual PI3K/mTOR inhibitors. Compounds may also display differential activity for wild-type and mutant PI3K proteins. Response rates with single-agent PI3K inhibitors are far below those of other kinase inhibitors in other cancer types (such as EGFR, ALK, or BRAF inhibitors). Frequent coexisting genetic alterations, compensatory feedback loops, and toxicity that precludes maintaining adequate dose intensity are possible explanations for this diminished efficacy.

Buparlisib (BKM120) is a pan-PI3K inhibitor with potent activity against mutant PI3Kα.[12] Early phase trials of buparlisib plus endocrine therapy reported activity and a manageable safety profile characterized by transaminitis, hyperglycemia, diarrhea, and mood disorders (anxiety, depression, irritability).[12,13] The randomized phase III BELLE-2 trial studied fulvestrant 500 mg plus buparlisib 100 mg daily or placebo in postmenopausal MBC progressing on AIs.[14] Buparlisib increased the median PFS by 1.9 months (6.9 months vs. 5.0 months, $p < .001$). For patients with PI3K/AKT pathway activation (defined as PIK3CA mutation or PTEN loss, assayed for the majority in the archival primary tumor) there was no difference in the benefit of buparlisib. However, in the subset of patients in whom *PIK3CA* mutation

was assessed by circulating tumor DNA at trial entry, buparlisib plus fulvestrant increased PFS in PIK3CA mutant cases compared with fulvestrant alone (7 months vs. 3.2 months; HR, 0.56; p < .001).

Using the same treatment arms as BELLE-2, the phase III BELLE-3 trial enrolled AI-experienced patients with disease progression in the past 30 days on an mTOR inhibitor plus endocrine therapy.[15] Median PFS for patients in the buparlisib arm was 3.9 months versus 1.8 months for fulvestrant/placebo, and 6-month PFS rates were 30.6% and 20.1%, respectively. Of 349 patients for whom *PIK3CA* mutation status from circulating tumor DNA was available, 147 had mutations in the gene. Among those with *PIK3CA* mutations, PFS was 4.7 months in the buparlisib arm versus 1.6 months in the placebo arm. A similar result was seen with *PIK3CA* status in tumor tissue.

PI3Kα is the isoform predominantly mutated in cancer, and studies have shown that selective inactivation of this isoform is enough to block PI3K/AKT signaling in response to different growth factor stimuli.[16-18] Early results with pan-PI3K inhibition suffered from substantial toxicity and reduced efficacy,[19] and inhibiting PI3Kα selectively is designed to achieve a better therapeutic index by targeting the driving isoform in a specific cancer. Two PI3Kα inhibitors are in clinical development for breast cancer in combination with endocrine therapy: alpelisib (BYL719) and taselisib (GDC-0032). Single-agent alpelisib showed preferential activity in solid tumors harboring *PIK3CA* mutations.[20,21] Alpelisib plus fulvestrant is being studied in a phase III trial for metastatic ER+ breast cancer progressing on AIs (SOLAR1, NCT02437318) and in a neoadjuvant phase II trial in combination with letrozole (NEO-ORB, NCT01923168). Taselisib is a is a potent inhibitor of p110α, p110δ, and p110γ but with 30-fold less inhibition of p110β relative to p110α and greater selectivity against *PIK3CA* mutant isoforms than wild-type.[22] Taselisib and fulvestrant is being tested in a randomized phase III study in the metastatic setting for women with previous exposure to AIs and enrichment for *PIK3CA* mutation (SANDPIPER, NCT02340221) and a neoadjuvant phase II trial in combination with letrozole (LORELEI, NCT02273973).

ESR1 Mutations

Mutations in the ligand binding domain of the ER gene *ESR1* result in estrogen-independent ER signaling and resistance to antiestrogen therapy.[23-26] *ESR1* mutations are uncommon in primary breast cancers at the time of diagnosis, but they have been identified in up to 55% of ER+ MBC previously treated with antiestrogen therapy.[27] *ESR1* mutations may have a role in determining optimal endocrine therapy. In the SoFEA phase III trial,[28] *ESR1* mutations were found in 39% of patients (63 of 161) with rates of mutation detection unaffected by delays in processing of archival plasma. Patients with *ESR1* mutations had improved PFS after taking fulvestrant (45 patients) compared with exemestane (18 patients; HR 0.52; 95% CI, 0.30–0.92; p = .02), whereas patients with wild-type *ESR1* had similar PFS after receiving either treatment (HR 1.07; 95% CI, 0.68–1.67; p = .77).[29] In PALOMA3, *ESR1* mutations were found in the plasma of 25.3% of patients (91 of 360), with mutations associated with acquired resistance to prior AIs. Fulvestrant plus palbociclib improved PFS compared with fulvestrant plus placebo in both ESR1 mutant (HR 0.43; 95% CI, 0.25–0.74; p = .002) and *ESR1* wild-type patients (HR 0.49; 95% CI, 0.35–0.70; p < .001).[29] *ESR1* mutations are often "polyclonal," with multiple different mutations detectable in the same patient.[29] There is considerable interest in developing antiestrogen therapies that are effective in the presence of *ESR1* mutations.

NEW APPROACHES IN TNBC: PARP INHIBITORS AND BEYOND

TNBC, which lacks all three predictive and prognostic immunohistochemical biomarkers, ER, progesterone receptor, and HER2, has few therapeutic options beyond chemotherapy which to date remains the standard of care. Clinically, TNBC has an aggressive tumor biology with the worst disease-specific outcome compared with other subtypes, representing an important challenge and unmet clinical need.[30,31] Survival data from clinical trials indicate that the median overall survival for patients with metastatic TNBC (mTNBC) is approximately 11 to 14 months and is indeed much shorter than among patients with other MBC subtypes.[32,33]

Subtypes of TNBC have been described on the basis of histopathologic features and gene expression profiling, highlighting the heterogeneity and complexity of these tumors.[34-37] Four distinct breast cancer subtypes (luminal A, luminal B, HER2-enriched, and basal-like) of prognostic and predictive significance were first described by Perou et al[38] in 2000 using microarray analysis. Of the four subtypes, basal-like tumors are typically of triple-negative phenotype, and the vast majority (approximately 80%) of TNBCs are of the basal-like subtype.[36,39] In analyzing gene expression profiles of TNBC, Lehmann et al[35] identified six distinct molecular subtypes (basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor). This was refined into four tumor-specific subtypes (basal-like 1, basal-like 2, mesenchymal, and luminal androgen receptor) following histopathology and laser-capture microdissection, which identified infiltrating lymphocytes and tumor-associated stromal cells contributing to the immunomodulatory and mesenchymal stem-like subtypes, respectively.[36] In addition to microarray-based studies, the genomic landscape of this disease has also been extensively interrogated, identifying alterations adding to our burgeoning knowledge of TNBC.[27,40] The features and alterations unique to these various subtypes have been incorporated into many ongoing, rationally designed trials to refine treatment strategies. In this article, we discuss notable novel approaches in the treatment of TNBC.

Cytotoxic Chemotherapy

The triple-negative paradox describes a higher responsiveness of TNBC to chemotherapy despite the overall unfavorable prognosis.[41] Currently, chemotherapy is the mainstay

to treating TNBC. Taxane and anthracycline-containing regimens remain the preferred chemotherapeutic options, and recent results have clarified the role of nab-paclitaxel and carboplatin. The Triple-Negative Albumin-Bound Paclitaxel Combination International Treatment Study (tnppAcity) is a phase II trial evaluating nab-paclitaxel in combination with either gemcitabine or carboplatin versus gemcitabine plus carboplatin in previously untreated mTNBC.[42] It found a significantly longer PFS (median PFS, 7.4 months vs. 5.4 months, p = .03, and 7.4 months vs. 6 months, p = .02) and overall response rate (ORR; 72% vs. 39% and 44%) in favor of nab-paclitaxel plus carboplatin compared with paclitaxel plus gemcitabine or gemcitabine plus carboplatin.[42] In the Triple Negative Breast Cancer Trial (TNT), 376 patients with previously untreated mTNBC were randomly assigned to receive either carboplatin or docetaxel monotherapy.[43] Although there was no difference in the ORR or PFS between the two arms in the overall population, the key finding was patients who harbored deleterious germline BRCA mutations fared better when treated with carboplatin, with greater ORR (68% vs. 33.3%, p = .03) and PFS (6.8 months vs. 3.1 months, p = .03) compared with docetaxel.[43] Thus, both platinum and nab-paclitaxel should be included in our armamentarium of treatment of TNBC as well as other standard chemotherapies used for other subtypes of breast cancer.

Targeting Defective DNA Repair

A significant proportion of BRCA-mutated breast cancers are TNBC[44] or have gene expression profiles similar to basal-like TNBC.[45] The BRCA gene complex plays an important role in maintenance of genomic stability via homologous recombination, one of the coordinated pathways that act to identify DNA aberrations and restore genomic stability. Loss of function of BRCA confers a defective homologous recombination phenotype. This affords an opportunity for achieving "synthetic lethality" by using PARP inhibitors.[46] Concurrent tumor intrinsic BRCA loss of function and pharmacologic inhibition of PARP results in tumor cell death with a high therapeutic index.[47]

As a proof of concept, clinical trials in the initial development of PARP inhibitors have focused largely on BRCA-mutated tumors.[48-50] In a phase II trial of olaparib monotherapy in two sequential cohorts of BRCA-mutated advanced breast cancer, an ORR of 11 of 27 (41%) was seen in the cohort treated at 400 mg twice daily and 6 of 27 (22%) in the cohort treated at 100 mg twice daily. A significant proportion of both cohorts had TNBC; 7 of 13 triple-negative cases (54%) responded to 400 mg twice daily, while 4 of 16 triple-negative cases (25%) responded to 100 mg twice daily.[49] Ongoing phase III trials evaluating PARP inhibition in BRCA-mutant MBC include olaparib in OlympiAD (NCT02000622), which will report at the 2017 ASCO Annual Meeting with a press release noting that the trial had reached its primary endpoint, niraparib in BRAVO (NCT01905592), and talazoparib in EMBRACA (NCT01945775). Ongoing efforts are focused on molecular diagnostics beyond BRCA testing to predict benefit from PARP inhibition as well as applying PARP inhibitors in a broader population through combination strategies.

Immunotherapy: Checkpoint Inhibition

Approximately 20% of TNBCs are classified as the immunomodulatory subtype and are characterized by genes involved in the immune system.[36] Early-stage TNBC has high levels of tumor-infiltrating lymphocytes, and increasing levels of tumor-infiltrating lymphocytes predict a better prognosis.[51] These tumor-infiltrating lymphocyte contribute significantly to the gene expression profiles and express immune checkpoint genes such as programmed cell death–1 (PD-1) and programmed cell death ligand–1 (PD-L1).[36,52] T-cell checkpoint inhibitors, which relieve the immunosuppressive tumor microenvironment and promote antitumor immune responses, have generated much excitement by demonstrating lasting efficacy in some patients across a broad array of tumor types, including TNBC.

In a multicohort phase IB study of monotherapy with the anti-PD1 monoclonal antibody pembrolizumab, the ORR was 18.5% in 28 evaluable patients with TNBC displaying PD-L1 expression (positive staining in stroma or on at least 1% of tumor cells by immunohistochemistry).[53] The median duration of response was not reached, and three responders remained on study for at least 1 year. These promising results led to the initiation of KEYNOTE-086 (NCT02447003), a larger single-arm phase II study to evaluate the role of pembrolizumab in advanced TNBC and identify biomarkers of efficacy. The preliminary results of this study will be reported at the 2017 ASCO Annual Meeting. In addition, KEYNOTE-119 (NCT02555657), a randomized phase III study of pembrolizumab versus physician's choice single-agent chemotherapy in pretreated advanced TNBC, is estimated to complete recruitment in late 2017. Finally, atezolizumab has also shown efficacy as a single agent in a phase IA trial in PD-L1–positive tumors where a cohort of 12 patients with mTNBC were treated, with an ORR of 33%.[54]

Combinations of immunotherapy and chemotherapy may be more efficacious in TNBC. It has been postulated that chemotherapy could promote an immune response to cancer and hence be synergistic with immune therapy.[55] Several trials are investigating combination strategies enhancing the efficacy of immunotherapy and expanding its reach to a broader population of patients. In a phase IB trial of atezolizumab in combination with nab-paclitaxel in mTNBC, the ORR (including unconfirmed responses) in all patients was an impressive 71%, with a range of 43% in those patients treated in the third line and beyond to 89% in those previously untreated.[56] Importantly, the regimen had a tolerable safety profile, and responses were seen in both PD-L1–expressing and PD-L1–nonexpressing tumors. IMpassion130 (NCT02425891), a phase III study of nab-paclitaxel with or without atezolizumab in previously untreated mTNBC, is ongoing and expected to enroll 900 patients across 270 sites globally. KEYNOTE-355 (NCT02819518) is a two-part phase III study evaluating the safety and efficacy of pembrolizumab in combination with three different chemotherapies, in the first-line setting.

Androgen Receptor Blockade

Gene expression microarray-based studies have identified the luminal androgen receptor subtype, which highly expresses androgen receptor (AR) messenger RNA in addition to downstream AR targets and coactivators.[7,35,57] Thus, it is postulated that AR inhibition would have antitumor activity in a well-defined subgroup of TNBC. A phase II trial of abiraterone acetate, an inhibitor of 17-α-hydroxylase/17,20-lyase (CYP17) in a cohort of heavily pretreated AR-positive (at least 10% by immunohistochemistry) TNBC demonstrated a 6-month clinical benefit rate of 20% (95% CI, 7.7%–38.6%) and PFS of 2.8 months.[58] Similarly, in a phase II trial of enzalutamide, a potent AR inhibitor, the 24-week clinical benefit rate was 29% (95% CI, 20%–41%), and median PFS of 14 weeks (95% CI, 8–19 weeks) was seen in the 57 evaluable patients.[59] In this study, an androgen-driven diagnostic gene signature was associated with greater clinical benefit, and the phase III ENDEAR trial of paclitaxel plus enzalutamide/placebo and enzalutamide monotherapy has been initiated in diagnostic signature positive TNBC (NCT02929576).[60]

Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) are a novel class of cancer therapeutics, which amalgamate the selectivity of a targeted treatment and cytotoxicity of chemotherapy, resulting in an improved therapeutic index. Sacituzumab govitecan (IMMU-132) is an anti-Trop-2 ADC consisting of humanized IgG antibody against Trop-2 linked to SN-38, an active metabolite of irinotecan. The Trop-2 protein is an epithelial cancer antigen found to be highly expressed in a majority of TNBC compared with normal tissues and is associated with a poor prognosis and aggressive disease.[61] In the first-in-human phase I trial, sacituzumab govitecan had an acceptable safety profile and evidence of efficacy including one confirmed response and two minor responses seen in three of four patients with TNBC.[62] In the ongoing multicenter phase II trial, promising PFS of 5.6 months (95% CI, 3.6–7.1 months), overall survival of 14.3 months (95% CI, 10.5–18.8 months), and a response rate of 29% were seen in a heavily pretreated (median of five prior therapies) population of TNBC.[63] Sacituzumab govitecan has been given breakthrough therapy and fast-track designation from the FDA, and a phase III international multicenter randomized trial versus treatment of physician's choice in refractory mTNBC is planned for initiation in 2017 (NCT02574455).

Glembatumumab vedotin (CDX-011) is a fully human IgG2 monoclonal antibody with high affinity for extracellular domain of glycoprotein nonmetastatic B linked to the microtubule inhibitor monomethyl auristatin E (MMAE). Glycoprotein nonmetastatic B is highly expressed in TNBC in relation to normal tissue, predicts breast cancer recurrence, and is associated with reduced overall survival.[64] Early activity was seen in mTNBC and high-gpNMB-expressing tumors in the phase II EMERGE study.[65] The METRIC trial, a randomized phase III study evaluating glembatumumab vedotin versus capecitabine, is ongoing in gpNMB overexpressing TNBC (NCT01997333).

Targeting the PI3K/AKT/mTOR Pathway

Numerous studies have shown that the PI3K/AKT/mTOR pathway is activated in TBNC either through loss of pTEN or INPP4B or mutations in PIK3CA or AKT.[66-68] A neoadjuvant study of weekly paclitaxel/doxorubicin/cyclophosphamide in combination with the AKT inhibitor MK-2206 versus chemotherapy alone showed a pathologic complete response rate of 40% in the combination arm compared with 22% in the chemotherapy alone arm.[69] In the metastatic setting, the LOTUS trial (NCT02162719), a phase III study of paclitaxel alone or in combination with the AKT inhibitor ipatasertib, has completed recruitment and results will be available in 2017. Finally, the luminal AR subtype is known to be enriched with *PIK3CA* mutations, and the combination of antiandrogens with PI3K inhibitors is currently being evaluated.[70]

NOVEL THERAPEUTIC DIRECTIONS FOR HER2-AMPLIFIED BREAST CANCER

HER2-overexpressing breast cancer exemplifies the concept of oncogene addiction as a highly rewarding treatment target. The success of trastuzumab and subsequent HER2 therapies (pertuzumab, T-DM1, lapatinib, neratinib) highlights that these breastcancers remain highly dependent on the HER2 pathway as treatment resistance develops. Hence the search for more potent agents against the HER2 pathway remains highly active. With the success of the trastuzumab and pertuzumab combination, de-escalation of chemotherapy in the early-stage setting will become a tractable goal. Most patients with advanced disease, however, present with de novo metastatic disease, and here are required therapies that can achieve long term disease control with a favorable toxicity profile and are effective in preventing and managing central nervous system (CNS) metastases. We speculate the treatment in advanced HER2+ disease will become focused on ER+ versus ER-negative status presence or absence and the stability of CNS disease as well as determining the presence of preexisting host immunity as major determinants for deciding ongoing therapy.

Novel HER2 Tyrosine Kinase Inhibitors

The role of HER2 tyrosine kinase inhibitors (TKIs) in the management of early- and late-stage HER2+ breast cancer is evolving. The toxicity of lapatinib and neratinib has hampered their widespread use, and it remains unclear how to best use these drugs in managing CNS disease, and in combination with trastuzumab, pertuzumab or T-DM1. Next-generation HER2 TKIs may ameliorate these issues. Tucatinib (formerly ONT-380, ARRY-380), is a highly selective HER2 tyrosine kinase small-molecule inhibitor.[71] This selectivity is expected to ameliorate the diarrhea and skin toxicity, which are the most troublesome side effects of existing HER2 TKIs such as lapatinib. Additionally, studies with an intracranial HER2 xenograft mouse model demonstrated superior survival with tucatinib treatment over lapatinib or neratinib.[72]

The preclinical rationale for reduced toxicity was confirmed in a phase I study of tucatinib in solid tumors with

HER2 overexpression.[73] The study included an expansion cohort of 17 patients with metastatic HER2+ breast cancer. The dose-limiting toxicity was elevated liver transaminases. At the maximum tolerated dose of 600 mg twice daily, grade 1 or 2 diarrhea occurred in 26% of patients, with no cases of grade 3 or 4 diarrhea. Grade 1 and 2 nausea occurred in 33% of patients. Among the patients with HER2+ breast cancer treated with the maximum tolerated dose or higher, three of 22 had a partial response (14%).

A phase IB trial tested tucatinib 300 mg twice daily in combination with capecitabine (100 mg/m^2) and/or trastuzumab (6 mg/kg thrice weekly) in patients with prior exposure to trastuzumab, taxane, and T-DM1 (NCT02025192).[74] The ORR was 83% for capecitabine plus tucatinib (6 patients), 40% for trastuzumab plus tucatinib (15 patients), and 61% for capecitabine plus trastuzumab plus tucatinib (23 patients). The median duration of response in the triplet arm was 10 months. In the capecitabine-containing arms, grade 1 or 2 diarrhea occurred in 68% of patients. The rate of grade 3 diarrhea was 9% (three of 34), similar to treatment with capecitabine alone. A follow-up phase IB trial tested tucatinib plus T-DM1 in a similar patient population that had not experienced T-DM1 (NCT01983501).[75] The recommended phase II dose of tucatinib 300 mg twice daily was used. The ORR was 47% in 34 patients with measurable disease, with similar benefit in those having received one or more prior HER2 agents. The most common grade 3 and 4 toxicities were thrombocytopenia (28%), increased alanine transaminase (16%), and fatigue (12%). Diarrhea incidence was 56% grade 1 or 2 and 4% grade 3.

CNS disease remains a challenging problem in the management of advanced HER2+ metastatic disease. Recently, neratinib and afatinib monotherapy have been tested in the setting of progressive CNS metastases, with relatively poor results. The LUX-Breast 3 trial found no benefit and increased toxicity with afatanib alone or afatinib and vinorelbine compared with physician's choice therapy.[76] The Translational Breast Cancer Research Consortium (TBCRC) 022 single-arm phase II trial tested neratinib monotherapy in patients with progressive CNS metastases after prior CNS-directed therapy. The partial response rate was 8%, and 21% of patients experienced grade 3 or worse diarrhea despite loperamide prophylaxis.[77] Encouraging results in the setting of CNS metastases have been seen with tucatinib in a combined analysis of patients with CNS metastases across the two phase IB trials described above. The partial response rate was 38% in asymptomatic untreated CNS metastases and 33% in progressive CNS metastases after prior radiotherapy or surgery.[78]

Considering these results, the phase III HER2CLIMB study is comparing tucatinib versus placebo in combination with capecitabine and trastuzumab (NCT02614794) in patients who have received prior taxane, trastuzumab, pertuzumab, and T-DM1. Asymptomatic CNS metastases and previously treated CNS metastases are permitted. The study enrollment has recently expanded to 480 patients.[79]

CDK4/6 Inhibitors

Preclinical data in mouse models of HER2+ breast cancer have shown that CDK4/6 inhibitors can restore sensitivity to anti-HER2 therapy in resistant tumors.[80] The randomized phase II monarcHER trial compares abemaciclib plus trastuzumab plus fulvestrant versus abemaciclib plus trastuzumab versus physician's choice, in ER+/HER2+ MBC with at least two prior anti-HER2 therapies (NCT02675231).[81] The phase II PATRICIA trial is delivering palbociclib and trastuzumab with or without letrozole in postmenopausal patients with advanced HER2+ breast cancer and includes ER+ and ER-negative groups (NCT02448420). A phase IB trial of palbociclib and T-DM1 (NCT01976169) and a phase I/II trial of ribociclib and trastuzumab or T-DM1 (NCT02657343) are also under way. A randomized phase III study of maintanence palbociclib with endocrine therapy, pertuzumab, and trastuzumab after chemotherapy in advanced ER+/HER2+ disease is also about to commence (PATINA: NCT02947685).

PI3K/mTOR Inhibitors

Activation of the PI3K pathway, including PIK3CA mutations and PTEN loss, has been noted preclinically to confer resistance to trastuzumab.[82] The BOLERO1 and BOLERO2 3 trials investigated the addition of the mTOR inhibitor everolimus to trastuzumab and paclitaxel in first-line therapy and trastuzumab and vinorelbine following trastuzumab resistance, respectively.[83,84] A combined analysis of these studies found that tumors lacking PIK3CA mutations, PTEN loss, and PI3K pathway activation did not benefit from everolimus.[85] A phase I study of buparlisib with trastuzumab in trastuzumab resistant advanced HER2+ breast cancer showed good tolerance and an ORR of 17% in 17 patients. Several early phase trials are in progress combining alpelisib (NCT02038010), taselisib (NCT02390427), or pictilisib (NCT00960960) with various combinations of trastuzumab, pertuzumab, and T-DM1.

Novel Antibody and Antibody Conjugates

Germline polymorphisms in CD16A, which encodes the activating Fc receptor FcγRIIIA, have been shown to affect clinical outcomes with trastuzumab.[86] Margetuximab is a novel antibody that targets the same epitope as trastuzumab but has a modified Fc portion designed for enhanced affinity for FcγRIIIA receptor and reduced engagement with the inhibitory FcγR receptor.[87] In a first-in-human phase I study of margetuximab monotherapy in HER2+ solid tumors, 19 evaluable patients with breast cancer who had received at least one prior anti-HER2 therapy showed an objective response rate of 26%.[88] PFS for this group was 5.5 months. Toxicity was favorable, with the most common grade 3 and 4 adverse events being lymphopenia (17%), elevated lipase (8%), and anemia (3%). The currently recruiting phase III SOPHIA trial is comparing margetuximab plus physician's choice chemotherapy to trastuzumab plus chemotherapy after previous treatment with pertuzumab, trastuzumab and T-DM1 (NCT02492711).[89]

Patritumab (U3-1287) is a fully human anti-HER3 monoclonal antibody. In a phase IB study of patritumab, trastuzumab,

and paclitaxel in patients with metastatic HER2+ breast cancer previously treated with trastuzumab, the objective response rate was 38.9% (18 patients), with median PFS of 274 days.[90] No dose-limiting toxicity was reached. The I-SPY-2 phase II neoadjuvant trial added a patritumab and trastuzumab arm in October 2016 (NCT01042379).

Following the efficacy and favorable toxicity of T-DM1, a number of ADCs entered early-phase trials. These next-generation ADCs incorporate novel linker chemistry and aim to have larger amounts of payload drug attached to each antibody. DS-8201a consists of trastuzumab conjugated with a novel topoisomerase I inhibitor. It has shown efficacy in a T-DM1 resistant PDX, as well as PDXs with low HER2 expression, and is capable of substantial bystander cytotoxicity.[91,92] In a phase I trial, no dose-limiting toxicities were seen, and the ORR in 12 patients with breast cancer previously treated with T-DM1 was 42%.[93]

The XMT-1522 ADC targets an HER2 epitope distinct from the trastuzumab epitope and is conjugated with the cytotoxic agent auristatin.[94] It has the possible benefit of avoiding interference with trastuzumab and pertuzumab activity. In preclinical studies, it displayed similar levels of HER2 inhibition as trastuzumab and was effective in T-DM1-resistant and low-HER2-expressing models. It also showed synergistic activity when combined with trastuzumab and pertuzumab.[94] A phase IB study is being conducted in both HER2 1–3+ and HER2-amplified advanced breast cancers, as well as other HER2-expressing tumor types (NCT02952729).

MM-302 is an ADC of liposomal doxorubicin and a HER2 targeted antibody. Despite an efficacy signal in a phase I trial, the phase II HERMIONE trial of MM-302 plus trastuzumab versus physician's choice chemotherapy plus trastuzumab was terminated early in December 2016 because of futility (NCT02213744).

Immunotherapy

Multiple lines of evidence support the importance of the immune microenvironment in HER2+ breast cancer and trastuzumab therapy.[95-97] The phase IB/II PANACEA trial is evaluating the combination of the anti–PD-1 antibody pembrolizumab with trastuzumab in patients with metastatic HER2+ breast cancer that has progressed after at least one line of therapy (NCT02129556). The trial is including patients with both PD-L1–negative and PD-L1–positive tumors by immunohistochemistry. The randomized phase II KATE2 study is comparing T-DM1 plus the anti–PD-L1 antibody atezolizumab to T-DM1 plus placebo in patients with prior trastuzumab and taxane treatment (NCT02924883).

A novel approach to skin metastases involves the application of the topical Toll-like receptor 7 agonist imiquimod directly to skin lesions. A single-arm phase II study of imiquimod and nab-paclitaxel in patients with treatment refractory breast cancer chest wall metastases showed an ORR of 72% in 14 patients, some of whom were HER2+.[98]

T-cell cellular therapies are a promising therapeutic intervention for refractory malignancies. In a phase I study, priming peripheral blood T-cells ex vivo with a HER2 vaccine before expansion in culture and reinfusion produced a response in 43% of patients (seven with HER2+ breast cancer, one with ovarian cancer).[99] Chimeric antigen receptor (CAR) T cells have had dramatic success in hematologic malignancies, where they target cell surface receptors such as CD19. This strategy is attractive for HER2+ advanced breast cancer, as HER2 overexpression represents an accessible target for the CAR. Early use of HER2-targeted CAR T cells was associated with substantial toxicity,[100] but more recently, improved CAR technology and optimized infusion protocols have been well tolerated and efficacious, as was seen in a phase I/II study of HER2 CAR T cells in HER2-expressing sarcomas.[101] CAR T-cell therapy could be an option in advanced refractory HER2+ breast cancers.

Vaccination with HER2-derived peptides has repeatedly shown that antigen-specific T-cell immunity can be induced. However, a strong efficacy signal has been lacking, and the benefit of vaccination against HER2 may be low in HER2 amplified tumors. The E75 HER2-derived peptide together with a GM-CSF as an adjuvant was tested in a phase I/II trial of 195 patients with early-stage breast cancer with a range of HER2+ expression. The nature of the vaccine requires that patients possess the HLA-A2 or A3 allele. In the optimally dosed group, 5-year disease-free survival was 94.6% compared with 80.2% in the control group ($p = .05$, log-rank test). With the E75 vaccine, the benefit of vaccination seems highest in tumors that are HER2 1+ or 2+.[102] A similar result was seen with the AE37 vaccine, consisting of a hybrid HER2 peptide designed to enable direct loading onto HLA class 2 molecules.[103] The E75 vaccine is being tested in the phase III PRESENT study, restricted to patients with HER2 1+ or 2+ expression. In the advanced disease setting, robust immune responses were noted with the combination of an anti-HER2 vaccine and trastuzumab.[104] The combination of T-cell checkpoint inhibitors and vaccines may also be a viable strategy in the advanced disease setting.[105]

CONCLUSION AND FUTURE DIRECTIONS

In the past year, ER+ disease has seen the debut of the highly active and well-tolerated CDK4/6 inhibitors. CDK4/6 inhibitors are now being evaluated in the adjuvant setting. In TNBC, immunotherapy holds much promise, particularly in combination with other therapies, and the subgroups that define patients most likely to benefit from specific therapies such as PARP inhibition or AR inhibition are becoming increasingly well defined. For HER2+ disease, next-generation HER2 TKIs with improved toxicity and better CNS activity will be a key development if preliminary data are confirmed, and the first results of the immunotherapy studies in combination with HER2-targeted agents are expected soon for advanced disease. As a platform, ADCs are expected to continue to bear fruit in HER2+ disease, and further evidence of efficacy in TNBC is eagerly awaited. The lengthening list of efficacious novel therapies is cause for cautious optimism about the future of breast cancer treatment, and results of ongoing clinical trials are eagerly awaited.

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Optimal Management of Early and Advanced HER2 Breast Cancer

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OVERVIEW

Approximately 15%–20% of breast cancer is HER2 positive, and patients with this subtype of disease historically had worse outcomes than patients with HER2-negative disease. However, the introduction of HER2-directed therapies has dramatically altered outcomes for these patients, especially for persons with early disease. However, despite these achievements, metastatic disease is still not curable. This review summarizes the current treatment approach for patients in the preoperative and adjuvant setting, including data regarding selecting the optimal chemotherapy partner as well as determining the duration and type of anti-HER–directed therapy. This article also reviews how to approach patients with advanced HER2-positive disease and discusses promising new therapies that are in development.

The initial studies of HER2-positive breast cancer focused on advanced disease, in which a novel monoclonal antibody directed against HER2 (which soon came to be known as trastuzumab) was shown to have single-agent activity in tumors that overexpressed HER2.[1,2] After the initial discovery of activity, the pivotal study by Slamon et al[3] showed benefit in terms of progression-free survival (PFS) and overall survival (OS) for both the combination of doxorubicin and cyclophosphamide with the antibody as well as the couplet of paclitaxel and trastuzumab. Although the anthracycline combination was more active, the cardiotoxicity that was reported led to the approval in 1998 of trastuzumab and paclitaxel as standard therapy for HER2-positive advanced breast cancer.[4]

WHERE ARE WE WITH THE TREATMENT OF ADVANCED HER2-POSITIVE BREAST CANCER?

The years after the 1998 approval of trastuzumab were dominated by studies examining the combination of trastuzumab with almost every known cytotoxic, exploring the prolonged administration of the antibody past progression and examining different dosing schedules (including the three-weekly scheduling that has become widely used).[5-7] In addition, many studies examined the optimal way to define HER2 in the laboratory, with the recognition that the best results were seen in those tumors that overexpressed HER2.[8] Although many individuals with true HER2-positive advanced disease respond to treatment, the majority of patients develop a resistance and disease progression, which has led to the pursuit of additional anti-HER2 agents or combinations to improve outcomes. Studies have tried to exploit other pathways in addition to HER2 to improve outcomes and to develop novel agents. This section briefly summarizes the work since trastuzumab became the standard of care, concentrating on those strategies that have influenced guidelines.

Targeting HER2 With Other Agents

Tyrosine kinase inhibitors. There were theoretical reasons to look at small molecules to target HER2, with the idea that they may have both mechanistic and practical advantages over a large antibody. Many of the small-molecule tyrosine kinase inhibitors (TKIs) had less specificity than trastuzumab, which was potentially of value in a tumor with heterogeneity. In addition, small molecules could potentially cross the blood-brain barrier, be given on a continuous schedule, be orally available, and possibly have less cardiac toxicity than the approved drug, trastuzumab. The first widely tested agent was lapatinib, which reversibly binds to and inhibits the intracellular domain of HER1 and HER2 and was shown to have both single-agent activity and be able to be combined with cytotoxics, including capecitabine and paclitaxel. The combination of capecitabine and lapatinib was compared with capecitabine alone, showing an improved time to progression with a hazard ratio (HR) of 0.49 (95% CI, 0.34–0.71; $p < .001$) but no OS benefit; this led to its approval in the second-line setting.[9,10] In addition, combined anti-HER2 therapy with trastuzumab and lapatinib showed activity in multiple pretreated patients with advanced breast cancer compared with lapatinib alone, with improved PFS

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(from 8 weeks to 11 weeks with the combination; HR, 0.74; 95% CI, 0.58–0.94; p = .011) and OS (from 10 months to 14 months; HR, 0.74; 95% CI, 0.57–0.97; p = .026).[11] In a head-to-head comparison in the first-line setting in combination with taxanes (MA31), lapatinib was shown to be inferior to trastuzumab. This trial demonstrated that trastuzumab in combination with a taxane had significantly longer intention-to-treat PFS of 11.3 months compared with lapatinib combined with a taxane of 9.0 months (HR, 1.37; 95% CI, 1.13–1.65; p < .001) and more toxicity, in terms of diarrhea and rash, was observed with lapatinib compared with trastuzumab combined with taxane (p < .001).[12] Although initial data suggested a benefit in brain metastases, this has not been clearly shown with specific studies such as CEREBEL or compared with other agents as in the EMILIA trial.[13-15] The toxicity of the drug with diarrhea (up to 60% any grade) and rash (up to 27% any grade), as well as the efficacy of newer agents such as trastuzumab emtansine (T-DM1), led to the changing role of lapatinib from the second-line setting to later lines.

Other small TKIs may have additional activity. Initial studies of neratinib, an irreversible pan-HER TKI of HER1, HER2, and HER4, suggest that it may be more active than lapatinib with single-agent activity. Burstein et al[16] reported a median PFS of 22.3 and 39.6 weeks, respectively, among patients previously treated with trastuzumab (66 patients) and those that were treatment naive (70 patients), with objective response rates of 24% for patients who received prior trastuzumab treatment and 56% for the trastuzumab-naive cohort.

Diarrhea, which is the major toxicity with neratinib administration, must be controlled early to derive the benefit from this drug and maintain dosing. The NEfERT trial was an open-label randomized study in first-line metastatic disease comparing neratinib and paclitaxel to trastuzumab plus paclitaxel. Median PFS was 12.9 months with neratinib/paclitaxel and 12.9 months with trastuzumab/paclitaxel (HR, 1.02; 95% CI, 0.81–1.27; p = .89).[17] With neratinib/paclitaxel, the incidence of central nervous system recurrences was lower (relative risk, 0.48; 95% CI, 0.29–0.79; p = .002) and time to central nervous system metastases was delayed (HR, 0.45; 95% CI, 0.26–0.78; p = .004). Common grade 3/4 adverse events were diarrhea (30.4% with neratinib/paclitaxel, 3.8% with trastuzumab/paclitaxel), neutropenia (12.9% vs. 14.5%), and leukopenia (7.9% vs. 10.7%); no grade 4 diarrhea was observed. The NALA phase III study is comparing neratinib in combination with capecitabine to capecitabine plus lapatinib for patients with HER2-positive metastatic breast cancer who have received two or more prior HER2-directed regimens (NCT01808573).

ONT-380 is a reversible TKI with selective HER2 inhibition with antitumor activity, and it is suggested to improve activity in brain metastases.[18,19] This agent is being combined with trastuzumab T-DM1 as well as capecitabine or both; further data are pending to further delineate this agent's potential benefit.

Antibodies. Although the initial development was rather slow, pertuzumab has now established its role in the first-line advanced setting. Activity was seen in phase II studies after preclinical studies showed the impact of blocking HER2 and HER3, which led to the CLEOPATRA study. CLEOPATRA randomly assigned patients with newly diagnosed advanced HER2-positive breast cancer to docetaxel and trastuzumab with or without the addition of intravenous pertuzumab.[20-22] This international phase III study showed a very powerful PFS of 18.5 months compared with 12.4 months in the trastuzumab arm and an OS benefit of 56.5 months in the trastuzumab/pertuzumab arm compared with 40.8 months in the trastuzumab cohort. Although the majority of patients in this study had de novo metastatic disease, the small number with prior exposure to trastuzumab in the adjuvant setting also responded. Studies have also shown benefit for pertuzumab with paclitaxel and vinorelbine, providing additional options for combination treatment and leading to its widespread use. This drug is well tolerated, causing only minimal increases in diarrhea for many patients and no notable additional cardiotoxicity. To date, there are no data to suggest a continued benefit of pertuzumab past progression.

T-DM1 is an antibody-drug conjugate linking trastuzumab with the powerful agent emtansine, a derivative of maytansine, an older microtubule cytotoxic initially evaluated in the 1970s.[23,24] A large phase III study, EMILIA, was launched in the second-line metastatic setting comparing single-agent T-DM1 to capecitabine and lapatinib for patients with prior trastuzumab and taxane exposure.[15] This study showed a statistically and clinically relevant benefit in PFS, response, duration of response, and OS for T-DM1, with a median 3.2-month PFS benefit (HR, 0.65; 95% CI, 0.55–0.77; p < .001) and a median 5.8-month OS benefit (HR, 0.68; 95% CI, 0.55–0.85; p < .001) compared with capecitabine plus lapatinib. The drug is very well tolerated, with the major side effects being thrombocytopenia (seen for 12.9% of patients) and occasional increases in liver enzymes (occurring for 2.9% and 4.3% of patients, for aspartate aminotransferase

KEY POINTS

- **The advent of anti-HER2 therapies have transformed the prognosis of HER2-overexpressing breast cancer.**
- **Dual targeting of HER2 with the antibodies pertuzumab and trastuzumab has been a successful strategy in both early and metastatic breast cancer.**
- **In the the metastatic setting, TDM-1, a novel antibody-drug conjugate, has become standard second-line therapy.**
- **In low-risk, early-stage breast cancer, modified protocols with limited chemotherapy are effective, although 12 months of anti-HER2 treatment remains the standard.**
- **Current neoadjuvant therapy results in higher pCR rates but also highlights the differences between estrogen receptor–positive, HER2-positive breast cancers and those that are HER2-positive but estrogen receptor negative.**

and alanine aminotransferase, respectively). An analysis of the EMILIA study showed that dose decreases may be associated with decreased efficacy, suggesting a rather narrow therapeutic window.[25] Of interest is that despite being a large antibody complex, there is activity against brain metastases seen in the EMILIA study and a number of other reports.

The TH3RESA study reported efficacy of T-DM1 for a heavily pretreated population, confirming the role of T-DM1 in advanced HER2-positive cancers. This randomized phase III study compared T-DM1 to physician's choice therapy and demonstrated an improved PFS of 6.2 months for T-DM1 compared with 3.3 months for physician's choice therapy ($p < .001$).[26]

In the first-line setting, a phase II study comparing T-DM1 to trastuzumab and docetaxel showed improvements in PFS of 14.2 months for T-DM1 compared with 9.2 months for trastuzumab, with an HR of 0.59 (95% CI, 0.36–0.97; $p = .035$).[27] MARIANNE was a three-arm randomized phase III study comparing trastuzumab plus a taxane (either paclitaxel or docetaxel) to single-agent T-DM1 or to the doublet T-DM1 and pertuzumab; it was hoped that this would to lead to the first-line approval for this well-tolerated drug.[28] Although expectations favored the experimental arms, there was disappointment for many when the addition of pertuzumab to T-DM1 did not improve the PFS of the monotherapy T-DM1. In addition, there was a noninferior PFS outcome for the two T-DM1 arms compared with the trastuzumab plus taxane arm. Fewer notable adverse events and better quality-of-life outcomes were seen for the two experimental T-DM1–containing arms. There was not a trastuzumab/pertuzumab arm similar to the CLEOPATRA cohort in the MARIANNE study. This trastuzumab/pertuzumab triplet remains the standard first-line treatment, except for selected patients who may not tolerate a taxane.

MM-302 is a new experimental agent comprising a HER2-targeted nanoparticle containing doxorubicin, a cytotoxic with well-known anti-HER activity.[28] MM-302 has been studied alone, in combination with trastuzumab, and in combination with cyclophosphamide and has demonstrated safety and preliminary efficacy. A phase II trial (HERMIONE) in anthracycline-naive advanced disease with prior progression on pertuzumab and T-DM1 that randomly assigned patients to receive MM-302 plus trastuzumab compared with physician's choice chemotherapy plus trastuzumab was recently closed early because an unfavorable futility analysis (NCT02213744).[29]

Other new agents. Ertumaxomab, a bispecific antibody targeting HER2 and cluster of differentiation-3 with selective binding to activatory Fcγ-type I/III receptors, has been shown to elicit an immune response and antitumor activity and is now in an open-label dose-escalating study of patients with HER2-expressing advanced solid tumors (NCT01569412).[30,31]

In addition, there are a number of studies of trastuzumab biosimilars being reported. These agents may have the role of providing choice for patients if these drugs are truly more advantageous economically.

Targeting of two pathways. Laboratory studies suggested that angiogenic pathways were active in HER2-positive cancers, leading to the idea of targeting both VEGF and HER2.[32] Many studies were initiated; in the advanced setting, the phase III trial of bevacizumab and trastuzumab in addition to docetaxel (AVEREL) did not show a statistically notable benefit for dual targeting of 424 patients who were randomly assigned to treatment, leading to a general abandonment of this combination strategy.[33] Other early strategies included combining heat shock protein agents with trastuzumab.[34] Although responses were seen, these have not led to large phase III studies or changes in guidelines.

With approximately half of HER2-overexpressing cancers also being estrogen receptor (ER)–positive, endocrine and anti-HER2 agents are an obvious combination in the advanced setting. An initial phase II study was done with trastuzumab and letrozole, with a 3.3-month PFS for the endocrine therapy alone and a 14.1-month PFS for the anti-HER2 therapy and endocrine therapy.[35] The phase III randomized TANDEM study of anastrozole and trastuzumab showed improvements in PFS with the addition of anti-HER2 therapy (from 2.4 months for anastrozole vs. 4.8 months for the combined anastrozole and trastuzumab).[36] The combination of lapatinib plus letrozole was studied in another large phase III trial. In the confirmed HER2-positive population, the median PFS rose from 3 months for the letrozole arm compared with 8.2 months for the lapatinib and letrozole arm, which led to the regulatory approval of this combination.[37] However, the results of both of these studies were inferior to those of trastuzumab with chemotherapy for this patient population, leading to a limited uptake of this strategy as upfront treatment of most patients with ER-positive, HER2-positive advanced breast cancer. This is an option for patients with low-burden disease or comorbidities. More recently, the phase II PERTAIN trial (NCT01491737) enrolled 258 postmenopausal women with HER2-positive, hormone receptor–positive, metastatic, or locally advanced breast cancer to receive first-line pertuzumab plus trastuzumab and an aromatase inhibitor (anastrozole or letrozole), or trastuzumab plus an aromatase inhibitor. Preliminary results showed that adding pertuzumab to trastuzumab and an aromatase inhibitor significantly reduced the risk of progression or death by 35% versus treatment with trastuzumab and an aromatase inhibitor alone (HR, 0.65; 95% CI, 0.48–0.89; $p = .0070$). The median duration of response was 27.1 months and 15.1 months in the pertuzumab arm and the trastuzumab-only arm, respectively (HR, 0.57; 95% CI, 0.36–0.91; $p = .02$).

Knowing that the phosphoinositide 3 kinase/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway has been implicated in resistance and that activating mutations in PI3KCA or PTEN (phosphatase and tensin homolog) are seen in a large number of HER2-positive metastatic tumors, initial phase II studies combined everolimus with trastuzumab and either vinorelbine or paclitaxel to target mTOR concurrently with HER2.[38,39] There are now reports from two phase III studies that randomly assigned

patients with advanced HER2-positive breast cancer to receive either paclitaxel plus trastuzumab (BOLERO I) or vinorelbine plus trastuzumab (BOLERO III), each with an experimental arm adding oral everolimus. In BOLERO I, which was in the first-line setting, there was no improvement in PFS, although an analysis of the HER2-positive/ER-negative cohort suggested an improved PFS from 13.1 months to 20.3 months.[40] In BOLERO III, which was done in the later setting for patients who had progressed with prior trastuzumab, there was a statistically significant improvement in PFS from 5.78 months to 7.0 months (HR, 0.78; 95% CI, 0.65–0.95; p = .0067).[41] There was considerable toxicity seen with the addition of everolimus and no improvement in OS was reported at this time. This lack of clinically relevant benefit coupled with toxicity has not led to changes in standard clinical practice although some individual patients may benefit. Correlative work suggested that patients with low PTEN concentrations may preferentially respond, but this needs further evaluation prior to being considered a predictive marker. Newer and more specific phosphoinositide 3 kinase inhibitors are in clinical trials in the advanced HER2-positive setting, including alpelisib, taselisib, and pictilisib. A phase II study of alpelisib, an alpha-specific inhibitor, has shown tolerability and responses among patients who had previously progressed during or following treatment with T-DM1.[42]

More recently, a number of studies have been initiated with checkpoint inhibitors and either trastuzumab or T-DM1 in advanced HER2-positive breast cancer. Preclinical laboratory work, as well as the demonstration of tumor-infiltrating lymphocytes (TILs) in HER2-positive breast cancer, has led to excitement in this area and a number of studies. These include the phase Ib/II PANACEA trial, which is combining the anti–PD-1 inhibitor pembrolizumab (MK-3475) with trastuzumab (NCT02129556). The Canadian Clinical Trials Group is combining durvalumab with trastuzumab in multiply pretreated patients with HER2-positive metastatic breast cancer to assess toxicity and biologic activity (NCT0264968). In addition, defining which cancers may respond to these costly therapies will be important. Vaccines are also being studied and initial reports have shown immune responses.

Finally, an area of new interest is the combination of CDK4/6 inhibitors and anti-HER2 agents, with the preclinical evidence of activity in this subtype suggesting in transgenic mouse models that resistance may be overcome by this strategy and the tumors become resensitized to EGFR/HER2 blockade.[43] Currently, studies of palbociclib and T-DM1 (NCT01976169) and abemaciclib plus trastuzumab are being done after preliminary activity has been reported (NCT02675231). The PATRICIA trial is comparing palbociclib plus trastuzumab with or without letrozole for patients with triple-positive advanced cancers who have had prior trastuzumab treatment (NCT0244840).

Ongoing Issues

Although there has been major progress in the treatment of HER2-positive advanced breast cancer, there are a number of ongoing issues that have not been resolved. First, as new agents are introduced into the neoadjuvant and adjuvant settings, including potentially pertuzumab, the selection of drugs and the optimal sequence in the advanced setting for previously treated patients may need to be revised. There are currently no data on how long to continue treatment for patients who appear to have a complete response, leading to a rather ad hoc approach to these rare cases. Most patients continue with anti-HER2 therapy indefinitely, because there is concern about tumor recurrence. We continue to struggle with tumor resistance, because this is the major cause of treatment failure. How much does tumor heterogeneity impact resistance and will this limit some of our more specific and HER2-directed treatments? What are the mechanisms of resistance? Although there have been clues, we are still a long way from defining them among most individual patients. Serial sampling and cell-free DNA studies may help our understanding. A notable number of patients still develop central nervous system disease, which continues to be difficult to treat despite studies of new agents and intrathecal drugs, including intrathecal trastuzumab. The development of new drugs is not easy with the small numbers of patients with advanced HER2-positive disease eligible for studies in some centers, generally requiring multicenter trials, which adds to the complexity and expense. This is a statement of our success but does extend the time to develop potentially active agents, particularly in later lines of therapy. Finally, will patients be able to afford new agents in the future or possibly continued treatment in the present?

OPTIMIZING NEOADJUVANT/ADJUVANT TREATMENT OPTIONS FOR THE PATIENT WITH HER2-AMPLIFIED BREAST CANCER

It has now been 12 years since trastuzumab was first reported to significantly improve disease-free survival (DFS) for HER2-positive breast cancer in the curative setting.[44] The positive impact of trastuzumab cannot be overstated, because its use has been shown to alter the natural course of this disease, transforming it from an aggressive subtype with poor outcomes to one that may be expected to have a prognosis as favorable as HER2-normal disease (Table 1).[45-48]

In the past decade, findings from multiple studies have become available to inform the optimal treatment of this form of breast cancer. These trials have addressed fundamental issues, including optimal duration of trastuzumab, timing with chemotherapy, chemotherapy backbone, and relative risks and benefits of adding other novel biologic therapies, including the use of dual HER2 targeting. Importantly, ongoing studies are now addressing the use of less toxic regimens with novel therapeutics and are evaluating prognostic or predictive biomarkers for long-term outcome. These data will no doubt be invaluable in maximizing the therapeutic index for patients diagnosed with early-stage HER2-driven disease. This section reviews how results from large adjuvant studies have significantly influenced management of this disease and describes major findings from neoadjuvant clinical trials that have provided essential clinical and molecular information in an efficient and cost-effective manner.

Four Trials, One Enormous Breakthrough

In February 2000, the first phase III clinical trial to evaluate the use of adjuvant trastuzumab (NSABP B-31) was launched; within less than 2 years, three additional large randomized adjuvant trials dedicated to evaluating trastuzumab in HER2-overexpressing or amplified breast cancer were activated, including the NCCTG N9831, BCIRG-006, and BIG 01-01 HERceptin Adjuvant (HERA) studies[44,51,52] (Table 2). Updated results for each of these trials, with 8 years[53] to 10 years[50,54] of median follow-up, demonstrated persistent substantial DFS and OS benefits associated with the addition of trastuzumab to standard chemotherapy. The designs of each of these clinical trials, as well as the design and results of subsequent studies, have provided important data to guide optimal treatment of early-stage disease. These will each be considered below.

Optimal Timing of Trastuzumab With Chemotherapy

Although several studies used concurrent chemotherapy and trastuzumab,[44,51,56] two were designed to give the trastuzumab after chemotherapy.[52,57] In HERA, 5,102 patients who had completed adjuvant chemotherapy were randomly assigned to either observation or 1- or 2-year treatment with trastuzumab.[52] With 10 years of follow-up, DFS (HR, 0.77; 95% CI, 0.68–0.86; p < .0001) and OS (HR, 0.74; 95% CI, 0.64–0.86; p < .0001) remained statistically significantly better with a year of trastuzumab compared with observation.[54] In a similarly designed study (FNCLCC-PACS-04),[57] 528 patients with HER2-positive breast cancer were randomly assigned after chemotherapy to receive trastuzumab for a year or to undergo observation, but they did not demonstrate a notable improvement in DFS with trastuzumab; the small size of the study, coupled with the fact that only 84% of the patients received at least 6 months of trastuzumab, may explain these discordant results.

To date, the N9831 trial is the only study that has prospectively compared the sequential or concurrent approaches.[58] With a median follow-up of 6 years, patients treated with concurrent paclitaxel chemotherapy and trastuzumab had a 5-year DFS of 84.4% compared with 80.1% for patients treated with paclitaxel followed by trastuzumab (HR, 0.77; 99.9% CI, 0.53–1.11; p = .0216). Although this did not cross the prespecified boundary for significance (p = .00116), this trend toward an increase in DFS with the concurrent administration led the authors to conclude that trastuzumab should be given concurrently with taxane chemotherapy.

Optimal Length of HER2-Targeted Therapy

Although the original decision to give trastuzumab for 1 year was relatively arbitrary, we now have the benefit of data from several studies that have addressed the ideal length of trastuzumab treatment. In addition, several other studies addressing the optimal length of trastuzumab treatment have enrolled patients but results are yet to be reported. The HERA trial was the first to address length of therapy by including not only an observation and 1-year trastuzumab arm but also a 2-year trastuzumab arm.[52] At a median 8 years of follow-up, there was no difference in DFS for patients treated for 1 or 2 years (HR, 0.99; 95% CI, 0.85–1.14; p = .86).[55] Importantly, the rates of grade 3/4 adverse events were higher for patients in the 2-year group (20.4%) compared with the 1-year group (16.3%). This included a higher rate of cardiac toxicity (4.1% and 7.2% for the 1-year and 2-year groups, respectively).

To date, two trials that evaluated whether a shorter course of trastuzumab yields similar outcomes to 1 year have been reported. FinHer was a 1,010-patient trial, in which patients were randomly assigned to receive three cycles of docetaxel or vinorelbine followed three cycles of 5′ fluorouracil/epirubicin/cyclophosphamide.[56] The 232 women with HER2-positive breast cancer were randomly assigned to receive a 9-week course of trastuzumab concurrently with the vinorelbine or docetaxel. Three-year recurrence-free survival was significantly improved for trastuzumab-treated patients (HR, 0.42; 95% CI, 0.21–0.83; p = .01) with a trend toward improved OS (HR, 0.41; 95% CI, 0.16–1.08; p = .07).[56] With longer follow-up, however,[48] the distant DFS benefit was no longer statistically significant but still tended to be in favor

TABLE 1. Overall Survival for HER2-Positive, Trastuzumab-Treated Early Disease Similar to or Better Than HER2-Normal Disease

Study	Reference	Median Follow-Up (Years)	No. of Patients With HER2-Positive Disease (%)		No. of Patients With HER2-Negative Disease (%)
			Yes Trastuzumab	No Trastuzumab	
BCIRG-005 and BCIRG-006	Mackey et al[49] and Slamon et al[50]	10	1,841/2,149 (86)*	870/1,073 (81)	2,647/3,298 (80)*
NOAH	Gianni et al[46]	5	87/117 (74)	74/118 (63)	75/99 (76)
Italian Registry	Musolino et al[45]	4.1	52/53 (98)*	140/161 (87)	1,108/1,186 (93)*
GeparQuattro	von Minckwitz et al[47]	5.4	392/446 (88)*		889/1,049 (85)*
FinHer[6]	Joensuu et al[48]	5	12/115 (90)	21/116 (82)	61/778 (92)

*Data from these studies indicate that, in general, HER2-positive trastuzumab-treated disease has a similar or better outcome than HER2-negative disease.

Studies that included patients with both HER2-positive (trastuzumab treated and trastuzumab nontreated) and HER2-negative disease are included (NOAH, Italian Registry, GeparQuattro, FinHer). In addition, BCIRG-005 (HER2 negative) and BCIRG-006 (HER2 positive) are included, because these studies were conducted at many of the same sites during similar time periods. Patients with HER2-positive disease were referred to BCIRG-006 and those with HER2-negative disease were referred to BCIRG-005.

TABLE 2. Four Large Initial Adjuvant Trastuzumab Trials

Trial	Reference	Arms	No. of Patients	DFS	OS	Hazard Ratio*		Median Follow-Up (Years)	Crossover (%)
						OS	DFS		
NCCTG N9831 and NSABP B-31	Perez et al[53]	NCCTG N9831**: AC → wP (group A), AC → wP → wH (group B),† and AC → wPwH (group C)	3,351	10-year DFS for groups C/2 vs. A/1: 73%, AC/PH; and 62%, AC/P	10-year OS for groups C/2 vs. A/1: 84%, AC/PH; and 75%, AC/P	0.63	0.60	8	20
		NSABP B-31‡: AC → P (group 1) and AC → PwH (group 2)							
HERA	Goldhirsch et al[55]	Standard chemotherapy and then observation vs. H for 1 years vs. H for 2 years	5,090	72%, H for 1 year; 66%, observation	84%, H for 1 year; 79%, observation	0.76	0.76	8	52
BCIRG-006	Slamon et al[50]	AC → T, AC → TH, and TCH	3,222	10-year: 75%, AC/TH; 73%, TCH; and 68%, AC/T	10-year: 86%, AC/TH; 83%, TCH; and 79%, AC/T	0.63, AC/TH; 0.76, TCH	0.72, AC/TH; and 0.77, TCH	10.3	3.1

*Statistically significant.

**NCCTG N9831: AC → P, doxorubicin/cyclophosphamide for four cycles followed by weekly paclitaxel 12×; AC→ wP → wH, doxorubicin/cyclophosphamide for four cycles followed by weekly paclitaxel 12× followed by weekly trastuzumab for 1 year; AC → wPwH, doxorubicin/cyclophosphamide for four cycles followed by weekly paclitaxel plus weekly trastuzumab 12× followed by weekly trastuzumab to complete a year.

†Not included in the joint analysis.

‡NSABP B-31: AC → P, doxorubicin/cyclophosphamide for four cycles followed by paclitaxel (weekly 12× or every 3 weeks 4×); AC → PwH, doxorubicin/cyclophosphamide for four cycles followed by paclitaxel (weekly 12× or every 3 weeks 4×) plus weekly trastuzumab followed by weekly trastuzumab to complete a year.

HERA: trastuzumab every 3 weeks for 1 year or 2 years.

BCIRG-006: AC/TH, doxorubicin/cyclophosphamide for four cycles followed by docetaxel/trastuzumab for four cycles, followed by maintenance with trastuzumab every 3 weeks to complete a year; AC/T, doxorubicin/cyclophosphamide for four cycles followed by docetaxel for four cycles; TCH, docetaxel/carboplatin/trastuzumab for six cycles followed by maintenance with trastuzumab every 3 weeks to complete a year.

Abbreviations: AC, doxorubicin; DFS, disease-free survival; H, trastuzumab; OS, overall survival; P, pertuzumab; PH, pertuzumab and trastuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab; wH, weekly trastuzumab; wP, weekly paclitaxel; wPwH, weekly paclitaxel plus weekly trastuzumab.

of trastuzumab-based therapy (HR, 0.65; 95% CI, 0.38–1.12; p = .12). Thus, although the safety and financial aspects of 9 weeks of trastuzumab treatment are attractive, the long-term benefits are not certain.

The second study reported to date to evaluate a shorter duration of trastuzumab is PHARE, a phase III noninferiority study aimed to evaluate 6 versus 12 months of trastuzumab for patients who had completed chemotherapy, surgery, and up to 6 months of trastuzumab treatment.[59] The prespecified noninferiority HR margin was set at 1.15. With a median follow-up of 42.5 months, the HR was 1.28 (95% CI, 1.05–1.56; p = .29); thus, noninferiority of 6 months of trastuzumab compared with 12 months was not demonstrated. An ongoing phase III study with a noninferiority DFS endpoint (PERSEPHONE) is also addressing 6 versus 12 months of trastuzumab. This study completed accrual of more than 4,000 patients in 2015. Cardiac safety data from the first 2,500 patients enrolled were reported in 2016, demonstrating a substantial reduction in cardiac events associated with 6 months of therapy compared with 12 months.[60]

Several studies addressing the optimal length of trastuzumab therapy are ongoing (Table 3). On the basis of currently available data, the standard of care remains 1 year of trastuzumab treatment. It should be noted that one phase III randomized study, EXTENET (described below), is evaluating a year of HER2-targeted therapy with neratinib for patients who already completed a full year of trastuzumab for early-stage disease.[61] Thus, in addition to evaluating a novel HER2-targeted therapy in the adjuvant setting, this study is addressing whether 2 years of HER2-targeted therapy improves outcomes compared with 1 year. A prespecified early analysis at the 2-year mark demonstrated that invasive DFS was significantly improved for patients who received neratinib, especially those with hormone receptor–coexpressing cancer. These intriguing data are in contrast with the 8-year HERA results, in which 2 years of trastuzumab did not provide additional benefit compared with 1 year, regardless of hormone receptor expression.[55] One theory to explain this differential outcome is that in contrast with trastuzumab, neratinib may more effectively interfere with receptor crosstalk between human EGFRs and ERs, leading to particular benefit in hormone receptor–positive tumors. Pending longer follow-up of this trial as well as data to guide management of the gastrointestinal toxicity associated with neratinib, 1 year of trastuzumab in the adjuvant setting remains the standard of care.

Optimizing the Cardiac Risk

Although the DFS and OS benefits of trastuzumab clearly support its use in the curative setting, the risk of cardiac

TABLE 3. Ongoing Studies Evaluating Duration of Trastuzumab

Study	No. of Patients (Enrollment Status)	ClinicalTrials.gov Identifier	Treatment Arms	Endpoint
PERSEPHONE	4,089 (closed)	NCT00712140	Chemotherapy concurrent or sequential with trastuzumab 12 vs. 6 months	DFS
SHORT-HER	2,500 (closed)	NCT00629278	AC or EC 4× → TH (H for 1 year) vs. TH 3× → FEC 3×	DFS
SOLD	2,168 closed)	NCT00593697	TH 3× → FEC 3× vs. TH 3× → FEC 3× → H for 1 year	DFS
BOLD-1	1,366 (open)	NCT02625441	THP 3× TH 3× → H for 1 year	iDFS
Hellenic Oncology Research Group	489 (closed)	NCT00615602	FEC 4× → TH 4× → H for 6 months FEC 4× → TH 4× → H for 12 months	DFS

Abbreviations: AC, doxorubicin/cyclophosphamide; DFS, disease-free survival; EC, epirubicin and cyclophosphamide; FEC, fluorouracil/epirubicin/cyclophosphamide; H, trastuzumab; iDFS, invasive disease–free survival; TH, trastuzumab; THP, trastuzumab/pertuzumab.

toxicity should be carefully considered, especially in the early-stage setting, in which a relatively substantial proportion of patients may be cured with local measures alone. A meta-analysis that included eight randomized controlled trials of trastuzumab (11,991 patients) reported a 5.11 times higher risk of congestive heart failure (2.5% vs. 0.4%) and a 1.83 times higher risk of left ventricular ejection fraction (LVEF) decline (11.2% vs. 5.6%) for trastuzumab-treated patients compared with control-treated patients.[62] Although these rates of cardiac dysfunction are relatively low compared with the improvements in DFS and OS, it is concerning to note that 7%–10% of patients who began anthracycline-based chemotherapy in the B-31[63] and N9831[64,65] trials were unable to ever receive trastuzumab-based therapy because of unacceptably low cardiac function.

This raises an important point relating to the chemotherapy backbone: the majority of adjuvant trastuzumab trials used an anthracycline, making it difficult to distinguish the relative impact on cardiac outcome contributed by trastuzumab and anthracycline. Seven-year follow-up of the B-31 trial reported cardiac events for 4.0% of patients treated with trastuzumab compared with 1.3% of patients in the control arm.[63] The prevalence of clinically occult cardiac damage is difficult to gauge, however, because this study was designed to measure LVEF data for asymptomatic patients for up to only 18 months. Of 947 trastuzumab-treated patients in the B-31 trial, 12% stopped taking trastuzumab because of an asymptomatic decline in LVEF; altogether, 15.5% stopped trastuzumab prematurely, owing to cardiac-related issues.[63]

The N9831 study also reported the rates of asymptomatic LVEF decline observed in the 18–21 months postrandomization. Of 1,944 patients who began post-AC (doxorubicin/cyclophosphamide) treatment, LVEF declined 10% or more for 26% of patients treated with AC/T (arm A), 35% of those treated with sequential paclitaxel and trastuzumab AC/T/H (arm B), and 40% of those treated with concurrent paclitaxel trastuzumab AC/trastuzumab (arm C).[65] A small proportion of patients (33%) consented to have another LVEF measurement at the 6-year time point. Data from these 651 patients showed that a substantial proportion in each treatment arm had a decrease in LVEF of at least 10% (arm A, 21%; arm B, 20%; and arm C, 23%), a decrease in LVEF of at least 15% (arm A, 9%; arm B, 7%; and arm C, 9%), and a decrease to below the lower limits of normal (arm A, 6%; arm B, 5%; and arm C, 5%). The percentage of patients with LVEF decline was similar among the treatment arms, and the median LVEF change from baseline to year 6 also appeared to be similar among the three treatment arms (−3.0%, −2.5%, and −3.0% in arms A, B, and C, respectively), leading the authors to speculate that one explanation for long-term LVEF dysfunction may be related to anthracycline exposure as opposed to trastuzumab exposure.[65]

To date, the only adjuvant study comparing a nonanthracycline regimen to an anthracycline regimen is BCIRG-006.[51] This study was prospectively designed to not only evaluate the relative efficacy of the two trastuzumab-containing arms (docetaxel/carboplatin/trastuzumab [TCH] and doxorubicin/cyclophosphamide followed by AC/trastuzumab) to the AC/T control arm but also aimed to prospectively follow cardiac function out to 5 years. Data from 48 months of follow-up demonstrated congestive heart failure for 2.0% of patients in the AC/trastuzumab arm, 0.7% in the AC/T arm, and 0.4% in the TCH arm. Moreover, a decline in mean LVEF of greater than 10 points was reported for 18.6% of patients in the AC/trastuzumab arm, 9.4% in the TCH arm (AC/trastuzumab vs. TCH: $p < .001$), and 11.2% in the AC/T arm.[51] With over 5 years of follow-up, the decline in mean LVEF did not appear to persist over time in the TCH arm.[50] However, persistence in this decline was observed among anthracycline-treated patients. In terms of efficacy, with a median follow-up of 10.3 years, both trastuzumab-containing arms demonstrated significant improvements in both DFS (AC/trastuzumab vs. AC/T: HR, 0.72; $p < .0001$; TCH vs. AC/T: HR, 0.77; $p = .0011$) and OS (AC/trastuzumab vs. AC/T: HR, 0.63; $p < .0001$; TCH vs. AC/T: HR, 0.76; $p < .0075$).[50] Although the study was not powered to test equivalence of the two trastuzumab-based arms, it is notable that 10-year DFS was quite similar in the two trastuzumab arms for higher-risk

patients with lymph node–positive (69.6%, AC/trastuzumab; 68.4%, TCH) or 4 or greater lymph node–positive disease (62.8%, AC/trastuzumab; 62.9%, TCH). To date, more than 5,000 patients have been treated with TCH-based therapy in clinical trials.[51,66-70]

Optimal Study Design to Evaluate Novel Therapies: Neoadjuvant Versus Adjuvant Settings

Around the same time that the large adjuvant trastuzumab studies were enrolling patients, two studies were started to evaluate the use of trastuzumab in primary breast tumors.[71-73] Both showed that trastuzumab more than doubled pathologic complete response (pCR) rates and also improved relapse-free/event-free survival.[46,71,73] Subsequently, several other trials were conducted to evaluate neoadjuvant trastuzumab.[74-76] Collectively, data from these studies support the routine clinical use of neoadjuvant trastuzumab, especially for larger tumors.

Traditionally, clinical trials of new agents have been conducted in the adjuvant setting. However, there are several potential advantages to the use of a neoadjuvant study design. First, the pCR rate appears to be a reliable surrogate marker of long-term outcome, especially for HER2-positive breast cancer.[77] This enables a relatively rapid readout of primary endpoints as well as smaller sample sizes. Neoadjuvant studies have been conducted to compare the activity and safety of trastuzumab to lapatinib[78-80]; to evaluate dual HER2 targeting with trastuzumab plus lapatinib,[68,81-85] trastuzumab plus pertuzumab,[67,86] and T-DM1 plus pertuzumab[87]; and to gauge activity of combining HER2- and hormonally targeted approaches (Table 4).[70,88,89] In addition, the neoadjuvant setting allows for serial biopsies to be performed, thus enabling in vivo molecular analyses to be conducted to assess for novel markers of response or resistance to therapy. This will be critical as we aim to personalize treatment regimens to provide an individual the highest therapeutic benefit with the least amount of toxicity. That said, although the design allows for more cost-effective trials to be done in an efficient manner, their small size makes it unlikely these studies will be powered to evaluate long-term outcomes. Thus, adjuvant studies are still needed to validate promising findings from the neoadjuvant setting. It is hoped that utilization of the neoadjuvant study design for the testing of novel targeted therapeutics will allow for weeding out of the less effective or more toxic agents, thus sparing the high expense, long follow-up, and large patient numbers required in the adjuvant setting.

Optimal HER2-Targeted Agents

Tyrosine kinase inhibitors. Evidence supporting activity of the oral TKI lapatinib in the preclinical and metastatic settings provided strong rationale for the evaluation of lapatinib alone and in combination with trastuzumab in the adjuvant setting.[9,11,90-92] In the TEACH trial, 3,147 patients with HER2-positive stage I–IIIC breast cancer who had completed adjuvant chemotherapy were randomly assigned to lapatinib (1,500 mg daily) for 12 months or placebo.[93] With a median follow-up of approximately 4 years, lapatinib-treated

TABLE 4. Ongoing Adjuvant/Neoadjuvant Studies

Study	No. of Patients (Enrollment Status)	ClinicalTrials.gov Identifier	Treatment Arms	Endpoint
KATHERINE	1,487 (closed)	NCT01772472	Adjuvant T-DM1 vs. trastuzumab (patients with residual disease after neoadjuvant treatment)	iDFS
APHINITY	4,806 (closed)	NTC01358877	Chemotherapy/trastuzumab vs. chemotherapy/trastuzumab/pertuzumab	iDFS
				Cardiac safety
KAITLIN	1,846 (closed)	NCT01966471	AC or FEC → T-DM1/pertuzumab	iDFS
			AC or FEC → taxane/trastuzumab/pertuzumab	
BOLD-1	1,366 (open)	NCT02625441	Taxane/trastuzumab/pertuzumab 3× → FEC 3×	iDFS
			Taxane/trastuzumab 3× → FEC 3× → trastuzumab for 1 year	
ATEMPT	500 (open)	NCT01853748	T-DM1 for 1 year vs. paclitaxel/trastuzumab for 12 weeks → trastuzumab for 1 year (stage I disease)	DFS
NeoPhoebe	50 (closed)	NCT01816594	Trastuzumab/paclitaxel/buparlisib vs. trastuzumab/paclitaxel/placebo	pCR
GeparOcto	950 (open)	NCT02125344	PMCb vs. ETC	pCR
			If HER2+, also pertuzumab/trastuzumab	
Predix-HER2	200 (open)	NCT02568839	Docetaxel/sq trastuzumab/pertuzumab vs. T-DM1	pCR
			Therapy arms switched if no response after cycle 2	
TEAL	30 (open)	NCT02073487	T-DM1/lapatinib → nanoparticle albumin–bound paclitaxel vs. trastuzumab/pertuzumab/paclitaxel	pCR

Abbreviations: DFS, disease-free survival; ETC, epirubicin/paclitaxel/cyclophosphamide; FEC, fluorouracil/epirubicin/cyclophosphamide; iDFS, invasive disease–free survival; pCR, pathologic complete response; PMCb, paclitaxel/nonpegylated liposomal doxorubicin/carboplatin; sq, subcutaneous.

patients had an 87% DFS compared with 83% for placebo-treated patients (HR, 0.83; 95% CI, 0.70–1.00; p = .053). It now appears, based on results from other comparative trials (discussed above and below), that lapatinib is less clinically active than trastuzumab. However, it is possible that the sequential administration of lapatinib after chemotherapy lessened its benefit. In addition, it is notable that a large proportion of patients enrolled when they were more than a year from their diagnosis of cancer (29% of lapatinib-treated patients were more than 4 years from their diagnosis) and, importantly, on central review, 21% of patients were found to have HER2-normal cancer. DFS analysis of the patients with centrally confirmed HER2-positive disease did suggest a significant reduction in risk (HR, 0.82; p = .04). That said, the DFS benefits were borderline at best, leading most to envision this as a negative study.

Another large study that evaluated lapatinib in the curative setting was ALTTO.[66,94] This study was unique, in that it not only compared a year of trastuzumab treatment (T) to a year of lapatinib, but it also evaluated a sequential arm (12 weeks of trastuzumab followed by 34 weeks of lapatinib) and an arm that used dual HER2 targeting. In 2011, the lapatinib arm was closed after an interim analysis determined futility to show noninferiority compared with trastuzumab/lapatinib. With a median follow-up of 4.5 years and a prespecified level of significance of .025 for each of the comparisons, lapatinib/trastuzumab was not shown to significantly improve DFS compared with trastuzumab (HR, 0.84; 95% CI, 0.70–1.02; p = .048), nor was trastuzumab followed by lapatinib shown to be different from trastuzumab (HR, 0.96; 95% CI, 0.80–1.15; p = .61). Moreover, compared to trastuzumab, lapatinib was associated with lower rates of completion of HER2-targeted therapy, owing to its notable toxicity.[94]

Lapatinib has also been evaluated in combination with chemotherapy in at least seven neoadjuvant clinical trials.[68,79-81,83-85] pCR rates with lapatinib were significantly inferior to trastuzumab in two trials making the head-to-head comparison.[79,80] The effects of single-agent lapatinib, trastuzumab, or their combination have been assessed in several of these trials.[68,81,83-85] Although all of these studies demonstrated numeric improvements in pCR with dual HER2 blockade, only two of these studies demonstrated a statistically notable improvement in pCR.[81,85] The toxicity associated with lapatinib resulted in lower rates of completion of HER2-targeted therapy in several of these trials.[81,83,85] Moreover, the pCR benefits noted in one of the studies (NeoALTTO) was not shown to translate into event-free survival benefits.[82]

Given its unfavorable safety profile and lack of demonstrated notable benefit in two large adjuvant studies and multiple smaller neoadjuvant studies, lapatinib is not considered appropriate therapy in the early-stage setting. That said, another TKI, neratinib, is showing promise in the adjuvant setting. As mentioned above, EXTENET is a phase III placebo-controlled study in which 2,840 patients who had completed trastuzumab were randomly assigned to 1 year of neratinib or placebo.[61] At 2-year follow-up, invasive DFS was 93.9% for neratinib-treated patients compared with 91.6% for the control arm (stratified HR, 0.67; 95% CI, 0.50–0.91; p = .0091). This benefit came at the expense of relatively severe gastrointestinal toxicity, with 40% of patients reporting grade 3 diarrhea. An ongoing study is being conducted to evaluate whether diarrhea can be mitigated with primary prophylaxis with loperamide (NCT02400476). At this point, neratinib is not available outside of a clinical trial.

Pertuzumab. In September 2013, based on the results of two relatively small phase II trials,[67,86] the U.S. Food and Drug Administration approved three neoadjuvant regimens for HER2-positive tumors greater than 2 cm in size. The three approved regimens all used dual HER2 targeting with pertuzumab and trastuzumab given concurrently with chemotherapy. One of the regimens approved (trastuzumab/pertuzumab 4×, followed postoperatively by fluorouracil/epirubicin/cyclophosphamide 3×) was based on the results of NeoSphere,[86] a four-arm randomized phase II trial that compared docetaxel plus either trastuzumab (TH), pertuzumab (TP), or both trastuzumab and pertuzumab. A fourth arm that used a chemotherapy-free regimen comprised of pertuzumab and trastuzumab was also included (HP). The pCR rates were significantly higher in the trastuzumab/pertuzumab arm and, importantly, the combination was shown to be relatively safe. The study was not powered to demonstrate event-free survival benefit but an exploratory analysis at 5-year follow-up showed a numerical trend in favor of the trastuzumab/pertuzumab arm compared with TH.[95] The other two regimens approved in 2013, docetaxel, carboplatin, trastuzumab and pertuzumab (TCHP) and fluorouracil/epirubicin/cyclophosphamide 3× followed by trastuzumab/pertuzumab 3×) were based on TRYPHAENA, a 225-patient, three-arm study primarily aimed to evaluate the cardiac safety of three pertuzumab/trastuzumab-based regimens.[67] pCR rates (in breast and lymph nodes) were similarly high among the three treatment arms (notably, 64% for TCHP and 55% for fluorouracil/epirubicin/cyclophosphamide followed by trastuzumab/pertuzumab). No long-term data from this study are currently available, but the tested regimens appeared to be safe from a cardiac perspective.

The largest neoadjuvant study reported to use pertuzumab and trastuzumab in combination with chemotherapy is GeparSepto.[96] This phase III trial was aimed to test noninferiority of nanoparticle albumin–bound paclitaxel–based chemotherapy to solvent-based paclitaxel. All patients with HER2-positive disease in this study (n = 396) received both pertuzumab and trastuzumab; thus, relative benefits imparted by dual HER2-targeted therapy compared with trastuzumab could not be assessed. pCR rates for the HER2-positive subset were 62% with nanoparticle albumin–bound paclitaxel and 54% with solvent paclitaxel (p = 0.13), providing further evidence of the activity of pertuzumab/trastuzumab-based therapy.

Although these data and the regulatory approval support the clinical use of trastuzumab and pertuzumab in the neoadjuvant setting, long-term safety and efficacy data from larger confirmatory studies are awaited (Table 3) before routine use of dual HER2 targeting in the adjuvant setting.

Optimizing Therapy for Hormone Receptor–Coexpressing Disease

At least half of HER2-positive breast cancer coexpresses one or both hormone receptors, and this coexpression may serve as a pathway for resistance to HER2-targeted therapy. This does not mean that HER2-targeted therapy is inactive in hormone receptor–positive breast cancer. In fact, analyses from the AC/trastuzumab and AC/T arms of the BCIRG-006[51] and B-31[53] trials show that the HRs for DFS are very similar for hormone receptor–positive (HR, 0.65 and 0.61 for BCIRG-006 and B-31, respectively) and hormone receptor–negative (HR, 0.64 and 0.62 for BCIRG-006 and B-31, respectively) disease. This also holds true for OS. Similarly, subset analysis of the HERA study at 10 years of follow-up also demonstrates long-term trastuzumab benefit for all patients regardless of HR status.[54] Although trastuzumab imparts DFS and OS benefit regardless of hormone receptor status, the presence of ER may indicate more indolent, luminal-like tumor behavior. For example, Kaplan–Meier curves from HERA indicate that although the long-term risk of recurrence is similar in hormone receptor–positive and hormone receptor–negative subtypes, patients with hormone receptor–negative disease have earlier recurrences, in keeping with more aggressive disease biology. Further evidence supporting the notion that disease behavior differs based on hormone receptor expression comes from neoadjuvant clinical trials, which have consistently shown that pCR rates are lower for hormone receptor–positive, HER2-positive breast cancer than for hormone receptor–negative disease.[67,77,81,83] That said, the longer follow-up of the NeoSphere trial[95] indicates that patients with hormone receptor coexpression have numerically higher PFS compared with those with tumors lacking hormone receptors (5-year PFS for patients who achieved pCR: 90% if hormone receptor positive, 84% if hormone receptor negative; 5-year PFS for patients who did not achieve pCR: 80% if hormone receptor positive, 72% if hormone receptor negative). Thus, patients with hormone receptor–positive tumors may do better in the long run. Intriguing biomarker analyses from HERA suggest that although ER-positive tumors with a high level of HER2 amplification (by FISH ratio) derive clear benefit from trastuzumab, those with a low level of HER2 amplification may not receive benefit from trastuzumab-based therapy.[97]

Several clinical trials aimed to evaluate cotargeting hormone receptor and HER2 have been conducted. The first of these, TBCRC-006, evaluated 12 weeks of neoadjuvant lapatinib plus trastuzumab (with letrozole for ER-positive tumors).[88] pCR (breast) in HER2-positive/hormone receptor–positive tumors was 21% in this proof-of-concept study, indicating that a relatively well-tolerated chemotherapy-free regimen might be highly effective for patients if accurate biomarkers for selection could be identified.

Trastuzumab emtansine has also been evaluated in the neoadjuvant and adjuvant settings. The WGS-ADAPT study compared four cycles of T-DM1, either alone or in combination with endocrine therapy, to trastuzumab plus endocrine therapy for patients with hormone receptor–positive, HER2-positive disease.[89] This relatively short course of T-DM1 was associated with an impressive pCR rate (breast and lymph nodes) of 41%, which was considerably higher than that achieved with trastuzumab plus endocrine therapy.

Although neither of these relatively small studies has changed the standard of care, the intriguing results should encourage the investigation of whether less toxic regimens like these might be beneficial for selected patient populations.

In December 2016, the results of the NSABP B-52 trial were presented. This study was designed to evaluate whether the addition of an aromatase inhibitor to standard chemotherapy plus HER2-targeted therapy (TCHP) would improve pCR rates for hormone receptor–positive/HER2-positive breast cancer, and to also test whether endocrine therapy would be antagonistic in combination with chemotherapy.[70] Although the addition of endocrine therapy to TCHP did not lead to a statistically notable improvement in pCR (41% for TCHP vs. 46% for TCHP plus endocrine therapy), it did not appear to be antagonistic, leaving room for future studies to test less toxic chemotherapy regimens concurrently with hormone therapy approaches.

In summary, in just over a decade, the management of early-stage HER2-positive breast cancer has changed drastically because of the development of highly effective biologically targeted therapy. The therapeutic options available to the patient in both the neoadjuvant and adjuvant settings are now nearly countless, making the choice of optimal therapy somewhat difficult at times. Our pursuit to provide patients with the safest and most effective therapies for their particular disease requires us to design carefully selected clinical trials with attention toward the discovery of molecular drivers of disease biology and markers of response to therapy.

DE-ESCALATING TREATMENT IN THE ADJUVANT SETTING IN HER2-POSITIVE DISEASE

Although there has been much work done to improve outcomes for patients with HER2-positive breast cancer by adding additional HER2-targeted agents to a standard chemotherapy backbone, it is important to consider that there may be some patients for whom we may be able to de-escalate treatment. One way to achieve this would be to use biomarkers that predict which patients are likely to benefit from less therapy. Although there are several biomarkers being explored, there is not yet one identified that can help us preselect patients for less therapy. Another approach would be to consider using clinical features to help determine which patients may be able to achieve good outcomes with less toxic regimens. Three clinical features we could consider to help us select patients

include tumor size, patient age, and response to preoperative therapy.

Using Biomarkers to De-escalate Therapy

Much work has been done to try to identify biomarkers that may help us identify patients that are likely to benefit to anti-HER2 therapy. A meta-analysis performed by Loibl et al[98] suggests that the presence of a PIK3CA mutation is associated with a significantly lower rate of pCR to anti-HER2 therapy; however, this difference in pCR was not associated with a difference in DFS. These data suggest that although those patients without a PIK3CA mutation may achieve better pCR rates than those with a mutation, the mutation is not predictive of long-term outcomes and thus cannot help us select patients that may be able to receive less therapy.

In a recent meta-analysis presented by Denkert et al,[99] high levels of TILs correlated with pCR rates among patients receiving anti-HER2 therapy and were associated with improved PFS. These data are in contrast with data from the N9831 study, which suggested that the presence of stromal TILs was associated with an improvement in recurrence-free survival of patients treated with chemotherapy alone but not of patients treated with chemotherapy and trastuzumab. In addition, high levels of stromal TILs were associated with lack of trastuzumab benefit.[100] Further work must be done to assess whether those patients with high TILs may achieve similar outcomes with less chemotherapy, and whether replacing chemotherapy with immunotherapy may be beneficial for these patients.

De-escalating Therapy Based on Clinical Parameters: Tumor Size

Systemic therapy for small (stage I) HER2-positive breast cancers has been a challenge for clinicians. This is largely attributable to the fact that the pivotal adjuvant trastuzumab trials included very few patients with stage I disease and even fewer with tumors smaller than 1 cm. In addition, as mammographic screening has become more widespread, the number of women diagnosed with T1 tumors has increased significantly. For example, among middle-aged women in the U.S. Surveillance, Epidemiology, and End Results registry, the diagnosis of T1 tumors increased from 143.5 per 100,000 to 163.5 per 100,000 women between 1990 and 1998.[101] Thus, providers face management of small, node-negative HER2-positive tumors with increasing frequency. Moreover, data from several retrospective studies looking at outcomes for patients with untreated tumors suggest that even the smallest node-negative HER2-positive tumors may have a substantial risk of recurrence (Table 5). Some of the most informative prognostic data for stage I HER2-positive breast cancers comes from a population-based cohort from British Columbia; this study demonstrated 10-year relapse-free survival of 71.6% for patients with stage I HER2-positive disease.[102] Similarly, a Finnish cohort of patients with pT1N0 disease had 72% 9-year distant DFS.[103] No patients in either cohort received trastuzumab therapy.

Studies looking at outcomes for T1abN0 tumors also suggest that even these tumors have a notable risk of recurrence. An MD Anderson Cancer Center study demonstrated that 5-year recurrence-free survival was 77.1% among 98 patients with untreated HER2-positive tumors that were less than or equal to 1 cm.[108] In a study examining a slightly larger population of patients within the National Comprehensive Cancer Network with similar disease characteristics, Vaz-Luis et al[110] demonstrated 5-year distant recurrence-free survival of 94%–96%. In a Kaiser Permanente study in which a minority of patients received chemotherapy and/or trastuzumab, 5-year distant invasive recurrence-free interval was 96.5%.[107,110] Although definitions for recurrence vary across retrospective studies and some trials included patients who received systemic therapy, the rates of recurrence across trials range from approximately 5% to 30%, indicating that these patients are at more than just minimal risk of recurrence.

Because these patients were excluded from the large adjuvant trials, the Adjuvant Paclitaxel and Trastuzumab (APT) trial was designed to prospectively address treatment of patients with small, node-negative HER2-positive breast cancer.[111] Eligible patients in this single-arm trial had a primary tumor size of less than or equal to 3 cm and had node-negative or N1mic disease (nodal disease greater than 0.2 mm but not more than 2 mm). Patients were treated with weekly paclitaxel and trastuzumab for 12 weeks, followed by completion of 1 year of trastuzumab. The study enrolled 406 patients, of which 67% had hormone receptor–positive tumors and 49.5% of tumors were less than or equal to 1 cm; 8.9% of patients had tumors greater than 2 cm and 1.5% of patients had N1mic disease (the remainder had N0 disease). Survival free from invasive disease, the primary endpoint of the trial, was 98.7% (95% CI, 97.7%–99.8%) at 3 years. Toxicity in the APT trial was minimal; 3.2% of patients experienced an asymptomatic but notable decline in cardiac ejection fraction, 0.5% of patients (2 patients) developed symptomatic heart failure. The majority of cardiotoxicity events were reversible after trastuzumab was held.[111] In a substudy of chemotherapy-related amenorrhea following the adjuvant trastuzumab regimen, which included 64 APT trial participants who were premenopausal at the time of APT trial enrollment, 28% of women were amenorrheic at a median of 51 months from study enrollment.[112] This compares favorably to the approximately 50% rate of chemotherapy-associated amenorrhea seen for premenopausal recipients of the standard AC/trastuzumab adjuvant regimen[113] and suggests that the trastuzumab regimen may have the added benefit of decreased fertility concerns among young, appropriately selected women with HER2-positive cancers.

Another prospective, single-arm phase II trial that looked at treatment of patients with early-stage HER2-positive breast cancer administered four cycles of docetaxel with cyclophosphamide and trastuzumab, followed by every-3-week trastuzumab to complete a year of therapy.

Of those patients enrolled, 284 (57.6%) had stage I HER2-positive disease. Three-year DFS for patients with node-negative disease was 97.8% (95% CI, 95.6–98.9).[114] Because this DFS is very similar to outcomes in the APT trial, there is likely little role for the addition of cyclophosphamide in the management of the lowest-risk HER2-positive tumors. Work is ongoing to determine whether even less toxic regimens may be effective in this population. The ATEMPT trial (NCT01853748) recently completed accrual and randomly assigned patients in a 3:1 fashion to T-DM1 or to the paclitaxel plus trastuzumab regimen used in the APT trial. This study was designed to compare clinically relevant toxicities between the two arms and to also examine DFS among those patients receiving T-DM1.

De-escalating Therapy Based on Patient Age

Elderly individuals comprise another group of patients for whom we should consider de-escalation of therapy. Data from Freedman et al[115] looking at the incidence of early-stage HER2-positive disease by age within the National Comprehensive Cancer Network showed that 26% of cases arise for patients older than age 60. These data also demonstrate that older patients were less likely to receive adjuvant trastuzumab, and those with notable comorbidity appear to be less likely to complete adjuvant trastuzumab therapy. Given evidence that shorter-duration trastuzumab adversely affects outcomes,[59] adherence to trastuzumab may be an important factor to consider when selecting an initial regimen. Previously conducted clinical trials of adjuvant trastuzumab-based regimens included few older patients, with women older than age 60 comprising approximately 15% of all participants. In addition, patients older than age 70, as well as those with cardiac conditions, were either excluded or poorly represented. Because trial eligibility is selective with regard to comorbidities, the landmark trials of trastuzumab provide limited data regarding tolerability and effectiveness of therapy among older patients. Multiple studies do, however, suggest that older women with more cardiac comorbidity may be at higher risk of cardiac toxicity with anthracycline-based therapy.[105,116,117]

When making decisions about these patients, it is important to factor in the potential benefits and toxicities of therapy, particularly in disease settings like HER2-positive cancer, in which recurrences can occur earlier rather than later. Older patients without notable comorbidities should be considered for standard adjuvant regimens; however, individuals with multiple medical problems may be those

TABLE 5. Observational Cohort Studies of Small HER2-Positive Breast Cancer

Reference	Type of Cohort	Tumors Included (Subgroups)	No. HER2+	Chemotherapy Treated (%)	Trastuzumab Treated (%)	Percent of DFS/ RFS (Years)	Percent of DDFS/ DRFS (Years)
Chia et al[102]	British Columbia	N0	206	16	0	65.9 (10)	71.2 (10)
		pT1abcN0	NR	NR	0	71.6 (10)	77.5 (10)
		pT1abN0	21	NR	0	NR	NR
Tovey et al[104]	United Kingdom	N0, grade 1–2	22	30	NR	NR	NR
Joensuu et al[105]	Finland	pT1abcN0	65	NR	0	NR	72 (9)
Rom et al[106]	Germany	pT1abcN0	87	NR	43	97.1 (1)	98.5 (1)
Fehrenbacher et al[107]	Kaiser Permanente	pT1abN0	234	25.6	8.1	94.1 (5)*	96.5 (5)*
Gonzalez-Angulo et al[108]	MD Anderson	pT1abN0	98	0	0	77.1 (5)	86.4 (5)
Curigliano et al[109]	European Institute of Oncology	pT1abN0HR+	71	25.4	0	92 (5)	NR
		pT1abN0HR−	79	43.7	0	91 (5)	NR
Rouanet et al[22]	France	pT1abN0	44	10	0	73 (10)	80 (10)**
Vaz-Luis et al[110]	NCCN database	pT1bN0HR+	89	0	0	NR	94 (5)
		pT1bN0HR−	17	0	0	NR	94 (5)
		pT1aN0HR+	102	0	0	NR	96 (5)
		pT1aN0HR−	49	0	0	NR	94 (5)

*Recurrence-free interval (invasive disease only).

**Metastasis-free survival.

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; DRFS, distant recurrence-free survival; NCCN, National Comprehensive Cancer Network; NR, not recorded; OS, overall survival; RFS, recurrence-free survival.

Data reported are from original publications, as referenced. Point estimates for outcomes are included; original publications include confidence intervals. Point estimates must be interpreted in the context of confidence intervals.

that should be considered for less toxic treatments. The ATOP trial (NCT02414646) is currently assessing a less toxic regimen for older patients; in this trial, patients older than age 60 with stage I–III HER2-positive breast cancer, for whom standard regimens are not felt to be appropriate, are treated with 1 year of adjuvant T-DM1. Another study looking at de-escalation of therapy for older patients is the RESPECT trial (NCT01104935) conducted in Japan, which is randomly assigning women age 69–81 with stage I–IIIA HER2-positive breast cancer to treatment with trastuzumab alone versus trastuzumab plus chemotherapy. This study will have the potential to address the question of whether trastuzumab monotherapy has a place in treated elderly patients with HER2-positive disease.

De-escalation of Therapy Based on Response to Preoperative Therapy

Consideration of de-escalation of therapy is also warranted for the group of patients who achieve a pCR to preoperative therapy. Data suggest that patients with HER2-positive breast cancer who achieve a pCR have better long-term outcomes, with improved DFS and OS.[77] In a pooled analysis of 12 international trials (11,955 patients), a notable association was found between pCR and event-free survival. There is, however, no association of treatment effects on long-term outcomes, suggesting that randomized trials with long-term follow-up are needed to understand outcomes for specific therapies. It is therefore critical that we begin designing clinical trials to assess outcomes for patients who achieve a pCR to a highly active regimen, rather than just administering further therapies with associated toxicities that may not be providing additional benefit. We should also consider using escalation of biologic therapy as a mechanism to de-escalate chemotherapy. If adding pertuzumab to trastuzumab-based chemotherapy is found to improve long-term outcomes in the APHINITY trial, perhaps patients may achieve similar outcomes with less chemotherapy and highly effective biologic therapy. One strategy would be to consider doing a prospective randomized trial of doxorubicin/cyclophosphamide/taxane with trastuzumab and pertuzumab compared with a taxane plus trastuzumab and pertuzumab regimen and see whether patients receiving less chemotherapy can do just as well.

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Optimizing Breast Cancer Adjuvant Radiation and Integration of Breast and Reconstructive Surgery

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OVERVIEW

Postmastectomy radiotherapy (PMRT) reduces the risk of locoregional and distant recurrence and improves overall survival in women with lymph node–positive breast cancer. Because of stage migration and improvements in systemic therapy and other aspects of breast cancer care, the absolute benefit of PMRT and regional nodal irradiation may be small in some favorable subsets of patients with very low nodal burden, and newer consensus guidelines do not mandate PMRT in all node-positive cases. The use and need for PMRT may considerably complicate breast reconstruction after mastectomy and therefore mandates multidisciplinary input that takes into account patient choice given potential risk of acute and long-term toxicities, benefits, life expectancy, the biology of the tumor, plans for systemic therapy, and actual tumor burden. Management of axillary lymph node metastases is changing with selective use of axillary lymph node dissection for advanced disease, sentinel lymph node biopsy alone for clinically and pathologic node-negative cases receiving mastectomy, and targeted axillary dissection alone among patients with eradication of initial biopsy-proven nodal metastases with neoadjuvant systemic therapy use. In general, when the need for PMRT is anticipated, autologous reconstruction should be delayed. This comprehensive article reviews the current indications and implications regarding integration of breast cancer surgery and timing of reconstruction with optimum radiation delivery to achieve the best possible patient outcomes.

In contemporary practice, there is uniform consensus that PMRT is indicated for patients at high risk of local regional failure, such as those with stage III breast cancers. However, locoregional and distant recurrence rates are lower than in past decades when randomized controlled trials demonstrated overall survival benefits in all patients with lymph node–positive disease.[1-3] Therefore, there is much controversy on the role of PMRT in patients with earlier stage breast cancer, particularly among those with low-volume nodal metastases identified with sentinel lymph node (SLN) dissection. Added to this treatment conundrum, recent evidence suggests that regional nodal irradiation (RNI) in itself may provide a survival benefit in patients with early-stage breast cancer despite only modest reductions in locoregional recurrence.[4-6] These RNI studies highlight the importance of long-term follow-up of prospective studies to fully assess the impact of locoregional therapies on breast cancer–specific and all-cause mortality. At the same time, stage migration from increased screening and improved diagnostic imaging, in addition to advances in systemic therapy, surgical techniques, pathologic evaluation, and radiotherapy delivery, all must be taken into consideration when applying the results from past locoregional studies to patients assessed in the clinic today.[7] These advances add complexity to counseling regarding the absolute risks and benefits of PMRT for each individual patient. In this context, new consensus guidelines related to the use of PMRT were recently released by the ASCO, the American Society for Radiation Oncology (ASTRO), and the Society of Surgical Oncology (SSO) to provide additional guidance on some continued areas of controversy, including the role of PMRT in patients with one to three positive lymph nodes, the role of PMRT in the setting of preoperative chemotherapy, as well as technical aspects of PMRT such as indications for internal mammary node irradiation (IMNI).[2]

Coupled with great institutional variability in applying PMRT and RNI guidelines is the complexity of integrating breast and nodal surgery together with plastic reconstructive surgery. Breast cancer nodal metastases plays a considerable role in determining radiotherapy indications and treatment targeting, yet recently there have also been marked changes in axillary management, starting with SLN biopsy for clinically node–negative disease and newer techniques to stage the axilla after neoadjuvant systemic therapy in node-positive breast cancer and new trial results related to use of adjuvant radiotherapy without completion dissection for SLN-positive breast cancer. Finally, patient decisions regarding whether to pursue immediate reconstruction

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may be impacted by a recommendation for PMRT, as PMRT may increase the risk of complications and adverse cosmetic outcome, and immediate reconstruction has been reported to pose challenges to PMRT delivery.[8-10] All of these factors underscore the imperative of close communication by multidisciplinary teams to best prospectively coordinate and deliver patient-centered breast cancer care. This special ASCO educational article will address the current indications and implications regarding integration of breast cancer surgery with optimum radiation delivery to achieve the best possible patient outcomes.

INDICATIONS AND IMPLICATIONS FOR OPTIMAL CONTEMPORARY ADJUVANT RADIATION THERAPY DELIVERY

The PMRT Randomized Controlled Trials

In the period from 1978 to 1990, three seminal randomized controlled trials (Table 1) were conducted (one in British Columbia, Canada, and two in Denmark) that evaluated the role of PMRT in patients receiving systemic therapy.[11-13] Eligibility criteria included one or more pathologically involved axillary lymph node. In addition, approximately 8% and 10% of patients in the premenopausal Danish Breast Cancer Cooperative Group (DBCG) 82b study and the postmenopausal DBCG 82c study, respectively, were node negative and enrolled on the basis of a primary tumor more than 5 cm or invasion of the skin or pectoral fascia. Each study reported similar findings, a 9% to 10% absolute improvement in 10-year overall survival with the addition of PMRT. However, there has remained heterogeneity in the uptake of PMRT, particularly in the subset of women with one to three positive nodes. Some physicians have favored offering PMRT in the majority of women meeting eligibility criteria (i.e., one or more positive lymph nodes) based on the high level of evidence provided by these prospective randomized controlled trials.[14] Others highlighted that inadequate axillary surgery and inadequate systemic therapy regimens without taxanes and anti-HER2 therapy have limited applicability to patients with low nodal burden in modern practice who have much lower recurrence rates.[15,16] In the DBCG 82b and 82c studies, a median of just seven lymph nodes were identified in pathologic specimens from axillary dissections. In the British Columbia study, the median number was 11. To address these concerns, the DBCG performed an analysis of patients with one to three positive lymph nodes from the DBCG 82b and 82c studies but in which they excluded patients with fewer than eight nodes removed. That analysis demonstrated a statistically significant overall survival benefit with the addition of PMRT (57% vs. 48%; p = .03).[14] In 2014, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published an individual patient data meta-analysis on the effects of PMRT. In it, they specifically assessed the role of PMRT in patients who underwent axillary lymph node dissection. For the 1,133 women with one to three positive nodes who underwent axillary lymph node dissection and received systemic therapy, PMRT reduced the 20-year breast cancer mortality rate from 49.4% to 41.5% (relative risk 0.78; p = .01).[17] These findings lead to unanimous agreement by an ASCO/ASTRO/SSO expert panel in 2016 that PMRT reduces recurrence and breast cancer mortality for patients with T1-T2 breast cancer with one to three positive axillary lymph nodes.[18] However, there was also recognition by the ASCO/ASTRO/SSO panel that patients with T1-T2 breast cancer and one to three positive nodes are a heterogeneous group with varying prognoses. They highlighted that subsets of patients in this population are likely to have such a low recurrence risk that the benefit of PMRT may be outweighed by the potential risks.[18]

Indeed, improvements in systemic therapy have significantly reduced both locoregional and distant recurrence risk because the three landmark randomized PMRT studies were conducted. It is noteworthy that patients included in the aforementioned EBCTCG analysis received cyclophosphamide, methotrexate, and fluorouracil (CMF), or tamoxifen, and the duration of tamoxifen for most patients was just 1 year.[17] These agents and schedules have since been replaced by more effective strategies, including anthracyclines, taxanes, HER2-targeted therapies, and prolonged endocrine therapy, frequently with aromatase inhibitors. In addition, the introduction of SLN dissection has resulted in the identification of smaller volume axillary macro- and micrometastases.[19] Therefore, improvements in both multidisciplinary management and stage migration have reduced

KEY POINTS

- **Prospective multidisciplinary review, communication, and coordination is necessary to optimize breast cancer local-regional control, survival, cosmetic outcome, and define a unified clear patient-centered path forward.**
- **PMRT reduces the risk of locoregional and distant recurrence and improves overall survival in women with lymph node–positive breast cancer. Because of stage migration and improvements in systemic therapy and other aspects of breast cancer care, the absolute benefit of PMRT may be small in some favorable subsets of patients with very low nodal burden.**
- **PMRT use may complicate breast reconstruction and requires multidisciplinary input that takes into account patient choice given potential risk of acute and long-term toxicities, benefits, life expectancy, the biology of the tumor, plans for systemic therapy, and actual tumor burden.**
- **Management of axillary lymph node metastases is changing with selective use of axillary lymph node dissection for advanced disease, sentinel lymph node biopsy alone, and targeted axillary dissection alone among patients with eradication of initial biopsy-proven nodal metastases with neoadjuvant systemic therapy.**
- **Immediate two-stage implant-based reconstruction is usually preferable in the majority of patients with breast cancer facing PMRT due to its preservation of autologous tissue and often acceptable outcomes, and PMRT can be administered either to the tissue expander or the final implant.**

TABLE 1. Select PMRT and RNI Randomized Controlled Trials

Study	Dates	No. of Patients	Inclusion Criteria	Systemic Therapy	Radiotherapy Target	Locoregional Recurrence	Distant Recurrence	Disease-Free Survival	Breast Cancer–Specific Survival	Overall Survival
British-Columbia	1979–1986	318	Premenopausal, pN+	CMF for 6–12 months	Chest wall, axillary, SC, and bilateral IMNs	20-yr ILRFS, 90 (RT) vs. 74% (no RT); p = .002. For 1–3 positive nodes, 91 vs. 79%	20-yr SBCFS, 48 (RT) vs. 31% (no RT), p = .004. For 1–3 positive nodes, 58 vs. 44%	20-yr BCFS, 48 (RT) vs. 30% (no RT); p = .001. For 1–3 positive nodes, 57 vs. 41%	20-yr BCSS, 53 (RT) vs. 38% (no RT); p = .008. For 1–3 positive nodes 64 vs. 53%	20-yr OS, 47 (RT) vs. 37% (no RT); p = .03. For 1–3 positive nodes, 57 vs. 50%
DBCG 82b	1982–1989	1,708	Premenopausal, pN+, or primary tumor > 5 cm, invasion of skin or pectoral fascia	CMF eight to nine cycles	Chest wall, axillary, SC and IMNs	Isolated LRR alone as first event 5 (RT) vs. 26% (no RT)	Distant metastases alone as first event 34 (RT) vs. 26% (no RT)	10-year DFS, 48 (RT) vs. 34% (no RT); p < .001. For 1–3 positive nodes, 54 vs. 39%	Not reported	10-yr OS, 54 (RT) vs. 45% (no RT); p < .001. For 1–3 positive nodes, 62 vs. 54%
DBCG 82c	1982–1990	1,375	Postmenopausal, age < 70, pN+, primary tumor > 5 cm, invasion of skin or pectoral fascia	Tamoxifen for 1 yr	Chest wall, axillary, SC and IMNs	Isolated LRR alone as first event 4 (RT) vs. 29% (no RT)	Distant metastases alone as first event 25 (RT) vs. 39% (no RT)	10-year DFS, 36 (RT) vs. 24% (no RT); p < .001. For 1 3 positive nodes 44% vs. 31%	Not reported	10-yr OS, 45 (RT) vs. 35% (no RT); p = .03. For 1–3 positive nodes, 55 vs. 44%
EORTC 22922/10925	1996–2004	4,004	Stage I, II, or III with a centrally or medially located primary tumor, irrespective of axillary involvement, or pN+ and externally located	According to institutional practice; of patients enrolled, 25% received chemotherapy, 30% received hormonal therapy, and 30% received both.	Breast or with/without chest wall vs. breast or with/without chest wall and RNI (axillary, SC, and IMNs)	Locoregional events 8 (RNI) vs. 10% (no RNI)	10-yr DDFS 78 (RNI) vs. 75% (no RNI); p = .02	10-yr DFS 72 (RNI) vs. 69% (no RNI); p = .004	10-yr breast cancer mortality 12 (RNI) vs. 14% (no RNI); p = .02	10-yr OS, 82 (RNI) vs. 81% (no RNI); p = .06

Continued

TABLE 1. Select PMRT and RNI Randomized Controlled Trials (Cont'd)

Study	Dates	No. of Patients	Inclusion Criteria	Systemic Therapy	Radiotherapy Target	Locoregional Recurrence	Distant Recurrence	Disease-Free Survival	Breast Cancer–Specific Survival	Overall Survival
NCIC MA.20	2000–2007	1,832	pN+ or primary tumor ±5 cm or primary tumor ±2 cm, < 10 axillary nodes removed, and one of grade 3, ER negativity, or lymphovascular invasion	According to institutional practice; of patients enrolled. 86% received an anthracycline; 25% received both an anthracycline and taxane; 57% received an aromatase inhibitor, and 19% received tamoxifen. After June 2005, trastuzumab was recommended for patients with HER2-positive disease.	Breast vs. breast plus RNI (axillary, SC, and IMNs)	10-yr ILRFS, 95 (RNI) vs. 92% (no RNI); p = .009	10-yr DDFS, 86 (RNI) vs. 82% (no RNI); p = .03	10-yr DFS. 82, (RNI) vs. 77% (no RNI); p = .01	10-yr breast cancer mortality, 10 (RNI) vs. 12% (no RNI); p = .11	10-yr OS, 83 (RNI) vs. 82% (no RNI); p = .38

Abbreviations: BCFS, breast cancer–free survival; BCSS, breast cancer–specific survival; CMF, cyclophosphamide, methotrexate, and fluorouracil; DDFS, distant disease-free survival; DFS, disease-free survival; ER, estrogen receptor; ILRFS, isolated local recurrence-free survival; IMNS, internal mammary node; LRR, locoregional recurrence; OS, overall survival; pN+, pathologically node positive; RNI, regional nodal irradiation; RT, radiotherapy; SBCFS, systemic breast cancer–free survival; SC, supraclavicular; yr, year.

the absolute risk of recurrence in patients with one to three positive lymph nodes considered for PMRT compared with years past and with it the absolute risk reduction that can likely be expected for some subsets with the addition of PMRT.[20-22] Yet more recently published prospective studies still demonstrated improvements in the therapeutic ratio with the addition of RNI (i.e., high axillary, supraclavicular, and internal mammary irradiation) in more contemporary treated populations with low axillary nodal burden.

IMNI, RNI, and the Relationship Between Locoregional and Distant Relapse

The National Cancer Institute of Canada MA.20 clinical trial assessed the role of the addition of RNI to whole breast irradiation (WBI) in women after breast-conserving surgery.[4] Fifty percent of the study population consisted of women with just one positive axillary lymph node, and 85% had one to three positive nodes. An additional 10% of women had high-risk node-negative disease. Eighty-six percent of patients received anthracycline-based chemotherapy, and 26% also received a taxane. Both tamoxifen and aromatase inhibitors were administered according to institutional practice, with 57% receiving an aromatase inhibitor alone or after a period of tamoxifen and 19% receiving tamoxifen alone. HER2-directed therapy was only recommended in the final 20 months that the study was open. MA.20 did not meet its primary endpoint of a 5% improvement in 5-year survival. Moreover, the 2% absolute improvement in 10-year rate of breast cancer mortality with the addition of RNI to WBI did not reach significance (hazard ratio 0.80; p = .11). However, RNI significantly improved the 10-year rate of disease-free survival from 77.0% to 82.0% (hazard ratio 0.76; p = .01). Interestingly, the absolute improvement in the rate of 10-year distant disease-free survival with the addition of RNI to WBI was 4.0%, greater than the 3.0% improvement in 10-year isolated locoregional disease-free survival. In the same journal issue, the European Organization for Research and Treatment of Cancer (EORTC) published results of EORTC 22922/10925, which also evaluated the role of RNI in patients with early-stage breast cancer.[5] The study population was slightly different than MA.20, with 44% of the population being node negative and 24% having undergone mastectomy. In this larger study, the 2% absolute improvement in breast cancer mortality with the addition of RNI reached statistical significance (hazard ratio 0.82; p = .02). Similar to MA.20, a provocative finding was that RNI prevented more distant events than locoregional events.

MA.20 and EORTC 22922/10925 evaluated the role of comprehensive RNI, including axillary, supraclavicular, and IMNI. Despite IMNI being a component of PMRT in 20 of the 22 trials in the EBCTCG analysis, the need for IMNI has been questioned, as the risk of isolated nodal failures in the IMNs has historically been reported to be 1% or less.[5,15] In addition, targeting the IMNs increases the dose to the heart and lungs, raising concern that IMNI could increase the late effects of treatment.[23] DBCG-IMN was a prospective population-based cohort study that specifically evaluated the effect of IMNI in patients with node-positive early-stage breast cancer.[6] All patients with right-sided disease were allocated to IMNI, whereas patients with left-sided disease received no IMNI to minimize cardiac exposure. The majority of patients enrolled had one to three positive nodes. With a median follow-up of 8.9 years, right-sided patients who received IMNI had an 8-year overall survival rate of 75.9% versus 72.2% for left-sided patients treated without IMNI (hazard ratio 0.82; p = .005). The results of these three studies evaluating nodal irradiation contradict a highly cited principle put forth in an earlier EBCTCG analysis of trials initiated between 1951 and 1991 that differences in radiotherapy and extent of surgery that result in a less than 10% difference in 5-year local recurrence risk are unlikely to impact breast cancer mortality.[24] Given the relatively high number of distant events prevented, the findings suggest that clinically substantial residual locoregional disease may go undetected or be only detected after a distant relapse has occurred. Therefore, caution should be exercised if de-escalating radiotherapy based on retrospective locoregional patterns of failure data alone.[16,25,26]

It is worth noting that most clinically detected locoregional recurrences after mastectomy occur on the chest wall, not in the regional lymphatics.[15,27] The data from MA.20 and EORTC 22922/10925 is not directly applicable to PMRT because the majority of patients in these studies underwent breast conservation therapy. However, because PMRT typically includes both chest wall and RNI, it is reasonable to infer that if patients with similar disease features were treated with mastectomy, the proportional and absolute reduction in recurrence with PMRT would have been at least as great. At the same time, favorable long-term breast cancer event rates have been reported in single-institution retrospective analyses of well-staged and carefully selected patients (a majority with T1, estrogen receptor–positive, and a single involved axillary micro- or macrometastases) treated with mastectomy and systemic therapy without PMRT.[1,28] In women with one to three positive lymph nodes being considered for PMRT, radiation oncologists must carefully consider individual patient and clinical features that not only influence the risk of locoregional relapse, but also distant relapse. Factors such as patient age, tumor size, number, size, and percentage of sampled nodes involved, grade, subtype, proximity of margins, and molecular profiling, if available, may all assist in estimating a patient's risk of recurrence and assist in identifying those with low nodal burden who are most likely to benefit from PMRT.[4,5,16,25,27,29-33]

PMRT in the Setting of Neoadjuvant Chemotherapy

Increasingly, patients are being treated with preoperative systemic therapy, and for most breast cancer subtypes, tumor response is the most important prognostic factor for recurrence in that setting.[34] Patients with residual disease in the lymph nodes after preoperative chemotherapy are at elevated risk of recurrence, and it is generally agreed that these patients should be treated with PMRT.[35,36] Patients who have a complete response in the breast but residual

disease in the axillary nodes after preoperative chemotherapy have a similar risk of recurrence as those with residual disease in both the breast and nodes and should also receive PMRT.[37] Whether such an approach is also appropriate for low-grade, slowly proliferating estrogen receptor–positive tumors (i.e., luminal A tumors) in whom preoperative endocrine therapy approaches are increasingly considered is uncertain and warrants further investigation.[38] Although retrospective analyses suggest locoregional recurrence risk is low, there is a dearth of prospective data on the benefits of administration or the safety of omitting PMRT in patients with lymph node–positive clinical stage II breast cancer who are converted to node negative after preoperative systemic therapy or who achieve a pathologic complete response in both the breast and axillary nodes.[39,40] The NRG Oncology Group 9353 trial randomizes patients with biopsy-proven axillary node involvement before preoperative chemotherapy who become pathologically node negative at the time of mastectomy to PMRT or no irradiation. In patients who undergo lumpectomy, the randomization is to WBI versus whole breast plus RNI (NCT01872975). Eligible patients are best treated as part of this clinical trial.

Toxicity of Radiotherapy in Modern Practice

Finally, the potential benefits in disease control with the administration of radiotherapy must be weighed with the risks of toxicity in each individual patient and take into consideration their values on minimizing treatment morbidity versus avoiding recurrence. For example, complications of PMRT are higher in women pursuing implant-based reconstruction (discussed below), as well as those who have previously undergone axillary lymph node dissection, relative to SLN biopsy.[41-43] Although toxicity outcomes of patients treated in past eras provide valuable lessons on the importance of optimizing radiotherapy delivery, the multidisciplinary team must be familiar with the expected acute and late toxicity of PMRT using the techniques and technology of today, not of decades past.[44,45] For example, a greater appreciation for the potential risks of low-dose cardiac irradiation and improved radiotherapy planning and delivery have led to much lower cardiac exposure in women undergoing radiotherapy today.[45] Proton therapy is being investigated for breast cancer and routinely enables heart, lung, and other nontarget normal tissue doses to be significantly lower than optimized photon and/or electron techniques and can further improve targeting of the IMNs in patients with challenging anatomy, such as those with bilateral reconstruction (Fig. 1).[46-50] Therefore, there is strong justification to support clinical trials and prospective registries investigating whether these newer techniques can further improve long-term outcomes.

PMRT Targeting and Techniques

PMRT should be delivered to both the chest wall and regional lymphatics, including the IMNs, provided that appropriate normal tissue constraints can be met.[18] At the Mayo Clinic in Rochester, MN, 50 Gy in 25 fractions is prescribed. We do not routinely boost the chest wall given concern about the potential additional risk to the reconstructed breast mound.[42] For photon PMRT, in cases of bilateral reconstruction, we routinely deflate the contralateral expander before CT simulation to avoid exposure from partially wide tangents that are generally used to target the IMNs. An added advantage of proton therapy is that contralateral tissue expander deflation is not necessary because protons are administered from anteriorly directed beams.[46] For both photon and proton PMRT, the ipsilateral expander is overinflated before simulation to facilitate the second stage of reconstruction and is maintained in the same state during treatment to ensure reproducibility of the radiotherapy plan. Evidence suggests that proton therapy further improves targeting in the setting of immediate reconstruction.[46,48,50] In patients undergoing WBI, hypofractionation resulted in less acute and late toxicity than conventional fraction.[51] Whether hypofractionated schedules can further improve the therapeutic ratio in patients undergoing PMRT, including those with reconstruction, is an important area of future investigation.

In summary, the absolute benefit of PMRT in some subsets of women with node-positive breast cancer is likely smaller in today's practice because of a lower baseline risk of recurrence. However, the relative benefit of PMRT may be greater because of improved systemic therapy, resulting in less risk of early systemic dissemination, better targeting of areas at risk with modern treatment planning, and reductions in dose to nontarget normal tissues. Thus, careful multidisciplinary consideration of individual risk factors for recurrence, toxicity, and patient values is crucial to optimize patient counseling. Investment by all stakeholders in locoregional therapy randomized studies will be required to address many of the controversies that persist.

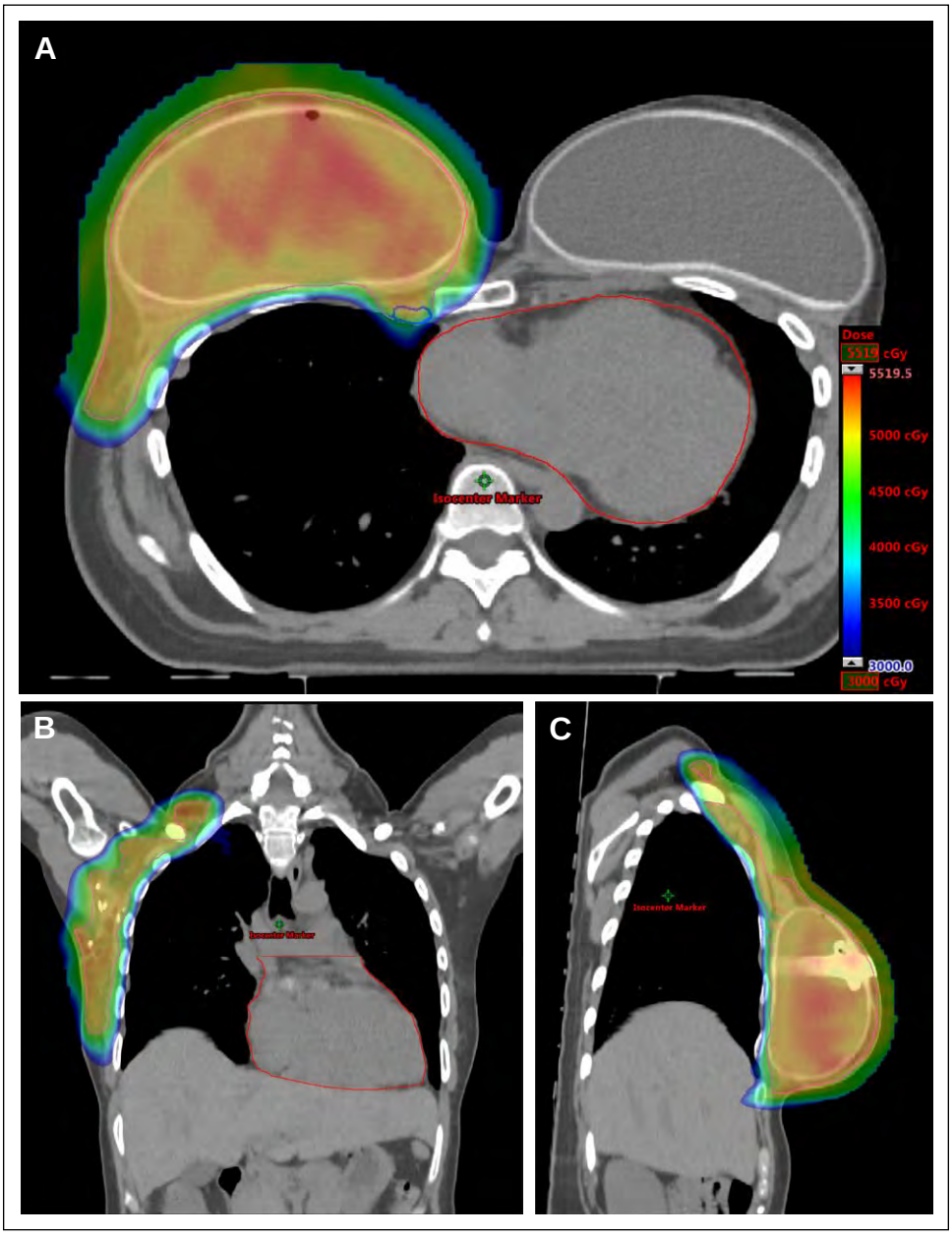
MANAGEMENT OF THE AXILLA IN PATIENTS WHO UNDERGO MASTECTOMY AND BREAST CONSERVATION

There have been many changes regarding the surgical management of node-positive breast cancer with respect to axillary surgery over the last 5 to 10 years. However, every day, all clinicians initially evaluating patients with breast cancer, and specifically the breast surgical oncologist, evaluate routine complexities that are discussed, including the need for or choice of mastectomy or choice of breast conservation. Further confounding these discussions is the potential for neoadjuvant systemic therapy in decisions regarding ultimate surgery and implications for PMRT. It becomes obvious and intuitive that these complex decisions are best made prospectively by a multidisciplinary team including the breast surgical oncologist, the radiation oncologist, the plastic surgeon, and the medical oncologists in conjunction, of course, with the patient.

SLN Biopsy for Clinically Node-Negative Patients

Simply stated, intraoperative lymphatic mapping and SLN biopsy for breast cancer is the accepted international standard for evaluating patients with a clinical node-negative axilla whether the patient receives breast-conserving therapy or mastectomy with or without immediate breast reconstruction.[52]

FIGURE 1. Axial (A), Coronal (B), and Sagittal (C) Colorwash Images of the Intensity-Modulated Proton Therapy Plan of a Patient With Bilateral Tissue Expander Reconstruction Undergoing PMRT



Chest wall (magenta) and internal mammary (blue) clinical target volume is well covered while sparing the heart (red) and contralateral reconstructed breast mound.

Before recently, it was more or less dogmatic that a patient with node-positive breast cancer and receiving mastectomy would be a candidate for PMRT. This concept is changing based on new consensus guidelines taking into account tumor biology as well as tumor burden such that any given patient with one or two positive SLNs may not be recommended PMRT.[2] However, despite these new guidelines, most patients who are younger with node-positive breast cancer and those patients with larger primary tumors and other risk factors will in fact be recommended for PMRT.[3] Currently, ultrasound with biopsy of suspicious axillary nodes is an excellent methodology to identify patients with axillary nodal metastases and can be quite valuable in making decisions regarding the use of neoadjuvant systemic therapy and planning for PMRT and reconstruction. Despite the utility of ultrasound, most imaging is neither sensitive nor specific for definitively identifying breast cancer nodal metastases.[53] A negative nodal ultrasound does not rule out metastatic carcinoma, and this has led some clinicians to perform a separate SLN procedure if the status of the lymph node would change systemic therapy sequencing and/or the type of reconstruction based on the potential need for PMRT. This has not been the MD Anderson approach—patients with a benign nodal ultrasound but with large primary tumors would either undergo preoperative systemic therapy if indicated or primary surgery and SLN biopsy,

usually with a tissue implant that could then easily be deflated for delivery of the PMRT if indicated and then be expanded for final reconstruction.[54]

Unsuspected Nodal Micrometastases Identified in SLNs

Patients receiving breast conservation and in whom unsuspected nodal metastases is identified in one or two lymph nodes do not have formal axillary lymph node dissection based on American College of Surgeons Oncology Group Z0011 randomized trial of axillary dissection versus observation for SLN-positive disease.[55] For those with more nodal metastases identified receiving breast conservation, a multidisciplinary decision is made for recommendation of axillary lymph node dissection as the current standard, although some patients decline dissection, and groups of clinicians do offer nodal radiotherapy for this group of patients if axillary dissection is not performed. For unsuspected nodal micrometastases in patients with mastectomy, the standard has been recommendation for completion axillary lymph node dissection, although many patients decline this surgery and opt for observation, particularly when systemic therapy is given with or without PMRT.[56] In this regard, although the National Comprehensive Cancer Network guidelines suggest that axillary radiotherapy could be used in this scenario instead of completion axillary dissection, the recent PMRT consensus guidelines specifically state that if completion axillary dissection is not performed after a positive sentinel node, patients should receive PMRT only if there is already sufficient information to justify its use.[2]

The International Breast Cancer Study Group (IBCSG) 23-01 noninferiority randomized clinically T1/2, N0 patients with micrometastases identified in SLNs to dissection versus observation.[57] Twenty-two percent of patients on that study who underwent breast-conserving surgery received no adjuvant radiotherapy or received intraoperative partial breast irradiation without any axillary treatment. An additional 9% underwent mastectomy without adjuvant radiotherapy. The 5-year local regional recurrence rates in both arms of the study were less than 3%, and no notable disease-free or overall survival difference was identified. Based on this additional study taken together with the Z0011 study, it has become standard practice to avoid axillary dissection among similar patients.

It is been well known for several decades that radiotherapy can be used to treat undissected breast cancer nodal disease. The EORTC 10981-22023 AMAROS (After Mapping of the Axilla, Radiotherapy or Surgery?) trial enrolled clinically node-negative patients with positive SLNs and a breast cancer less than 3 cm in diameter (approximately 17% of each group underwent mastectomy, and about 5% of cases in each arm had three or more positive SLNs).[41] The study reported a 5-year axillary recurrence rate of 0.43% after dissection and 1.19% in the axillary radiotherapy group with no overall or disease-free survival difference yet significantly lower rates of clinical lymphedema in the radiotherapy arm compared with dissection group (23% compared with 11%; $p < .0001$).[41] Thus, axillary radiotherapy seems to control regional residual microscopic disease among patients with positive SLNs, although, taken together with the results from the Z00011 and IBCSG study, may potentially overtreat some patients.

Management of Biopsy-Proven Axillary Nodal Metastases: SLN Biopsy and Targeted Axillary Dissection

Neoadjuvant systemic therapy can eradicate documented breast cancer axillary nodal metastases in 40%–74% of patients.[53,58] Therefore, it was of interest to see if the SLN procedure could accurately identify patients without residual disease to avoid axillary lymph node dissection and potential complications associated with that type of surgery. Retrospective and prospective clinical trials demonstrated that the false-negative rates of SLN biopsy alone were often higher among patients with documented nodal metastases treated with neoadjuvant systemic therapy compared with patients receiving surgery first.[59-62] The false-negative rates markedly decreased after placing a marker within the lymph node with documented carcinoma, such that it could be localized and tested after neoadjuvant systemic therapy as an accurate reflection of the remaining lymph nodes.[41,63] The concept intuitively makes sense, as the lymph node to test would be an actual lymph node that had carcinoma before the introduction of systemic therapy. The new technique, called targeted axillary dissection (TAD), in which a radioactive seed is placed within the previously biopsy-proven positive clipped node after preoperative chemotherapy and removed along with any other SLNs, reduced the false-negative rates to about 2% in The University of Texas MD Anderson Cancer Center clinical trial.[64] Ensuring removal of the clipped lymph node seems to improve the accuracy of sentinel lymphadenectomy after preoperative chemotherapy, because approximately 25% of the time, the clipped node with documented carcinoma is not retrieved as a standard SLN, probably because of fibrosis in the lymphatics and nodes secondary to treated carcinoma.[64] Patients at MD Anderson who do not have residual nodal metastases found on TAD do not go on to full completion axillary lymph node dissection. Patients with residual nodal metastases with TAD have an approximately 50% chance of harboring additional nodal disease and undergo completion dissection or are enrolled in the Alliance for Clinical Trials in Oncology 11202 (NCT01901094), a trial with the primary aim to determine whether axillary radiation alone is not inferior to axillary lymph node dissection with radiotherapy among patients with initial documented nodal disease both before and after receipt of neoadjuvant systemic therapy.

RECONSTRUCTION IMPLICATIONS OF PMRT

General Approach to Breast Reconstruction in the Patient Needing Radiation

PMRT is used with increasing frequency in the treatment of patients with advanced breast cancer. The plastic surgeon is faced with the challenge of reconstructing a breast before

radiotherapy or sometimes in a previously radiated field. In these patients, the timing and sequence of mastectomy, reconstruction, chemotherapy, and radiation has not been clearly established. A reasonable algorithm for management of these complex patients is outlined in Fig. 2. Generally, if radiation is anticipated, immediate two-stage implant-based reconstruction is recommended. This allows for reconstruction of a usually acceptable breast mound and leaves autologous tissue as a potential salvage in the case of failure of the implant-based reconstruction. This section will outline why it is generally preferable not to do immediate autologous reconstruction and the outcomes and timing for immediate two-stage reconstruction with implants in the setting of PMRT.

AUTOLOGOUS RECONSTRUCTION AND RADIOTHERAPY

Immediate Autologous Flap Reconstruction

Immediate breast reconstruction with a flap followed by PMRT remains controversial and is usually not recommended.[65,66] This is principally the result of multiple studies that have demonstrated higher complication rates, flap fibrosis, fat necrosis, and poor aesthetic outcomes in flap reconstructions that receive radiation.[65,67,68] Although free flap reconstruction can result in high flap-survival rates, these patients frequently require additional procedures and often a second flap for salvage of the reconstruction. Although there are some proponents of immediate autologous reconstruction followed by PMRT who believe that acceptable aesthetic results are feasible,[69] this approach remains controversial, and most guidelines do not routinely recommend autologous reconstruction in patients who will definitely need PMRT.[70]

DELAYED AND DELAYED-IMMEDIATE AUTOLOGOUS FLAP RECONSTRUCTION

The most acceptable approach for the patient choosing autologous reconstruction is to perform reconstruction after the completion of mastectomy, chemotherapy, and radiation. Alternatively, a two-stage reconstruction can be performed by first placing a tissue expander underneath the mastectomy flaps and then radiating the tissue expander after early, rapid expansion. Once radiated, a flap reconstruction can be performed after a delay. This approach has been described as "delayed-immediate reconstruction" and in concept preserves more native mastectomy skin for the delayed reconstruction, potentially to the benefit of the aesthetic outcome. However, this approach does involve an additional surgical procedure. Further, it is not clear whether performing the flap reconstruction within a very short period of time after radiation therapy may actually increase the chances of perioperative complications as compared with traditional delayed autologous breast reconstruction.

ALLOPLASTIC RECONSTRUCTION AND RADIOTHERAPY

Two-stage implant-based reconstruction is the most common approach to breast reconstruction, and it is well-established that the long-term reconstructive failure rate of prosthetic reconstruction is significantly lower in nonradiated versus radiated reconstruction. The largest prospective series of immediate two-stage breast reconstruction has demonstrated that patients who undergo PMRT after implant reconstruction will lose the implant reconstruction in 9.1% of cases as compared with only 0.5% in the nonirradiated group. In addition, the high-grade capsular contracture rate is greater

FIGURE 2. Breast Reconstruction Management Algorithm When Postmastectomy Radiation Is Anticipated

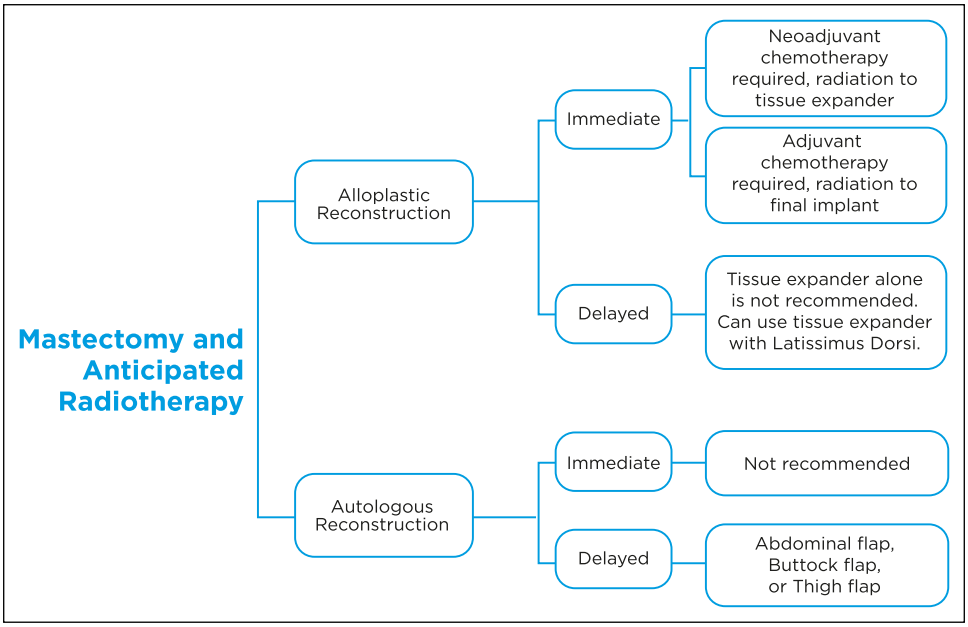
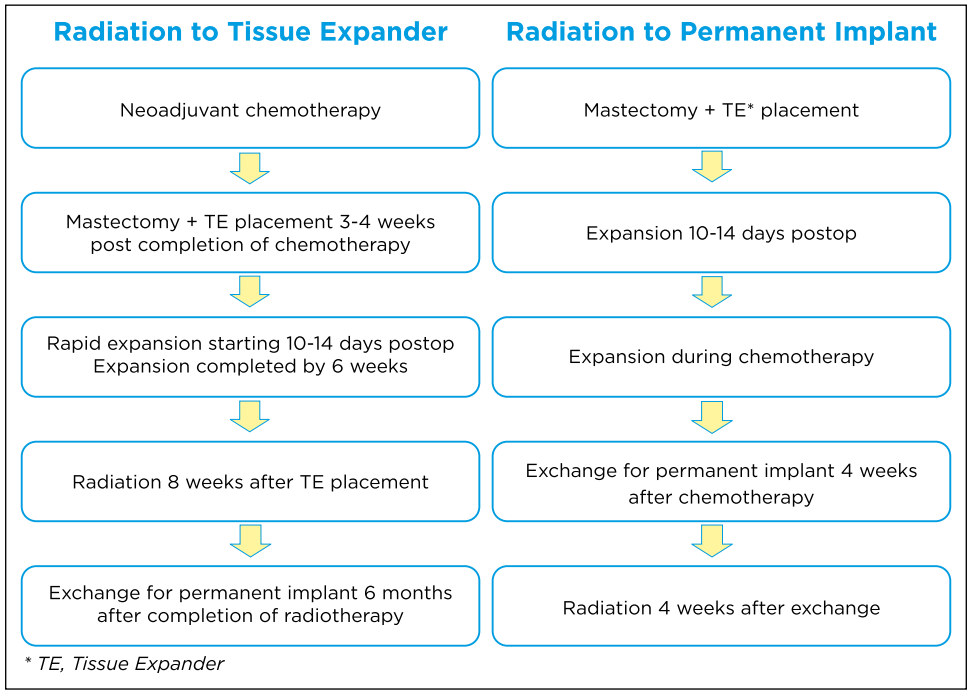


FIGURE 3. Timing and Sequence of Immediate Two-Stage Prosthetic Breast Reconstruction With Mastectomy, Chemotherapy, and Radiation



(6.9% in radiated versus 0.5% nonradiated), and the aesthetic outcomes are generally inferior in patients with radiated reconstruction.[71] It is an open question whether immediate alloplastic reconstruction is still acceptable given these inferior outcomes and more importantly whether this procedure can be timed and sequenced appropriately within the oncologic treatment scheme.

TIMING AND SEQUENCE OF IMMEDIATE RECONSTRUCTION WITH MASTECTOMY, CHEMOTHERAPY, AND RADIATION

How can the reconstructive surgeon best collaborate with the oncologic surgeon, oncologist, and radiation oncologist to provide the patient with a successfully reconstructed breast mound in the face of PMRT? Figure 3 outlines the two principal approaches with regard to the sequencing of surgery and PMRT in patients who undergo two-stage prosthetic breast reconstruction: either the expander can be exchanged for permanent implant before radiation or the tissue expander is first radiated and then exchanged for the permanent implant. There have been numerous proponents for both of these approaches, although the literature primarily consists of small, retrospective series, often without control subjects.[42]

The protocol at Memorial Sloan Kettering Cancer Center (Fig. 2) was derived primarily for patients who underwent mastectomy, adjuvant chemotherapy, and then PMRT. These patients underwent immediate reconstruction with a tissue expander at time of mastectomy, expansion during adjuvant chemotherapy, and exchange for permanent implant 4 weeks postchemotherapy. The final implant reconstruction was then radiated 4 weeks later. This timing and sequence of oncologic treatment and reconstruction is not possible in patients undergoing neoadjuvant chemotherapy followed by mastectomy followed by radiation. In patients for whom treatment follows the neoadjuvant chemotherapy to mastectomy to PMRT sequence, exchange before radiation is not feasible because of the resulting 4- to 5-month gap between chemotherapy and PMRT. Thus, the approach to these patients involves rapid expansion within 6 weeks and radiation to the tissue expander within 8 weeks postsurgery. The exchange to permanent implant is performed 6 months after completion of PMRT.

The largest prospective series that compares long-term outcomes of patients receiving prosthetic breast reconstructions with PMRT to the expander versus those receiving radiation to the permanent implant demonstrates that reconstructions undergoing radiation therapy to the tissue expander before exchange to the permanent implant have doubled the 6-year predicted failure rate (32%) of those receiving radiation after placement of the permanent implant (16%).[8] Therefore, in principle, the final implant should be radiated to minimize reconstructive failure. The data on long-term aesthetic outcomes of the two approaches are not entirely clear. Nava et al[72] found that subjective evaluations of shape and symmetry assessed by several surgeons and the patient's opinion of the final reconstruction favored radiation of the final implant. However, the data from Cordeiro et al[8] suggest that patients with radiation to the tissue expander might have slightly better aesthetic outcomes

and slightly lower capsular contracture grades than patients with radiation to the permanent implant. With either approach, one must keep in mind that it is still possible to have good-to-excellent outcomes in approximately 50% of patients.

What then is the ideal timing of reconstruction and PMRT? What is the timing of radiation to the tissue expander or to the permanent implant? For patients who have already undergone neoadjuvant chemotherapy, the decision is a priori dictated by the oncologic treatment because these patients cannot delay radiotherapy and should receive radiation to the tissue expander. In the case of patients who undergo mastectomy followed by adjuvant chemotherapy, the reconstructive surgeon is faced with the dilemma of choosing to recommend radiation therapy to the tissue expander, accepting that approach's higher rate of reconstructive failure as worthwhile given its potentially superior aesthetic result? Or should long-term viability of the reconstruction be more important than a lesser aesthetic result? The pros and cons of these options should be discussed with the patient. Perhaps the best approach is to provide the patient with the data, review her goals and expectations, and then let the patient make the final decision.

One could argue that because the overall implant survival rate, aesthetic outcomes, and capsular contracture rates are significantly worse in patients who undergo immediate prosthetic breast reconstruction in the face of PMRT, these patients should not be reconstructed and should instead undergo delayed breast reconstruction. However, patients who undergo mastectomy and PMRT alone would likely never undergo delayed two-stage prosthetic reconstruction because they cannot be expanded successfully. These patients would then be relegated to delayed reconstruction with autologous tissue. Many may not be candidates for autologous reconstruction because of age, comorbidity, or inadequate tissue at donor site; may not survive long enough to ever undergo delayed reconstruction; or may simply not be interested in further extensive, complicated operations given what they have already experienced in the course of cancer treatment. One could also argue that by providing a very simple reconstructive approach consisting of small operations and quick recoveries, most of these patients are still extremely happy to have some form of reconstructed breast and are accepting of the aesthetic tradeoff. Patient-reported outcomes data demonstrate lower satisfaction levels in those patients with radiated implant reconstructions as compared with those that are not radiated.[71] However, overall satisfaction in many patients remains high enough that it is certainly worthwhile. We therefore still strongly advocate immediate two-stage implant-based breast reconstruction in any patient who might be interested, despite the potential need for PMRT.

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Standard and Genomic Tools for Decision Support in Breast Cancer Treatment

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OVERVIEW

Over the past few decades, comprehensive characterization of the cancer genome has elucidated pathways that drive cancer and mechanisms of resistance to therapy and provided important insights for development of new therapies. These advances have resulted in the development of prognostic and predictive tools for use in clinical settings, which can assist clinicians and patients in making informed decisions about the benefits of established therapies. In early-stage breast cancer, multiparameter genomic assays are now available for decision making about the duration of adjuvant endocrine therapy and the use of adjuvant chemotherapy. Similarly, in metastatic disease, there are multiple commercially available next-generation sequencing options for identifying genetic alterations in tumors that may be targeted with a drug. Although these tools hold great promise for providing precision medicine, it can be difficult for the treating physician to evaluate their clinical utility and appropriately select tools for individual clinical situations. This review summarizes the currently available genomic tools in breast cancer, the data underlying their clinical validity and utility, and how they can be used in conjunction with standard clinicopathologic data for making adjuvant and metastatic treatment decisions.

The knowledge generated by The Cancer Genome Atlas on the genetic profile of breast and other cancers along with the development and widespread availability of sophisticated technologies for commercial testing of the cancer genome in clinical settings has led to a desire to use these tools to improve patient care and outcomes. This has catalyzed the development of a variety of prognostic and predictive tools designed to assist clinicians and patients in making informed decisions about the benefits of established therapies, as well as potentially identifying new treatment options. Although these tools hold promise for personalized care and rational molecularly based treatments, it can be difficult for the treating physician to evaluate their quality and clinical utility and select tools that are appropriate for an individual patient and/or clinical situation. This review summarizes the framework for evaluating new genomic tools in breast cancer and the data underlying their utility for making adjuvant and metastatic treatment decisions.

QUALITY OF BIOMARKERS

All biomarkers, including genomic and molecular tools, require rigorous development and evaluation prior to incorporation into clinical care.[1] According to the Evaluation of Genomic Applications in Practice and Prevention framework, biomarkers must have analytic validity, clinical validity, and clinical utility.[2] The assay for the biomarker must be accurate and reproducible. Once an assay is analytically valid, it must be shown in multiple independent cohorts to have the ability to divide a population of interest into separate groups, and it must be demonstrated that use of the biomarker adds to current clinical care in a meaningful way without introducing substantial risk to the patient. Although it would be ideal to evaluate all biomarkers in prospective trials, similar to what is done for medications, this is not practical, so the Tumor Marker Utility Grading System was developed to assess the level of evidence supporting the clinical utility of individual biomarkers,[3] which allows all potential new biomarkers to be evaluated in a standardized way.

USING MOLECULAR TOOLS TO MAKE ADJUVANT ENDOCRINE THERAPY DECISIONS

Prognostication Without Treatment

Adjuvant endocrine therapy reduces the risk of breast cancer recurrence and improves survival[4] for hormone receptor–positive (HR^+) breast cancer irrespective of age, menopausal status, involvement of axillary lymph nodes, or tumor size.[5] A variety of molecular tools, including the 21-gene recurrence score assay (Oncotype DX),[6-8] the 70-gene signature (MammaPrint),[9-11] the PAM50 risk-of-recurrence assay (Prosigna),[12] the Breast Cancer Index,[13,14] and EndoPredict,[15,16] can identify subsets of patients who are HR^+/

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TABLE 1. Summary of Available Multiparameter Genomic Assays for Decision Making in Early Breast Cancer

Name	Description	Results	References
Breast Cancer Index	HoxB13/IL17BR plus molecular-grade index	Low vs. high risk for both prognosis and prediction	13,14,17
EndoPredict	11-gene signature	Low vs. high risk	15,18,19
uPA/PAI-1 (Femtelle)	Urokinase plasminogen activator plus plasminogen activator inhibitor type 1	Low vs. high risk	20
70-gene breast cancer recurrence assay (MammaPrint)	70-gene signature	Low vs. high risk	
Mammostrat	5-gene signature	Low vs. moderate vs. high risk	
21-gene recurrence score assay (Oncotype DX)	21-gene signature	Low vs. intermediate vs. high risk	6,7,21
PAM50 risk of recurrence score (Prosigna)	46-gene signature plus 18-gene proliferation score plus tumor size	Low vs. intermediate vs. high risk	12,22,23

HER2$^-$ and have a low risk of distant recurrence (< 5% at 5 years and/or < 10% at 10 years; Table 1). However, the vast majority of patients included in these series were treated with adjuvant endocrine therapy (and some also received chemotherapy). There are less data regarding prognostic performance for patients who were untreated.

MammaPrint (70-gene signature) was initially developed from a cohort of 78 patients with lymph node–negative breast cancer who were younger than age 55 by using distant metastasis-free survival at 5 years from diagnosis to derive the "good prognosis" from "poor prognosis" 70-gene signature.[9] All patients who were distant metastasis-free at 5 years, as well as 29 of 34 patients who developed metastases, had not received adjuvant endocrine therapy or chemotherapy. A subsequent independent validation by the TRANSBIG consortium included 302 patients from six European institutions with node-negative breast cancer diagnosed between 1980 and 1998 who had not received adjuvant endocrine therapy or chemotherapy.[24] The 10-year distant metastasis-free survival in the "low-risk" 70-gene profile group approached 90%. Similarly, a subset of 198 patients with available RNA from this cohort were analyzed for a 76-gene prognostic profile,[25] independently developed by investigators at the Erasmus Cancer Center in Rotterdam, the Netherlands, with minimal gene overlap with the 70-gene profile.[26] The 10-year distant metastasis-free survival in the "good risk" 76-gene profile group was 94% in the absence of systemic therapy.[25]

The Oncotype DX assay, a 21-gene signature, was initially validated in a cohort of 668 patients with HR$^+$, node-negative breast cancer treated with adjuvant tamoxifen and no chemotherapy in NSABP B-14.[6] This trial randomly selected patients to receive 5 years of tamoxifen versus placebo. For patients in the placebo group, a low-risk recurrence score lower than 18 was associated with a 10-year distant disease-free survival of 85.9% compared with 93.1% in patients who received tamoxifen.[27]

Recent data from prospective clinical trials demonstrate excellent outcomes for patients with HR$^+$ breast cancer with "low-risk" gene-expression profiles treated with endocrine therapy alone. In the TAILORx trial, patients with HR$^+$, HER2$^-$, node-negative breast cancer with an Oncotype DX recurrence score of 10 or lower were treated with tamoxifen or an aromatase inhibitor, and their rate of 5-year freedom-from-distant recurrence was 99.3%.[7] Similarly, in the West German Study Group Plan B, trial patients with HR$^+$, HER2$^-$, breast cancer with recurrence scores of 11 or lower (including patients with 1–3 involved lymph nodes) were treated with endocrine therapy alone without chemotherapy, and their 3-year disease-free survival was 98%.[28] In the MINDACT trial, patients with HR$^+$, HER2$^-$ breast cancer with up to three positive lymph nodes who were low risk based on clinical (based upon Adjuvant! Online) and genomic (based upon MammaPrint) criteria had a 5-year distant disease-free survival of 97%.[11]

KEY POINTS

- **Numerous multiparameter genomic assays have been developed that provide prognostic information for HR$^+$, HER2$^-$, node-negative breast cancer, and a subset are also predictive of the benefit from adjuvant chemotherapy and endocrine therapy.**
- **Studies are underway examining the clinical utility of multiparameter genomic assays for determining benefit from extended adjuvant endocrine therapy.**
- **Comprehensive next-generation sequencing approaches are being developed to identify targetable lesions, and clinical tests focused on actionable mutations are currently available.**
- **Liquid biopsies, which can be used to identify circulating tumor cells and circulating tumor DNA, are less invasive, may better reflect tumor heterogeneity, and can be used to identify tumor mutations that are complementary to those found in tumor biopsies.**
- **Prospective trials using genomic tumor testing for treatment selection in the metastatic setting have not demonstrated clinical utility in improving patient outcomes. Thus, this testing is not recommended by ASCO for this purpose, although it may be useful for eligibility in investigational trials.**

These excellent outcomes raise the question of whether these patients might also fare well without endocrine treatment. Outside of well-controlled clinical trials, up to 40% of patients with early-stage HR+ breast cancer are nonadherent with tamoxifen or aromatase inhibitor therapy.[29,30] Persistence with endocrine treatment decreases over time, due in part to side effects, including vasomotor and mood symptoms, arthralgias, weight gain, and sexual dysfunction. Intriguingly, a retrospective analysis of the randomized Stockholm Tamoxifen trial (STO-3) reported a 20-year disease-specific survival rate of 94% in node-negative women who received no adjuvant systemic therapy and who had a predefined "ultra-low-risk" MammaPrint score; in the tamoxifen-treated group, the 20-year disease-specific survival was 97%.[31] Although only 15% of patients in this analysis had an ultra-low-risk MammaPrint score, molecular tools may identify a higher proportion of patients with indolent biology in the modern era of mammographic breast cancer screening.[32] However, considering the long natural history of recurrence risk for HR+ breast cancer, the generally favorable safety profile of tamoxifen and aromatase inhibitors, and the continued reduction in recurrence risk beyond the duration of endocrine treatment,[4] the current evidence is insufficient to withhold endocrine therapy based upon the results of molecular testing.

Prediction of Benefit From Endocrine Treatment

Data for prediction of endocrine treatment benefit with molecular tools are even more limited. In the NSABP B-14 trial, the greatest benefit with adjuvant tamoxifen versus placebo was observed in patients with low (< 18) and intermediate (18–30) Oncotype Dx scores compared with high (≥ 31) scores (for low scores: 10-year distant relapse-free survival [DRFS], 93.1% vs. 85.9%; p = .039; for intermediate: 10-year DRFS, 79.5% vs. 62.2%; p = .02; for high: 10-year DRFS, 70.3% vs. 68.7%; p = .82).[27] The National Cancer Institute of Canada Clinical Trials Group MA.12 trial randomly selected premenopausal women with stage I–III breast cancer of any hormonal status to receive tamoxifen versus placebo following adjuvant chemotherapy.[33] A retrospective analysis using the PAM50 assay showed a benefit in disease-free survival for tamoxifen (hazard ratio 0.52; 95% CI, 0.32–0.86) in the luminal (A + B) subtypes compared with nonluminal subtypes (hazard ratio 0.80; 95% CI, 0.50–1.29), although the interaction test was not statistically significant (p = .24).[34] There are no randomized data available for prediction of endocrine treatment benefit with other molecular tools. These data are insufficient to inform endocrine treatment decisions for patients with HR+ breast cancer identified using standardized immunohistochemistry testing methods.[35]

Data to evaluate the differential predictive benefit of one endocrine treatment approach versus another are also limited. In the TransATAC study, the prognostic value of recurrence score was compared for postmenopausal patients who were HR+ and randomly selected to receive 5 years of anastrozole versus tamoxifen using a multivariate model adjusted for tumor size, tumor grade, nodal status, and age.[8] The hazard ratios for distant recurrence per 50-point change in recurrece scores were similar in each treatment group, and tests for recurrence score × treatment interactions were not noteworthy. The TEAM trial compared 5 years of upfront exemestane versus a switch regimen of tamoxifen (2 years to 3 years) followed by exemestane (3 years to 2 years). No differential effect in DRFS prognostication was observed in patients treated with 5-year exemestane or the switch regimen according to Mammostrat score, which stratifies patients based on five immunohistochemical markers.[36]

Prognostication of Late Relapse

HR+ breast cancer has a unique natural history, with a relatively constant ongoing annual hazard of distant relapse following an initial peak within the first 5 years of diagnosis.[37,38] Recent studies demonstrate a reduction in recurrence risk with extended adjuvant endocrine therapy with tamoxifen[39,40] or an aromatase inhibitor[41-43] following 5 years of upfront tamoxifen. Data regarding the benefit of extended adjuvant endocrine therapy after 5 years of upfront aromatase inhibitor or a switch regimen of 2 year to 3 years of tamoxifen followed by 2 year to 3 years of aromatase inhibitor are conflicting.[44-47] Extended adjuvant endocrine treatment is associated with bothersome side effects and potentially serious risks, such as endometrial cancer and venous thromboembolism with tamoxifen and bone fracture and cardiovascular events with aromatase inhibitors.

A variety of molecular tools may identify patients at very low risk of late relapse more than 5 years from diagnosis who might be spared extended adjuvant endocrine treatment. In NSABP B-14, node-negative patients treated with 5 years of tamoxifen who had high *ESR1* mRNA expression and recurrence scores lower than 18 had a low risk of distant recurrence in years 5–15 (6.8%) compared with scores of 18–30 (11.2%) and scores 31 or higher (16.4%; p = .01).[48] The risk-of-recurrence score model integrates the expression profile of a subset of 46 genes from the PAM50 intrinsic subtype classifier with an 18-gene proliferation score and tumor size. In TransATAC, recurrence score and risk of recurrence were associated with relapse risk during years 5–10 from diagnosis in multivariate analysis,[49] although risk-of-recurrence scoring was a stronger prognosticator of late recurrence than recurrence scoring. A combined analysis of TransATAC and the ABCSG-8 trial found that the risks of distant relapse in years 5–10 for women with low, intermediate, and high risk-of-recurrence scores were 2.4%, 8.3%, and 16.8%, respectively.[50] For women with node-positive disease, the 5–10-year distant recurrence risk with a low risk-of-recurrence score was only 3.3%.

Likewise, a combined analysis of the ABCSG-6 and ABCSG-8 trials found that EPclin, which combines the EndoPredict score with tumor size and nodal status, was prognostic for late distant recurrence (> 5 years) in patients with HR+, HER2− breast cancer.[51] At 10 years of follow-up, the rate of distant metastasis was 1.8% for EPclin-low patients compared with 17.1% for EPclin-high patients. BCI combines the two-gene HOXB13/IL17BR ratio with the five proliferation

gene Molecular Grade Index. A cubic risk model was developed using the tamoxifen arm of the STO-3 and was found to be prognostic of late recurrence in an independent validation cohort of HR$^+$, node-negative patients.[17] Risks of distant recurrence in years 5–10 were 2.5%, 16.9%, and 15.0% for the low-, intermediate-, and high-risk cohorts, respectively. A linear risk model was also shown to prognosticate for late recurrence in TransATAC[13] and restratify low and intermediate reucrrence score groups into distant recurrence risk subsets.[52]

A recently published ASCO guideline using data available through August 2014 did not recommend any molecular tools to inform extended adjuvant endocrine therapy.[53] The review panel concluded that clinical validity for late recurrence was not shown for any individual assay in more than one study, and clinical utility had not been demonstrated. Although there are limitations of the available evidence, the consistency of highly favorable outcomes for late recurrence risk reported for “low-risk” patients across studies suggests that these molecular tools that are driven by quantification of proliferation may play an increasingly prevalent role in extended adjuvant treatment decisions.

Tools for Chemotherapy Decision Making

Clinicopathologic tools. Breast cancer is heterogeneous. At diagnosis, patients can present with breast tumors that differ by stage, histology, and pathologic characteristics. When deciding whom to treat with cytotoxic chemotherapy, providers synthesize the data for individual patients to develop a personalized treatment recommendation. In particular, treatment decisions are driven by clinical factors such as patient age and comorbidities, as well as pathologic factors such as disease stage, tumor grade, and receptor status, including estrogen receptor and progesterone receptor overexpression as well as overexpression or amplification of HER2. A number of organizations have developed guidelines for chemotherapy use in patients with stage I–III breast cancer based on these standard clinicopathologic characteristics, including the National Comprehensive Cancer Network, ASCO, and the St. Gallen International Expert Consensus Panel.[54-57]

Quantitative decision aids have been developed for use by providers making treatment recommendations. One of the first to be widely used was Adjuvant! Online (www.adjuvantonline.com), in which providers input details including age, tumor size, nodal involvement, grade, and estrogen and progesterone receptor status and receive estimates of likelihood of recurrence or mortality within 10 years based on different treatment options. The data used to develop the tool were derived from Surveillance, Epidemiology, and End Results data for estimates of prognosis as well as data from the Early Breast Cancer Trialists’ Collaborative Group meta-analysis for estimates of response to endocrine and cytotoxic chemotherapy.[58] Although useful, the tool has limitations, including lack of incorporation of HER2 status into the estimates. In addition, the site is currently offline for updating.

A second decision aide has been developed that addresses some of the limitations of Adjuvant! Online. This model, called PREDICT (www.predict.nhs.uk), is derived from a database of patients treated in the United Kingdom between 1999 and 2003 and provides survival estimates for patients based on clinicopathologic factors, including HER2, Ki67, and mode of detection of breast cancer.[59] It has been validated using a number of independent data sets.[60,61] In addition to providing 5- and 10-year survival data, the site also provides information about likelihood of benefit from second- and third-generation chemotherapy regimens as well as endocrine therapy.

Although these decision aides can be used for treatment decision making for patients with estrogen receptor–negative, progesterone receptor–negative, and HER2$^-$ breast cancer (termed "triple-negative" breast cancer), decisions regarding use of chemotherapy are primarily driven by tumor size and lymph node involvement.[54,55,57,62] Similarly for patients with HER2$^+$ disease, use of chemotherapy plus anti-HER2 therapy is recommended for most patients with tumor size greater than 5 mm and/or lymph node involvement because of the reduction in risk of recurrence with chemotherapy and the additional 40% improvement in disease-free survival from the addition of trastuzumab.[54,55] Therefore, although these decision aids can estimate prognosis for an individual patient, they are often less useful for making decisions about treatment. In contrast, for patients with HR$^+$ disease, the Adjuvant! Online and PREDICT decision aids may be more useful for informing decision making regarding treatment with chemotherapy in addition to endocrine therapy.

Multiparameter genomic assays. More recently, multiparameter genomic assays have been developed that complement standard clinicopathologic data for treatment selection (Table 1). A subset of these has been recommended for use in the most recent ASCO biomarker guidelines[53] because of demonstrated clinical utility, including Oncotype DX,[6,7,63] EndoPredict,[15,18,21] PAM50/Prosigna,[12,19,22] Breast Cancer Index,[13,14,17] and the combination of urokinase plasminogen activator and plasminogen activator inhibitor type 1.[23] Importantly, current ASCO guidelines recommend these assays for use in patients with HR$^+$, HER2$^-$, node-negative breast cancer.[53] The guidelines do not recommend use of these assays for guiding adjuvant systemic therapy decisions in patients with HR$^-$, HER2$^+$, or node-positive disease.[53] Selected assays will be discussed in more detail below; details about the other assays can be found in the provided references.

The first assay to be incorporated into routine clinical use in the United States was Oncotype DX.[6] The assay was originally developed using samples from patients with HR$^+$, node-negative breast cancer treated with tamoxifen on a randomized clinical trial. The assay analyzes the expression of 16 tumor-related genes and five housekeeping genes from formalin-fixed, paraffin-embedded tumor specimens to generate a recurrence score that corresponds with the 10-year risk of distant disease recurrence assuming 5 years of treatment with tamoxifen.

Subsequent studies using samples derived from a separate trial demonstrated that the recurrence score is also predictive of response to chemotherapy. Patients with low scores (0–17) were shown to have no benefit from adjuvant chemotherapy in addition to endocrine therapy, whereas those with high scores (31–100) were shown to benefit from chemotherapy followed by endocrine therapy.[63] For those with intermediate scores (18–30), the optimal treatment approach remains uncertain and is currently being investigated in the TailoRX clinical trial (NCT00310180). Observational studies have demonstrated that incorporation of the assay into routine clinical care has resulted in decreased use of chemotherapy for women with node-negative breast cancer.[20] In addition, data from prospective-retrospective trials have demonstrated there is similar benefit from use of Oncotype DX in patients with node-positive disease[8,64]; the prospective SWOG 1007 RxPONDER clinical trial (NCT01272037) is ongoing to provide more definitive results.

The use of a different multiparameter genomic assay, MammaPrint, for chemotherapy decision making has also been studied in a large prospective randomized trial, MINDACT.[11] MammaPrint separates patients into two categories, either good or poor prognosis. In MINDACT, the investigators evaluated patient prognosis based on both standard clinicopathologic factors using Adjuvant! Online and genomic factors using MammaPrint. Those patients who were discordant, with high clinical risk but low genomic risk, were randomly selected to receive chemotherapy or not, in additional to endocrine therapy. The 5-year rate of survival without distant metastases in those patients who did not receive chemotherapy was 94.7% (CI, 92.5% to 96.2%), which met the criteria for success in this trial. They concluded that those patients at low genomic risk of recurrence might not require chemotherapy, despite being at high risk based on standard clinicopathologic factors. Of note, the results of this trial were published after the development of the most recent ASCO biomarker guidelines.[53,65]

In summary, multiparameter gene expression assays complement standard pathologic factors and provide additional information to support treatment decision making. The primary use of multiparameter assays, therefore, is to inform the decision about adjuvant systemic therapy in situations in which chemotherapy in being considered. For patients who definitely will or will not be receiving chemotherapy based on standard clinicopathologic factors, including comorbidities and patient preferences, testing is unnecessary because it will not alter the planned treatment. Additional high levels of evidence data are forthcoming regarding use of these assays in other patient populations, including those with node-positive disease.

THE ROLE OF GENOMIC TESTING IN THE METASTATIC SETTING

Breast cancer is the second leading cause of cancer death in women.[66] Approximately 30% of women diagnosed with the disease will ultimately recur, and over 40,000 women die annually of metastatic breast cancer.[66] Standard treatment is guided by expression of HR or HER2, with sequential endocrine therapies initially in most HR^+ disease, chronic anti-HER2 therapy (with or without chemotherapy) in $HER2^+$ disease, and sequential chemotherapy in triple-negative and endocrine-resistant disease.[67] Development of resistance is universal, and patients are in a continual state of alternating disease control and progression.

Receptor expression and genetic changes can differ between a breast primary and metastases,[68] as tumors continue to evolve both stochastically and in response to treatment. Several meta-analyses[69] have documented that pooled estimates for the absolute frequency in changes from positive to negative ranged from 5.7% to 9.5% for estrogen receptor status and 17% to 24% for progesterone receptor status, whereas ranges for changes from negative to positive ranged from 3% to 8.8% and 6.9% to 7.3% for estrogen receptor and progesterone receptor, respectively. The overall rate of absolute change in HER2 status (in either direction) was approximately 6%, and some studies have demonstrated that discordance is associated with shorter survival.[70-72] Next-generation sequencing (NGS) technologies have led to the development of numerous commercial assays that can detect genomic variability both within tumors and in the circulation through the identification of intact circulating tumor cells (CTCs) and shed tumor DNA (patient tumor DNA [ptDNA]). A number of studies have reported on the spectrum of mutations identified by massively parallel sequencing in primary and metastatic breast cancer,[73-76] and similar recurrent genomic alterations have been identified both in tumor and blood.[77-81] Although these data have the potential to improve prognostication, expand therapeutic targets,[82-85] or enable tracking of therapeutic response,[86] evidence supporting the clinical utility of either tumor- or blood-based genomic assays for these purposes is scant.

Available Tools for Genomic Testing of Metastatic Disease

Approaches to evaluating the spectrum of genetic mutations or other alterations, such as copy number changes, generally use NGS approaches to enable simultaneous evaluation of many genes, with commercial and proprietary panels in widespread use. This requires tumor biopsy, which can be difficult or risky depending on the location of disease, limits the amount of tissue that can be obtained, and may not be representative of the entire tumor because of tumor heterogeneity. Technologies underlying these panels use whole-exome sequencing on paraffin-embedded tumor specimens and bioinformatics approaches to identify driver mutations, mutational hot spots, and those that are actionable—that is, for which there are potentially effective targeted therapies. Those approved for use in making treatment decisions must be done in a Clinical Laboratory Improvement Amendments–certified laboratory, meeting requirements for clinical and analytic validity. Platforms can vary substantially in sensitivity, specificity, and the spectrum of mutations that can be detected, and there are biologic

challenges to identifying true drivers in this context of tremendous biologic heterogeneity.[87] In addition to identifying mutations, amplifications in many genes are also biologically important, and thus, copy-number changes are typically included in these tests.

Concurrently, technologies have developed to measure circulating markers of tumor burden, including CTCs and tumor-derived DNA. These technologies are appealing as a way to provide a liquid biopsy from the blood, obviating the difficulties in procuring surgical tumor specimens. However, these technologies also differ in sensitivity and specificity, require specific blood processing and storage protocols, and, in the case of CTCs, require immediate processing. CTCs can measure tumor burden and be profiles for surface receptors, including estrogen receptor, progesterone receptor, and HER2. ptDNA can detect specific mutations but with the same limitations as tumor NGS. Prior studies of concordance between tumor and ptDNA in breast cancer have been mainly restricted to analysis of pathogenic mutations, demonstrating concordance rates above 70%[88-90] when the same platform is used. In addition, as shown in a prospective study of 32 patients comparing NGS data sets from three distinct patient-matched samples types (formalin-fixed, paraffin-embedded and CTC-DNA ptDNA) using common amplicon-based resequencing panels, CTC-DNA and ptDNA evaluation yielded complementary molecular information from the same blood sample.[85,91] However, in clinical practice, the need for rapid turnaround times for clinical decision making and differences in commercial platforms can lead to lack of concordance between tumor and blood due to purely technical reasons, such as differences in test coverage of genes, laboratory variant reporting practices, variant classification, and allele frequency thresholds for detection based on total sequencing depth. Consideration of these limitations is are extremely important for practicing oncologists when ordering and interpreting the results of such tests to avoid erroneous conclusions about potential therapeutic targets or the gain or loss of specific mutations or overall changes in mutational burden under the pressure of therapy.

Current Knowledge of the Unique Biology of Metastatic Disease

The development of massively parallel sequencing technologies such as NGS has led to a proliferation of studies that have characterized primary tumors and enable comparison of metastatic breast tumors to matched primaries. The Cancer Genome Atlas characterized the genomic landscape of early breast cancer, demonstrating that approximately one-third of tumors have *TP53* or *PIK3CA* mutations, and up to 20% have amplifications in *ERBB2*, *FGFR1*, and *CCND1*.[73] Studies taking a broad approach with NGS have demonstrated that whole-exome or whole-genome sequencing uncovers discordant, novel mutations in both primaries and matched metastases.[79,92-94] Studies using comparative genomic hybridization to detect copy number changes between matched primary and distant metastases have been contradictory, with some but not all studies finding increased copy number changes in metastases compared with primaries.[95-97] The largest metastatic profiling study to date, examining 216 metastatic breast tumors/blood pairs compared with 712 TCGA primary tumors as reference, found that 12 genes (*TP53*, *PIK3CA*, *GATA3*, *ESR1*, *MAP3K1*, *CDH1*, *AKT1*, *MAP2K4*, *RB1*, *PTEN*, *CBFB*, and *CDKN2A*) were identified as significantly mutated in metastatic breast cancer (false discovery rate < 0.1). Eight genes (*ESR1*, *FSIP2*, *FRAS1, OSBPL3*, *EDC4*, *PALB2*, *IGFN1*, and *AGRN*) were more frequently mutated in metastatic breast cancer as compared with early-stage breast cancer (false discovery rate < 0.01). *ESR1* was identified both as a driver and as a metastatic gene (n = 22; odds ratio 29; 95% CI, 9–155; p = 1.2e-12) and also presented with focal amplification (n = 9) for a total of 31 metastatic breast cancers with either *ESR1* mutation or amplification, including 27 HR^+ and $HER2^-$ metastatic breast cancers (19%). $HR^+/HER2^-$ metastatic breast cancers presented a high prevalence of mutations in genes located in the mTOR pathway (*TSC1* and *TSC2*) as compared with $HR^+/HER2^-$ early-stage breast cancer (6% and 0.7%, respectively; p = .0004). Other actionable genes were more frequently mutated in HR^+ metastatic breast cancer, including *ERBB4* (n = 8), *NOTCH3* (n = 7), and *ALK* (n = 7). Analysis of mutational signatures revealed a notable increase in APOBEC-mediated mutagenesis in $HR^+/HER2^-$ metastatic tumors as compared with primary TCGA samples (p < 2e-16). These data and others that are emerging paint a picture of the enormous genetic heterogeneity of metastatic breast cancer.

Clinical Utility of Genomic Testing for Patient and Treatment Selection in Metastatic Trials and Practice

Despite advances in technology and our understanding of metastatic tumor biology as well as the proliferation of clinical and commercial tools to perform genomic assessment of tumor genomics and ptDNA, the clinical utility of these tests has not yet been established in metastatic breast cancer. Clinical utility of a genomic test in this context is defined as the identification of targetable alterations (those causing perturbations in proteins, pathways, or both that can be specifically intercepted pharmacologically[98]) with the use of such agents leading to a favorable outcome over standard of care. As stated earlier, high-level evidence supporting the use of such tools in clinical practice relies on prospective studies designed and powered for clinically meaningful outcomes.

Only one trial to date, the SAFIR trial,[77] has prospectively profiled metastatic breast tumors and assessed treatment responses based upon genomically guided decision making. This trial, conducted in 18 centers in France, enrolled 423 patients with biopsy-accessible tumors. Biopsy samples from 407 patients underwent comparative genomic hybridization, genome-wide single nucleotide polymorphism array, and Sanger sequencing of *PIK3CA* (exons 10 and 21) and *AKT1* (exon 4). The primary outcome was the proportion of patients for whom genomic analysis identified a targeted therapy, with a goal of achieving a 30% or higher success

rate. Overall, 46% of patients were found to have actionable mutations, and therapy could be personalized in 13%. Of the 43 assessable patients, 9% had partial response to therapy, and 21% had stable disease for at least 16 weeks. Although these results are promising and demonstrate feasibility, they do not provide evidence that using this approach is superior to use of estrogen receptor, progesterone receptor, or HER2 overexpression for clinical decision making.

Similar multidisease trials are either completed or underway. To date, results are mixed, and it is too early to define a role for testing specifically in breast cancer. However, there are hints that such an approach could have traction. In the MOSCATO trial,[99] patients were used as their own control subjects. The progression-free survival (PFS) from the most recent therapy on which the patient had just experienced progression before enrollment in MOSCATO was compared with the PFS observed under the targeted therapy selected within the MOSCATO trial based upon molecular genomic testing of the patient's tumor, which was selected from over 60 phase I trials at the study center. A total of 33% of patients treated within the MOSCATO trial had an improved outcome, defined as at least a 30% increase in their PFS with the targeted therapy as compared with their baseline reference PFS. Moreover, 62% of the patients had an objective response or stable disease. The SHIVA trial[100] took a slightly different approach. This was an open-label, randomized, controlled phase II trial that included adult patients with any metastatic solid tumor refractory to standard of care, provided they had good performance status, disease that was accessible for a biopsy or resection of a metastatic site, and at least one measurable lesion. The molecular profile of each patient's tumor was established with large-scale genomic testing, and the trial enrolled only patients for whom a molecular alteration was identified within one of three molecular pathways (HR, phosphoinositide 3-kinase/AKT/mTOR, and RAF/mitogen-activated protein kinase kinase), which could be matched to 1 of 10 regimens, including 11 available molecularly targeted agents. Patients were randomly assigned (1:1) to receive a matched molecularly targeted agent (experimental group) or treatment of the physician's choice (control group). This trial was not limited to breast cancer, although patients with breast cancer constituted 20% of the study population, and patients with tumor alterations that matched a standard-of-care therapy (such as tamoxifen for HR^+ disease) were not included in the analytical group. With 11.3 months of follow-up, there was no considerable difference in PFS between those who received a matched therapy and those who received physician's choice (hazard ratio 0.88; 95% CI, 0.65–1.19; p = .41) nor were the findings noteworthy within each of the specific types of alterations. The small size of the subset of patients with breast cancer precluded analysis for that group specifically. Similar trials, including MATCH,[101] SAFIR02, and TAPUR, are ongoing and enrolling patients with breast cancer.

Given the current state of evidence on the biology of breast cancer metastases and the lack of definitive utility of genomic testing tools for treatment selection, ASCO guidelines[102] currently recommend using ER, PR, and HER2 status of the metastatic tumor for treatment selection and support biopsy of metastatic sites for this purpose. The panel considered any use of NGS testing to be investigational and does not recommend the use of this testing to initiate systemic therapy or direct selection of new therapy outside a research setting.

FUTURE DIRECTIONS

In the past decade, there have been considerable advances in the development of genomic assays and incorporation of these tools into routine clinical care, primarily for chemotherapy decision-making. Increasingly, there are also data evaluating use of these same assays for making decisions about extended adjuvant endocrine therapy, although use of these tools has not yet been incorporated into treatment guidelines. In the arena of metastatic breast cancer, comprehensive genomic analysis of metastatic lesions is being intensively studied to determine if the identified changes have sufficient clinical utility to guide treatment. Continued technological advances will lead to more comprehensive findings from both tumors and liquid biopsies, at lower cost. Results of studies examining the impact of this knowledge on disease outcomes, and the clinical utility of these results for guiding patient care, are eagerly awaited.

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Therapeutic Bone-Modifying Agents in the Nonmetastatic Breast Cancer Setting: The Controversy and a Value Assessment

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OVERVIEW

Clinical trials and meta-analyses investigating bisphosphonates as an adjuvant breast cancer therapy have shown a consistent trend, with postmenopausal women and women receiving ovarian suppression with gonadotropin-releasing hormone therapy gaining improved breast cancer outcomes with the use of adjuvant bisphosphonate therapy. The interpretation of these data is controversial, because the primary endpoints of the majority of adjuvant bisphosphonate studies have been negative. Pros and cons as well as the value of adjuvant bisphosphonate therapy are discussed here.

Despite notable recent advances in therapy, breast cancer remains one of the leading causes of cancer deaths among women worldwide. Adjuvant endocrine therapy is the state-of-the-art adjuvant treatment for all patients with estrogen receptor–positive early-stage breast cancer. For postmenopausal patients, aromatase inhibitors have been identified as one standard of care for this endocrine treatment, owing to their superior efficacy compared with tamoxifen, as demonstrated in several large clinical trials.[1-8] The main side effect of aromatase inhibitors is their ability to compromise bone health,[9-11] based on the (oncologically intended) reduction of estradiol levels.[12] Thus, the concomitant use of bone-targeted agents has been extensively investigated to protect patients from these side effects and to prevent treatment-induced bone loss and fractures.[13]

Several trials using antiresorptive agents such as bisphosphonates have demonstrated that treatment-induced bone loss can be successfully prevented.[13-21] It remains controversial whether these successful interventions actually lead to a notable reduction in the incidence of fractures. More recently, the anti–receptor activator of nuclear factor kappa-B ligand denosumab was shown to dramatically reduce fractures in a pivotal phase III trial. As a result, most clinical practice guidelines recommend monitoring of bone mineral density, as well as treatment with bisphosphonates or denosumab.[22]

In addition to their ability to protect and restore bone health for patients with early breast cancer, antiresorptive drugs have also been investigated for their oncologic benefits as adjuvant therapy. This was based on their antineoplastic potential, which was well described in preclinical in vitro and in vivo studies, as well as on putative indirect effects of antiresorptive therapies on the bone microenvironment.[23]

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THE CASE FOR USING BONE-MODIFYING AGENTS AS ROUTINE ADJUVANT THERAPY

Early Studies

More than 2 decades ago, several trials investigated the adjuvant effects of the first-generation bisphosphonate clodronate. In a pivotal German trial,[24] 302 patients were selected because of the presence of disseminated tumor cells (DTCs) in their bone marrow and they were randomly assigned to receive oral clodronate or not. Early results from this trial demonstrated significant improvements in disease-free survival (DFS; 87% vs. 71% at 3 years; $p < .0001$) and even overall survival (96% vs. 85%; $p = .0001$); however, later updates did not confirm these findings. In addition, the Royal Marsden trial examining 2 years of clodronate treatment versus placebo yielded notable outcome improvements (HR at 5

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years, 0.69).[25] A third adjuvant clodronate trial not only failed to confirm these promising results, but it even reported a detrimental effect of adjuvant clodronate on outcomes (i.e., increasing nonbone metastases).[26] As a result of these controversial trial results, oral bisphosphonates never became accepted as a standard of care.

More Recent Studies With Oral Bisphosphonates

Oral bisphosphonates were also studied in more recent larger trials. NSABP B-34 is a randomized, double-blind, placebo-controlled study among more than 3,300 patients with breast cancer. Patients were stratified by age, axillary nodal status, and hormone receptor status and were randomly assigned to either 1,600 mg of oral clodronate per day for 3 years or placebo. After a median follow-up of almost 8 years, overall DFS did not differ between the groups (hazard ratio [HR], 0.91); however, a beneficial effect was observed for postmenopausal patients (see below).[27] This was also seen in the GAIN study, a multicenter, open-label, randomized controlled phase III trial that recruited more than 3,000 patients to investigate the adjuvant effect of ibandronate in node-positive early breast cancer. Patients were randomized in a 2:1 ratio to either 50 mg of ibandronate per day or placebo for 2 years. Again, the overall results of this trial were negative: oral ibandronate did not improve outcomes of patients but there was a positive trend for DFS in the postmenopausal subgroup,[28] fueling the discussion about differential effects of adjuvant bisphosphonates according to menopausal status.

Adjuvant Studies With Intravenous Aminobisphosphonates

Most adjuvant bisphosphonate studies have used zoledronic acid, the most potent bisphosphonate. With respect to DTCs, smaller studies among women with high-risk early breast cancer have reported that monthly zoledronic acid in addition to treatment with cytotoxic anticancer therapy can effectively increase DTC clearance and can reduce DTC numbers and persistence in bone marrow compared with standard therapy alone.[29-31] These bisphosphonate-mediated decreases in DTC have been suggested as a potential mechanism underlying the observed clinical benefits in the large adjuvant studies.

In the ABCSG-12 trial, anticancer effects with zoledronic acid were seen both in and outside bone. When patients who received zoledronic acid were compared with those who did not, improved DFS and fewer locoregional, visceral, and nonvisceral recurrences were observed.[32] After longer-term follow-up (median 76 months), a persistent benefit in DFS more than 3 years after completion of treatment suggests a sustained "carryover" benefit from adding zoledronic acid to endocrine therapy.[33] In addition, zoledronic acid also produced a significantly improved overall survival (HR, 0.59; p = .042). Further analyses on the mature dataset from ABCSG-12 revealed a significant difference in zoledronic acid treatment effects based on patient age at enrollment[33]: although no significant decrease was observed in women age 40 or younger, zoledronic acid produced a 42% reduction in the risk of DFS events among premenopausal women older than age 40 at study entry (HR, 0.58; p = .003). In addition, zoledronic acid was associated with a strong trend toward a 43% reduction in the risk of death for this older subset of patients (HR, 0.57; p = .057).

These results were supported by two adjuvant zoledronic acid trials (ZO-FAST and Z-FAST) among postmenopausal women, in which DFS was a secondary end point. In ZO-FAST,[34] the zoledronic acid group showed a significant DFS improvement of 41% (HR, 0.588; log-rank p = .0314) after a median follow-up of 3 years. The sibling study, Z-FAST,[35] showed similar results, in which zoledronic acid yielded reduced disease recurrence at 61 months of follow-up.

In the AZURE trial, however, the addition of zoledronic acid to standard adjuvant breast cancer therapy did not significantly increase DFS compared with the overall population.[36] Notably, a differential effect of the bisphosphonate was observed with respect to menopausal status of trial patients. There was no difference in DFS with zoledronic acid among pre- or perimenopausal patients; however, among patients who were postmenopausal for at least 5 years before study entry, zoledronic acid significantly reduced the risk of DFS events by 24% (p = .02) and the risk of death by 29% (p = .017).[37]

Thus, the indirect metastasis-preventing effect of bisphosphonates is confined to postmenopausal women and to premenopausal women who receive ovarian function suppression, but not younger patients without ovarian function suppression. This suggests that estrogen effects on the bone microenvironment play a substantial role in determining who may benefit most from adjuvant bisphosphonate therapy.[38]

Eventually, the large Early Breast Cancer Trialists Collaborative Group meta-analysis confirmed this by assembling patient-level data on the majority of patients included in any

KEY POINTS

- **Adjuvant breast cancer systemic therapy is given with curative intent.**
- **Data are evolving to suggest that the adjuvant use of a bone-modifying agent (bisphosphonate or denosumab) may have anti–breast cancer effects for postmenopausal women (or women receiving ovarian-suppressing therapy).**
- **The primary endpoints of the majority of adjuvant bisphosphonate studies to date have been negative, with the positive anticancer findings identified through subset analyses.**
- **Controversy exists over whether the existing data are sufficient to influence adjuvant breast cancer treatment recommendations.**
- **The value of adjuvant bone-modifying agents for adjuvant breast cancer care will be discussed, taking into account the clinical benefit and toxicity of these agents and their cost.**

adjuvant clinical bisphosphonate trial. Based on data from almost 19,000 patients, the results of this meta-analysis were clearly positive: bisphosphonates were demonstrated to have a positive effect on the recurrence of bone metastasis and overall survival for postmenopausal patients with breast cancer.[39] It is important to note that outcome benefits appear to be confined to patients who are postmenopausal (either naturally or therapy induced) at diagnosis; clinically important benefits were seen for these women, with improvements in overall breast cancer recurrence, distant recurrence at any site, bone recurrence, and breast cancer-specific mortality (relative risk of 0.86, 0.82, 0.72, and 0.82, respectively).

DFS Results of Adjuvant Denosumab

In an early and premature analysis of the ABCSG-18 data,[40] adjuvant denosumab appears to yield DFS benefits that are similar to what was observed in the bisphosphonate meta-analysis. Further follow-up of this trial as well as the results of the large D-CARE trial are expected for 2018 and will clarify the outcome effects of adjuvant denosumab.

RESERVATIONS ON THE USE OF BONE-MODIFYING AGENTS AS ANTICANCER THERAPY IN THE NONMETASTATIC SETTING

Adjuvant breast cancer studies investigating bone-modifying agents with a bisphosphonate or denosumab have been reported, and additional studies are ongoing.[41] The majority of reported studies have identified a positive effect of the bone-modifying agent in secondary or exploratory analyses. The anticancer benefits are particular to postmenopausal women. For the purposes of this discussion, the term "postmenopausal" applies to women who are clinically not pre- or perimenopausal and includes women receiving ovarian suppression with gonadotropin-releasing hormone therapy.

The fundamentals of bisphosphonate pharmacology are known, including absorption, distribution, elimination, pharmacokinetics, and pharmacodynamics and the impact that structural alterations to the bisphosphonate chemical structure have on potency.[42] Bisphosphonates enter the osteoclast by endocytosis. Nitrogen-containing bisphosphonates, such as zoledronic acid and ibandronate, inhibit farnesyl pyrophosphate synthase and prevent the prenylation of small guanosine 5′-triphosphatase proteins essential for the function and survival of osteoclasts. The non–nitrogen-containing bisphosphonates, such as clodronate, are incorporated into adenosine 5′-triphosphate analogs in the osteoclast and promote apoptosis.[42]

Bisphosphonates may have direct or indirect antitumor effects within the bone and may impact tissues outside of the skeleton. There are data suggesting that bisphosphonates alter tumor behavior; affect host or tumor vasculature, the tumor microenvironment, and its associated immune cells, fibroblasts, stromal cells, and macrophages; and effect circulating factors.[43,44] It is not known whether any, or which, of these properties are related to the potential anticancer effects seen with adjuvant bisphosphonate therapy for postmenopausal women with breast cancer.

Incorporating an adjuvant bone-modifying agent into the care plan of postmenopausal women may reduce the risk of osteoporosis, osteoporotic fractures, and possibly the risk of breast cancer outcomes. The risk of serious toxicities affecting the gastrointestinal tract, renal system, osteonecrosis of the jaw, and atypical fractures appears to be lower than the potential benefits in anticancer outcomes. Yet the use of adjuvant bisphosphonates for postmenopausal women with early-stage breast cancer does not appear to be uniformly embraced by clinicians, patients, or health care payers. Indeed, the Canadian Bone and the Oncologist New Updates meeting debated "are adjuvant bisphosphonates now standard of care in early stage breast cancer" and the majority of the meeting attendees voted "no."[45]

Ten potential reasons to hesitate before adopting adjuvant bisphosphonates in the care of postmenopausal women with breast cancer are outlined here.

1. The adjuvant bisphosphonate clinical trials were not designed to test the hypothesis that there would be an effect in postmenopausal women that differs from pre- and perimenopausal women.
2. Meta-analyses do not substitute for well-designed, randomized clinical trials testing an a priori hypothesis.
3. Confidence in the data and the durability of the anticancer findings may be questioned. First, ZO-FAST and Z-FAST are "twin" studies in which zoledronic acid was used up front or in a delayed manner for postmenopausal women receiving an adjuvant aromatase inhibitor.[46] These parallel studies do not report the same cancer outcomes at 5 years. ZO-FAST reports improved DFS with the use of immediate use of zoledronic acid (HR, 0.66; 95% CI, 0.44–0.97; p = .0375), and Z-FAST does not have statistical significance for disease recurrence or death between the arms.[34,47] Second, the long-term follow-up of ABCSG-12 does not show retained statistical improvement in DFS.[48] The long-term follow-up of AZURE does not show maintained statistical significance for improved overall survival with use of zoledronic acid for participants who were more than 5 years since menopause.[37]
4. No proven mechanism to explain the different cancer outcomes among pre-, peri-, and postmenopausal women has been identified.
5. For postmenopausal women, adjuvant bisphosphonates appear to affect the risk of bone metastases. Estrogen receptor–positive breast cancers are more likely to metastasize to bone than estrogen receptor–negative, progesterone receptor–negative, and HER2-negative (triple-negative) breast cancers.[49] Yet tumor characteristics (i.e., estrogen receptor status) did not correlate with benefit from adjuvant bisphosphonate use.
6. Patient selection factors that may be used in the decision to treat with adjuvant bone-modifying therapy are not refined. The use of adjuvant bisphosphonate

therapy for all postmenopausal women with a risk of breast cancer recurrence seems indiscriminate.

7. If the decision is made to use an adjuvant bone-modifying agent, the data do not provide clarity on the optimal time to start an adjuvant bone-modifying agent or on the drug selection, dose, dosing interval, or duration of therapy.
8. If there are challenges in tolerating adjuvant therapy, it is not known whether the bone-modifying agent should be discontinued or perhaps changed to an alternative drug and/or dosing schedule.
9. Polypharmacy can negatively influence compliance with, adherence to, and persistence of medication use. These factors must be investigated as related to adjuvant bone-modifying therapy.
10. The value of using an adjuvant bone-modifying agent and the financial toxicities to the patient and the health care system have not been prospectively defined.

In summary, confidence in the data is undermined by the limited hypothesis testing and the absence of a proven biologic mechanism to account for the reported anticancer outcomes among postmenopausal women treated with adjuvant bisphosphonate therapy. This is complicated by challenges in identifying which postmenopausal women to treat and an optimal treatment regimen. Guiding principles in medical care address having an understanding of the drug to be used, its mode of action, the risk-benefit profile for the patient to be treated, the dosage to be prescribed, the dosing interval to be used, the duration of therapy, and the toxicity profile (which may include financial toxicities) prior to prescribing a medication. Today, there remains uncertainty on many of these key factors. Additional data are needed to optimally understand the utility of adjuvant bone-modifying agents and to identify those patients most likely to benefit from therapy.

BISPHOSPHONATES AS ADJUVANT THERAPY FOR EARLY BREAST CANCER: A VALUE ASSESSMENT

The value associated with the use of bisphosphonates as adjunctive therapy for early breast cancer is controversial. Administration of bisphosphonates has two plausible goals: one is to abrogate bone loss (particularly when using aromatase inhibitors) and the other relates to potential beneficial effects on disease recurrence, as well as mortality, for postmenopausal women. Multiple studies have addressed this question, yet controversy remains. The following remarks attempt to view the question of the utility of these agents in the context of the value framework developed by ASCO.

ASCO's Value in Cancer Care Task Force has been committed to identifying approaches that support the highest quality of cancer care, while bending the cost curve downward. The basic assumption is that provision of high-quality cancer prevention and treatment practices at the lowest reasonable cost is the embodiment of high-value care. Examples of the initiatives the ASCO task force has undertaken thus far include participation in the "Choosing Wisely" campaign of the American Board of Internal Medicine Foundation and *Consumer Reports*.[50,51] Ten commonly used practices in medical oncology were identified on the basis of there being no evidence that they add clinical value but do have high associated costs. These included unnecessary imaging, unnecessary staging in early cases of breast and prostate cancer, proper use of cytokines and high-quality end-of-life care that shifts from cancer-directed to symptom-directed treatment,[50,51] and the development of a model system with which to assess the value of antineoplastic therapies.[52,53] ASCO's model framework enables assessment of the incremental benefit associated with a new drug or regimen when compared in a prospective randomized clinical trial. The original intent of the framework was to provide physicians and patients with a rapidly accessible, easily comprehensible way of viewing comparative options for management of a specific cancer, as well as to demonstrate the cost associated with administering the therapies both from the perspective of societal and out-of-pocket costs to the patient. The latter have been a steadily growing burden, frequently resulting in emotional stress, physical symptoms, personal bankruptcy, and possibly earlier mortality.[52,53] The use of tools such as this and other frameworks is another area that is receiving substantial attention from the payer community.

The ASCO Value Assessment Framework[54,55] measures the incremental clinical impact (termed the net health benefit [NHB]) of a new therapy compared with a control treatment when these have been evaluated in a prospective randomized trial. The framework includes several parameters, each of which is assigned a maximum point score that reflects the difference between the arms in a trial. Two distinct frameworks have been developed, one for advanced disease and the other for the potentially curative setting. The elements within the framework are as follows:

1. Clinical benefit: the maximum score is 100 when comparing magnitude of difference of the test regimen and its control.
2. Toxicity: a maximum of 20 points can be added or subtracted from the clinical benefit score depending on the relative toxicity or lack thereof of the new therapy compared with the comparator.
3. Bonus points: these are awarded for specific milestones reached such as improved symptom control in advanced disease.
4. NHB: the NHB represents the sum of clinical benefit and bonus scores from which is subtracted (or added) the toxicity score.
5. Cost for adjuvant regimens or the total cost (based on average sale price of the control and test regimens): the cost of the new regimen is not factored into a final value assessment but is represented in parallel with the clinical benefit. The goal is to promote discussion between physician and patient about the clinical impact of a therapy and whether the extent of benefit is justified by the financial cost to the patient and family unit.

The Early Breast Cancer Trialists Collaborative Group performed a meta-analysis of all prospective randomized trials and concluded that "some years of adjuvant bisphosphonate treatment can reduce breast cancer recurrence rates in bone and improve breast cancer survival, but have provided clear evidence of benefit only in women who are postmenopausal (natural or induced) at the time bisphosphonates are started."[39] The European Society of Medical Oncology has evaluated the aggregated data from a large number of clinical trials and has published guidelines that support the use of adjuvant bisphosphonates as part of the systemic treatment of early-stage breast cancer for postmenopausal women, whether they are postmenopausal through a natural menopause or as a result of ovarian suppression.[41]

The value assessment of adjuvant bisphosphonate is based on a subset of 11,767 postmenopausal women included in the meta-analysis of trials comparing bisphosphonate use versus no bisphosphonate use in early breast cancer. The included studies used durations of bisphosphonate treatment varying between 2 and 5 years, with no conclusion as to the optimal period of treatment.

The meta-analysis demonstrated an 18% reduction in the risk of breast cancer mortality at 10 years among postmenopausal women who took a bisphosphonate compared with those treated with placebo. In absolute terms, the advantage is quite small (3.3%). When using the ASCO value framework, this difference in outcome yields a clinical benefit score of 18 points (of a possible 100). Most studies of bisphosphonates registered small increases in toxicity. Were there no toxicity, the ASCO framework would yield no added or subtracted points. Because the toxicities were generally few and mild, for the purposes of this analysis, the clinical benefit will be reduced by 5%, thereby subtracting 1 from the clinical benefit score to yield an NHB of 17. To place this in perspective, in the study comparing ibrutinib to chlorambucil as first-line therapy for chronic lymphocytic leukemia, the NHB score was 77 based upon a reduction in risk of death of 84%. In a comparison between chemotherapy (doxorubicin, cyclophosphamide, and paclitaxel vs. the same agents plus trastuzumab), the NHB score in favor of the trastuzumab-containing regimen was 47. The cost of the adjuvant endocrine therapy plus bisphosphonate will be presented in parallel with the NHB calculations. Comparisons with clinical trials in which the lest agent yielded a larger NHB will be shared to demonstrate the range of possible outcomes in the value analysis.

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CANCER PREVENTION, HEREDITARY GENETICS, AND EPIDEMIOLOGY

European/U.S. Comparison and Contrasts in Ovarian Cancer Screening and Prevention in a High-Risk Population

Marian J. Mourits, MD, PhD, and G. H. de Bock, PhD

OVERVIEW

The history of screening and prevention of ovarian cancer among high-risk women in the United States and Europe is one of mutual inspiration, with researchers learning from each others' findings and insights and collaborating with investigators from both sides of the Atlantic ocean. Examples of simultaneous and joint development of knowledge and scientific points of view include the paradigm shift from ovarian to fallopian tube high-grade serous cancer and the cessation of simultaneous adoption of ovarian cancer screening by clinicians in both the United States and Europe. Examples of joint efforts with fruitful results include international collaboration in large population-based, genome-wide association studies and in epidemiologic database studies. Research in the field of hereditary ovarian cancer is a great example of mutual inspiration and joint efforts for the purpose of improving knowledge and health care for women with hereditary ovarian cancer.

Ovarian cancer is the most lethal of all gynecologic cancers. The poor prognosis of ovarian cancer is largely attributable to the fact that patients with the disease present late. Although the symptom index for ovarian cancer may help to identify women with the disease, symptoms are not early signs, and most women are diagnosed at an advanced stage.[1,2]

Once the malignancy is detected, usually when classified at International Federation of Gynecology and Obstetrics stages III to IV, standard treatment consists of a combination of debulking surgery and chemotherapy, and survival rates have shown little improvement.[3] Over the last decade, it became clear that ovarian cancer is not a single disease; different histologic subtypes of epithelial ovarian cancer with different molecular pathogeneses and prognoses can be identified.[4] This knowledge will guide future research initiatives to improve early detection of and prognosis for epithelial ovarian cancer.[5]

OVARIAN CANCER SCREENING

Although ovarian cancer screening cannot prevent cancer, it was long hoped that screening might permit detection at an early stage when a cure is possible. Data from general population screening were disappointing; therefore, a large, more sophisticated screening study began in the 1990s in the United Kingdom.[6] Postmenopausal women age 45 or older were randomly assigned to a screening or control group. Women randomly assigned to screening were offered three annual screens that included: cancer antigen 125 (CA125) measurements; pelvic ultrasonographies if the CA125 measurement was greater than 30 U/mL; and referrals for gynecologic counseling if the ovarian volume reached 8.8 mL or greater. The development of epithelial ovarian cancer was the study endpoint. The median survival of women with index cancers was longer for the screened group than for the control group (72.9 vs. 41.8 months; p = .01), however, the number of deaths attributable to ovarian cancer did not differ.[6] To further improve screening results, a new ovarian cancer risk algorithm was designed using pelvic ultrasonography and trends in serum CA125. This algorithm was developed by the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) group, another large screening study.[7] Outcomes of the UKCTOCS study showed a favorable stage distribution using the risk of ovarian cancer algorithm, however, there was no notable survival benefit in the screened group compared with the control group.[8] In the United States, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial investigators randomly assigned women between age 55–74 to an annual screening group and a control group. The screened group underwent an annual pelvic ultrasound and serum CA125 measurement. Increased morbidity was reported owing to high false-positive results (8%) in the screening group, which resulted in women undergoing surgery, however, no reduction in ovarian cancer mortality by screening was found.[9]

Because the positive and negative predictive value of screening depends on the incidence of the disease, screening was

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expected to be more effective for a high-risk population. The U.K. Familial Ovarian Screening Study (UKFOCSS) was developed as a prospective cohort study to assess the value of screening in a high-risk population specifically. The UKFOCSS recruited more than 5,000 high-risk women between 2002 and 2009, and screening was performed with four monthly CA125 measurements analyzed by the risk of ovarian cancer algorithm. Although the final UKFOCSS results are not yet available, screening is not expected to improve ovarian cancer–specific survival nor to be cost-effective.

HEREDITARY OVARIAN CANCER

Since the *BRCA* genes were discovered in 1994 and 1995,[10,11] clinicians worldwide have begun developing guidelines for a systematic ovarian cancer screening program for women with *BRCA1/2* mutations, consisting mostly of an annual pelvic ultrasound and serum CA125 measurement.[12-16]

Lynch syndrome (LS) is another hereditary syndrome with an increased ovarian cancer risk. LS is an autosomal dominant predisposition characterized by germline mutations in one of four DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[17] For female carriers with LS, endometrial cancer is, after colon cancer, the most common tumor type with a cumulative lifetime risk of 21%–71%; the risk of ovarian cancer is between 6% and 12%.[18] Because of these high cancer risks, women with LS are regularly surveyed. Endometrial cancer surveillance seems to be effective in early detection of endometrial cancer[19-21]; however, the value of surveillance for ovarian cancer has not yet been proven.[19,22]

In a recent review on ovarian cancer in LS, the mean age of women with LS and ovarian cancer was 45.3 years and patients had a wide age range of onset (between age 19–82).[23] For these patients, ovarian cancer was mostly diagnosed at an early stage (International Federation of Gynecology and Obstetrics stage I–II), exhibited a variety of histopathological subtypes (frequently endometrioid or clear cell), and had a survival rate of 86%.[23] Data on the role of surveillance in the detection of ovarian cancer in women with LS were scarce, and the early stage could not be attributed to screening.[23]

KEY POINTS

- **Ovarian cancer screening is not effective in early detection of the disease.**
- **Most, if not all, high-grade serous ovarian cancers arise in the fallopian tube.**
- **All women with epithelial ovarian cancer should be offered genetic counseling and testing to reduce morbidity and mortality for patients and their relatives.**
- **The only effective strategy to prevent high-risk women from dying of the disease is to remove the ovaries and fallopian tubes before the cancer incidence rises.**
- **Research in the field of hereditary ovarian cancer is an example of a joint effort and fruitful collaboration between researchers on both sides of the Atlantic ocean.**

TIME TO STOP OVARIAN CANCER SCREENING

After 2 decades of ovarian cancer screening, and despite major efforts in large prospective trials, no evidence of a survival benefit of screening has been reported. Clinicians, almost simultaneously in the United States and European Union, began to omit gynecologic screening and instead adopted risk-reducing salpingo-oophorectomy (RRSO) and reported on their results.[24-30] In 2009, a meta-analysis on risk-reduction estimates showed that RRSO, performed at ages 35–40 for BRCA1 and 40–45 for BRCA2 mutation carriers (i.e., before the cancer incidence rises[31]), is effective in the detection of more than 96% of BRCA-associated ovarian cancers (hazard ratio, 0.21; 95% CI, 0.12–0.39).[32]

NEW PARADIGM OF OVARIAN CANCER IN BRCA1/2 MUTATION CARRIERS

Since the adoption of RRSO for BRCA1/2 mutation carriers, increasing percentages of fallopian tube (pre)malignancies have been found. In 1998, Dubeau[33] was the first to propose that the various ovarian cancers (serous, endometrioid, mucinous, and clear cell) resemble the epithelium of the fallopian tube, endometrium, endocervix, and gastrointestinal tract, respectively. In 2001, a group of Dutch researchers published a small series on the fallopian tubes of high-risk women and found preneoplastic lesions in benign fallopian tube tissue, not in controls.[34] One patient, a BRCA1 mutation carrier, showed loss of the wild-type BRCA1 allele in a severely dysplastic lesion of the distal fallopian tube.[34] The publication by Piek et al[34] opened the eyes of many pathologists around the world, including Crum and colleagues[35] in Boston, Massachusetts, who were the most successful in further elaborating the new paradigm. They were the first to describe the phenomenon of tubal intraepithelial carcinomas, later designated serous tubal intraepithelial carcinomas. From that point, fallopian tubes were more carefully examined, which resulted in an increasing incidence of premalignant and early stages of high-grade serous cancer in prophylactically removed fallopian tubes.[36-39] Many research projects have since been initiated and are still ongoing to find definitive evidence that the fallopian tube is the tissue of origin of pelvic high-grade serous cancer.[40,41]

IDENTIFICATION OF MUTATION CARRIERS

Since the isolation of *BRCA1/2*, the National Comprehensive Cancer Network, which is an alliance of leading U.S. cancer centers, and various family cancer clinics in Europe have developed guidelines for surveillance and prophylactic surgery.[12,14,16] More recently, with the introduction of next-generation sequencing and the availability of gene panels, genetic testing for patients with ovarian cancer and family members of mutation carriers is within reach of many women. Year by year, the costs for genetic testing have dropped dramatically, and genetic counseling and testing was recently incorporated in practice guidelines in the United States and Europe.[42,43] However, referral for genetic counseling and testing is not implemented among all patients with ovarian cancer in the United States and Europe, and

accessibility differs among patient groups. A recent study on adherence to National Comprehensive Cancer Network guidelines showed differences in genetic testing for patients with ovarian cancer in the United States: women were more frequently tested if they were younger at diagnosis, had a lower stage of ovarian cancer, were white, had private/managed care insurance, and had a family history of cancer.[44] Adherence and access to genetic counseling guidelines in different European countries has not yet been studied. Because genetic counseling and testing of all patients with ovarian cancer can reduce morbidity and mortality from ovarian (and breast) cancer among their relatives, and because prophylactic surgery is cost-effective, referral of all women with epithelial ovarian cancer should be encouraged, regardless of age, histologic type, and family history.[42,43]

COMPARISON AND CONTRASTS BETWEEN THE UNITED STATES AND EUROPEAN UNION

The knowledge and understanding of inherited ovarian cancer has expanded greatly since the discovery of *BRCA1/2*. Scientific expertise has developed on both sides of the Atlantic ocean, and researchers all over the world are sharing new findings and insights on the implications of the hereditary cancer syndrome and the ovarian cancer paradigm shift. Collaboration between geneticists and epidemiologists from Western countries resulted in large cohorts of BRCA1/2 mutation carriers (e.g., CIMBA, IBCCS, kConFab, BCFR, GEO-HEBON, EMBRACE, GENEPSO), resulting in numerous important studies on risk estimates, genetic modifiers and correlation of cancer incidence, and lifestyle and reproductive factors.

There are no scientific controversies on the pathogenesis and extraovarian origin of high-grade serous ovarian cancer, and the paradigm shift concerning the cell of origin arising from the fallopian tube is an excellent example of mutual inspiration and collaboration.[34,45] Regarding clinical implications, no controversies exist regarding the cessation of ovarian cancer screening, which was adopted almost simultaneously on both sides of the ocean.[42,43] If there are contrasts between countries and continents, they exist mostly in the field of access to genetic counseling and testing for all patients with ovarian cancer and in models of care for women at increased risk.[46,47]

One contrast across the ocean seems to be the extent of risk-reducing surgery, with or without hysterectomy. Although the overall risk of uterine cancer after RRSO is not increased, more clinicians in the United States than in Europe are inclined to offer a hysterectomy with RRSO.[47]

In conclusion, research and guidelines on hereditary ovarian cancer is a great example of mutual inspiration and joint efforts of researchers from all over the world, for the purpose of improving knowledge and health care for women with hereditary ovarian cancer.

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Social Media and Mobile Technology for Cancer Prevention and Treatment

Judith J. Prochaska, PhD, MPH, Steven S. Coughlin, PhD, and Elizabeth J. Lyons, PhD, MPH

OVERVIEW

Given the number of lives affected by cancer and the great potential for optimizing well-being via lifestyle changes, patients, providers, health care systems, advocacy groups, and entrepreneurs are looking to digital solutions to enhance patient care and broaden prevention efforts. Thousands of health-oriented mobile websites and apps have been developed, with a majority focused upon lifestyle behaviors (e.g., exercise, diet, smoking). In this review, we consider the use and potential of social media and mHealth technologies for cancer prevention, cancer treatment, and survivorship. We identify key principles in research and practice, summarize prior reviews, and highlight notable case studies and patient resources. Further, with the potential for scaled delivery and broad reach, we consider application of social media and mHealth technologies in low-resource settings. With clear advantages for reach, social media and mHealth technologies offer the ability to scale and engage entire populations at low cost, develop supportive social networks, connect patients and providers, encourage adherence with cancer care, and collect vast quantities of data for advancing cancer research. Development efforts have been rapid and numerous, yet evaluation of intervention effects on behavior change and health outcomes are sorely needed, and regulation around data security issues is notably lacking. Attention to broader audiences is also needed, with targeted development for culturally diverse groups and non-English speakers. Further investment in research to build the evidence base and identify best practices will help delineate and actualize the potential of social media and mHealth technologies for cancer prevention and treatment.

New cancer cases in the United States number nearly 1.7 million annually. With earlier detection and improved treatments, the 5-year cancer survival rate increased from 49% during 1975 to 1977 to 69% during 2005 to 2011. Yet, cancer remains the second leading cause of death in the United States, with a substantial proportion of cancers preventable. Tobacco use alone is estimated to cause 29% of all cancer deaths,[1] and more than one in five cancer diagnoses are related to lifestyle factors of obesity, physical inactivity, alcohol consumption, dietary factors, sexual health, and sun exposure.[2] Vaccinations and regular cancer screening also are important for cancer prevention and early intervention. Among cancer survivors, quitting smoking and maintaining a healthy body weight through physical activity and healthy nutrition reduces the risk of disease recurrence or progression.

Given the number of lives affected by cancer and the great potential for optimizing well-being via lifestyle changes, patients, providers, health care systems, advocacy groups, and entrepreneurs are looking to digital solutions to enhance patient care and broaden prevention efforts. In this review, we consider the use and potential of social media and mHealth technologies for cancer prevention and cancer care. Social media are websites and applications (apps) that allow users to create, share, and participate via virtual communities and networks. Social media can provide fellowship with others, because of sharing common attitudes, interests, goals, or experiences, person-to-person, in real time, at low or no cost. mHealth, more broadly, refers to the delivery, facilitation, and communication of health-related information via mobile telecommunication and multimedia technologies (e.g., handheld devices, smartphones, tablets). The boom in mHealth has been made possible by the high penetration of internet access and increased use of smartphones. An estimated 89% of United States adults are now online, with smartphone ownership at 72%.[3] As such, social media and mHealth technologies offer the ability to scale and engage entire populations, develop supportive social networks, connect patients and providers, encourage adherence with cancer care, and collect vast quantities of data for advancing cancer research.

Our review attends to the use of social media and mHealth technologies in cancer prevention, cancer treatment, and survivorship. The field is broad and emerging rapidly with

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the need for determination of evidence base and identification of best practices for patient care and data security. Given the breadth of our interest, a comprehensive review is not feasible. Instead, we identify key principles in research and practice, summarize prior reviews, and highlight notable case studies and patient resources. Further, with the potential for scaled delivery and broad reach, we consider application of social media and mHealth technologies in low-resource settings and best practices for dissemination.

SOCIAL MEDIA APPLICATIONS TO CANCER PREVENTION AND CANCER CARE

Social media come in several forms with differing audiences and emphases (Table 1). Among United States adults online, 79% use Facebook, 32% Instagram, 31% Pinterest, 29% LinkedIn, and 24% Twitter.[4] Further, social media use in the United States has become routine, with daily use reported by 76% of Facebook users, 51% of Instagram users, and 42% of Twitter users.

Most health-oriented research has been performed on general social media outlets such as Facebook and Twitter, with relatively little information available on smaller or specialized networks such as Snapchat. Yet, the emphases of specialized networks may make some platforms more optimally suited for specific intervention components. For example, video on YouTube or photos on Instagram may be effective for instruction and role modeling. Smaller and more private social networks may be preferred when discussing sensitive topics such as weight, tobacco, heavy alcohol use, or sexual activity. If using a larger and more general social medium, it may be prudent to consider private invitation-only groups, such as the example presented on use of Twitter to deliver private, peer-to-peer, quit-smoking groups (Sidebar 1). Closed quit-smoking groups targeting young adults also have been tested on Facebook[5,6] and WhatsApp[7] with encouraging short-term effects.

KEY POINTS

- **Innovations in mHealth and social media applications are occurring across the cancer spectrum, from primary prevention to screening, early diagnosis, treatment, survivorship, and end-of-life care.**
- **Thousands of health-oriented mobile websites and apps have been developed, with most focused upon lifestyle behaviors (e.g., exercise, diet, stress, smoking).**
- **Advantages of social media and mHealth technologies include low- or no-cost, high scalability, self-tracking and tailored feedback functionalities, use of images and video for enhanced health literacy, broad reach, and data sharing for large-scale analytics.**
- **Although development efforts have been rapid and numerous, evaluation of intervention effects on behavior change and health outcomes are sorely needed, and regulation around data security issues is notably lacking.**
- **Targeted development is also needed for culturally diverse groups and non-English speakers.**

TABLE 1. Categories of Existing Social Media and Popular Examples

Category	Examples
Major general-purpose social media outlets	Facebook; Twitter
Social media with a chronic illness focus	Smartpatients; CaringBridge; PatientsLikeMe
Photo-emphasizing social media	Instagram; Snapchat
Video-emphasizing social media	YouTube; Periscope
Blogs and message board–style networks	Tumblr; Reddit; Medium
Social video game or simulation networks	Xbox Live; Apple GameCenter; Second Life

Social media can provide varying degrees of anonymity, which may be attractive for stigmatized behaviors or medical conditions. When faced with the unknowns of a new diagnosis and a menu of treatment options, each with particular risks and benefits, social media can provide a unique connection with others who have direct personal experience. For example, with a focus on empowering patients, *PatientsLikeMe* is a free website, organized by medical conditions, where people can share health data, track their progress, connect with others, and contribute to big data analytics. *PatientsLikeMe* reports nearly 450,000 registered users and offers communities on nine cancer types.

With a specific focus on cancer survivors, *Springboard Beyond Cancer* addresses more than 20 symptoms and health behaviors. The site promotes skills training and use of strategies for active self-management among cancer survivors with the aim of lessening the impact of disease and treatment side effects and improving quality of life.[9] The mobile-optimized website draws existing information from Cancer.org, Cancer.gov, and literature related to survivorship and health behavior interventions.

With social media sites that are largely uncurated or expert moderated, patients should be forewarned that negative or inaccurate health information might be posted. For example, user communities may encourage excessive dieting, vaccine avoidance, or use of nonevidence-based treatments (e.g., laser or herbs for quitting smoking). Harassment also can be a problem on more open networks such as Twitter and Reddit. Review of online content on breast cancer identified difficulty finding accurate information because of the lack of regulated sites.[10] Although social media has become an important channel for disseminating findings from medical studies, the problem of fake news, including fake health news, is real, with growing recognition of the need for countermeasures.[11,12]

KEY PRINCIPLES OF SOCIAL MEDIA TO ENHANCE CANCER PREVENTION AND TREATMENT

At the foundation of social media applications for cancer prevention and control are techniques related to social support, health communication, self-regulation, and motivation enhancement.

SIDEBAR 1. *Tweet2Quit* Smoking-Cessation Intervention

Description

In private and by invitation-only 20-person groups, *Tweet2Quit* fostered peer-to-peer support and accountability for maintaining commitment to quit smoking. The Twitter-based intervention encouraged engagement via two scheduled automessages a day: (1) discussion questions based on tobacco treatment clinical practice guidelines and (2) individualized autofeedback based on past-day participation. A customized computer program automatically downloaded the group's tweets daily, analyzed those who tweeted versus not, and sent prewritten and varied messages that praised tweeters for participating and encouraged nontweeters to do so. The groups lasted 100 days.

Study Design

In a two-group randomized controlled trial with 160 tobacco smokers, *Tweet2Quit* was combined with a web guide (smokefree.gov) and nicotine patch. The comparison group received the web guide and nicotine patches without the Twitter support group. Tobacco abstinence was reported at 60 days follow-up.

Examples of Group Tweeting

M1: I've smoked.:-(but I hide when I do bc I'm ashamed.:-p
M2: Who you hiding from? YOU are the one that wants to quit…start over and try again!
M3: Its ok to trip u just need to get back on track it sounds like u want to quit maybe u need more patches
M1: I am going to get more and start fresh. Ty!!!
M4: It's ok to stumble. just keep getting back up. you can do it!
M1: When I saw myself failing I stopped tweeting so much. Didnt want to bring the rest of you down.:-/
M2: You need to keep tweeting! Maybe WE can bring you back UP!
M3: Know we r all here to help anytime day or night u want to smoke txt us we r here for u

Study Findings

Tweet2Quit participants reported significantly greater sustained tobacco abstinence compared with control subjects: 40% vs. 20%; p = .012. Engagement was high, with participants averaging 57 tweets over an average of 47 days. More tweeting was associated with quitting (p = .003).[8]

Study Limitations

The sample was largely non-Hispanic white (88%), and outcomes were self-reported and short term (60 days). A larger randomized controlled trial is underway with an ethnically diverse sample and 6-month bioconfirmed outcomes of tobacco abstinence.

Future Applications

Social media may be leveraged to create support groups to attend to other cancer-related behaviors such as diet, physical inactivity, and excessive alcohol use.

Social Support, Influence, and Norms

Online social networking for fostering social support has a long research history, from online mailing lists and message boards to more modern iterations such as Instagram. Social support is important for behavior change broadly,[13-15] and ample evidence indicates that existing social media groups can provide informational and emotional support to cancer survivors and caregivers.[16-18] Online communities have been linked to increased empowerment[19] and retention[20]; engagement with the communities has been linked to behavior change success for weight loss, smoking cessation, and other cancer-related behaviors,[8,21,22] although some effects are small.[23-25] Additionally, structured short message service and text messages to generate forum discussions, provide reminders, or offer tips and strategies have been effective build-ins.[26] Ideally, social support is bidirectional, and attention should be paid to facilitate receipt as well as provision of social support. A recent intervention study found that expressing social support was associated with perceived bonding within the social media group and positive coping strategies, whereas receipt alone of supportive messages was not.[27]

With a focus on influencing perceived social norms, social media interventions have demonstrated preliminary efficacy for reducing problematic alcohol consumption.[28,29] Yet, of concern, the literature also finds social networking associated with negative outcomes related to social comparison, such as poor body image and depression.[13,30] When designing interventions for cancer prevention and survivorship, it is important to consider potential unintended negative consequences and attempt to avoid or ameliorate them. For example, implementing weight-related programming

in photo-sharing media may require private groups, stricter rules, or additional intervention to reduce negative social comparisons to participants with lower weights, "thinspiration" accounts, or slim celebrities.

Health Communication

Communication campaigns using social media such as Twitter and Facebook are increasingly popular. Both large-scale national and international campaigns as well as smaller campaigns by local organizations and clinics have demonstrated engagement with their target audiences using social media.[14,15] Role model narratives are effective methods of persuasion with demonstrated positive impacts on cancer prevention behaviors[19-21] and can easily be delivered using video and photo tools in most popular social media systems. Evaluation of a breast cancer awareness campaign launched on Facebook by the Centers for Disease Control and Prevention found greatest engagement for posts with photos rather than status/links or videos; posts released in the early morning and afternoon (2:00 PM to 6:00 PM) versus other time periods; and posts shared earlier (2014) than later (2016) in the campaign.[31] Social media also can provide opportunities for truly interactive intervention methods. For example, a study found that participation in cocreating antismoking campaign content on Facebook produced greater information searching and intention to quit than simply viewing the content online.[22]

Self-Regulation

Self-regulation techniques, such as goal setting and feedback, are the foundation of many interventions that seek to change health behaviors, both for cancer prevention and adherence with cancer treatment regimens. Social networks are incorporated into some health-related apps and websites to promote self-regulatory skill-building,[26] and many general social networks include large subcommunities related to these topics. Some forms of these media may be particularly well suited to promoting self-regulation. For example, video-sharing services can provide highly detailed instruction and rich feedback from peers as well as experts.[32]

Motivation Enhancement

Social media shows promise for delivery of general and social rewards. In fact, several scholars have suggested that virtual rewards such as badges may be more effective when implemented within some form of social network, to emphasize personal status, group affiliation, and reputation.[33,34] Recommendations for gamification emphasize the importance of social engagement, personal reflection, and nurturing game elements for producing long-term motivation,[35,36] all of which can be facilitated via social media.

Engagement

Inadequate engagement can be a major limitation to cancer-related social media interventions.[37] Research consistently has found that posting photos results in a greater amount of engagement than other post types.[31,38,39] A study of scientific communication with the public across social media platforms by the European Organization for Nuclear Research found that "wow" photographs (i.e., awe-inspiring photographs) produced the most engagement, especially when posted on the photo-emphasizing platform Instagram.[40] Another recurring finding is that users may prefer different social media platforms, making formative research and/or use of multiple channels an important consideration.[7,41]

MHEALTH APPS AND WEARABLE DEVICES FOR CANCER PREVENTION AND CANCER CARE

A full range of mHealth apps are available for download from digital marketplaces (e.g., iTunes, Google Play) for use on smartphones, tablets, and other handheld devices. Thousands of health-oriented apps have been developed, with most focused upon lifestyle behaviors (e.g., exercise, diet, stress, smoking).[42] Yet, a mere 36 comprise half of the downloads. The focused use is attributed to the very limited functionality of most mHealth apps: just 10% can connect to a device or sensor, only 2% sync with providers' systems, and few incorporate social networking functions.[43] Table 2 presents categories and examples of mHealth apps relevant to cancer prevention and cancer care.

Several reviews have been published on mHealth apps. With attention to the prevention, detection, and management of cancer, one review identified 295 mHealth apps available in 2012.[44] Most common were apps on breast cancer (47%) or cancer in general (29%), apps aimed at raising cancer awareness (32%), providing cancer education (26%), supporting fundraising (13%), assisting in early detection (12%), or promoting a charitable organization (10%). Far fewer were apps designed to support disease management (4%), cancer prevention (2%), or social support (1%). The authors conducted a companion systematic review of the

TABLE 2. Categories of mHealth Apps With a Cancer Focus and Examples

Category	Examples
General health apps	Find a Health Center; Medscape
Health risk assessment apps	BRisk; BCSC; Rotterdam Prostate Cancer Risk Calculator
Quit-smoking apps for patients/providers	ASPIRE; QuitStart; QuitGuide; QuitMedKit
Diet and fitness apps	SuperTracker; SWORKIT; Endomondo
Self-regulation apps with social networking	Fitbit; Lose It!; My Fitness Pal; QuitNet
Symptom navigator apps	My PearlPoint Cancer Side Effects Helper
Patient portals	OhMD
Health condition trackers	My Breast Cancer Journey
Screening exam apps	ePrognosis Cancer Screening
Environmental exposure apps	Detox Me, Healthy Living Mobile App
Cancer treatment and survivorship apps	Cancer.Net (ASCO), iCancerHealth; National Comprehensive Cancer Network

health literature (1990–2012) and could not identify a single empirical evaluation of a cancer-focused mHealth app.

With a focus on breast health, a search of breast symptoms and diseases in major app stores identified 185 mHealth apps, of which 139 (75%) focused on breast cancer. Most of the apps (51%) were educational, 16% were self-assessment tools, only 14% were deemed evidence-based, and a mere 13% involved medical professionals in their development. Potential patient safety concerns were identified in 29 (16%) of the apps. Needed are mHealth cancer prevention apps informed by behavior change theory that attend to multiple risk factors and are appropriate for patients with low health and e-health literacy. As an illustrative example, the purposeful design of a breast cancer prevention app is summarized in Sidebar 2.[45]

A recent study conducted with 54 women at elevated risk for breast cancer evaluated, in a randomized controlled design, the combination of a wearable technology to monitor physical activity (Fitbit One) with a smartphone app to monitor diet (My Fitness Pal), and coaching calls from trained counselors. The goal was weight loss. Women randomized to the wearable plus mHealth app plus coaching achieved significantly greater weight loss (4.4 vs. 0.08 kg; p = .004) than women randomized to usual care.[46]

With a focus on managing symptoms following breast cancer treatment, The-Optimal-Lymph-Flow health IT system is an mHealth site with an electronic assessment and education on self-care strategies for lymphedema symptom management.[47] Evaluated over 12 weeks with 355 survivors of breast cancer, 97% reported high satisfaction with ease of use, and participants reported less pain, less soreness, less aching, less tenderness, fewer lymphedema symptoms, and improved symptom distress (all p values < .05).

In the area of tobacco control for cancer prevention, a number of apps have been developed with good interest. A 2014 search identified 546 smoking-cessation apps in the Apple Store and Google Play, which were downloaded an estimated 3.2 million times in the United States and 20 million times worldwide.[48] A review specifically of Android apps for quitting smoking identified 225 apps available between 2013 and 2014.[49] Most provided simplistic tools (e.g., calculators, trackers). Use of tailoring was limited, though positively related to app popularity and user ratings of quality.

The numbers are anticipated to rise as interest in mHealth apps and wearable health devices continues to grow. The past 2 years (2014–2016) saw a doubling in consumer use. One in three adults now report using an mHealth app and

SIDEBAR 2. Development of the Physical Activity and Your Nutrition for Cancer (PYNC) Prevention App

Objective
To promote healthy diet, nutrition, physical activity, and weight loss among women at risk of breast cancer who have varying levels of health literacy and e-health literacy.

Methods
An eight-step process is being followed to ensure that the intervention materials are appropriate for the intended audience. Development to date has included literature reviews, conceptual design, drafting informational and motivational content, acceptability review with community members, and scientific review by the research team. Remaining steps include prototyping materials, assessment of health literacy level, usability testing with community members, and final modifications.

Framework
The app uses Leventhal's Common Sense Model of Health Behavior, which describes how thoughts and beliefs about health and disease risk influence behavior.

Components
The app draws upon commercially available technology for monitoring physical activity, caloric intake, diet, and nutrition (Fitbit, LoseIt!, and USDA's ChooseMyPlate) while providing evidence-based information about breast cancer and ways that women can reduce their risk of the disease.

Prototype Feedback
Recommendations included use of "more relaxed language" and presentation of information "in a more visual way." Other suggestions included ideas for easy-to-prepare healthy foods, instruction on how to read food labels, and information on environmental contaminants and chemicals that may influence cancer risk, such as cleaning and beauty products.

Future Directions
Next steps are testing the efficacy of the mHealth intervention in increasing physical activity, improving diet and nutrition, and managing weight through a randomized controlled trial.

21% a wearable device, with use greatest among adults age 18–34. The most popular mHealth app segments are fitness (59%) and diet/nutrition (52%), followed by symptom navigators (36%), patient portals (28%), health condition trackers (25%), medication trackers (12%), and disease-management apps (10%). Most consumers (77%) and doctors (85%) view health wearables as helping to engage patients in their health, and over a third of physicians have recommended mHealth apps to their patients.[43,50] In the area of cancer care, novel wearable technology concepts include balance sensors for patients with chemotherapy-induced peripheral neuropathy[51] and Google glasses with a fluorescence imaging system for complete resection of tumors in surgical oncology.[52]

The demonstrated evidence, however, for mHealth apps in promoting and sustaining behavior change is still limited. A 2016 review of 38 articles of mobile phone applications for behavior change, four specific to cancer, was unable to identify a single best practice approach to evaluate mHealth apps, which the authors noted was further complicated by a general lack of regulation.[53] Similarly, a systematic review of randomized controlled trials testing the efficacy of mHealth apps for cancer prevention identified only four trials for smoking cessation and two for sun safety and concluded a meta-analysis was premature in this area.[54]

Health apps also have been developed to help consumers reduce exposures to known or suspected carcinogens and other toxicants in work or home environments. App functions include education, scanning of product bar codes at point-of-purchase, and self-tracking. With the same limitations acknowledged above, to date, the environmental health apps have not been tested for acceptability, feasibility, or effectiveness in randomized controlled trials.[55]

PRIVACY AND CONFIDENTIALITY CONCERNS WITH SOCIAL MEDIA AND MHEALTH TECHNOLOGIES

Although technologies such as smartphone mHealth apps and other remote monitoring devices have the potential to transform oncology care,[56] they also raise new considerations with regard to patient privacy and confidentiality. Apps may support a patient's self-report of symptoms or passively record location and other information using global positioning systems, accelerometers, and physiologic sensors. The ability to collect large amounts of personal data over long periods of time provides clinicians and researchers with insights into disease treatment and progression and also raises unique ethical issues.[57,58] We consider in this study the privacy and confidentiality concerns of social media and consumer-oriented mHealth technologies; patient safety, data security, and confidentiality of mHealth technologies; and regulatory developments. With direct application to practice, we also consider clinician-patient discussion points regarding the risks and benefits of using mHealth technologies.

Patients who purchase consumer-facing smartphone apps and other mHealth technologies (e.g., apps for weight loss and wearable devices for monitoring steps, heart rate, and sleep) may not be well informed of privacy practices. Systematic reviews of health and wellness apps available from generic app stores have identified deficiencies in the extent to which data uses are documented and appropriate security measures are implemented.[59,60] Among the most commonly used apps available for iOS and Android, only 183 of 600 (31%) had privacy policies, and 66% of the privacy policies did not specifically address the app.[59]

Consumers may be unaware that smartphone apps may share sensitive information such as sensor data on location with third parties such as advertisers. Many apps sold direct to consumers send unencrypted data to third party sites for advertising or analytics.[61] The main security risk is unauthorized access to data during collection, transmission, or storage. Unencrypted data (e.g., global positioning system coordinates, telephone numbers, email addresses, health information) transmitted over the internet can be intercepted. Efforts have been made to create secure devices and apps, but many contain serious flaws.[62]

Security threats also exist for provider-facing mHealth technologies. Ethical and regulatory issues related to mHealth technologies used by providers for patient care relate to patient safety and the security and confidentiality of patient data transmitted and stored in mobile medical apps.[63] Hackers and malware pose an increasing threat to the security of mobile medical apps.

REGULATION AND CERTIFICATION OF MEDICAL APPS AND MHEALTH TECHNOLOGIES

In some countries, government agencies have begun to regulate or curate medical apps.[63-65] In 2013, the U.S. Food and Drug Administration (FDA) released guidance for mobile medical apps that draws a distinction between unregulated apps and mobile medical apps that are subject to overt FDA regulation.[66] Apps that convert a mobile platform such as a smartphone or tablet computers into a medical device are regulated by the FDA.[63] The FDA regulates mobile apps that pose a greater risk to patients if they do not function as intended (e.g., apps that perform clinical tests such as blood or urine analysis, apps that display diagnostic images from x-rays and MRI, and apps that remotely display data from bedside monitors). The FDA focuses on technical issues related to patient safety and the security and integrity of information but not patient privacy.[62] Consumer-oriented apps for general health education are mostly unregulated.[66] In Europe, an Irish app (ONCOassist) for the iPhone and iPad that contains prognostic tools and calculators for oncologists at the point-of-care, has received Conformite Europeenne certification indicating that it complies with relevant European Union legislation.[67] The European Medical Device Directive MDD 93/42/EEC mentions software in its definition of a medical device.

In the United States, the Health Insurance Portability and Accountability Act (HIPAA) contains the primary set of regulations that guide the privacy and security of health

information.[68] HIPAA regulations require covered entities and their business associates (e.g., physicians, hospitals, health plans) to protect health information that identifies an individual and that relates to an individual's physical or mental health or health care services provided to the individual.[69] Developers of mobile apps and sensors must consider whether the software and information technology will be used by a covered entity and whether it will include any protected health information. For example, an app that assists a health care provider with following up patients must be designed to allow the provider to comply with HIPAA.[69] HIPAA requires that identifiable health information be encrypted so that only those authorized to read it can do so.[68] In the United Kingdom, the National Health Service established a Health Apps Library that endorses apps considered to be relevant to people in Great Britain and that provide trustworthy information, comply with data storage regulations, and do not pose potential risks if used improperly.[70] A recent assessment of 79 apps certified as clinically safe and trustworthy by the Health Apps Library found systematic gaps in compliance with data protection principles.[70] None of the 79 apps encrypted personal information stored locally, 66% (23 of 35) of apps sending identifying information over the internet did not use encryption, and 20% (7 of 35) did not have a privacy policy.[70] The authors noted that app users cannot see into the inner workings of apps or the services to which they connect; hence, they must trust developers to comply with privacy regulations and security best practices.[70] Medical information stored on apps or transmitted via the internet or Bluetooth should be secured using encryption.[71]

WHAT SHOULD CLINICIANS TELL THEIR PATIENTS ABOUT PRIVACY AND CONFIDENTIALITY?

Clinicians can only provide limited guarantees about privacy protection. Data collected on mobile phones can be subpoenaed as part of legal proceeds in civil or criminal cases.[57] Because of the potential for hacking of personal data from mHealth apps, the security of data collected via mobile phones cannot be guaranteed.[57] As stated, many mHealth apps do not use encryption when transferring data.[72] A further issue is that telecommunication companies record metadata and data transferred over their networks and sell them to third parties.

Patients' trust in their clinicians contributes to treatment adherence and continuity of care and, in turn, plays an important role in the adoption of mHealth technologies.[68] Clinicians should discuss the risks and benefits of using mHealth technologies as part of patient-centered care.[68] Providers should be aware of their institutions' privacy and security policies as part of their ethical obligation to ensure patient-physician confidentiality. Before using mHealth technologies, clinicians should obtain informed consent from patients so that they understand the benefits, risks, and potential harms. The rapid pace of development, early efforts at regulation, and the complex nature of the risks posed by using mHealth technologies raise challenges in communicating risks to patients.[57] Discussion of the potential risks (e.g., data harvesting, data breaches), benefits (e.g., self-awareness/self-management, attention to adherence and lifestyle behaviors, patient-provider communications), and unknowns (e.g., optimal balance of tech to touch) is warranted.

USING SOCIAL MEDIA AND MHEALTH APPS IN LOW-RESOURCE SETTINGS

Globally, by 2030, the burden of cancer is predicted to worsen significantly in low-income (82% increase in incidence) and lower-middle income (70% increase) countries.[73] The rise in mobile phone access worldwide[74] affords opportunity for delivering social media and mHealth technologies to improve cancer awareness, encourage timely screening, and secure follow-up care.[75] In the United States, mobile technologies have bridged the digital divide.[76] By ethnicity, African Americans and English-speaking Hispanics are just as likely as whites to own a mobile phone and use it for a wider range of activities.[76] In a survey of female public housing residents in Boston, nearly all reported mobile phone use for calls (97%) and texts (84%); recent use (past day) of the internet was 65%, social media 59%, and email 28%; 70% had a Facebook account and 12% a Twitter account.[77] Social media users were more likely to be Hispanic and Spanish speaking.

Broad reach, low or no cost, and high scalability make social media and mHealth apps particularly well suited for application in resource-poor settings. Social media can be used across platforms (i.e., Android, iOS, and personal computers) and can connect individuals over long distances, which can be valuable to individuals in rural areas with rare cancers who do not have peers or role models readily available otherwise. Even for those with more common cancers, online social media allows social interaction without the burden of travel to clinics or support group locations. Research indicates barriers to engaging in care among some low-income groups, such as residents in public housing.[78] Social media and mHealth technologies may aid outreach efforts with appropriate messaging and support for cancer prevention efforts.

Needed and worthy of evaluation is the extent to which people with lower levels of health literacy or numeracy find cancer-related use of social media and mHealth apps to be helpful or practical and whether apps are effective in helping culturally diverse groups to reduce their risk of cancer. Emphasized is the thoughtful development and use of mHealth applications to solve health disparities, not widen them.

To inform development of a social media smoking-cessation intervention, focus groups were conducted with 33 Hispanic, Spanish-speaking, current and former smokers in the San Francisco Bay area.[79] Most participants owned a smartphone (84%), and the majority of cell phone owners reported daily texting (81%) and Facebook use (69%). The participants valued the communal aspect of social media

and suggested strategically tailoring groups based on key features (e.g., age, gender, language preference). Participants reported preferring visual, educational, and motivational messages connected with existing services.

Development of social media and mHealth programs for diverse settings and communities can be achieved with limited investment by drawing upon existing resources. Content analyses of various social media groups (e.g., Facebook groups, individuals using the same Twitter hashtag) have identified several types of social support provided,[16,80] and numerous interventions have shown that behavior change techniques can be effectively delivered via existing social media tools.[7,23,81] Hence, expending resources to create new cancer-focused mobile apps or websites may not be necessary to deliver effective prevention and treatment interventions. Even if the long-term goal is to create an entirely new system, existing tools can provide a method for prototype testing. For example, combinations of personal emails and group sessions via social media can be used to test out the potential effects of face-to-face or app-based delivery of these techniques. An example of effective low-cost leveraging of mobile technologies comes from work in Ambanja, Madagascar, where smartphones were used to take and transmit high-definition images for the detection of cervical intraepithelial neoplasia of grade 2 or worse as an adjunct to standard on-site examination.[82]

CONCLUSION

Exciting innovations in mHealth and social media applications are occurring across the cancer spectrum, from primary prevention to screening, early diagnosis, treatment, survivorship, and end-of-life care. These new platforms and technologies avail social engagement and support as well as personalized data points for patients and providers to inform care decisions. Cancer-prevention applications include attention to tobacco use, diet, physical activity, and sleep; there are screening apps and cancer risk calculators to raise awareness; and links to patient communities or providers for symptom management. Advantages of social media and mHealth technologies include low or no cost, high scalability, self-tracking and tailored feedback functionalities, use of images and video for enhanced health literacy, broad reach, and data sharing for large-scale analytics. Although development efforts have been rapid and numerous, frameworks and investigations of efficacy for achieving and sustaining behavioral change and positive health outcomes are sorely needed, and regulation concerning data security issues is notably lacking. Targeted development is also needed for culturally diverse groups and for non-English speakers. Further investment in research to build the evidence base and identify best practices will help delineate and actualize the potential of social media and mHealth technologies for cancer prevention and treatment.

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CARE DELIVERY AND PRACTICE MANAGEMENT

Challenges in Opening and Enrolling Patients in Clinical Trials

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OVERVIEW

Clinical trials are key elements of the processes that account for many of the recent advances in cancer care, including decreased mortality rates and increased survivorship; better supportive care; and improved understanding of cancer risk, prevention, and screening. This research also has led to the validation of numerous exciting new types of cancer treatments, such as molecularly targeted therapies and immunotherapies. Clinical trials, however, are becoming more and more challenging to conduct. Research programs must comply with legal and regulatory requirements that can be inefficient and costly to implement and often are variably interpreted by institutions and sponsors and sponsors' representatives, including contract research organizations. Some of these requirements are essential to protect the safety of trial participants, to promote the scientific integrity of research, or to ensure that trial conduct is efficient and adequately resourced. Such requirements are important to preserve. However, some requirements do not fulfill any of these goals and, in fact, hinder research and slow patient access to safe and effective treatments. This article discusses some of the identified issues that are slowing the process of cancer clinical trials, such as conservatively interpreted guidelines by pharmaceutical companies and contract research organizations; overprotective language for contracts; and patient protections by health systems and universities. The article also discusses possible solutions to these problems that are slowing down the cancer therapies that patients need.

Clinical trials are key elements of the processes that account for many of the recent advances in cancer care, including decreased mortality rates and increased survivorship; better supportive care; and improved understanding of cancer risk, prevention, and screening. This research also has led to the validation of numerous new types of cancer treatments, such as molecularly targeted therapies and immunotherapies.

Clinical trials, however, are becoming more and more challenging to conduct. Research programs must comply with legal and regulatory requirements that can be inefficient and costly to implement and often are variably interpreted by institutions and sponsors and sponsors representatives, including contract research organizations. Some of these requirements are essential to protect the safety of trial participants, to promote the scientific integrity of research, or to ensure that trial conduct is efficient and adequately resourced. Such requirements are important to preserve. However, some requirements do not fulfill any of these goals and, in fact, hinder research and slow patient access to safe and effective treatments.

To address the problem of administrative and regulatory burden on cancer clinical trials, the American Society of Clinical Oncology (ASCO) partnered with the Association of American Cancer Institutes on the Best Practices in Cancer Clinical Trials Initiative (the Initiative). The purpose of the Initiative is to promote practical solutions to meeting existing regulatory and administrative requirements on research. Both ASCO and the Association of American Cancer Institutes have previously explored various strategies to streamline the conduct of clinical trials, such as the development of supportive tools and templates, networking sessions, and the development of common guidelines and standards. This Initiative was an opportunity to expand on the current work in this area.

The Initiative was overseen by a multidisciplinary working group, including hematologists and oncologists, research nurses, administrators, managers, and industry representatives. Officials from the U.S. Food and Drug Administration (FDA) and the National Cancer Institute, contract research organization staff, and patient advocates attended. The main elements of the project included (1) a stakeholder survey to identify the most pressing issues in clinical trials that could be addressed by the Initiative and to gather data on use of existing tools and resources, (2) an invitational workshop, which convened many leading oncology professionals and policy makers to identify potential solutions for improving the efficiency and conduct of cancer clinical trials, and (3) dissemination of the recommendations from the workshop through publication; the ASCO Annual Meeting; and the

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development of practical resources, toolkits, and follow-up meetings with relevant organizations and individuals. This article provides a summary of the stakeholder survey and of the workshop.[1]

ADVERSE EVENT REPORTING: FDA GUIDANCE

As stated in the Code of Federal Regulations (CFR), the primary objective of the FDA in reviewing an investigational new drug application (IND) is "to assure the safety and rights of subjects" (21 CFR §312). One of the principle ways that this is accomplished is by monitoring adverse events that occur during the course of clinical trials. Sponsors of clinical trials conducted under an IND are required under 21 CFR §312.32 to report any suspected adverse reaction that is both serious and unexpected as an IND safety report to the FDA and to all participating investigators.

In September 2010, the FDA published a final rule that amended the safety reporting requirements for INDs.[2] This rule became effective on March 28, 2011. This rule was adopted to clarify the requirements for safety reporting to improve the quality of reporting, reduce the number of uninformative reports, expedite the FDA review of important safety information, and improve the ability to detect valid safety signals. Sponsors often submitted IND safety reports of individual events that were a result of the underlying disease—events that occurred often in the population evaluated, or events that were study endpoints. This resulted in submission of a large number of uninterpretable and uninformative safety reports that strained the limited resources of the FDA, investigators, and institutional review boards and did not contribute meaningfully to the development of a drug safety profile.

The FDA published two guidance documents to help sponsors and investigators comply with the requirements of the 2010 final rule: Safety Reporting Requirements for INDs and BA/BE Studies, in December 2012,[3] and Safety Assessment for IND Safety Reporting, in December 2015 (Draft Guidance).[4] A brief review of the these guidance documents with a focus on reporting events from clinical trials is below, followed by a review of results of an internal FDA audit about the quality of safety reporting in oncology and efforts to improve the problem of ongoing uninformative safety reporting.

KEY POINTS

- **Some steps that have been shown to dramatically improve the efficiency of the clinical research process include establishing clear timelines; developing transparent metrics; and defining the appropriate role for center clinical investigators.**
- **Another key step is the development of standardized study budgets, based on fair market value as applicable to the center's level and location, with dynamic benchmarking with comparable centers.**
- **The ratio of and relative priority given to commercially sponsored studies, investigator-initiated studies/trials, the National Clinical Trials Network, or federally funded trials should be addressed.**
- **The FDA guidance documents on adverse event reporting should be followed by all sponsors, contract research organizations, and investigators for cancer clinical trials.**
- **Health care institutions should work with the investigators and the sponsors on reasonable terms for master contracts that should be universally accepted.**

Review of FDA Guidance on IND Safety Reporting

The final rule clarified the following definitions to be used for reporting purposes:

- Adverse event: any untoward medical occurrence associated with the use of a drug, whether it is considered drug related or not
- Suspected adverse reaction: any adverse event for which there is a reasonable possibility that the drug caused the adverse event (i.e., evidence to suggest a causal relationship between the investigational drug and the adverse event)
- Life-threatening adverse event or life-threatening suspected adverse reaction: an event that, in the view of either the investigator or sponsor, places the patient at immediate risk of death
- Serious adverse event or serious suspected adverse reaction: an adverse event that, in the view of either the investigator or sponsor, results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that do not meet the above criteria may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Unexpected adverse event or unexpected suspected adverse reaction: An adverse event is considered unexpected if it is not listed as occurring with the particular drug in the investigator brochure or other risk information, or is not listed at the specificity or severity as the current event.

Sponsors of clinical trials conducted under an IND application must notify the FDA and all participating investigators in an IND safety report (a 7- or 15-day report, depending on the type of event) of potential serious risks from clinical trials or other sources. In the IND safety report, the sponsor must identify all reports of similar events previously submitted to FDA, and the sponsor should take these events and any other relevant information into consideration for the assessment of causality and significance of the suspected adverse reaction being reported.

Sponsors must report suspected adverse reactions that are both serious and unexpected. Reports that do not satisfy all three criteria should not be submitted to the FDA as IND safety reports.

The issue of causality is often the most difficult to assess, but it is the most critical to avoid uninformative reporting. The regulations state that there must be a reasonable possibility that the adverse event was caused by the drug. This should be interpreted as the presence of enough evidence to suggest a causal relationship. Per FDA regulations, the determination of causality for the purposes of reporting rests with the sponsor, not the investigator. The sponsor has access to the most up-to-date and comprehensive information available about the drug and is best able to make informed and consistent decisions about causality. This is a difference between the FDA regulations and the ICH E2A guideline,[5] which allows the determination of causality to be made by the investigator or the sponsor. Sponsors should consider the following when assessing causality:

- Single adverse events usually are uninterpretable and would not meet the criteria for expedited reporting except in cases of events that are uncommon and known to be associated with use of a drug, such as Stevens-Johnson syndrome or angioedema.
- Multiple occurrences of events not commonly associated with drug exposure but otherwise not common in the population (e.g., tendon rupture), may be informative. Single events with strong evidence of causation, (i.e., a strong temporal relationship or recurrence on rechallenge) may constitute sufficient evidence for an expedited report, but generally more than one similar event is needed to suspect a causal relationship.
- Adverse events that are likely to occur (i.e., are anticipated) in the population under evaluation, whether as a result of the age of the patient, nature of the disease, or concomitant therapy (e.g., cardiac disease in older patients with risk factors or fever and neutropenia in patients receiving cytotoxic chemotherapy) should not be reported as single events, because there is inadequate information to determine a reasonable possibility of causality. These events require aggregate analysis across the development program to determine if they truly occur more often in patients exposed to the drug. These aggregate analyses require that the sponsor have a system in place for ongoing review and analysis of safety data throughout the development of the drug. If these analyses reveal there is an imbalance between patients who did and those who did not receive the investigational drug, this information should be reported in an IND safety report.

An event is considered unexpected if it is not listed in or if it occurs at a severity or frequency that is unusual from that listed in the investigator brochure or other risk information. The investigator brochure should contain a list of adverse events that have been observed with use of the drug and for which a causal relationship is suspected or confirmed. Clinical judgment is required to establish and then maintain this list after periodic review of safety information from ongoing clinical investigations.

Adverse events that qualify for IND safety reporting must be submitted to the FDA and participating investigators as soon as possible, but no later than 15 calendar days after the sponsor determines that the information qualifies for reporting. Unexpected fatal or life-threatening suspected adverse reactions must be reported as soon as possible, but no later than 7 days after the sponsor receives the information. Follow-up reports are only required for relevant information that is necessary to evaluate the suspected adverse reaction.

For clinical trials that are blinded, the blind generally should be broken for IND safety reports submitted to FDA and investigators, because information about drug exposure is necessary to interpret the event, treat the patient, and institute any changes in trial conduct, such as increased monitoring or changes to the informed consent document. This unblinding should not affect the integrity of the trial, because it should be infrequent for single events. A data monitoring committee or independent safety team should review safety data to determine if aggregate reporting of any particular adverse event is appropriate.

Sponsors also are required to submit safety information from other clinical studies, epidemiologic studies, and pooled analyses of multiple studies; findings from in vitro studies that suggest a notable risk in humans; and any increased rate of serious suspected adverse reactions other than that listed in the protocol or IB. Clinical judgment is required to determine what is a clinically meaningful increase on the basis of the trial population(s), nature and severity of the adverse event, and the magnitude of increase. The submission of an IND safety report for the findings listed above should be enough to require a change to the protocol (e.g., monitoring or eligibility criteria) or to the informed consent document.

Internal Audit of Expedited Safety Reports in the Office of Hematology and Oncology

From the years 2006 to 2014, the Office of Hematology and Oncology Products received an average of 17,686 expedited safety reports per year. Additional analysis of the number of reports per IND per year that were submitted before and after the implementation of the 2010 final rule on IND safety reporting showed that, not only was there no change since the implementation of the final rule, there was actually a slight increase.[5] In 2015, medical officers in the Office of Hematology and Oncology Products who were responsible for evaluating IND safety reports conducted a review of 160 initial safety reports submitted to commercial INDs and concluded that only 14% met criteria for reporting.[6] The remaining 86% of the reports were determined to be uninformative for a variety of reasons: 54% of the reports were for adverse events that were expected on the basis of information in the investigator brochure or product labeling, in 50% of the reports, the sponsor did not conclude that the adverse event was related to the drug; and, of the reports that met all three criteria of serious, suspected, and unexpected events, 42% of the events were determined to be anticipated on the basis of the FDA review (e.g., febrile neutropenia in a patient who received a backbone of cytotoxic chemotherapy).

Steps Toward Process Improvement

The FDA has been encouraging sponsors to develop mechanisms to reduce uninformative reporting. Several sponsors have been successful at dramatically decreasing the number of initial and follow-up safety reports through a variety of measures, including establishing dedicated teams of physicians to review safety reports, implementing consistent thresholds for determination of causality, and identifying and reporting only clinically relevant follow-up information that directly contributes to the assessment of the suspected adverse reaction.[7]

In addition, 21 CFR § 312.32 (c)1(v) allows for submission of IND safety reports in an "electronic format that FDA can process, review, and archive." The FDA is exploring the digital submission of expedited safety reports based on ICH E2B guidelines—Technical Requirements for Registration of Pharmaceuticals for Human Use—for postmarket safety report submissions[5] on the basis of a successful pilot study conducted by the Office of Hematology and Oncology Products and the Office of Surveillance and Epidemiology.[7] This move to standardize reporting and submit safety information as data sets uses mechanisms already in place for safety reporting in the postmarket setting. This method of submission will allow for a more consistent and streamlined way to receive, process, and analyze safety information, the ability to better detect safety signals and ensure the protection of patients, and the identification of relevant events at time of reporting.

Efficient and timely submission and review of relevant safety data are imperative to ensure patient safety in clinical trials. Unfortunately, revisions to the IND safety reporting requirements instituted in the final rule in 2010 did not result in the desired decrease in the number of uninformative safety reports, which continue to be burdensome for the FDA, investigators, and investigational review boards to process and review; these reports also make the detection of genuine safety signals more difficult. Perceived barriers by sponsors to implementation of the provisions of the 2010 final rule include a lack of international harmonization on all elements of reporting as well as concerns related to unblinding during the course of clinical trials and to thresholds for reporting serious and unexpected adverse reactions.[8] Efforts to improve and streamline the reporting process are ongoing, but successful implementation will require all sponsors to identify barriers to and institute mechanisms for decreasing uninformative IND safety reporting; efforts also will require regulators to continue to engage with all stakeholders to optimize the process for IND safety reporting.

BREAKING DOWN THE BARRIERS: THE PATH FORWARD

The barriers to patient participation in cancer clinical studies are numerous; less than 5% of patients participate in a clinical trial. Conducting relevant public education campaigns; addressing financial and other study access barriers; and increasing physician advocacy for, and conduct of, clinical trials are important ways to address this major challenge.

In cancer centers where the conduct of clinical studies is an important core activity, there is increasing concern about the escalation of attendant financial and personnel costs of study conduct. Efforts to standardize and streamline the process of opening, conducting, and closing studies at cancer centers are ongoing. Some key steps that have been shown to dramatically improve the efficiency of this process include:

1. Map the institutional processes used to open, conduct, close, and report a study. The involvement of all relevant stakeholders and of professional process improvement colleagues is critical to the success of this step. It is important to leverage an underlying proven, data-driven, process-improvement methodology, such as Define, Measure, Analyze, Improve, Control (i.e., DMAIC), that can be scaled according to the scope and depth of current and desired clinical study activity.
2. Eliminate all unnecessary duplicative steps in the process, and pay particular attention to steps that are necessary for full compliance with applicable mandatory standards (e.g., National Cancer Institute–designated cancer centers). Establish clear timelines for—and definitions of roles, responsibilities, and deliverables of those involved in—the remaining essential steps. Develop an ongoing dynamic feedback system to monitor the efficiency of these key steps.
3. Develop transparent metrics for expected productivity and outcomes of key administrative, financial, and research staff.
4. Define the appropriate role for center clinical investigators in study budget development and study institutional resource allocation, with appropriate consideration of conflict-of-interest issues, academic freedom, and operational efficiency. Develop standardized study budgets that are based on fair market value as applicable to the level and location of the center. Ensure that such fair-market-value budgets are dynamically benchmarked with comparable centers and are offered in a transparent manner to all sponsors for all studies, regardless of whether the study is offered directly from a sponsor or via intermediary entities.
5. Develop policies, in conjunction with comparable clinical research sites, on institutional responses to site evaluation/screening questionnaires; on responses to sponsor/contract research organization requests for site evaluation/qualification visits; on minimal qualifications/experience levels of external staff who conduct or monitor the study; on the nature and frequency of remote and on-site study monitoring activities; and on standards for authorship/acknowledgment expectations in study-related publications.
6. A specific issue that merits the development of institutional policies is the ratio of, and relative priority given to, studies or trials that are commercially

sponsored and investigator initiated, that are National Clinical Trials Network studies, or that are federally funded. Additional specific issues include the role of central institutional review boards, participation in multicenter groups with common consensus administrative and budget policies, and the development of specific alliances with sponsors to improve the investigator-initiated studies/trials process.

Major opportunities for standardization of approaches to clinical research conduct between cancer centers exist. Key steps will involve central registers/repositories of commonly requested study conduct documents and central records of investigator and institutional research capabilities, interests, infrastructure/resources and productivity. Increasing the role of central key organizations, such as ASCO, in developing, monitoring, and refining policies and procedures to optimize clinical research conduct also will be crucial.

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mHealth: Mobile Technologies to Virtually Bring the Patient Into an Oncology Practice

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OVERVIEW

Accompanied by the change in the traditional medical landscape, advances in wireless technology have led to the development of telehealth or mobile health (mHealth), which offers an unparalleled opportunity for health care providers to continually deliver high-quality care. This revolutionary shift makes the patient the consumer of health care and empowers patients to be the driving force of management of their own health through mobile devices and wearable technology. This article presents an overview of technology as it pertains to clinical practice considerations. Telemedicine is changing the way clinical care is delivered without regard for proximity to the patient, whereas nonclinical telehealth applications affect distance education for consumers or clinicians, meetings, research, continuing medical education, and health care management. Technology has the potential to reduce administrative burdens and improve both efficiency and quality of care delivery in the clinic. Finally, the potential for telehealth approaches as cost-effective ways to improve adherence to treatment is explored. As telehealth advances, health care providers must understand the fundamental framework for applying telehealth strategies to incorporate into successful clinical practice.

Telehealth encompasses a broad variety of technologies with clinical applications to deliver virtual health care services. Because there is no universal definition, the terms telehealth, telemedicine, eHealth, digital health, or mobile health (mHealth) often are used interchangeably. However, the U.S. Department of Health & Human Services defines telehealth as the use of electronic information and telecommunication technologies to support and promote long-distance clinical health care, patient and professional health-related education, public health, and health administration.[1] Although this broad definition includes both clinical and nonclinical applications, the term telemedicine is confined to clinical services in remote locations and is defined as allowing health care professionals to remotely evaluate, diagnose, and treat patients using telecommunications technology.[2] These clinical applications encompass services that support remote electronic clinical consultation, such as diagnosis, patient communication, disease management, remote monitoring, and clinician support. Meanwhile, nonclinical applications can include distance education for consumers or clinicians, administrative meetings, research, continuing medical education, or health care management.[3] Telehealth innovations enable the delivery of care irrespective of geographic location, bringing about a fundamental shift in U.S. health care by bringing health care to the patient. Moreover, the need to improve quality, access, equity, and affordability of health care supports the utilization of telehealth across several medical disciplines. The potential shortage of oncology services is pointed out in ASCO's report, *The State of Cancer Care in America: 2016*[4]; evidence-based health research supports the use of telehealth in the oncology setting and its ability to increase access to patients with cancer.[5-7] For example, in a systematic review of experiences for patients with cancer who have participated in telehealth interventions, telehealth was noted to be an advantageous approach to reduce treatment burden and disruption to patient lives.[8] Health care professionals who use telehealth to export their clinical expertise enable patients to experience decreased travel time, immediate access to care, early detection of health issues, increased patient autonomy, reduced caregiver burden, and increased patient satisfaction with health care.

TELEHEALTH TECHNOLOGY

The most commonly used telehealth technology employs video conferencing to connect a patient to a health care provider.[9] Video conferencing integrates telecommunications

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technology to allow patients and providers to "electronically collaborate face to face, in real time, and share all types of information, including data, documents, sound, and picture."[9] This type of interactive video conferencing environment allows for patient-provider consultation, discussion, education, and patient monitoring. The use of telehealth technology offers great promise and currently is being used in health care in a number of ways. The clinical applications of telehealth range from drug formulary apps to reference programs, educational apps, medical tools (patient documentation apps, patient monitoring apps, nursing apps, imaging apps, and clinical apps), payer tools, decision support tools, and patient support tools.[10] The technological advances of telehealth include wearable sensors (pedometer/accelerometer, or sensors of sleep, weight, blood pressure, heart rate, temperature, environment exposure, blood levels, falls, and geolocation), data entry technologies (exercise testing, diet, mood/stress levels, symptoms, health-related quality of life, functional status, social support, medication, tobacco use, pillbox sensors, and alcohol use), ingestible/implantable sensors, biometric sticker sensors, and the ability of smartphones to be used as otoscopes, ophthalmoscopes, and microscopes. This technology can be used to remotely collect and send data for interpretation by a health care provider.[11] Telehealth interventions also have been expanded to social media sites such as Twitter to foster healthy lifestyles through the use of wearables for self-monitoring and social media to facilitate support for behavioral changes.[12] The U.S. Food and Drug Administration also has approved imaging apps, which allow radiologists to interpret images or ophthalmologists to use color vision plates for clinical evaluation when a more traditional outlook is not available. Digital images also are a type of store-and-forward technology, which permits the electronic transmission of medical files to be used at the convenience of providers to then make diagnoses, recommendations, and treatment plans. Whether the device exists as a standalone item, such as a smartphone, wearable, or hybrid (e.g., smartwatch), the information can be used by remotely monitoring health, medical behavior (e.g., compliance, movement, symptoms, vital signs, diet) or a person's location.[11]

Moreover, the demand to satisfy uniform quality of telehealth services has been met recently through the American Telemedicine Association. These practice guidelines and technical standards include practice guidelines for videoconferencing-based telemental health, evidence-based practices for telemental health, core standards for telemedicine operations, practice guidelines for teledermatology, telehealth practice recommendations for diabetic retinopathy, home telehealth clinical guidelines, and clinical guidelines for telepathology.[13] The standardization of telehealth guidelines may help reduce the cost of equipment and increase adoption by making telecommunication independent of hardware used.

HEALTH CARE CONSUMER AND PROVIDER PERSPECTIVES

The goal of telehealth is equal efficiency with in-person care, and physician-patient encounters via telehealth recently have reported consistent performances compared with standard face-to-face care.[14] In a randomized, controlled trial for patients with prostate cancer that used telehealth after radical prostatectomy to assess the efficiency, satisfaction, and cost of remote virtual visits versus traditional office visits, telehealth was equivalent in patient and provider satisfaction and time allocated to care.[15] In another study to evaluate the opinion on the use of telehealth in oncology, a majority of responders cited advantages of oncologic apps that included better documentation, improved and continual care for patients, enhancement of communication between provider and patient, improved patient compliance, possible use of data for scientific evaluation, and potential for patient-independent information.[16] Overall, 84.3% supported the use of oncologic apps complementary to traditional treatment.[16] Critics of telehealth cited issues related to legal uncertainty, data privacy, and insecure data transfer and storage.[16] Moreover, in a group of surveyed health care professionals, the most common medical app functions included drug-referencing tools, clinical decision-support tools, communication, electronic health record (EHR) access, and medical education materials.[17] The amount of scientific material that clinicians must memorize is large, so reference programs and educational apps help enable clinicians to choose clinically appropriate and cost-effective drugs, quickly search and access information/textbooks, perform calculations, log experiences, communicate, and input specific patient information for diagnosis.[10]

The adoption of telehealth technology relies on patient participation and the motivation of patients to become partners in their health care. With a consumer-based foundation, telehealth shifts medicine to more participatory care and an improved health care system composed of patient empowerment. This paradigm shift in responsibility allows patients to manage their health, health network, and heath information, and it leverages emerging technologies for a patient-centered ecosystem. In a survey to assess patient

KEY POINTS

- **Oncology health care is ripe for digital health disruption with the convergence of mobile technology, platforms, networks, and the introduction of machine learning.**
- **Digital platforms that include telemedicine, internet of things, and wearables are scalable.**
- **mHealth technology, including virtual scribes, real-time location systems, and peer-to-peer messaging apps, has the potential to improve the efficiency and quality of clinical cancer care.**
- **Treatment nonadherence in oncology occurs at a high rate and is associated with worse outcomes.**
- **Innovative, collaborative research will be pivotal to transform mHealth into a standard part of modern cancer care relevant to the 21st century health care marketplace.**

attitudes toward telehealth, patients had a positive overall attitude and cited an opportunity for improved self-efficacy and improved provider-driven medical management.[18] Moreover, respondents mentioned comfortableness in being remotely monitored with confidence in privacy protection. Findings about telehealth from the experience of a cancer survivor illustrated analytic themes that included how telehealth limited the disruption to people's lives, how telehealth could enable close and personalized relationships between cancer survivors and service providers, and how survivors felt that they had immediate access to professional advice, which acted as a safety net for possible issues in treatment.[8] Nevertheless, individual differences in digital literacy (i.e., the competency and technical skills to operate digital devices and conceptually understand their functionality) have the potential to widen health disparities and must be addressed as telehealth becomes more widespread.[19,20]

TELEHEALTH CHALLENGES FOR CLINICAL PRACTICE

Despite its potential, telehealth issues of privacy and security remain ongoing concerns for health care professionals and patients alike. For telehealth to complement traditional approaches in the delivery of health care, it must be delivered to both clinicians and patients with confidence that the privacy, confidentiality, and security of their data will be safeguarded within compliance of the Health Insurance Portability and Accountability Act (HIPAA). In an emerging field, the means for securing data includes understanding the roles of cybersecurity and developing a mobile technology policy to ensure that protected health information data are safe. Moreover, patient portals tethered to EHRs include advanced technology as part of their system to provide scheduling, billing, and clinical support, but there is no policy for telehealth applications to be fully integrated into health information systems in hospitals or provider organizations.[21] The variation in telehealth data and a patient's EHR displays the difficulty of management for telehealth and need for integration. In the progression of telehealth, health care institutions must establish a method for health care providers to access the EHR at the time of a telehealth encounter and establish a foundation of interoperable standards.

Multiple factors on both the individual and organizational levels are crucial to clinician acceptance and adoption of telehealth technology. Clinician acceptance of telehealth technology depends on a full integration into the workflow, added value to patient care, administrative convenience, and facilitated communication among multidisciplinary teams.[22] Although usefulness and ease of use were cited as important factors to the adoption of telehealth, the argument of whether it is an affordable option is still in discussion among health care professionals, who have referenced cost issues as limiting the adoption of telehealth tools.[23,24] Elements related to costs (e.g., the question of how to bill for telehealth) act as barriers to its adoption. Reimbursement regulations for medical services were planned before telehealth technology, which thus gives each state the option of whether to cover telehealth. These variations in reimbursement relate to service coverage, payment methodology, distance requirements, eligible patient populations, authorized technology, and patient consent.[25] Moreover, traditional concepts of liability and malpractice still apply to telehealth practitioners, who are more vulnerable to legal issues and who may face an additional fee for malpractice insurance.[26]

Despite technological advances, legal and regulatory challenges concerning provider licensure, credentialing, and privileging processes remain an obstacle for all allied health professionals. Mutual recognition models such as the multistate Nurse Licensure Compact or the Interstate Medical Licensure Compact are just beginning to develop to help facilitate telehealth interactions across state boundaries and into the mainstream. Additionally, the mandate for credentialing and privileging in multiple, separate health care facilities offer similar challenged for health care providers to deliver telemedicine.

FUTURE DIRECTIONS FOR TELEHEALTH

Telehealth is the future to improved access to specialized medicine, preventive care, monitoring of chronic conditions, and improved patient outcomes and satisfaction. It has the potential to reduce fragmentation of care and allow access to care despite the distance from major medical centers. In a 2014 study, telehealth industry growth and its potential to decrease care costs within the health care system were demonstrated; the study outlined $5 billion in savings on the basis of an estimated 100 million telemedicine visits across the world.[27] Demands for improved access to care in rural areas or to underserved populations that have been a challenge historically because of a shortage of clinicians or because of financial or geographic barriers also create the potential for a new telehealth ecosystem and novel health care model. Telehealth can overcome many of these barriers; it already has increased the quality of care and reduced costs by reducing the readmissions and emergency visits in rural communities.[28] Telehealth effectiveness also has been demonstrated through research in rural and remote areas, where telehealth satisfaction reached 94%.[29] These findings suggest a general acceptance of therapies delivered via telehealth, which advocates for its unparalleled opportunity. Growing interest in tele-oncology also shows the potential to increase access from a comprehensive cancer center to patients in rural areas by offering consultations, supervision of chemotherapy administration, oral medication adherence, or symptom management.[30]

THE POTENTIAL OF MHEALTH TECHNOLOGY TO IMPROVE EFFICIENCY AND CLINICAL CARE

mHealth technology has a tremendous potential to improve clinical care; its uses range from telemedicine patient encounters to the collection of patient-reported outcomes and improved adherence to therapies with apps and mobile devices. However, there is a lack of research about what patients will benefit the most, what the efficiency of telehealth

is at saving costs or time, and whether its contribution to a greater provider burden significantly hinders the advancement of telehealth. Apps for electronic patient-reported outcomes are available now from the Apple and Android app stores. One example is the Strength Through Insight app (Fig. 1).[31] The Strength Through Insight study aims to assess the feasibility of collecting survey data from patients through digital technologies and hand-held devices.[31] Practitioners may worry about the impact these technologies have on their day-to-day workflows and how demands for increasing technological innovation may interfere with their primary job of caring for patients. To what extent are these changes taking into account improvements in the efficiency of patient care? Efficiency has not been a major consideration in the design of much of health care technology, but there are a number of areas in which mHealth tools can be used not just to improve compliance or billing but also to benefit day-to-day practices.

REDUCING THE BURDEN OF DOCUMENTATION IN THE EHR WITH VIRTUAL SCRIBES

The primary components of health care technology that practitioners interact with on a day-to-day basis are the EHR, clinical decision support tools, and clinical physician order entry.[32] The primary intent behind adoption of these tools has been the reduction in preventable medical errors, as outlined in the Institute of Medicine report "To Err is Human; Building a Safer Health Care System,"[33] and their use is encouraged through the Health Information Technology for Economic and Clinical Health (HITECH) Act.[34] Although much time and money have been spent on their adoption, little time has been spent making these systems user friendly or efficient. Additional requirements specific to oncology, such as meeting criteria for participation in the Oncology Care Model,[35] only worsen the bureaucratic burden. There is a growing realization that documentation in the EHR places a substantial time burden on practitioners and is drastically reducing the amount of time physicians can spend face to face in direct patient interaction. This has consequences in reduced patient and physician satisfaction as well as in reduced clinical productivity and income.[36]

The need for documentation in an EHR is not going away anytime soon, so a workaround, the medical scribe, has allowed practitioners to spend more time with patients. Scribes, who usually are unlicensed professionals hired to retrieve from and transcribe data into the EHR, have been shown in various clinical settings to decrease time spent in documentation and to improve both the quality of documentation and patient satisfaction.[37] Scribes introduce challenges too, including space issues in the exam room, patient discomfort with a stranger in the room during sensitive conversations, and—of course—expense and availability of trained scribes issues. However, the capacity of telemedicine for instantaneous, real-time communication anywhere in the world now means that the scribe does not have to be in the same room or even in the same country as the practitioner.

Virtual scribes, connected by audio and video to the patient and practitioner through a wireless connection such as Google Glass,[38,39] could provide the same advantages as an in-person scribe but without the space issues or intrusiveness of an additional person in the room. There could also be cost advantages, such as reduced expense in hiring and training scribes in a HIPAA-compliant location that can link out to clinics around the world, even, potentially, in countries where highly educated individuals are available at reduced cost. Patients would still have to consent to this service, and there are important issues related to protection of protected health information and data security that must be addressed, but hospital systems around the country already are adopting this model with some success.[39] A pilot study to investigate the impact of virtual scribes on documentation time and on patient and physician satisfaction is planned (unpublished observation).

REAL-TIME LOCATION SYSTEMS

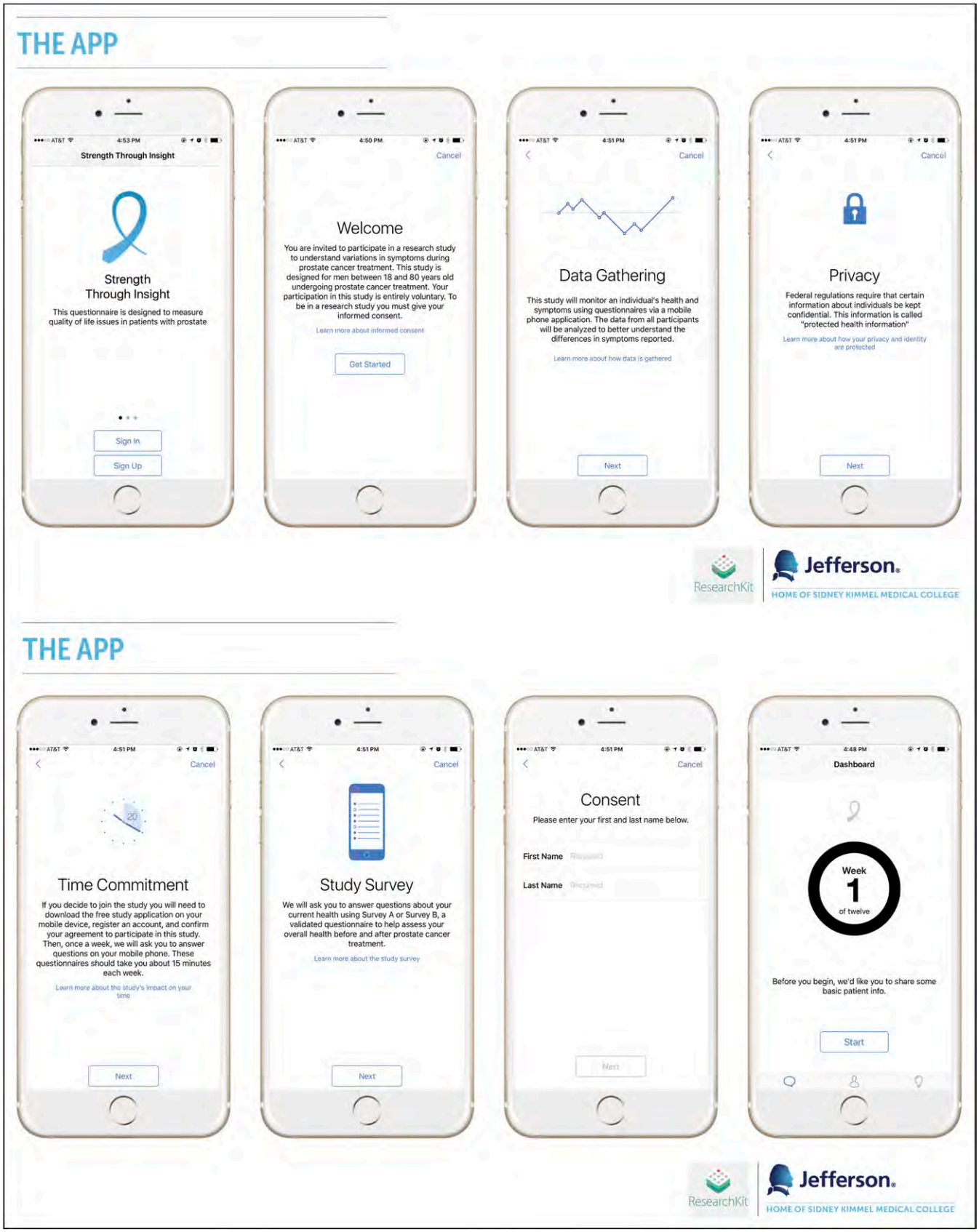
mHealth technology does not always have to connect to the outside world. Real-time location system (RTLS) technology is emerging as a useful tool to help improve patient flow within clinics and hospitals by allowing real-time localization of patients and practitioners.[40,41] In general, patients or practitioners wear a badge that allows them to be tracked in real time by a variety of possible means (e.g., wireless local area networking (Wi-Fi), radio-frequency identification (RFID), or global positioning system (GPS), and the patterns of movement and time spent in a particular location can be recorded. This can help with clinic flow and treatment chair management, and it can decrease room turnover time.[40,42] RTLS also can allow rapid localization (which can be a tedious process) of individual practitioners to sign orders, for example. Some RTLS systems allow hands-free verbal communication through the badges.[43]

Although little data exist specifically in the oncology field about the use of RTLS to improve efficiency, data in other health care settings supports RTLS as a viable option, and a number of prominent institutions, including a cancer center affiliation of one author (N. A. P.), has adopted this technology.[44,45] In an example of how RTLS can be used, a timer starts when patients are roomed; if no practitioner enters the room within 15 minutes, a nurse is alerted to find the practitioner and to reassure the patient. As a result of the positive effect on clinic flow as well as the possible impact of the Hawthorne effect (i.e., that watching someone tends to influence their behavior), studies have shown the patient wait times can be lowered and satisfaction scores can be improved by RTLS.[42]

USE OF MOBILE TECHNOLOGY FOR PHYSICIAN-TO-PHYSICIAN COMMUNICATION

Communication between health care practitioners is critically important to high-quality health care, especially in a field as multidisciplinary as oncology. This is true whether it occurs between nurse and physician, between resident and supervising physicians on a health care team, or between

FIGURE 1. The Strength Through Insight App



The app allows patients and their caregivers to build a partnership for communication throughout their cancer treatment. The survey uses standard questions that can be answered digitally via an app at a set schedule.

consulting services. Although there are a great many ways that practitioners communicate, ranging from alphanumeric pagers to email, the ubiquity of mobile phones and texting/instant-messaging apps opens up a whole new arena of opportunity for communication.

Mobile phones have been tested in medical settings and compared with pagers in terms of speed of communication and reduction in medical errors; results generally are in favor of mobile phones.[46] However, the speed and ease with which practitioners can be reached with mobile phones has drawbacks. Although replacement of pagers with mobile phones has been shown to improve efficiency and decrease the time needed to reach physicians, it may not improve nursing satisfaction with communication. In fact, in one study, use of mobile phones reduced face-to-face communication of nurses with doctors. Instead communication primarily occurred by texting or phone calls, which were considered less meaningful.[47] Studies also have suggested that the ease of mobile phone–based communication significantly increases the number of messages, which can be disruptive to workflow.[48] Finally, questions about the security of protected health information depend on the specific application used for texting; institutions that choose texting as a preferred communication method must provide a properly secure environment.[49]

Despite the risks of increased interruptions and security, mobile phones seem likely to replace pagers and other types of physician-to-physician communication, given their prominence in all other aspects of our lives. In middle-income countries, mobile phones may represent the best available means of communication. An example of the use of mobile technology in this manner is the widespread use of the web-based messaging app, WhatsApp (WhatsApp, Inc., Mountain View, CA), which has approximately one billion users worldwide and has been tested in a number of health care settings.[50]

WhatsApp has advantages compared with short message service texting in that closed groups can be created, and all communications can be viewed securely by all group members, which allows supervision of team communications. Notifications can be sent when a message has been read, and the app is fairly inexpensive, because practitioners can use their own phones and communicate with the wireless network of the institution. In some countries, such as Israel, WhatsApp is used by up to 96% of physicians, and up to 71% use it for communication of patient information and for consultations.[50] Several studies have shown WhatsApp to be a viable method of communicating patient information, asking questions of supervising physicians, and getting feedback among members of a health care team.[51,52]

Given the importance of teamwork and multidisciplinary care to oncology,[53] the availability of a secure and rapid method for team communication would have tremendous potential to aid patient care. However, there are concerns about the security of WhatsApp for communicating protected health information,[54] because the app security is end-to-end encrypted only if all members of a communication group have the most up-to-date version of the software. WhatsApp represents an intriguing illustration of the potential for web-based messaging for clinical communication. However, before adoption of a specific app for professional communication, the policy of the institution about the use of such technology must be clear.

Many oncologists and other practitioners view health information technology as a burden that decreases their face-to-face time with patients and contributes to burnout, but it is important to point out that technology also has the potential to improve efficiency and reduce time spent on low-value tasks. Although this is by no means a comprehensive list, the examples of virtual scribes to reduce time spent typing on the EHR, RTLS to reduce time spent moving patients or searching for providers, and use of mobile apps for better team communication should illustrate how technology may reduce burdens in caring for patients with cancer. As these technologies advance, however, it will be critically important to study their effects on patient care and practitioner well-being and to make sure that the rapid pace of technological development does not conflict with laws in place to protect patient confidentiality.

MHEALTH APPROACHES TO IMPROVING TREATMENT ADHERENCE

Decreased adherence to treatment is well documented for many chronic diseases. Adherence rates vary across diseases and patient factors, with an overall nonadherence rate of 24.8%.[55] This is an important topic, given that decreased treatment efficacy is a consequence of nonadherence.[56] The empiric data specific to adherence in oncology is more limited. Innovative use of mobile technology is well suited to support strategies to improve adherence in oncology, although study of these approaches is still limited. Given that use of telehealth approaches may provide a cost-effective way to improve outcomes for patients with cancer, validated approaches to use of this technology are highly desirable.

Although there are decades of experience in measuring and improving adherence in many chronic diseases, this topic has not received the same attention in oncology. Given the historical dominance of infused therapies in oncology, the concept of adherence as understood in other therapeutic areas was not relevant—antineoplastic treatment was delivered in direct view of the health care team. Empiric work conducted to understand adherence to cancer treatment is more limited, and strategies to optimize patient adherence have not been incorporated into usual care. A preponderance of the empiric work on treatment adherence in oncology has focused on imatinib for chronic myeloid leukemia, or on hormonal therapy for breast cancer (e.g., tamoxifen, aromatase inhibitors), because these were among the first widely used oral medications to require long-term administration in oncology.[57] Adherence rates in these indications are similar to those documented in other therapeutic areas; adherence to oral chemotherapy has ranged in empiric studies from 50% to 89%, depending on the definition of adherence and the study methodology.[57-59]

An important methodologic consideration in adherence research is the measure of adherence used. Measures can be described as direct measures (e.g., blood levels, provider observation) or indirect measures that are further subdivided into objective (e.g., prescription fills) or subjective (e.g., patient self-report) measures. Comparison of objective and subjective measures shows that patients systematically over-report adherence behavior.[60]

Treatment adherence is a critical issue for oncology, because studies consistently have shown that nonadherence leads to worse outcomes, including decreased survival.[61] Data from studies of infused therapies are instructive to define the risk of missed doses. A study of relative dose intensity of adjuvant chemotherapy delivered to patients with breast cancer found that the cohort of patients who received a relative dose intensity of less than 65% achieved an overall survival equivalent to a control group who received no adjuvant chemotherapy.[62] Increased mortality underscores another difference between the consequences of poor adherence in oncology and those in other diseases, in which the risk is limited to increased morbidity.

Nonadherence also leads to increased health care utilization and increased cost.[63] Predictors of nonadherence include patient factors (e.g., age, gender, amount of social support), treatment factors (e.g., frequency and severity of adverse effects), and health care team factors (e.g., education from physician about disease linked to treatment information).[58] Cost of treatment also has been linked to decreased adherence rates.[64,65] Given the emerging focus on improving outcomes while containing health care costs, the need to implement cost-effective strategies to improve treatment adherence is paramount. In addition, the ability to connect to patients outside clinical settings is a compelling approach, given the importance of patient engagement and symptom management in promoting adherence for patients with cancer. For both of these reasons, research into mHealth approaches to manage treatment adherence is desirable.

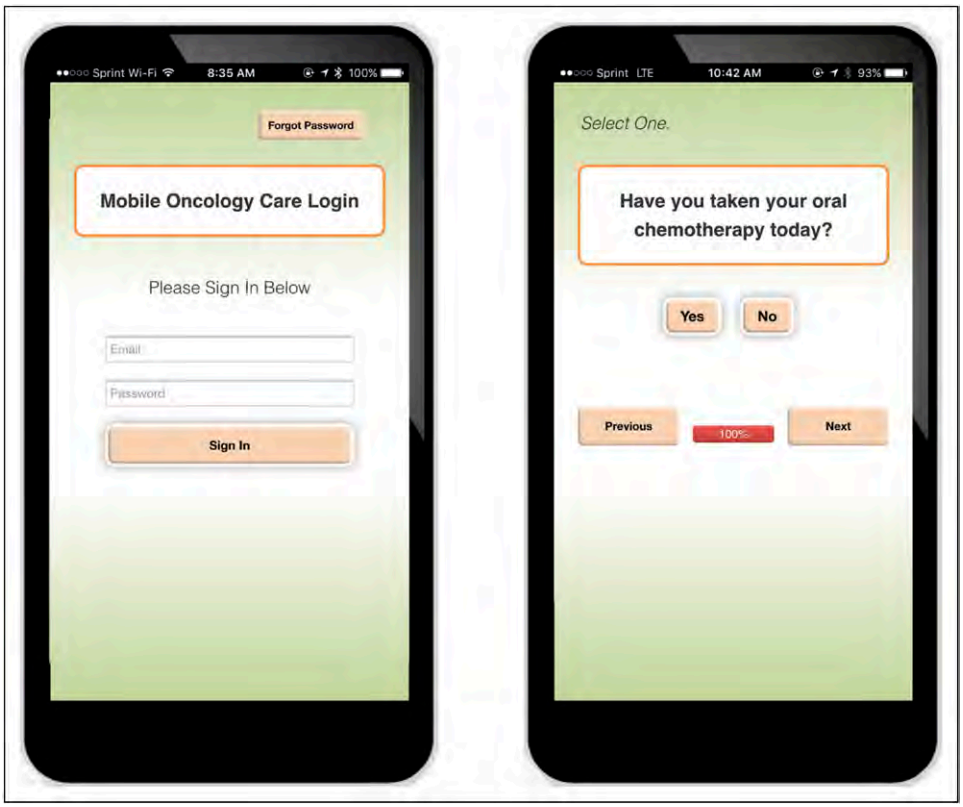
Given that smartphones are becoming ubiquitous, interventions to improve medication adherence through smartphone applications are broadly available.[66] Greater than 90% of American adults owned a cell phone in 2015, an increase from 65% in 2005.[67] There is a growing body of evidence that even simple interventions, such as text message reminders, improve adherence in a variety of chronic diseases.[68] Greater than 80% of cell phone users report sending or receiving text messages.[69] Essentially all (99%) texts are opened, and 90% are read within 3 minutes.[70] Short message service–and multimedia message service–based texting programs and smartphone applications are being introduced into the health care setting.[71-73] Prospective research remains limited, but early studies indicate that digital mHealth interventions can improve patient engagement and adherence to treatment.[69,74] Real-time mobile links between patients and providers can relieve logistic burdens of facility-based care, improve symptom tracking, enhance patient compliance, and shift symptom control to the at-home setting.[75] However, it is also true that the features present in basic smartphone apps vary enormously; therefore, not all apps can be expected to have the same usability or outcomes.[76] An evaluation of the features of 272 mobile phone apps purported to promote medication adherence, and readily available in an app store, found that only six of these apps had even half of the desirable features.[76] For example, flexible scheduling was the most common feature found across the 272 apps but was still available in only 56.3% of the apps. Password protection, as desired to optimize data privacy, was available for only 13.2% of these apps. Standard approaches to evaluate the quality of apps as required to meet their stated goals are needed to facilitate decision making by patients and providers.

In contrast to standard treatments for many chronic diseases, treatments in oncology are often associated with risks for toxicity. This cause of nonadherence may require a different approach than those effective in other therapeutic indications. That is, a text message reminder may not increase treatment adherence in a patient with severe diarrhea who is electing not to take his oral chemotherapy in response to treatment-related symptoms. Instead, approaches that include symptom monitoring of emerging toxicity that prompt the health care team to conduct proactive management would be expected to provide value to improve adherence in oncology. Basch et al[77] used an electronic system to routinely collect patient reported outcomes on common symptoms as part of usual care. Patients in this experimental condition continued to receive therapy for an average of 2 months longer, and they experienced increased 1-year survival, compared with a control group treated with usual care. These data provide evidence that symptom assessment and management may help improve outcomes in the context of oncology care.

A recent pilot study combined symptom monitoring and adherence assessment in patients with early-stage breast cancer who initiated treatment with aromatase inhibitors (Fig. 2).[78] Patients were stratified to receive text and/or email alerts reminding them to complete surveys or to a group that logged onto a website to complete surveys on an ad lib schedule. The group receiving text/email alerts completed 74% of surveys compared with 38% in the ad lib group. Post-study interviews found a high level of acceptance for the mobile surveys; patients stated that they felt that weekly surveys better captured their symptoms compared with waiting for their in-clinic appointment. Additionally, the alert group had nominally better quality of life than the ad lib group.

Beyond systemic therapy, patient-facing technology also may improve broader patient acceptance of their complex care journey, including locoregional treatment. Adherence to immediate postoperative care is ripe for mHealth engagement. Surgical recovery is a traumatic part of the overall cancer care continuum and is punctuated by discomfort, disability, and anxiety. For example, the emotional burden of cancer surgery in the head and neck region is heightened by disfigurement and debilitation. Surgeons and allied

FIGURE 2. Screen Shots From the Patient Care Monitor (Vector Oncology, Memphis, TN) Used for Mobile Health Adherence Monitoring



providers field drop-in visits to manage minor problems, but these visits distract from their urgent duties. Real-time or asynchronous mobile communication could empower appropriate patient self-care, preempt needless anxiety, and decompress clinic schedules. A pilot study that involved a surgical specialty team was conducted at an academic referral center and used a commercial automated text-based intervention to address the immediate postoperative care engagement needs of patients with head and neck cancer.[79] Thirty-two patients were approached, and 23 patients (72%) enrolled. All enrolled patients texted their providers, although frequency (median, seven texts; range, two to 44 texts) varied. Socially isolated patients and those who faced surgical complications used the platform more frequently. Patient satisfaction with the platform was high (mean,3.8 on a four-point Likert scale).

Radiation treatment is complex, lengthy (often 30 to 35 daily treatments during 6 to 7 weeks), costly, and toxic. It has been shown that gaps in treatment yield poorer outcomes for patients as a result of accelerated tumor regrowth during breaks in treatment. Compliance is crucial to ensure the best chance for local control and cure; unfortunately, adherence to radiation is a challenge. A review of 564 patients with head and neck cancer who received radiotherapy at a tertiary academic center was conducted to quantify the extent of this problem in a modern patient population covered by a spectrum of private insurance and public indigent care.[80] Three-hundred sixteen patients (56% of all enrolled) suffered a treatment break; 114 missed a single session, 202 missed multiple treatments. Seventy percent of uninsured patients had treatment delays compared with 47% of privately insured patients ($p \leq .0001$). Uninsured patients most often missed treatment because of nonmedical/logistic reasons. Delay was predictive for local recurrence ($p = .0002$) and overall survival ($p < .0001$). Among noncompliant patients, there was a higher likelihood for local recurrence in indigent patients. Our results highlight cancer control needs specific to disadvantaged communities at risk for poor radiotherapy adherence. A complex mix of social and human elements—including patient trust in providers, effectiveness of toxicity management, and quality of patient support—create a constellation of determinate factors. Emerging research has shown that mHealth informatics platforms can positively affect health care delivery in indigent cancer populations.[74,75] Interestingly, a pilot study published by Percac-Lima et al[81] found that telephone navigation directed to at-risk patients significantly improved cancer clinic visit adherence.

In summary, early patient-centered studies leveraging mHealth applications to engage patients with cancer about their treatments confirm an exciting beginning. However, these are just the first steps in a longer journey, on which all hype will wear thin quickly. Careful work is needed to refine personalized telehealth tools/utility measures, propel

stakeholder enthusiasm, and secure sustainable reimbursement models. Momentum toward mobile consumer self-fulfillment in our modern economy is undeniable. Our patients soon will demand dependable, useful, and thoughtfully designed mobile tools to optimize the acute, recuperative, and long-term survivorship phases of their cancer care. Inclusive multidisciplinary teams will be necessary to keep the cancer care experience relevant to the 21st-century patient, and the changes will require the buy-in and expertise of clinicians, social scientists, computer/data scientists, product designers, health systems experts, and health care policy makers among others. Additional work must focus on best practices to improve outcomes and balance patient and provider burden. Comparing approaches will be challenging because of the variability in features of apps and tools grouped under the mHealth label. Attention to scientific methodology will be especially important to ensure that potentially cosmetic improvements in patient satisfaction and adherence that we engender with technology actually lead to meaningful downstream clinical outcome improvements.

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Perspectives on the Use of Clinical Pathways in Oncology Care

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OVERVIEW

Pathways and guidelines are valuable tools to provide evidence-based care in oncology. Pathways may be more restrictive than guidelines because they attempt (where possible) to reduce cost, add efficiency, and remove unwarranted variability. Pathways offer an opportunity to measure, report, and improve quality of care; they can drive to evidence-based targeted therapy where appropriate; they can enhance efficiency through standardization; and, finally, they can be a vehicle to enhance participation in clinical trials. Pathway implementation requires understanding and commitment on the part of the physician and leadership as they may initially disrupt workflow, but ultimately have the ability to enhance patient care. ASCO criteria have been published for the development and implementation of high-quality oncology pathway programs. Future challenges for pathways include incorporation of molecular testing and appropriate targeted care in a real-time precision oncology approach.

Pathways have been used for more than a decade in the oncology space, with the aims of improving patient care and communication while focusing on outcomes and maximizing resource utilization by reducing unwarranted variation and promoting the use of higher value therapy. However, the magnitude and growing importance of pathways is evident in the role of reimbursement, already implemented by some payers, and pathway utilization expansion, such as in the Oncology Care Model. Additionally, with the statutory implementation of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA), the U.S. health care system of reimbursement is transitioning away from a volume-incentivized, provider-centric model to a value-based, patient-centered model. Well-designed pathways have the potential to help us adapt to this transformation by serving as a foundation for comprehensive patient care, while promoting efficient, higher quality care. This in turn can potentially control costs and better position practices to assume financial risk for our patient populations, while assuring best care for the patient. Pathways could possibly serve as a central component of oncology practice and as a cornerstone of future payment methodologies.

DEFINITION: GUIDELINES VERSUS PATHWAYS

The terms "guidelines" and "pathways" are used frequently in discussions regarding quality and cost-effective oncology care. A guideline is a listing of all treatments that are considered (by a panel of experts) to be within a "standard of care" for a given presentation of disease. Practice guidelines assist practitioner and patient decisions about appropriate care, defined by empirical evidence, addressing specific clinical circumstances and aligning practice with state of the art oncology. Guidelines do not formally address cost and resource utilization. The primary aim for guidelines is not standardization, but rather to ensure that care delivered has been demonstrated to be effective by evidential review. In a Venn diagram, pathway treatment recommendations would be included within the scope of the guidelines, but with a much smaller numerical set. An exception to this might be when a pathway is updated more frequently than a guideline, incorporating new evidence.

Pathways are also known as care pathways, critical pathways, care maps, or integrated care pathways. A pathway references the same literature sources, but attempts to choose a single therapy from the acceptable options that is best for a given presentation of disease. This process involves committees of physician peers with disease expertise and uses consensus to determine the best option based on a platform of efficacy, toxicity, and cost. Characteristics of a pathway program include the pathway serving as a multidisciplinary management tool, based on high-level evidence applicable to a specific group of people, wherein interventions are defined, optimized, and sequenced. Generally, pathways will support the Triple Aim of health care, which is better perception of care by the patient, improved professional effectiveness and coordination of care, while

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controlling/reducing costs. Ideally, pathways should be available at the point of care for a patient for real-time clinical decision support. The pathway system should also be able to document the decision making of the clinician for future study, reporting, and compliance.

RATIONALE FOR USE OF PATHWAY PROGRAMS

Whereas access to the ASCO and the National Comprehensive Cancer Network guidelines is open, pathway systems are currently only commercially available and thus require substantial commitments of time and resources for practice implementation. However, there are multiple compelling reasons to support pathway use. First, the status quo of relying upon the individual expertise of any one physician to decide appropriate care is no longer acceptable in our current age of accountability. There is now a need to prove the quality of care to stakeholders (e.g., patients, referring providers, and payers) rather than the "trust me" mantra of old. Measuring care is an indispensable part of care delivery, but, unfortunately, our current electronic platforms for documenting care are not up to the task as they cannot have the innate flexibility needed to react to the rapidly changing science of oncology. Pathway systems can provide such data demanded by new legislation, such as MACRA and Merit-based Incentive Payment System.

Second, the costs of all medical care are rising faster than inflation with oncology care contributing significantly to this increase. By standardizing care—where feasible and appropriate—to best evidenced-based care, pathways programs offer the possibility of driving down costs, increasing quality, and improving outcomes. Standardization also offers the potential for improved patient flow, error reduction, and cost savings without compromising patient access or care. Limiting "unwarranted variability" is in everyone's best interest.

Finally, as oncology care becomes more personalized, the options for care more numerous, and the volume of information that informs decision making ever more complex, it becomes increasingly difficult for a single provider to remember the nuanced details of treatment of every state and stage of disease presentation. At the same time, restrictions in provider availability will likely tighten as the baby boomers continue to age and patients live longer and better lives with their cancer diagnoses. The need for a point-of-care decision support tool is increasingly becoming self-evident. For institutions committed to advancing the knowledge-base of cancer treatment through research, a pathway can simplify and potentially enhance accrual of patients by being able to incorporate open clinical trials into the treatment algorithm.

KEY POINTS

- **Pathways are a subset of guidelines designed to standardize care with best evidence and reduce unwarranted variability and cost.**
- **Pathways offer the hope of improved quality by standardization around best evidence, enhancing clinical trial availability, offering decision support at the point of care, and providing measurable outcomes.**
- **Implementation of pathways requires significant understanding and commitment of the provider institution, but has the promise of being an important quality and cost tool.**
- **Pathways may be influenced by the viewpoint of the developer. ASCO members are often most comfortable with the implementation of provider-based pathways in clinical care.**
- **Pathways may enhance the use of appropriate targeted (personalized) care.**

THE ROAD MAP TO SUCCESSFUL PATHWAY IMPLEMENTATION

After the decision has been made to proceed with the adoption of clinical pathways, there are several key aspects to a successful launch. The initial "big picture" buy-in of all of the clinicians in the institution is critical; they must understand and agree that a provider-based solution is preferable to a payer- or government-based solution both for patient care and provider satisfaction. The big picture will necessarily look different to an academic physician compared with a clinical physician, but can be equally compelling.

Once buy-in is obtained, the system chosen for use should be integrated into the normal physician workflow as seamlessly as is possible. Clinician expectations have to be managed, stressing that all efforts are being made to minimize disruption in the clinic, but that it is impossible to add a variable without some alteration in flow. Adjustments to workflow or the product should not be based upon a perception of what it will be like, but rather upon the experience of hands-on usage and subsequent thoughtful adjustment to obtain the goal of quality patient care and good workflow. This iterative process is possibly the single most important aspect of implementation. Each clinic may have its own uniqueness and character demanding slight variations in rollout that are often easily accommodated.

After initial implementation, giving feedback to the physician and monitoring that feedback are vital to success. Clinician feedback regarding the advantages of a decision support tool and data collection are helpful in maintaining compliant use of the system. For example, the ability to provide data on eligible patients throughout a network to academic physicians for screening or clinical trials development is an immediate positive byproduct. Facilitating workflow by offering all the information necessary for patient care in one location is appreciated by busy clinicians trying to get through a busy clinic. Saving time to look up side effects or dose reductions allows for more time spent with each patient. Changes in workflow are always difficult to manage, especially when physicians already have their own established care preferences. Attempting change in a stepwise fashion is preferable to allow time for adoption.

The content of a pathway may differ based upon the principles and priorities of the pathway developer. A transparent

SIDEBAR 1. ASCO Recommendations to Improve the Development and Use of Clinical Pathways in Oncology

1. Pursue a collaborative, national approach to reduce the unsustainable administrative burdens associated with the unmanaged proliferation of oncology pathways.
2. Adopt a process for development of oncology pathways that is consistent and transparent to all stakeholders.
3. Ensure that pathways address the full spectrum of cancer care, from diagnostic evaluation through medical, surgical, and radiation treatments, and include imaging, laboratory testing, survivorship, and end-of-life care.
4. Update pathways continuously to reflect new scientific knowledge and insights gained from clinical experience and patient outcomes, to promote the best possible evidence-based care.
5. Recognize patient variability and autonomy and allow physicians to easily diverge from pathways when evidence and patient needs dictate.
6. Implement oncology pathways in ways that promote administrative efficiencies for both oncology providers and payers.
7. Promote education, research, and access to clinical trials in oncology clinical pathways.
8. Develop robust criteria to support certification of oncology pathway programs; pathway programs should be required to qualify based on these criteria, and payers should accept all oncology pathway programs that achieve certification through such a process.
9. Support research to understand the effect of pathways on care and outcomes.

and evidence-based development process of pathways is vital to assure the confidence of those affected by the pathway: the provider, patient, and payer. Many practices have found that implementation of a well-designed pathway program is both doable and advantageous in the delivery and measurement of quality oncology care.

THE ASCO PERSPECTIVE OF CLINICAL PATHWAYS

On January 12, 2016, the ASCO Policy Statement on Clinical Pathways on Oncology[1] was released with recommendations to ensure that clinical pathways in oncology enhance—and not diminish—patient care (Sidebar 1). The intent of the statement was to elevate awareness about clinical pathways in oncology and to convey a cautionary note that no current mechanism exists to ensure the integrity, efficient implementation, and outcome assessments for these treatment management tools. The release came within 1 year of the establishment of the Task Force on Clinical Pathways, which was charged with better understanding the concerns and barriers to providing high-quality, evidence based care, as articulated by ASCO members and other stakeholders. Specifically, ASCO's State Affiliate Council and Clinical Practice Committee cited a number of concerns, including: lack of transparency in disclosing conflict of interest and disclosure describing the methodology used in development, a focus on cost savings with efficacy and safety as secondary considerations, a cumbersome appeals process and lack of reimbursement for off-pathway treatment, lack of pathways for rare and in-patient–treated cancers, implementation concerns, as well as lack of publicized analytics supporting pathway utilization. Members especially highlighted the associated unsustainable administrative burdens related to the multitude of oncology pathways some providers are required to track and manage, as well as the continued requirement of pre-authorization when pathway compliant.

The Clinical Pathways Task Force has continued its efforts to ensure that pathways are consistently developed and transparent to all stakeholders, and used in the way they are intended—to guarantee quality care while helping to reduce unwanted variations in care and controlling costs. Recently, the Task Force developed and published ASCO criteria for the development and implementation of high-quality oncology pathway programs while actively seeking and respecting input—through direct stakeholder meetings and interviews—with patient advocates, payers, vendors, and providers (Table 1).[2] The criteria focus on three key areas: development, implementation/use, and analysis and are intended for use by multiple stakeholders to evaluate clinical pathway programs and guide their future development.

TABLE 1. ASCO Criteria for High-Value Pathways

Development	Implementation and Use	Analytics
Expert driven and reflects stakeholder input	Clear and achievable expected outcomes	Efficient and public reporting of performance metrics
Transparent, evidence-based, patient-focused, clinically driven, and up-to-date	Integrated, cost-effective technology, and decision support	Outcomes-driven incentives
Comprehensive and promotes participation in clinical trials	Efficient processes for communication and adjudication	Promotion of research in value and effect on pathways and care transformation

BENEFITS OF USING ASCO CLINICAL PATHWAY CRITERIA FOR PRACTICING ONCOLOGISTS

Regardless of the site of service, ASCO criteria are intended to be used in a manner that enhances the ability of the provider to evaluate pathway programs for their practice. Because providers are becoming increasingly focused on optimizing efficiencies, including reducing costs while preserving high quality care for the patient, the criteria may help in assessing programs that may best attain practice management goals. Furthermore, as various stakeholders collaborate to improve the delivery of care, pathway utilization may intensify. Cancer care is generally a multidisciplinary effort, and pathways, if comprehensively developed as proposed in the criteria, can be widely used by the caregiver team to optimally coordinate patient care. Reducing redundancy and unnecessary testing while assuring the necessary evaluations and treatments are delivered would be paramount to the success of a pathway program in this collaboration. On a broader scale, there are differences between payer- and provider-facing pathways. Collaboration between payers and providers regarding pathway utilization and criteria compliance may offer opportunity to help minimize some of the administrative issues for both stakeholder groups, be leveraged as a measure to control costs, and inform reimbursement discussions.

EVOLUTION OF CLINICAL PATHWAYS: CHALLENGES OF PRECISION ONCOLOGY

The ASCO criteria promote a much needed benefit of continually updated comprehensive pathways to help with the management of rapidly developing clinical advances. All stakeholder groups, including payers and patients, are quick to point out variation of care and resource utilization between providers. As pathways integrate scientific advances, including precision medicine and rapid learning system–validated evidence, there should be opportunity to maximize resource alignment and promote value. In addition, informed pathways will assist the provider in delivering appropriate, equitable care for all patients. To serve as example, pathway programs can potentially assist providers in ensuring the growing complexity of molecular testing is used optimally so patients can receive targeted and other personalized care to achieve best outcomes. Currently, the utilization of U.S. Food and Drug Administration–approved and National Comprehensive Cancer Network guideline-approved tests, such as EGFR testing in patients with newly diagnosed advanced lung cancer, is not known. One study estimates 18% of patients with newly diagnosed lung cancer undergo testing within 6 months of diagnosis, with 37% patients with presumed nonsquamous histology (receiving bevacizumab or pemetrexed) undergoing EFGR testing.[3] Certainly, pathway use can help to ensure and track the use of appropriate molecular tests.

Precision oncology now refers to the use of molecular testing to identify mutation-based treatment options such as vemurafenib and dabrafenib for patients with BRAFV600 mutations or erlotinib for EGFR mutations. With the increasing uptake of genomic testing, in part enabled by reduced cost, many clinicians and patients are faced with trying to understand the implications of molecular testing results on treatment decisions. For example, should patients with various disease types who have BRAFV600 mutations receive targeted therapy, even if the drugs have not yet been tested or approved for those specific disease-types? Two meta-analyses have shown that trials utilizing molecularly-based treatments led to better outcomes compared with those with nontargeted therapies.[4,5] However, the prospectively randomized French SHIVA trial did not show benefit in progression-free survival for patients who were treated with molecularly targeted agents versus investigator's choice. In this trial, patients with any metastatic solid tumor that had progressed on standard treatments underwent mandatory tumor biopsy to obtain tissue for genomic testing. Patients who had molecular alterations that mapped to the PI3K/AKT/mTOR, or RAF/MEK, or hormone receptor pathways were randomly selected to receive standard of care versus molecularly targeted agents including erlotinib, lapatanib plus trastuzumab, sorafenib, imatinib, dasatinib, vemurafenib, everolimus, abiraterone, letrozole and tamoxifen. Of 741 patients screened, 293 (40%) had at least one molecular mutation identified; 92 patients were randomly selected to receive the control standard-of-care arm and 99 patients to the experimental molecularly targeted arm. The median progression-free survival was 2.0 months compared to 2.3 months (HR 0.88; p = 0.41) in the control versus experimental arms, respectively.[6]

There are several reasons for the lack of benefit seen in patients receiving targeted therapy in the SHIVA trial. Mutations in driver genes identified by sequencing may be silent passenger mutations or mutations that are resistant to therapies, such as EGFR exon 20 insertions that are not associated with response to EGFR inhibitors. Alternatively, some cancers may require multiple hits in different signaling pathways or involve epigenetic or post-transcriptional control. Finally, discrepancies between commercially available tests or discordance between primary, metastatic, or just heterogeneous tumors may complicate the use of molecular alterations for treatment. Although there is no doubt that some molecularly based treatments based on single mutations (e.g., erlotinib and crizotinib in lung cancer) can improve patient outcomes and should be incorporated into clinical pathways, much work remains to be done before large-scale genomic testing and subsequent targeted therapies becomes standard of care.

VALUE-BASED CARE AND PATHWAYS: FUTURE CHALLENGES

Several current initiatives aim to improve quality of care and care delivery, including the development of learning health care systems and value-based frameworks. These initiatives, along with pathways, are influenced by the different perspectives and needs of the stakeholders. For example, the definition of value may differ between health systems,

payers, patients, oncologists, and manufacturers. Similarly, the perspectives of payer- and provider-facing pathways may differ. Because there is limited published data regarding pathway performance, escalation of widespread pathway program analysis as it pertains to patient outcomes and the financial aspects surrounding cost and value, is needed. Additionally, learning health care systems have challenges pertaining to data sharing, interoperability of electronic health care systems, and patient-reported outcomes. These initiatives, although currently being developed independently, have the potential to enhance patient-centered care as an integrated strategy while still achieving the goals of quality, value, and cost control. As pathway programs continue to evolve, improvements in patient care will be achieved as value and learning health system learnings are integrated as essential components.

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Precision Oncology: Who, How, What, When, and When Not?

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OVERVIEW

Precision oncology, defined as molecular profiling of tumors to identify targetable alterations, is rapidly developing and has entered the mainstream of clinical practice. Genomic testing involves many stakeholders working in a coordinated fashion to deliver high-quality tissue samples to high-quality laboratories, where appropriate next-generation sequencing (NGS) molecular analysis leads to actionable results. Clinicians should be familiar with the types of genomic variants reported by the laboratory and the technology used to determine the results, including limitations of current testing methodologies and reports. Interpretation of genomic results is best undertaken with multidisciplinary input to reduce uncertainty in clinical recommendations relating to a documented variant. Non–small cell lung cancer has emerged as a prototype disease where genomic data from at least several well-documented alterations with approved targeted agents are essential for optimal treatment from diagnosis of advanced disease. Due to the development of resistance to targeted therapies, resampling and retesting of tumors, including using liquid biopsy technology after clinical progression, may be important in making treatment decisions. The value of molecular profiling depends on avoiding both underutilization for well-documented variant target-drug pairs and overutilization of variant-drug therapy without proven benefit. As techniques evolve and become more cost effective, the use of molecular testing may prove to add more specificity and improve outcomes for a larger number of patients.

The goal of precision medicine is simply to deliver the right cancer treatment to the right patient at the right dose and the right time. Several lines of investigation came together nearly simultaneously to usher in the beginning of the precision oncology era. In 1998, the *BCR-ABL* rearrangement in chronic myeloid leukemia was successfully targeted by the small molecule imatinib, leading to dramatic clinical remissions and U.S. Food and Drug Administration approval in 2001. The first draft sequence of the human genome was accomplished the same year,[1] followed by the first cancer genome.[2] Rapid discovery of multiple, nonoverlapping driver mutations and tyrosine kinase inhibitors with clinically effective inhibitory properties in non–small cell lung cancer and melanoma led to assays of alterations performed by polymerase chain reaction (PCR) quickly and inexpensively. Use of these biomarkers to drive treatment decisions in solid tumors raised expectations and interest in molecular profiling. Sequencing technology and costs improved rapidly during the early 2000s, particularly with the advent of NGS on formalin-fixed, paraffin-embedded tissue whereby massive parallel sequencing allows determination of alterations in a large number of genes through a timely, cost-effective process.

Underpinning precision oncology is the concept of somatic mutations as the foundation of cancer development.[3] Mutations in oncogenes rendering them constitutively active are considered driver mutations and are central control points for progression of malignancies. Conversely, tumor suppressor genes, involved naturally in controlling tumor pathogenesis, can cause cancer progression when inactivated through mutation or allele loss. Multiple processes result in dysregulation of the genetic machinery in DNA RNA or protein, leading to altered expression of the protein coded for by the gene. To capture the entire spectrum of potential alterations, multiple technologies, termed a multi- or pan-omic approach, are best considered. The vast number of choices of technologies, commercial entities offering testing, and sometimes conflicting results have overwhelmed clinicians looking to obtain molecular information that will result in clinical utility for their patients. Even in academic centers, oncologists report varying confidence in their ability to use the genomic findings appropriately.[4]

At its most fundamental level, a genomic test with clinical utility should be predictive of a treatment response from a targeted agent. An early example in solid tumor oncology was the ability to test for *HER2* positivity as defined as fluorescent in situ hybridization–based gene amplification or immunohistochemistry to demonstrate overexpression of the protein. Positive results predicted response to

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trastuzumab-based therapies, whereas *HER2*-negative tumors did not derive benefit from this approach. As we have moved into multiplex testing of many genes or other biologic species, including messenger RNA and proteins, the same criteria should apply—is the variant alteration sufficiently predictive of response to a paired agent?

To date, success in using precision approaches to treatment have been mixed. A prospective phase II study of molecular profiling to assign matched therapy did not show superior outcomes for the matched group but suffered from serious methodologic design issues.[5] Large retrospective series have documented that 80%–90% of patients tested will have potentially actionable genomic alterations, although the definition of actionable can vary substantially.[6-9] However, only a minority of patients to date actually receive genomically directed therapy, usually on a clinical trial.

TECHNICAL ASPECTS OF NGS TESTING FOR THE CLINICIAN

Types of Alterations Detected

A range of genomic somatic variants can be ascertained with NGS, including single nucleotide variants (SNVs), also known as point mutations, and small insertions or deletions of bases (indels), which can lead to a nonfunctional or absent protein. Additionally, copy number variants, which reflect amplifications and deletions of genes and/or larger portions of a chromosome, gene rearrangements and fusion genes can be detected.

Read Depth and Coverage

This criterion refers to the number of times a particular base position in the DNA is read during the NGS analysis. The greater the coverage of a particular alteration, the more likely it is to be detected, which is especially important in tumor samples with low tumor content. By covering the same area of the gene fragment multiple times, the likelihood of picking up a variation of low allelic frequency is enhanced.

KEY POINTS

- **The goal of precision oncology has begun to be realized through multiplex molecular testing including NGS.**
- **Oncologists should be familiar with technical aspects of NGS to facilitate selecting the most appropriate and cost-effective testing platform.**
- **Considerations for molecular testing include which tissue type to utilize, timing of profiling in the disease course, extent of panel to order, and degree of clinical annotation reported.**
- **Actionable biomarkers of non–small cell lung cancer make this disease a paradigm for precision oncology at diagnosis of advanced disease, during therapy, and at time of progression.**
- **Interpretation of molecular data to facilitate best practice remains a challenge; clinical trial participation and sharing of linked molecular/clinical data sets are strongly encouraged.**

For hot spot testing, coverage of at least 100–300X is recommended.

Breadth and Scope of Testing

How many genes are included and what areas of the gene are analyzed. The most frequent NGS offerings today are hot spot testing, where alterations in exons or intron/exon junction areas of a preselected panel of cancer genes, including known activating oncogenes and tumor suppressor genes, are analyzed. Targeted hot spot panels focus on the best-annotated cancer genes, typically 35 to 350 genes, and provide high depth of coverage. The greater depth allows for assessing lower allele frequency and can account for intratumoral heterogeneity and low allele frequency of the alteration. NGS panels are not ideal for large-scale rearrangements and/or deletions and certain fusion genes. Addition of RNA sequencing can help identify these alterations.

Recently, whole-exome sequencing and whole-transcriptome sequencing have become available at academic and some commercial laboratories. At the moment, the value of whole-exome sequencing information is largely confined to the translational research space, where it offers enormous potential to produce novel variant-pathogenic associations leading to clinical trials investigating new agents. Lengthy turnaround time and lack of clinical associations for the large majority of genomic alterations preclude current effective clinical use.

Variant Calling

The bioinformatics approach to lining up the vast amount of information obtained in an NGS sequence, and accurately calling variants, is important to achieve quality results. Variant quality scores are generated for each test within a laboratory. Technical validity results can be provided to the practitioner upon request and may be useful in determining which assay to use due to interlaboratory differences. Federal guidelines for technical validity do not currently exist for NGS tests, which are classified as laboratory developed tests.

Variant Allele Frequency

This reflects the percentage of reads identifying a variant divided by the overall coverage of that locus. If tumor cells represent 100% of the sample DNA analyzed, heterozygous loci such as seen in germline mutations should be near 50% variant allele frequency, homozygous loci should be near 100% and reference loci should be near zero. In actual practice, the contamination from normal cells, local copy number alterations and tumor heterogeneity often yield unpredictable variant allele frequency.

Variant Meaning

Particularly for single nucleotide variants, it is not always easy to determine if a mutation is pathogenic or not. Publicly available databases, such as the Catalogue of Somatic Mutations in Cancer (COSMIC),[10] and the laboratory's internal databases, are reviewed by the evaluating pathologist, and a

determination is made whether the alteration is pathogenic, probably pathogenic, probably benign (meaning that it is likely a single nucleotide polymorphism without functional significance), benign representing a known single nucleotide polymorphism or a variant of unknown significance. As panel testing grows larger, the reporting of a variant of unknown significance has grown dramatically. It is hoped that in the future, sharing of genomic data will settle the issue for the growing number of alterations without a clinical correlate to call pathogenic or not. At the moment, utilizing a laboratory with deep molecular expertise, including molecular pathologists and geneticists on staff to help make the call, is extremely important. Alternatively, third-party organizations like N-of-1 use extensive resource capabilities to perform this function for laboratories or health care systems. Their role is to generate content relevant to the spectrum of variants so that clinically appropriate decisions can be made.

Tumor Only Versus Tumor Normal

When a tumor alone is tested, variants are compared with databases such as COSMIC and ClinVar[11] to determine whether the variant is a known pathogenic variant or a known single nucleotide polymorphism. Simultaneously sequencing tumor and normal tissue allows more precise calling of somatic mutations. Moreover, germline cancer predisposition genes can be clearly distinguished from somatic mutations in the same genes. As bioinformatics improves, value from the additional cost and complexity of sequencing both tumor and normal tissue routinely appears to be diminishing.[12] Though advances in bioinformatic techniques and reference germline databases are improving the accuracy of tumor-only sequencing, matched-tumor and normal-tissue sequencing is still the gold standard for somatic mutation detection.

IMPLEMENTING PRECISION ONCOLOGY TESTING AND INTERPRETATION IN PRACTICE

Doing precision oncology optimally depends on getting operational issues of testing right. Many considerations factor into selecting the right molecular test (Sidebar 1). Communication between medical oncologists and local pathologists becomes more critical than ever, particularly when the material will be sent to an outside facility. Local pathologists control the tissue, and the rationale for testing and the technical needs of the outside laboratory must be clearly stated. Standard operating procedures for molecular testing are useful to facilitate the process and improve the likelihood of timely, successful and accurate molecular result reporting. Importantly, tissue blocks must be assessed for adequate tumor tissue so that the results are interpretable and infrequent mutations can be characterized. Formalin-fixed, paraffin-embedded samples, including fine-needle aspirates and cytology samples with sufficient cellularity, can be used for NGS. The amount of DNA needed, expressed either in nanograms or the number of slides necessary to do testing, should be considered upfront to avoid a quantity-not-sufficient result. NGS technology requires at least 10 to 20 slides for a complete analysis, so the pathologist may have to evaluate multiple blocks to pick the sample with the most tumor tissue likely to yield an interpretable result.

SIDEBAR 1. Diagnostic Considerations in Molecular Testing

- Choice of assay and design
- Cost
- Tissue quality
- Turnaround time
- Clinical Laboratory Improvement Amendments and/or College of American Pathologists certification
- Bioinformatics analysis
- Clinical interpretation

Many patients undergo fine-needle aspiration or core biopsies for histologic diagnosis of malignancy, so remnant tissue may be sparse and careful decision making weighing the risks and benefits of biopsy for the express purpose of genomic testing is essential. For patients likely to require molecular testing at some point in their course, it is helpful to plan the initial biopsy of metastatic disease with this need in mind, so that tissue will be available later. Decisions to rebiopsy are complex and include morbidity and cost associated with the procedure versus the value of assessing the current tumor biology, particularly after exposure to genomic-altering agents.

Typically, specific informed consent for testing in the context of clinical decision making is not required for molecular profiling. An oncology clinic's general consent form for testing and treatment should cover molecular testing under the scope of medical practice. If patient results will be used in a prospective registry maintained by the practice, the institution, the testing laboratory or an academic consortium, informed consent based on a collection and analysis protocol is advisable. Should molecular alterations render a patient eligible for a clinical trial, the patient will be required to provide consent again to use this information for the study.

Who and When?

Many patients with metastatic disease may be good candidates for genomic testing at varying times in their clinical course. Patients with disease with fewer or no standard treatment options are candidates for early molecular profiling in the hope that they will be a candidate for a clinical trial evaluating a particular alteration. Such trials are called basket studies and typically are agnostic to the tissue of origin as long as specific variants are identified. When no trial is available or the patient is not eligible, using an approved agent for a specific alteration in another disease state (e.g., BRAF V600E mutation) might be appropriate after failure of standard therapy. Often there is no definitive trial data to base decisions on appropriateness of molecular targeted therapy in noninvestigational settings, and a balance of risks and benefits of an unknown approach should be carefully

TABLE 1. Online Knowledge Bases to Aid Clinical Decision Making

Resource	Website
My Cancer Genome	www.mycancergenome.org
JAX Clinical Knowledgebase	https://ckb.jax.org
Clinical Interpretation of Variants in Cancer	https://civic.genome.wustl.edu
Oncology Knowledge Base	https://oncokb.org
Clinical Genome	https://clinicalgenome.org

weighted. One potential hierarchy for decision making is presented in Table 1. Emerging evidence suggests overall tumor mutational load, analyzed in either large target gene panels of 300 to 600 genes or utilizing whole-exome sequencing, can be predictive of response to immune checkpoint inhibitors.[13,14] Additionally, mismatch repair deficiency assessment through genomic analysis is another valuable molecular assay with applicability to immune-oncology therapies.[15]

In general, early-stage patients undergoing definitive treatment do not typically require somatic gene panels. They will not have actionable alterations provided by NGS beyond what can be ascertained from standard histologic evaluation (e.g., estrogen receptor, progesterone receptor, and HER2 in the case of early-stage breast cancer). Broader molecular information will be of research use only.

For certain diseases where a first-line decision depends on multiple molecular markers, such as advanced non–small cell lung cancer, the use of a multiplex NGS panel at diagnosis becomes increasingly attractive given the growing number of targetable genes, the ability to simultaneously obtain the information from one sample and the ever lower cost of multiplex testing. Conversely, when other disease states exhaust evidence-based lines of standard therapy, panel testing is often appropriate if the patient remains a good candidate for further treatment.

A decision must be made whether to send a new biopsy or use archival tissue. Discordant genomic results may be seen between primary tumors and metastases, although this is highly disease site specific. For instance, *RAS* mutations in colorectal cancer are an early event in tumorigenesis, and reliable actionable information regarding use of anti-EGFR antibodies in the metastatic setting can obtained from the primary tumor.[16] Conversely, estrogen receptor 1 mutations conferring resistance to aromatase inhibitors in breast cancer appear to occur as a consequence of exposure to aromatase inhibitors and are unlikely to be present in the primary tumor.[17]

Molecular evolution of the tumor has been documented in many cancers under the selective pressure of prior therapy. This is most apparent in patients receiving targeted therapy whereby one of the mechanisms of resistance is secondary mutations in the gene of interest or along the relevant pathway.[18] In these circumstances, repeat biopsies may be very informative. Currently, the degree of heterogeneity exhibited by metastatic lesions in various sites is unclear. When heterogeneity is suspected, liquid biopsies for circulating tumor DNA or circulating tumor cells may reflect the clinical situation better, presumably integrating tumor status from a variety of sites and reflecting a composite mutational landscape.[19] This concept is attractive but far from established and requires further study. However, minimal invasive tissue sampling using blood samples to yield components such as circulating tumor DNA and circulating tumor cells is likely to become standard as an alternative to biopsy in clinically risky situations and in monitoring progressive alterations over tumor during exposure to targeted agents.

Molecular Tumor Board

As precision oncology expands, there is an increased need to include multiple domain experts in decision making to best harness the massive amount of information wisely. In the community setting where generalist oncologists now have to add management of genomic data to the clinical information, having access to additional expertise is enormously valuable. Either virtual or real-time molecular tumor boards can be accomplished in a practice setting. Ideally, members would include medical, surgical, and radiation oncologists as would be found in any conventional tumor board complimented by pathologists, genetic counselors, and research staff. Additional expertise is often available from commercial laboratories in the form of molecular pathologists and molecular geneticists. In more robust practice settings, access to biostatisticians, bioinformaticists, epidemiologists, and translational scientists may be available to participate. Multiple databases are publicly available for searching during molecular tumor boards to help in making variant-therapy associations. A number of free, frequently updated, and deeply curated websites offer information on a large number of variants and can be very useful to the practicing clinician in helping ascertain whether a particular therapy is right for a patient (Table 2). Archived, online molecular tumor boards such as those provided by ASCO are a good reference source.[20]

Data Integration

Integration of molecular data into electronic health records remains in the infancy of development. Typically, genomic results are sent to the oncologist in Portable Document Format and are therefore not available in structured fields that are searchable, filterable, and linked to clinical data. Integration of clinical and genomic data are a necessary goal to aid electronic matching of patients to molecular-based trials and to aggregate multiple N-of-1 experiments on individual patients to develop real-world evidence of benefit. Custom interfaces can be developed through relationships with third-party genomic laboratories and information technology companies or as a standalone in larger institutions that possess deep bioinformatics and information technology resources. Several laboratories now offer resources, such as the Caris Life Sciences Molecular Intelligence portal[21] and the Foundation Medicine Interactive Cancer Explorer

TABLE 2. U.S. Food and Drug Administration–Approved Drugs and Companion or Complementary Diagnostics for Non–Small Cell Lung Cancer

Targeted Agents	Tumor	Blood
EGFR		
Erlotinib	cobas EGFR Mutation Test v2	cobas EGFR Mutation Test v2
Gefitinib	Therascreen EGFR RGQ PCR Kit	
Afatinib	Therascreen EGFR RGQ PCR Kit	
Osimertinib	cobas EGFR Mutation Test v2	cobas EGFR Mutation Test v2
ALK/ROS1		
Crizotinib	ALK IHC (D5F3, Ventana)	
	ALK Break Apart FISH Probe Kit (Vysis)	
Ceritinib		
Alectinib		
PD-L1		
Pembrolizumab	PD-L1 IHC (22c3, Dako)	
Nivolumab	PD-L1 IHC (28-8, Dako)	
Atezolizumab	PD-L1 IHC (SP142, Ventana)	

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PCR, polymerase chain reaction, RGQ, Rotor-Gene Q.

portal,[22] which allow result searches with some data-basing capability, and provide documentation of available preclinical and clinical research pertaining to observed variants and therapies. The clinical interpretation of molecular alterations is at the heart of providing the value of precision oncology.

NON–SMALL CELL LUNG CANCER AS THE PARADIGM OF PRECISION ONCOLOGY

Recently, lung cancer, after several decades of choosing platinum-based doublets for every patient, has undergone a transformation integrating precision medicine. There are now numerous biomarkers needed for treatment assessment in patients with lung cancer (Table 3), and this number will continue to increase as new molecularly defined subsets are identified. When diagnosing a patient, measuring *EGFR* mutation, and *ALK* or *ROS1* fusions, will help determine whether a tyrosine kinase inhibitor (TKI) should be used in lieu of cytotoxic chemotherapy.[23] Recently, PD-L1 expression (tumor proportion score ≥ 50%) has proven to be effective in enriching patients with lung cancer who may benefit from immunotherapy (pembrolizumab) instead of chemotherapy.[24] When considering patients who are diagnosed with non–small cell lung cancer, these biomarkers may alter treatment decisions in approximately 50% of patients to biologic agents instead of cytotoxic chemotherapy.

Increasing utilization of targeted therapies also brings to the forefront the growing clinical challenge of acquired drug resistance, currently a very active area of research. This is best exemplified by the emergence of the EGFR T790M mutation, which occurs in 50% of patients previously treated with an EGFR-TKI.[25] These gatekeeper mutations, which directly interfere with drug-target interactions, are a recurring theme across many kinase-driven tumors treated with kinase inhibitors.[26] Propelling their significance is the accompanying development of (1) therapies designed to target these mutations and overcome resistance (e.g., T790M/osimertinib), and (2) noninvasive assays that can monitor status of the resistance mutations (e.g., cobas EGFR Mutation Test v2), sequentially and in real time.

The complexity associated with acquired resistance is compounded by intra- and intertumor heterogeneity[27] and adaptive tumor biology that is facilitated by genetic instability.[25] The selective pressure of kinase inhibition can lead to the disappearance of drug resistance mutations,[28] emergence of varying resistance mechanisms at different metastatic sites,[29] histology transformation to small cell lung cancer,[30] or emergence of new resistant clones (e.g., C797S, Leu792).[31] Each of these situations presents unique treatment approaches. For example, there are reported responses to specific small cell lung cancer treatments for tumors that have transformed into small cell lung cancer.[30] Rechallenge with first-generation EGFR TKIs in patients where the T790M clone disappearshas also been successful.[32]

The utilization of the evolving genetic landscape of tumors to inform treatment decisions will be made possible through sequential and real-time monitoring of the patient. Rebiopsy with traditional biopsy techniques at time of progression, which may occur at multiple time points through the treatment course, is not safe for the patient, nor feasible from a practical perspective. Furthermore, patients may have multiple tumors. Therefore, the challenge is also identifying the tumor that would yield the best-quality biopsy; however, that approach still does not address the potential for intertumor heterogeneity.

Much progress has been made to address these complex and evolving issues through the development of noninvasive plasma-based assays for the detection of emerging

resistance mutations. The U.S. Food and Drug Administration approved the first liquid biopsy–based companion diagnostic to detect the T790M resistance mutation in patients whose disease is progressing on erlotinib, gefitinib or afatinib, for consideration of osimertinib. Furthermore, the search for assays, utilizing PCR- or NGS-based detection methods, that have high sensitivity and specificity, are cost-effective, and have high concordance with tumor biopsies is intensifying.[33-35] Some studies note, however, that liquid biopsy is still not ready for replacement of tumor biopsies but, in some instances, such as monitoring response or progression, may be prioritized.[36,37] Therefore, in cases in which a liquid biopsy test is negative for a resistance mutation, guidelines recommend a tissue biopsy.[23]

Collectively, these research efforts are converging to create a new paradigm in precision medicine in oncology. The discovery of resistance mutations, designing new drugs that target these resistance mechanisms, and development of noninvasive techniques to monitor emergence of resistance are all integral components advancing the field forward. The following case highlights the precision medicine revolution occurring in lung cancer.

Case Example

Mr. G, a 55-year-old man, has felt fatigued during the last couple months. A persistent cough led to a doctor's appointment. He did not have a history of smoking, although his parents did smoke cigarettes. His performance status was good, and he did not have any other chronic medical conditions. Radiographic imaging with CT identified several lesions in the lungs bilaterally. A CT–guided biopsy revealed a well-differentiated adenocarcinoma. The rest of the staging scans revealed stage IV disease in the bilateral lungs. Molecular testing was performed and revealed an exon 19 deletion. The patient started treatment with afatinib 40 mg daily. He had grade 1 acne and grade 1 diarrhea. Follow-up CT after 2 months of treatment revealed significant response of the tumors. He continued treatment, eventually dose reducing to 30 mg after several months of treatment. The patient continued taking afatinib for 20 months when a restaging scan revealed new disease bilaterally. The disease was peripherally located, with the largest lesion approximately 1 cm. Performing a tissue biopsy would be challenging but feasible. A serum circulating tumor DNA test revealed a T790M mutation. The patient then started treatment with osimertinib 80 mg daily. Restaging after 2 months revealed shrinkage of the tumors. He is tolerating the therapy well and continues at this time.

PRECISION ONCOLOGY IN THE ERA OF VALUE-BASED MEDICINE

The goal of precision testing is to identify the optimal therapy for the patient that will maximize their survival and quality of life. In some cases, there are well-validated biomarkers in a specific tumor context with high-quality clinical evidence (often approved by the U.S. Food and Drug Administration) of improved efficacy using a specific targeted agent or class of agents vis-à-vis an unselective therapy. For example, every new diagnosis of metastatic non–small cell lung cancer should undergo molecular testing for *EGFR* mutation, *ALK* rearrangement, *ROS1* rearrangement and *PD-L1* expression, all of which have demonstrated improved benefit with targeted agents for tumors positive for these biomarkers compared with chemotherapy in the first-line setting. In contrast, mutated *RAS* is a contraindication for the addition of anti-EGFR therapy for metastatic colorectal cancer due to well-demonstrated lack of efficacy in this setting. Testing for these biomarkers in the appropriate clinical context is the standard of care and is covered by insurance. With proven benefits, clear indications and financial coverage, the major challenge in this subset is underutilization of testing and dissemination and implementation of timely adoption to maximize benefits for all patients. The National Comprehensive Cancer Network, ASCO, and other tumor-specific societies provide regularly updated guidelines and are good references for evidence-based testing. Examples of these validated context-biomarker-drug combinations are listed in Table 3.

However, there is a much longer list of context-biomarker-drug combinations without sufficient evidence to make standard of care (Table 4). The cost of NGS has decreased by orders of magnitude in recent years. Cancer centers and other academic medical centers often have their own "home-grown" panels of cancer genes, anda number of companies offer gene panel sequencing for several thousand dollars within a few weeks. Given the reasonable cost, rapid turnaround time, and the potential for discovery of

TABLE 3. Examples of U.S Food and Drug Administration–Approved Biomarkers/Drug Pairs for Specific Tumors

Biomarker	Drug	Tumor Context
HER2/neu (ERBB2) expression	Trastuzumab, pertuzumab	Metastatic breast cancer
EGFR L858R	Erlotinib	Metastatic NSCLC
*BCR-ABL*1 fusion	Imatinib	Chronic myeloid leukemia
17p deletion	Venetoclax	Chronic lymphocytic leukemia
KIT expression	Imatinib	Gastrointestinal stromal tumor
BRAF V600E	BRAF and MEK inhibitors	Metastatic melanoma

Abbreviation: NSCLC, non–small cell lung cancer.

TABLE 4. Examples of Precision Tests Without Established Clinical Utility

Biomarker	Drug	Tumor Context
EGFR L858R	EGFR TKI	Non-NSCLC tumor
BRAF V600E mutation	BRAF and MEK inhibitors	Nonmelanoma
BRAF L597 mutations	BRAF and MEK inhibitors	Any tumor
ATM mutation	PARP inhibitor + alkylator	Any tumor

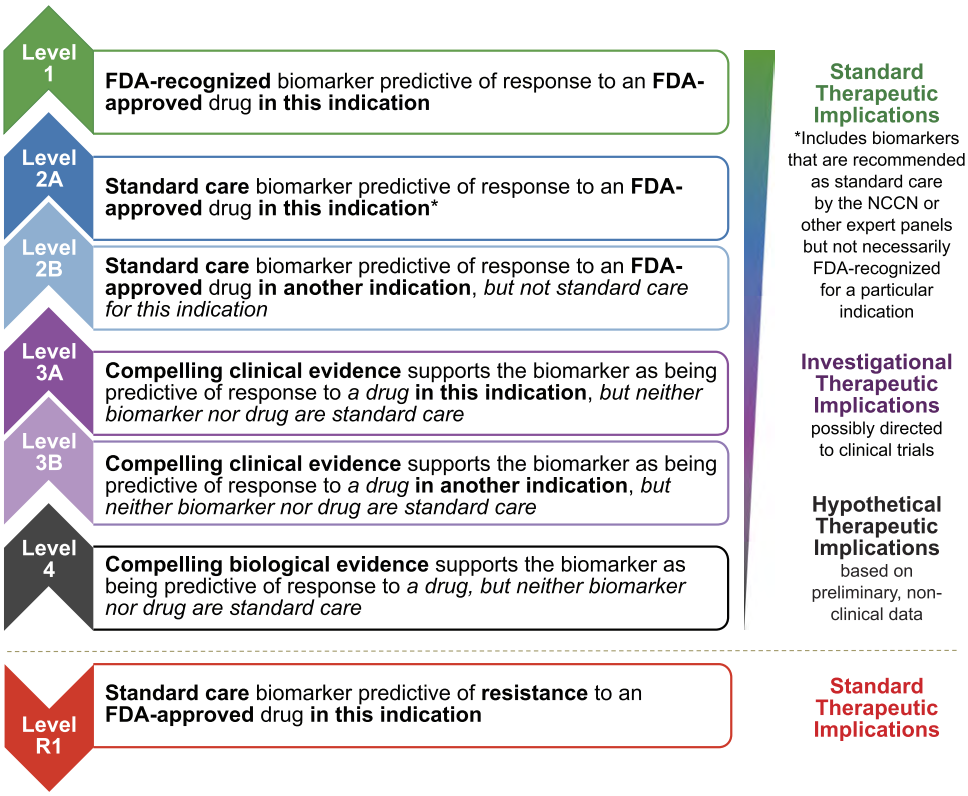
Abbreviations: NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

new biomarkers that are targetable, the use of panel testing has proliferated in academic medical centers and the community. Standard biomarkers are tested in these gene panels, but in addition, alterations in genes without sufficient evidence of corresponding efficacious therapy are also routinely presented.

Interpretation and communication of this data to patients and translation into therapeutic interventions is a daunting challenge for clinicians. For example, *BRAF* V600E–mutated melanomas respond exceptionally well to *BRAF* and *MEK* inhibitors, but the response in colorectal cancers to these drugs as monotherapies has been disappointing.[38,39] Closely curated databases of genomic alterations such as OncoKB[40] and MyCancerGenome[41] have developed frameworks to assist prioritization of therapies for genomic alterations (Fig. 1). However, use of these biomarkers to select therapy is still largely experimental and should be done in the setting of a clinical study at an experienced center, where structured support is available for the patient and data can be appropriately collected and aggregated to answer clinical and research questions. It should be emphasized that in communication with patients, clinicians should make clear that beyond the limited set of validated tests with corresponding validated therapies, selection of therapy based on tumor genomic profiles is experimental and with no clearly established benefit.

Whenever possible, patients should be encouraged to participate in clinical studies. Molecular stratification of patient tumors increases the challenge of accruing sufficient patients to power detection of benefit (or lack thereof) in these tumor subsets. A variety of clinical trial designs have been developed to validate predictive biomarkers, including random assignment of patients stratified by biomarkers (IPASS,[42] MARVEL[43]), enrichment studies with assignment to study arms by biomarker status (BATTLE,[44] I-SPY 2[45]) and adaptive trial designs.[46] NCI-MATCH (NCT02465060) is a National Cancer Institute–sponsored clinical trial designed to

FIGURE 1. Example of Hierarchy of Evidence of Genomic Alterations



Used with permission.[40]

handle the problem of low accrual by combining multiple tumor types as a basket trial based on molecular alteration rather than tumor type, as well as to maximize the number of participating sites to optimize enrollment.[47] ASCO has initiated the Targeted Agent and Profiling Utilization Registry Study (TAPUR), which will collect real-world data on use of approved agents to treat molecular targeted variants across disease types.[48] Umbrella trials, such as the National Cancer Institute–sponsored Lung MAP trial (NCT02154490), recruit patients of a given tumor type (recurrent metastatic squamous cell carcinoma) and place them into arms based on biomarkers (e.g., *PI3KCA* mutation) with targeted therapies (e.g., taselisib).[49]

The vast majority of patients do not participate in biomarker-driven clinical studies, and their genomic and clinical data would be a huge boon for research if able to be collected, aggregated and structured appropriately. This has prompted initiatives to share and pool data between multiple institutions, such as the American Association for Cancer Research–sponsored GENIE project[50] and ORIEN.[51] Further, direct patient collaborations such as the Metastatic Breast Cancer Project,[52] in which individual patients directly give permission for clinical data and tumor tissue to be collected from disparate medical centers and centrally analyzed, could provide important data in low-frequency disease. ASCO is further developing the CancerLinQ[53] program to create a data platform in which clinical (and genomic, where available) data from the much larger group of patients treated in a broader range of settings can be collected and analyzed both for clinical and research benefit. The Cancer Moonshot Initiative[54] identified data aggregation and a common data ecosystem as key components of accelerating the pace of cancer research.

Beyond the current set of existing tests, new promising technologies are being developed. Cell-free tumor DNA found in blood plasma has been detected in multiple metastatic tumor settings[19]; a liquid biopsy avoids the morbidity of traditional biopsies and allows more frequent monitoring, enabling earlier detection of response or development of resistance. Further, tumor genomic heterogeneity has been demonstrated between primary and metastatic lesions and [55] different metastatic lesions[56,57] and even in different regions[58] of the same lesion. A liquid biopsy may thus present an integrated profile of the tumor. Further, novel techniques using bio-informatic approaches to infer deficiencies in DNA repair pathways from genomic data[59] may predict response to DNA-damaging therapies. Single-cell RNA sequencing,[60] or deconvolution of bulk RNA sequencing[61] to identify specific immune cell subsets in the tumor microenvironment,[62] may assist in predicting which tumors are likely to respond to immune therapy. It is likely that in the future mulitple omic approaches including genomic DNA alterations, epigenetic modifications, transcriptome-based expression of mRNA, proteomic expression, and alterations in regulatory molecules such as microRNA and immune factors will provide a more integrated portrait of the tumor and microenvironment.

In a value-based reimbursement world, where quality is defined by outcome/cost, it is essential for oncology practices to maintain up-to-date lists of biomarker/target–driven pairs for which there is compelling evidence that biomarker testing identifies an important therapeutic opportunity (e.g., crizotinib for *ALK*-rearranged lung cancer) or allows for avoidance of a toxic therapy (e.g., cetuximab in *KRAS* mutant colorectal cancer). Quality metrics will increasingly focus on avoiding underutilization of these established tests, as clinical evidence has already established biomarker selected therapy as a superior strategy.

In contrast, use of broad panel tests is more complex. Payers may have prior authorizations built in to limit use of panel testing in certain clinical circumstances. Panel tests may be valuable if they are used to identify a batch of validated biomarker/target–driven pairs as well as to support investigation. However, overuse of panel tests should also be avoided. It is critical that when these tests are obtained, oncologists have access to the necessary support for interpretation. Finally, it is anticipated that linking these genomic reports with detailed treatment histories and clinical outcomes such as response, duration of response and survival will accelerate discovery of efficacious therapeutic strategies.

CONCLUSION

Precision oncology has clinical utility in the here and now, but the promise for the future is much greater. With rapid improvements in technology, enhanced ability to probe beyond single DNA alterations to other molecular components that influence tumor behavior and represent targets for new therapeutics is clearly in sight. Responsible use of this remarkable technology will depend on generating evidence through new clinical trial designs, aggregation of molecular and clinical data in real-world databases and careful analysis to determine relevant target-agent associations. Ultimately, the approach must prove value across specific patient populations. The practicing oncologist should make an effort to understand the power and limitations of the current testing and treatment landscape to help patients make the best informed decisions.

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CENTRAL NERVOUS SYSTEM TUMORS

American Society for Radiation Oncology 2016 Annual Meeting: Central Nervous System Abstracts

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OVERVIEW

The American Society for Radiation Oncology's (ASTRO) 2016 scientific program presented a number of excellent abstracts focusing on brain and spine tumors. Selected abstracts will be reviewed in this article.

There were a number of excellent abstracts regarding central nervous system tumors presented at ASTRO's 2016 Annual Meeting. This review will highlight some of these abstracts, but is not meant to be comprehensive. The exclusion of some abstracts does not reflect on the quality of those abstracts, as all abstracts presented were superb.

GLIOBLASTOMA/GLIOMA

EORTC 26981-22981 defined the current standard of care for glioblastoma, showing that the addition of temozolomide resulted in a survival advantage.[1] In a secondary analysis, Hegi et al[2] demonstrated that the methylation of O-6-methylguanine-DNA methyltransferase resulted in better survival and response to temozolomide. However, there has not been an updated nomogram to help predict survival that incorporates O-6-methylguanine-DNA methyltransferase methylation. Gittleman et al[3] used data from the Radiation Therapy Oncology Group (RTOG) 0525 and 0825 studies to develop this nomogram. They found that older age at diagnosis, male gender, lower Karnofsky performance status (KPS), lack of a gross total resection, and unmethylated O-6-methylguanine-DNA methyltransferase predicted for worse survival. A nomogram was developed and can be accessed through this website: http://cancer4.case.edu/rCalculator/rCalculator.html.

Treatment options for recurrent glioblastoma are limited. A phase I trial was conducted at Yale looking at mibefradil and reported by Lester-Coll et al.[4] This drug is a calcium channel blocker, but was found to have activity in gliomas as a radiation sensitizer. In this study, mibefradil was given 5 days prior to resection, and the tissue was analyzed for the presence of drug. Radiation was given to a total dose of 30 Gy in five fractions. Drug dose was escalated in a 3 + 3 design. The study was able to escalate to a final dose level of 200 mg per day. Median progression-free survival was 5.25 months, and median overall survival (OS) was 12.75 months. One patient had a complete response. Drug levels in the tumor correlated to what was required for tumor cell sensitization. The researchers are currently doing a phase I trial in upfront glioblastoma.

Other studies included one that looked at salicylic acid (Zhang et al[5]), which appears to affect growth inhibition and apoptosis related to c-Jun-N-terminal kinase and AMPK (AMP-activated protein kinase) activation and arrest in the G2/M phase in vitro. This may have promise for a future study.

A couple of studies specifically looked at institutional data regarding low-grade gliomas. The Mayo Clinic looked at their series of patients with low-grade glioma. Kreofsky et al[6] found that the median OS was 11.8, 8.1, 14.2, and 14 years for observation, radiation therapy (RT) alone, chemotherapy alone, and RT and chemotherapy, respectively ($p = .02$). They recommended that observation is reasonable for appropriately selected patients with low-grade glioma, in particular those younger than age 40 and with a gross total resection. Wahl et al[7] looked at patients treated at the University of California, San Francisco, and found that patients with 1p19q codeletion and pretreatment tumor volume of less than 68 cc had 0% risk of progression during treatment. Median progression-free survival was 4.9 years, and median OS was not reached. This suggests that there may be a subgroup of patients who can avoid radiation.

BRAIN METASTASES

Studies to date looking at stereotactic radiosurgery (SRS) alone versus SRS with whole-brain RT (WBRT) have failed to demonstrate a strong role for WBRT upfront given its effect on neurocognitive function and quality of life.[8,9] It is recognized, however, that there might be patients who may benefit, as a subset analysis of a prospective trial

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demonstrated a potential survival benefit to WBRT.[10] Churilla et al[11] performed a secondary analysis of EORTC 22952-26001 that randomly selected patients who received SRS or surgical resection to observation versus WBRT. They asked the question whether WBRT translates into a survival benefit for patients with a limited competing risk from their extracranial disease. They found no interaction from the effect of WBRT and time to extracranial progression. There was no difference in OS between patients with favorable versus unfavorable graded prognostic assessment, so the patients with the best survival did not seem to benefit from WBRT. The study authors concluded that WBRT could be omitted in patients undergoing SRS or surgical resection.

It is clear from these studies, however, that withholding WBRT does increase the risk for intracranial recurrence.[8,10,12-14] Thus, patients who do not receive WBRT have a higher rate of needing salvage therapies, including more SRS. Given the costs of SRS, there is concern that withholding WBRT will increase the overall costs of brain metastases management in a patient. Miller et al[15] used single-institutional data comparing various costs including cancer-specific costs, brain metastases–specific cost, and cumulative total costs of health care between those receiving SRS alone and those receiving SRS and WBRT upfront. The study authors showed that there was no difference in the various costs between the two cohorts. Additional sensitivity analyses and modeling were recommended by the authors to identify if there is a subset of patients for which SRS with WBRT is most cost-effective.

Brown et al[16] reported as a late-breaking abstract the results of NCCTG N107C. This was a phase III trial comparing WBRT and SRS to the resection cavity for patients with resected brain metastases. In total, 194 patients were enrolled in this study. Median follow-up was 15.6 months. There was shorter cognitive deterioration-free survival of 2.8 months in those receiving WBRT compared with 3.2 months for those that received SRS to the resection cavity ($p < .0001$). As expected, overall intracranial tumor control at 12 months was 78.6% with WBRT and was better compared with SRS alone, which was 54.7% ($p = .0001$). However, quality of life was better in the SRS arm. One interesting result was that surgical bed relapse at 12 months was rather high at 44.4% compared with SRS at 21.8% for WBRT. The final manuscript is eagerly awaited to see if these factors contributed to a higher than expected surgical bed relapse rate for the SRS-only group.

Mahajan et al[17] reported the results of an MD Anderson Cancer Center prospective study comparing observation and SRS to the resection cavity for completely resected brain metastases. In this phase III study, 132 patients with 140 resected brain metastases were randomly selected to receive SRS to cavity versus observation. Median follow-up was 12.6 months. The authors found that local control was better in the SRS arm at 72% at 12 months compared with 45% for observation. There was no difference in distant brain metastasis control. OS was the same in both arms. Those with a preoperative tumor size of more than 3 cm in diameter benefitted the most. Adjuvant SRS is recommended postresection for local control over no additional therapy.

There has been interest in using systemic agents to manage brain metastases upfront. Magnuson et al[18] performed a multi-institutional analysis comparing upfront epidermal growth factor receptor tyrosine kinase inhibitor therapy compared with upfront RT. From four institutions, 162 patients were pooled. Median OS was longer in the upfront RT group at 29.4 months compared with upfront epidermal growth factor receptor tyrosine kinase inhibitor therapy at 20.5 months ($p = .0015$). Upfront SRS had significantly improved survival, but upfront WBRT did not. Median intracranial progression-free survival was improved in patients receiving upfront RT compared with upfront epidermal growth factor receptor tyrosine kinase inhibitor therapy (21.1 vs. 13.4 months; $p = .003$). The authors stressed the importance of a prospective study given these results.

KEY POINTS

- **For gliomas, and in particular glioblastoma, there is a need to better determine prognosis for treatment selection.**
- **Systemic therapies need further study. This includes a better understanding of patients who may avoid radiation, particularly in low-grade gliomas.**
- **More studies seem to prove stereotactic radiosurgery alone is the best approach for patients with a limited number of brain metastases. In this era, an understanding of the costs of stereotactic radiosurgery is necessary.**
- **Resection cavity radiosurgery may be an alternative to whole-brain radiation for patients with resected brain metastases. Systemic agents need further study in the management of brain metastases.**
- **Spine stereotactic radiosurgery has become an established technique in treating spine metastases. The presented abstracts focused on understanding the toxicities and survival rates following spine radiosurgery.**

SPINE STEREOTACTIC RADIOSURGERY

The role of spine stereotactic radiosurgery is being studied by RTOG 0631, a phase II/III study with the phase III component comparing single-fraction conventional radiation with spine SRS.[19] One toxicity that has been noted by those treating with SRS is vertebral compression fractures (VCF). Prior studies have shown that a dose of 20 Gy and more per fraction increases the risk of VCF.[20] Thibault et al[21] used CT-based segmentation to assess the volume of lytic vertebral body metastatic disease and predict the risk of VCF for spine radiosurgery. In 55 patients, 100 spine segments were analyzed. Of these, 56% had lytic disease. Median dose was 24 Gy in two fractions. Those who developed fractures had pre-existing osteolytic disease. The threshold for VCF was a lytic tumor burden of 11.6% or more. One may consider prophylactic stabilization or vertebral augmentation in this group of patients.

Using the patients treated at MD Anderson Cancer Center, Deegan et al[22] looked at long-term toxicities from spine SRS. This includes grade 4 myelopathy in 1.7%, sensory radiculopathy in 8.5%, and vertebral body collapse in 13.6%, with 10.2% requiring vertebroplasty or surgery. Most of these occur within 2 years of treatment. The only toxicity that occurred after 4 years was a VCF.

There is no good way to predict how patients receiving spine SRS will do with regard to survival. This is important, as spine SRS is a relatively expensive treatment but is felt to improve local control with good pain relief compared with conventional RT. Spine SRS may be offered to patients with better survival, but those who have short anticipated survival may be best treated with conventional RT. Balagamwala et al[23] used a database comprising 444 patients and looked at factors that contribute to survival. On univariate analysis, patients with a KPS higher than 70, controlled systemic disease, single-level spine disease, absence of visceral metastases, and longer time from diagnosis of primary had improved survival. The authors did recursive partitioning analysis. Class I patients were defined as KPS higher than 70 and controlled systemic disease and had a median OS of 26.7 months. Class II patients were defined as KPS higher than 70 and uncontrolled systemic disease or KPS 70 or lower, age 54 or older, and no visceral metastases. These patients had a median OS of 13.4 months. Recursive partitioning analysis class III patients had KPS 70 or lower, age 54 or older, and visceral metastases or KPS 70 or less and age younger than 54. The median OS was only 4.5 months in this group. The authors felt that spine SRS as upfront treatment is best reserved for patients who are recursive partitioning analysis class I and II. For class III patients, conventional RT may be favored, and spine SRS can be reserved as salvage treatment.

CONCLUSION

There were numerous excellent abstracts presented at ASTRO's 2016 Annual Meeting. Only a few of these were reviewed in this summary. With continuing research like this, better treatments with lower toxicities and improved survival may be discovered.

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Beyond Alkylating Agents for Gliomas: *Quo Vadimus*?

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OVERVIEW

Recent advances in therapies have yielded notable success in terms of improved survival in several cancers. However, such treatments have failed to improve outcome in patients with gliomas for whom surgery followed by radiation therapy and chemotherapy with alkylating agents remain the standard of care. Genetic and epigenetic studies have helped identify several alterations specific to gliomas. Attempts to target these altered pathways have been unsuccessful due to various factors, including tumor heterogeneity, adaptive resistance of tumor cells, and limitations of access across the blood-brain barrier. Novel therapies that circumvent such limitations have been the focus of intense study and include approaches such as immunotherapy, targeting of signaling hubs and metabolic pathways, and use of biologic agents. Immunotherapeutic approaches including tumor-targeted vaccines, immune checkpoint blockade, antibody-drug conjugates, and chimeric antigen receptor–expressing cell therapies are in various stages of clinical trials. Similarly, identification of key metabolic pathways or converging hubs of signaling pathways that are tumor specific have yielded novel targets for therapy of gliomas. In addition, the failure of conventional therapies against gliomas has led to a growing interest among patients in the use of alternative therapies, which in turn has necessitated developing evidence-based approaches to the application of such therapies in clinical studies. The development of these novel approaches bears potential for providing breakthroughs in treatment of more meaningful and improved outcomes for patients with gliomas.

The past decade has seen important breakthroughs in the treatment of newly diagnosed gliomas with the publication of mature and practice-changing results of several clinical trials. However, nearly all these trials have been based on the combination of radiation therapy and alkylating agents. The promise of targeted therapies, which has resulted in notable successes in several other cancers, has not been realized in patients with gliomas despite numerous trials of agents targeting the most common signaling pathways altered in these tumors.[1] Although ongoing studies are actively examining the mechanisms for the failure of targeted therapies in gliomas, alternative approaches that seek to attack tumor cells in ways that circumvent tumor resistance and heterogeneity are being increasingly explored. One of the more exciting of therapeutic strategies that has emerged in recent years involves immunotherapy involving a variety of methods including cell-free and cell-based vaccines, antibody-drug conjugates, and checkpoint blockade, which exploit the expression of tumor-specific antigens and neutralize tumor-mediated immunosuppression.[2] Another emerging area is the identification and targeting of tumor-specific metabolic and protein-processing pathways that act as hubs for converging cellular processes vital for tumor cell survival.[3] Targeting such hubs has the potential to disable the complex signaling networks that tumor cells depend on for survival and resistance to therapy. However, the slow progress in developing effective therapies against gliomas has also resulted in patients seeking alternative and often untested therapies that are used concurrent with or as alternatives to standard therapy[4]; the rigorous assessment of such treatments through systematic studies is emerging as an equally important aspect of cancer care. The following sections examine the current state of these varied approaches and their impact on the treatment of patients with gliomas.

NEW APPROACHES TO GLIOMA THERAPY: TARGETED THERAPIES AND BEYOND

Current Standards of Care for Gliomas

Recent studies have established new standards of care for patients with gliomas. For adults with World Health Organization (WHO) grade II glioma after maximum safe resection, radiation therapy (RT) followed by chemotherapy using a combination of procarbazine, lomustine, and vincristine resulted in improvement of survival compared with RT alone, particularly for patients with low-grade oligodendroglioma.[5] The same regimen also resulted in improved overall survival (OS) in patients with WHO grade III (anaplastic) oligodendrogliomas that had codeletions of chromosome 1p and 19q.[6,7] Further characterization of this benefit is being

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explored in a randomized CODEL trial that seeks to compare the benefits of RT with procarbazine, lomustine, and vincristine with that of RT with temozolomide (TMZ) against 1p/19q codeleted anaplastic gliomas.[8] The optimal standard of care for patients with anaplastic gliomas without 1p/19q codeletion is currently being explored in a multicenter CATNON trial that randomly assigned patients to four different treatment arms to assess the benefit of adding TMZ as adjuvant or concurrent therapy with RT. Recently reported interim results of this study indicated that the two arms with adjuvant TMZ had a better outcome compared with the two without.[9] Based on these data, the trial has been modified to eliminate the arms without adjuvant TMZ and now continues with two arms (RT followed by TMZ vs. RT with TMZ followed by TMZ), the results of which are awaited. In the setting of recurrent grade II or grade III gliomas, there are no clear new standards of care; currently used treatments include reirradiation, alkylating agents, and treatment of secondary glioblastoma (GBM) with bevacizumab. Lastly, the current standard of care for adults up to age 70 with newly diagnosed GBM after maximum safe resection consists of chemoradiation therapy (6 weeks) with concurrent daily TMZ followed by up to six monthly cycles of adjuvant TMZ, which improved survival particularly in the subgroup of patients in whom tumors have promoter methylation of methyl-guanyl methyltransferase (*MGMT*).[10,11] Efforts to intensify adjuvant TMZ dosing or to add bevacizumab to this regimen have failed to improve survival in this setting. However, recent data showed that the addition of low-intensity alternating electrical fields to the standard of care therapy along with adjuvant TMZ, using transducer arrays applied to the scalp for more than 18 hours a day (tumor-treatment fields; Optune) improved OS in adults with newly diagnosed GBM independent of the *MGMT* promoter status.[12] In elderly patients, a shortened course of chemoradiotherapy (3 weeks) followed by up to 12 months of adjuvant TMZ was both tolerated and improved OS compared with RT alone.[13] Treatments for recurrent GBM includes bevacizumab, nitrosoureas, tumor-treatment fields, and several other chemotherapeutic agents that are currently less frequently used given their limited benefit. None of these treatments have provided a survival benefit, although bevacizumab received regulatory approval based on response rate and improved progression-free survival (PFS).[14,15]

KEY POINTS

- **Alkylating therapies remain the cornerstone of standard-of-care therapy for gliomas despite advances.**
- **Identification and targeting of specific signaling pathways most commonly altered in gliomas have failed to yield improvement in outcomes in patients with these tumors.**
- **There is urgent need for a broader targeting of the diverse pathways that mediate adaptive resistance to treatment and facilitate tumor recurrence.**
- **Novel strategies include immunotherapeutic approaches, targeting of metabolic pathways, and harnessing of newer insights into the biology of gliomas.**
- **Additionally, the lack of curative therapies for gliomas has also increasingly encouraged patients to use alternative therapies with little scientific support. Critical assessment and systematic study of such treatment options is essential for providing the best care for patients with gliomas.**

Targeted Therapies Against Gliomas: Rationale and Limitations

Extensive genetic, epigenetic, and molecular studies have been conducted to delineate the key signaling pathways and alterations in gliomas.[16-20] Early studies had identified key roles for three major pathways in gliomagenesis and progression including (1) the receptor tyrosine kinase/phosphoinositide 3-kinase (PI3K)/Akt pathway, including alterations in *EGFR*, *Her2*, *PDGFR*, *FGFR*, and *cMET* (approximately 90%), (2) the p53 pathway including alterations in *TP53*, *MDM2*, and *MDM4* (approximately 85%), and (3) the Rb and cell cycle–related pathways including defects in *RB, CDKN, CDK,* and cyclins (approximately 80%).[16] More in-depth analysis has revealed the striking complexity of genetic and epigenetic changes in both low- and high-grade gliomas.[19,20] These data provided strong rationale for several clinical trials targeting key GBM relevant pathways, especially those of receptor tyrosine kinase inhibitors initially in the setting of recurrent GBM and subsequently in the newly diagnosed setting; however, it was soon evident that single-agent trials of these agents were largely ineffective in providing benefit in either PFS or OS for this patient population.[21-23] Focusing on the strategy of overcoming bypass pathways that the tumor cells deploy to establish resistance to the action of single agents, combination strategies targeting multiple pathways were subsequently tried but were again strikingly unsuccessful in providing an improvement in outcome.[24] These results point to limitations in our understanding of the complexity of survival and resistance mechanisms adopted by glioma cells and the need for more concerted effort to delineate the adaptive mechanisms of these cells that can be new targets for therapy.

Recent Advances in Understanding the Biology of Gliomas

In-depth genetic and epigenetic analyses of large numbers of low- and high-grade gliomas have recently yielded novel insights into the complexity of the alterations in these tumors.[25] From a clinical perspective, this has also provided evidence that histologic diagnosis may not accurately correlate with outcome; this has led to a revision of the WHO classification of brain tumors with modifications that allow incorporation of such molecular markers into conventional diagnostic approaches to align better with clinical outcome.[26] Although some of these markers have shown potential to be predictive markers that can help selection of treatment options, most are prognostic in nature and inform largely of the intrinsic behavior of the tumors without

specificity to the treatments used.[6,7,11,27-29] From the perspective of the basic biology of the tumors, the studies have shown that tumor heterogeneity is one of the most critical factors that dictates tumor behavior. Such heterogeneity is seen to be not only spatial (with different regions of the same glioma evolving along distinct pathways) but also temporal (with emergence of new mutations and hence biologic behavior with tumor treatment and progression).[30-32] It is also becoming clear that treatments can induce mutations that can contribute to clonal evolution of gliomas.[33] Such heterogeneity has provided an explanation for why therapies targeting single or even multiple pathways in gliomas fail to uniformly affect the majority of tumor cells or eliminate emergent clones during the course of tumor growth and therapy.

Emergent Targets for Antiglioma Therapies

Novel therapies for gliomas must overcome tumor heterogeneity and disable resistance mechanisms to treatment to be effective in improving outcome. The search for such strategies has resulted in the identification of novel targets that promise to change conventional approaches and are in advanced clinical studies or in early stages of investigations. Immunotherapy has emerged as one of the most promising strategies against gliomas currently in clinical trials and is aimed at either disabling immunosuppression induced by tumor cells or enable tumor targeting of immune cells by identification of overexpressed proteins or neoantigens. Several other emerging areas that bear promise to change therapeutic outcome of patients include targeting signaling hubs, use of biologic agents, disabling tumor-specific metabolic pathways, and activating death pathways that can eliminate tumor cells independent of internal tumor heterogeneity. The following sections briefly review these approaches and outline ongoing or potential clinical trial strategies related to these approaches.

The high frequency (approximately 80%) of mutations in isocitrate dehydrogenase 1 (*IDH1*) in WHO grade II and III gliomas as well as secondary GBM[34] associated with increased levels of 2-hydroxyglutarate (2HG), a putative oncometabolite that is believed to drive gliomagenesis,[35] has provided a strong rationale for targeting mutant IDH1 as a therapy against gliomas[36]; this has led to development of pharmacologic inhibitors of IDH1 that are currently in early clinical trials. A phase II trial of IDH-305, a selective R132H-IDH1 inhibitor against progressive WHO grade II and III gliomas, is due to open shortly (NCT02977689). Another trial aimed at low-grade gliomas that have high 2HG as measured by magnetic resonance spectroscopy proposes to assess changes in 2HG in tumor tissue and clinical outcome in terms of tumor response (NCT02987010). Another agent, AGI-5198, was shown to inhibit the ability of mutant IDH1 to produce 2HG in glioma cells, suggesting a potential for clinical activity in these tumors.[37]

Tumor cells including glioma cells, unlike normal cells, when subject to hypoxic environments, preferentially continue to use the anaerobic tricarboxylic acid cycle even after normoxic conditions are restored, the so-called Warburg effect.[3] Hypoxic regions are a key feature of GBMs and associated with areas of pseudopallisading necrosis, which also show increased expression of hypoxia-inducible factor α (HIF1α), a key player in inducing the Warburg effect.[38] HIF1α is stabilized in the setting of hypoxia and acts as a transcription factor that triggers a number of changes in gene expression and protein signaling aimed at increasing levels of tumor cell defense mechanisms include resistance pathways, accelerated metabolism, and angiogenic factors.[39] Therapeutic agents that target upstream effectors that stabilize HIF1α such as PI3K and mTOR have failed to yield substantial responses or improved outcome in early trials, likely because of activation of bypass pathways. Agents that directly target HIF1α have been tested in early trials, but data regarding their efficacy have not been promising.[39] More recently, the identification of phosphokinase M2 (PKM2) as being highly expressed in cancers, being transcriptionally upregulated by HIF1α, and promoting the Warburg effect,[40,41] has triggered efforts to develop PKM2 inhibitors as anticancer agents.[42,43] Depletion of PKM2 in cancer cells reverses the Warburg effect and inhibits tumor formation, providing a strong rationale for targeting PKM2 to inhibit cancer metabolism and tumor growth. Novel inhibitors to inhibit PKM2 are currently under development and may provide a novel therapeutic option against GBM (Fig. 1).[42,43]

Targeting basic cellular processes common to oncogenic pathways could potentially disable resistance mechanisms deployed by GBM cells and overcome the effect of heterogeneity. Heat shock response is one such highly conserved process that protects cells against adverse environmental stresses (e.g., oxidative stress, acidosis, or metabolic stress).[44] Heat shock response is mediated by the heat shock protein (HSP) family, which directs protein folding, oligomerization, and secretion, enabling the cell to generate potent resistance and survival mechanisms. Hsp90, a key member of this family, regulates folding and stabilization of several oncoproteins and is overexpressed in cancer cells; a high-affinity form of the protein is specifically expressed by cancer cells, allowing them to rapidly process proteins unlike normal cells.[45] Targeting Hsp90 can destabilize client oncoproteins, leading to their proteosomal degradation disabling crucial defense mechanisms used by GBM and sensitizing them to treatment.[46] Several Hsp90 inhibitors that block ATPase activity in a tumor-selective manner are in clinical trials.[47] Their use against GBM has been limited due to their inability to cross the blood-brain barrier, short duration of action, or unacceptable toxicity profile.[48] Second-generation Hsp90 inhibitors such as AUY922,[49] Onalespib,[50,51] and Debio0932,[52] some of which cross the blood-brain barrier, are currently in clinical trials against cancer and being considered for clinical trials against gliomas.

Another central regulator of protein processing involves the unfolded protein response (UPR), which is an evolutionally conserved central defense mechanism activated when protein that protects allows cells to adapt to endoplasmic reticulum (ER) stress.[53] ER stress results in the incorrect

folding and improper glycosylation of newly synthesized proteins. UPR allows cells to re-establish homeostasis by inducing a cell cycle arrest and blocking of protein translation, which prevents new protein formation during the period of ER stress.[53] Cancer cells including glioma cells are frequently subject to hypoxia and nutrient deprivation triggering tumor-specific ER stress, as a result of which they become highly reliant on the UPR for survival, making it an ideal target for therapeutic targeting.[54] Given that the UPR has also emerged as a mechanism for resistance to conventional therapies in solid tumors,[55] inhibitors of the UPR may serve to overcome resistance to standard antiglioma treatments and enhance their antitumor efficacy. The UPR is mediated by the dissociation of GRP78 from its inhibitory association with three transducer proteins—protein kinase R–like ER kinase, inositol-requiring enzyme 1, or activating transcription factor 6—allowing it to bind to and chaperone unfolded proteins.[55] Once released, protein kinase R–like ER kinase, inositol-requiring enzyme 1, or activating transcription factor 6 initiate downstream signals that cause transcriptional arrest and assist in alleviating ER stress. Inhibitors of GRP78 can disrupt signaling through the UPR, facilitate the reversal of ER, and consequently sensitize tumor cells to conventional treatments. AR-12, a novel orally bioavailable agent, has been reported to downregulate GRP78 and affect the UPR.[56] Inhibitors of the mitogen-activated protein kinase kinase/extracellular signal–regulated kinase pathways also decrease levels of GRP78 and can potentially inhibit the UPR. Novel inhibitors of GRP78 pathway are in continued development, and these agents are expected to enter clinical trials.[57]

Several novel and unconventional agents are currently entering clinical trials that have shown promising preclinical data against gliomas. BXQ-950 is a first-in-class agent that is a lipid-protein complex composed of Saposin C (SapC), a lysosomal protein, and a phospholipid (dioleoylphosphatidylserine [DOPS]) assembled into nanovesicles (SapC-DOPS), which selectively kill tumor cells through targeting of phosphatidylserine on the cancer cell surface, activating the ceramide cell death pathway as demonstrated in recent preclinical studies in gliomas.[58] The agent is currently in a first-in-human phase I trial including in patients with recurrent GBM (NCT02859857). G-202 (mipsagargin) is another novel prodrug that is activated by prostate-specific membrane antigen, which is expressed by GBM and tumor-associated vasculature but not in normal tissue, and is currently in phase II trials against recurrent GBM (NCT02876003 and NCT02067156). Glioma stem cells have also been assessed as novel targets in GBM; BBI608 (napabucasin), an orally bioavailable STAT3 inhibitor that targets cancer stem cells,[59] is currently in a phase I/II trial against recurrent GBM in combination with TMZ (NCT02315534).

IMMUNOTHERAPY FOR GLIOMA

Immunotherapy has emerged as one of the most exciting of therapeutic strategies against gliomas with a variety of approaches that harness the recent insights gained into cell based and humoral immune responses against cancer. The following section outlines several key strategies and associated ongoing clinical trials including a summary or early results available to date (Table 1).

Checkpoint Inhibitors

Checkpoint inhibitors (CPIs) work by interacting with molecules involved in the normal immune-inhibitory pathways of the body, tasked with limiting immune responses and avoidance of autoimmune reactivity.[60] A phase III trial (Checkmate 143; NCT02017717) is underway, looking at treatment of patients with recurrent GBM with nivolumab, a PD-1 inhibitor, and ipilimumab, a CTLA-4 inhibitor.[61] Preliminary data for this trial showed 90% of patients receiving a combination of nivolumab and ipilimumab having grade 3 or 4 adverse events in response to treatment. Preliminary efficacy results showed a 12-month OS of 40% for nivolumab (3 mg/kg), 30% for nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg), and 25% for nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg). Another phase III trial (Checkmate 498; NCT02617589) is investigating treatment with nivolumab combined with RT in adults with newly diagnosed MGMT promoter unmethylated GBM compared with standard therapy. KEYNOTE-028 is a phase I trial looking at the use of pembrolizumab (PD-1 inhibitor) for solid tumors and includes a GBM cohort of 26 patients.[62] A total of 73.1% of patients experienced treatment-related adverse events, with 15.4% experiencing grade 3 or 4 adverse events. One patient exhibited a partial response to treatment, whereas 12 patients exhibited stable disease. Results regarding PFS and OS did not show noteworthy improvements from current standard therapy. Additional studies are underway. The relatively modest effect of CPIs in trials to date may be because of the fact that GBM is not generally primed for immune response. Future studies using CPIs in combination therapies that may increase the degree of immune activity against GBM cells may provide better outcomes

T-Cell Therapies

Adoptive T-cell therapy is a novel approach to glioma immunotherapy that allows the targeting of treatment to a patient's specific tumor-associated antigen (TAA) profile, thus limiting the off-target effect to surrounding nonmalignant cells. Autologous lymphocytes are harvested and grown ex vivo, allowing for modification and recognition of specific TAAs prior to implantation in the patient.[64,65] Another novel approach uses chimeric antigen receptor (CAR) T cells, which uses autologous T-cell extraction and transduction to express modified tumor antigen T-cell receptors on the cell surface, allowing for chimeric T-cell activation independent of surface major histocompatibility complexes.[66] Brown et al[67] recently published a case report of one patient involved in a phase I trial (NCT02208362), treating patients with recurrent GBM using CAR T-cells targeting the TAA interleukin-13 receptor alpha 2 (IL-13Rα2). The patient exhibited tumor regression from 70%–100% in all lesions, an effect that was maintained for 7.5 months. Furthermore, this group

TABLE 1. Active Clinical Trials for Immunotherapy in Glioma

Intervention (Target/Origin)	Phase	Population	Design	Estimated Primary Completion Date	NCT Identification
Peptide Vaccines					
IMA950 (multiple tumor antigens)	I/II	Newly diagnosed GBM	Open-label, single-group assignment	March 2016	NCT02343406
PEPIDH1M (IDH1)	I	Recurrent grade II glioma	Open-label, single-group assignment	May 2017	NCT02193347
IDH1 peptide vaccine (IDH1R132H)	I	Grade III/IV glioma	Open-label, single-group assignment	August 2018	NCT02454634
HSPPC-96 (heat shock protein)	II	Recurrent GBM	Randomized, open-label, parallel assignment	July 2017	NCT01814813
DC Therapies					
ICT-107 (allogenic TAAs)	III	Newly diagnosed GBM	Randomized, double-blind, parallel assignment	December 2019	NCT02546102
DC vaccine (allogenic tumor lysate)	I	Newly diagnosed or recurrent GBM	Nonrandomized, open-label, parallel assignment	October 2018	NCT02010606
DC vaccine (autologous tumor lysate)	Pilot	Newly diagnosed GBM	Open-label, single-group assignment	November 2016	NCT01957956
DC vaccine (tumor lysate)	I	Recurrent GBM	Nonrandomized, open-label, parallel assignment	July 2018	NCT01808820
Human CMV pp65-LAMP mRNA-pulsed DC vaccine	II	Newly diagnosed GBM	Randomized, double-blind, parallel assignment	March 2019	NCT02366728
ICT-121 (CD 133)	I	Recurrent GBM	Open-label, single-group assignment	November 2017	NCT02049489
DCVax-L (autologous tumor lysate)	III	Newly diagnosed GBM	Randomized, double-blind, parallel assignment	November 2016	NCT00045968
CPIs					
Pembrolizumab (PD-1 inhibitor)	I	Solid tumors (Recurrent GBM)	Open-label, single-group assignment	August 2017	NCT02054806
Nivolumab (PD-1 inhibitor) with/without ipilimumab (CTLA-4 inhibitor)	III	Recurrent GBM	Randomized, open-label, parallel assignment	February 2017	NCT02017717
Durvalumab (PD-1 Inhibitor)	II	Newly diagnosed or recurrent GBM	Nonrandomized, open-label, parallel assignment	July 2017	NCT02336165
Pembrolizumab	II	Recurrent GBM	Randomized, open-label, parallel assignment	August 2016	NCT02337491
Nivolumab	III	Newly diagnosed GBM	Randomized, open-label, parallel assignment	March 2019	NCT02617589
Indoximod (IDO inhibitor)	I/II	Recurrent GBM	Nonrandomized, open-label, parallel assignment	December 2016	NCT02052648
T-Cell Therapies					
Genetically modified T cells (IL-13Rα2)	I	Recurrent GBM	Nonrandomized, open-label, parallel assignment	December 2018	NCT02208362
CAR T cells (EGFRvIII)	I/II	Recurrent GBM	Nonrandomized, single-group	December 2018	NCT01454596
CAR T cells (CMV, HER2)	I	Recurrent GBM	Open-label, single-group assignment	June 2014	NCT01109095
CAR T cells (EphA2)	I/II	Newly diagnosed or recurrent GBM	Randomized, open-label, parallel assignment	September 2016	NCT02575261
Viral Therapy					
MV-CEA (measles virus)	I	Recurrent GBM	Nonrandomized, open-label, parallel assignment	June 2017	NCT00390299
PVSRIPO (poliovirus)	I	Recurrent GBM	Open-label, single-group assignment	January 2017	NCT01491893
DNX2401 (adenovirus)	I	Recurrent GBM	Open-label, single-group assignment	December 2015	NCT01956734
Toca 511 (retrovirus) + Toca FC	II/III	Recurrent GBM	Randomized, open-label, parallel assignment	November 2017	NCT02414165

Continued

TABLE 1. Active Clinical Trials for Immunotherapy in Glioma (Cont'd)

Intervention (Target/Origin)	Phase	Population	Design	Estimated Primary Completion Date	NCT Identification
Combination Therapy					
DNX2401 + pembrolizumab	II	Recurrent GBM	Open-label, single-group assignment	December 2019	NCT02798406
DC vaccine + nivolumab	I	Recurrent GBM	Randomized, open-label, parallel assignment	May 2018	NCT02529072
Nivolumab + galunisertib (TGF-βR1K inhibitor)	I/II	Refractory solid tumors (recurrent GBM)	Nonrandomized, single group, open label	April 2018	NCT02423343
Pembrolizumab + HSPPC-96	II	Newly diagnosed GBM	Randomized, parallel assignment	May 2018	NCT03018288

Abbreviations: NCT, National Clinical Trial; GBM, glioblastoma; DC, dendritic cell; TAAs, tumor-associated antigens; CPIs, checkpoint inhibitors; IDO, indoleamine 2,3-dioxygenase; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; TGF, transforming growth factor.
Data derived from https://clinicaltrials.gov.

reported 10 patients currently undergoing treatment, with minimal side effects, and CAR T cells detected in cerebrospinal fluid or tumor cyst fluid for more than 7 days.[68] These findings suggest that CAR T cells may be well tolerated by patients and are capable of producing a relevant treatment response in vivo. Other early-stage CAR T-cell trials include NCT01454596 (National Cancer Institute), treating patients in whom GBM expresses EGFR type III (EGFRvIII), a known tumor-specific antigen, and NCT01109095, testing the safety of CAR T cells targeting HER2, a tumor-specific antigen expressed on 87% of GBM cells.[69,70] For this second study, the gene expressing the HER2 antibody was transduced into T cells selected for their reactivity to cytomegalovirus (CMV), postulating that these cells would be more reactive as they would respond to both tumor cells and CMV, a viral antigen found in many patients with GBM.

Peptide Vaccine Therapies

Vaccination strategies for GBM are aimed at creating vaccines targeting specific tumor antigens, such as EGFRvIII and isocitrate dehydrogenase 1 (IDH1).[60,66,71] The ACT III trial was a phase II trial of newly diagnosed patients with GBM treated with rindopepimut (CDX-110), a vaccine targeting EGFRvIII. Early results showed a survival benefit, with patients exhibiting a PFS at 5.5 months of 66% and median OS of 21.8 months.[72] However, the phase III trial (ACT IV) was terminated early when it failed to show a survival benefit.[73] It has been speculated that the results may have been influenced by the patients in the control arm faring better than would be expected of typical control subjects with GBM.[66,73] Reardon et al[74] reported the results of a phase I/II trial of SL-107, a peptide vaccine targeting three tumor antigens—IL-13Rα2, Ephrin A2 (EphA2), and Survivin—in patients with recurrent GBM. Early results showed a partial response in one patient (more than 33 weeks in duration) and stable disease in 15 patients (median duration 8 weeks). Migliorini and Dutoit[75] reported results of a trial using IMA950, a peptide vaccine composed of 11 tumor-specific peptides.[66] For the six patients treated under the initial protocol, median OS was 17.5 months (range 11–21 months). Another target of interest under investigation for potential vaccination therapy is HSP.[76,77] A phase II trial (NCT01814813) is evaluating heat shock protein–peptide complex 96 (HSPPC96) with bevacizumab in patients with recurrent glioma. Similarly, IDH1 is a novel target for vaccine therapy, with one phase I trial in patients with grade III/IV glioma testing an IDH1 vaccine (NOA-16; NCT02454634).

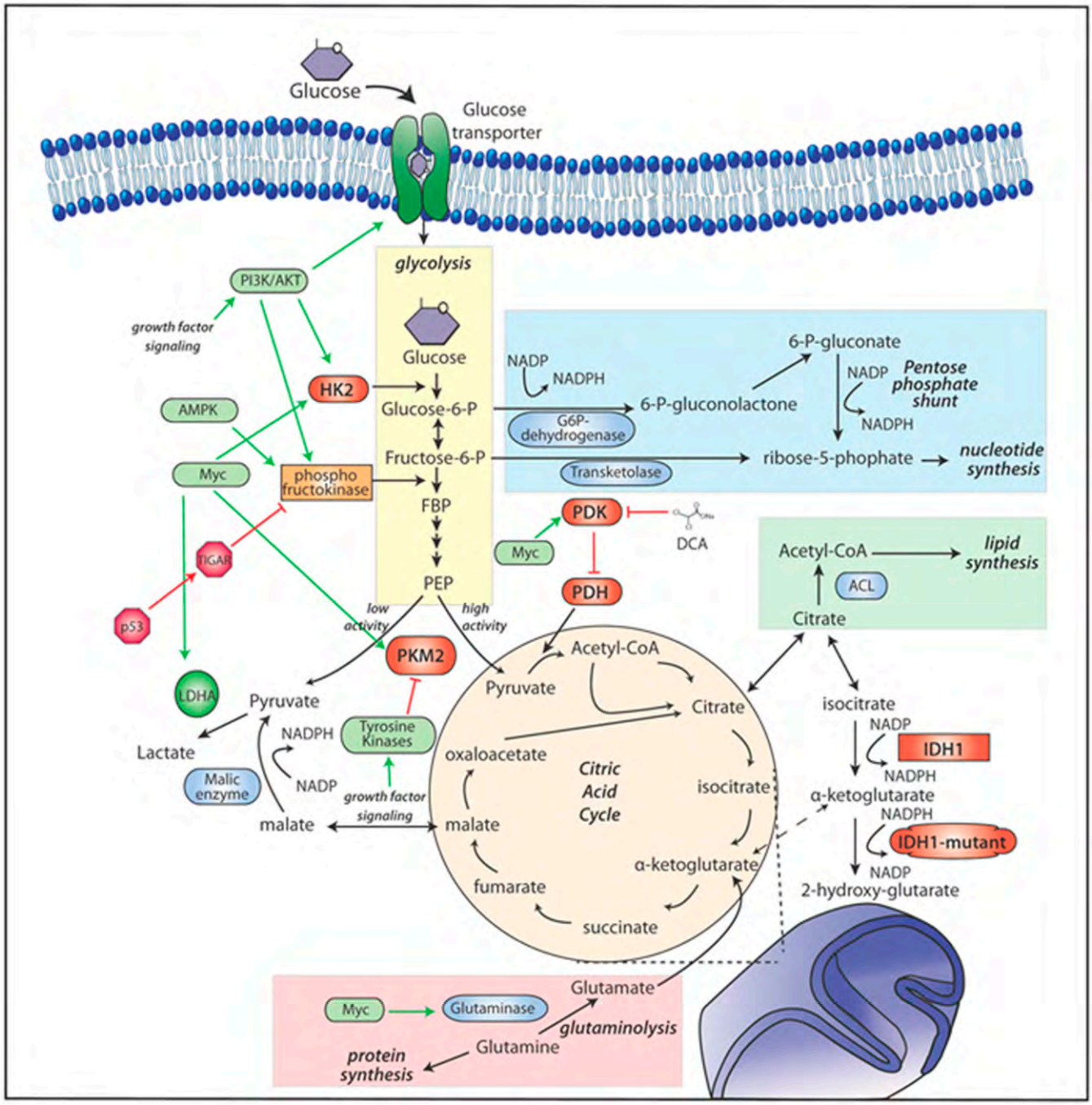
Dendritic Cell Therapies

Dendritic cell (DC) therapies function by harvesting DCs from the patient and exposing them to the tumor-specific peptides or tumor lysate ex vivo, prior to being injected back into the patient.[5,18] Previous clinical trials using DC therapy have shown encouraging results, with improvement in OS and 2-year survival compared with the current therapy.[60] Santos et al[78] published data from a phase II (NCT01280552) trial using ICT-107, a DC vaccine encompassing autologous DCs incubated ex vivo with six tumor-specific peptides. The data showed a relationship between HLA-A2–positive patients and an immune response to treatment, associated with both OS and PFS. The Mayo Clinic group reported a trial (MC1272; NCT01957956) of DC therapy in patients with newly diagnosed GBM.[79] Autologous DCs were pulsed with allogenic tumor lysate from two human GBM cell lines. Mean follow-up was roughly 1 year (range 0.19–1.77), with 80% OS. The University of California, Los Angeles group reported recently on a phase IIa trial (NCT01635283) of DC therapy in patients with grade II glioma treated with autologous DCs pulsed with autologous tumor lysate.[80] No difference was noted in time to progression between study patients and a matched cohort. One phase III trial (NCT00045968) using a tumor-lysate pulsed DC vaccine (DCVax-L) was recently completed in December 2016 with results not yet reported.

Oncolytic Viral Therapies

Oncolytic virus therapy uses genetically modified viral vectors that have the ability to both directly attack malignant cells as well as produce a durable host immune response to them.[81,82] NCT00390299 is a phase I trial for patients with recurrent GBM, assessing the safety and efficacy of measles virus transfected with human carcinoembryonic antigen as a marker for replication in vivo.[66] The PVSRIPO trial (NCT01491893) is evaluating a recombinant poliovirus (PSVRIPO) and has shown promising early results.[83,84] Patel

FIGURE 1. Metabolic Pathways Active in GBM Involving Enzymes of Glycolysis, the Pentose Phosphate Pathway, Fatty Acid and Glutamine Metabolism, and Their Regulation by Known Oncogenes and Tumor Suppressor Genes in Proliferating Cells



Growth factor/PI3K/AKT signaling stimulates glucose uptake and flux through the early part of glycolysis. Tyrosine kinase signaling negatively regulates flux through at PKM2, making glycolytic intermediates available for macromolecular synthesis. Myc has been found to promote glutamine metabolism and inhibit oxidative metabolism by activating pyruvate dehydrogenase kinase (PDK). p53 decreases metabolic flux through glycolysis in response to cell stress.

Abbreviations: Acetyl-CoA, acetyl coenzyme A; ACL, ATP citrate lyase; AMPK, 5' adenosine monophosphate–activated protein kinase; DCA, dichloroacetate; FBP, fructose 1,6-bisphosphate; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate; PDH, pyruvate dehydrogenase; PEP, phosphoenolpyruvate.

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et al[85] recently reported on a new clinical trial using a recombinant oncolytic herpes simplex virus that functions through direct oncolytic action against malignant cells and transfection of a viral payload causing malignant cells to secrete IL-12. Tejada et al[86] reported preliminary results from a phase I trial (NCT01956734) using an oncolytic adenovirus (DNX-2401) and TMZ with noteworthy results: one patient alive 30 months after treatment with no evidence of progression and two further patients alive at 23 months. Aghi et al[87] also reported the preliminary results of three phase I trials using replicating retrovirus Toca 511 in patients with recurrent GBM, delivered via three distinct methods. Toca

511 is a recombinant retrovirus that transfects yeast cytosine deaminase into malignant cells, allowing for subsequent treatments with Toca FC (a 5-fluorocytosine derivative) to convert to 5-fluorouracil within the malignant cells.[87,88] Median OS for all three trial groups was 12.1–13.6 months.

Combination Immunotherapy Approaches

Several trials are investigating the use of combinations of immunologic agents to elicit the synergistic effects of such therapies. These include the CAPTIVE trial (NCT02798406), a phase 2 trial combining pembrolizumab with DNX-2401 (oncolytic adenovirus), the AVERT trial (NCT02529072), a phase I trial testing a combination of nivolumab and a DC vaccine (pp65) against recurrent glioma, a phase I/II trial (NCT02423343) for several solid malignancies, including recurrent GBM, testing nivolumab in conjunction with galunisertib, a transforming growth factor-beta receptor I kinase inhibitor, and a trial (NCT03018288) using pembrolizumab in conjunction with HSPPC96, an HSP peptide vaccine. Further research is likely needed to understand the critical interplay of immunosuppressive mechanisms within GBM, but combination trials such as these will hopefully provide us with useful information regarding concurrent immunotherapy treatments.

INTEGRATIVE MEDICINE AND ALTERNATIVE THERAPIES AGAINST GLIOMAS

Scope and Definition of Integrative Medicine

Integrative medicine, a new name for an ancient field of medicine, was previously known as alternative medicine, but because the term "alternative" implies in lieu of traditional medical therapy, the name has been recently been changed to the more inclusive name. Practitioners in oncology often encounter patients seeking advice about integrative oncology practices but whom are often ill equipped to address such questions, which may result in minimizing or avoidance of discussion regarding these queries. This common practice could lead to the patients becoming reluctant to discuss such therapies with their clinical team and potentially withholding information about the integrative techniques that they may be using. It is noted that up to 65% of cancer survivors report using integrative medicine practices at some time during their clinical course,[89] making it a highly relevant issue in the management of oncology patients. It has hence become important for practitioners in oncology to address this issue, encourage a discussion with the patients related to integrative therapy, and provide evidence-based information to help them make appropriate choices. Although reducing the potential for unreported use of integrative medicines by patients and encouraging open dialogue is a major reason for practitioners to educate themselves about integrative medicine, there are also evidence-based practices that demonstrate not only improvement in quality of life measures but also an increase in OS and PFS in patients with cancer.

Role of Stress and Mitigation of Stress

Stress and stress reduction is one of the most difficult fields to study in medicine because of often-subjective measures but is also the most interesting of all integrative medicine fields. Thaker et al[90] used a validated stress model to test the hypothesis that stress can induce tumorigenesis through stimulation of the B-adrenergic receptor on tumor cells. Nude mice were placed in a stress-inducing restraint system, and human ovarian carcinoma cells were inoculated into the peritoneal cavity. As compared with the control nonstressed mice, the ovarian cancer cells grew by up to 275% in the stressed-out mice. The pathophysiology of this response is poorly understood but is thought to be secondary to stimulation of the B-adrenergic receptor on tumor cells and transcriptional upregulation of VEGF. A legitimate question hence is whether decreasing stress can cause a decrease in tumor burden and improve survival. In this context, a randomized trial showed a considerable survival benefit of stress reduction in patients with metastatic breast cancer.[91] Patients undergoing adjuvant breast cancer therapy were randomized to an intervention arm that taught strategies to "reduce stress, improve mood, and alter health behaviors" for 1 year (26 sessions). At 11 years of follow-up, there was a striking improvement in median survival in the intervention arm (6.1 years) versus the assessment-only arm (4.8 years). Multivariate analyses confirmed that patients randomized to the intervention arm had a significantly lower risk of death because of breast cancer (hazard ratio 0.44; $p = .016$). Although there is a paucity of such trials, the importance of mental health in patients with cancer, often minimized in routine care, has been shown to improve quality of life measures and now even survival in a statistically meaningful way. Incorporating stress reduction techniques such meditation, psychologic therapy, and psychiatric intervention to address issues such as anxiety and depression into routine oncological clinical practice hence must be an integral part of the management of the patient with cancer in a modern era of medicine.

Exercise and Its Impact on Cancer

All areas of medicine accept that regular exercise is important for maintaining mental and physical health, but the question of whether exercise can actually affect cancer growth has only recently been systematically addressed. In a laboratory study, mice were randomized to a cage with a wheel for running or into a cage without a wheel, and mice in both groups were inoculated with B16F10 melanoma cells. Strikingly, after 4 weeks of running, the exercise mice had a 61% ($p < .01$) reduction in tumor as compared with the mice that were not exercising. Exercised mice had increased natural killer cell mobilization that was believed to be the pathophysiology due to which tumor progression was decreased.[92] In an era of immunotherapy, these data suggest that exercise may have an important part in therapy.

Primary brain tumors such as high-grade gliomas are highly aggressive and treatment resistant. A very interesting trial examined the role of exercise in patients with

recurrent grade III and grade IV malignant gliomas in which 243 patients with a Karnofsky performance status 70 or higher were prospectively given a self-administered questionnaire that assessed exercise behavior and performed a 6-minute walk test to assess functional capacity.[93] Exercise was an independent predictor of survival (p = .0081), although, interestingly, functional capacity was not. Exercise was also a better predictor of survival than Karnofsky performance status, age, sex, grade, and number of prior progressions. The adjusted hazard ratio mortality was 0.64 (95% CI, 0.46–0.91) for patients reporting strenuous exercise. That strenuous exercise was an independent predictor of survival is a striking finding in an extremely treatment-resistant tumor given that to date, no chemotherapy, radiation therapy, nor surgical therapy have been shown to improve survival in a meaningful way in recurrent high-grade gliomas. Patients often stop exercising after the diagnosis of cancer because of several factors, including fatigue and concerns regarding the impact of physical exercise on their fragile health status, an attitude that may be inadvertently encouraged by clinicians. The data presented above and in many animal models point to the contrary and suggest that patients should continue to exercise as vigorously as possible not only to maintain performance status but also for its potential effect on controlling tumor growth and improving survival.

Diet and Nutrition

One of the most controversial areas of integrative oncology is related to diet and nutrition and its effect on cancer. There are often concerns about weight loss and poor protein intake in patients with a hypermetabolic state. The prevalent belief among clinicians that diet has no notable effect on tumors has been challenged by emerging data in animals as well as humans. This is highlighted by the intriguing results of a randomized, double-blinded, placebo-controlled study assessing the role of flax seed in postmenopausal patients with breast cancer conducted by Thompson et al.[94] After initial biopsy, patients were randomized to a diet taking 25 grams of flaxseed daily in a muffin versus one with no flaxseed and with no other changes in their regular diets. At the time of lumpectomy, the flaxseed arm was found to have a considerable decrease (median 34.2%) in Ki-67 labeling index and considerable increase in apoptotic index (30.7%). No quantifiable changes on these indices were noted in the placebo group. Other similar studies have shown that even small changes in diet for a short period of time can induce changes at a cellular level. However, the question of whether diet can change tumorigenesis in a clinically meaningful way has been challenging to answer because of the difficulties in evaluating the effect of diet in an evidenced-based manner. Randomized controlled trials are virtually impossible, and so clinicians have to often rely on retrospective trial data, which are fraught with statistical bias. One large randomized control trial, the PREDIMED study, conducted in Spain on 4,282 women age 60 to 80 at high cardiovascular risk, showed compelling results in this context. These subjects were randomized to a Mediterranean diet with olive oil, a Mediterranean diet with nuts, or a low-fat control diet and monitored for development of breast cancer. There were 35 cases of breast cancer in a median follow-up of 4.8 years; intriguingly, the multivariable-adjusted hazard ratios for the Mediterranean diet plus olive oil group versus the control group was 0.32 (95% CI, 0.13–0.79).[95] The impact of these results can be considered in the context that a chemotherapy agent that showed similar results in preventing breast cancer would have been considered highly successful.

Other specialties in medicine such as cardiology have willingly embraced the impact of stress reduction, exercise, and diet in the prevention and treatment of disease. In oncology, such acceptance has lagged behind despite cumulative data that support the direct beneficial effects of such modalities on quality of life and survival. The reasons for the resistance in accepting the value of such measures in the therapeutic strategies against cancer are unclear. It can be speculated that this may be due to the lack of a direct and verifiable logical link between cancer and, for instance, exercise. It is also possible that the lack of conventionally accepted evidence based on robust clinical trials raise skepticism about the results of small uncontrolled studies or anecdotal experience. Further, in the era of highly specific and targeted therapies, it is possible that the role of a broader and less specific intervention such as diet or exercise may have lesser acceptance as a legitimate anticancer therapy. Perhaps clinicians also have concerns that patients may choose integrative practices in lieu of traditional medical therapy with potential medical consequences. Equally likely, however, is that clinicians trained in oncology receive little or no training in aspects of integrative medicine given the traditional stigma and biases associated with this field in traditional training programs as being a nonspecific science. However, it is highly encouraging that Integrative Oncology as a field is moving forward and that there is a growing recognition of the obligation in clinicians to familiarize themselves with the fundamentals of this field and to critically examine the evidence in the field as well as generate carefully designed studies, including through new study designs and clinical trial approaches to provide evidence-based results on which practice can be based. This is imperative for the benefit of our patients who are currently bombarded with nonevidence-based recommendations from a variety of nonmedical sources, including the internet and social media, every day.

CONCLUSION AND FUTURE DIRECTIONS

Recent advances in treatment have yielded incremental improvement in the outcomes of patients with gliomas; however, paradigm-shifting therapies that provide considerable prolongation of survival and improvement in quality of life for these patients have been elusive. The need for unconventional approaches to targeting gliomas has led investigators to explore targets and strategies that go beyond traditional chemotherapeutic agents, including the ones outlined in the sections above. A variety of other strategies,

including gene editing, noncoding RNAs, biologic therapies including viral and nonviral vectors, in addition to cell-based therapies, heat-based therapies, novel surgical techniques, and local delivery using blood-brain barrier disruption and convention-enhanced deliveries, as well as novel approaches with radiation therapy techniques, are under development. An exhaustive coverage of these techniques is outside the scope of this review, but it is recognized that these equally cutting-edge approaches are under active study. These novel strategies bear great promise in providing the long overdue improvement in quality of life and survival for patients with gliomas.

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Practice-Changing Abstracts From the 2016 Society for Neuro-Oncology Annual Scientific Meeting

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OVERVIEW

The most relevant practice-changing presentations at the 2016 Society for Neuro-Oncology (SNO) Annual Scientific Meeting revolved around the topic of the new 2016 World Health Organization (WHO) classification of central nervous system (CNS) tumors. The most notable change in this new classification is the introduction of molecular markers into the morphologic classification of diffuse gliomas (isocitrate dehydrogenase [IDH] mutation, 1p19q codeletion, and H3K27M mutation), ependymomas (RELA fusion), medulloblastomas (WNT- and sonic hedgehog–activated), and other embryonal tumors (C19MC amplification), thus allowing for more precise diagnosis of these entities compared with the use of morphologic features alone. Among the clinical trials presented, only one phase III trial evaluating a device therapy for treatment of newly diagnosed glioblastoma (EF14; tumor-treating fields) met prespecified statistical criteria for success, showing a modest benefit in progression-free survival and overall survival in patients without progression after radiation and concurrent temozolomide. Other topics of interest included the spatial and temporal heterogeneity of primary brain tumors and the prevalence of burnout among neuro-oncologists.

The new 2016 WHO classification of CNS tumors and its practice-changing implications were discussed in detail in several presentations during the 2016 SNO Annual Scientific Meeting.[1-6]

Historically, gliomas and other primary brain tumors have been classified based on morphology, with glioma grading depending on cellularity, nuclear pleomorphism, and presence of microvascular proliferation and necrosis. It is widely accepted that tumor grade is the primary predictor of biologic behavior and prognosis. However, recent data demonstrate that the molecular marker IDH mutation provides better prognostication than grade in malignant gliomas, and anaplastic gliomas without IDH mutations (IDH wild-type) have a similarly dismal prognosis as glioblastoma. Additionally, the presence of 1p19q codeletion is linked to the oligodendroglioma lineage and also associated with better prognosis and response to therapy than tumors of astrocytoma lineage.

This current 2016 update of the WHO classification of tumors of the CNS is the result of the collaboration of 117 contributors from 20 countries and discussion of the most controversial issues by a working group of 35 neuropathologists, neuro-oncological clinical advisors, and scientists at a 3-day consensus conference. The changes introduced in this 2016 update to the 2007 edition are detailed by Louis et al.[7]

The 2016 WHO CNS tumor classification moves beyond the classic histology description toward an integrated diagnosis, adding molecular-genetic markers to define many CNS tumors, although the grade determination is still being defined primarily on histologic criteria. As a result, the classification now includes a major restructuring of diffuse gliomas, with incorporation of new molecularly defined entities and deletion of some variants lacking diagnostic and/or biologic relevance (Table 1). The WHO grade II diffuse astrocytomas, WHO grade III anaplastic astrocytomas, and WHO grade IV astrocytomas (glioblastoma), are now each divided into IDH-mutant, IDH wild-type, and not otherwise specified (NOS) categories.

The diagnosis of WHO grade II oligodendroglioma and WHO grade III anaplastic oligodendroglioma requires the demonstration of both an IDH mutation and combined whole-arm losses of 1p and 19q (1p/19q codeletion). In the absence of testing or the setting of inconclusive genetic results, an otherwise histologically typical oligodendroglial tumor should be diagnosed as NOS. In instances in which histology and molecular genetic features are discordant (e.g., a diffuse glioma with morphologic features of astrocytoma, but harboring an IDH mutation and 1p/19q codeletion, or a tumor with appearance of oligodendroglioma, but with IDH, ATRX, and TP53 mutations), the genotype features determine the final diagnosis. Importantly, a molecularly defined

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TABLE 1. 2016 WHO Changes to the Classification of Diffuse Gliomas

New Molecularly Defined Entities	Entities or Variants Deleted	Variants Added
Diffuse astrocytoma, IDH-mutant	Gliomatosis cerebri	Epithelioid glioblastoma
Diffuse astrocytoma, IDH wild-type	Protoplasmic and fibrillary astrocytoma variants	
Diffuse astrocytoma, NOS		
Anaplastic astrocytoma, IDH-mutant		
Anaplastic astrocytoma, IDH wild-type		
Anaplastic astrocytoma, NOS		
Glioblastoma, IDH wild-type		
Glioblastoma, IDH-mutant		
Glioblastoma, NOS		
Diffuse midline glioma, H3K27M-mutant		
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted		
Oligodendroglioma, NOS		
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted		
Anaplastic oligodendroglioma, NOS		
Oligoastrocytoma, NOS*		
Anaplastic oligoastrocytoma, NOS*		

Abbreviations: WHO, World Health Organization; IDH, isocitrate dehydrogenase; NOS, not otherwise specified; CNS, central nervous system.

*The diagnosis of mixed gliomas is strongly discouraged in the 2016 WHO classification of CNS tumors. Diagnostic molecular testing should be used for further classification as a "molecularly" astrocytic or oligodendroglial tumor, whenever possible.

NOS is to be used in the absence of diagnostic molecular testing or when results are inconclusive; for oligoastrocytomas, NOS category should also be used in the very rare instance of a dual genotype oligoastrocytoma.

group of tumors, diffuse midline gliomas, H3K27M-mutant, has been introduced in the new 2016 WHO classification. These are tumors primarily seen in children (but also in adults), characterized by K27M mutations in the histone H3 gene *H3F3A* (or less commonly in the *HIST1H3B* gene) and a diffuse growth pattern, midline location (thalamus, brain stem, or spinal cord), and poor prognosis.

Even though the changes in the classification of diffuse gliomas are the most relevant due to the frequency of diffuse gliomas in clinical practice, other important changes have been introduced in this 2016 classification. New glioma variants have been included, such as epithelioid glioblastoma and anaplastic pleomorphic xanthoastrocytoma, as well as a new mixed neuronal-glial tumor entity, diffuse leptomeningeal glioneuronal tumor. A genetically defined ependymoma variant has also been included that is called ependymoma, RELA fusion-positive, which accounts for the majority of supratentorial ependymomas in children.

Medulloblastomas and other embryonal tumors are also being reclassified based on molecular subtypes when possible, and the general term PNET, or primitive neuroectodermal tumor, has been removed and substituted by the wastebasket diagnosis of CNS embryonal tumor, NOS, to be used when further histologic and/or molecular characterization is not possible (Table 2). Resembling the new classification of diffuse gliomas, medulloblastomas should also be classified following an integrated diagnosis model, with incorporation of both molecular group and histologic phenotype. The classification of embryonal tumors is expected to continue to evolve when molecular markers allow more precise cataloguing of these tumors and their subtypes in the near future. Other noteworthy changes to the 2016 WHO classification of CNS tumors include the introduction of brain invasion as a criterion for atypical meningioma and a soft tissue-type grading system

KEY POINTS

- **The new 2016 WHO classification of CNS tumors introduced molecular markers into the morphological classification of diffuse gliomas, ependymomas, medulloblastomas, and other embryonal tumors, allowing for more precise diagnosis of these entities.**
- **The 2016 CNS WHO classification includes a major restructuring of diffuse gliomas; WHO grade II diffuse astrocytomas, grade III anaplastic astrocytomas, and grade IV astrocytomas (glioblastoma) are now each divided into IDH-mutant, IDH wild-type, and NOS categories.**
- **Only one randomized phase III non–placebo-controlled trial was presented that met prespecified statistical criteria for success, evaluating the role of tumor-treating fields for treatment of newly diagnosed glioblastoma in combination with maintenance temozolomide.**
- **Recognition of spatial and temporal hetereogeneity of gliomas is key for the development of the new generation of clinical trials.**
- **A survey among SNO members revealed a high prevalence of symptoms of burnout and high levels of stress, and showed that patient care was the most satisfying career aspect.**

for the new combined entity of solitary fibrous tumor/hemangiopericytoma.

The WHO CNS tumor classification remains a work in progress. Of note, only markers with widely recognized diagnostic value and standardized, widely available methods of detection have been incorporated. Prognostic markers such as MGMT promoter methylation in glioblastoma have therefore not been incorporated, because of the lack of diagnostic value and lack of consensus on methods for detection. One of the major shortcomings is the difficulty to rapidly incorporate diagnostically relevant new molecular findings into standard WHO updates. For this reason, a new initiative will soon commence that will facilitate input and consensus review of novel molecular data, perhaps facilitating incorporation into future CNS tumor classifications. This initiative has been named cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) and is sponsored by the International Society of Neuropathology.[8]

FINAL ANALYSIS OF TUMOR-TREATING FIELDS PHASE III CLINICAL TRIAL FOR NEWLY DIAGNOSED GLIOBLASTOMA

The final results of NovoCure EF-14, an industry-sponsored, multicenter, non–placebo-controlled, randomized phase III trial in newly diagnosed glioblastoma testing the efficacy of tumor-treating fields (TTFields) in combination with maintenance temozolomide after initial treatment with chemoradiation were presented at this 2016 SNO meeting.[9]

TTFields are low-intensity (1–3 V/cm), intermediate-frequency (200 kHz) alternating electric fields applied to the shaved scalp via transducer arrays, connected to a portable device set to generate the electric fields (Optune; Novocure Ltd.). In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase.[10] Notably, a prior randomized phase 3 trial in 237 patients with recurrent glioblastoma comparing treatment with TTFields to physician's choice standard chemotherapy failed to demonstrate an improvement in overall survival (OS) or progression-free survival (PFS), although adverse effects were generally minor.[11]

The current study in newly diagnosed glioblastoma aimed to evaluate the efficacy and safety of TTFields used in combination with maintenance temozolomide after completing therapy with radiation and concurrent temozolomide. The interim results were previously reported at SNO 2014 and published in *JAMA* in 2015.[10] Randomization was 2:1 favoring the experimental arm. The primary endpoint of the study was PFS in the intent-to-treat population, assessed by a blinded central review panel, with OS in an as-treated population as a powered secondary endpoint. OS was to be tested statistically only if the primary was met to avoid an increase in the risk of a false-positive result. The as-treated population was defined as patients who were able to receive at least one adjuvant cycle of temozolomide (i.e., started cycle 2) and also excluded patients in the control arm who received TTFields therapy outside the protocol (a total of 35 patients were removed for analysis of OS at the time of interim analysis). Blinded central review was not performed in real time to dictate treatment decisions, and some discrepancies in interpretation between local and central review were identified in both the experimental and standard arm.[10] An unusual feature of this trial was that, in the TTFields arm, patients were allowed to continue TTFields in combination with second-line chemotherapy until the second radiologic progression or clinical deterioration, for a maximum of 24 months.

At the published prespecified interim analysis, which included data from 315 patients,[10] the difference in PFS was 4.0 versus 7.1. months (i.e., an increase in 3.1 months favoring the TTFields arm, with a hazard ratio of 0.62), whereas the final analysis with 695 patients[9] found the difference was 4.0 versus 6.7 months with a hazard ratio of 0.63 (i.e., an increase of 2.7 months favoring the TTFields arm). In terms of OS in an as-treated population (powered secondary endpoint), there was a difference of 5 months both at interim and final analysis with a hazard ratio of 0.65, although the difference in intent-to-treat population at interim analysis was smaller (3 months). The respective 2-, 3-, and 4-year OS rates (secondary objective) were 43% (CI, 38%–47%) versus 30% (CI, 24–37), 24% (CI, 19–29) versus 16% (CI, 11–23), and 17% (CI, 13–23) versus 10% (CI, 6–18), respectively

TABLE 2. 2016 WHO Changes to the Classification of Medulloblastomas and Other Embryonal Tumor

New Molecularly Defined Entities	Entities or Variants Deleted	Entities Added
Medulloblastoma, WNT-activated	Primitive neuroectodermal tumor	CNS embryonal tumor, NOS
Medulloblastoma, SHH-activated and TP53-mutant		
Medulloblastoma, SHH-activated and TP53 wild-type		
Medulloblastoma, non-WNT/non-SHH		
Medulloblastoma, group 3		
Medulloblastoma, group 4		
Medulloblastoma, NOS		
Embryonal tumor with multilayered rosettes, C19MC-altered		
Embryonal tumor with multilayered rosettes, NOS		

Abbreviations: WHO, World Health Organization; CNS, central nervous system; NOS, not otherwise specified; SHH, sonic hedgehog.

TABLE 3. Comparative Outcome Data From RTOG 0525, RTOG 0825, EF-14 Interim Analysis, and EF-14 Final Analysis

			EF-14†	
	RTOG 0525 (2013)*	RTOG 0825 (2014)**	Interim (*JAMA* 2015)	Final (SNO 2016)
Median PFS (Months) Standard/ Experimental	5.5/6.7	7.3/10.7	4.0/7.1	4.0/6.7
Median OS (Months) Standard/ Experimental	16.6/14.9	16.1/15.7	15.6/20.5‡	16/21
***N* (Standard/Experimental)**	411/422	309/312	105/210	695

Abbreviations: JAMA, *Journal of the American Medical Association*; SNO, Society for Neuro-Oncology; PFS, progression-free survival; OS, overall survival.

*Randomization after chemoradiation.

**Randomization by day 10 of chemoradiation.

†Randomization after chemoradiation.

‡Defined as per protocol population (prespecified analysis). Median OS in intent-to-treat population also reported: 16.6 vs. 19.6 months.

($p < .05$ for all time points). Therefore, this phase III trial met prespecified statistical criteria for success, with a modest improvement in both PFS and OS. This is in striking contrast with the negative results of the previous phase III trial in recurrent glioblastoma.[11]

Table 3 summarizes EF-14 outcome data (median PFS and median OS) and provides the results of two other recent phase III trials, RTOG 0525 (standard vs. dose-dense temozolomide)[12] and RTOG 0825 (bevacizumab vs. placebo in addition to chemoradiation),[13] both large, multicenter randomized trials in newly diagnosed glioblastoma. Although direct comparison of patient outcomes among different trials is not statistically appropriate, RTOG 0525 and RTOG 0825 provide a reference of expected outcome of patients with newly diagnosed glioblastoma treated in clinical trials, and it is worth discussing in some detail to highlight potential limitations of this trial.

In RTOG 0525 and EF-14, patients were randomly assigned after chemoradiation, whereas in RTOG 0825, random assignment occurred at the beginning of chemoradiation (patients had to be randomly assigned by day 10 of chemoradiation). In all three trials, PFS and OS were measured from random assignment. When comparing outcome data, notably, the temozolomide control arm in EF-14 trial showed worse PFS than in RTOG 0525 and RTOG 0825, whereas OS seemed equivalent. In both RTOG 0525 and RTOG 0825, patients with suspected treatment effect rather than true tumor progression (pseudoprogression) were allowed to continue therapy, unless there was a new lesion or clinical decline. In the EF-14 trial, patients with suspected progression after chemoradiation were excluded from participation.

One potential factor that can account for differences in PFS in a given trial or among trials is the misclassification of true early tumor progression and pseudoprogression. Unfortunately, both traditional imaging criteria and clinical criteria are often misleading when trying to differentiate true progression from early treatment effect, thus being challenging to correctly include or exclude patients from trial participation and to estimate PFS. It is known that the peak of pseudoprogression happens within 3 to 4 months of completion of chemoradiation. Unfortunately, a blinded central radiologic review does not eliminate the problem of having inadequate tools to determine true versus false tumor progression. If, inadvertently, more patients with true progression right after chemoradiation were included in the temozolomide-only control arm of EF-14 (as suggested by worse PFS than in previous RTOG trials), this may have introduced an involuntary source of bias into the randomized study, favoring the experimental arm.

In summary, the positive results of EF-14 bring one additional therapy (TTFields) into the treatment arsenal against newly diagnosed glioblastoma. However, in view of the previous negative phase III trial in recurrent glioblastoma and the modest differences found in PFS and OS, it is still unclear which patients truly derive most benefit from this therapy, a question particularly relevant in the context of globally increasing health care costs. Unfortunately, patients with the most aggressive tumors (i.e., showing rapid tumor progression early during their course) are still lacking valid treatment options. In many cases, these tumors are also likely to have high MGMT activity as well as other unfavorable molecular markers. Additional research to investigate novel therapies for newly diagnosed and recurrent glioblastoma must continue to achieve much better improvement in survival, in the order of years rather than several months, as is the reality today. We must see the progress in OS for high-grade gliomas that has occurred in other malignancies like chronic myeloid leukemia or her2$^+$ metastatic breast cancer.[14,15]

OTHER TOPICS OF INTEREST

Spatial and Temporal Heterogeneity of Tumors

It is well known that gliomas represent a group of highly heterogeneous tumors, not only spatially (with different areas of the same tumor demonstrating different morphology, grade, or even molecular findings), but also temporarily, with an evolving molecular makeup during tumor treatment and evolution.[16] In this regard, Costello[17] presented intriguing data regarding IDH mutations during glioma evolution. Despite being an early oncogenic molecular event, IDH status can change during subclonal evolution and tumor recurrence via epigenetic mechanisms.

It is becoming increasingly clear that the failure of molecularly targeted therapies for recurrent tumors may be due, at least in part, to dynamic changes in the molecular alterations

driving the growth of the recurrence as compared with the original tumor. In consequence, taking therapy decisions based on molecular analysis on original tumor tissue is likely inappropriate in most cases. Recognition of this phenomenon should lead to changes in research practice, obtaining new tumor tissue for analysis whenever feasible before enrollment to clinical trials. In addition, it is also apparent that we do not have targeted drug therapies today that are sufficiently brain penetrant to access infiltrating cells, able to inhibit cellular targets long enough to exert sufficient antitumor activity, or specific enough in their action to be safely combined with other targeted therapies,[18] and a summary of the 2nd CNS Anticancer Drug Discovery and Development Conference will be published in *CNS Oncology* in the next few months.[18]

Investigating Burnout and Career Satisfaction Among Neuro-Oncologists

Professional burnout is common among U.S. physicians, but prevalence, root causes, and consequences of burnout syndrome in the neuro-oncology community had not been studied until now. Barbara O'Brien, MD, Shlomit Yust-Katz, MD, and Alvina Acquaye, MS, spoke on Education Day at the SNO meeting about their ongoing study on burnout in neuro-oncology and its preliminary findings.[19] Among 324 SNO members from the U.S. and Canada who completed an anonymous online survey, 30% reported current symptoms of burnout and 45% reported experiencing burnout in the past. More than 70% of the participants reported working more than 50 hours per week and administrative burden was high. Nearly half of participants reported significant stress and did not meet exercise and sleep recommendations for a healthy lifestyle. Interestingly, despite the unique challenges of caring for patients with brain or spinal cord tumors, patient care was reported as the most satisfying career aspect. Data collection and analysis are still ongoing, but these preliminary results reflect a high prevalence of burnout and stress in the neuro-oncology community and point toward the need for interventions to reduce undue administrative burden.

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DEVELOPMENTAL THERAPEUTICS AND TRANSLATIONAL RESEARCH

Adoptive T-Cell Therapy for Solid Tumors

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OVERVIEW

Chimeric antigen receptor (CAR) T-cell therapy is an innovative form of immunotherapy wherein autologous T cells are genetically modified to express chimeric receptors encoding an antigen-specific single-chain variable fragment and various costimulatory molecules. Upon administration, these modified T cells traffic to, and recognize, cancer cells in an HLA-independent manner. CAR T-cell therapy has shown remarkable success in the treatment of CD-19–expressing B-cell acute lymphocytic leukemia. However, clinical gains to the same magnitude have not been reported in solid tumors. Several known obstacles to CAR T-cell therapy for solid tumors include target antigen identification, effective trafficking to the tumor, robust activation, proliferation, and in vivo cytotoxicity. Beyond these T-cell intrinsic properties, a complex and dynamic immunosuppressive tumor microenvironment in solid tumors hinders T-cell efficacy. Notable advancements in CAR design to include multiple costimulatory molecules, ligands, and soluble cytokines have shown promise in preclinical models, and some of these are currently in early-phase clinical trials. In this review, we discuss selected solid tumor malignancies and relevant preclinical data and highlight clinical trial results that are available. Furthermore, we outline some obstacles to CAR T-cell therapy for each tumor and propose strategies to overcome some of these limitations.

CAR T-cell therapy for solid tumor malignancies is an exciting frontier in cancer immunotherapy. The general architecture of a CAR consists of a single-chain variable fragment (scFv) derived against a predetermined tumor-associated antigen (TAA) followed by a CD3ζ domain required for provision of signal 1 and T-cell activation upon antigen recognition.[1] Upon transfection into autologous T cells, first-generation CAR T cells targeting *HER2*/*Neu*-expressing breast and ovarian cancer cell lines showed increased interleukin-2 (IL-2) production and cytotoxicity.[2] However, it was subsequently realized that sustained activity and proliferation after receptor engagement required a secondary signal, or signal 2.[1] Additional genetic modifications to include costimulatory molecules, such as CD28[3] and 4-1BB,[4] to the CD3ζ signaling domain led to second-generation CARs (28ζ and 4-1BBζ, respectively). Acting in concert, provision of both signal 1 and signal 2 mitigated the anergy and activation-induced cell death observed with first-generation CAR T cells.[5] Direct comparison of first- and second-generation CARs directed against CD19, a TAA expressed on malignant B cells, revealed superior expansion, tumor infiltration, and persistence in favor of the second-generation CAR design.[6] Additional genetic modifications have yielded third-generation CARs composed of two distinct costimulatory domains, such as CD28/4-1BB/CD3ζ or CD28/OX-40/CD3ζ, all with varying degrees of efficacy.[7-9] More recently, other approaches to optimize CAR T-cell efficacy via engineered expression of tethered or soluble ligands, cytokines, or scFvs[10,11] also have been reported.

However, despite ongoing success in the management of CD19+ B-cell hematologic malignancies, progress in the solid tumor landscape has been met with many obstacles. One is the identification of suitable neoantigens or TAAs to serve as targets for CAR T-cell therapy. The biologic heterogeneity of solid tumor malignancies does not lend to an approach of one antigen fits all. This difficulty is compounded by the frequent expression of putative target antigens on normal tissues that leads to on-target, off-tumor toxicity.[12] Despite this, acceptable antigens, such as EGFR variant III (EGFRIII),[13] GD2,[14] mucin 1 (MUC-1),[9] mucin 16 (MUC-16),[15] carcinoembryonic antigen,[16] mesothelin,[17] CA-IX,[18] and prostate-specific membrane antigen (PSMA)[19] have been characterized and are in various stages of clinical development (Table 1). Besides identification of a suitable TAA, trafficking of administered CAR T cells to the tumor is another challenge to effective therapy. Consequently, experimental models to improve innate CAR T-cell trafficking via coexpression of chemokine receptors[20] and compartmental/intercavitary administration of CAR T cells are being investigated.[21] Perhaps the most notable limitation lies in the dynamic, complex, and often inhibitory tumor microenvironment present in many solid tumor malignancies. For instance, myeloid-derived suppressor cells and tumor-associated macrophages (TAMs) decrease local tryptophan levels in

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the tumor microenvironment,[22] depriving CAR T cells of an essential amino acid necessary for optimal function. In addition, regulatory T cells, myeloid-derived suppressor cells, and TAMs elaborate inhibitory cytokines such as IL-4, IL-10, leukemia inhibitor factor, and transforming growth factor β—all of which further repress T-cell function.[23-25] Strategies aimed at overcoming these limitations are currently areas of intense investigation.

GLIOBLASTOMA

IL-13 receptor α2 (IL-13Rα2) and EGFRIII are two major targets that have been investigated for CAR T-cell therapy against glioblastoma. IL-13Rα2 is overexpressed in more than 50% of glioblastomas, but limited expression on normal brain tissue is retained.[34] Importantly, IL-13Rα2 expression has been reported on both stem-like and more differentiated malignant cells, making it a favorable target with the potential to eliminate tumor-initiating cells and prevent tumor recurrence. Kahlon et al[35] generated a first-generation IL-13Rα2–specific CAR that redirected human CD8+ cytotoxic T lymphocytes to eradicate established glioblastoma tumor in an orthotopic xenograft model. In a separate study, IL-13Rα2–specific CAR T cells targeted glioma stem–like cancer-initiating cells and abrogated their tumor-initiating activity in mice.[36] A phase I trial was conducted in three patients with recurrent glioblastoma who received repetitive intracranial infusions of first-generation IL-13Rα2–specific CAR T cells without nonmyeloablative preconditioning.[26] Only transient antiglioma responses were observed in two patients. The unsatisfactory response may be explained by poor expansion and persistence of CAR T cells in vivo, because the trial used first-generation CAR T cells. As previously mentioned, first-generation CAR T cells show diminished expansion upon repeated antigen stimulation.[37] In a recent case report, a patient showed tumor regression after multiple intracranial infusions of second-generation IL-13Rα2–specific CAR T cells.[38] Interestingly, CAR T cells with intracavitary administration prevented only local tumor recurrence but failed to control tumor progression at distant sites. In contrast, intraventricular infusions resulted in tumor regression in all intracranial and spinal tumors. *EGFRIII* is a tumor-specific, mutated form of wild-type *EGFR* and is commonly expressed in glioblastoma. Because of an absence in normal tissues, EGFRIII is ideally suited to minimize on-target, off-tumor toxicity. Multiple preclinical studies demonstrate that EGFRIII-specific CAR T cells recognize and eliminate antigen-positive glioblastoma tumors in vitro and in vivo without cross-reacting with wild-type receptors present on normal tissues.[13,39-41]

KEY POINTS

- **CAR T-cell therapy has emerged as a promising immunotherapeutic approach for solid tumor malignancies and several promising candidates are in early-phase clinical trials.**
- **Despite tumor and antigen heterogeneity, several TAAs such as MUC-16, GD2, EGFRIII, mesothelin and PSMA have been identified as targets for CAR T-cell therapy.**
- **Clinical responses have been reported in a small subset of solid tumor malignancies; however, increased response rates and responses across a broader range of tumor types are required.**
- **CAR T-cell efficacy is limited by various intrinsic and extrinsic factors, including poor trafficking to tumor site and an immunosuppressive tumor microenvironment.**
- **Further genetic engineering to optimize CAR design (armored CAR T cells) or combinatorial approaches with cytotoxic, targeted therapy, and immunomodulatory agents are currently under investigation.**

NEUROBLASTOMA

In contrast to glioblastoma, neuroblastoma originates from immature neurons and mostly occurs in infants and young children. Multiple targets, including GD2 and CD171, have been identified and tested for development of CAR T-cell therapy. GD2 is expressed on tumors of neuroectodermal origin, including neuroblastoma and melanoma.[42] In a preclinical study, GD2-specific CAR T cells exhibited potent cytotoxicity and cytokine production in response to antigen stimulation.[43] A phase I clinical trial by Louis et al[27] reported a complete remission rate of 27% (three of 11 patients) in patients treated with first-generation GD2-specifc CAR T cells without lymphodepletion. Furthermore, CAR T-cell persistence was observed for up to 192 weeks in this study.[27] CD171 is a surface antigen expressed on many types of cancer, including neuroblastoma. Functionally, CD171 has been reported to enhance tumor cell activity.[44] The first CD171-specifc CAR was developed by Gonzalez et al,[45] and the engineered T cells displayed robust antitumor activity in vitro. However, subsequent treatment with first-generation GD2-targeting CD8+ lymphocytes in clinical trials failed to control disease progression, and CAR T-cell persistence was inversely correlated with disease burden.[28] The authors speculated that the minimal antitumor response was due in part to the lack of coadministration of IL-2, which is especially critical to support the function of first-generation CARs. It is also worthwhile to note that absence of a CD4+ subset in transferred T cells may have compromised function and persistence; emerging data indicate that optimal CAR T-cell efficacy requires both CD4+ and CD8+ compartments.[46]

Prospects

Efficient CAR T-cell trafficking and localization to the tumor site are prerequisites for optimal antitumor efficacy. This is especially challenging for neuro-oncological malignancies such as glioblastoma because of limited T-cell infiltration in brain. CAR T cells modified to express chemokine receptors, such as chemokine receptor 2, have shown improved trafficking and tissue homing in a neuroblastoma model.[47] An alternative strategy is to target the tumor vasculature. Local delivery of tumor necrosis factor α (TNF-α) has been reported to upregulate the expression of adhesion molecules, such

TABLE 1. Selected Clinical Trials of CAR T-Cell Therapy for Solid Tumors

Trial	Tumor	Target	CAR Design	Phase	Best Response Data
Brown et al[26]	Glioblastoma	IL-13Rα2	CD3ζ	I	*
Louis et al[27]	Neuroblastoma	GD2	CD3ζ	I	CR, 27%; 19 patients**
Park et al[28]	Neuroblastoma	CD171	CD3ζ	I	PD
Feng et al[29]	Non–small cell lung cancer	EGFR	4-1BB/CD3ζ	I	PR, 18%; SD, 45%; 11 patients
Beatty et al[17]	Mesothelioma/pancreatic cancer	Mesothelin	4-1BB/CD3ζ	I	PR, 50%; 2 patients
Junghans et al[30]	Prostate cancer	PSA	CD3ζ	I	PR, 40%; 5 patients
Lamers et al[18,31]	Renal cell carcinoma	CAIX	FcRγ	I	PD
Kershaw et al[32]	Ovarian cancer	Folate receptor α	FcRγ	I	PD
Ahmed et al[33]	Sarcoma	*HER2*	CD28/CD3ζ	I/II	SD, 24%; 17 patients
NCT02209376	Glioblastoma	EGFRIII	4-1BB/CD3ζ	I	N/A
NCT01454596	Malignant glioma	EGFRIII	CD28/CD3ζ	I/II	N/A
	Glioblastoma				
	Brain cancer				
NCT02664363	Glioblastoma	EGFRIII	†	I	N/A
NCT02208362	Glioblastoma	IL-13Rα2	4-1BB/CD3ζ	I	N/A
NCT02311621	Neuroblastoma	CD171	4-1BB/CD3ζ	I	N/A
	Ganglioneuroblastoma		CD28/41BB/CD3ζ		
NCT01822652	Neuroblastoma	GD2	CD28/OX40/CD3ζ	I	N/A
NCT01818323	Head and neck cancer	*ErbB*	CD28/CD3ζ	I	N/A
NCT02547961	Breast cancer	*HER2*	CD28/CD3ζ	I/II	N/A
NCT02349724	Lung cancer	CEA	†	I	N/A
	Colorectal cancer				
	Gastric cancer				
	Breast cancer				
	Pancreatic cancer				
NCT02414269	Malignant pleural disease	Mesothelin	CD28/CD3ζ	I	N/A
	Mesothelioma				
	metastases				
	Lung cancer				
	Breast cancer				
NCT02159716	Pancreatic cancer	Mesothelin	4-1BB/CD3ζ	I	N/A
	Ovarian cancer				
	Mesothelioma				
NCT01583686	Cervical cancer	Mesothelin	†	I/II	N/A
	Pancreatic cancer				
	Ovarian cancer				
	Mesothelioma				
	Lung cancer				
NCT01140373	Prostate cancer	PSMA	CD28/CD3ζ	I	N/A
NCT02498912	Ovarian cancer	Muc-16	CD28/CD3ζ	I	N/A
NCT00902044	Sarcoma	*HER2*	CD28/CD3ζ	I	N/A

Continued

TABLE 1. Selected Clinical Trials of CAR T-cell Therapy for Solid Tumors (Cont'd)

Trial	Tumor	Target	CAR Design	Phase	Best Response Data
NCT02107963	Sarcoma	GD2	OX40/CD28/CD3ζ	I	N/A
	Osteosarcoma				
	Neuroblastoma				
	Melanoma				

*Patients underwent craniotomy before CAR therapy.

**Patients with NED before CAR therapy were not included in denominator of responders.

†Not listed on clinicaltrials.gov.

Abbreviations: CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CR, complete response; EGFRIII, EGFR variant III; FcR, fragment crystallizable receptor; GD2, disialoganglioside GD2; IL-13Rα2, interleukin-13 receptor α2; MUC-16, mucin 16; N/A, not applicable; NED, no evidence of disease; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SD, stable disease.

as vascular cell adhesion protein 1 and intracellularadhesion molecule 2 on endothelial cells, and to enhance T-cell infiltration.[48] Therefore, genetically modifying CAR T cells to secrete TNF-α is one potential approach to overcome this limitation and improve CAR T-cell efficacy. Combining CAR T cells with lenalidomide has been reported to enhance the formation of immune synapses and improve persistency of CAR T cells in vivo,[49] providing a rationale for combinatorial approaches for CAR T-cell therapy.

HEAD AND NECK CANCER

A target of particular interest is the ErbB receptor family, which contains four members, designated EGFR (or ErbB-1), ErbB-2 (HER2 or neu), ErbB-3, and ErbB-4.[50] ErbB receptors are transmembrane tyrosine kinase proteins that promote cell growth and inhibit apoptosis. Overexpression of these receptors, especially ErbB1 and ErbB2, have been observed in many malignancies, such as head and neck, breast, and lung cancers.[51-53] ErbB receptors can exist either in homodimeric or heterodimeric configurations,[54] and it has recently been appreciated that the transforming potential of the heterodimeric configuration is superior.[55] In addition, targeting individual ErbB receptors often results in acquired resistance because of enhanced activity of nontargeted receptors. In light of this, Davies et al[56] developed a second-generation CAR that incorporates a chimeric polypeptide, T1E, designed to achieve broad specificity for the ErbB network. ErbB-specific CAR T cells recognized and lysed several ErbB-positive tumor cell lines in vitro. These cell lines showed expression of a broad range of receptor combinations. In SCID-beige mice, CAR T-cell administration led to the eradication of established xenografts derived from ErbB1/2-overexpressing and ErbB2/3-overexpressing tumors. All four ErbB receptors are widely expressed in normal tissues, albeit at lower levels, which could lead to on-target, off-tumor toxicity. Van der Stegen et al[57] examined treatment toxicity in SCID-beige mice after delivery of the ErbB-specific CAR T cells via different routes. Compared with the intraperitoneal route, intratumoral delivery promoted tumor regression without eliciting any cytokine release syndrome. Consideration of intratumoral delivery has been proposed in clinical trials.[58]

Prospects

Multiple mechanisms have been exploited by cells in head and neck squamous cell carcinoma to escape immune surveillance. Data suggest that 55% to 65% of head and neck squamous cell carcinomas express PD-L1, which binds to its cognate receptor PD-1 on T cells, and suppress immune responses.[59] The presence of infiltrating regulatory T cells also contributes to the immunosuppressive tumor microenvironment via secretion of IL-10 and transforming growth factor β and via direct inhibition of T cells.[60] Therefore, strategies to optimize T-cell efficacy for head and neck squamous cell carcinoma could involve rational combinations of anti-PD-1/PD-L1 antibody with CAR T cells or armored CAR T cells modified to secrete blocking PD-1/PD-L1 scFvs.

BREAST CANCER

HER2 and mesothelin are two TAAs currently under investigation. Amplification of *HER2* oncogene leads to uncontrolled cell proliferation and occurs in approximately 20% of breast cancers.[61] Globerson-Levin et al[62] generated a HER2-specific, second-generation CAR containing CD28 and fragment crystallizable receptor (FcγR) signaling domains and tested its efficacy in a syngeneic mouse mammary tumor model. Transduced T cells exhibited potent cytotoxic capacity and cytokine secretion upon antigen recognition.[62] In addition, repeated injections of HER2-directed CAR T cells eliminated spontaneous HER2-positive tumors and enhanced survival in transgenic mice. Mesothelin is a glycoprotein expressed on a broad range of solid tumors, with limited expression on normal tissues.[63] Mesothelin expression has been shown to be enriched in triple-negative breast cancer and is associated with poor outcomes.[64] Patients with triple-negative breast cancer are not suitable for targeted therapy or hormone therapy, so adoptive transfer of mesothelin-specific CAR T cells offers an alternative option. Tchou et al[65] engineered mesothelin-specific CAR T cells and reported a cytolytic capacity against primary breast tumor cells in vitro. However, in vivo antitumor activity was not evaluated in this study.

Prospects

A major therapeutic challenge to therapy in breast cancer is acquired resistance that results from antigen escape. For instance, under selective pressure, HER2 can undergo proteolysis to cleave the extracellular domain without compromising kinase activity. One approach to overcome this limitation is to use a dual-targeting CAR system, in which engineered T cells coexpress two CARs that recognize two distinct antigens. Redirected T cells can be activated in the presence of either antigen, in essence creating an or-switch, to mitigate antigen-loss escape.[66] Alternatively, CAR T cells can be modified to secrete inflammatory cytokines, such as IL-12, or costimulatory ligands, such as 4-1BB ligand, to stimulate an endogenous immune response against tumor cells via epitope spreading.[67,68]

NON–SMALL CELL LUNG CANCER

Overexpression of *EGFR* is commonly seen in patients with non–small cell lung cancer, and small molecules inhibiting EGFR kinase activity have shown therapeutic benefits. Feng et al[29] reported efficacy of second-generation EGFR-specific CAR T cells that incorporate CD137 and CD3ζ signaling domains. In vitro antitumor efficacy was demonstrated via potent cytotoxicity and by interferon γ (IFN-γ) and IL-2 secretion in response to EGFR-positive lung carcinoma cells. In a phase I clinical study, two of 11 patients with refractory non–small cell lung cancer experienced a partial response after treatment with second-generation EGFR-specific CAR T cells after lymphodepletion. CAR T cells were detected in the peripheral blood of treated patients along with detection of CAR T cells at tumor sites, and eradication of EGFR-positive tumor cells was noted in post-treatment biopsies.[29] Mesothelin and carcinoembryonic antigen are also two attractive targets because of their elevated expressions in non–small cell lung cancer.[69,70] Multiple preclinical studies have reported antitumor efficacy of mesothelin- and carcinoembryonic antigen–specific CAR T cells against antigen-positive tumors, such as ovarian and liver cancers. However, direct evidence of antitumor efficacy against primary tumor samples or lung cancer cell lines has not been evaluated.[71-74]

MESOTHELIOMA

In addition to breast and lung cancer, mesothelin is overexpressed on the majority of mesotheliomas. Carpenito et al[71] engineered several mesothelin-specific CARs that used different combinations of costimulatory domains and compared their antitumor efficacy. Despite equivalent cytotoxicity in vitro, third-generation CARs, which contained CD137 and CD28 costimulatory domains in tandem, showed marginally superior tumor rejection in a subcutaneous mesothelioma tumor model compared with second-generation CARs that had either costimulatory domain alone. In a separate study, a fully humanized second-generation anti-mesothelin CAR mediated tumor elimination in vitro and in vivo.[72] Importantly, CAR T-cell activation was not subverted by soluble tumor-secreted or recombinant mesothelin. This mitigates the concern that CAR T cells could be blocked or preoccupied by the soluble portion of mesothelin detected in some patients. In addition to CAR development, identifying an optimal route of administration has been explored. Using an orthotopic mesothelioma xenograft model, Adusumilli et al[73] showed that intrapleural delivery of second-generation mesothelin-directed CAR T cells vastly outperformed intravenous delivery, requiring 30-fold fewer CAR T cells to induce tumor eradication. In a phase I clinical trial, four patients with advanced mesothelioma or pancreatic cancer were treated with repetitive intravenous infusions of second-generation mesothelin-specific CAR T cells. Moderate antitumor responses were observed, and CAR T cell persistence and trafficking to the tumor site were detected. Interestingly, this study also reported induction of an antitumor humoral immune response after CAR T-cell therapy, evidenced by an elevated antibody response to a variety of tumor-associated proteins. This observation highlights the potential of CAR T-cell therapy to elicit a systemic immune response targeted to a broader range of antigens mediated via epitope spreading.[17] One patient experienced anaphylaxis and cardiac arrest after the third infusion on this trial, and this adverse event was believed to be associated with the development of antibodies against the murine-derived scFv.[75]

Prospects

Like many other solid tumors, lung cancer and mesothelioma possess an immunosuppressive microenvironment. Overexpression of inhibitory molecules, such as PD-L1 and indoleamine 2,3-dioxygenase (IDO) by tumor cells and myeloid-derived suppressor cells have been reported in patients with non–small cell lung cancer or mesothelioma.[76-78] Multiple strategies, including additional modification of CAR T cells and combinatorial approaches, can be adopted to overcome these obstacles and enhance CAR T-cell efficacy. For instance, CAR T cells can be engineered to express dominant negative PD-1 receptors[79] or anti–PD-1/PD-L1 agents to promote resistance to such inhibition.[11] In addition, rational combinations with PD-1/PD-L1 blockade antibody or IDO inhibitors may restore CAR T-cell activity.

OVARIAN CANCER

Several antigens have been exploited as targets for CAR T-cell therapy in ovarian cancer. Barber et al[80] engineered a first-generation NKG2D receptor CAR that recognizes the cognate NKG2D ligand expressed on ovarian cancer cell lines and patient-derived primary ovarian cancer samples. In both cell lines and primary samples, these CAR T cells were activated, secreted proinflammatory cytokines, and lysed tumor cells in an NKG2D-dependent fashion. In vitro efficacy and repression of flank-implanted ovarian cancer cells in a xenogeneic model using HER2/neu-directed second-generation CAR T cells also have been reported.[81] The Lewis-Y (Le^{Y+}) antigen is a carbohydrate molecule that has been shown to be overexpressed on 70% of epithelial-derived tumors.[82-84] Westwood et al[85] designed a CD28ζ

second-generation CAR directed against Le^{Y+} tumors, one of which included ovarian cancer in an OVCAR-3 tumor model. These CAR T cells showed significantly enhanced IFN-γ production, proliferation, and cytotoxicity when exposed to Le^{Y+} OVCAR-3 cells.[85] Furthermore, treatment with Le^{Y+}-specific CARs inhibited growth of flank-implanted OVCAR-3 in immunodeficient NOD-SCID mice. Another TAA under development is MUC-16. MUC-16 is a membrane-associated molecule that belongs to the mucin family of glycoproteins.[86] The extracellular domain of MUC-16 is cleaved into a soluble antigen (cancer antigen 125 [CA-125]), leaving a retained portion (MUC-16-CD) that can be targeted by adoptively transferred engineered T cells.[15] Chekmasova et al[15] engineered a second-generation (CD28ζ) MUC-16-CD–directed CAR that showed efficacy against OVCAR-3 and patient-derived tumor samples. Armored CAR T-cells which have been engineered to secrete IL-12 directed against MUC-16-CD have been shown to be superior in vitro and in vivo to second-generation MUC-16-CD–directed CARs.[87] Similarly, mesothelin, a glycoprotein molecule expressed on pleural, pericardial, and peritoneal cells[88] has been explored as a TAA in ovarian cancer. Carpenito et al[71] reported notable in vitro cytotoxicity using mesothelin-directed third-generation (CD28/4-1BBζ) CAR T cells. Folate receptor α(FRα) is a cell surface–anchored glycosylphosphatidylinositol molecule[89] that is highly expressed on ovarian cancer cells,[90] and it has been shown to be predictive of negative outcomes in patients with ovarian cancer.[91] On the basis of the preclinical efficacy of folate receptor–directed CAR T cells,[92] Kershaw et al[32] conducted a phase I clinical trial using first-generation FR-positive–specific CAR T cells with or without exogenous IL-2 in patients with relapsed/refractory epithelial ovarian cancer. All 14 patients treated in this study had progressive disease. There was no reported decline in CA-125 or antitumor response.[32] In one of the cohorts in this study, the adoptively transferred cells were labeled with indium-111 to facilitate in vivo imaging. After intravenous administration, most of the labeled T cells persisted in the lungs, without any evidence of specific localization to the tumor sites. This finding partially explained the decreased systemic persistence and lack of efficacy in this trial.

Prospects

The inhibitory tumor microenvironment in ovarian cancer, including the highly suppressive ascitic microenvironment,[93] is an important obstacle that needs to be addressed for CAR T cells to be successful in this disease. One approach is to armor the CAR T cells with soluble cytokines, such as IL-12,[21] a proinflammatory cytokine that has been shown to enhance the cytotoxic capability of effector T cells[94] and to reprogram dendritic cells and myeloid-derived suppressor cells.[95] Potential combinations of checkpoint blockade with second-generation or armored CAR T cells also could be explored as a means to augment CAR T-cell efficacy via recruitment of endogenous effector T cells.[96,97]

PROSTATE CANCER

Prostate stem-cell antigen and PSMA are two of the most commonly used target antigens for CAR T-cell therapy for prostate cancer. Predominantly found on prostate tissue, prostate stem-cell antigen is a glycosylphosphatidylinositol-anchored antigen located on the cell surface.[98] In contrast, PSMA is a type II transmembrane protein that reportedly is present at low levels on the cytosolic/apical surface of normal prostate tissue.[99] However, during malignant transformation to prostate adenocarcinoma, it translocates to the extracellular/luminal side of the epithelium.[100] Zhong et al[8] generated a PSMA-directed third-generation CAR by engineering the 4-1BB receptor costimulatory molecule in tandem with CD28 and CD3ζ (named P28BBζ) and tested its efficacy against a human prostate cancer cell line in an SCID/beige mouse model. These CAR T cells showed robust proliferation and cytotoxicity in vitro. In tumor-bearing mice, treatment with P28BBζ greatly enhanced survival compared with control mice. Mechanistically, these T cells showed increased intracellular signaling and enhanced production of granzyme, IFN-γ, TNF-α, and granulocyte-macrophage colony-stimulating factor. Hillerdal et al[101] also have reported efficacy of a prostate stem-cell antigen–directed third-generation CAR that uses CD28 and OX-40 costimulatory molecules. In addition to robust proliferation, cytokine production, degranulation, and cytotoxicity upon recognition of prostate stem-cell antigen–expressing cells, these CAR T cells also were able to significantly delay subcutaneous tumor growth and prolong survival in nude mice. A phase I clinical trial by Junghans et al[102] reported a response rate, by prostate-specific antigen level, of 40% (two of five patients) with a first-generation PSMA-directed CAR after nonmyeloablative preconditioning and concurrent IL-2 administration. In another phase I report, Slovin et al[30] reported tolerability and systemic persistence of up to 2 weeks with second-generation PSMA-directed CAR T cells.

Prospects

TAMs have been implicated in prostate cancer.[103] Specifically, TAMs are recruited to and infiltrate the tumor stroma in a colony stimulating factor-1 (CSF-1)/CSF-1 receptor (CSF-1R) –dependent fashion,[104] where it has been shown to promote tumor and vascular growth[105] and to mediate resistance to hormonal therapy.[106] In experimental models, clodronate-mediated depletion of TAMs led to notable inhibition of tumor growth.[105] One approach to optimize CAR T-cell therapy for prostate cancer might involve preconditioning therapy with either pharmacologic (AZD6495) or antibody-mediated (anti–CSF-1R) depletion of TAMs before CAR T-cell administration. Alternatively, second-generation CAR T cells can be armored via additional genetic modifications to secrete soluble CSF-1R inhibitors.

RENAL CELL CARCINOMA

Carboxy-anhydrase-IX (CA-IX) expression in metastatic renal cell carcinoma has been exploited as a target for adoptive transfer of engineered T cells.[18] CA-IX is a metalloprotease

that reversibly catalyzes the hydration of carbon dioxide.[107] Although it is useful as a TAA in renal cell carcinoma, it also is expressed on several normal tissues, such as the gastric mucosa epithelium, small intestine epithelium, duodenum, and biliary tree.[108] In addition, expression of CA-IX is inducible in many other tissues under hypoxic conditions.[109] In preclinical studies, Weijtens et al[110] showed robust cytokine production and cytotoxic activity of first-generation CA-IX–directed engineered T cells against renal carcinoma cells. Lamers at al[31] initially treated three patients with CA-IX–positive metastatic clear cell renal cell carcinoma with first-generation CA-IX–specific CAR T cells and exogenous IL-2 administration without nonmyeloablative preconditioning. Two of these patients developed grade 2 to 4 liver enzyme toxicity, and liver biopsies showed cholangitis that involved T-cell infiltration around bile ducts and confirmation of CA-IX expression on the biliary ductal epithelium. Furthermore, all three patients developed antibodies against the murine-derived scFv. To abrogate any more toxicity, the investigators pre-administered unmodified antibody from which the scFv was derived (cG250) to saturate and protect the liver before CAR T cell administration. With this amended approach, Lamers et al[18] successfully eliminated treatment-associated hepatoxicity in all four patients who received antibody pretreatment. Curiously, they were unable to detect any human anti-mouse antibodies against the cellular product in patients who underwent antibody pretreatment, which suggests that perhaps the nonspecific inflammation caused by the cholangitis contributed to the generation of human anti-mouse antibodies. Despite CAR T-cell persistence of 3 to 5 weeks, there were no clinical responses.[18]

Prospects

Myeloid-derived suppressor cells[111,112] have been shown to facilitate T-cell suppression via arginase-mediated downregulation of the T-cell receptor ζ chain.[113] Increased levels of circulating regulatory T cells also have been reported in patients with renal cell carcinoma[114] and are inversely correlated with survival.[115] Sunitinib is a U.S. Food and Drug Administration–approved multikinase inhibitor for the treatment of metastatic renal cell carcinoma, and it has been shown to decrease myeloid-derived suppressor cells,[116] enhance type-I IFN responses, and decrease regulatory T cells function in patients with renal cell carcinoma.[117] Could sunitinib be used as preconditioning and maintenance therapy after CAR T-cell administration? This hypothesis could readily be subject to testing with a second-generation or armored CARs in a syngeneic model of metastatic renal cell carcinoma.[118]

SARCOMA

Although sarcomas represent a heterogeneous group of mesenchymal-derived neoplasms, there has been some success in identifying TAAs that are expressed across different sarcoma subtypes. Ahmed et al[119] exploited the expression of HER2 on osteosarcomas by engineering a second-generation HER2-directed CAR construct. These HER2-specific T cells showed robust cytokine production, proliferation, and cytotoxicity in vivo. Adoptive transfer of these genetically modified T cells effectively treated both localized and metastatic osteosarcoma in SCID mice. Second-generation (CD28ζ) NKG2D ligand-directed CAR T cells also have shown efficacy in preclinical in vitro models of Ewing sarcoma.[120] Another approach reported by Huang et al[121] involved generation of an anti–IL-11 receptor α chain (IL-11Rα) second-generation CAR. IL-11Rα expression has been reported on multiple tumor types, including osteosarcoma,[122] prostate cancer,[123] and breast cancer.[124] Signaling via the IL-11/IL-11Rα pathway has been shown, among many other things, to promote osteoclastogenesis.[125,126] IL-11Rα–specific CAR T cells were effective against both primary tumors and pulmonary metastasis in a nude mouse model of osteosarcoma.[121] In a phase I/II trial by Ahmed et al,[33] 19 patients with HER2-positive sarcoma were treated with second-generation HER2-specific CAR T cells without nonmyeloablative preconditioning. Adoptively transferred cells were detectable for up to 9 months in a fraction of treated patients. Furthermore, in patients who underwent metastatectomy 9 to 15 weeks after CAR T-cell therapy, HER2-specific CAR T cells were detected in the tumor samples by qualitative polymerase chain reaction.[33] Of the 17 evaluable patients, four had stable disease for as long as 12 weeks to 14 months. Three patients who underwent metastatectomy after CAR T-cell therapy remained in remission for up to 16 months.

Prospects

The importance of angiogenesis and vascular invasion in sarcoma has been well described.[127] In addition, the presence of M2-polarized TAMs has been reported, and these cells also could contribute to pathologic vasculogenesis via VEGF production.[128] Could CAR T cells be additionally modified to secrete soluble VEGF inhibitors? Perhaps they could be used in combination with anti-VEGF antibodies or multikinase inhibitors like pazopanib or sunitinib? Preconditioning or combination with immune-modifying agents, such as trabectedin[129] or mifamurtide, which act against monocytes/macrophages, could be explored as a means to optimize CAR T-cell efficacy for this disease.

CONCLUSION

Despite enthusiasm for adoptive immunotherapy, many obstacles must be addressed before CAR T-cell therapy joins the armamentarium for management of solid tumors. In tumor types that have more than one TAA, there is the question of which is the optimal target to minimize tumor escape via antigen loss/downregulation. When more than one TAA is expressed, could scFvs against both antigens be engineered in an or-activation or and-activation configuration to combat tumor heterogenicity or to improve safety, respectively? The prerequisite for nonmyeloablative preconditioning also must be rigorously assessed in syngeneic solid tumor models and clinical trials. There might be a hypothetical benefit to remodeling the endogenous lymphoid populations in anticipation of activation/recruitment

by specifically armored CAR T cells, but this remains to be tested. Appropriate preclinical models and mechanisms of efficacy and resistance to CAR T-cell therapy also should be explored, ideally before clinical development. Driven mostly by the importance of demonstrating antitumor efficacy against human cancer cell lines, the clear majority of preclinical CAR T cell validation experiments have been in the context of SCID/beige or other immunodeficient tumor models. These models potentially could underestimate the immunomodulatory effect of the endogenous immune systems of the hosts and the effects of the immunosuppressive tumor microenvironment on adoptively transferred T cells. Consequently, more effort is being directed at understanding the interaction of the tumor microenvironment and the endogenous immune system in immunocompetent mouse models in addition to the prerequisite xenogeneic research. The route of CAR T-cell administration also could be tailored to each solid tumor malignancy according to what is known about each tumor's biology. For example, clinical trials of intrapleural and intraperitoneal administration of CAR T cells for mesothelioma and ovarian cancer, respectively, are in progress. Lingering issues with toxicities in the form of cytokine release syndrome, neurotoxicity, and off-tumor cytotoxicity also are being investigated. Ultimately, knowledge of how best to mitigate these toxicities, coupled with rational combinations of chemotherapy, surgery, radiotherapy, or immunomodulators, will pave the way for the next breakthroughs in CAR T-cell therapy for solid tumor malignancies.

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Biomarkers for Checkpoint Inhibition

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OVERVIEW

The identification of predictive biomarkers for the benefit of cancer immunotherapy is the holy grail of the burgeoning immunotherapy field. Recent work has shown that there are a core of concepts that establish the presence of an immune cell–infiltrate, an inflammatory signature of the tumor microenvironment, and the availability of target antigens defined by mutated neoantigens, as critical for the success of the checkpoint blockade. Genetic analyses have shown that resistance to PD-1 blockade, either innate or adaptive, may be due to existing or de novo mutations in signaling pathways critical for T-cell function in a modest proportion of cases. Major hurdles in the field that remain to be overcome are the difficulty of obtaining tumor biopsies for biomarker assessment, the heterogeneity of biomarker expression within tumors and within different tumors from the same patient, and the inducibility of some biomarkers by disease-related processes. Although assessment of peripheral blood or serum biomarkers would be ideal, few data suggest that they would reliably predict outcome with checkpoint blockade. Ultimately, some amalgamated biomarker that includes tumor and host factors will be required to predict which patients are likely to benefit from, or be resistant to, the effects of checkpoint inhibition.

The field of cancer immunotherapy has expanded enormously over the last decade, with many new trials and multiple new approvals of checkpoint inhibitors for solid tumors in 2016. Ipilimumab, nivolumab, and pembrolizumab have become mainstays of treatment for metastatic melanoma,[1-6] lung cancer,[7-10] and other solid tumors, and numerous combination trials are underway in efforts to optimize the use of checkpoint inhibition. Recently, atezolizumab, the first anti–PD-L1 antibody to be approved by the U.S. Food and Drug Administration for the treatment of platinum-resistant bladder cancer.[11] Lessons learned from evaluating biomarkers of toxicity and outcome in patients with melanoma will undoubtedly help accelerate the development of checkpoint inhibition for other cancers, and may suggest new strategies for overcoming innate and adaptive resistance to checkpoint inhibition.

The most critical question in the field of cancer immunotherapy is whether biomarkers can be defined that predict benefit from the use of these drugs and allow oncologists to choose patients most likely to respond to them. In melanoma and non–small cell lung cancer (NSCLC), a variety of studies have suggested that tumors have three potential immune profiles: (1) those that are infiltrated with T cells and express an "inflammatory" signature of genes, which could be amenable to checkpoint inhibition; (2) tumors that are devoid of any T-cell or inflammatory infiltrate on histologic examination and have a noninflamed, or "cold" gene expression profile and could be amenable to adoptive cell therapy; (3) and tumors that have T cells and other immune cells present, but only at the periphery or within the stromal tissue and not within the tumor itself and might be amenable to antiangiogenic therapy.[12] The "hot" tumors are most likely to respond to PD-1/PD-L1 blockade and have been associated with a previously primed immune response, but have been infiltrated with T cells with high levels of PD-1. Cold tumors that lack a T-cell infiltrate may be good candidates for an adoptive cell therapy strategy, and tumors that have immune cells that fail to infiltrate the tumor tissue may be appropriate for strategies employing antiangiogenesis agents or other drugs that promote T-cell migration.

PD-L1

PD-L1 is the critical ligand for the checkpoint molecule PD-1 on T cells. Its overexpression on tumor cells is a form of adaptive resistance to the presence of T cells that are infiltrating tumors.[13,14] A number of studies have evaluated the association of PD-L1 expressed on tumor cells and/or immune cell expression assessed by immunohistochemical staining and its clinical effect on the efficacy of PD-1/PD-L1 blockade.[15] Although most studies are in agreement that the higher the level of tumor cell membrane PD-L1 expression, the better the outcome with PD-1/PD-L1 blockade, it is clear that patients whose tumors stain negatively for PD-L1 may still gain benefit from checkpoint inhibition.[16]

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This compromises the utility of PD-L1 as a biomarker to choose patients for therapy, because the investigators are unable to define patients who should not receive immunotherapy. In current studies, no less than three different antibodies are routinely used for PD-L1 staining assays, with three different scoring systems. The Ventana SP263, Dako 22C3, and Dako 28-8 antibodies have been most commonly used, and when evaluated for the pathologists' concordance in scoring using NSCLC specimens, a 90% rate was achieved.[17]

Nonetheless, some trials include tumor staining, others allow staining of tumor and immune cells, and yet others include staining of the immune-infiltrating cells only within the scoring system. Nonetheless, PD-L1 is an important biomarker for some tumors, and it has been used as a companion biomarker for the approval of pembrolizumab in patients with NSCLC.[9,10] In NSCLC and melanoma, patients with the highest levels of PD-L1 tumor staining have an excellent chance of achieving a response to PD-1 blockade. PD-L1 expression, a cytolytic or gamma interferon–related gene expression signature, CD8 density, and mutational load have been evaluated for their utility as biomarkers for the efficacy of PD-1 blockade, and mutational load appeared to be independent of the expression of T-cell and PD-L1 markers (Weber et al, unpublished data, 2017).

T-CELL INFILTRATION

The number of CD8 T-cells infiltrating the tumor microenvironment and expressing PD-1 and/or CTLA-4 appears to be a key indicator of success with checkpoint inhibition, and both PD-1 and CTLA-4 blockade may increase the proportion of infiltrating T cells. The best parameter associated with response to PD-1 blockade was a high density of CD8+ T cells at the invasive tumor margin.[18] Assessment of CD8+ cells in the tumor itself were less useful, as was tumor and invasive margin PD-1 expression or the expression of PD-L1 on the tumor cells and invasive margin cells. The number of intratumoral CD8+ T cells that were PD-1+ may also be associated with response to PD-1 blockade. In a different study, the number of double positive PD-1+/CTLA-4+ CD8 T cells within the tumor-infiltrating population was most strongly associated with outcome.[19] In patients receiving sequential PD-1 then CTLA-4 blockade with a planned switch, the CD8 T-cell infiltrate detected by immunohistochemistry was strongly associated with response to treatment in the cohort that received PD-1 antibody first (Weber et al, unpublished data, 2017).

Immune T-cell receptor (TCR) DNA sequencing utilizes a multiplex polymerase chain reaction (PCR) assay with forward primers specific for each V-gene segment and reverse primers specific for each J-gene segment. The TCR repertoire from circulating peripheral blood T cells was determined prior to and after anti–CTLA-4 antibody therapy. There was a substantial increase in the diversity (the number of unique TCR V-beta sequences) of the peripheral blood T cells. This increase demonstrated that no specific clone or subgroup of clones was expanded preferentially. These data suggest that a number of important clones have been disinhibited and allowed to proliferate by CTLA-4 blockade.[20,21] Interestingly, the immune-related toxicity associated with anti–CTLA-4 antibodies was also associated with increases in the TCR diversity, suggesting that some of the clones that were disinhibited and allowed to proliferate generated proinflammatory or autoimmune hyper-responsiveness. In another study, tumor biopsies from patients with metastatic melanoma were analyzed by TCR V-beta chain immune sequencing before anti–PD-1 antibody therapy.[18] Patients whose tumors had more clonal T-cell repertoire were most likely to respond to PD-1 blockade. When a metric of T cell number and clonality of the TCR was calculated, those with progressive disease had the lowest values. Analysis of tumors obtained after starting anti–PD-1 therapy showed that patients whose tumors exhibited high expansion of preexisting T-cell clones were most likely to respond to therapy.

A "focused" TCR repertoire, defined by DNA sequencing of the rearranged beta chain variable regions of the TCR within tumors, was associated with a good outcome with PD-1/PD-L1 blockade,[18] whereas a more "diverse" repertoire infiltrating tumors was associated with benefit from anti–CTLA-4 antibodies, as indicated above.[20-22] The focused repertoire would seem likely to encode TCRs specific for neoantigens, and many of the TCR sequences associated with a good outcome with PD-1 blockade can be found in the periphery in patients with melanoma. TCR diversity is also independent of the T-cell infiltrate or PD-L1 staining, both of which are dependent variables as a marker of outcome.

KEY POINTS

- **PD-L1 staining of tumors is associated with response and survival after treatment with PD-1 blockade.**
- **The magnitude of the CD8 T-cell infiltrate is an important correlate of benefit from anti–PD-1 therapy.**
- **An inflammatory tumor signature is also associated with benefit from anti–PD-1 therapy.**
- **T-cell receptor diversity is associated with benefit from CTLA-4 blockade; in contrast, T-cell receptor clonality is associated with benefit from PD-1 blockade.**
- **Mutational and neoantigen load have a modest association with benefit from PD-1 blockade.**

MUTATION AND NEOANTIGEN LOAD

The T-cell repertoire reflects the host immune response to cancer, but the tumor itself is a key determinant of success with checkpoint inhibition because there is a relationship between increased nonsynonymous variants or somatic mutations in tumors and outcome with checkpoint inhibition.[23] Patients who had tumors, which, like melanoma, possessed a high frequency of somatic mutations,were more likely to respond to checkpoint inhibition with anti–CTLA-4 and anti–PD-1 antibodies. In lung cancer, the number of smoking-related mutations,[24] and in gastrointestinal cancers,[25] the level of mutations dictated by the presence of mismatch repair deficiency were associated with the benefit of PD-1 blockade. Mismatch repair deficiency occurs in a small proportion of colorectal cancers as well as cancers

of the uterus, stomach, biliary tract, pancreas, ovary, prostate, and small intestine. Tumors that possess defects in the mismatch repair pathway have thousands of somatic mutations in regions of repeated DNA, known as microsatellites. Many different mismatch repair deficient tumors possess a prominent immune infiltrate and a cytokine-rich tumor microenvironment in which the tumors express PD-L1 and the effectors express different immune checkpoints including PD-1, CTLA-4, and LAG-3, which is consistent with a primed immune response.[26] The number of neoantigens—mutated proteins that are expressed and could be recognized in the context of MHC class I or II molecules as a processed peptide antigen by T cells, which is related to the total mutational burden—is critically associated with outcome for checkpoint inhibitors. However, the correlation between the burden of neoantigens and clinical benefit was less clear-cut when increasing rigorous thresholds for the binding affinity of peptides were applied and the neoantigens thus defined did not possess any shared sequences or features that were preferentially observed in patients who were responding.[27] These data suggest that the clinical relevance of neoantigens depends on the proper antigen processing and affinity of the neo-epitope peptide and HLA expression by the tumor, which is frequently aberrant. An additional issue is that of clonality, the likelihood that the majority of tumor cells express the neo-epitope in question, as opposed to a "branched" mutation that might be expressed by a small proportion of tumor cells and not clinically relevant. Better algorithms might also be needed to assess the immunogenicity of mutation-derived neo-epitopes.[28,29]

Interestingly, *BRCA2* mutations, which are associated with increased rates of DNA damage and a higher mutational load, are also associated with response to PD-1 blockade.[30]

TUMOR GENE EXPRESSION PROFILE

The nature of the tumor microenvironment also plays an important role in resistance or susceptibility to checkpoint inhibition. A tumor gene expression signature that reflects a series of gamma interferon–inducible genes may define a "hot," inflamed tumor, and is associated in several studies with a good outcome with checkpoint inhibition; its loss is associated with resistance to ipilimumab therapy.[30,31] Melanomas that are class II MHC–positive respond to PD-1/PD-L1 blockade and may share the interferon responsive signature.[31] In a recent study that included whole-exome sequencing of tumors from 16 patients with melanoma, multiple copy-number alterations resulted in the loss of interferon gamma pathway genes in 12 patients whose disease did not respond to ipilimumab.[32] Mice bearing melanoma tumors that lacked one of these genes, *IFNGR1*, also had an impaired response to anti–CTLA-4 therapy and substantially reduced overall survival compared with their counterparts whose tumors had wild-type *IFNGR1*. Tumor samples were collected from patients with melanoma treated with CTLA-4 blockade followed by PD-1 blockade at progression at multiple time points during therapy. Tumor biopsies during CTLA-4 blockade demonstrated higher density of CD8+ T cells in responders compared with nonresponders, suggesting a pharmacodynamic effect of the treatment that was associated with benefit.[33] When tumor gene expression profiling for patients exposed to either PD-1 or CTLA-4 blockade was performed, there was only a modest overlap in the genes that were increased at baseline or during early therapy and associated with outcome with either therapy, indicating a very different mode of action of the two antibodies. Response to PD-1 blockade was associated with pathways of cytolytic activity, antigen processing, and interferon gamma signaling. Expression of *VEGFA* was decreased in responders and increased with therapy in nonresponders, suggesting a mechanism of therapeutic resistance, as observed by others, and a potential target for therapy. In contrast, resistant tumors displayed a transcriptional signature (called the innate anti–PD-1 resistance, or IPRES), which was associated with increased expression of genes involved in the regulation of the epithelial-mesenchymal transition, cell adhesion, extracellular matrix remodeling, angiogenesis, and wound healing.[30] In addition to mesenchymal transition genes, immunosuppressive genes including *IL10*, *VEGFA*, *VEGFC*, and monocyte and macrophage chemotactic genes such as *CCL2*, *CCL7*, *CCL8*, and *CCL13* were associated with a poor outcome with PD-1 blockade. Those signatures of mesenchymal-invasive transition, angiogenesis, and wound-healing signatures have been detected in the resistant melanomas from patients receiving BRAF-inhibitor therapy, suggesting that induction of these signatures may negatively impact responsiveness to combinatorial anti–PD-1/PD-L1 therapy.[30,34] The IPRES signature was found to be increased in metastases compared with primary melanomas and was also detected in most different types of malignancy. Deletion of the *PTEN* gene, commonly found in melanoma, has a deleterious effect on antitumor immunity with checkpoint inhibition, and leads to a "cold" tumor with high levels of immune suppressive cytokines with sparse and inactive T cells.[35] The *PTEN*-deleted population had increased Akt signaling, and consistent with that finding, high levels of *p*-Akt expression in pretreatment tumor cells. In addition, CTLA-4 expression on the tumors and infiltrating T cells of patients with melanoma was associated with poor response rate and overall survival.[36]

There is also an association between tumor activation of the WNT/β-catenin signaling pathway and absence of a T-cell gene expression signature, which leads to deficiencies of infiltrating dendritic cells and a "cold" tumor microenvironment.[37] This might be overcome with the use of a STING agonist, which can augment expression of interferon gamma pathway genes.[38] Clinical examination of host biomarkers from large clinical trials of PD-1 blockade has shown that neutrophil-to-lymphocyte ratios, baseline lactate dehydrogenase, and eosinophil numbers are associated with outcome to checkpoint blockade, although none of these markers can reliably identify a patient who will not benefit from treatment.[39-41]

When tumors become resistant to PD-1 blockade after an initial response, exhibiting adaptive resistance to therapy, the induction of tumor *JAK1* and *JAK2* mutations, or deletion of beta 2-microglobulin may be responsible, leading to

impaired T-cell immunity and inability to detect tumor antigens.[42] In patients with innate resistance to anti–PD-1 antibodies that never respond to treatment, inactivating *JAK1/JAK2* mutations are not common, but are associated with low PD-L1 expression and lack of antitumor response.[43]

PERIPHERAL BLOOD AND MICROBIOME

The definition of serum biomarkers associated with the benefit of PD-1 blockade is still immature. In one series of patients receiving either nivolumab or pembrolizumab, a mass spectrometry–defined signature of proteins included those associated with acute phase reactant, complement, and wound-healing pathways.[44] The complement pathway has not been clearly shown in the past to play a role in T-cell activation, but recent work suggests that, in murine models, T cells have complement receptors, and that C5a and C3a can inhibit T-cell proliferation and activation.[45,46] High pretreatment serum levels of angiopoetin-2 was found to be associated with reduced overall survival in patients who were treated with anti–CTLA-4 or anti–PD-1 antibodies.[47] CTLA-4 and PD-1 blockade increased serum angiopoietin early after treatment initiation in a cohort of patients, whereas the addition of bevacizumab to ipilimumab resulted in decreased serum concentrations of angiopoietin. Increased angiopoietin levels were associated with reduced response to checkpoint inhibition.

Although immune populations detected in the peripheral circulation may not reflect events in the tumor microenvironment, a recent study demonstrated that baseline frequencies of myeloid-derived suppressor cells, CD4+/DF25+/FOXp3+ T regulatory cells, and high levels of eosinophils were associated with clinical benefit in patients with melanoma treated with ipilimumab.[40] High baseline frequencies of circulating CD4+/CD25-high/FOXp3+ T regulatory cells were associated with improved overall survival in this cohort.

There is a long history of work suggesting that the composition of the host microbiota in mice is associated with a favorable outcome with immunotherapy and checkpoint blockade, and recent data suggest that both clinical outcome and the immune-related adverse events often seen with checkpoint blockade may be associated with specific microbial taxa.[48-51]

CONCLUSION

In conclusion, there is no clear-cut and clinically useful single biomarker associated with the benefit of checkpoint blockade, or which could be used to select patients that would not benefit from this treatment. Developing the tools to define pathways of benefit, and that have the negative predictive value to predict innate and adaptive resistance to PD-1/PD-L1 and CTLA-4 inhibition, will undoubtedly require an amalgamated biomarker that combines tumor cell–intrinsic and host T-cell specific determinants. Current efforts in which peripheral blood cells, tumor and serum, as well as microbiome specimens are routinely collected in patients before and after treatment with checkpoint inhibition will be critical to research in defining biomarkers of response and resistance to immunotherapies.

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Pharmacokinetic/Pharmacodynamic Modeling for Drug Development in Oncology

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OVERVIEW

High drug attrition rates remain a critical issue in oncology drug development. A series of steps during drug development must be addressed to better understand the pharmacokinetic (PK) and pharmacodynamic (PD) properties of novel agents and, thus, increase their probability of success. As available data continues to expand in both volume and complexity, comprehensive integration of PK and PD information into a robust mathematical model represents a very useful tool throughout all stages of drug development. During the discovery phase, PK/PD models can be used to identify and select the best drug candidates, which helps characterize the mechanism of action and disease behavior of a given drug, to predict clinical response in humans, and to facilitate a better understanding about the potential clinical relevance of preclinical efficacy data. During early drug development, PK/PD modeling can optimize the design of clinical trials, guide the dose and regimen that should be tested further, help evaluate proof of mechanism in humans, anticipate the effect in certain subpopulations, and better predict drug-drug interactions; all of these effects could lead to a more efficient drug development process. Because of certain peculiarities of immunotherapies, such as PK and PD characteristics, PK/PD modeling could be particularly relevant and thus have an important impact on decision making during the development of these agents.

High drug attrition rates in oncology have been a major concern during recent years.[1] Only 5% of agents that show anticancer activity in preclinical development ultimately are approved upon demonstration of efficacy in a phase III clinical trial. Although the advent of molecular targets has led to a reduction in attrition rates—to 55% in the case of kinase inhibitors—rates remain unacceptably high,[2] which has led to an unsustainable economic model of drug discovery for the pharmaceutical industry and to spiraling costs of drugs that finally receive approval.[2,3]

These high attrition rates compared with those of other therapeutic areas can be explained in part by particular characteristics of oncology drugs,[4] including a narrow therapeutic index, complex pharmacology, the lack of data from healthy patients, a sparser PK sampling, high interindividual variability, and frequent use of therapies in combination to achieve maximum efficacy. Also, major differences in cancer targets and mechanisms of action of anticancer drugs (from conventional cytotoxic chemotherapies to small-molecule targeted agents to immune checkpoint targeted therapies) reject a one-size-fits-all model for PK and PD analyses.

Different solutions, including adaptive trial design[5]; a more extensive use of biomarkers from the early stages[6-8]; and novel tools, such as PK/PD modeling and simulation to aid the different steps of drug development, have been discussed.[9,10]

PHARMACOLOGICAL AUDIT TRAIL

The Pharmacological Audit Trail (PhAT) is a conceptual framework developed by Banerji and Workman[11] to facilitate rational decision making during drug development. By integrating PK and PD data, this tool allows for the codification of a series of biomarker-driven questions that should be raised in a sequential way at the appropriate stages of drug development. When these relevant issues or benchmarks are addressed, the likelihood of failure of a drug would decrease. The PhAT allows us to address critical aspects though out all the process, from the identification of the population most likely to respond and thus to define the target population, to the development of biomarkers of response, to understand the mechanisms of resistance once the treatment fails and finally to establish potential mechanisms to overcome such resistance (such as defining a new combination regimen or the identification of a potential new target).

Pharmacokinetics

PK is the study of the drug concentrations in the body during a period of time, and it includes the processes by which the drug is absorbed, distributed, metabolized, and excreted (also known in colloquial terms as what the body does to the drug).

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Both the importance and utility of PK studies in early drug development have long been recognized.[4,12] Different questions must be addressed. Are we reaching an appropriate PK exposure in humans? What is the correct schedule of administration? What is the correlation of the PK values with the toxicities observed during the trial? The answer to this specific question, for example, could help manage different toxicity profiles that could correlate with the maximum drug concentration and the area under the curve, which could help determine a different schedule of administration.[7] Finally, is there a relevant food effect or drug-drug interaction?

Pharmacodynamics

PD is the study of the relationship between drug concentration and its biologic effects (also known in colloquial terms as what the drug does to the body). Overall, there are two main types of biomarkers in this field[13]: (1) predictive biomarkers that constitute any measurement associated to response/lack of response or toxicity and (2) mechanism-of-action biomarkers that reveal insights into the PD effects of a drug.

Selection of the correct biomarker remains an important challenge, and the bottom-line questions surely must be these: are we modulating the intended target, and does this modulation translate into clinical benefit? Just one example to illustrate this point is the phase I trial of the protein tyrosine kinase Src inhibitor saracatinib.[14] The maximum-tolerated dose was achieved, and the recommended phase II dose was determined. Importantly, different schemes of treatments were tested, and PK analysis confirmed the proposed dose as optimal for PD effects in the tumor, with substantial reduction in Src activity. Another example is a PD study performed to evaluate the effects of different doses and schedules of cetuximab.[15] Results showed that every-other-week dosages of cetuximab had the same functional PD effect as weekly administration in patients with metastatic colorectal cancer; these results confirmed that the every-other-week dosage could be the appropriate one to treat this patient population.

KEY POINTS

- **There is a clear need to improve the speed and efficiency of clinical drug development in oncology.**
- **A deeper, more systematic knowledge of the PK and PD properties of a particular drug is required to better guide rational decision making during drug development.**
- **The use of computational models and simulation can help quantify and understand the relationship between exposure (i.e., PK) and response (i.e., PD).**
- **PK/PD modeling is a useful tool throughout all stages of drug development, and applications differ during the preclinical and clinical stage.**
- **Given the particular characteristics of immune therapies, PK/PD modeling could be particularly relevant during the immune therapy development.**

Despite the fact that PK/PD biomarkers remain crucial for phase I trials, incorporation of the use of predictive biomarkers from the outset clearly could be crucial for acceleration of drug development.[16] This is especially true with molecular targeted therapies, for which the cancer patient subpopulations that are most likely to respond to treatment can be identified to increase the probability of success. The development of anaplastic lymphoma kinase inhibitors in patients with *ALK* rearrangements,[17] or BRAF inhibitors in patients with mutant V600E *BRAF* melanoma,[18] is a clear example of this molecular enrichment approach. Complete validation of the biomarker probably will be carried out in subsequent phase II and III trials; incorporation of the biomarkers earlier, though, will potentiate more informative study designs about the biology of the tumor and treatment resistance mechanisms.

Pharmacokinetics/Pharmacodynamics Modeling

Model-based drug development employs mathematical and statistical models to describe disease progression, PK, and PD; to improve study design; and to better enable decision making.[19] It works as a tool to respond more certainly to the questions raised in the PhAT at a lower cost.

The term PK/PD modeling refers to a PK- and PD-driven exploratory analysis, which is based on a mathematical model.[20] These models can help to better understand the relationship between exposure (PK) and response (PD) as well as the change between these relationships as a function of drug intake. The normal assumption for a study design is the linear relationship between exposure to a medication and its activity; however, this relationship is not always so simple. For example, many monoclonal antibodies exhibit nonlinear PK behavior.

PK/PD modeling can be used throughout all the stages of clinical development.[21] Because models work with data in an iterative manner, the PK/PD model will be more reliable and valuable when more data are available. For the tool to reach its full potential, the tool should be developed from the preclinical stages to incorporate new data as the drug moves forward, which thus refines and improves the model. The updated model will help with the next steps of development. At the end of this building process, a well-defined model will include different submodels, which will be able to predict trial outcomes through the use of data of hundreds of multiple individual patients and multiple trial designs (Fig. 1). PK/PD modeling allows us to address a number of key questions at the various stages of the drug discovery and development process (i.e., PhAT).

Pharmacokinetics/pharmacodynamics modeling in preclinical stages. The main objective of early drug development is to select promising compounds that will be screened for efficacy and safety. The most promising agents will be studied more, and those with an acceptable efficacy/safety profile will enter the clinic. However, the translation of the efficacy and safety results from a preclinical level to the patient population remains a major challenge.

One of the key aims of translational, mainly mechanistic, PK/PD modeling is to generate a priori simulations that help support predictions about efficacy between different species (e.g., in vitro-in vivo predictions and xenograft-to-clinical correlations); thus, the importance of this tool lies at the preclinical-to-clinical interface.[21,22] The biggest cost-saving potential of drug modeling would be a determination of which compounds should move forward and which should be dropped.

The use of these models in the preclinical setting has several potential advantages.[23,24] It can improve lead optimization and the selection of the optimal compound, predict clinical potency estimates (e.g., effective concentration of a drug that gives half-maximal response), and predict the drug exposure needed. It also can provide guidance about the initial tested dose in clinical trials, the dose range, the suggested administration scheme, and even the optimal sampling required in the trial (Fig. 2).[25] Other advantages include prediction of oral bioavailability and assessment of the potential for drug-drug interactions. Other types of modeling, such as synergy-response surface modeling, can help predict the result of drug combinations and can better define a whole development strategy.

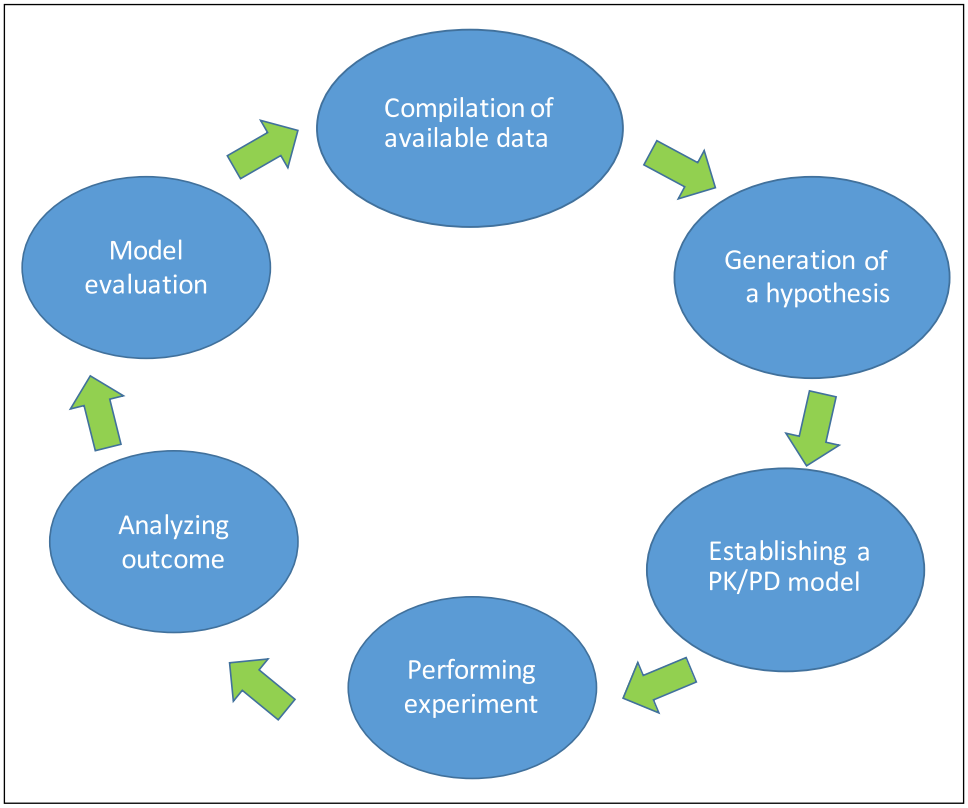
Pharmacokinetics/pharmacodynamics modeling in the clinical stage. There are several applications of PK/PD modeling in clinical development.[24,26] This include effective establishment of the relationship between exposure and biomarker, exposure and response, or biomarker and response relationships; earlier decision making about go or no-go plans on the basis of PK and PD characteristics of the drug; reduced numbers of phase II trials needed to obtain enough data for a phase III trial or for registration; and evaluation of different schemes of drug administration and study designs.

One important aspect of modeling is that it can increase prediction of drug-drug interactions. In the field of oncology, these interactions are a substantial problem, because many agents have a narrow therapeutic index and because most of the anticancer agents will be metabolized by cytochrome P450. The use of modeling can unmask these interactions and the importance of these interactions, and such data can be sent to the health authorities. With this approach, additional drug-drug interaction studies were avoided during the development of ceritinib, for example.[27]

Population PK/PD models also are becoming more important; in addition to the characterization of PK and PD, the models include relationships between covariates such as patient characteristics (e.g., age, body weight, renal function). This enables the assessment and the quantification of potential sources of variability in exposure and response within a specific target population, even under sparse sampling conditions. This approach is extremely relevant for assessments of special populations (e.g., pediatric population, frail patients, renal or liver impairment).[28]

A comprehensive example that illustrates the use of PK/PD modeling in the clinic is the development of everolimus. Everolimus blocks the mammalian target of rapamycin, or

FIGURE 1. The Model-Building Process



mTOR, pathway and inhibits the downstream S6 kinase 1. PK/PD models predicted that the inhibition of S6 kinase 1 in peripheral blood mononuclear cells was related to tumor effect and suggested that, although a weekly dose of 20 to 30 mg of everolimus already was associated with an antitumor effect, daily administration could cause a greater effect with higher dose intensity.[29,30] This supported the incorporation of S6 kinase 1 as a PD biomarker of mTOR signaling and guided the selection of the doses explored during the phase I studies. The phase I trial showed that everolimus administered as 10 mg daily or as 50 mg weekly would be the recommended phase II dosage, although the PD effect was more sustained with the daily dosage.[30,31] Subsequently, a phase III trial showed an increased overall survival in patients with renal cancer who received 10 mg of everolimus daily; approval for this indication was obtained.[32] Another phase III trial showed that 10 mg of everolimus daily increased progression-free survival in patients with pancreatic neuroendocrine tumors.[33]

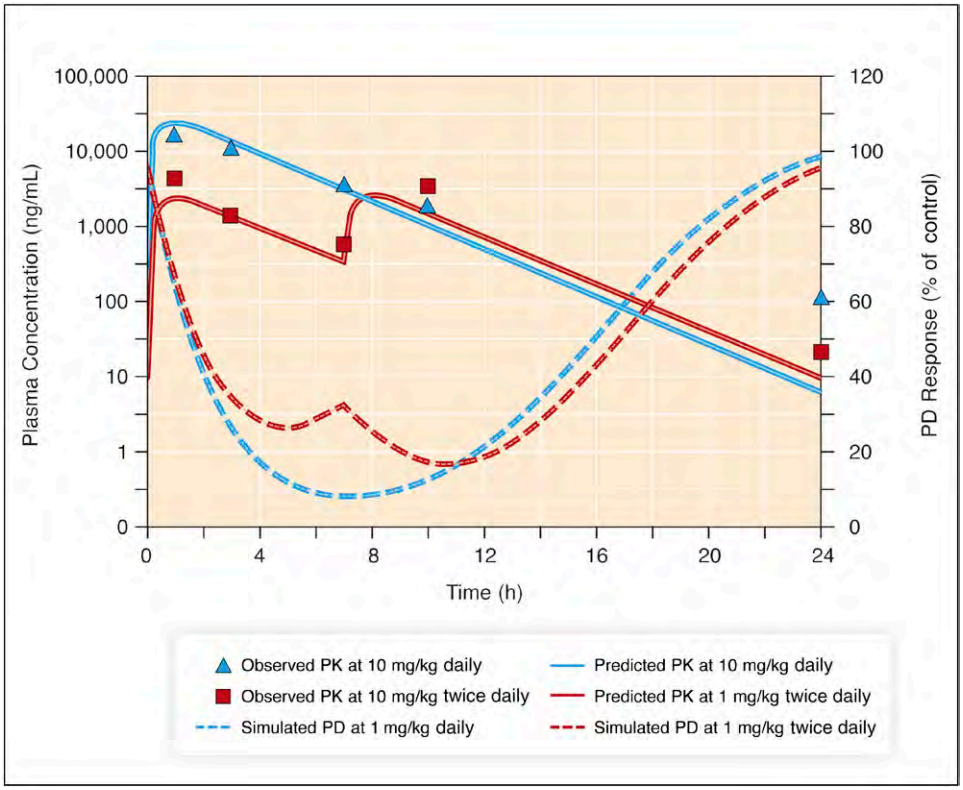
One area in which PK/PD modeling is especially reliable is that of biologics (drugs such as monoclonal antibodies that are produced by using biologic organisms or purified from a natural source) because of their ability to translate across species.[34] In general, the determination of the first-in-human dose is based mainly on toxicology properties and consideration of the no-observed-adverse-effect level, which is determined in preclinical safety studies and then reduced by an appropriate safety factor. However, with monoclonal antibodies, particularly agonist therapies, an additional approach is recommended—an approach that uses the minimal anticipated biologic effect level (MABEL) approach. The MABEL approach considers the pharmacological properties of the drug and the anticipated dose level that leads to a minimal biologic effect level in humans. MABEL is calculated mainly by integrating all of the available in vitro and in vivo information by PK/PD modeling.

DRUG MODELING WITH IMMUNOTHERAPIES

The advent of immune therapy represents a groundbreaking milestone for the treatment of patients with cancer, and the number of immuno-oncology agents entering drug development has continued to increase. However, because of the particular characteristics of these agents, their development has different challenges that must be considered.

Until recently, because most agents have had a direct dose-response curve, determination of the maximum-tolerated dose (MTD) has been the principal parameter for definition of the recommended phase II dose. However, the safety profile of most immunotherapies is different from those of targeted therapies or cytotoxic agents, and

FIGURE 2. Simulation of Exposure and Efficacy Data of Hypothetical Dosing Regimens in a Preclinical Mouse Model



A mouse xenograft model was treated with a drug with two different regimens: 30 mg/kg once daily or 1 mg/kg twice daily. Observed and predicted plasma levels were plotted with the simulated PD responses. This strategy can help determine what dose should be further tested.

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic.

Modified from Tuntland et al.[5]

the MTD generally is not reached; this provides an optimal setting for PK/PD-based dose recommendations. Moreover, the relationships between dose, response and toxicity are more complex with immunotherapies than with other drugs, so the old paradigms of the higher the dose the better, and the higher the dose the higher the toxicity profile is completely obsolete.[35]

To date, most of these immunotherapeutic agents are antibodies and have much more complex PK profiles than small molecules that have specific absorption, distribution, and metabolism characteristics. The size of an immunotherapy agent is much bigger, they are mainly administered intravenously, their distribution is more limited, and their elimination mainly depends on proteolytic degradation rather than biliary and renal excretion. The PD characteristics also are different. For example, although the toxicity of small molecules can be as a result of an on-target or off-target mechanism, the toxicity that has been observed with immunotherapies is mainly because of an activation of the immunogenicity, with a delayed onset of most of the immune adverse events. This will be especially relevant when combination therapies are considered.[36] Another potential advantage of immuno-oncology therapies is that, given their mechanisms of action, repeated PD measurements can be tracked for dynamic biomarker assessment and immunologic monitoring (e.g., $CD4^+$ and $CD8^+$ cells or the levels of different cytokines), which potentially could add value as predictive biomarkers or surrogates of tumor response. Despite these considerations, most phase I studies of immune agents lack PK and PD data. Additional knowledge of these parameters clearly would enrich PK/PD models and optimize the development of these treatments.[35]

A clear example of the importance of modeling in drug development is the case of pembrolizumab. The large phase I KEYNOTE 001 trial started with a standard 3 + 3 design, dose-escalation cohort to explore the MTD of pembrolizumab. Several dosages, from 2 to 10 mg/kg every 2 and 3 weeks, were evaluated.[37] Despite the safety of the higher dosage studied (10 mg/kg every 2 weeks), the mechanism-based translational model, which focused mainly on intratumor exposure prediction, suggested that robust clinical activity would be observed from a dosage of 2 mg/kg every 3 weeks.[38] This dosage, therefore,was recommended to be tested for clinical efficacy in additional clinical trials. Model-based characterization of the PK of pembrolizumab also was performed,[39] and it indicated an absence of covariate effects and supported the pembrolizumab dosage of 2 mg/kg every 3 weeks. Pembrolizumab at a dosage of 2 mg/kg every 3 weeks now is approved for non–small cell lung cancer tumors that express programmed death-ligand 1 and for metastatic melanoma. This clearly illustrates how drug modeling can transform early PK and PD results into a robust clinical trial design and can increase knowledge about the pharmacological properties of a drug. Given the costs of these agents and the challenge of reimbursement for health authorities and insurers, determination of the most appropriate dose is paramount. Notably, pembrolizumab was approved just 4 years after the phase I clinical trial started, through breakthrough designation by the FDA. This timeframe clearly contrasts with the 10 or greater years that former drugs traditionally took to be approved.[40]

CONCLUSION

As we progress in drug development, the importance of strategic thinking and rational decision making aimed at improvements of results remains clear. The PhAT represents a stepwise approach that allows for critical decision making that is based on biomarker and clinical endpoints, and it should be adopted and embraced more widely in clinical research.

Implementation of PK/PD modeling from early drug development promises a substantial impact on general efficiency as an excellent tool to help address critical questions and to evaluate different scenarios. For optimal modeling, the groundwork must begin early in preclinical development and the model must be finely tuned as results are obtained and sequentially analyzed.

Because of the common practice of using an MTD measurement, model-based drug development generally has not been considered during development decisions for anticancer therapies. This will probably change with novel drugs such as immunotherapeutics, because the MTD often is not reached. For PK/PD modeling to deliver on its promise the entire drug development community will need to learn and understand this approach in order to trust the models and be reassured of their utility.

As drug development evolves from determinations of MTDs to determinations of the optimal biologic (or immunologic) dose, the need for validated biomarkers will be of critical importance. Newer trial designs, coupled with new response and efficacy assessments, also will be required to optimize and expedite the development of novel agents, immunotherapies in particular.

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Strategies to Maximize Patient Participation in Clinical Trials

Eric H. Rubin, MD, Mary J. Scroggins, MA, Kirsten B. Goldberg, MA, and Julia A. Beaver, MD

OVERVIEW

Despite considerable interest and success in oncology drug development, the minority of patients with cancer diagnoses enroll in clinical trials. Multiple obstacles account for this low enrollment rate. An improvement in patient participation in clinical trials could increase patient access to novel and potentially promising agents, provide faster trial results, and, with implementation of rational eligibility criteria, allow for a better understanding of the drug's safety and efficacy in a heterogeneous population. We present barriers and potential solutions to maximize patient participation, including a review of the ASCO and Friends of Cancer Research (FoCR) Modernizing Eligibility Criteria Project, U.S. Food and Drug Administration (FDA) regulatory considerations, an industry perspective, and a patient perspective.

The goal of oncology clinical trials is to understand the risks and benefits of a therapy and to facilitate and expedite the development of safe and effective drugs to treat patients with cancer. Clinical trials also provide patients with access to investigational agents; however, U.S. oncology clinical trials only enroll approximately 3% of patients diagnosed with a new cancer.[1] Multiple barriers can contribute to this low rate of enrollment, including those at the patient, physician, institutional, and protocol levels.[2,3]

Patient-level barriers to enrollment in clinical trials result from the fear that clinical trials will delay initiation of antineoplastic drugs (particularly if biopsy and genomic sequencing are required), fear of undergoing additional testing and procedures, or concerns about enrolling in randomized trials that might include a placebo or perceived inferior investigational or control arm. Other patient barriers include socioeconomic issues, such as concerns over travel costs with increased frequency of follow-up visits in a clinical trial. The lack of clinical trial access and/or a decline in functional status are additional commonly reported reasons that patients are not enrolled in clinical trials.[4] Physician-level barriers such as lack of knowledge about new agents and available clinical trials may also present obstacles to enrollment. Institutional-level barriers are reflected by the number of available protocols at one institution, and the fact that for many community practices, knowledge about the potential for referral to clinical trials may be limited. Overly restrictive eligibility criteria are a major protocol-level barrier. Given these obstacles, strategies are needed to maximize patient participation in clinical trials.

MAXIMIZING CLINICAL TRIAL PARTICIPATION AND IMPLEMENTATION OF MODERN ELIGIBILITY: INDUSTRY PERSPECTIVE

From an industry perspective, key parameters in clinical trial implementation and participation are as follows: (1) speed and efficiency in evaluating the safety and efficacy of an experimental oncology agent, (2) investigator and site experience with investigational drug trials (including obtaining patient informed consent and assessing adverse events), (3) speed of trial initiation at sites, (4) site accrual rates, (5) site data quality, and (6) investigator experience with the pathway targeted by the experimental agent.

Protocols for industry-sponsored clinical trials undergo a rigorous internal review process, typically involving multiple review committees with members possessing expertise in trial design, statistics, and regulatory, safety, data management, and operational aspects of clinical trials. During protocol development, industry sponsors typically obtain investigator input and ensure that the patient perspective is understood in order to confirm feasibility and maximize accrual rates.

Single-arm, personalized treatments (e.g., trials that select among various treatments based on a biomarker evaluation of a tumor biopsy) are often attractive to patients; thus, these trials tend to accrue rapidly. Single-arm trials may be sufficient for regulatory approval in some cases, such as rare cancers and/or where initial data suggest a remarkable improvement relative to existing treatment options. However, in most cases, randomized controlled trials will be necessary to demonstrate clinical benefit. In these trials, accrual rates can vary widely depending on patient perspectives on the potential benefits of the experimental and control arms.

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Clinical Trial Designs to Improve Enrollment

Depending on the molecular target for an investigational agent, it may be preferable to use clinical trials that use enrichment designs (i.e., eligibility is dependent on having a "positive" result from a biomarker test performed on a tumor or blood specimen from the patient), particularly if the target is a mutated gene that has a low prevalence among a given tumor type. Using adaptive trials (e.g., trials that include prespecified changes based on accumulating data) may improve efficiency relative to use of multiple sequential trials, each requiring several internal and external committee reviews as well as separate site contracting and trial initiation efforts.[5-7] However, there may be tension in terms of the degree of flexibility desired by an industry sponsor versus prespecification of sample sizes based on statistical evaluations of efficacy and safety. In addition, adaptive trials increase protocol complexity, particularly if multiple amendments are required even if the adaptive changes are prespecified.

In some types of enrichment trials, it may be expected that that the biomarker test may identify responsive patients regardless of tumor type. In this case, "basket" trials have become increasing popular, in which eligibility is determined by the biomarker test rather than the tumor type.[8] However, this approach may create challenges in terms of selection of site principal investigators, because cancer centers are not organized by biomarkers but by tumor type. Thus, it may be difficult to identify an optimal principal investigator in terms of patient accrual to the trial.

KEY POINTS

- **Despite considerable interest and success in oncology drug development, the minority of patients with cancer diagnoses enroll in clinical trials, owing to barriers at the patient, physician, institutional, and protocol levels.**
- **An ASCO and FoCR Modernizing Eligibility Criteria Project, in collaboration with the FDA and other stakeholders, is working toward evaluating clinical trial entrance criteria that may unnecessarily restrict clinical trial access and providing recommendations for a more rational approach to determining inclusion and exclusion criteria.**
- **Working groups with representatives from ASCO, FoCR, FDA, patient advocacy programs, industry, and others have prioritized assessments on criteria for patients with brain metastases, organ dysfunction, history of prior malignancy, and HIV and for those younger than age 18 to come up with recommendations for a more nuanced approach to determining eligibility.**
- **Creative clinical trial designs such as enrichment designs, master protocols, and "basket" trials in the right clinical scenario can maximize patient participation and efficiency.**
- **Clinical trials hold the promise of providing benefit to patients/survivors and patient-level barriers to enrollment can be addressed through reasoned interventions.**

Master protocols are another trial design that has become increasingly popular as a means of improving efficiency of oncology drug development for a particular tumor type.[9] When testing multiple drugs with non-overlapping eligibility criteria (e.g., drugs targeting non-overlapping gene mutations), these designs have advantages over use of multiple two-arm randomized registration trials. First, grouping these trials under a single protocol, with a common control arm, reduces the overall screen failure rate. For example, assuming a prevalence of 20% for biomarkers A, B, C, and D in a given histologic cancer type (with no overlap among each subpopulation) and a need for 200 biomarker-positive patients each on an experimental arm and in the treatment-control arm, 8,000 patients would need to be screened in the case of four separate randomized studies, whereas only 2,163 would need to be screened in the case of a single five-arm study with four experimental arms and one control treatment arm. Second, process and operational efficiencies are improved through the ability to amend a single master protocol as needed as drugs enter and exit the trial. For example, after implementation, sponsors enrolling new drugs would benefit from the presence of a preexisting infrastructure. Although master protocols can improve the efficiency of drug development, they may not be fully endorsed by industry, particularly if trial arms include similar agents.

Implementation of Modern Eligibility

Although there are already examples of industry sponsors embracing changes in traditional eligibility criteria that have been suggested recently by various stakeholders (see section on modernizing eligibility criteria), challenges remain. Because industry typically desires to register new drugs in many different countries, registration trials usually involve sites from many different countries, and in certain countries, the view on reducing eligibility restrictions may differ from that of the United States, particularly as related to age. Furthermore, although mitigating factors have been described, allowing patients with impaired organ function or performance status may bias evaluation of safety and efficacy, potentially leading to premature discontinuation of the development of a particular agent. In some trials, accrual may be dominated by non-U.S. sites as a result of limited access of patients in some countries to investigational drugs or newly approved drugs. This can result in U.S. filing applications consisting of patient data from predominantly non-U.S. sites.

Strategies to Address Low Enrollment

Some studies enroll poorly, which may relate to several possible issues. These reasons may include lack of interest in the investigational agent or the control arm treatment, overly restrictive eligibility criteria, complex requirements (e.g., prolonged inpatient stays, uncomfortable procedures, or multiple invasive biopsies), or, in the case of enrichment trials, a low prevalence of biomarker positivity. Another possible reason for slow enrollment is the existence of similar studies competing for the same patient population,

particularly if the eligible population is uncommon (e.g., a biomarker-selected population in which the prevalence of biomarker positivity is low). Although many sites attempt to limit the number of trials competing for the same population, this does not address competition for patients between sites.

Sponsors may evaluate several options in cases of slow enrollment. A commonly used option is to simply add additional sites. If there is a high rate of screen failures, eligibility criteria may be re-evaluated, particularly if one criterion is a predominant reason for screen failures. For example, the number and types of previous treatment allowed may be too restrictive. In addition, for randomized trials, patients and investigators may not view the control arm as an attractive treatment option. In this case, adding additional treatment options to the control arm (e.g., allowing investigators to choose among a list of treatments), or allowing crossover to the investigation arm upon disease progression, may improve accrual rates.

MODERNIZING ELIGIBILITY CRITERIA FOR CLINICAL TRIALS

Historically, eligibility criteria were appropriately put in place because of concerns over safety in selected populations but, in many cases, clinical trial protocols are copied forward between and within drug development portfolios and are not always based on a rational analysis. It is critically important for developers of clinical trials to take a more thoughtful approach to the selection of eligibility criteria, not only to provide improved access to clinical trials for patients with cancer but also to understand a drug's safety and efficacy in a more representative population. Despite years of recognition of this issue, inclusion and exclusion criteria remain prohibitive for many patients.[10-13] Certain populations in particular are frequently excluded from oncology clinical trials, including patients with HIV, brain metastases, history of prior malignancies, poor performance status, and comorbidities and those younger than age 18.[13] Of approximately 300 commercial Investigational New Drug Applications submitted to the FDA's Office of Hematology and Oncology Products in 2015, only 3.7% included pediatric patients; 60% required Eastern Cooperative Oncology Group performance status of 0–1; 77% excluded known, active, or symptomatic central nervous system or brain metastases; 47% allowed treated or stable brain metastases; and 84.2% excluded patients with known or active HIV (with only 1.7% allowing patients to enroll with adequate CD4 counts).[14] Multiple stakeholders realize that taking a more rational approach to eligibility criteria will result in improved patient benefit.

ASCO/Friends of Cancer Research/FDA Modernizing Eligibility Criteria Project and Working Groups

The ASCO and FoCR Modernizing Eligibility Criteria Project, in collaboration with the FDA and other stakeholders, is working toward evaluating clinical trial entrance criteria that may unnecessarily restrict clinical trial access and providing recommendations for a more rational approach to determining inclusion and exclusion criteria.[13,15] Working groups were formed with representatives from ASCO, FoCR, FDA, patient advocacy programs, industry, the National Cancer Institute, biostatisticians, pharmacologists, and clinical investigators to come up with recommendations for a more nuanced approach to determining eligibility. These groups have prioritized assessments on criteria for patients with brain metastases, organ dysfunction, history of prior malignancy, and HIV and those younger than age 18.

Working Group Preliminary Recommendations

Publications from these working groups are pending; however, preliminary recommendations presented at the FoCR Annual Meeting in November 2016 detail current working group thinking.[16] The brain metastases working group endorsed the routine inclusion of patients with treated or stable brain metastases in all phases of clinical trials unless there is a compelling rationale for exclusion.[16] In certain instances, patients with new, active, or progressing brain metastases may also be included, taking the history of the patient's disease, trial phase and design, drug mechanism, and potential for central nervous system interaction into account. Patients with leptomeningeal disease may also have specific situations that warrant an eligible cohort in early-phase trials. The minimum age working group proposed that pediatric-specific cohorts be included in dose-finding studies in which strong scientific rationale is present. This rationale could be based on preclinical data or an understanding of the mechanism of the disease. In later stages of drug development, the group proposed that trials in diseases that span adult and pediatric populations should enroll pediatric patients, particularly patients age 12 and older. Others, including the FDA, have also suggested the inclusion of patients age 12–17 in appropriate adult disease-specific trials.[17] The working group also proposed that HIV-related eligibility criteria be rationally developed and focus on current and past CD4 and T-cell counts, a history of AIDS-defining conditions, and status of HIV treatment.[16] The working group advised that HIV should be considered a comorbidity and antiretroviral therapy should be considered a concomitant medication. The organ dysfunction working group proposed that eligibility regarding renal function should be based on creatinine clearance rather than serum creatinine levels, and knowledge of a drug's excretion by a specific organ system could inform exclusion criteria cutoffs. In addition, it was advised that exclusions based on prior malignancy be liberalized.

Regulatory Considerations of Eligibility

Regulatory incentives that might encourage a thoughtful approach to eligibility are also possible. For example, an expanded marketing claim could be granted if an adequately studied patient cohort included a previously excluded population such as patients with brain metastases. In addition, postmarketing requirements or commitments, such as the study of organ impairment, might be unnecessary if these

populations were included previously. Pediatric incentives include the ability to address requirements from the Pediatric Research Equity Act to study the effects of drugs on children. So that efficacy is not compromised in trials intended to support registration, a broader clinical trial population could include a prespecified, more narrowly defined population for the primary efficacy evaluation.

ASCO/FoCR/FDA Eligibility Criteria Future Directions

Appropriate eligibility criteria define a patient population that will result in patient protection, but strict eligibility criteria can negatively affect patient participation and result in failure to understand a drug's safety and efficacy in a representative population. Future endeavors of the ASCO/FoCR/FDA project will focus on approaches to appropriately defining drug washout periods, exclusion of concomitant medications, and inclusion of elderly patients.[16,18] The Modernizing Eligibility Criteria Project advocates for a culture shift in the approach to inclusion and exclusion criteria and will continue to pursue a broad implementation of this rational approach to eligibility.

IMPROVING ACCESS TO CLINICAL TRIALS: A PATIENT PERSPECTIVE

Although it is important to acknowledge that there is no single patient or patient advocate perspective or consensus on clinical trials. The views and suggestions offered here are those of an individual advocate informed and enriched by more than 20 years of active engagement across numerous advocacy groups.

A Goal of Patient Benefit

Simply put, clinical trials hold the promise—the enormously hopeful potential—of providing benefit to patients/survivors. Patient advocates, some as research advocates, support the clinical trial enterprise in numerous ways and participate in clinical trials for many reasons—one being the hope of personal benefit and another being the desire to contribute to the likelihood of benefit to future generations. Low trial enrollment decreases the speed and likelihood of trial progress and thus ultimate patient benefit (practice changing or incremental), wastes precious human and funding resources, and compromises confidence in the entire enterprise (thus becoming an additional barrier to enrollment).

Overview of Patient Barriers

Barriers to participation in clinical trials vary widely across institutions, professions, and populations. Low trial enrollment, relative to the available pool of participants, is a recurring topic or theme at nearly all conferences, meetings, and other gatherings of individuals involved in the clinical trial enterprise, seeking access to trials, or hoping to benefit from them. The long list of often-overlapping barriers includes (1) a history of unethical trials, (2) lack of understanding of clinical trials or the availability of specific trials, (3) lack of trust in the medical system, (4) uneven or unequal recruitment (including physician conscious and unconscious bias), (5) patient-physician communication (or the lack thereof), (6) access and logistical considerations (including financial, geographic, and educational considerations), and (7) the fear factor (e.g., of being randomized or of randomization not being so random and of being the object of unfettered experimentation).

These barriers and others combine to create limited and unequal participation in clinical trials, with differing effects on various populations, partially depending on their experience with the health care system. For example, "history" is often cited as a barrier to participation by populations described as vulnerable or "special" (a misnomer); however, history can be a barrier for any population and any individual who understands the medical misconduct and infamous studies that litter the research landscape. When known and understood, events such as the Nazi experiments (1940s), the Willowbrook studies (1956–1972), the Jewish Chronic Disease Hospital studies (1963), the AIDS trials (1980s), and the Tuskegee syphilis study (1932–1972), which is perhaps the most often cited example, prompt or exacerbate distrust in the system and increase reluctance to participate even with the potential of benefit to the participant or to others.

Distinguishing Myth From Reality

Important overarching concerns related to clinical trial participation include limited understanding of clinical trial terminology, standards, and protections. These concerns support the rise and maintenance of myths, such as those described in Table 1.

Trial Participation in the Age of Personalized Medicine

Clinical trial participation is the primary route through which biospecimens are obtained and banked, thus serving as a gateway for individual access to personalized medicine and health care. As such, it is increasingly important for all populations to be represented in the clinical trial enterprise. Because they are not equally represented, it is not surprising that banked biospecimens do not represent the diversity of the general population and that the findings derived from these biospecimens are not widely generalizable to segments of the population. Without trial participation across populations, underrepresented populations will have little or no "skin in the game." An unintended consequence is likely to be an increase in cancer health disparities. Therefore, with a substantial share of research efforts and research dollars focused on personalized medicine and health care, representative trial participation is a must.

Potential Strategies and Interventions

Like the barriers to clinical trial participation and low enrollment, potential solutions are frequently offered, if not implemented. The following potential solutions are offered as doable, feasible, and measurable:

1. Acting on what we know and have researched (including using best practices),

TABLE 1. Myths and Realities of Clinical Trial Participation

Myth	Reality
The Tuskegee syphilis study is the reason for low enrollment of black patients and perhaps other vulnerable populations.	The Tuskegee syphilis study or what it represents is a reason (i.e., one among many others), not the reason. In fact, it can become an excuse for the opportunity to participate not being offered.
Black and Hispanic patients are less likely to participate in clinical trials than white patients.	Although both groups are less likely to be invited to participate in trials than white patients, when asked, they are slightly more likely to enroll.
Trial participants are guinea pigs and may be experimented on in ways beyond their consent.	Numerous regulations and safeguards, including 45CFR46, ensure that human participants are protected and that research is ethical. All U.S. research involving human participants is reviewed and monitored by an institutional review board, whose focus is to protect participants.
Clinical trials are or should be an option only when potential participants have no other treatment options.	Clinical trial participation can and should be an option for any patient who meets specific trial eligibility requirements and wants to participate. Not all patients will choose to participate, but all should be given the option to do so when appropriate.
Some clinical trial participants will receive treatment inferior to standard of care, perhaps through randomization or placebo use.	All clinical trial participants will receive at least standard of care. Randomization and placebo strike fear in the hearts of potential participants. This fear can be educated away.

2. Focusing on recruitment of—as opposed to continuously studying—vulnerable and special populations (as a largely untapped resource and as a matter of good conscience and good science),
3. Funding and implementing bidirectional clinical trial education and awareness (to include a sustained public awareness campaign, communications skills, and cultural sensitivity training for the public, patients and survivors, health care providers, and researchers),
4. Developing trial-specific educational material (as well as trial-general material with substantial meaningful patient advocate involvement),
5. Instituting accountability relative to uneven/unequal recruitment and unmet goals (to include the requirement for rigorously reviewed population-specific recruitment goals and the implementation of consequences where warranted),
6. Reviewing and modernizing eligibility requirements (understanding, for example, that exclusion of potential participants with comorbidities—unless scientifically warranted—has a profound effect on eligibility by population and that trial participants should more closely align with the general population that might benefit from the trial),
7. Formalizing engagement of patient advocates beyond recruitment and throughout and beyond protocol development and review, and
8. Requiring an informed consent process as well as a signed informed consent document.

This may seem a smorgasbord or data dump of possibilities. It is not. Instead, it is a listing of potential solutions that can and should often be combined and fashioned into interventions that move from discussing low enrollment and the concomitant barriers to overcoming them.

In Summary—A Patient Advocate's Perspective

This cancer survivor and patient advocate's perspective focuses on the implementation of interventions old and new, alone and in combination. The breadth and depth of research on clinical trial participation have been extensive and the conversation is ongoing; however, to effect measurable change, we must move from conversation to research-based and best practice–informed action, that is, reasoned interventions.

CONCLUSION

Although restrictions on clinical trial entry for the protection of patients are appropriate and supported by all stakeholders, an examination of more nuanced eligibility is appropriate in many cases. This rational approach to defining eligibility will benefit patients by providing clinical trial access and ultimately resulting in a greater knowledge of a drug upon approval. Additional barriers can also be approached with similar efforts to expand and maximize patient participation in clinical trials. Through collaborative efforts across academia, government, industry, and advocacy, there is great promise and potential for maximizing patient participation in oncology clinical trials.

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Tissue-Agnostic Drug Development

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OVERVIEW

The U.S. Food and Drug Administration (FDA) has approved drugs to treat patients with tumor types based on a single anatomic site, such as renal cell carcinoma or melanoma, rather than on a biomarker alone. This standard approach is based on a number of factors, including heterogeneity of drug effects in different biomarker-positive tumor types. Additionally, drug development for some drugs was primarily directed toward a specific genomic abnormality in a specific tumor type (e.g., drugs for anaplastic lymphoma kinase [ALK] fusion-positive non–small cell lung cancer). In such cases, differences in biology, differences in natural histories of different cancers, differences in mutation frequencies among cancers, or differences in concomitant therapies may have necessitated diverse development considerations. As described in U.S. regulations [21 CFR 201, CFR 201.57(c)(2)], the indications and usage section of drug labeling "must state that a drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition." Such regulations, however, do not require that disease be defined solely as a specific tumor type. This manuscript will highlight scientific/biologic issues, clinical trial designs, and regulatory issues pertaining to the development of drugs agnostic of tumor type. Although the manuscript will discuss regulatory considerations as understood by the authors regarding tissue-agnostic drug development, it should not be considered formal or binding FDA guidance or policy.

Some of the earliest successes in developing targeted therapy for genetically defined subsets of cancer occurred by targeting genetic alterations that, in retrospect, were nearly restricted to one or two cancer types. This was the case for abl kinase targeting with imatinib, EGFR inhibitors for *EGFR* activating mutations, and ALK inhibitors for *ALK* fusions. As the tools to unravel the molecular biology of cancer have enabled complete characterization of the hundreds of cases of all common cancers and many uncommon ones, it is clear that cancers arise from common somatic genetic building blocks.

SCIENTIFIC/BIOLOGIC CONSIDERATIONS AND TARGET SELECTION FOR TRIALS TO IDENTIFY PATIENTS FOR TREATMENT AGNOSTIC OF TUMOR TYPE

The Cancer Genome Atlas project and other publicly funded studies rediscovered common genetic alterations that were variably represented across cancer types defined by site of origin (e.g., *PIKC3A*, *RAS*, *BRAF*, *Her-2*, *TP53*, *PTEN*, *CDKN2A*, etc.).[1] New insights were also gleaned into the commonness of genetic changes in components of complex, multicomponent molecular machinery (such as the SWI-SNF and spliceosome complexes). In the case of *Her-2* amplified and *BRAF* mutant tumors, it has become clear that the spectrum of efficacy observed in one tumor type can vary substantially when comparing various cancer types harboring a specific genetic alteration.[2-5] Perhaps most striking is the case of BRAF, where BRAF inhibitor monotherapy has profound efficacy in melanoma that is not yet equaled in colorectal cancer, even with triple-drug regimens targeting BRAF, MEK, and EGFR.[6] This precedent established the principle that one should assume heterogeneity, not homogeneity when investigating novel targeted therapy strategies. More recently, even immunotherapy has been subject to similar considerations. For the field-changing class of PD-1/PD-L1 antibodies, it has been established that higher mutation burden, infiltration of CD8+ T cells, and expression of PD-L1 on tumor and/or infiltrating immune cells can predict response.[7] But, the predictive accuracy varies across cancer types.[8] As new immunotherapies are being developed, the question arises as to whether their development would be accelerated by understanding whether new single agents or combinations building on a PD-1/PD-L1 antibody backbone might confer benefit similarly or differently in various cancer types that are profiled at the level of these analytes.

Preclinical models that might aid in predicting the most-responsive or most-resistant tumor types for a given therapy are poorly developed for many cancer types. Models that reflect the full genetic complexity of human cancer,

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in a representative microenvironment, and in the setting of an intact immune system, are a particular unmet need in cancer therapeutic development. Thus, new therapies are brought into clinical development with little ability to predict which cancer types would be most impacted.

Principles of Variable Response to Oncogene/Signal Transduction Targeted Therapy

In cases of single-agent targeted therapy development, variable response within a single tumor type is the rule. The full spectrum of durable responses and de novo refractory disease has been well cataloged in the case of BRAF in melanoma, EGFR in *EGFR* mutant non–small cell lung cancer,[9] and ALK in non–small cell lung cancers harboring *ALK* fusions.[10] The addition of Her-2 antibodies to conventional cytotoxic chemotherapy in *Her-2* amplified breast cancer follows the same pattern.[2] Extensive investigation into the causes of de novo resistance and susceptibility have highlighted the contribution of cells in the tumor microenvironment providing growth factor-mediated survival signals, compensatory signaling as a consequence of dysregulated feedback mechanisms, and concomitant somatic genetic alterations present at baseline that mediate compensatory signaling. Even the contribution of tumor/immune interactions has been implicated in responsiveness of *BRAF* mutant melanomas to BRAF inhibitors.[11] It is logical to hypothesize that heterogeneity in one or more of these features would account for variable response to a new therapy being prospectively investigated. Taking the case of BRAF, sensitivity was equally demonstrated in melanoma and colorectal cancer (CRC) cell lines harboring V600 BRAF mutations.[12] But, only after observing widespread unresponsiveness in the colorectal population treated as one of two expansion cohorts in the phase I trial of vemurafenib were preclinical investigations launched that uncovered the ability of EGFR receptor signaling to rescue MAP kinase signaling and maintain PI3K pathway signaling in colon cancer models.[13,14] Interestingly, upregulation of EGFR has been implicated as a component of receptor tyrosine kinase–mediated resistance in melanoma, but as a component of acquired, not de novo, resistance.[15] Whereas the presence or absence of concomitant genetic alterations beyond the index alteration that is being therapeutically targeted can be assessed relatively easily in the era of clinical next-generation sequencing, predictive adaptive resistance mechanisms that do not have a hard-wired somatic genetic basis are not readily diagnosed a priori.

KEY POINTS

- **Most somatic genetic alterations in cancer are distributed across several to many cancer types.**
- **Preclinical model systems poorly predict relative sensitivity or resistance to therapies targeting these alterations.**
- **Early-phase clinical trials increasingly explore comparative efficacy across the spectrum of biomarker-defined tumor types.**
- **To date, durable objective responses have been observed in patients across different microsatellite instability–high/mismatch repair–deficient tumor types when treated with checkpoint inhibitors.**
- **If scientifically and clinically appropriate, investigating the effects of a drug agnostic of tumor type may be one pathway for drug development; however, every drug presents unique circumstances in regard to the population of patients who might benefit from it.**

Somatic Genetics Features

Concomitant genetic alterations that might mediate resistance to a targeted therapy (such as *PTEN* or *CDKN2A* loss in concert with a V600 BRAF mutation in melanoma) can be considered as effect modifiers. To mediate de novo resistance, such alterations must be present in the vast majority of tumor cell clones, presuming that cells that lack such alterations would be sensitive to therapy. Subclonal events that are present in a small minority of cells would be expected to account for resistance and disease progression following an initial period of disease control or response. Extreme examples of this are the presumed presence of gatekeeper mutations that impair drug binding to EGFR and ALK inhibitors that co-occur with an activating mutation that activates the kinase domain of EGFR or a translocation that drives ALK overexpression.[16,17] Such gatekeeper mutations are rarely found in the untreated state but commonly emerge under selective pressure of targeted therapy over the course of months. As such, these types of acquired resistance mechanisms seem to have little to do with variable initial response to treatment.

Another possibility has recently emerged in the targeted therapy development landscape: subclonal presence of the targeted oncogene itself. This appears to be the case in certain *PIK3CA* mutant cancers.[18,19] For years, *PIK3CA* mutant cancers were minimally impacted by the first generation of nonspecific PI3K inhibitors. With the emergence of inhibitors that are relatively selective for the alpha isoform of PI3K, which is the isoform that is activated by the mutation, muted responses have been observed across cancer types that harbor these common mutations (including breast cancers, head and neck cancers, and endometrial cancers). Genetic characterization of tumor specimens procured at baseline and at the time of disease progression has revealed that *PIK3CA* mutations are commonly subclonal and that *PIK3CA* wild-type tumors cells become over-represented in progression samples. In cases where mutant *PI3KCA* is clonal, concomitant genetic loss of PTEN can mediate resistance, providing a mechanism analogous to the other oncogene targeted therapy precedents described above. The *PIK3CA* case provides another dimension that may account for variable response and resistance across cancers that harbor genetic features: truncal versus subclonal target gene alteration.

Lineage-Specific Resistance

Beyond the somatic genetic makeup of cancers, the large remainder of resistance mechanisms to oncogene/signal

transduction targeted therapy lies in the epigenetic domain. On the surface, this refers to any de novo or adaptive resistance mechanism that reflects altered gene expression or signaling without requirement of an upstream genetic alteration that activates or inactivates. For the case of variable response to BRAF inhibitors in melanoma versus colorectal cancer, an epigenetic mechanism appears to underlie the utilization of EGFR signaling to maintain CRAF-MEK-ERK signaling in the face of BRAF inhibition.[14,20] Interestingly, this program does not appear to be as readily accessible to melanoma, raising the hypothesis that cell of origin might be an important factor for lineage-specific therapeutic resistance. Extensive research has highlighted the baseline transcriptional state of BRAF mutant melanomas and how that state is altered upon exposure to BRAF inhibitors. It appears that coordinated alteration in the melanocyte-specific transcription factor MITF and other TFE-3 family transcription factors can, but does not always, facilitate utilization of the beta-catenin signaling pathway and altered cellular metabolism.[21,22] These downstream consequences of BRAF inhibitor therapy might have their analog in other cancers that harbor BRAF mutations, but are almost certainly mediated by other transcription factors that play a role in the tissue-specific identity of those cells.

The relative contribution of concomitant genetic alterations and epigenetic phenomena is far from completely understood in any of the cases of successfully developed oncogene/signal transduction targeted therapy. In each case, it is only after a therapeutic effect has been observed that analysis of patients' tumor samples and parallel investigation in preclinical models have shed light on variable response within and across tumor types. It is this unmet need that, in part, informs the rise of functional diagnostics as an approach for judging response in minimally manipulated tumor samples ex vivo or, using novel microdevices for local delivery of drugs, in vivo.[23,24] These technologies are in their infancy with regard to use in cancer drug development. As such, it remains challenging to anticipate how the currently standard preclinical methods alone will enable prediction of therapeutic effects of a new class of therapies being brought forward.

The Clinical Trial Paradigm

In light of the current state of preclinical prediction, the standard paradigm for early-phase clinical trials is to perform dose escalation in unselected or biomarker-selected patients across tumor types followed by an exploration of efficacy in expansion cohorts. In the case of the vemurafenib phase I trial, unselected patients were enrolled in dose escalation (in part because diagnostic methods for *BRAF* mutation testing in real time were lacking), and two expansion cohorts were explored in which patients with melanoma and CRC were required to have a V600 BRAF mutation.[4,5] The target population was initially 20 patients. As opposed to formal phase II trials with statistical power to rule out a meaningful response rate, dose expansion cohorts of this size serve roughly the same purpose as the first stage of accrual in a Simon two-stage design. Depending on the clinical context with regards to unmet medical need, different threshold levels of response might be sought. The 20-patient CRC cohort was sufficient to declare vemurafenib as unworthy of further investigation as a single agent, whereas the response rate of greater than 60% in melanoma provided a clear signal that further single-agent development was warranted. Additionally, other cancer types in which BRAF mutations are less commonly found were investigated systematically in a dedicated phase II trial in which patients with any type of solid tumor could be enrolled.[25]

As in the vemurafenib example, a new oncogene/signal transduction targeted therapy is most commonly evaluated in the most-prevalent tumor-defined populations and/or the ones with the greatest unmet clinical need. With a path forward clearly established in melanoma, a parallel phase II investigation in other cancers harboring V600 BRAF mutations could be conducted while the confirmatory phase II trial in melanoma was performed for the purposes of regulatory approval. This approach effectively created a staggered drug development strategy, one that was driven by prevalence as well as observed efficacy. Out of an intention to streamline the process of drug development, pharmaceutical companies now typically embrace dynamic decision making and adaptation of phase I/II trials to enable broad exploration across cancer types and acceleration within cancer types in the setting of variable efficacy.[26] Of course, if heterogeneity is not seen, then the possibility exists of maintaining a tumor type–agnostic approach to development through phase II. This topic will be discussed in more detail later in the article.

One additional point in regards to drug development for oncogene/signal transduction targeted therapies is the difficulty in finding sparsely distributed, genetically defined populations. In the case of a genetic alteration that is present in 1% of a certain cancer type, it is both inefficient and costly to perform tests seeking alterations in such a single gene. Next-generation sequencing platforms for routine clinical use can solve this problem by simultaneously sequencing many cancer genes at one time, but have only recently been introduced and are used systematically in only a small number of major academic medical centers. Diagnostic companies have developed these platforms for centralized testing so that individual pathology laboratories need not develop their own capacity. However, in both scenarios, medical insurance payers are reluctant to cover the cost of these tests. Absent more widespread availability of next-generation sequencing tests, it becomes prohibitive to screen 100 patients to find one. The ongoing NCI-MATCH trial performs a sequencing analysis that identifies alterations in more than 150 genes for the purpose of empowering dozens of parallel phase II trials. But, with a total sample of only 6,000 patients, this trial simply demonstrates the efficiency of such an approach.

As originally conceived, NCI-MATCH placed priority on determining the genetic make-up of tumors at the time of study entry, rather than relying on archival tumor material

that might have been obtained at the time of primary tumor resection and potentially confounded by selective pressure of intervening therapy. To execute this, fresh biopsies were required at the time of study entry. This design decision reflects optimization of diagnostic accuracy, while introducing cost, risk associated with invasive procedures for research purposes, and a time delay while next generation sequencing is performed and analyzed. While this approach would have little impact on the representation of truncal mutations in a given tumor sample, it ensured that subclonal genetic alterations that may arise through tumor evolution and therapeutic resistance would be captured. During conduct of the trial, a modified approach was incorporated to allow submission of biopsies procured within the preceding 6 months prior to study entry provided that an intervening response to therapy had not occurred.

APPROACH TO THE DEVELOPMENT OF DRUGS FOR PATIENTS WITH MSI-H TUMORS

The promise of developing mismatch repair (MMR) deficiency as the first predictive biomarker across multiple tumor types for response to a novel therapeutic is supported by strong biologic rationale, availability of commercially used diagnostics for patient identification, and the urgent, unmet medical needs of patients with refractory cancers. The accumulation of evidence that PD-1 inhibition can provide durable benefit in patients with MMR deficiency, coupled with the explosion of technologies to identify these patients, leaves traditional approval pathways that require substantial evidence of effectiveness for each tumor type inadequate to help those in desperate need of therapy today.

MMR deficiency refers to the deficiency in proteins responsible in DNA repair when a mismatch occurs in the replication process. Specifically, these proteins are MLH1, PMS2, MSH2, and MSH6. Tumors deficient in these proteins accumulate many mutations because they lack the capacity to repair these mistakes. A tumor may acquire these deficiencies as part of an inherited disorder in one of these genes known as Lynch syndrome, a double somatic mutation in the tumor, or by hypermethylation of the MLH1 gene.[27-29] Immunohistochemistry testing for the absence of the MMR proteins can be used to identify these tumors.[30] Regardless of the mechanism for deficiency, this leads to the phenomenon of microsatellite instability. Microsatellites are repetitive DNA sequences that are prone to accumulation of mutations when tumors are MMR deficient. Microsatellite instability-high (MSI-H) refers to a tumor that, by polymerase chain reaction–based testing, has been shown to have shifts in more than 30% of specific microsatellite loci. As the shifts are compared with normal DNA, polymerase chain reaction–based testing does require normal tissue.

The recognition that MMR-deficient tumors were potentially immunogenic predated the current era of immune checkpoint blockade therapeutics. One of the pathologic characteristics of MSI-H CRC is the presence of immune infiltrating cells.[31-34] In particular, the presence of cytotoxic T cells in the tumor microenvironment suggests recognition of tumor antigen by these cells. The presence and progression of the tumor despite immune cell infiltration, however, support immune evasion by the cancer. The mechanism of immune recognition is not completely understood; however, these tumors are considered "hypermutated" due to accumulation of 10- to 100-fold the number of mutations as their microsatellite-stable counterparts.[35,36] These mutations can lead to the presentation of neoantigens to the immune system, making the prospect of immune recognition more likely.

Biologic Commonalities Among MMR-Deficient Tumors

The frequency of MSI varies across tumor types and stages within a tumor type but can be found in diverse histologies, ranging from those with higher frequencies such as colon, gastric, and endometrial cancers to those less commonly associated with MSI such as prostate cancer.[35,37] However, among those tumor types that have been studied histologically and by sequencing, the characteristics that may be predictive of response to immunotherapy are shared among MSI tumors: T-cell infiltration, PD-L1 expression, and high mutation burden. These features are found in both Lynch-associated and sporadic tumors.

CRC

MSI is present in 15% of CRC, with a majority of cases sporadic in etiology and 3% due to Lynch syndrome.[29] In advanced-stage disease, the frequency is 3% to 5%. Testing is already part of the National Comprehensive Cancer Network guidelines for CRC (version 1.2017).[38] Testing is recommended for the identification of patients with possible Lynch syndrome, a negative predictive marker for adjuvant therapy for stage II colon cancer, and now as a positive predictive biomarker for PD-1 inhibition. Better prognosis in early-stage disease is possibly due to immune recognition of these tumors. However, this is not true in metastatic disease, and MSI may portend a worse prognosis.[39,40] Pathologists can often identify these tumors without molecular diagnostics, as they tend to originate from right-sided primaries and have medullary differentiation, signet cell features, mucin production, poor differentiation status, and dense T-cell infiltration.[31,32,34] PD-L1 expression is also more frequent in MSI cancers than microsatellite-stable cancers.[41] In the Cancer Genome Atlas analysis of CRCs, 77% of the 30 hypermutated tumors with a complete data set were MSI-H.[42] Nineteen of these were due to MLH1 hypermethylation.

Endometrial Cancer

Universal testing of endometrial tumors for MMR deficiency is now recommended for the identification of patients with Lynch syndrome (National Comprehensive Cancer Network guidelines, version 1.2017). Data correlating MSI status to patient outcomes has been mixed. In a Japanese study, 40% of 191 cases of surgically resected endometrial cancer were found to be MMR deficient by IHC and this correlated with

better OS.[43] However, in a study of patients younger than age 40, MMR deficiency was associated with worse outcomes.[44] Similar to CRC, MSI-H endometrial cancers have higher CD3+ and CD8+ T-cell infiltrates than their microsatellite-stable counterparts.[45,46] Furthermore, PD-L1 expression is also mostly seen on immune-infiltrating cells.[45] Integrated genomic analysis of 373 endometrial cancers including MSI testing found MSI in 40% of endometrioid tumors and 2% of serous tumors.[47] MSI tumors fell into the hypermutated group, with most of them falling into the MLH1 hypermethylated group.

Gastric Cancer

Although MSI testing is not routinely performed in gastric cancer, some studies report an MSI-H frequency as high as 30%.[37] In a post hoc analysis of a large trial of perioperative chemotherapy versus surgery alone, MMR deficiency was a positive prognostic factor in those undergoing surgery alone but negative in those treated with chemotherapy.[48] This is reminiscent of the adjuvant story in colon cancer. Pathologically similar to other MSI-H cancers, they are associated with tumor-infiltrating lymphocytes and mucin phenotypes.[49,50] These tumors are predominantly intestinal in type. As part of the Cancer Genome Atlas analysis, 295 gastric cancers were analyzed. Four subtypes of gastric cancer were proposed: Epstein-Barr virus (EBV)–associated tumors that are associated with PD-L1 and PD-L2 amplification; microsatellite-unstable tumors; genomically stable tumors; and tumors with chromosomal instability.[51] The MSI-H cancers were again characterized to have high mutation rates. Likewise, PD-L1 expression on tumor and tumor immune infiltrates are more commonly associated with EBV+ or MSI-H gastric cancers.[50,52,53]

Other MSI-H Cancers

Microsatellite instability can be found across multiple tumor types at varying frequency.[35,37] These variations may be due to the baseline characteristics such as geographic region, stage of disease, and family history. Furthermore, the assay for detection of MMR or MSI varied as well. MSI can be detected in 2% of pancreatic adenocarcinomas, 10% of ampullary cancers, and 10% of ovarian cancers. The availability of data regarding the prognostic implications of MSI status varies among different histologies; however, once metastatic, the cancers are uniformly fatal. It is hypothesized that regardless of histology, the common features of immune cell infiltration, PD-L1 expression, and high mutation frequency will make MSI an important predictive marker for susceptibility to immune checkpoint blockade. Furthermore, routinely used assays are already being used to identify these patients, and MSI/MMR status is now also being reported on molecular profiling and next-generation sequencing panels.

Hints of PD-1 Antibody Activity in MSI-H Cancers

Intriguingly, PD-1 inhibition has shown some level of activity in these specific histologies known to have a subset of cancer with MSI. In CRC, single-agent PD-1 inhibition has only been active in MSI-H tumors. The single response in the first nivolumab study and the response in the PD-L1–positive selected study of pembrolizumab in CRC were found to be MSI-H.[54,55] PD-L1 was not a good predictive biomarker of response in the latter study. The overall response rate (ORR) was 13% in PD-L1–selected endometrial cancer.[56] MSI status has not been reported on these patients. However, in a study of pembrolizumab in PD-L1–positive gastric cancer, a 22% ORR was observed, with all eight responders achieving partial responses. Twenty-four tumors were tested for MSI and 17% (four tumors) were determined to be MSI-H. Of these, two MSI-H tumors were noted to have responded to treatment, accounting for at least 25% of the responses.[57,58]

In an analysis of 319 esophagogastric cancers by investigators at Memorial Sloan Kettering Cancer Center, they identified 12 patients with MSI-H tumors, of which three were treated with anti–PD-1 with best response of complete response, partial response, and stable disease. One patient with an EBV+ cancer had a complete response to combination PD-1 and cytotoxic T lymphocyte antigen-4 inhibition.[59]

MMR Deficiency as a Predictive Biomarker for PD-1 Inhibition

In a prospective study, MMR deficiency was explored as a predictive biomarker of response to pembrolizumab.[60] Patients with CRC were identified as MMR deficient based on immunohistochemistry testing for the MMR proteins or by polymerase chain reaction–based testing for MSI. An additional cohort of MSI-H non-CRC patients was also treated. The original article reported on 11, 21, and nine patients with MMR-deficient CRC, MMR-proficient CRC, and MMR-deficient non-CRC with ORR of 40%, 0%, and 71%, respectively. Importantly, in the MMR-deficient cohorts of patients who were all previously treated with standard therapies, the median duration of response and overall survival were not reached. Median follow-ups were 36 and 21 weeks for the MMR-deficient CRC and non-CRC cohorts, respectively. As expected, whole-exome sequencing resulted in a mean of 1,782 somatic mutations per tumor in MMR–deficient tumors and 73 in MMR-proficient tumors. Updated data reported at the 2016 ASCO Annual Meeting [61,62] showed the ORR was 57% with 11% complete response rate in the MMR-deficient CRC cohort and 53% with a 30% complete response rate in the MMR-deficient non-CRC cohort. The disease control rates were 89% and 73%, respectively. Responses were seen in CRC and endometrial, gastric, pancreaticobiliary, small bowel, and prostate cancers. At the same meeting, preliminary data with nivolumab was reported that showed an ORR of 26% with an additional 30% stable disease in MSI-H CRC.[63]

Based on a clinically significant response rate with longer-than-expected response duration in traditionally incurable advanced cancers, physicians and patients are optimistic that the evidence is accumulating that will allow access to these agents for patients outside of clinical trials and access programs.

REGULATORY CONSIDERATIONS REGARDING TISSUE-AGNOSTIC DEVELOPMENT

General Considerations

Federal regulations governing drug development do not require disease to be defined based on a single tumor type. Food-labeling regulations contain the following definition of disease: "… damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition."[64] Nevertheless, prior to determining whether a drug can be developed based on a molecular pathway, investigators or drug developers should determine whether the approach is scientifically and clinically appropriate. In the BRAF example cited above, tissue-agnostic development may not have been appropriate. Importantly, the mechanistic explanation for lack of response in CRC has been elucidated, and this has led to clinical trials that are investigating the effects of BRAF inhibitors in combination with other inhibitors of the MEK or EGFR pathways.[6,14,65]

Ultimately, determining whether a sponsor should develop a drug irrespective of histology will depend on several preclinical and clinical factors, including data supporting the scientific rationale (e.g., as discussed above) and the context of treatment of patients with different tumor types. For example, if a drug is most effective in combination regimens, tissue-agnostic development may not be appropriate given the differences in standard therapies administered to patients across tumor types. It may be more appropriate to consider tissue-agnostic development in situations where a drug-target combination appears to demonstrate very high activity (e.g., breakthrough-like) across multiple tumor types where the clinical effect can easily be demonstrated. Other developmental considerations may include differences in natural history across diverse cancers and how investigators or sponsors will propose to generate data in a sufficient number of patients with various tumor types.

Pediatric Development

An indication that is truly tissue agnostic would allow for the treatment of both adults and children. Such a tissue-agnostic approach, if appropriate, could therefore benefit children by bringing drugs to treat children with cancer more expeditiously. Sponsors who are assessing the effects of a drug across various tumor sites based on a biomarker should consider how they will address the needs of children who have a tumor that possesses that biomarker. For example, the FDA has recommended the inclusion of adolescents (age 12–17) in disease- and target-appropriate adult oncology trials.[66] Sponsors should determine whether additional formulations of a drug would be necessary to address the needs of younger children so that younger children can enroll in clinical trials and potentially benefit from that therapy.

Companion Diagnostic

A companion or complementary in vitro diagnostic (IVD) device provides essential information for the safe and effective use of a corresponding therapeutic product.[67] An analytically and clinically validated device reduces the risk of withholding appropriate therapy from a patient who is mutation/biomarker positive who receives a false negative test result or administering inappropriate therapy in the case of a false positive result.[67] From a practical perspective, for rare mutation-tumor combinations, it may be preferable to develop an IVD test as part of a larger panel of tests (e.g., as part of a next-generation sequencing panel). Factors unique to IVD development for tissue-agnostic use may include differences in amount of tumor collected at biopsy among different tumor types, differences in tumor heterogeneity among tumor types, and differences in stromal tissue surrounding tumors. The FDA recently published a perspective regarding both the potential benefits and challenges of complex IVD signatures.[68]

Sponsors are encouraged to meet with the FDA early to facilitate companion diagnostic development. FDA can provide advice to sponsors to determine whether an investigational device exemption is necessary to use an IVD in the trial and to provide guidance in regards to what data would be necessary to approve a companion IVD if the device is necessary for the safe use of the drug.

Residual Uncertainty

Uncertainty may arise in a development program about a drug's effectiveness in all tumor types with a specific fusion, mutation, or biomarker, particularly because some tumor-biomarker combinations may be exceedingly rare. The rarity of certain tumor-biomarker combinations may also make it impossible to conduct randomized trials, especially in settings where equipoise would not exist based on unprecedented antitumor activity observed in single-arm trials. For example, the FDA granted regular approval of crizotinib for ROS-1–positive non–small cell lung cancer based on the benefit of an objective response rate of 66% (95% CI, 51–79) by independent review and a median duration of response of 18.3 months.[69]

Depending on the strength of evidence across tumor types, multiple regulatory mechanisms exist to address this residual uncertainty. These range from requiring additional data in the premarket setting to requiring postmarketing data in the setting of accelerated approval. If data are adequately collected, "real-world" evidence also may provide supportive data regarding tumor response or lack thereof across rare tumor types.[70] Postmarketing requirements for drugs granted accelerated approval would not necessarily need to include randomized trials. Alternatively, if there is a histology-biomarker combination that is more common (e.g., ALK in lung cancer), a randomized trial (if necessary) in that dominant tumor type could be conducted to provide supportive evidence of safety and clinical benefit of a high (durable) response rate observed in other tumor types.

CONCLUSION

Ultimately, the goal of drug development is to bring effective drugs that benefit patients as quickly as possible.

Investigating the effects of a drug agnostic of tumor type may be one pathway for drug development; however, every drug presents unique circumstances in regard to the population of patients who might benefit from it. Furthermore, development agnostic of tumor type could actually slow drug development if there are differential effects across tumor types by diverting resources from enrolling patients in a predominant population or in the tumor type most likely to respond. Therefore, input from all stakeholders is recommended prior to embarking on such an approach.

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GASTROINTESTINAL (COLORECTAL) CANCER

Personalizing Adjuvant Therapy for Stage II/III Colorectal Cancer

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OVERVIEW

This review focuses on three areas of interest with respect to the treatment of stage II and III colon and rectal cancer, including (1) tailoring adjuvant therapy for the geriatric population, (2) the controversy as to the optimal adjuvant therapy strategy for patients with locoregional rectal cancer and for patients with colorectal resectable metastatic disease, and (3) discussion of the microenvironment, molecular profiling, and the future of adjuvant therapy. It has become evident that age is the strongest predictive factor for receipt of adjuvant chemotherapy, duration of treatment, and risk of treatment-related toxicity. Although incorporating adjuvant chemotherapy for patients who have received neoadjuvant chemoradiation and surgery would appear to be a reasonable strategy to improve survivorship as an extrapolation from stage III colon cancer adjuvant trials, attempts at defining the optimal rectal cancer population that would benefit from adjuvant therapy remain elusive. Similarly, the role of adjuvant chemotherapy for patients after resection of metastatic colorectal cancer has not been clearly defined because of very limited data to provide guidance. An understanding of the biologic hallmarks and drivers of metastatic spread as well as the micrometastatic environment is expected to translate into therapeutic strategies tailored to select patients. The identification of actionable targets in mesenchymal tumors is of major interest.

Although there is no uniform number at which physiologic aging occurs, there is little known about optimal treatment of colon cancer involving lymph nodes following surgical resection for adults age 75 or older.[1,2] A substantial number of patients with colorectal cancer (CRC; 40%) are adults age 75 or older.[3] Standards for adjuvant chemotherapy following resection of colon cancer were established based on results of three large randomized clinical trials: MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer), NSABP C-07 (National Surgical Adjuvant Breast and Bowel Project), and XELOXA NO16968 (XELOX in Adjuvant Colon Cancer Treatment). Yet with less than 1% (MOSAIC) and 5% (NSABP C-07), respectively, of those trials including older adults, it proves difficult to extrapolate standards of adjuvant chemotherapy to older adults in the real-world setting (the proportion age 75 or older is not reported in XELOXA NO16968). Several pooled analyses show potential for survival benefit among some older adults; however, nearly two-thirds do not receive adjuvant treatment.[3,4] Nonreceipt of systemic chemotherapy is particularly prevalent among those older adults diagnosed with colon cancer who also have geriatric syndromes (e.g., delirium, frailty) or active comorbid medical conditions.[5] Expertise in delivering care to this growing subset of patients is predominantly driven by provider experience and possible bias, given the limited clinical trial data available to guide use of adjuvant chemotherapy in the older adult population. Here, we review the available data and recommendations for adjuvant treatment recommendations for adults age 75 or older diagnosed with stage III colon cancer.

TAILORING ADJUVANT THERAPY FOR THE GERIATRIC POPULATION

Adjuvant Chemotherapy for Stage III Colon Cancer

General population. The benefit of adjuvant chemotherapy has been clearly established in the adjuvant setting for node-positive colon cancer. Standard treatment options include fluorouracil (FU) or capecitabine with or without oxaliplatin (Table 1). The addition of FU to surgical resection led to 17% improvement in disease-free survival and 13% improvement in overall survival among patients with node-positive colon cancer.[6] The addition of capecitabine led to similar improvements in disease-free (hazard ratio [HR], 0.87; 95% CI, 0.75–1.00) and overall survival (HR, 0.84; 95% CI, 0.69–1.01) compared with bolus FU/leucovorin (p for equivalence < .001, with median follow-up of 3.8 years).[7] The addition of oxaliplatin to FU further leads to an absolute improvement in disease-free and overall survival at 10 years by an additional 8%.[8] The addition of oxaliplatin

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to capecitabine results in a similar improvement, with reductions of 20% and 17% in the relative risk of recurrence or death (95% CI, 0.69–0.93; p = .004) and risk of death (95% CI, 0.70–0.99; p = .04), respectively.[9] The extent to which older adults derive benefit from adjuvant chemotherapy was not established in these trials, given that most trials limited participation to those younger than age 75[7,10] or limited the number of adults age 75 or older.[3,4]

Older adults. A number of pooled and subpopulation analyses have been conducted to fill the gap in knowledge regarding survival benefit of older adults receiving adjuvant chemotherapy for stage III colon cancer (refer to Table 1[23,24]). In a pooled analysis of seven randomized clinical trials of adjuvant chemotherapy included in the ACCENT (Adjuvant Colon Cancer End Points) study, older adults did not experience substantial benefit from adjuvant fluoropyrimidine or combination chemotherapy regimens regarding disease-free survival (HR, 1.05; 95% CI, 0.94–1.19), overall survival (HR, 1.08; 95% CI, 0.95–1.23), or time to recurrence survival (HR, 1.06; 95% CI, 0.93–1.22).[22] Older adults seemed to have a reduced overall survival benefit from oxaliplatin-based chemotherapy with a similar disease-free survival benefit compared with younger adults receiving oxaliplatin-based chemotherapy. There was no difference in rates of death within experimental or control arms, suggesting that it is unlikely that the substantial interaction noted between treatment and age would be explained by early deaths attributable to treatment-related toxicity.[22]

In contrast, comorbidity and age did not appear to affect disease-free or overall survival among older adults enrolled in four randomized clinical trials evaluating adjuvant fluoropyrimidine with or without oxaliplatin including comorbidity data defined by the Charlson Comorbidity Index or the National Cancer Institute Combined Index.[15] The ACCORE study evaluated 191 patients age 70 or older and 338 patients younger than 70 receiving adjuvant 5-fluorouracil (5-FU) or capecitabine with or without oxaliplatin for CRC in Denmark from 2001 to 2012.[25] Older adults experienced similar 10-year CRC-specific overall survival compared with younger patients but did experience higher rates of mortality owing to other causes after controlling for performance status and presence of comorbid medical conditions. Older adults received equivalent doses of capecitabine but fewer doses of oxaliplatin and 5-FU compared with younger patients. Disease-free survival and CRC-specific mortality were not affected by reductions in chemotherapy dose intensity. This and other pooled analyses from clinical trials are limited by the relatively small number of older adults enrolled. Despite this, rates of use of oxaliplatin found in the Surveillance, Epidemiology and End Results (SEER) database increased rapidly in adults age 65 or older diagnosed with stage III colon cancer (from 52% in 2004 to 73% in 2007, albeit at reduced rates among individuals older than 85 and those with comorbid medical conditions).[26]

In the general population of 5,489 adults 75 or older, 2,395 (44%) received chemotherapy within 120 days of surgery and 3,096 (56%) did not.[3] Rates of chemotherapy administration were higher in academic centers (75% in a National Comprehensive Cancer Network assessment [61% oxaliplatin]) versus nonacademic and community sites (42% in a SEER-Medicare analysis [42% oxaliplatin], 45% in a New York State Cancer Registry-Medicare study [28% oxaliplatin], and 52% in the CanCORS study). Oxaliplatin receipt decreased with increasing age, from 46% of adults age 75–79 to 7% among those age 85 or older. However, the benefit of adjuvant chemotherapy in this heterogeneous older population was comparable to that observed in pooled analyses of selected fit older adults participating in clinical trials, suggesting retention of survival benefit among subsets of older adults amenable to and receiving adjuvant chemotherapy within 120 days of surgical resection.

Older adults appear to receive a benefit from adjuvant chemotherapy in some, but not all, studies. Survival seems to differ across age categories, with decreasing survival benefit with increasing age. A review of the National Cancer Institute SEER database linked to the Medicare database (SEER-Medicare) noted a predicted increased 5-year survival benefit of 14% among patients age 70–74 compared with 8% among those age 80–84.[17] Survival benefit persists in older adults age 80–89, despite only 43% of the 8,141 octogenarians included in the National Cancer Database from 2006 to 2011.[4] Regardless of potential benefit for some older adults, older age remains the strongest determinant of initiation, duration, and completion of adjuvant chemotherapy.[3,27-29] Older adults are also more likely to have delays in initiation of adjuvant chemotherapy and are less likely to complete the full 6 months of adjuvant therapy, factors that also increase mortality risk.[25,30,31]

KEY POINTS

- **Age is the strongest predictive factor for receipt of adjuvant chemotherapy, duration of treatment, and risk of treatment-related toxicity.**
- **Available data support disease-free and overall survival benefit after adjuvant therapy among older adults age 70–74 years with colon cancer, but variable outcomes for those age 75 years or older.**
- **Attempts at defining the optimal rectal cancer population that would benefit from adjuvant therapy remain elusive.**
- **In stage II disease, microsatellite instability and/or high "immunoscores" associate with very good prognosis and support a no-adjuvant-treatment approach. On the other hand, empirical evidence for the addition of supervised gene expression classifiers to the clinical decision-making paradigm is scarce.**
- **Irrespective of tumor stage, activation of a gene expression signature of epithelial-mesenchymal transition correlates with an invasive-inflamed microenvironment infiltrated with stromal and immunosuppressive cells, which confers poor prognosis and limited benefit with standard adjuvant chemotherapies.**

TABLE 1. Survival Outcomes for Adjuvant Chemotherapy Among Older Adults

Trial (Year), Study Design	Treatment Arms	Older Adult Cohort, Age (No. of Patients)	Regimen-Specific Data	Disease-Free Survival	Relapse-Free Survival	Time to Recurrence	Overall Survival
NSABP C-06 phase III (2006[11])	UFT/LV vs. 5-FU/LV	≥ 60 (939)		1.41 (1.18–1.69); p = .002 (referent = age < 60)	N/A	N/A	1.40 (1.12–1.74); p = .03 (referent = age < 60)
National Cancer Database (2005[12]), retrospective study	Adjuvant chemotherapy	All (1990–1991: 12,413; 2001–2002: 14,187)	Receipt of chemotherapy (%):	N/A	N/A	N/A	Similar OS regardless of age
		70–79 (1990–1991: 4,103; 2001–2002: 4,086)	69	N/A	N/A	N/A	
		≥ 80 (1990–1991): 2,593; 2001–2002: 3,305)	39	N/A	N/A	N/A	
NO16968 phase III (2015[9])	XELOX vs. bolus 5-FU/LV	≥ 70 (409)		0.86 (0.64–1.16); p = NR	N/A	N/A	0.91 (0.66–1.26); p = NR
7 randomized clinical trials (2004[6]), pooled analysis	5-FU/LV vs. surgery alone	≥ 60 (1,864)		63% vs. 55%; p = .001 at 5 years	N/A	N/A	69% vs. 62%; p = .0005 at 5 years
SEER-Medicare (2002[13]), retrospective study	5-FU/LV vs. surgery alone	≥ 65 (4,768)		N/A	N/A	N/A	0.66 (0.60–0.73)
ACCENT (2001[14])	5-FU/LV vs. surgery alone	> 70 (506)	Similar DFS and OS regardless of age	Overall 0.68 (0.60–0.76); p < .001	N/A	N/A	Overall 0.76 (0.68–0.85); p < .001
XELOXA, AVANT, X-ACT, NSABP C-08 (2015[15]), pooled analysis	5-FU or capecitabine vs. XELOX or FOLFOX	5-FU: ≥ 70 (424); XELOX or FOLFOX: ≥ 70 (480)		0.77 (0.62–0.95); p = .014	N/A	N/A	0.78 (0.61–0.99); p = .045)
Phase II dose escalation study of capecitabine (2012[16])	Capecitabine	≥ 70 (82)	50% completed planned therapy at 80% relative dose intensity; stable QoL during treatment; 26% grade 3 hand-foot syndrome	N/A	N/A	N/A	N/A
SEER-Medicare, NYSCR, CanCORS, NCCN (2012[3]), retrospective study	Fluoropyrimidine (5-FU, capecitabine) ± oxaliplatin	≥ 75 (5,489)	SEER-Medicare	N/A	N/A	N/A	Adjuvant chemotherapy: 0.60 (0.53–0.68); p = NR
							Oxaliplatin: 0.84 (0.69–1.04); p = NR

Continued

TABLE 1. Survival Outcomes for Adjuvant Chemotherapy Among Older Adults (Cont'd)

Trial (Year), Study Design	Treatment Arms	Older Adult Cohort, Age (No. of Patients)	Regimen-Specific Data	Disease-Free Survival	Relapse-Free Survival	Time to Recurrence	Overall Survival
			NYSCR	N/A	N/A	N/A	Adjuvant chemotherapy: 0.76 (0.58–1.01); p = NR
							Oxaliplatin: 0.82 (0.51–1.33, p = NR)
			CanCORS	N/A	N/A	N/A	Adjuvant chemotherapy: 0.48 (0.19–1.21), p = NR
							Oxaliplatin: N/A
			NCCN	N/A	N/A	N/A	Adjuvant chemotherapy: 0.42 (0.17–1.03); p = NR
							Oxaliplatin: 1.84 (0.48–7.05); p = NR
SEER-Medicare (2009[17]), retrospective study	Adjuvant chemotherapy	≥ 66 (7,182)	Receipt of chemotherapy (%):	N/A	N/A	N/A	Overall survival by age:
		66–69	19	N/A	N/A	N/A	0.47 (0.33–0.65); p < .001
		70–74	30	N/A	N/A	N/A	0.32 (0.25–0.40); p < .001
		75–79	30	N/A	N/A	N/A	0.41 (0.34–0.50); p < .001
		80–84	16.5	N/A	N/A	N/A	0.59 (0.49–0.72); p < .001
		≥ 85	5	N/A	N/A	N/A	0.54 (0.41–0.71); p < .001
MOSAIC phase III (2012[18])	FU/LV vs. FOLFOX4	70–75 (315)		69.1% (61.3%–75.8%) vs. 65.8% (57.8%–72.7%)	N/A	78.8% (71.2%–84.6%) vs. 69.9% (61.9%–76.5%);	75.8% (0.73–1.65) vs. 76.1% (68.6–82.1)
				0.93 (0.64–1.35); p = .710 at 5 years (referent = age < 70)		0.72 (0.47–1.11); p = .14 at 5 years (referent = age < 70)	1.10 (0.73–1.65); p = .661 at 6 years (referent = age < 70)
NO16968 phase III (2011[19])	FU/FA vs. XELOX	< 65 vs. ≥ 65 (1,886 overall)		No change in DFS/OS by age reported			No change in DFS/OS by age reported
NSABP C-07 phase III (2011[20])	FU/LV vs. FLOX	≥ 70 (396)		62% vs. 62.8%;1.17 (0.94–1.46); p = .16 (referent = age < 70)	N/A	N/A	76.3% vs. 71.6% 1.32 (1.03–1.70), p = .30 (referent = age < 70)

Continued

TABLE 1. Survival Outcomes for Adjuvant Chemotherapy Among Older Adults (Cont'd)

Trial (Year), Study Design	Treatment Arms	Older Adult Cohort, Age (No. of Patients)	Regimen-Specific Data	Disease-Free Survival	Relapse-Free Survival	Time to Recurrence	Overall Survival
NSABP C-06 phase III (2006[11])	FU/LV vs. UFT/LV	≥ 60 (939)		1.41 (1.18–1.69); p = .002 at 5 years (referent = age < 60)	N/A	N/A	1.40 (1.12–1.74), p = .03 at 5 years (referent = age < 60)
X-ACT phase III (2012[21])	Bolus FU/LV vs. capecitabine	≥ 70 (397)		58.1% vs. 55.8%; 0.97 (0.72–1.31) at 5 years	N/A	N/A	68.8% vs. 65.0%; 0.91 (0.65–1.26) at 5 years
ACCENT (2013[22]), pooled analysis of 7 adjuvant studies	Oral/IV FU ± irinotecan or oxaliplatin	≥ 70 (2,575)	Oxaliplatin-based regimens (1,119)	0.94 (0.78–1.13); p = .09	N/A	0.86 (0.69–1.06); p = .36	1.04 (0.85–1.27); p = .05
			Oral fluoropyrimidine (757)	0.92 (0.92–1.41); p = .13	N/A	1.20 (0.93–1.54); p = .09	1.13 (0.90–1.41); p = .16

Abbreviations: 5-FU, fluorouracil; CanCORS, Cancer Care Outcomes Research and Surveillance Consortium; DFS, disease-free survival; FA, folinic acid; FLOX, bolus fluorouracil/leucovorin/oxaliplatin; FOLFOX, fluorouracil/leucovorin/oxaliplatin; FU, fluorouracil; IV, intravenous; LV, leucovorin; MOSAIC, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer; N/A, not available; NCCN, National Comprehensive Cancer Network; NR, not reached; NSABP, National Surgical Adjuvant Breast and Bowel Project; NYSCR, New York State Cancer Registry; OS, overall survival; QoL, quality of life; SEER, Surveillance, Epidemiology and End Results; UFT, uracil tegafur; XELOX, capecitabine/oxaliplatin.
Data are presented as hazard ratios (95% CIs) unless otherwise indicated.

Molecular Profile of CRC Among Older Adults

Could a molecular profile determine those older adults unlikely to benefit from adjuvant chemotherapy? We sought to identify a subset of molecular markers unique to older adults diagnosed with colon or rectal cancer. We examined the presence of the CpG island methylator phenotype; microsatellite instability (MSI); *KRAS*, *BRAF*, and *PIK3CA* mutations; and nuclear CTNNβ1 expression status by age at CRC diagnosis within a large prospective cohort study. Tumor nuclear CTNNβ1 appeared to be associated with higher mortality among older adults diagnosed with CRC.[32] However, subsequent examination of the impact of nuclear CTNNβ1 and a host of additional molecular factors on prognosis for older adults diagnosed with colon or rectal cancer did not confirm a particular molecular phenotype among older adults diagnosed with colon or rectal cancer (N. J. McCleary, MD, MPH, and A. J. Bass, manuscript in preparation, 2017). Additional study is underway to examine whether a particular molecular phenotype predicts survival among a cohort of older adults receiving chemotherapy for colon or rectal cancer.

Modifying Risk, Enhancing Benefit of Adjuvant Chemotherapy for Older Adults

Potential benefit from adjuvant chemotherapy in older adults must be balanced by the potential for risk attributable to increased toxicity, reduced organ function, sarcopenia, limited social support, or unanticipated decline in physical function.[33] Although prospective clinical trials cannot delineate patients most at risk for poor clinical or physical outcomes from specific adjuvant chemotherapy regimens, doses, or duration of treatment, we can glean recommendations for treatment decisions from a few notable studies.

First, we can predict treatment-related toxicity across multiple cancer types for older adults. Moving beyond the limitations of the Eastern Cooperative Oncology Group or Karnofsky performance status, the comprehensive geriatric assessment has been shown to predict those older adults at risk for toxicity across a number of cancer types and stages, including colon cancer.[34,35] The comprehensive geriatric assessment is a feasible, validated instrument that allows both patient and provider evaluation of functional status, medications, social support, cognition, nutrition, psychologic state, and comorbidity to better assess overall fitness. This assessment may identify issues affecting treatment decision making for both patient and provider. The geriatric assessment can predict overall morbidity and mortality but, more specifically, it can anticipate chemotherapy-related toxicity.[36-39] A cancer-specific comprehensive geriatric assessment has shown benefit in treatment selection for older adults diagnosed with lung cancer in the ambulatory setting[40] and for hospitalized older adults.[41] It is now being embedded within a prospective multicenter treatment clinical trial to assess its ability to risk-stratify patients (A. Hurria, personal communication, ALLIANCE meeting, Chicago, IL, November 2016). This and other indices of frailty,[42] or risk of increased morbidity and mortality associated with chemotherapy, will not only provide parameters for discussion with older adults regarding the additive risks versus benefits of adjuvant chemotherapy, but they will also potentially inform provider decision making regarding initiation and dosing of treatment.[43-45]

Second, we can consider the potential impact of particular adjuvant chemotherapy regimens on organ function and physical function absent from any specific comorbid medical condition. Common measures of performance status underestimate the physiologic changes in organ function occurring with aging.[24] Bone marrow reserves decrease with increasing age. Chemotherapy treatment can lead to depletion of the bone marrow, thereby increasing the risk of cytopenias and subsequent risks of bleeding or infection. Aging is also associated with decreases in renal and hepatic function, bone and muscle mass, and risks of altered cognition, potentially increasing the risk of treatment-related toxicity.[24] Exercise is recommended for secondary cancer prevention following resection of colon cancer and may serve as a useful adjunct during the postoperative treatment course.[46,47] However, older adults receiving chemotherapy are susceptible to a decline in physical function, potentially limiting their ability to exercise. Oxaliplatin-induced neuropathy further affects this physical decline and increases the potential risk of falls and limits independence.[24,48-50]

Third, we can discuss the relative benefit of adjuvant chemotherapy among those older adults with active, unmanaged comorbid medical conditions and competing risk of death or disability. Comorbid medical conditions appear to have a greater effect on older adults diagnosed with advanced CRC.[51] Comorbid medical conditions may impact drug absorption and clearance. The presence of comorbid medical conditions predict for concomitant medications and risk of drug interactions.[52] Regular careful review of patient medications, as promoted by geriatric assessment, can limit the potential risk of drug-drug interactions.[53] In the adjuvant setting, renal excretion of both capecitabine and oxaliplatin requires dose adjustment for creatinine clearance below 50 mL/min.[24] Capecitabine also requires dose adjustment for patients taking warfarin. Cognitive impairment increases the risk of nonadherence to capecitabine.

Finally, it is incumbent on us as oncology providers to understand the full impact of adjuvant chemotherapy on older adults beyond disease-free and overall survival.[54] Disease-free and overall survival are the primary outcomes used to determine the standards for adjuvant chemotherapy regardless of age at diagnosis. However, other clinical and quality outcomes may be of interest to patients. Although outcomes of interest have not yet been specifically identified for older adults, few clinical trials evaluate outcomes beyond traditional outcomes of disease-free and overall survival to include outcomes potentially pertinent to older adults, such as the impact of adjuvant chemotherapy on "quality of survival and functional independence."[34] Given this, we can consider the traditional outcomes as a measure of treatment response, but we cannot fully comment on other benefits that older adults may experience as a result of adjuvant chemotherapy. Adults age 65 or older reported greater decline in physical and mental health within the first 6 months of diagnosis of CRC compared with age-matched controls as part of the Medicare Health Outcomes Survey, particularly among patients diagnosed with stage III or IV CRC.[55] How do we best define "functional independence" and "quality of survival" over the course of adjuvant chemotherapy administration and afterward? What is an acceptable threshold for additional outcomes beyond which treatment should not be recommended regardless of potential disease-free or overall survival benefit? We must begin exploring those additional outcomes of importance to older adults to determine the full impact of adjuvant chemotherapy on older adults and develop strategies to improve outcomes globally.

CONTROVERSIES IN THE ADJUVANT SETTING

Adjuvant Chemotherapy for Rectal Cancer

For many years, the standard of care for patients with locally advanced clinical stage II to III rectal cancer included surgery, often resulting in a permanent ostomy, followed by adjuvant chemotherapy and chemoradiation.[11-14,16,18-21] This strategy improved both overall survival and the risk of locoregional failure. An example of the outcome benefits of combined adjuvant chemoradiation, published more than a decade ago, include the U.S. Intergroup 0144 trial, which evaluated the so-called sandwich approach of chemotherapy followed by chemoradiation followed by additional chemotherapy and compared bolus versus infusional 5-FU regimens for patients with T3-4N0M0 or T1-4N1,2M0 disease.[56] The locoregional failure rate for those who received low anterior resection was between 3% and 5%. Three-year overall survival was between 81% and 83%. A pooled analysis of North American phase III combined modality adjuvant trials identified three different risk groups defined by TN stage, including T1-T2N1 and T3N0 (intermediate); T1-2N2, T3N1, and T4N0 (moderately high); and T3N2, T4N1, and T4N2 (high), which correlated with survival and disease control.[57,58] Five-year overall survival rates for the intermediate group were 78%–85% compared with 25%–57% for those with high-risk lesions. Different treatment strategies depending upon risk were therefore implied. Subsequently there was a profound shift in the treatment approach for clinical stage II to III rectal cancer as data emerged supporting the use of neoadjuvant chemoradiation; however, this therapeutic evolution generated considerable controversy as to the role of adjuvant chemotherapy, a controversy that has persisted.

Neoadjuvant chemoradiation has become the preferred treatment of locally advanced rectal cancer because of evidence demonstrating improved outcomes, better tolerability, and, in many cases, considerable downstaging resulting in sphincter-preserving surgery and thus avoiding a permanent ostomy. A hallmark study from the Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the Germany Cancer Society (CAO/ARO/AIO-94) compared preoperative chemoradiotherapy with postoperative chemoradiotherapy for locally advanced rectal cancer, demonstrating significant improvement in 5-year cumulative incidence of local relapse favoring a preoperative approach (6% vs. 13%; $p = .006$).[59] There were considerably less acute and long-term toxic effects in the preoperative group, although 5-year overall survival

rates were similar (76% vs. 74%). Patients also received four cycles of postoperative 5-FU. Long-term follow-up data showed improved outcomes for the preoperative patients who achieved complete and intermediate tumor regressions and the overall 10-year cumulative incidence of local relapse continued to favor the patients treated preoperatively (7.1% vs. 10.1%; p = .048); there was no change in overall survivorship (59.6% vs. 59.9%).[60,61] A recent meta-analysis of more than 10,000 patients who participated in randomized controlled trials confirmed the improved rate of local control with neoadjuvant chemoradiation, including after total mesorectal excision, although there was no improvement in long-term survival.[62]

Although incorporating adjuvant chemotherapy for patients who have received neoadjuvant chemoradiation and surgery would appear to be a reasonable strategy to improve survivorship as an extrapolation from stage III colon cancer adjuvant trials, attempts at defining the optimal rectal cancer population that would benefit from adjuvant therapy remain elusive. This paucity of consistent evidence has resulted in variability in practice patterns. For example, a National Comprehensive Cancer Network CRC database assessment of nearly 2,000 patients with stage II/III rectal cancer who received neoadjuvant chemoradiation showed that a sizable minority of patients did not receive adjuvant chemotherapy.[63] A SEER-Medicare database analysis noted that one in three patients did not receive adjuvant therapy after neoadjuvant chemoradiation and resection.[64]

Some investigations have attempted to select patients who may not require adjuvant therapy after neoadjuvant chemoradiation and surgery. For example, a study of 176 patients reported that those who achieved a complete response (15.3% of patients staged as ypT0M0) had 5-year disease-free and overall survival rates of 96% and 100%, respectively, suggesting that adjuvant therapy would provide no further meaningful benefit for these individuals.[65] In a retrospective study of 851 patients, 330 received preoperative short-course radiation (2,500 cGy administered in five fractions without chemotherapy) and 123 received adjuvant chemotherapy.[66] A subgroup analysis showed that adjuvant therapy improved disease-specific survival and overall survival only for those patients who had at least two high-risk features such as pT4 tumor, inadequate lymph node sampling, lymphovascular invasion, perineural invasion, poor differentiation, obstruction, or perforation.

EORTC 22921 was a randomized trial of 1,011 patients evaluating FU-based adjuvant chemotherapy after preoperative chemoradiation for patients with clinical stage T3 or T4 resectable rectal cancer.[67] Patients were assigned to one of four treatment arms including preoperative radiotherapy with or without chemotherapy and preoperative radiotherapy with or without chemotherapy followed by adjuvant chemotherapy. There was relatively poor adherence to adjuvant chemotherapy, because only 43% of patients received the planned dose. At a median follow-up of 10.4 years, there was no substantial difference in overall survival among the four treatment groups (48.4%–51.9%), nor were there differences in disease-free survival rates and cumulative incidence of distant metastases. Most recurrences were noted within 5 years. A recently reported Italian study of 634 evaluable patients concluded that adjuvant 5-FU did not improve 5-year overall or disease-free survival, including among those who obtained a complete pathologic response and overall downstaging rates; 28% of patients, however, never received the assigned adjuvant chemotherapy.[68] A Dutch study of 437 eligible patients closed prematurely for accrual reasons; however, there was no difference in 5-year cumulative incidence for either local regional recurrence or in 5-year distance recurrences after postoperative fluoropyrimidine monotherapy.[69]

Systematic reviews and meta-analyses also were recently reported to address the role of adjuvant chemotherapy after neoadjuvant therapy and surgery. An analysis of four phase III clinical trials of nearly 1,200 patients with ypTNM stage II and III rectal cancers and a R0 resection found no difference in overall survival comparing those who received adjuvant chemotherapy versus observation.[70] There were patients with tumors located at 10 to 15 cm from the anal verge who had improved disease-free survival and fewer distant metastases when treated with adjuvant chemotherapy. Another analysis of randomized controlled trials in retrospective studies of nearly 5,500 patients reported improvement in both 5-year overall survival and disease-free survival for those patients treated with neoadjuvant chemoradiation, surgery, and adjuvant chemotherapy.[71] The improvement in 5-year overall survival was largest among patients who were downstaged and in the retrospective series. A third systematic review and meta-analysis of five randomized trials including 2,398 patients did not show an advantage for those who received adjuvant chemotherapy although there was a substantial adjuvant chemotherapy effect for patients who were randomized after surgery (753 patients).[72] In two trials, there was a difference in disease-free survival for those who received FU and oxaliplatin compared with single-agent 5-FU; however, in two other trials, FU and oxaliplatin did not show a substantial difference. Overall, the authors concluded that adjuvant chemotherapy provided no "strong scientific evidence" to support its use for those who received preoperative chemoradiation.

A number of treatment strategies have been the subject of recent clinical trials and have informed current or planned global clinical trial portfolios[73,74] (Table 2). For example, there is interest in the "wait and watch" approach for patients who have obtained a complete response after chemoradiation and in strategies to encompass neoadjuvant chemotherapy while reserving radiation for those with suboptimal response.[73,74] The overall goal is to avoid more extensive intervention with the associated risk of toxicity and long-term sequelae for patients who may not need such an approach and to intensify therapy for those who are at highest risk for recurrence. Current National Comprehensive Cancer Network guidelines recommend a number of options for patients with clinical stage II and III rectal cancer, including (1) neoadjuvant therapy comprising long-course chemoradiation with either

capecitabine or infusional 5-FU, short-course radiation, or a preferred chemotherapy regimen with oxaliplatin and a fluoropyrimidine followed by chemoradiation; or (2) adjuvant therapy is recommended after surgery for those who have received neoadjuvant oxaliplatin and a fluoropyrimidine followed by chemoradiation surveillance, whereas adjuvant chemotherapy with oxaliplatin and a fluoropyrimidine is recommended as the preferred regimen for those treated with chemoradiation or short-course radiation.[75]

Adjuvant Therapy for Resectable Metastatic Disease

It has long been known that there is a subgroup of patients with colon or rectal cancer who have potentially resectable metastatic disease and can enjoy long-term survival after surgery. The introduction of combination chemotherapy for metastatic CRC has resulted in improvement in response, progression-free survival, and overall survival. In addition, there is a perceived benefit of combination chemotherapy for patients with resectable metastatic disease or those who obtain a substantial response to therapy rendering them with resectable disease. An advantage of preoperative chemotherapy for patients with resectable or potentially resectable metastatic disease is to determine "chemosensitivity" and also to identify those individuals who may be resistant to therapy and develop more rapid disease progression. For patients with rectal cancer and potentially resectable

TABLE 2. Select Current and Planned Rectal Cancer Trials

Trial	Treatment
NO148 PROSPECT phase III	FOLFOX × 6 → response ≥ 20% → TME → FOLFOX × 6
	FOLFOX × 6 → response < 20% → 5-FU/capecitabine RT → TME → FOLFOX × 2 *versus*
	5-FU/capecitabine RT → TME → FOLFOX x 8
NRG G1-002 (TNT) phase II	
High risk	FOLFOX × 8 → RT + capecitabine → surgery
	FOLFOX × 8 → RT + capecitabine + veliparib → surgery
	Additional arms planned
CCTG CO28 NeoTEMS phase II	cT1-3N0 FOLFOX/CAPOX → TEMS/TAMIS → ypTO/T1^{Good} → surveillance
	cT1-3N0 FOLFOX/CAPOX → TEMS/TAMIS → ypT1$^{Bad\ or\ higher}$ → TME[a]
OPRA (13-213) phase II	ChemoRT + chemotherapy → TME
	ChemoRT + chemotherapy → surveillance
RIA trial phase II	
High risk	FOLFOX/aflibercept × 6 → capecitabine RT → surgery
	FOLFOX × 6 → capecitabine RT → surgery
PIER phase II	
Intermediate risk	FOLFOX/panitumumab → no progression → TME
	FOLFOX/panitumumab → progression → capecitabine RT
ARISTOTLE NCRI phase III	Capecitabine RT → surgery
	Irinotecan + capecitabine RT → surgery
AIO/ARO/A10-04	ChemoRT → surgery → FOLFOX → 5-FU
AIO/ARO/A10-12 phase II	Chemotherapy → chemoRT → surgery
	ChemoRT → chemotherapy → Surgery
AIO/ARO/A10-16	
Low risk	Surgery → FOLFOX (pN+) *versus*
	Capecitabine RT → surgery → capecitabine
High risk	Capecitabine RT → surgery → capecitabine *versus*
	5-FU/oxaliplatin RT → FOLFOX → surgery
RENO	ChemoRT → cCR → watch and wait
RAPIDO phase III	ChemoRT → MRI/CT → response → TME → CAPOX *versus*
	RT → CAPOX → MRI/CT → response → TME

[a]ypT1^{Bad}, RI, high grade.

Abbreviations: 5-FU, fluorouracil; CAPOX, capecitabine/oxaliplatin; cCR, complete clinical response; chemoRT, chemoradiotherapy; FOLFOX, fluorouracil/leucovorin/oxaliplatin; pN+, pathologically node positive; RI, microscopic positive margin; RT, radiotherapy; TAMIS, transanal minimally invasice surgery; TEMS, transanal endoscopic micro-surgery; TME, total mesorectal excision.

metastatic disease, preoperative chemoradiotherapy is often considered to reduce the risk of local regional recurrence, particularly when the goal of surgery is curative intent.

A perioperative approach for those with resectable metastatic disease incorporates a total chemotherapy treatment period of approximately 6 months including preoperative therapy followed by surgery and adjuvant chemotherapy. The role of adjuvant chemotherapy, however, has not been clearly defined because of very limited data to provide guidance. A systematic review of 642 evaluable patients with liver metastases evaluated surgery versus surgery and chemotherapy, demonstrating improvement in disease-free and progression-free survival favoring chemotherapy without a survival advantage.[76] A meta-analysis of 10 studies including nearly 1,900 patients showed no survival benefit for patients who received perioperative chemotherapy for resectable liver metastases compared with surgery alone; however, a disease-free survival benefit was noted.[77] Similar results were observed in additional analyses.[78,79] EORTC 40983 evaluated six cycles of fluorouracil/leucovorin/oxaliplatin before and after surgical resection of liver metastases compared with surgery alone, demonstrating a 40% response to preoperative fluorouracil/leucovorin/oxaliplatin and improvement in progression-free survival for eligible patients who were resected with no overall survival benefit.[80] There is consensus in the National Comprehensive Cancer Network guidelines that adjuvant chemotherapy after resection of metastatic disease remains an option of care.[75]

MOLECULAR PROFILES AND THE FUTURE OF ADJUVANT THERAPY: MICROENVIRONMENT MATTERS

Retrospective biomarker analyses of multiple clinical trials in the adjuvant setting strongly support the feasibility of refining prognostic stratification in CRC by factoring in molecular features with pathologic tumor staging.[81] However, validated predictive markers of adjuvant therapy benefit for stage II or III CRCs are still lacking.[81] To date, the only molecular marker with proven clinical utility in early-stage CRC is MSI, which associates with very good prognosis in stage II disease irrespective of adjuvant chemotherapy, supporting a no-adjuvant-treatment approach.[82] On the other hand, patients with MSI stage III CRC derive benefit from adjuvant chemotherapy, with no differential benefit compared with the microsatellite stability (MSS) population in clinical trials assessing 5-FU or oxaliplatin-based regimens.[83] Interestingly, there is a possible interaction between MSI status and primary tumor location in stage III treated disease, with a better prognosis limited to right-sided tumors.[84] This association reinforces the known intrinsic biologic differences between proximal and distal CRC.[85]

Mounting evidence indicates that an enhanced lymphocytic reaction in CRC is a critical determinant of the risk of dissemination to distant metastasis.[86] A clinical translation of this finding was the establishment of a scoring system, called the "immunoscore," based on the abundance of two distinct lymphocyte populations ($CD8^+$ cytotoxic T cells and $CD3^+$ T memory cells) at the tumor center and at its invasive margin. In a large validation study, time to recurrence and overall survival were significantly longer for patients with stage II and III colon cancer with immunoscore high tumors, independent of clinicopathological factors.[87] MSI cancers characteristically exhibit strong infiltration of the tumor microenvironment with immune cells, which relates to hypermutation rates and higher neoantigen loads.[88] However, a subset of MSS tumors also have increased intratumoral adaptive immune gene expression and high immunoscores. These "immune-activated" tumors, irrespective of stage, have improved survival outcomes and the immunoscore was shown to be superior to MSI in predicting patients' disease-specific recurrence and survival in multivariable models.[89] These data strengthen the concept that reduced immune cytotoxicity is a major factor driving metastases in CRC. However, most patients with early-stage CRC have MSS and/or a medium/low immunoscore, which associate with an intermediate to poor prognosis and do not help prioritize adjuvant chemotherapy in stage II or III disease. The same is true for tumors harboring *BRAF* V600E mutations, which are an independent prognostic factor of reduced overall survival in multiple studies, particularly in MSS left-sided disease, but not a marker of chemosensitivity/resistance to 5-FU or oxaliplatin-based regimens in the adjuvant setting.[81]

In addition to microsatellite status and gene mutations, which did not demonstrate predictive value for standard chemotherapy benefit in early-stage CRC, different groups explored the potential clinical utility of gene expression signatures in this context. The transcriptomic profile of a tumor, encompassing cancer cell, immune, and stromal signals, is intimately linked to its phenotype and clinical behavior. Gene expression profiling has been used extensively to identify biologically homogeneous subtypes of the disease through unsupervised clustering. An international effort dedicated to large-scale data sharing and coordinated analytics cross-compared independent transcriptomic-based CRC subtyping systems and resulted in a consensus molecular classification that allows the categorization of most CRC tumors into one of four robust intrinsic subtypes.[90] The consensus molecular subtype (CMS) features are summarized in Table 3. There are striking differences in prognosis with this unsupervised gene expression signature, confirming that the biologic processes implicated in each subtype are clinically relevant.[90] The CMS4 mesenchymal group is associated with a significantly higher risk of distant relapse and death for patients diagnosed with early-stage CRC, irrespective of validated clinicopathological features, MSI status, and *BRAF* V600E mutations.[81] These tumors exert a proangiogenic and stromagenic influence on the microenvironment, which is highly infiltrated with endothelial cells and cancer-associated fibroblasts. In addition, CMS4 mesenchymal tumors are enriched with immunosuppressive cells, such as regulatory T cells, B cells, and myeloid-derived suppressor cells, which are negative regulators of cytotoxic T cells.[91-93] This effect is explained in part by high expression of transforming growth factor-β and chemokines attracting myeloid cells (C-C motif chemokine ligand CCL2) and related cytokines

(interleukin-23 and interleukin-17).[92,93] The proangiogenic/stromagenic/immunosuppressive phenotype of CMS4 mesenchymal tumors, with their invasive-inflamed microenvironment, is intimately linked to higher chances of metastatic spread and resistance to therapy.[94,95] Indeed, retrospective biomarker analysis of the NSABP C-07 randomized clinical trial showed poor prognosis and no benefit from adjuvant oxaliplatin-based chemotherapy in the subset of patients with stage III CRC whose tumors displayed a mesenchymal phenotype.[96] However, the clinical utility of using intrinsic CRC subtyping to identify patients for oxaliplatin treatment requires validation in independent clinical trial cohorts.

Similarly, the value of supervised gene expression classifiers for adjuvant chemotherapy selection remains to be proven. Different prognostic signatures, such as Oncotype DX Colon Cancer, ColoPrint, Veridex, and GeneFx Colon, have been widely evaluated retrospectively in clinical cohorts.[81] Irrespective of assay, gene panel size, and tissue source (fresh, frozen, formalin fixed, paraffin embedded), analysis of the various transcriptomes in CRC can effectively classify patients into subgroups at low and high risk of disease relapse. The original hypothesis was that patients whose tumors are categorized as high risk have increased benefit from adjuvant chemotherapy. In theory, the prognostic information provided by these signatures could have the greatest clinical utility when used as a complement to T stage and MSI status, specifically for patients who have pT3pN0 MSS disease.[97] However, the relative chemotherapy benefit for Oncotype DX Colon Cancer was shown to be similar across risk groups.[98,99] Despite the fact that gene expression–based risk scores seem to add little to risk models with known prognostic factors,[100] incorporation of the signature results into clinical practice was associated with changes in treatment recommendation for nearly 50% of patients with pT3pN0 MSS CRC compared with traditional clinicopathological assessment variables alone.[101] Prospective validation of these signatures has not yet been presented, and currently only one trial (PARSC [Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients]) is comparing risk assessment using the ColoPrint profile versus a clinical risk assessment based on the investigator's judgment and American Society of Clinical Oncology recommendations for high-risk disease. Furthermore, economic studies assessing the cost-effectiveness of using gene expression signatures to select patients with CRC who have a high risk of relapse (and to base adjuvant chemotherapy decision making on this criterion) are not yet available. Given the fact that high risk scores in supervised signatures have substantial overlap with a mesenchymal phenotype,[102] it is understandable that these prognostic classifiers have limited predictive value for adjuvant chemotherapy selection. This finding is in stark contrast with prognostic gene expression classifiers in early-stage breast cancer, in which high risk scores associate with high proliferation rates and increased benefit from more aggressive adjuvant chemotherapy.[103]

In summary, pathways that coordinate the creation of an immunosuppressive microenvironment and stromal invasiveness are the key drivers of a prometastatic state in CRC.[86] These processes are strongly enriched in the CMS4 mesenchymal CRC population,[90] which is poorly responsive to standard chemotherapies.[95,96] The following investigations should be pursued by the scientific community: (1) correlating response patterns of targeted agents and immunotherapies with the CMS classification in existing clinical trials; (2) adapting the design of future trials, such as adding stratification factors or increasing their power to allow these retrospective correlative analyses to be performed; and (3) designing prospective clinical trials in CRC that incorporate new biomarkers with drug repositioning and/or novel matched targeted agents and immunotherapies.[91] Different academic groups are working on a practical and robust CMS classifier that works on formalin-fixed, paraffin-embedded primary CRC tissues (either gene expression or immunohistochemistry based).[104] Molecular classifiers based on

TABLE 3. Clinical and Molecular Features of Intrinsic Gene Expression–Based CRC Subtypes

Feature	CMS1 (MSI Immune)	CMS2 (Canonical)	CMS3 (Metabolic)	CMS4 (Mesenchymal)
Prevalence in early-stage CRC, approximate %	15	40	15	30
Primary tumor site	Enriched right side of the colon	Enriched left side of the colon and rectum	Enriched right side of the colon	Enriched left side of the colon and rectum
Cancer cell features	MSI, hypermutated, hypermethylated, enriched for *BRAF* mutations	MSS, chromosomal instability, EGFR, and ERBB2 upregulation	Mixed MSI/MSS status, chromosomal instability, metabolic deregulation, enriched for *KRAS* mutations	MSS, chromosomal instability, epithelial-mesenchymal transition and stemness
Microenvironment features	Infiltrated with cytoxic T, helper T, and natural killer cells	Limited immune cell or stromal cell infiltration	Limited immune cell or stromal cell infiltration	Highly infiltrated with stromal cells, regulatory T cells, B cells, and myeloid-derived suppressor cells
Prognosis	Better relapse-free survival and worse survival after relapse	Better relapse-free and overall survival	Better relapse-free and overall survival	Worse relapse-free and overall survival

Abbreviations: CMS, consensus molecular subtype; CRC, colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stability.

intrinsic tumor phenotypes are already being investigated in prospective clinical trials in the metastatic setting, such as in the MoTriColor project, a large pan-European effort pioneering novel molecularly guided trials in metastatic CRC, but the biologic differences between micro- and macrometastatic disease must be taken into account when translating data garnered from advanced-stage CRC into early-stage disease regarding treatment decisions.[91] The recent failures with cetuximab and bevacizumab in adjuvant trials in stage III CRC exposed this challenge and call into question our traditional paradigm of drug development (namely, considering agents for testing in the curative setting only after they are found to be beneficial in the treatment of patients with metastatic disease). We believe that this new biologic understanding is expected to guide drug selection in future adjuvant clinical trials and is hoped to increase cure rates and survival in CRC.

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Systemic Therapy for Metastatic Colorectal Cancer: From Current Standards to Future Molecular Targeted Approaches

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OVERVIEW

Over the past 20 years, substantial advances have been made in the treatment of patients with metastatic colorectal cancer (mCRC). In particular, there is now a wide range of options for the front-line treatment of mCRC. Sophisticated molecular technologies have been developed to identify novel prognostic and predictive biomarkers for CRC. DNA sequencing technology has made remarkable advances in recent years, primarily as a result of the development of next-generation sequencing and whole exome sequencing, which are powerful new tools for the discovery of predictive molecular biomarkers to facilitate the delivery of personalized medicine. In addition to tumor tissue, recent efforts have focused on analyzing circulating tumor DNA in peripheral blood. Herein, we review the evolution of standard chemotherapy and targeted therapy strategies for the treatment of mCRC in the front-line setting, the molecular technologies that are presently being used to facilitate our ability to practice individualized medicine, and the practical aspects of applying molecular biomarkers to everyday clinical practice.

CRC remains a major public health problem in the United States and worldwide. In 2017, there will be an estimated 135,000 new cases diagnosed in the United States.[1] CRC is the second leading cause of cancer deaths, with an estimated 50,000 deaths each year. Approximately 20% of newly diagnosed CRC is metastatic at the time of initial presentation. Perhaps more importantly, up to 50% of patients who initially present with early-stage CRC will eventually be diagnosed with metastatic disease. Substantial progress has been made in the treatment of mCRC during the last 2 decades, so that median overall survival (OS) is now in the 30-month range.

For patients with mCRC, systemic chemotherapy has been the main treatment approach.[2,3] For nearly 40 years, from the mid-1950s to 1996, the fluoropyrimidine 5-fluorouracil (5-FU) was the only agent approved for the treatment of mCRC. However, since 1996 with the approval of the topoisomerase I inhibitor irinotecan, considerable advances have been made with the approval of several cytotoxic, biologic, and targeted agents by the U.S. Food and Drug Administration. In addition to irinotecan, the cytotoxic agents include oxaliplatin, a third-generation platinum analog, and two oral fluoropyrimidines, capecitabine and TAS-102. Bevacizumab, an anti-VEGF antibody, was approved in 2004, along with cetuximab, an anti-EGFR antibody. In 2006, panitumumab, an anti-EGFR antibody, was approved for use in the disease-refractory setting, and in 2012, the anti-VEGF recombinant fusion protein, Ziv aflibercept, and regorafenib, a multikinase small molecule inhibitor, were approved.

OXALIPLATIN VERSUS IRINOTECAN

Four randomized clinical trials have directly compared the clinical efficacy of oxaliplatin-based chemotherapy with irinotecan-based chemotherapy in the first-line treatment setting.[4-7] The most well-known was the GERCOR C97-3 study conducted by Tournigand et al[4] in France, and this was the first large, randomized clinical trial investigating leucovorin plus 5-FU (46-hour infusion) and oxaliplatin (FOLFOX6) compared with leucovorin plus 5-FU and irinotecan (FOLFIRI) for the front-line treatment of mCRC. This study clearly documented the virtually identical clinical efficacy of FOLFOX6 and FOLFIRI chemotherapy with respect to overall response rate (ORR; 56% vs. 54%, respectively), median time to tumor progression (8.5 vs. 8.1 months), and median OS (20.6 vs. 21.5 months). Similar results were subsequently reported by the Gruppo Oncologico Dell'Italia Meridionale in Italy and the U.S. CALGB Cooperative Group (CALGB 80203).[5,6] The Hellenic Oncology Group in Greece conducted a clinical study in which the bolus weekly schedule of 5-FU was used instead of an infusional schedule as the backbone fluoropyrimidine regimen in combination with irinotecan or oxaliplatin, and they also showed no difference between irinotecan and oxaliplatin with respect to clinical efficacy.[7]

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ORAL VERSUS INTRAVENOUS 5-FU

FOLFOX Versus XELOX

The NO16966 randomized phase III study was initially designed as a two-arm, open-label study to compare the clinical efficacy of leucovorin plus 5-FU (22-hour infusion) and oxaliplatin (FOLFOX4) with oral fluoropyrimidine plus capecitabine and oxaliplatin (XELOX).[8] When it was clear that bevacizumab was going to receive approval by the U.S. Food and Drug Administration, this study was subsequently amended to a two-by-two, placebo-controlled design with two of the arms including bevacizumab.[9] In the initial cohort of 634 patients who were treated with only FOLFOX4 or XELOX, no differences were observed with respect to ORR, progression-free survival (PFS), and OS. Both combination regimens were relatively well-tolerated. However, FOLFOX4 was associated with more grade 3/4 neutropenia (44% vs. 7%), febrile neutropenia (4.8% vs. 0.9%), and grade 3/4 venous thromboembolic agents (6.3% vs. 3.8%) than XELOX. In contrast, XELOX was associated with an increased incidence of grade 3 diarrhea (19% vs. 11%) and grade 3 hand-foot syndrome (6% vs. 1%) compared with FOLFOX4. Of note, the rates of grade 3/4 neurotoxicity were similar between XELOX and FOLFOX4.

Ducreux et al[10] conducted a randomized study of XELOX compared with FOLFOX6 in the first-line treatment of mCRC, and the primary endpoint of this study was overall ORR. The secondary endpoints were PFS, OS, quality of life, and pharmacoeconomics. No differences were observed between the XELOX and FOLFOX6 arms in terms of the clinical efficacy endpoints of ORR (42% vs. 46%, respectively), PFS (8.8 vs. 9.3 months, respectively), and OS (19.9 vs. 20.5 months, respectively). However, as had been previously reported in the N016966 study, the incidence of grade 3/4 myelosuppression was higher in patients treated with FOLFOX6 (47%) compared with XELOX (5%). Patients treated with XELOX experienced more grade 3/4 thrombocytopenia (12% vs. 5%) and diarrhea (14% vs. 7%) than those treated with FOLFOX6. In contrast to the NO16966 study, FOLFOX6 was associated with a higher incidence of neurotoxicity (26% vs. 11%) compared with XELOX.

KEY POINTS

- **Anti-VEGF and anti-EGFR antibodies can be effectively used in combination with cytotoxic chemotherapy for the first-line treatment of metastatic colorectal cancer.**
- **The sidedness of the primary tumor is an important factor in determining the potential role of anti-VEGF and anti-EGFR antibodies for the first-line treatment of metastatic colorectal cancer. Anti-EGFR antibody therapy should not be administered in patients with a right-sided primary tumor.**
- **Genomic testing should be performed at the time of diagnosis of metastatic disease to evaluate for potential alterations in the *KRAS*, *NRAS*, and *BRAF* genes, which will guide patient selection for anti-EGFR antibody therapy, and to also inform decisions about potential curative-intent resection of metastases.**
- **Induction chemotherapy with FOLFOXIRI, with or without bevacizumab, should be considered in patients with a *BRAF* mutation and good performance status.**
- **Treatment with the immune checkpoint inhibitors nivolumab or pembrolizumab should be considered in patients with microsatellite unstable/mismatch repair defective tumors, as per the 2017 NCCN guideline (U.S. Food and Drug Administration approval is pending).**

FOLFIRI Versus XELIRI

A meta-analysis of six clinical studies was conducted by Guo et al[11] to investigate the clinical efficacy of the oral capecitabine plus irinotecan (XELIRI) and FOLFIRI combination regimens in the first-line treatment of mCRC. No significant differences in clinical efficacy, as reflected in ORR, PFS, and OS, between XELIRI and FOLFIRI were identified. In terms of side effects, both treatment regimens were relatively well-tolerated with similar safety profiles.

The FNCLCC ACCORD 13/053 study was a randomized phase II clinical trial that investigated the efficacy and safety of XELIRI and FOLFIRI as first-line therapy of mCRC.[12] Patients were randomly assigned to receive XELIRI or FOLFIRI, and bevacizumab was included in both treatment arms. The 6-month PFS was 82% in the XELIRI arm and 85% in the FOLFIRI. In general, both XELIRI and FOLFIRI were well-tolerated with a manageable safety profile, and the most frequent toxicities were grade 3/4 neutropenia (18% vs. 26%, respectively) and grade 3 diarrhea (12% vs. 5%, respectively).

Triplet Cytotoxic Chemotherapy

In patients with good performance status and who are believed to be able to tolerate aggressive combination chemotherapy, it is clear that doublet chemotherapy has superior clinical efficacy over single-agent fluoropyrimidine chemotherapy, whether it is infusional 5-FU or oral capecitabine. The next issue to consider is whether triplet chemotherapy with all three of the active cytotoxic agents, 5-FU, oxaliplatin, and irinotecan, could provide improved clinical efficacy in the up-front treatment setting. To directly address this question, the Gruppe Oncologico Nord Ovest (GONO) of Italy conducted the first randomized phase III study to compare leucovorin plus 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI) with FOLFIRI in the front-line setting.[13] A total of 244 patients were randomly assigned, and Falcone et al reported improved ORR, PFS, and median OS in patients treated with the FOLFOXIRI triplet combination regimen when compared with FOLFIRI. Moreover, treatment with FOLFOXIRI compared with FOLFIRI resulted in improved R0 surgical resection rate for all patients (15% vs. 6%, respectively) and for those specific patients with liver-limited disease (36% vs. 12%, respectively). The triplet combination regimen was fairly well-tolerated, although there was an increase in grade 2/3 neurotoxicity (19% vs. 0%) and grade 3/4 neutropenia (50% vs. 28%) compared with FOLFIRI. However, the incidence of febrile neutropenia and grade 3/4 diarrhea was not significantly different between the two treatment arms. A final analysis was conducted after a median follow

up of 5 years that confirmed the superiority of the FOLFOXIRI regimen.[14] In addition, a risk-stratified analysis based on the Köhne prognostic model was performed, which showed that FOLFOXIRI, when compared with FOLFIRI, was associated with improved PFS and OS in all risk subgroups.

FOLFOXIRI chemotherapy is associated with improvements in PFS and OS; the absolute benefit in OS is 7% at 5 years. In a relatively fit patient population, this triplet combination regimen is feasible and is associated with a manageable safety profile. Moreover, in patients who are able to undergo R0 surgical resection of liver-limited disease, there does not appear to be an increase in liver toxicity. Finally, initial treatment with FOLFOXIRI does not appear to have a negative effect on the outcomes of patients who received subsequent treatment in the second-line setting.

ANTI-VEGF VERSUS ANTI-EGFR THERAPY IN COMBINATION WITH CYTOTOXIC CHEMOTHERAPY

PEAK was a phase II study in which modified FOLFOX6 (mFOLFOX6) was used as the chemotherapy backbone, and patients were randomly assigned to receive the anti-VEGF antibody bevacizumab or the anti-EGFR antibody panitumumab.[15] A total of 285 patients were enrolled, and the primary endpoint of the study was PFS, with secondary endpoints of ORR, OS, and safety. Overall, ORR and median PFS were nearly identical between the arms treated with bevacizumab or panitumumab (54% vs. 58%, respectively, and 10.1 vs. 10.9 months, respectively). However, median OS was significantly improved in patients treated with panitumumab when compared with bevacizumab (34.2 vs. 24.3 months; hazard ratio [HR] 0.62; p = .009). When an extended *RAS* analysis was performed and the clinical data were re-analyzed, the improvement in OS was maintained with panitumumab compared with bevacizumab (41.3 vs. 28.9 months; HR 0.63). Moreover, median PFS in patients treated with panitumumab was found to be significantly improved by 4.5 months compared with bevacizumab (13 vs. 9.5 months; HR 0.65; p = .029).

FIRE-3 was a study conducted in Germany in which patients with previously untreated mCRC with wild-type *KRAS* were treated with the FOLFIRI chemotherapy backbone, and patients were randomly assigned to receive either bevacizumab or cetuximab.[16] The primary endpoint of this study was ORR, with secondary endpoints of PFS, OS, R0 surgical resection rate, and safety. In the original analysis of this study, ORR and PFS were virtually identical between the arms treated with bevacizumab or cetuximab (58% vs. 62%, respectively, and 10.3 vs. 10.0 months, respectively). However, a significant 3.7-month improvement in OS was observed in patients treated with cetuximab, which represented a 23% reduction in the risk of death (HR 0.77; p = .017). The safety profiles of the two arms of the study were as expected and manageable. This was the first direct head-to-head comparison of cetuximab and bevacizumab in the front-line treatment setting, and although ORR and PFS were identical, cetuximab treatment resulted in a potentially clinically meaningful improvement in OS. At the time of the initial publication and the presentation of this work at the 2013 ASCO Annual Meeting, the potential effect of the improvement of the FOLFIRI plus cetuximab combination remained unclear given the somewhat limited information relating to duration of second-line and subsequent salvage therapies.

In the United States, the CALGB/SWOG 80405 phase III randomized study compared the potential benefit of cetuximab and bevacizumab added to cytotoxic chemotherapy.[17] In contrast to the FIRE-3 study, the primary endpoint of this study was OS, and patients could receive either FOLFOX or FOLFIRI as their cytotoxic regimen depending on physician preference. Of note, 74% of patients received FOLFOX whereas 26% received FOLFIRI. Overall, no significant differences were observed in PFS (10.4 vs. 10.8 months, respectively) and OS (29.9 vs. 29.0 months, respectively) in patients treated with cetuximab compared with bevacizumab. When the specific chemotherapy regimen was analyzed, no significant differences in OS were identified among patients treated with FOLFOX or FOLFIRI chemotherapy. This was the largest randomized study in the front-line setting conducted to date, and the take-home conclusions were that FOLFOX/FOLFIRI in combination with either bevacizumab or cetuximab were effective treatment options and that an OS of approximately 30 months established a new benchmark for first-line treatment.

Venook et al[18] recently investigated the potential effect of primary tumor location on the clinical efficacy of patients treated on CALGB/SWOG 80405, and these findings were reported at the 2016 ASCO Annual Meeting. In a careful chart review, they determined that 68% of the primary tumors came from the left side of the colon or rectum and 27% of the tumors came from the right side. When OS was determined by sidedness of the primary tumor, there was an improvement in OS for patients with left-sided tumors compared with right-sided tumors (33.3 vs. 19.4 months, respectively), which was highly significant (p < .0001). For patients treated with bevacizumab, the improvement in OS was maintained in patients with left-sided tumors compared with right-sided tumors, albeit still higher for left-sided primary tumors (31.4 vs. 24.2 months, respectively). However, in patients treated with cetuximab, there was a striking 19.3-month difference in which OS was 36.0 months for left-sided tumors and only 16.7 months for right-sided tumors. These findings are important as they highlight the importance of sidedness as an important predictive marker and the role of sidedness in determining response to anti-EGFR antibody therapy and has now been confirmed in other clinical studies.[19,20] Patients with right-sided tumors clearly derive greater benefit from bevacizumab compared with cetuximab and, in fact, derive little benefit from cetuximab. In contrast, patients with left-sided tumors derive benefit from both cetuximab and bevacizumab, although it appears that the median OS is improved by nearly 5 months with cetuximab.

Triplet Cytotoxic Chemotherapy in Combination With Biologic Agents

TRIBE was a multicenter, phase III study conducted in 34 Italian oncology centers in which patients with mCRC were randomly assigned to receive FOLFOXIRI plus bevacizumab or FOLFIRI plus bevacizumab as first-line treatment.[21,22] A total of 508 patients were enrolled in this study. The median PFS was 12.1 months with FOLFOXIRI plus bevacizumab compared with 9.7 months with FOLFIRI plus bevacizumab (HR 0.75; p = .003), and ORR was increased to 65% compared with 53% for patients treated with FOLFIRI plus bevacizumab. The median OS was 31 months in the FOLFOXIRI plus bevacizumab group compared with 25.8 months in patients treated with FOLFIRI plus bevacizumab, and this difference approached significance (HR 0.79; p = .054). Of note, the FOLFOXIRI/bevacizumab combination was equally effective in wild-type and mutant *KRAS* tumors, and although the numbers were small, this combination appeared to be especially active in the mutant *BRAF* subgroup.

To date, only phase II studies have investigated FOLFOXIRI in combination with the anti-EGFR antibodies cetuximab and panitumumab. Saridaki et al[23] conducted a pilot phase II study of FOLFOXIRI plus cetuximab, and they reported an ORR of 70%, with median time to progression of 10.2 months and median OS of 30.3 months. In addition, R0 surgical resection was performed in 37% of patients. Although this combination regimen was relatively well-tolerated, the incidence of grade 3/4 diarrhea was 53%. The GONO group in Italy investigated the combination of FOLFOXIRI plus panitumumab in patients with wild-type *RAS* and *BRAF* mCRC, and they reported an 89% ORR and a median PFS of 11.3 months.[24] In addition, R0 surgical resection was achieved in 35% of the treated patients. Once the 5-FU infusion dose was reduced from 3,000 mg/m^2 to 2,400 mg/m^2 after two of the first three patients experienced grade 3/4 diarrhea, this combination regimen was found to be well-tolerated, and the most common grade 3/4 toxicities were neutropenia (48%), diarrhea (35%), asthenia (27%), mucositis (14%), and skin conditions (14%).

CURRENT TREATMENT OPTIONS FOR MCRC

In 2017, there is now a wide range of treatment options for the first-line therapy of mCRC.[25] The current standard of care for first-line treatment is combination cytotoxic chemotherapy using the fluoropyrimidine backbone (5-FU or capecitabine) with either oxaliplatin (FOLFOX or XELOX) or irinotecan (FOLFIRI or XELIRI) in combination with the anti-VEGF agent bevacizumab or anti-EGFR agents (cetuximab or panitumumab) for patients with wild-type *RAS* and *BRAF*. The choice between bevacizumab and anti-EGFR agents for the first-line setting in patients with wild-type *RAS* depends on clinical presentation and individual patient factors. Recent studies suggest that the sidedness of the primary tumor is an important predictive biomarker and that patients who present with right-sided primary tumors derive little benefit from anti-EGFR therapy. Patients with left-sided primary tumors derive clinical benefit from either bevacizumab or cetuximab, although it appears that the benefit may be greater with cetuximab.

MOLECULAR PROFILING OF CRC: WHAT, WHEN, AND HOW

Genomic analysis of mCRC provides both prognostic and predictive information. Genomic analysis should be performed in all patients with mCRC, including patients with limited tumor burden who are being evaluated for hepatectomy or other metastasectomy. The National Comprehensive Cancer Network (NCCN) guideline recommends genomic testing at the time of diagnosis of metastatic disease.[25] An array of sequencing tests, which differ in the number of genes analyzed, depth of sequencing, and evaluation of mutations and/or copy number alterations, are currently available.

For clinical care, genomic analysis should evaluate for the presence of activating mutations in the *KRAS*, *NRAS*, and *BRAF* genes to guide the selection of patients for the anti-EGFR therapies, cetuximab or panitumumab. The *KRAS*, *NRAS*, and *BRAF* are oncogenes that encode proteins involved in the classic mitogen-activated protein kinase (MAPK) pathway that regulates cell proliferation and survival, and mutations in these genes are found in about 45%, 4%, and 8% of mCRC, respectively.[26] Activating mutations in these genes occur as an early event in colorectal tumorigenesis[27] in defined hotspots, and *KRAS*-, *NRAS*-, and *BRAF*-activating mutations are nearly universally exclusive.[28] In mCRC, either the primary tumor or metastasis can be analyzed. Studies of paired tumors suggest near complete concordance for mutations in *KRAS*, *NRAS*, and *BRAF* between colorectal primaries and metastases.[29,30]

Genomic alterations in the *KRAS*, *NRAS*, and *BRAF* genes provide predictive information for the selection of patients for the anti-EGFR antibodies cetuximab or panitumumab. Activating mutations in these genes result in constitutively activated proteins, whose activation does not require upstream signaling, such as through EGFR, and whose activation leads to negative feedback loops that limit EGFR activation. Multiple clinical trials indicate that colorectal tumors harboring activating *KRAS* or *NRAS* mutations do not benefit from anti-EGFR therapies and may actually experience accelerated growth with use of these drugs.[26,31,32] Thus, prior to the consideration for treatment with the anti-EGFR antibodies, *RAS* mutation testing should be performed to analyze for mutations, both at the more common sites in exon 2 (codons 12 and 13) and outside exon 2 (exon 3 at codons 59 and 61, and exon 4 at codons 117 and 146). In colorectal tumors harboring BRAF V600E mutations, increasing evidence through subset analysis of clinical trial and retrospective data also suggest lack of response to EGFR inhibitors, both as single agents and in combination with chemotherapy. In addition, two meta-analyses found no PFS benefit for EGFR inhibitors in BRAF-mutant mCRC.[33,34] These data are limited by the overall low frequency of BRAF V600E mutation and the aggressive nature of mCRC with this mutation (see below).

Genotyping the *KRAS*, *NRAS*, and *BRAF* genes also provides important prognostic information. Several studies have evaluated the effect of *KRAS* mutations on the outcomes of patients with mCRC. Although early results were inconsistent, as some studies found no effect and others found harm associated with *KRAS* mutations, recent data increasingly suggest that the presence of a *KRAS* mutation is associated with worse outcomes. A retrospective analysis of 918 patients with mCRC at Memorial Sloan Kettering Cancer Center identified an HR of 1.6 (95% CI, 1.29–1.90; p < .001) for OS with the presence of a *RAS* mutation on multivariate analysis adjusting for age at diagnosis of metastatic disease, gender, location of primary tumor, synchronous or metachronous disease, and occurrence of metastasectomy or hepatic arterial infusion treatment treated as a time-dependent covariates.[35] Few series have looked at outcomes in *NRAS*-mutant mCRC. An updated analysis from Memorial Sloan Kettering Cancer Center found that, compared with *RAS*–wild-type mCRC, *NRAS*-mutant and *KRAS*-mutant mCRC had an HR of 2.0 (95% CI, 1.3–2.8; p < .01) and 1.5 (95% CI, 1.2–1.8; p < .01) for OS, respectively, on multivariate analysis (Rona Yaegar, unpublished data). The presence of the BRAF V600E mutation is a strong negative prognostic marker in mCRC. Data from the randomized phase III Medical Research Council COIN trial in mCRC, for example, identified an OS of 8.8 months for patients with *BRAF*-mutant mCRC, 14.4 months for *KRAS* exon 2–mutant mCRC, and 20.1 months for *KRAS* exon 2–wild-type mCRC.[36] Similarly, many series have reported median OS of less than a year for *BRAF*-mutant mCRC.[26,37] The presence of a *BRAF* mutation in mCRC has been associated with T4 primary tumors, poor tumor differentiation, and peritoneal metastasis.[37-40]

The presence of mutations in the *RAS* and *BRAF* genes may also influence recurrence risk after metastasectomy, and patients with *RAS*-mutated or *BRAF*-mutated tumors should be carefully selected for surgical treatment with curative intent. In patients undergoing hepatectomy for colorectal liver metastases, the presence of a *RAS* mutation, in comparison with wild-type the wild-type variant, was associated with significantly worse recurrence-free survival (RFS) and OS, with similar liver RFS at 3 years, but lower lung RFS at 3 years.[41] In *RAS*-mutant mCRC, there is a high risk of recurrence as well as shorter survival after hepatectomy in node-positive primary tumors, larger tumors, and after more than 7 cycles of preoperative chemotherapy. The presence of a *BRAF* mutation is associated with a high risk of recurrence after metastasectomy of liver, lung, or peritoneal disease, and patients with *BRAF*-mutant mCRC experience shorter survival after metastasectomy compared with patients with *BRAF*–wild-type disease.[42] Patients with *BRAF*-mutant mCRC should be carefully selected and informed of the increased risk of recurrence before metastasectomy; and, unless metastatic disease is truly limited, systemic clinical trial options (see below) should be considered rather than aggressive surgical debulking.

Prior to an appreciation for the need to perform extended *RAS* genotyping, clinical testing should focus on hotspot alterations in exon 2 of *KRAS*. Genotyping of codons 12 and 13 in exon 2 of *KRAS* was often done with Sanger sequencing or real-time polymerase chain reaction (PCR).[43] Sanger sequencing is limited by low sensitivity with a limit of detection of about 20% and is laborious. Real-time PCR is more sensitive, but requires unique primers for each possible mutation. PCR-based assays have been expanded to cover all hotspots in *RAS* and can be used for extended *RAS* testing. However, with the decreased cost of sequencing, many groups have shifted to multiplexed genotyping platforms that include more genes. A mass spectrometry based multiplatform assay can detect alterations with a sensitivity limit of detection of about 5%. For this assay, the target DNA is amplified, a single base extension is performed, and then the small DNA products with unique mass value according to the mutation generated are measured by a mass spectrometer. These assays can analyze several genes in a single sample and genotype multiple hotspots, but require prior knowledge of all potential mutation sites of interest. In recent years, target enrichment by hybrid capture has allowed next-generation sequencing (NGS) of subsets of the genome of clinical interest, as done by FoundationOne, Caris Life Sciences, and Tempus.[44] NGS assays are highly sensitive, can analyze a large panel of genes, and detect novel mutations, small insertions and deletions (indels), copy number alterations, and select gene fusions and rearrangements from small amounts of DNA.

In addition to providing predictive and prognostic information, when using a multigene NGS panel to perform molecular profiling of mCRC, the number of mutated genes identified can be used to discriminate between somatic mCRC and microsatellite-unstable mCRC.[45] Microsatellite instability–high (MSI-H) mCRC results from mutations in the mismatch repair (MMR) genes that cause a malfunctioning gene product or from promoter methylation causing epigenetic silencing of MMR protein expression and is diagnosed with a PCR assay to identify changes in length of dinucleotide/trinucleotide repeats or with immunohistochemical analysis for retained expression of the MMR proteins (MLH1, MSH2, MSH6, PMS2). MSI-H tumors exhibit a higher mutation burden. Using a small number of test cases with known MSI status, a mutation number cutoff to discriminate between microsatellite-stable (MSS) and MSI-H cases can be identified.[46] The mutation number cutoff varies by the assay and the number of genes analyzed. Information about MSI status of mCRC now has important clinical implications, and the updated 2017 NCCN guideline recommends that all mCRC be evaluated for MMR deficiency, and the anti-PD1 antibodies, pembrolizumab and nivolumab, have been added as treatment options for patients with unresectable MSI-H or MMR-deficient mCRC.[25] Use of a single assay may provide a cost-effective option to both evaluate *RAS* and *BRAF* mutation status and screen for microsatellite instability in mCRC.

Because activating mutations in the *KRAS*, *NRAS*, and *BRAF* genes are nearly universally exclusive, some groups use a hierarchical system of genotyping to improve cost-effectiveness

of genomic analysis. Genomic alterations are analyzed sequentially—usually first in *KRAS* exon 2, then extended *KRAS* testing, BRAF V600E, and finally *NRAS* testing based on frequency of these alterations—with the analysis halted if a mutation is detected. In tumors that are wild-type at all three genes, it may be worth considering alternative driver alterations that may impact response to EGFR inhibition and may be targetable. *ERBB2* amplification and *MAP2K1* mutations appear to predict resistance to EGFR inhibition and may be targetable.[46-49] NTRK fusions, although very rare in mCRC, are potentially targetable and early clinical trials with novel agents that target NTRK alterations have reported promising initial results.[50]

Cell-free fragments of DNA are shed into the bloodstream by cells undergoing apoptosis and necrosis, and the circulating free DNA (cfDNA) released by tumor cells can be collected and amplified to look for somatic mutations. Looking to the future, cfDNA may represent a novel method to perform molecular profiling in mCRC, obviating the need to obtain tumor tissue and potentially allowing for a noninvasive method to perform genomic analysis at multiple time points during therapy, evaluating for clonal evolution, as well as molecular mechanisms of response and resistance. Both focused analysis for several genes and multigene NGS assays have been applied to detect somatic alterations within circulating tumor DNA in mCRC.[51] Genomic analysis of cfDNA has been done most often in patients with response to targeted therapy who then acquire resistance.[52,53] The use of cfDNA to characterize *KRAS*, *NRAS*, and *BRAF* mutation status and guide the use of EGFR inhibitor treatment is not standard in mCRC and may be limited by the lower sensitivity of the assay.

TRANSLATING BIOMARKERS INTO CLINICAL PRACTICE

RAS Mutations

If a mutation is detected in *KRAS* or *NRAS* at codons 12, 13, 61, 117, or 146, the recommendation is for cetuximab or panitumumab to not be considered as potential treatment options.[54] RAS remains an elusive target, although many early phase trial strategies are aimed at targeting RAS and/or its downstream effectors. One study that has generated a great deal of interest is the phase 1B study of the MEK inhibitor, cobimetinib, combined with the anti-PD-L1 agent, atezolizumab.[55] Based on prior clinical data, neither drug along would be expected to produce responses in *KRAS*-mutated, MSS mCRC tumors. In combination, however, the ORR to cobimetinib plus atezolizumab was 20% in 20 *KRAS*-mutant tumors, with the majority of responses or disease stabilization persisting for more than 6 months. It is now hypothesized that MEK inhibitor–mediated intratumoral T-cell infiltration and MHC I upregulation is a *RAS* mutation–independent effect. For this reason, the follow-up phase III trial (NCT02788279) allows up to half of patients to have *RAS* wild-type tumors.

If a tumor is found to be *RAS* wild-type, additional biomarker testing should be considered to try to identify potentially actionable targets. It should also be noted that as per the 2017 NCCN guideline, cetuximab and panitumumab therapy are only recommended for left-sided tumors, further refining the appropriate patient population for anti-EGFR antibodies.[25]

MSI/MMR

The anti–PD-1 antibodies, pembrolizumab or nivolumab, have been included as treatment options for patients with unresectable MSI-H or MMR-deficient CRC in the recently updated 2017 NCCN guideline[25]; although, as of this writing, neither agent is U.S. Food and Drug Administration–approved for mCRC. The data to support the NCCN recommendation come from the interim results of KEYNOTE-016, a phase II study of pembrolizumab in MSI-H tumors (NCT01876511), and CheckMate 142, a study of nivolumab or nivolumab combinations in recurrent or mCRC (NCT02060188).[56-58] Given the limitations of cross-study comparisons, these results are summarized in Table 1. With immunotherapy, time to response may be long, such that response rates tend to increase as the data matures. Whereas primary progression occurs quickly, responses and stable disease are impressively durable.

KEYNOTE-164 is a phase II trial of pembrolizumab as monotherapy in patients with previously-treated MSI-H/MMR-deficient mCRC, and this study is now closed to accrual after reaching the planned enrollment of 120 patients.[60] For newly identified patients with MSI-H/MMR-deficient mCRC, KEYNOTE-177 is an ongoing phase III study of first-line pembrolizumab compared with standard of care chemotherapy with a planned enrollment of 270 patients (NCT02563002).[61]

In response to those patients with MSS mCRC who ask about immunotherapy, none of the 25 patients with MMR-proficient mCRC who received pembrolizumab during the phase II study achieved objective responses (median

TABLE 1. MSI-H/dMMR CRC: Interim Results of Anti–PD-1 Antibody Trials

Therapy	No. of Patients	Confirmed ORR, %	Median DOR (Months)	Median PFS (Months)	Median OS (Months)	Reference
Pembrolizumab*	28	57	NR	NR	NR	59
Nivolumab	74	27	NR	9.6	NR	58
Nivolumab + ipilimumab**	27	33	NR	NR	NR	57

*Median follow-up of 9.3 months.

**At least 12 weeks of follow-up.

Abbreviations: MSI-H, microsatellite instability high; CRC, colorectal cancer; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NR, not reached.

TABLE 2. *BRAF*-Mutated Metastatic Colorectal Cancer: Phase II Trial Results

Therapy	No. of Patients	Confirmed ORR, %	Median DOR (Months)	Median PFS (Months)	Median OS (Months)	Reference
Vemurafenib (V)	21	5	5	2.1	7.7	[72]
V + cetuximab (C)	27	4	9	3.7	7.1	[73]
C + irinotecan (I)	52*	4	NA	2	NA	[75]
V + C + I	54*	16	NA	4.4	NA	[75]
Dabrafenib (D) + trametinib (T)	43	7	NA	3.5	8.7	[76]
D + panitumumab (P)	20	10	6.9	3.5	13.2	[77]
T + P	31	0	NR	2.6	8.2	[77]
D + T + P	91	21	7.6, estimate	4.4	9.1	[77]
Encorafenib (E) + C	50	22	4.6	4.2	12.4	[78]
E + C + alpelisib	52	27	9.9	5.4	13.1	[78]

*Patients were randomly assigned to treatment.

Abbreviations: ORR; objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NA, not available; NR, not relevant.

PFS, 2.4 months); comparable results were observed for the 20 patients with MSS mCRC treated with nivolumab with or without ipilimumab.[56,57] Research efforts are underway to identify a subset of patients with immune-infiltrated MSS tumors who may benefit from checkpoint blockade.[62] In addition, several combination strategies are being developed to prime MSS tumors for immunotherapy by first inducing intratumoral T-cell accumulation, including the cobimetinib plus atezolizumab trial discussed above.

BRAF Mutations

The presence of a BRAF V600E mutation predicts aggressive disease biology and poor response to standard therapies including anti-EGFR antibodies.[26,37,63-66] However, the potential treatment implications of favorable prognosis *BRAF* mutations at codons 594 and 596 are less clear.[67,68] With a BRAF V600 mutation, the ability to achieve disease control with first-line therapy may be a critical determinant of survival outcomes.[69] In patients with good performance status, induction therapy with FOLFOXIRI should be considered.[70] The TRIBE study showed that the median OS of 53 patients with *BRAF*-mutated CRC was 19 months when treated with first-line FOLFOXIRI plus bevacizumab compared with 10.7 months with FOLFIRI plus bevacizumab (HR 0.54; 95% CI, 0.24–1.20).[22] Additionally, approximately a quarter of BRAF V600E–mutated mCRCs also exhibit MMR/MSI. Responses to checkpoint inhibitor therapy have been observed in the presence of a *BRAF* mutation and MMR/MSI.[58,71] As such, immunotherapy options, such as enrollment on the KEYNOTE-177 trial (NCT02563002) and/or other immunotherapy-based clinical studies should be considered in this setting.

Several studies have investigated the role of BRAF inhibitors as single-agents and in various combination strategies, for the treatment of BRAF V600E–mutated mCRC[72-79] (Table 2). What we have learned thus far is that BRAF inhibitor monotherapy is ineffective, although inclusion of a BRAF inhibitor in a combination strategy appears to be important, and three-drug therapies are somewhat more active than doublets. In the first randomized comparison with a standard of care regimen, the S1406 cooperative group study found that the addition of vemurafenib to irinotecan plus cetuximab significantly improved PFS (HR 0.42; 95% CI, 0.26–0.66; p < .001).[76]

Some patients clearly benefit from targeted inhibitor strategies, although disease stabilization is more common than radiographic response. Early emergence of drug resistance remains a challenge. For newly identified patients with *BRAF* V600E-mutated mCRC, an ongoing phase III trial that is expected to enroll 645 patients, BEACON CRC, is testing the combination of binimetinib (MEK inhibitor) with encorafenib and cetuximab, as compared with standard therapy (NCT02928224).

HER2 Amplification/Overexpression

The presence of HER2 amplification or a HER2-activating mutation may predict resistance to anti-EGFR antibodies. However, the current NCCN guideline does not yet discourage the use of cetuximab or panitumumab.[25,48,80-82] Several HER2-directed treatment strategies have been, or are being, evaluated in mCRC.[49,83-85] HERACLES (HER2 Amplification for Colorectal Cancer Enhanced Stratification) was the first large, phase II clinical trial to evaluate the tyrosine kinase inhibitor lapatinib in combination with the HER2-targeted monoclonal antibody trastuzumab in patients with HER2-amplified mCRC. HER2 positivity was defined as 2+/3+ by immunohistochemistry or fluorescence in situ hybridization–positive. The HERACLES study found that 27 patients with HER2-amplified mCRC refractory to standard therapy, including anti-EGFR antibodies, had a 30% response rate to lapatinib plus trastuzumab, with an 8.9-month median duration of response and a median PFS of 4.9 months.[49] A follow-up study, HERACLES-RESCUE, is evaluating T-DM1 after progression during trastuzumab and lapatinib treatment is underway.[86] T-DM1 is an antibody-drug conjugate whereby trastuzumab (the T portion) is connected via a stable

thioether linker to emtansine (the DM1 portion), a potent microtubule chemotherapy agent. Once trastuzumab binds to HER2-expressing cells, the linker is broken down, releasing DM1 intracellularly.

Considerations for patients with newly identified HER2 overexpression include ongoing basket trials. NCI-Molecular Analysis for Therapy Choice (NCI-MATCH, NCT02465060) is testing T-DM1 in HER2-amplified cancers and afatinib, an irreversible tyrosine kinase inhibitor that targets HER2, EGFR, and HER4, in HER2-mutated cancers. The MyPathway study is testing the combination of trastuzumab with pertuzumab, a monoclonal antibody that inhibits HER2 homodimerization and heterodimerization with other HER family members, in HER2-amplified and mutated tumors (NCT02091141).[85] The interim efficacy data from 34 patients enrolled in MyPathway is similar to what has been reported with the HERACLES study: 38% ORR, with a 10.3-month median duration of response, and a median PFS of 4.6 months. Notably, none of the nine patients with mutant KRAS and HER2-amplified/overexpressed mCRC responded to trastuzumab plus pertuzumab.[85,86]

Emerging Biomarkers

The aforementioned basket trials and several smaller studies contain rational therapeutic options for a large number of genetic aberrations found in CRC, including *EGFR*, *AKT*, *PIK3CA*, and *MAP2K1* mutations, as well as *MET* and *FGFR* amplification. Additionally, PARP inhibitors may be effective for *BRCA1/2*-mutated CRCs. Other emerging CRC-relevant DNA damage response targets include ataxia-telangiectasia–mutated (*ATM*) and ataxia-telangiectasia and Rad3-related (*ATR*).[87] Oncogenic fusions are of particular interest, as their targeting has led to exquisite responses in other cancer types. As proof-of-concept, patients with mCRC with a *NTRK1* and an *ALK* gene rearrangement were treated with entrectinib, a selective pan-TRK, ROS1, and ALK inhibitor.[50,88] Both patients experienced partial responses. A basket study of entrectinib for the treatment of patients with NTRK, ROS1, or ALK fusions is ongoing (NCT02568267). For patients with high *RSPO3* gene expression, which may arise from translocations of *RSPO3* and *PTPRK*, a trial of the anti-RSPO3 antibody, OMP-131R10, is in progress (NCT02482441).

In 2017, *KRAS*, *NRAS*, *MSI/MMR*, and *BRAF* are the main molecular markers that currently influence standard-of-care practice. However, enrollment of patients with these and other potentially actionable biomarkers in clinical trials holds promise for making increasingly personalized and effective treatment options available to future patients with mCRC.

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

Best Practices and Practical Nuances in the Treatment of Gastric Cancer in High-Risk Global Areas

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OVERVIEW

Gastric cancer is an aggressive disease that is very frequent in Latin America. The reasons for this increased incidence is not clear. Associated with the lack of minimum health care opportunities, lack of accurate statistics and reporting data beyond epidemiologic data, and raw nonreliable data, there is little known of the actual clinical course and treatment of these patients. Understanding epidemiologic data may allow us to encourage the adequate use and distribution of the meager resources that exist.

The incidence of gastric cancer in Latin America and in Central America is quite high. In the neighboring countries of Central America—Guatemala, El Salvador, and Honduras—the incidence of gastric cancer is high enough to be considered the most common malignancy. Actual statistics and information about the number of occurrences and the clinical course of this condition are unknown. In Central America, with the exception of Panama and Costa Rica, a mature, well-developed cancer registry program is sorely lacking.[1] Internet sites like www.WorldAtlas.com quote a gastric cancer incidence in Guatemala as high as 23.7 in 100,000. Limited information gathered through National Cancer Institute of Guatemala states that gastric cancer remains the leading cause of cancer-related deaths.[1] Regardless, gastric cancer is the second most common cause of cancer mortality worldwide and is the leading infection-associated cancer.[2,3] Gastric cancer has clear geographic and ethnic variability.[3,4] The highlands of the Pacific coast of Latin America have the highest incidence and mortality rates of the sites studied so far; the areas affected include Mexico, Guatemala, Honduras, Costa Rica, and Colombia.[5] As already mentioned, with the exception of Panama and Costa Rica, any type of information or literature about the epidemiology of gastric cancer in Central America is limited.[1,3]

Gastric cancer development has to be considered a multifactorial process, in which many conditions play a role; historically, the roles of diet, infection, ethnic background, socioeconomic conditions, and the altitude enigma[6] have been addressed. The impact of these factors may actually affect the histologic type of cancer (personal observation on the frequency of signet ring type histology) and the anatomic location of the sites of the cancer (proximal vs. distal). It should be noted that, without much data and on the basis of personal observations, at least in Guatemala, gastric cancers in lower socioeconomic populations tend to present with signet ring morphology and a more virulent behavior; anatomically, they tend to be distal cancers. This article attempts to outline the known facts associated with this condition in Guatemala and northern Central America.

RISK FACTORS

Dietary factors may induce cancer, but dietary habits also may be protective; diet is being studied aggressively. Historically, worldwide studies have documented protection from diets high in vegetables and fruit. Conversely, high intake of processed, red meat or smoked preserved foods seems to increase the risk of gastric cancer. A meta-analysis of Latin American studies done by Bonequi et al[4] showed that a trend toward this protection did exist, but the association was considered weak. Results for the association with the intake of red meat, processed meat, and salt did not vary from other global studies and did not indicate an increase in risk for the development of gastric cancer.[4] Smoking and drinking clearly showed a notable impact on the development of this malignancy. Smoking increased the incidence of gastric, overall risk increased 60% between smokers and nonsmokers. The dose response meta-analysis for this cancer documented an increase in gastric cancer risk of 12% per exposure of 10-pack years.[4] Alcohol use seemed to increase the risk of gastric cancer by 61%, but there was notable variability on the amounts of exposure reported.[4]

Education and ethnicity may go hand in hand as surrogate indicators of socioeconomic status and income potential in countries where the median income of the population is approximately $1.60 per day.[1] Clearly, ethnicity has been

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studied worldwide, but, in Latin America, where 10% of the population is indigenous,[7] the lack of information is widespread, and even the more advanced economies of the area lack statistics and data with which to work.[1,8] We know that poverty is associated with poor outcomes of cancer care; this has been attributed to poor access to medical care either because of low availability or, probably more important, because of the high cost of care and the lack of accessible, affordable resources in these low-income countries.[7] Also, poverty and ethnic background fuel persistent cultural beliefs, which hinder both access and availability to medical care.[4,8] The lack of adequate educational and medical resources at the national level in these societies also affects the incidence of gastric cancer.

Other risk factors worth mentioning include the association with infections and the site of residence. We have known for some time that the presence of infections, in particular *Helicobacter pylori (H. pylori)*, clearly increases the risk of gastric cancer. This association, identified in the 1990s, has been aggressively studied worldwide.[9]

In association with presence of infections, the site of residence for this population may play a role. Interesting data have been published on the role of high altitude and the development of gastric cancer. Torres et al[6] reviewed published statistics and data that documented clearly higher gastric cancer mortality in the Americas and a higher incidence of disease concentrated in the nations along the Pacific Rim. Observational analysis cited in the article document notable changes in incidence of this disease in short distances, sometimes as small as 150 miles, but the most distinct difference between the communities was the altitude.[6] Implications of these observations are important; these observations have led to the development of the altitude enigma concept. Historically, geographic barriers like mountains or large bodies of water allow development of diverse genetic patterns in humans and in bacteria or other organisms. If we include the impact of population changes triggered by immigration, slavery, and historical events, the implications are staggering. Implications and associations studied so far include evaluation of *H. pylori* genotypes and haplotypes on the basis of altitude. The ancestral origin of the *H. pylori* strain studied by phylogenetic haplotypes has been documented by de Sablet et al,[10] who noted clear variation between the African ancestries populations that live in the coastal regions of Colombia compared with the mestizo population (European/Amerindian) in the highlands. It was determined that the incidence of *H. pylori* from European ancestry was more common in the highlands with the mestizo population, whereas the coastal populations had 66% African-originated *H. pylori*.[10] These researchers also observed an increase in more severe gastritis and DNA damage in the populations affected by the European-ancestry *H. pylori*, but they still could not explain, by this finding alone, the 25-fold difference in incidence of gastric cancer between coastal and mountain regions of Colombia. Clearly, other risk factors do exist. The possibility of coinfections, either chronic helminthiasis or Epstein-Barr virus, has been suggested.[11,12] Diet, as previously mentioned, also has been strongly evaluated.

KEY POINTS

- **In the Americas, the highest incidence of gastric cancer is found the mountain areas of the Pacific Rim.**
- **Gastric cancer has ethnic and geographic variability.**
- **Dietary issues may not play as large a role in the pathogenesis of gastric cancer.**
- **Altitude may be a surrogate for bacterial, dietary, and environmental factors that may predispose to gastric cancer.**
- **Interactions between *H. pylori* serotype and population genetic makeup could explain some of the epidemiological variability for gastric cancer.**

EPIDEMIOLOGY OF GASTRIC CANCER IN CENTRAL AND LATIN AMERICA

A difference in the type of gastric cancers according to socioeconomic status has been noted. As documented in all of the previously mentioned citations, gastric cancers in low-income countries tend to be noncardia, affect the poor more often, and have a male-to-female ratio of 2:1.[3] In contrast, the higher socioeconomic, more educated, and more affluent groups tend to suffer from cardia-based gastric cancer, which presents with a ratio of 5:1 in men to women and 2:1 in white to black individuals.[13] To explain the different pattern of development for gastric cancer in the cardia in the developed countries, other dietary behavioral issues—in particular, obesity and tobacco use—have been suggested.[14] These suggestions carry many concerns. Does the different carcinogenesis pattern develop a different kind of biologic behavior? Does the different pattern of development imply a different pattern of genetic amplification and overexpression that would affect how we treat this condition? Clearly, these are all good questions that, without adequate databases, will be hard to answer. Corral et al[3] observed that, as Hispanic people have migrated to the United States, there has been a slight shift proximal of the site of origin of the malignancy; however, malignancies remain noncardia in origin. Cancers of the antrum in Central America occurred in 73.6%; cancer of the corpus was slightly more common, at 54%, in the U.S. Hispanic population. Thus, there is either a genetic predisposition or a residual epidemiologic drift brought on by cultural and social affinities; it is hard to know which is true.

IMPLICATIONS

This brief review outlines the issues created by the inequities in medical care. Cancer is one of the most common medical conditions across all continents and social strata and should be considered a public health issue. The problem of adequate care is compounded by the multiple other social issues surrounding illness and public health cost that exist, in particular in low-income countries, which results in a lack of information worldwide. Few studies outside the

high-income countries have been done to provide indicators, to identify the magnitude and scope of this problem, and to plan an approach to tackle it. Treatment patterns and outcomes in Latin American countries, in particular in Central America, usually are underreported; any accurate static or information is elusive. Cancer control can be achieved only if we develop a system to acquire relevant data that could be analyzed to allow development of a systematic approach to address this problem across all countries and socioeconomic strata.

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Gastric Cancer in Southern Europe: High-Risk Disease

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OVERVIEW

Gastric cancer is an aggressive disease. Several risk factors are involved in gastric cancer pathogenesis, likely *Helicobacter pylori (H. pylori)* infection, genetic factors in hereditary syndromes, lifestyle, and diet. However, well-implemented screening strategies are lacking in most countries, including those in Southern Europe. Nevertheless, gastric cancer outcomes are better in some Southern European countries than in others, likely because of the incidence and distribution of different histologic types. Robotic surgery has been gaining favor as a treatment of early-stage disease, and the need for perioperative chemotherapy or adjuvant chemoradiotherapy (CRT) for locally advanced disease has been debated. In the metastatic setting, trastuzumab in combination with chemotherapy has helped to extend survival compared with chemotherapy alone for HER2-positive disease. This article will describe how gastric cancer is assessed and treated in Southern Europe in an attempt to correlate these approaches from a global perspective.

Gastric cancer is a very aggressive disease worldwide.[1] Specifically, it is the third most important cause of cancer-related death, and in Southern Europe, it is the sixth most common malignancy. Therefore, Southern Europe is considered a high-risk area for gastric cancer.[1-3] In Europe, the incidence of gastric cancer is not homogeneous, and the risk is low in some areas, such as Central Europe. The mortality rate is 9.7% in men and 4.6% in women.[1] Moreover, some familial syndromes, such as hereditary diffuse gastric cancer syndrome, which is related to the *CDH1* gene mutation, play an important role in the etiology of gastric cancer.[4,5] Furthermore, the incidence of *H. pylori* and genetic factors are responsible for a variety of related diseases and their presentation. Currently, *H. pylori* infection is considered a component of gastric cancer development. In addition, factors related to the improvement of the population's living conditions, a better diet, and improved food preservation may improve the course of the disease.[1,6] Although the incidence of gastric cancer continues to decrease in the United States and Europe, gastric cancer remains an important leading cause of cancer death worldwide.[7] Geographic differences in the disease burden of gastric cancer (highest in Japan, Korea, and regions of Latin America) suggest that environmental and dietary factors play major roles in gastric cancer risk. Histologically, gastric adenocarcinomas are classified as intestinal or diffuse; diffuse-type gastric cancers make up 15% to 10% of cases and are characterized by the submucosal spread of neoplastic signet ring cells. In this article, we discuss how gastric cancer is assessed and treated in Southern Europe in an attempt to correlate these approaches from a global perspective.

RISK FACTORS AND HEREDITARY SYNDROMES

Several genetic and hereditary factors have been identified to interact with gastric cancer pathogenesis. Nevertheless, environmental risk factors have been studied on a population basis because they can be modified to reduce the prevalence of this disease. Although Western Europe is considered an overall low-risk area, gastric cancer is a challenge for oncology health care professionals in Southern Europe, which is considered a high-risk area. However, gastric cancer mortality has been decreasing in recent decades (since 1971).[8] Although most gastric adenocarcinomas are presumed to be sporadic, approximately 5% to 10% arise in individuals with a family history of gastrointestinal cancer, and 3% to 5% of these cases are estimated to be associated with inherited cancer predisposition syndromes.[8] Following the decreases observed since the 1970s in Portugal, further declines in gastric cancer mortality were projected for 2015 and 2020, with an expected number of deaths of approximately 1,400 and 1,300 in men and 900 and 800 in women, respectively, corresponding to crude rates of 28.9/100,000 and 28.2/100,000 in men and 16.9/100,000 and 16.1/100,000 in women, respectively.[7-10] Another important issue is the prevalence of *H. pylori*, which increases with age, from childhood to age 45 to 50 in adults. In addition, the prevalence of *H. pylori* has not exhibited consistent trends in adults and children since the

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1990s. Regarding overall survival (OS), some screening programs implemented in certain areas, such as Korea, may improve survival because of early diagnosis. Nevertheless, survival is higher in Portugal than in Europe overall. This difference is likely because of a higher incidence of tumors with a better prognosis, such as noncardia tumors and intestinal histologic type tumors and not because of generalized screening programs.[7,9,11] Furthermore, efforts to reduce the prevalence of *H. pylori* infection are important because such efforts reduce gastric cancer mortality, as reported in previous studies of developed countries such as the United States and Central Europe.

PATHOLOGY AND MOLECULAR PROFILE

Genetic alterations are closely associated with the development of neoplasia, and the body of evidence identifying molecular factors that affect gastric cancer is continuously growing. Specifically, approximately 140 genes have been identified to drive cancer, a subset of which have been implicated in hereditary cancer syndromes. However, the types and patterns of these mutations are highly variable and heterogeneous within a single entity as well as between different tumor categories. For example, the hyperactivation of the phosphatidylinositol-3 kinase (PI3K)/Akt/mTOR signaling pathway in gastric cancer has frequently been identified to be related to mutations and/or amplifications of the *PIK3CA* gene and a loss of function of PTEN, which play a crucial role in the regulation of this pathway. The PI3K/Akt/mTOR signaling pathway plays an important role in mediating multiple cellular functions including cell growth, proliferation, metabolism, survival, and angiogenesis. In 2014, researchers from The Cancer Genome Atlas (TCGA) research network studied 295 stomach tumors and found that 80% harbor different grades of mutations in the *PIK3CA* gene and amplifications of receptor tyrosine kinase genes, such as *ERBB3*, *ERBB2*, and *EGFR*, which increase the activities of these proteins in gastric cancer.

Akt acts as a central regulator of cell survival by transcriptionally and post-translationally interacting with antiapoptotic signals. In addition, Akt phosphorylates Bad, a member of the BCL2 family of antiapoptotic proteins, at SER136 and Caspase9, a protease, and at SER196, which partially inhibits cell death and supports cell survival signals. Akt also regulates antiapoptotic transcriptional functions by translocating to the nucleus and regulating the transcription of the forkhead box O (FoxO) family of transcription factors. The FoxO family of transcription factors regulates cell death signals by expressing various members of both intrinsic and extrinsic modes of apoptosis as well as cyclin-dependent kinase inhibitors. Upon nuclear translocation, Akt represses the transcription of FoxO1, FoxO3, and FoxO4, thereby enhancing cell survival signals.

In 2014, researchers from TCGA examined 295 stomach tumors and identified subtypes using complex statistical analyses of molecular data obtained from six molecular analysis platforms. Thereafter, they described a new molecular characterization that defines four major genomic subtypes of gastric cancer: positive for Epstein-Barr virus, microsatellite instability, chromosomally instability, and genomic stability. At least three of these subtypes, which includes 80% of the studied gastric cancer cases (Epstein-Barr virus–positive, microsatellite instability, and chromosomally instability subgroups), house different grades of mutations in the *PIK3CA* gene and amplifications of receptor tyrosine kinase genes, such as *ERBB3*, *ERBB2*, and *EGFR*. In a recent Chinese study, the authors suggested that a mutation in the GTPase *RHOA* gene and its oncogenic signaling pathway represent a strong biomarker-driven therapeutic target for Asian gastric cancer. This comprehensive strategy represents a promising approach for the development of hit compounds. *RHOA* is frequently overexpressed in the gastric cancer tumors of Japanese and Chinese patients, whereas gastric cancer datasets from TCGA depository exhibited *RHOA* mutations, not mere overexpression, in diffuse-type gastric cancer tumors. More recent evidence suggests that changes in PHOSPHO2-KLHL23 mRNA expression were the most significant in gastric adenocarcinoma. PHOSPHO2 is important for metabolism and the vitamin B6 metabolism pathway, and KLHL23 is implicated in cone-rod dystrophy and the vitamin B6 metabolism pathway. Ribosomal protein L17 (RPL17), also known as RPL23, is a component of the large 60S ribosome subunit and promotes multidrug resistance in gastric cancer cells by suppressing drug-induced apoptosis. In a Korean study, Choi and colleagues[12] screened read-through transcription events from stomach adenocarcinoma RNA-seq data and selected three candidates, PHOSPHO2-KLHL23, RPL17-C18orf32, and PRR5-ARHGAP8, to assess their biologic role in gastric cancer. They suggested that PHOSPHO2-KLHL23 was the most significantly upregulated transcript in stomach tumor tissues ($p < .0001$), and our investigation revealed that the KLHL23 protein is related to this tumorigenic effect.

One to three percent of all gastric cancers may be considered hereditary diffuse gastric cancer.[13] Furthermore, consistent with the biallelic *CDH1* inactivation and consequent E-cadherin loss of function, E-cadherin protein expression,

KEY POINTS

- **Gastric cancer is a very aggressive disease with a higher incidence in Latin America, Southern Europe, and Asia compared with other areas.**
- **Several genetic and hereditary factors have been identified to interact with gastric cancer pathogenesis.**
- **The eradication of *H. pylori* reduces the incidence of gastric cancer and peptic ulcers as well as the prevalence and cost of managing dyspepsia.**
- **Minimally invasive surgery has been demonstrated to improve the short-term outcomes in selected patients compared with open surgery, especially the rate of perioperative complications.**
- **Irinotecan in combination with 5-FU (FOLFIRI or IF) is an option for the treatment of patients with chemotherapy-naive disease with a poor performance status.**

as assessed by immunohistochemistry, is almost always abnormal in hereditary diffuse gastric cancer, in contrast to the normal complete membranous expression in adjacent normal (nontumoral) epithelium.[3,5,14-16] The E-cadherin gene, *CDH1*, is located on chromosome 16q22.1, and heterozygous germline *CDH1* mutations have been described in 18% to 40% of hereditary diffuse gastric cancer families.[4,17] The 120 kDa glycoprotein encoded by *CDH1* features a large extracellular domain, a transmembrane segment and a short cytoplasmic domain. E-cadherin is a transmembrane calcium-dependent protein that is mainly expressed at the basolateral membrane of epithelial cells, where it plays important roles in cell-cell adhesion at the adherens junctions to maintain epithelial integrity. Furthermore, several other genes are involved in hereditary diffuse gastric cancer predisposition, including *CTNNA1*. Like *CDH1*, *CTNNA1* is involved in intercellular cell adhesion, and *CTNNA1* encodes the protein α-E-catenin, which functions in a complex with β-catenin, where it binds the cytoplasmic domain of E-cadherin to the cytoskeleton.[14,18]

CLINICAL APPROACHES AND TREATMENT

Currently, screening strategies are not well implemented throughout European and Latin American countries. Nevertheless, the eradication of *H. pylori* reduces the incidence of gastric cancer and peptic ulcers as well as the prevalence and cost of managing dyspepsia. Specifically, economic analyses suggest that the eradication of *H. pylori* is cost-effective in controlling gastric cancer for high-risk populations.[19-21] Table 1 summarizes current clinical trials involved in gastric cancer prevention and/or early detection.

In terms of molecular approaches, a single molecular alteration that has been universally accepted as an independent prognostic factor in gastric cancer has not been identified. Instead, many gene expression signatures have been used to classify tumors into intrinsic subtypes and predict the survival of patients with gastric cancer,[22,23] and carriers of germline mutations in different genes associated with cancer predisposition have an increased risk for various tumor types.[24] The identification of germline mutations in families offers the opportunity for early intervention in relatives as yet unaffected by cancer who may be at high risk. Specifically, 25 frequently mutated genes have been identified in gastric adenocarcinoma (e.g., *PIK3CA*, *RHOA*, *ARID1A*, *KRAS*, *MUC6*, *RNF43*, *CNGA4*, *TP53*, *SMAD4*, *CDH1*, *APC*, *MLH1*, *MSH2*, *MSH6*, *STK11*), and these mutations correspond to four tumor subtypes: positive for Epstein-Barr virus, microsatellite stable (hypermutated), genomically stable (predominantly diffuse subtype), and chromosomally instable.[25] However, well-implemented strategies and policies to correlate these data with screening tools to avoid familiar gastric cancer cases are lacking. Furthermore, populations at a low risk for gastric cancer may also benefit from screening and treatment because of the effects on nonmalignant upper gastrointestinal diseases. However, public health authorities have been slow to consider the benefits of population-based screening and treatment as a means of reducing the morbidity and mortality associated with *H. pylori* infection.[21]

Nevertheless, novel techniques are revolutionizing approaches for the treatment of gastric cancer. For example, robot-assisted surgery has recently improved conventional minimally invasive surgery. Specifically, Ceccarelli and colleagues[26] reported an interesting retrospective Italian review of 363 consecutive patients undergoing robot-assisted surgery at an Italian general surgery unit from September 2012 to June 2016. The entire cohort and subgroups that underwent three of the most-performed surgeries (i.e., gastric resections, right colectomy, and liver resections) were analyzed. This analysis suggested that the benefits of minimally invasive surgery compared with open surgery have improved short-term outcomes in selected patients, as evidenced by lower perioperative complication rates and earlier recovery, resulting in an improved quality of life. These benefits were also suggested in elderly populations; the risk of death or morbidity was not increased among elderly patients compared with younger patients in the three groups examined in their retrospective cohort. Thus, their study showed robot-assisted surgery to be a safe and effective technique for the aging patient population, especially for major abdominal cancer surgery.[26]

Early Disease

Endoscopic resection may be suitable for well differentiated, early-stage gastric cancer that is smaller than 2 cm, confined to the mucosa, and is not ulcerated. Intestinal Lauren histology and no evidence of lymphovascular invasion also indicate mucosectomy in the following tumors: intramucosal cancers without ulceration, irrespective of tumor size; ulcerated intramucosal cancers less than 3 cm; or cancers with early invasion into the submucosa measuring less than 3 cm. Endoscopic submucosal dissection has proven more effective than endoscopic mucosal resection but requires greater skill and instrumentation and entails a significant risk for complications, including perforation.[23,27]

For locally advanced disease, complete resection with adequate margins remains the cornerstone of curative treatment. In gastric cancer, the type of resection, subtotal compared with total gastrectomy, depends on the anatomic location of the primary tumor. A total esophagectomy with a partial gastrectomy or an extended gastrectomy is generally performed for esophagogastric junction cancers, but the extent of lymph node dissection remains a subject of controversy. Nevertheless, consensus exists regarding lymphadenectomy: it must include at least 15 lymph nodes, and gastrectomy with D2 lymph node dissection is a recommended procedure.[27]

Neoadjuvant Chemotherapy

The indication for neoadjuvant chemotherapy is also a subject of great interest. According to the European Organisation for Research and Treatment of Cancer trial, which examined 40,954 inpatients with locally advanced gastric cancer, neoadjuvant chemotherapy did not provide a

survival benefit.[28] However, a meta-analysis by Sjoquist and colleagues showed that neoadjuvant chemotherapy provided a significant survival benefit to patients with gastroesophageal cancer (p = .005).[29] Thus, the Spanish Society of Medical Oncology recommends neoadjuvant chemotherapy for patients with stage IB disease.

The POET[30] and CROSS[31] studies assessed the role of neoadjuvant CRT for locally advanced gastric and gastroesophageal carcinoma. The pathologic complete response was significantly higher for patients in the CRT group, but OS did not significantly differ between groups.[30,31] However, the meta-analysis by Sjoquist and colleagues supports an increase in OS for patients who have undergone CRT.[29]

Perioperative Chemotherapy

At many centers in Portugal, Spain, and most European countries, perioperative chemotherapy has been adopted as an interesting option for medically fit patients with resectable locally advanced (cT2 or higher, any N) distal esophageal, esophagogastric junction, or gastric tumors. The British MAGIC trial,[32] the French FNLCC/FFCD 9703 study,[33] and a meta-analysis[34] have shown that perioperative chemotherapy significantly increases R0 rates and survival outcomes without significantly increasing perioperative complications or mortality. Moreover, the approach based on 3-cytotoxic agent combination also exhibits a quite tolerable grade 3 to 4 toxicity rate, however it is not normally used.[34]

Adjuvant Chemoradiotherapy/Chemotherapy

Based on the evidence of the INT-0116 trial and CALGB 80101 study, adjuvant CRT is indicated in patients with stage IB–IV (M0) resected gastric or gastroesophageal junction adenocarcinoma.[35,36] The MacDonald regimen (CRT based on fluorouracil [5-FU]/leucovorin [LV]) improved progression-free survival (PFS; hazard ratio [HR], 1.52; p < .001) and OS (HR, 1.35; p = .005) compared with surgery alone. Furthermore, the CALGB study compared the INT-0116 regimen with epirubicin, cisplatin, and 5-FU (or ECF) before and after 5-FU/radiotherapy in resected gastroesophageal junction or gastric cancer without observing differences in the 3-year OS (52% and 50% for ECF and 5-FU/LV, respectively). The role of adjuvant trastuzumab for patients with HER2-positive disease is still being assessed in the phase II TOXAG trial. Nevertheless, patients with stage II or III gastric cancer submitted to D2-resection significantly benefited from S-1 at 1 year in the ACTS-GC randomized phase III trial (HR, 0.708; 95% CI, 0.510–0.983).[37,38] However, the CLASSIC phase III trial[39] also demonstrated that XELOX (capecitabine, oxaliplatin) significantly (p = .0015) benefited patients with stage II and III disease: the median 5-year PFS was 68% compared with 53%, and the estimated 5-year OS was 78% compared with 69% in the XELOX and the surgery-only groups, respectively.[37-39]

Currently, adjuvant approaches (chemotherapy vs. CRT) are controversial for patients with stage II-III D2 disease after resection. The ARTIST trial is an important study that compared CRT (cisplatin and capecitabine, or XP) with concurrent radiotherapy) with chemotherapy alone (XP every 3 weeks for 6 cycles) in patients with at least D2 lymphadenectomy and R0 resection. The long-term follow-up analysis showed no differences in the outcomes (PFS and OS; p = .527). However, a subgroup analysis showed that CRT significantly improved PFS (p = .04) in patients with node-positive, intestinal-type gastric cancer.[40] Furthermore, the ARTIST II trial is expected to demonstrate the role of S-1 with or without oxaliplatin and radiotherapy. Currently, CRT has a limit role when surgery is D2 quality; and it is commonly reserved for patients with node-positive disease, insufficient lymphadenectomy, or questionable surgery precedence[41].

Metastatic Disease

Advanced gastric cancer is a challenge for oncologists, especially because the clinical status of some patients is too poor to begin chemotherapy. However, chemotherapy is mandatory for patients with a good performance status to improve OS. Specifically, the combination of cisplatin and fluoropyrimidine is the treatment cornerstone for patients with HER2-negative disease. Both CF (cisplatin and 5-FU) and ECF can be considered standard combinations that extend OS in Southern Europe.[16] However, head-to-head studies comparing the efficacy of these treatment modalities are not available. Furthermore, docetaxel, cisplatin, and 5-FU–based chemotherapy is considered a more effective option than CF, but it exhibits a worse toxicity profile.[42] Regarding platinum toxicity and efficacy, some studies demonstrated that oxaliplatin can replace cisplatin because of its improved tolerability.[3,43] Furthermore, trastuzumab in combination with chemotherapy significantly improved OS according to the ToGA trial (p = .0046), and this drug is also being used in Southern Europe in a metastatic setting for patients with HER2-positive disease.[3,44] Conversely, irinotecan combined with 5-FU (FOLFIRI or IF) is an option for patients with chemotherapy-naive disease.[23,45,46] However, less than 60% of patients receive second or later lines of therapy for gastric cancer in clinical practice.[44,47] Therefore, first-line treatment should be maximized for these patients to attain clinical outcomes and quality of life.

Nevertheless, several efforts are being made to develop tolerable drugs for patients with advanced, previously treated gastric cancer, such as antiangiogenic drugs. For example, ramucirumab showed significant efficacy as a monotherapy (REGARD) or in combination with paclitaxel (RAINBOW). Specifically, the REGARD trial randomly assigned 445 patients to ramucirumab or placebo, and ramucirumab produced a significant OS benefit (5.2 vs. 3.8 months; HR, 0.77) over placebo.[48] In addition, the RAINBOW trial randomly assigned 665 patients to ramucirumab plus paclitaxel or paclitaxel plus placebo, and the ramucirumab plus paclitaxel arm showed a significantly superior OS (9.6 vs. 7.3 months; HR, 0.80, p = 0.017) over paclitaxel monotherapy.[49] More recently, apatinib was also shown to be superior to best supportive care in previously treated patients,[47] and an Italian study[50] showed that the combination of irinotecan and 5-FU is a manageable and acceptable regimen. Moreover, third-line

FOLFIRI has been shown to benefit patients with heavily pretreated disease without excessive toxicity. In particular, almost half of patients experienced disease control in their study.[50] Furthermore, immunotherapy acquired an important role in gastric cancer. In January 2017, a randomised phase III study, NCT02267343, indicated that nivolumab (a human monoclonal IgG4 antibody which blocks the human PD-1 receptor) has superior survival ($p < .0001$) when compared to placebo in pretreated patients with advanced gastric cancer.[51] Thus, it also could be considered a promising option for treat these patients in later lines.

FUTURE DIRECTIONS

Gastric cancer is a challenge to health care professionals worldwide, especially in high-risk areas. Moreover, the landscape of gastric cancer is different in Southern Europe and Mediterranean countries than in other Central and Northern European countries. Environmental and genetic factors constitute an important background to understand the disease trajectory, mainly in the diagnosis and screening phases. However, well-implemented screening programs are lacking in these high-risk countries, and most patients consequently present with late-stage gastric cancer at diagnosis. Moreover, the eradication of *H. pylori* infection is important to decrease this manageable risk factor. Currently, novel target drugs and immune-checkpoints inhibitors could be promising options to prolong the outcomes of advanced patients with good quality of life. Further epidemiologic studies are warranted to improve the disease outcomes and implement preventive strategies.

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Deploying Immunotherapy in Pancreatic Cancer: Defining Mechanisms of Response and Resistance

Gregory L. Beatty, MD, PhD, Shabnam Eghbali, and Rebecca Kim

OVERVIEW

The immune reaction to pancreatic ductal adenocarcinoma (PDAC) is a strong prognostic determinant of clinical outcomes and may be a promising therapeutic target. We use multiplex immunohistochemistry to illustrate distinct patterns of T-cell and myeloid cell infiltration seen in PDAC that have therapeutic implications and discuss the current state of immunotherapy in this disease. Based on collective findings from clinical and preclinical studies, two conceptual models have emerged for applying immunotherapy in PDAC that involve (1) restoring elements of T-cell immunosurveillance and (2) redirecting myeloid cells to condition tumors with increased sensitivity to cytotoxic therapies. Overall, the success of immunotherapy in PDAC will most likely rely on strategic combinations of therapies that are informed by well-designed correlative analyses that consider the spatial heterogeneity of immune responses detected in malignant tissues.

Therapeutic resistance to standard cytotoxic therapies (e.g., radiation and chemotherapy) is a hallmark of PDAC, a disease for which the 5-year overall survival rate has remained below 10% for the past two decades despite considerable efforts to improve clinical outcomes.[1] The recent advent of immunotherapy has brought new hope to this disease with the possibility of redirecting the immune system to recognize and eliminate malignant cells. However, PDAC is capable of orchestrating several mechanisms of immune escape that can thwart the therapeutic potential of immunotherapy.[2] Thus, unlike many solid malignancies for which a sizable subset of patients have demonstrated remarkable responsiveness to immunotherapy, PDAC has shown striking resistance. Nonetheless, lessons learned from preclinical models and several clinical trials investigating immunotherapy in PDAC have provided critical insight into strategies to circumvent immune resistance in this disease. This knowledge is now guiding the next generation of immunotherapy in PDAC with an emphasis on rationally designed and novel treatment combinations.

THE IMMUNE REACTION TO PDAC

The tumor microenvironment is a critical determinant of treatment resistance. In PDAC, this microenvironment is commonly marked by a dense fibrotic reaction with recruitment of fibroblasts and leukocytes, which together can impede the efficacy of therapeutics.[3] The leukocyte infiltrate seen in PDAC is complex and heterogeneous. Myeloid cells are the most prominent component of this infiltrate and are associated with a worse prognosis in patients with surgically resected PDAC.[4,5] In contrast, $CD3^+$ T-cell infiltration has been found in some studies to correlate with improved overall survival for at least a subset of patients with resected PDAC.[4,6] Other reports, though, have failed to demonstrate a correlation between T-cell density and overall survival, suggesting that for many patients, the mere presence of T cells may have little clinical significance.[7,8] This is consistent with the notion that the type and location of T cells within tumors is equally as important as their density.[9]

The location of T cells in PDAC may inform resistance mechanisms to productive T-cell immunosurveillance. For example, $CD3^+$ T-cell infiltrates are more prominent in regions of chronic pancreatitis than in PDAC.[7] In addition, $CD3^+$ T cells have been identified more commonly at the invasive front of PDAC with fewer cells detected in the center, suggesting mechanisms of T-cell exclusion orchestrated by malignant cells.[4] Within primary resected PDAC tumors, $CD3^+$ T-cell infiltrates have been found associated with tertiary lymphoid structures which include B cells, dendritic cells, and other immune cell populations.[10,11] Tumor-infiltrating $CD3^+$ T cells also cluster adjacent to nests of malignant cells (Fig. 1A) and are commonly found diffusely scattered and trapped within stromal tissue (Fig. 1B). In contrast, direct interaction between $CD3^+$ T cells and malignant cells is infrequent (Fig. 1C and D). Thus, although $CD3^+$ T-cell infiltrates can be found in the majority (approximately 75%) of resected primary PDAC tumors, they appear to be trapped within the stroma.[10,12]

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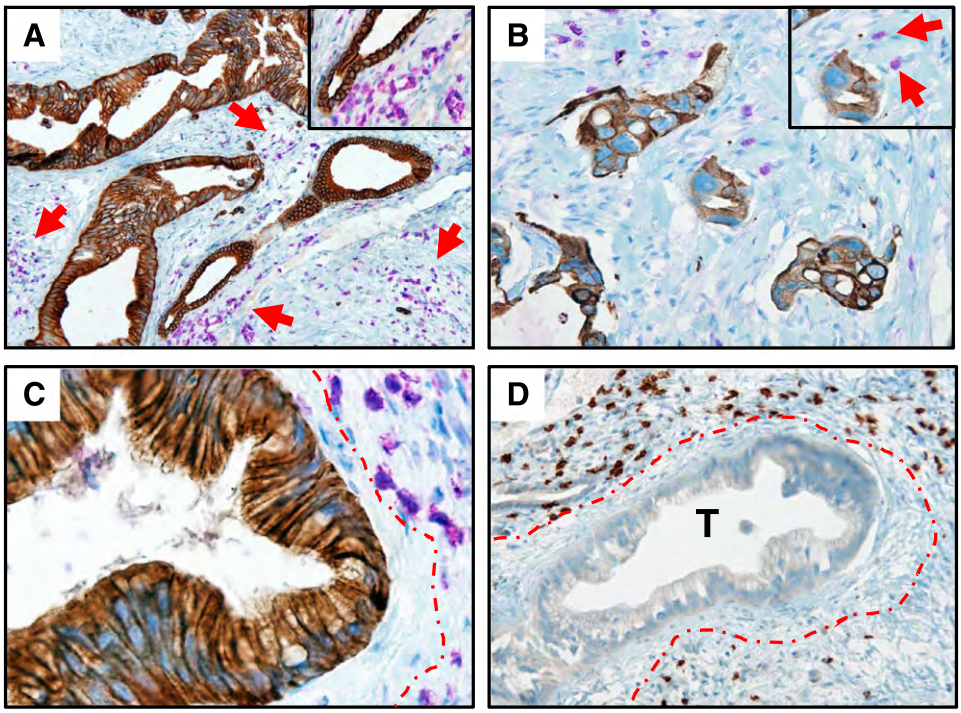
FIGURE 1. Patterns of T-Cell Infiltration in Human PDAC



Shown are representative images of $CD3^+$ T cells (purple) seen clustering (A, red arrows) adjacent to $CK19^+$ tumor cells (shown in brown) and trapped (B, red arrows) in stromal tissue adjacent to $CK19^+$ tumor cells. Insets show higher magnification. $CD3^+$ (C, purple) and $CD8^+$ (D, brown) T cells are seen adjacent to but excluded from interacting with tumor cells. Dotted red line illustrates stromal barrier between T-cell infiltrates and malignant cells. Nuclear staining (light blue) is illustrated by hematoxylin counterstain. Immunohistochemical staining was performed on surgically resected human PDAC specimens using the Ventana Discovery Ultra automated staining system. T, tumor.

The presence of tertiary lymphoid structures in surgically resected PDAC has led to the suggestion that this disease may be more immunogenic than previously appreciated.[10]

KEY POINTS

- **$CD3^+$ T-cell infiltrates are associated with favorable clinical outcomes in pancreatic ductal adenocarcinoma (PDAC), whereas myeloid cell recruitment to tumors portends a poor prognosis.**
- **Multiplex immunohistochemistry can be used to define the quality and quantity of distinct patterns of $CD3^+$ T cell infiltration in PDAC including formation of tertiary lymphoid aggregates, clustering adjacent to tumor cell nests, trapping within stromal tissue, and interaction with malignant cells.**
- **Strategies designed to harness the potential of T cells for the treatment of PDAC may need to address a state of functional paralysis associated with tumor-infiltrating $CD3^+$ T cells.**
- **Clinical experience with immunotherapy and preclinical modeling suggests a need for rationally designed combination treatment strategies that consider elements of immunosuppression imparted by the tumor microenvironment.**
- **Two conceptual models for applying immunotherapy to PDAC have emerged: restoring elements of T-cell immunosurveillance and redirecting the myeloid reaction to PDAC for enhancing the efficacy of cytotoxic therapies.**

These lymphoid structures are detected by immunohistochemistry in most samples analyzed via serial tissue sectioning.[10] Moreover, characterization of the T-cell receptor repertoire in primary PDAC by deep sequencing analysis has found that the majority of the T-cell infiltrate is represented by only a few T-cell clones.[10] However, it is unknown whether these clones are confined to tertiary lymphoid structures or represent true tumor-infiltrating T cells. As T-cell entry into tumors is via the bloodstream and not lymphatics, the antitumor potential of T cells found in tertiary lymphoid structures is uncertain. Indeed, the clonal repertoire of T cells detected in tertiary lymphoid structures, as defined by Vβ T-cell receptor expression, appears to be distinct from T cells detected infiltrating the tumor stroma.[10] As a result, analysis of the immune microenvironment of PDAC using techniques (e.g., RNA and flow cytometry) that do not consider the spatial location of T cells within tumor tissue may overestimate the quality and quantity of the lymphocyte infiltrate in PDAC.[13-15] Nonetheless, despite their unclear role in regulating PDAC biology, tertiary lymphoid structures are associated with a more favorable prognosis in surgically resected PDAC.[16,17]

Expansion of tumor-infiltrating $CD3^+$ T cells isolated from surgically resected PDAC tumors has showed that at least a subset of T cells in PDAC has tumor reactivity.[10,18] However, the frequency of the expanded T cells displaying tumor reactivity is usually low (less than 1%).[10] In addition, within the majority of PDAC specimens (more than 80%), $CD3^+$ T cells show a considerable decrease or loss of CD3zeta chain

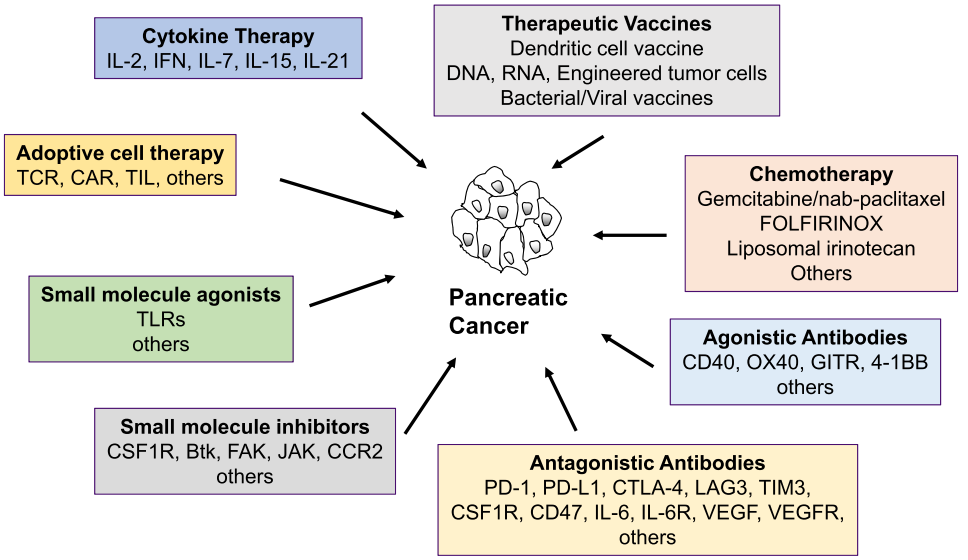
expression, which is required for T-cell receptor signaling and activation.[12] A notable decrease in CD3ζ expression on T cells has also be detected in nearly half (9 of 19) of peritumoral lymph nodes analyzed and is seen in the peripheral blood of patients with metastatic PDAC compared with healthy control subjects.[12,19] Decreased CD3zeta expression correlates with limited T-cell capacity to secrete cytokines, in particular interferon (IFN)-gamma.[19] Moreover, consistent with the notion of poor T-cell activation in PDAC, genomic profiling of human PDAC tumors suggests that despite potentially targetable neoantigens being present in nearly all PDAC samples, albeit at much lower levels than seen in other tumors such as melanoma, T cells detected in tumor tissue lack an activation gene signature.[13] Thus, strategies designed to harness the potential of T cells for the treatment of PDAC must address a state of functional paralysis associated with tumor-infiltrating and circulating $CD3^+$ T cells in this disease.

CLINICAL EXPERIENCE WITH IMMUNOTHERAPY IN PANCREATIC CANCER

The success of immunotherapy is reliant on activating potent and durable T-cell immunity against PDAC. T-cell immunosurveillance is dependent on elements of the cancer immunity cycle that proposes that tumors harbor unique antigens capable of being recognized by T cells and that these antigens, when appropriately presented by antigen-presenting cells, can prime and activate T cells to infiltrate tumors, where they then recognize and eliminate malignant cells.[2,20] Multiple clinical-grade therapeutics are available for bolstering elements of the cancer immunity cycle (Fig. 2). The most extensively evaluated approach in PDAC has involved the use of vaccines (Table 1).

Vaccines can induce T-cell responses against PDAC. In a phase I study, vaccination with GVAX, an irradiated allogeneic whole tumor cell vaccine expressing granulocyte-macrophage colony-stimulating factor (GM-CSF), stimulated delayed-type hypersensitivity responses to autologous tumor cells in a subset of patients and induced the development of mesothelin-specific $CD8^+$ T cells that correlated with improved disease-free survival.[21,44] Based on this finding, GVAX combined with low-dose cyclophosphamide (Cy), as a strategy to deplete regulatory T (Treg) cells, was subsequently tested with or without an attenuated *Listeria*-based mesothelin vaccine (CRS-207) in a prime/boost strategy intended to stimulate and maintain tumor-specific immunity.[24] In this phase II study, Cy plus GVAX followed by CRS-207 compared with GVAX alone was associated with improved overall survival (6.1 vs. 3.9 months) in patients with previously treated metastatic PDAC. Moreover, the development of mesothelin-specific $CD8^+$ T cells in response to treatment was associated with longer overall survival. These promising results led to a phase IIB study comparing Cy/GVAX plus CRS-207 with CRS-207 alone or chemotherapy alone in patients with previously treated PDAC. However, the combination of Cy/GVAX plus CRS-207 produced no survival benefit over chemotherapy alone. Similarly, algenpantucel-L, an irradiated allogeneic tumor cell vaccine expressing murine alpha-1,3-galactosyltransferase, was recently found in a phase III study of patients with resected PDAC to not significantly impact overall survival when combined with standard of care versus standard of care only.[23] A large phase III study evaluating sequential or simultaneous telomerase peptide vaccination in combination with chemotherapy in patients with locally advanced or metastatic PDAC also demonstrated no notable improvement in overall survival with chemoimmunotherapy with a potential trend toward worse outcomes in the sequentially treated group.[35] Limited-efficacy data have also been observed for a range of other tumor-specific peptide-based vaccines despite their capacity to stimulate tumor-specific T-cell immune responses

FIGURE 2. Immunotherapeutic Strategies for the Treatment of PDAC



Multiple therapeutic options with clinical-grade agents capable of restoring distinct elements of the cancer immunity cycle exist for the treatment of PDAC.

TABLE 1. Completed Phase II/III Clinical Trials of Immunotherapy in PDAC

Treatment	Trial Phase	Setting	No. of Patients	ORR, *N* (%)	Median PFS (Months)	Median OS (Months)	Reference
GVAX/CRT	II	Stage I-II res	60	NR	17.3*	24.8	21
Algenpantucel-L + CRT following surgery	II	Stage I-II res	73	NR	14.1*	NR	22
Chemo	III	Stage I-II res	722	NR	NR	30.4	23
Chemo + algenpantucel-L						27.3	
Cy/GVAX + CRS-207	II	Met	90	0	NR	6.1	24
Cy/GVAX						3.9	
Chemo	II	Met	303	NR	NR	4.6	25
CRS-207						5.4	
CRS-207 + Cy/GVAX						3.8	
Postoperative K-ras vaccine	I/II	Res	22	NR	NR	27.5	26
KIF20A/VEGFR1,2/Gem	II	Stage III-IV	68	8 (12.1)	4.7–5.2	9.0–10.0	27
PPV	II	Stage IV	41	0	NR	7.9	28
KIF20A	I/II	UR, met	31	8 (25.8)	1.8	4.7	29
Ras	I/II	UR	5	0	NR	5	30
Ras	II	Stage II-III	5	NR	36+* (PDAC)	47+ (PDAC)	31
Ras + GM-CSF	I/II	Res or LA	48	1 (2)	NR	25.6	32
Gem	II/III	UR or met	159	NR	3.71 (active)	8.36 (active)	33
Gem + VEGFR2					3.75 (placebo)	8.54 (placebo)	
Antisense oligo TGF-β2	I/II	UR	37	1 (2.7)	NR	NR	34
Gem/capecitabine	III	UR LA, met, res	1,062	63 (18)	6.4	7.9	35
+ GV1001 sequential				31 (9)	4.5	6.9	
+ GV1001 concurrent				55 (16)	6.6	8.4	
Anti–CTLA-4 (ipilimumab)	II	LA or met	20	0	NR	~4	36
CIK	II	Met	20	0	2.75	6.65	37
CapCell + ifosfamide	I/II	UR (stage II-IV)	14	4 (28.6)	NR	10.25	38
FU	III	Res	68	NR	11.5*	28.5	39,40
FU + Cis + IFN-α-2b + RT			64		15.2*	26.5	
Surgery	NS	Stage III	41	NR	14.2*	18.8	41
Surgery + chemo			46		21.7*	25	
Surgery + chemo + IL-2			44		27.52*	31.07	
Gem	II	UR	110	(2.9)	2.4	5.6	42
Gem + IMM-101				(10.7)	4.1	6.7	
I(131) KAb201	I/II	UR	19	1 (6)	NR	5.2	43

Abbreviations: CapCell, encapsulated CYP2B1; chemo, chemotherapy; CIK, cytokine-induced killer cells; cis, cisplatin; CRT, chemoradiation therapy; FU, 5-fluorouracil; gem, gemcitabine; I(131) KAb201, radiolabeled anti-CEA antibody; KIF20A, Rab6-binding kinesin-derived peptide; IFN, interferon; IL, interleukin; LA, locally advanced; met, metastatic; NR, not reported; NS, not specified; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PPV, personalized peptide vaccine; res, resected; TGF, transforming growth factor; UR, unresectable.
*Disease-free survival reported.

(Table 1). Together, these data collectively demonstrate the capacity of vaccines to elicit tumor-specific T-cell responses in patients that are in some cases associated with improved clinical outcomes, but suggest the importance of immune resistance mechanisms that regulate the efficacy of T-cell immunosurveillance in this disease.

T-cell effector activity is an exquisitely regulated process that is controlled by a balance of positive and negative signaling pathways. In this regard, immune checkpoint molecules (e.g., CTLA-4 and PD-1/PD-L1) provide negative signals to T cells to limit their expansion and effector activity in tissues.[45] Disruption of these signals using blocking antibodies has demonstrated remarkable success in stimulating antitumor T-cell immunity in a subset of patients across a wide range of malignancies.[46] However, for patients with PDAC, treatment with checkpoint inhibitors against CTLA-4, PD-L1, and Lag-3 has not produced considerable clinical activity.[36,47] Interestingly, *PD-L1* transcriptional expression in PDAC,

unlike other solid malignancies, is correlated with worse disease outcomes in patients with surgically resected PDAC.[48] Nonetheless, emerging evidence suggests that a subset of patients with cancer with mismatch repair (MMR) deficiency may be particularly sensitive to PD-1/PD-L1 blockade.[49] However, while this population may represent as much as 15–20% of PDAC patients,[50-52] it is noteworthy that the predictive value of MMR deficiency, as seen in colorectal cancer, is correlated with an enhanced quality and density of tumor-infiltrating T cells.[49,53] It is currently unclear, though, whether a similar correlation will be observed in PDAC. Thus, ongoing studies are investigating the prospect of PD-1–blocking antibodies for this population. Nonetheless, for the majority of patients with PDAC, exceptional resistance to checkpoint immunotherapy has emerged as a common theme.

The ability of vaccines to modulate the immune microenvironment in PDAC by stimulating the formation and activation of tertiary lymphoid aggregates in tumor tissue has suggested that immune checkpoint inhibitors may enhance the efficacy of vaccines.[11] Combining CTLA-4–blocking antibodies with chemotherapy and vaccines, though, has been largely ineffective in PDAC.[54-56] However, multiple studies are underway that seek to provide further insight into the capacity of vaccines and chemotherapy to combine with immune checkpoint inhibitors as a strategy to convert PDAC from immunoresistant to immunosensitive (Table 2). The ultimate goal is to sequentially restore major elements of the cancer immunity cycle by layering in therapies that can stimulate tumor-specific T-cell expansion, activation, trafficking, and effector activity.

An alternative approach to stimulating tumor-specific T-cell activity in patients is to adoptively transfer tumor-reactive T cells. This approach bypasses the need for in vivo T-cell priming and allows for assessment of downstream mechanisms that may regulate T-cell infiltration and effector activity within tumors.[57] For example, engineering T cells with a chimeric antigen receptor (CAR) that recognizes mesothelin, which is expressed on the surface of malignant cells, can yield potent major histocompatibility complex (MHC)–independent cytolytic activity in vitro against autologous PDAC tumor cells.[58] In PDAC, expression of MHC class I molecules is frequently altered in primary and metastatic lesions with poor infiltration by T cells seen in MHC class I–negative tumors.[8] Thus, CARs offer a unique strategy for overcoming elements of immune escape mediated by downregulation or loss of antigen processing and presentation machinery in tumor cells. CARs combine the protein recognition capacity of antibodies with intracellular stimulatory components of the T-cell receptor to redirect T cells against a tumor-specific target protein.[57] However, clinical benefit with CAR T cells in PDAC has thus far been limited, despite evidence for potential clinical activity.[59] For instance, one patient with metastatic PDAC responded to CAR T-cell therapy with a complete metabolic response in the liver detected on fluorodeoxyglucose-PET/CT imaging, but ultimately succumbed to disease because of progression of their primary pancreatic lesion. Similar mixed clinical responses have been seen in patients with advanced-stage PDAC treated with intravenous infusions of MUC1-specific lymphocytes in combination with intradermal vaccination using MUC1-expressing dendritic cells.[60] The finding of mixed tumor responses seen in these studies implies tumor lesion heterogeneity but also suggests that T cells may be capable of producing, in some cases, remarkable clinical activity.

Chemotherapy alone may also alter the immune microenvironment in PDAC. In patients with surgically resectable disease, preoperative therapy with chemoradiotherapy or chemotherapy has shown the capacity to decrease myeloid cell and Treg infiltrates, leading to an increase in the ratio of CD8 T cells to Treg cells.[15] Similarly, a separate study showed that neoadjuvant chemoradiotherapy can increase T-cell infiltrates, which is a stronger predictor of long-term outcomes than pathologic response to treatment.[61] To enhance the immunostimulatory capacity of chemotherapy, cytokines such as IFN-alpha-2b have been investigated in the adjuvant setting but have not been found to produce noteworthy improvement in clinical outcomes.[39]

The use of molecularly targeted therapies to disrupt signaling pathways may enhance cancer immunogenicity. For example, an early-phase clinical trial has suggested the capacity of MEK inhibitors to uncover therapeutic benefit with PD-L1 checkpoint blockade in patients with MMR-proficient colorectal cancer.[62] The potential immune-enhancing effects of inhibiting the MEK pathway is suggested by preclinical studies showing enhanced expression of cancer differentiation antigens and MHC expression in the setting of MEK inhibition.[63,64] Similarly, in preclinical models of PDAC, MAPK has been found to regulate PD-L1 expression on malignant cells which can inhibit CD8 T cell antitumor activity.[65] In this model system, combining MAPK inhibition with PD-1 blockade produced T-cell–dependent antitumor immunity. Epigenetic modulation may also have a significant role in defining the immunogenicity of cancer cells.[66] To this end, epigenetic modifiers, such as inhibitors of DNA methyltransferase (DNMT) or histone deacetylase (HDAC), have been found to enhance cancer cell immunogenicity through increased MHC expression and in preclinical models, combine with checkpoint immunotherapy to produce increased T cell–dependent antitumor activity.[67] Thus, incorporating molecular targeted therapies to improve cancer cell immunogenicity may be a promising therapeutic avenue for shifting PDAC from immune-resistant to immune-sensitive. Overall, findings from clinical trials investigating immunotherapy in PDAC suggest that many patients, although not all, respond to vaccines by eliciting tumor-specific T-cell responses. However, the productivity of vaccine-induced T cells as well as adoptively transferred T cells has been marginal, and based on histologic analyses of tissues showing discreet patterns of infiltration and activation, attention has turned to the tumor microenvironment as a major determinant and barrier to the efficacy of T-cell immunotherapy in PDAC.

TABLE 2. Immune Targets Under Active Clinical Investigation in Pancreatic Cancer

Target Category	Target	Target Agent (Active Clinical Trials)
Checkpoint molecules	CTLA-4	Tremelimumab (NCT02311361, NCT02639026)
		Ipilimumab (NCT01896869)
	PD-1/PD-L1	Pembrolizumab (NCT02713529, NCT02331251, NCT02305186, NCT01174121)
		MEDI4736 (NCT02311361, NCT02639026, NCT02826486)
		Nivolumab (NCT02451982, NCT02423954)
	B7-H3	Enoblituzumab (NCT02475213)
	B7-H3 × CD3	MGD009 (NCT02628535)
	IDO	Indoximod (NCT02077881)
Myeloid recruitment	CSF-1R	AMG820 (NCT02713529)
	BTK	Ibrutinib (NCT02562898)
	CXCR4	BL-8040 (NCT02826486)
Immune-suppressive molecules	PI3K	INCB050465 (NCT02646748)
	FAK	Defactinib (NCT02546531)
	JAK	INCB039110 (NCT02646748)
Vaccines	Whole tumor cell vaccine	GVAX (NCT02451982, NCT01896869)
	Kras	TG01 (NCT02261714)
	p53	P53MVA (NCT02432963)
	WT1	DSP-7888 (NCT02498665)
	p97	CB-5083 (NCT02243917)
	hTERT	INO-1400 (NCT02960594)
	MUC16	DMCU4064A (NCT02146313)
	VEGFR2	Ramucirumab (NCT02581215)
	CA-125	Oregovomab (NCT01959672)
Immune agonists	CD40	RO7009789 (NCT02588443)
	CD40/4-1BBL oncolytic virus	LOAd703 (NCT02705196)
Adoptive cell therapy	Anti-PSCA CAR	BPX-601 (NCT02744287)
	Anti-mesothelin CAR	NCT01583686
Cytokines	IL-12	INO-9012 (NCT02960594)
	IL-15	ALT-803 (NCT02559674)
	IL-2	Aldesleukin (NCT01174121)
	IL-10	AM0010 (NCT02009449, NCT02923921)
Other	Young TIL	NCT01174121

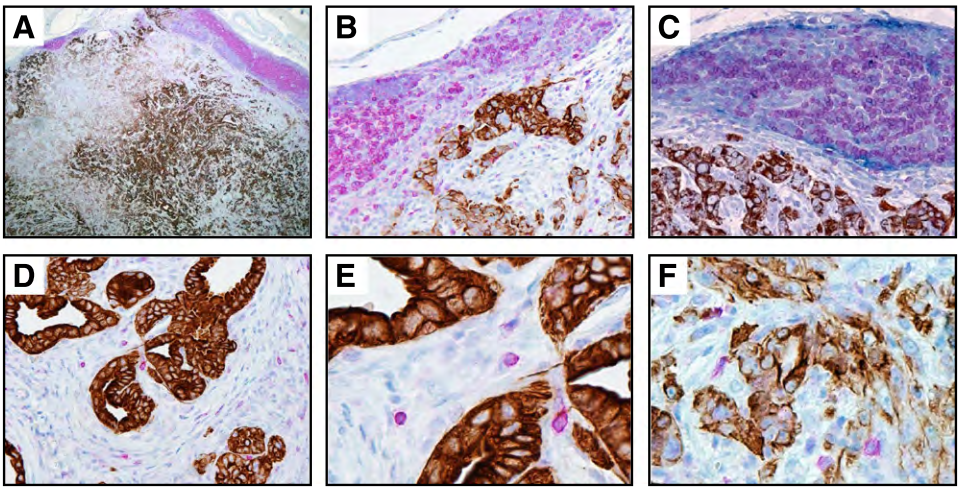
Abbreviations: hTERT, human catalytic reverse transcription subunit of telomerase; IDO, indoleamine 2,3-dioxygenase; LOAd703, oncolytic adenovirus; P53MVA, modified vaccinia virus Ankara vaccine expressing p53; PI3K, phosphatidylinositide 3-kinase; TIL, tumor-infiltrating lymphocyte.

PRECLINICAL MODELING TO GUIDE THE APPLICATION OF IMMUNOTHERAPY IN PDAC

The development of genetic mouse models that recapitulate salient features of human PDAC, including the immune reaction, offer an opportunity to rapidly study the tumor microenvironment, novel therapeutic targets, and combination treatment regimens.[68,69] In these genetic mouse models, similar to human disease, $CD3^+$ T-cell infiltrates can be detected in lymphoid aggregates adjacent to tumors (Fig. 3A) and are sometimes found diffusely scattered within tumor tissue (Fig. 3B), but infrequently seen to interact directly with malignant cells (Fig. 3C). In contrast, myeloid cells are a common component of the immune reaction to both mouse and human PDAC and can be found in close contact with malignant cells (Fig. 4). Moreover, inducing pancreatic inflammation pharmacologically[70-72] or with radiotherapy[73] has been shown to drive pancreatic cancer development and accelerate tumor progression, implying that the myeloid reaction to PDAC can have a protumor role.

Depletion of myeloid cell subsets in genetic mouse models of PDAC has been shown to alter the immune dynamics in tumors with increased $CD3^+$ T-cell infiltration.[74] In addition, pharmacologic inhibition of macrophages has been suggested as a strategy to inhibit metastasis formation.[75] Disrupting myeloid cell recruitment to tumors can also alter tumor sensitivity to cytotoxic therapies. For example, inhibiting

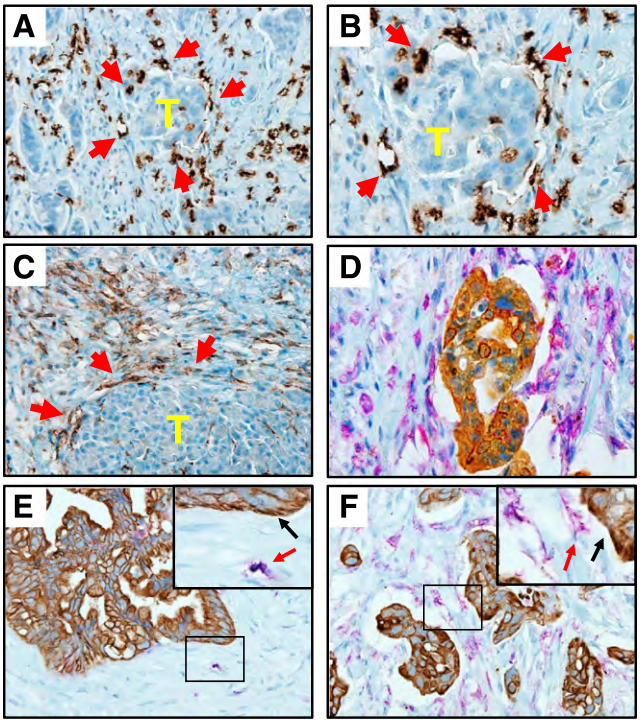
FIGURE 3. Patterns of T-Cell Infiltration in Murine PDAC Tumors



Shown are representative immunohistochemical images showing low-power (A) and high-power (B) magnifications of $CD3^+$ T cells (purple) detected in lymphoid aggregates adjacent to $CK19^+$ PDAC cells (brown). (C) $CD3^+$ T cells (purple) are confined to lymphoid structures demarcated by Lyve-1 (dark blue). Shown are low-power (D) and high-power (E) magnification images of $CD3^+$ T cells (purple) seen trapped in stromal tissue adjacent to $CK19^+$ PDAC cells (brown) and rare direct cell-cell interaction between $CD3^+$ T cells (purple) and malignant $CK19^+$ cells (brown; F). Nuclear staining (light blue) is illustrated by hematoxylin counterstain. Immunohistochemical staining was performed on PDAC specimens obtained from *Kras*$^{G12D/+}$; *Trp53*$^{R172H/+}$; *Pdx-1Cre* mice using the Ventana Discovery Ultra automated staining system.

myeloid cell infiltration by antagonizing the CCL2/CCR2 pathway has been found to increase the efficacy of chemotherapy[76,77] and radiotherapy[78] in mouse models of PDAC. Blockade of macrophage colony-stimulating factor using neutralizing antibodies has also been shown to decrease myeloid accumulation in PDAC and in doing so, enhance the efficacy of radiotherapy.[73] CXC chemokines, involved in the recruitment of neutrophils and immature myeloid cells, are

FIGURE 4. Patterns of Myeloid Cell Infiltration in Human PDAC



Low-power (A) and high-power (B) magnification images showing $CD15^+$ granulocytes (brown) surrounding tumor cells (yellow T). (C) $CD14^+$ macrophages (brown) are seen closely interacting with the periphery of a nest of tumor cells (yellow T). Red arrows indicate cellular localization patterns in A–C. (D) $CD14^+$ macrophages (purple) are seen to encompass $CK19^+$ malignant cells (orange). $CD14^+$ macrophage (purple) recruitment to $CK19^+$ tumor cell structures (brown) is heterogeneous within tumor tissues, with some tumor clusters showing rare single cells excluded from interacting with malignant cells and other tumor clusters (E) showing robust macrophage infiltration and close interaction with PDAC cells (F). The black arrows in E and F mark tumor cells, and the red arrows mark macrophages to illustrate the distance separating macrophages and tumors in each image. Nuclear staining (light blue) was detected by hematoxylin counterstain. Immunohistochemical staining was performed on surgically resected human PDAC specimens using the Ventana Discovery Ultra automated staining system.

also detected at increased levels in both mouse and human PDAC. Chemokine (C-X-C motif) receptor (CXCR) 2–dependent recruitment of neutrophils and myeloid cell progenitors has been found to limit the efficacy of cytotoxic chemotherapy and immune checkpoint inhibition with PD-1–blocking antibodies in mouse models of PDAC.[79] Promising early phase clinical results investigating small-molecule inhibitors of CCR2 in patients with both borderline resectable/locally advanced[80] and unresectable[81] disease support a role for inhibiting myeloid cell recruitment to tumor tissues for improving the efficacy of cytotoxics in PDAC.

Although blocking myeloid recruitment to tumors is one strategy for shifting the immune reaction in PDAC from tumor-promoting to tumor-inhibitory, the biology of myeloid cells is inherently pliable such that under the appropriate conditions, they can also acquire antitumor properties.[82] This biology creates an opportunity to leverage myeloid cell recruitment to tumors for potential therapeutic benefit. For example, CD40 agonists have been found to impart antitumor and antifibrotic properties on tumor-infiltrating myeloid cells in vivo.[83,84] This myeloid-dependent antifibrotic activity induced by CD40 agonists can shift PDAC tumors from resistant to chemotherapy to sensitive to chemotherapy, thereby implying a potential role for immunotherapy in enhancing the efficacy of cytotoxic therapies.

CD40 agonists are best appreciated for their capacity to license antigen-presenting cells with T-cell stimulatory properties.[85] In mouse models of spontaneously arising PDAC, CD40 agonists can reverse functional T-cell paralysis detected in lymphoid structures adjacent to tumor tissue.[83] However, the capacity of CD40 agonists to restore productive T-cell immunosurveillance is exquisitely regulated by macrophages residing outside of the tumor microenvironment.[86] This finding implies that strategies to reverse elements of immune suppression imposed by myeloid cells may be critical to the success of T-cell immunotherapy.

Inhibition of myeloid cell activation through targeting of Bruton's tyrosine kinase (BTK) has been found to inhibit tumor progression.[87] Moreover, combining BTK inhibition with chemotherapy produces T-cell–dependent tumor regressions in an orthotopic model of PDAC.[87] T-cell–dependent antitumor activity can also be induced in orthotopic models when chemotherapy is combined with inhibitors of CCR2, CSF1R, and CXCR2, which all limit myeloid accumulation in tumors.[73,77,79] These findings suggest that redirecting or disrupting the myeloid reaction in tumors may be a cardinal feature for the success of T-cell immunotherapy in PDAC.

The inflammatory reaction that surrounds PDAC is likely directed, at least in part, by tumor cell-intrinsic signaling pathways. For example, Kras activation can drive the release of factors (e.g., interleukin [IL]-8 and GM-CSF) that induce the recruitment and accumulation of myeloid cells in tumor tissue.[88,89] In addition, hyperactivation of focal adhesion kinase (FAK) activity in malignant cells has been found to stimulate the release of chemoattractants involved in myeloid cell recruitment.[90] Disruption of FAK signaling genetically or pharmacologically delays tumor progression, reduces fibrosis, and decreases myeloid cell accumulation in mouse models of PDAC. In patients with resected PDAC, FAK activity has been associated with decreased $CD8^+$ T-cell infiltration.[90] Moreover, FAK inhibition can enhance the efficacy of both chemotherapy and PD-1 antagonists in mice with spontaneously arising PDAC tumors.[90]

Overall, genetic mouse models have suggested that the tumor microenvironment is a key determinant of T-cell efficacy in PDAC. However, whether the microenvironment acts as a physical barrier to T-cell infiltration is less clear. Adoptive transfer studies in a genetic mouse model of PDAC has shown that tumor-reactive T cells can effectively penetrate the fibrotic matrix that surrounds malignant cells.[91] However, the functional capacity of tumor-infiltrating T cells is fleeting and associated with upregulation of multiple negative regulatory molecules.[91] In essence, tumor-infiltrating T cells may ultimately become trapped in the stromal compartment, as is also seen in human disease.[12] Elements of the stroma, including fibroblasts, have been implicated in this active sequestration of T cells away from malignant cells through secretion of chemokines including CXCL12.[92,93] Inhibiting the interaction of CXCL12 with its receptor, CXCR4, which can be found on T cells among many other cell types including myeloid cells, has shown potential to restore T-cell infiltration and, in doing so, uncover therapeutic activity with immune checkpoint inhibitors including CTLA-4 and PD-L1–blocking antibodies.[92] Thus, elements of the tumor microenvironment including fibroblasts and myeloid cells possess properties capable of inhibiting the efficacy of immunotherapy in PDAC.

STRATEGICALLY APPLYING IMMUNOTHERAPY TO PDAC

Unlike other malignancies in which monotherapy with immune checkpoint inhibitors can produce extraordinary activity in some patients, PDAC is a disease that has demonstrated remarkable immunologic resistance. Applying immunotherapy to PDAC will undoubtedly require strategically designed combinations of therapies. Genetic mouse models of PDAC have been strongly predictive of immunotherapy outcomes and thus can offer a high-throughput platform for the study of treatment combinations.[69] From clinical and preclinical studies, two conceptual models for applying immunotherapy in PDAC have emerged: (1) restoring elements of the cancer immunity cycle to stimulate productive T-cell immunosurveillance and (2) redirecting the immune reaction to PDAC for enhancing the efficacy of cytotoxic therapies. Although strategies capable of invoking T-cell immunity are critical for treatment response durability, leveraging the immune microenvironment in PDAC to improve outcomes with cytotoxic chemotherapy and radiotherapy may be particularly relevant for tumor debulking.[85]

Effective T-cell immunity in PDAC will likely require a multipronged approach that involves (1) conditioning the tumor microenvironment by reversing elements of immunosuppression and therapeutic resistance, (2) activation of tumor-specific T-cell responses using vaccines, targeted

therapy, chemotherapy, radiotherapy, or transfer of T-cell immunity, and (3) maintenance therapy to sustain T-cell effector activity and counteract negative regulatory signals encountered within tumors. Well-designed correlative analyses applied to early phase clinical trials that incorporate tissue analysis using genomic and proteomic assays (e.g., multiplex immunohistochemistry) that consider the spatial heterogeneity of tumors will be fundamental to rapidly learning from each patient treated and interpreting treatment responses and failures based on expected biologic activity.

Given considerable heterogeneity seen in the immune microenvironment in PDAC, it is also likely that immunotherapy must ultimately be personalized. One approach to this is actively being explored and involves applying genetic determinants (e.g., MMR deficiency and BRCA1/2 mutations) to identifying patient subgroups that may be more likely to respond to a particular immunotherapeutic strategy. For example, MMR deficiency has been suggested from clinical studies to be a potential biomarker for clinical activity with PD-1 antagonists.[49] Similarly, in mouse models of BRCA mutant PDAC, IL-6–neutralizing antibodies enhance the efficacy of PD-L1 antagonists.[94]

The application of immunotherapy to PDAC has been associated with mixed clinical responses. This has been seen with adoptive cell therapy using CAR T cells as well as MUC-1–specific lymphocytes.[59,60] In addition, CD40 agonists administered in combination with chemotherapy have produced heterogeneous treatment responses in individual lesions detected within the same patient.[95] Together, these findings suggest that tumor heterogeneity could emerge as a major challenge to the success of immunotherapy in PDAC.

In conclusion, immunotherapy is a novel treatment approach to PDAC that leverages the specificity and diversity of the immune system for cancer therapy. Multiple clinical trials evaluating immunotherapy in PDAC are ongoing (Table 2). However, PDAC has repeatedly triumphed over novel therapeutic strategies in the past. Thus, for immunotherapy to be different and successful in this disease, it must be applied strategically and guided by rigorous "bedside-to-bench and back" research.

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Gastric Cancer in Asia: Unique Features and Management

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OVERVIEW

Gastric cancer (GC) poses a burden to patients across the globe as the third leading cause of cancer deaths worldwide. Incidence of GC is particularly high in Asian countries, which is attributed to the prevalence of *Helicobacter pylori* (*H. pylori*) infection and has prompted the establishment of unique treatment strategies. D2 gastrectomy, which was established in the 1950s in Japan, has served as a gold standard for locally advanced GC for over half a century. Since the beginning of the 21st century, endoscopic resection (ER) techniques and minimally invasive laparoscopic surgery have greatly changed the treatment of patients with early GC. S-1, which showed a striking survival benefit in a large randomized trial in Japan, has been used as adjuvant therapy for the last decade. Likewise, S-1–based chemotherapy regimens are currently the standard of care for the treatment of unresectable/metastatic GC in Asia. Along with the development of standardized therapy, novel techniques and new drugs have been rapidly brought into clinical practice. State-of-the-art sentinel node (SN) navigation surgery enables clinicians to perform truly minimally invasive surgery for early GC, and appropriate chemotherapy regimens are now determined by a tumor's molecular expression. New classifications based on gene signatures are proposed and may replace conventional clinical classifications. Such highly individualized treatment has the potential to alter our clinical practice in GC in the near future. The best practice in each geographic region should be shared and integrated, resulting in the best practice without borders.

GC is the fifth most common cancer worldwide with 952,000 new patients diagnosed in 2012, and the third leading cause of cancer deaths in both men and women.[1] Geographic distribution of incidence and mortality of GC is known to be disproportionate, namely it is particularly high in Asian countries and low in the Western hemisphere. This uneven distribution has been closely correlated with the prevalence of *H. pylori* infection, which is undoubtedly the primary cause of noncardia GC (Fig. 1).[2-4] GC has therefore been one of the leading causes of cancer mortality in Asia.

In Japan, as well as other high-risk areas, the infection rate of *H. pylori* was very high a hundred years ago with an estimated prevalence of 80% in people born in the 1900s; however, the prevalence has gradually declined and no more than 10% of people born in the 2000s harbor *H. pylori*.[5] This fact is well associated with the trend of incidence and mortality of GC in Japan. At that time, because surgical resection of the stomach was the only treatment of GC, Japanese surgeons struggled to determine how to manage this intractable cancer that presented with extensive lymph node metastasis and systemic dissemination. They finally devised two approaches: one approach was the elucidation of lymphatics around the stomach followed by the establishment of classification of GC, and the other approach was implementation of a screening program for GC.

Meticulous analysis of gastric lymphatics was initially studied by Inoue et al in 1936. Based on the study, Tamaki Kajitani and other Japanese gastric surgeons established systematic lymph node dissection of the stomach in the 1950s, namely today's D2 lymphadenectomy. The fundamental concept of D2 gastrectomy was resection of the primary tumor with whole dissection of the lymphatic system around the stomach, which was most likely to involve not only macroscopic (visible) but also microscopic (invisible) nodal metastases. Gastrectomy with adequate lymphadenectomy was reasonable in light of cancer surgery and thus has been widely accepted by Japanese surgeons. Careful, organized findings about GC was exhaustively collected and finally published in the first edition of the *Japanese Classification of Gastric Carcinoma* in 1964. Surgical resection has been the predominant treatment of GC thereafter.

In contrast, a major problem was that the cancer was already advanced and metastatic when many patients presented with their symptoms. Thus, it was crucial to find cancer at an early stage to achieve cure. Toshio Kurokawa et al first performed a mass screening program for GC in

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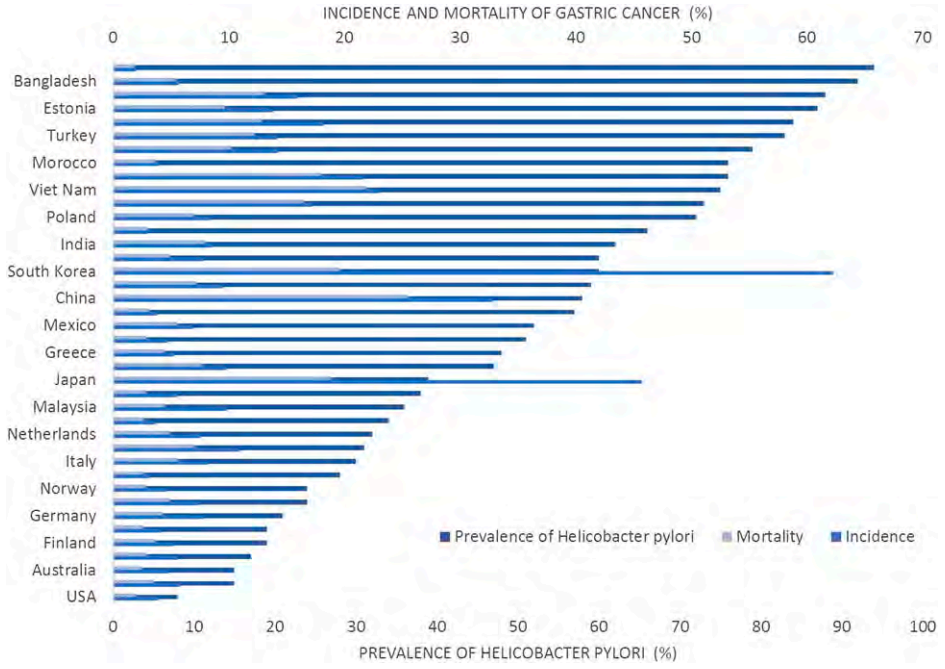
FIGURE 1. Prevalence of *Helicobacter pylori* Infection by Country Along With the Incidence and Mortality of Gastric Cancer



the 1950s "with the intention of early discovery and prevention of cancer through the diagnosis of people who felt they were perfectly healthy."[6] His tremendous effort also led to the development of diagnostic tools and techniques used today, represented by endoscopy and double-contrast barium radiography. Owing to the screening program, over half of GCs were detected at an early stage in the early 1980s, whereas less than 5% were detected before 1955. Although the question whether mass screening programs for GC can ultimately reduce mortality of GC is still open to debate,[7] it is no longer in doubt that such a program detects a large number of early GCs that are curable.

These unique features have greatly influenced the management of GC in Asian countries, particularly in Japan. Nowadays, much evidence comes from Western countries where evidence-based medicine has been widely accepted for many years. Guidelines and clinical practices in Asian countries, for example in breast cancer and colorectal cancer, depend much on external evidence from the West. In contrast, by taking advantage of the large numbers of patients with GC, we have developed best practices not by extrapolating external evidence, but by establishing our own evidence. In this review, we outline how the management of GC has been established, by tracing back the history of GC treatment in Japan and then discuss whether in future we should follow our own path as done so far, or should collaborate with other countries in the West to establish common evidence.

KEY POINTS

- **As a result of the large numbers of patients with GC in Asia, we have established our own evidence-based best practices.**
- **The sentinel node concept was demonstrated to be applicable in certain early GCs, enabling highly individualized sentinel node navigation surgery.**
- **Conventional D2 gastrectomy followed by adjuvant chemotherapy using S-1 or capecitabin plus oxaliplatin serves as a gold standard for locally advanced GC in Asia.**
- **S-1 is one of the key drugs used in the Asian population and S-1–based chemotherapy regimens currently achieve the best survival in unresectable/metastatic GC.**
- **In the new era of precision medicine, the best treatment strategy is determined by a tumor's molecular expression and gene signatures including Epstein-Barr virus status, microsatellite and/or chromosomal instability, genomic stability, epithelial mesenchymal transition, p53 activity, cytokine signaling, cell proliferation, and DNA methylation.**

SURGICAL MANAGEMENT OF EARLY GC: TRULY MINIMALLY INVASIVE SURGICAL THERAPY

The high incidence of early-stage GC in Japan has had considerable influence on its surgical management, and has resulted in the development of endoscopic treatment and minimally invasive surgery. ER was first reported by Tsuneoka et al in 1969, which has since become the standard of care for early GCs in which the risk of lymph node involvement is most likely to be zero.[8,9]

Early cancers that are not eligible for endoscopic therapy are primarily treated by surgical resection of the stomach with D1+/D2 lymphadenectomy, as is performed for

patients with locally-advanced GC, because there is a high risk (approximately 15%) of lymph node metastasis.[10,11] Open gastrectomy was the standard of care until a decade ago; however, since 1991, when laparoscopic gastrectomy as minimally-invasive surgery for patients with gastric cancer was first performed by Seigo Kitano et al, laparoscopic surgery has become popular worldwide. The Japan Clinical Oncology Group (JCOG) is now conducting a large, randomized phase III trial comparing laparoscopic gastrectomy with conventional open gastrectomy in patients with early GC (JCOG0912), and short-term outcomes showed the safety of the procedure in line with the result from a large phase III trial in Korea (KLASS-01).[10,11] Although many randomized, controlled trials of laparoscopic gastrectomy for early GC have demonstrated surgical and oncologic noninferiority, only a limited study provided evidence of its superiority over conventional surgery. This is in part because the procedure in the abdomen is more or less the same between open and laparoscopic surgery (i.e., gastrectomy with lymphadenectomy).[12] Therefore, how to avoid gastrectomy without compromising radicality, which is truly minimally invasive, is one of the long-standing issues surgeons have attempted to solve for decades.

SN biopsy was first introduced by Cabanas et al in penile carcinoma in 1977, and also dramatically altered the surgical and oncologic management of breast cancer.[13] If nodal status can be pathologically confirmed prior to gastrectomy, radical lymphadenectomy would not be necessary for patients without lymph node involvement, which accounts for up to 90% of all early GCs. Hence, if the SN concept can be applied to the gastric lymphatic drainage, which is relatively complicated, it would be possible to mitigate the burden of gastrectomy.[14] To evaluate whether the SN theory can be applied to GC, a large, prospective, multicenter phase II study was implemented by the Japan Society of SN navigation surgery, in which a standardized protocol and technique with an endoscopic dual tracer injection method were used.[15] A total of 397 patients with cT1/T2 gastric adenocarcinoma smaller than 4 cm were analyzed, and the SN detection rate was 97.5% and the overall accuracy of nodal evaluation for metastasis was 99.0% with only four false-negative cases (1.0%). The study confirmed that the SN theory can be applied to the complicated gastric lymphatic drainage and a large phase III study is currently being conducted in which long-term oncologic safety and quality of life will be evaluated.

D2 gastrectomy alone has been the standard of care for early GCs as well as locally advanced cancers. According to the SN study, 96% of metastatic nodes reside within the D2 area, which indicates the need for the radical and complete technique of D2 gastrectomy. However, D2 gastrectomy might be overtreatment for patients who are at very low risk of lymph node metastasis. Gastric surgeons have long confronted this dilemma, that it is hard to please everybody. Hence, SN navigation surgery can help individualize surgical treatment, thereby appropriately providing radical and less-invasive procedures for patients with early GC.

On the basis of the SN theory, a new rendezvous-style surgical procedure using endoscopy and laparoscopy was developed for early GC. The concept of the procedure, which is called laparoscopy-endoscopy cooperative surgery (LECS), was originally developed for submucosal tumors of the gastrointestinal tract and various modified methods have been currently proposed.[16] Nonexposed endoscopic wall–inversion surgery is one of the modified procedures, in which a full-thickness gastric wall resection can be achieved in a closed manner.[17] By combining nonexposed endoscopic wall–inversion surgery with SN navigation, Goto et al reported the first case of stomach-preserving surgery in a 55-year-old female patient with 2-cm diffuse-type early GC that was not eligible for ER.[18] (Fig. 2)

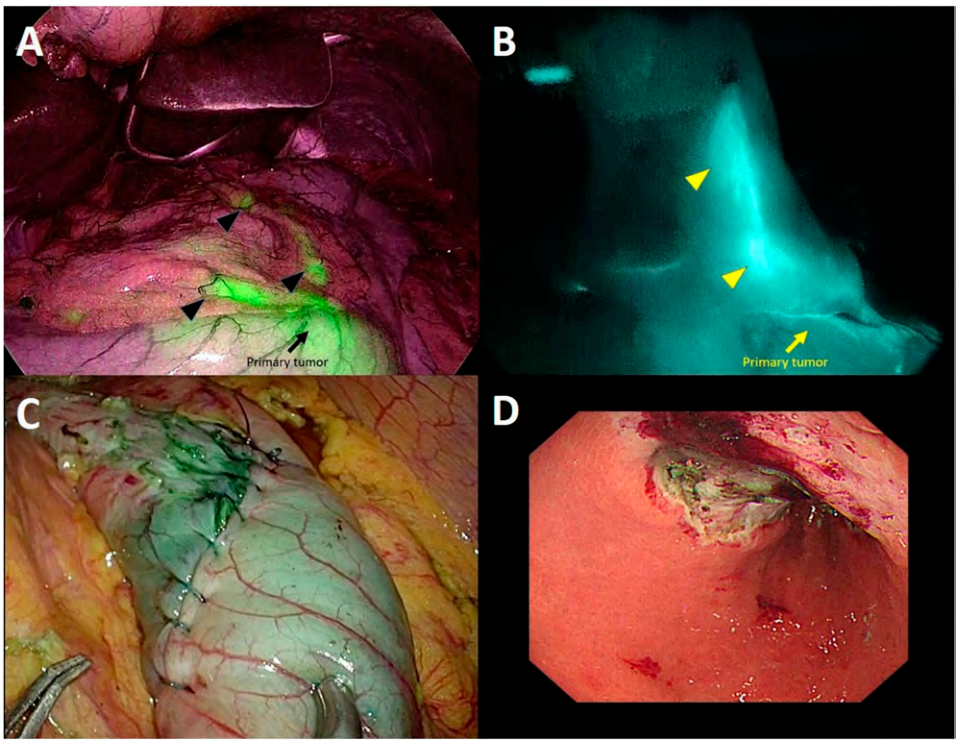
Although this minimally invasive technique is just being developed and thus needs to be carefully evaluated, it has great potential to change the role of gastrectomy for early GC, which has served as a gold standard for decades.

TREATMENT STRATEGY FOR LOCALLY ADVANCED GC: PERIOPERATIVE TREATMENT

Since Kajitani et al established D2 gastrectomy alone as the standard of care for locally advanced GC for many years until S-1 (an orally-administered combination drug of tegafur and gimeracil plus oteracil) was introduced as adjuvant therapy in 2006. In the late 1990s, results from two randomized trials from Holland (Dutch trial) and the United Kingdom (MRC trial) comparing D2 with D1 were published, in which D2 gastrectomy yielded no survival benefit and showed more postoperative complications and high mortality.[19,20] However, Japanese surgeons did not accept high morbidity and in-hospital death rates in the D2 group as sufficient reason to change their management practices, and D2 gastrectomy remained the standard of care in Japan. Results of a 15-year follow-up analysis of the Dutch trial were published in 2010, which demonstrated advantages of D2 gastrectomy in terms of locoregional recurrence (22% in D1 vs. 12% in D2) and GC-related death (48% in D1 vs. 37% in D2; hazard ratio [HR] 0.74; 95% CI, 0.59–0.93; p = .01), although there were no significant differences in disease-free survival (p = .31) or risk of recurrence (p = .10).[21] Based on these results, and that it is currently performed safely in Western high-volume centers, D2 gastrectomy is currently recommended for medically-fit patients in the guideline of the National Comprehensive Cancer Network and European Society of Medical Oncology.[22,23]

Five large, randomized, controlled trials were conducted in Japan by JCOG to evaluate the survival benefit of extended lymphadenectomy and surgical procedure because there had been much discussion among Japanese surgeons about the optimal extent of lymphadenectomy (Table 1).[24-27] JCOG9501, the first big surgical randomized trial that evaluated survival benefit of prophylactic paraaortic lymph node dissection, demonstrated a negative result. The results between the two groups were strikingly similar for 5-year overall survival (OS; 69.2% for D2 and 70.3% for extended D2; HR 1.03; 95% CI, 0.77–1.37) and other relevant outcomes.[24] The

FIGURE 2. Sentinel Node Navigation Surgery for Early Gastric Cancer in Combination With Nonexposed Endoscopic Wall-Invasion Surgery



(A) Fluorescence image after indocyanine green was injected around the primary tumor. (B) Visualization of indocyanine green through infrared camera. (C) Circumferential seromuscular incision followed by linear suturing. (D) Endoscopic removal of the primary lesion.

second trial tested noninferiority of spleen-preservation during gastrectomy in patients with locally-advanced cancer that was not located in the greater curvature (JCOG0110).[26] Because standard D2 total gastrectomy had included the nodal station 10 (splenic hilar nodes), splenectomy was necessary to complete D2 dissection. The study demonstrated noninferiority of spleen preservation in regards to 5-year OS (75.1% for splenectomy and 76.4% for spleen preservation; HR 1.21; 90.7% CI, 0.67–1.16 with noninferiority margin 1.21; p = .025), having altered the definition of D2 since January 2017. The third study, JCOG1001, started in 2010 and compared bursectomy with nonbursectomy in patients with cT3/T4 GC. As a result, pancreatic fistula was twofold more likely to occur in the bursectomy group, whereas bursectomy failed to provide significant 5-year OS benefit (HR 1.07; 95% CI, 0.81–1.42; one-sided p = .68), and the data monitoring committee recommended early publication after all patients completed recruitment as planned.[27] None of the trials showed a benefit of extended surgery, and conventional D2 gastrectomy without splenectomy and bursectomy is currently recognized as the standard procedure for locally-advanced cancer. Therefore, perioperative treatments should have promising potential to improve survival in patients with locally advanced GC.

Although surgery was regarded as the most effective treatment, the importance of perioperative therapy was also recognized; however, there was no evidence to support this. The first large, randomized phase III trial by JCOG commenced in 1988 in which surgery plus adjuvant mitomycin C (MMC) and 5-fluorouracil (5-FU) followed by tegafur demonstrated no survival benefit compared with surgery alone in patients with serosa-negative GC (Table 2).[29] Importantly, T1 cancer accounted for 32.8% of all tumors in this study, suggesting that surgery alone for T1 cancer yielded good survival without need for any adjuvant therapy. Other JCOG studies compared curative surgery alone with MMC, 5-FU, cytosine arabinoside followed by oral 5-FU in serosa-negative GC (JCOG9206-1),[30] and intraperitoneal and intravenous cisplatin followed by oral 5-FU in serosa-positive GC (JCOG9206-2).[31] However, both trials yielded negative results, failing to show the advantage of adjuvant chemotherapy.

In 1984, an oral tegafur/uracil drug named UFT was developed in Japan and has become commercially available. Taking advantage of this "homemade" drug, a national randomized trial comparing surgery alone with surgery plus adjuvant UFT was conducted (*N*-SAS-GC).[32] The patient accrual was slow and only 190 patients (38% of initially-planned) were finally included in the study. The result was favorable for the adjuvant therapy group; however, the 5-year recurrence-free survival rate was relatively poor, calling for a replication of the study to validate the result.

Meanwhile, another homemade agent named S-1 was developed and launched in 1999. S-1, commercially available as TS-1 in Asia and Teysuno in Europe, is an orally bioavailable fluoropyrimidine antagonist consisting of tegafur

TABLE 1. Practice-Changing Randomized Phase III Trials in Gastric Cancer Surgery in Asia

Ref	Recruit Time	Country	Trial	Registry	No. of Patients	Target	Arms	Primary Endpoint	Result	HR (95% CI)	p Value
24	1995–2001	JP	JCOG9501	NCT00149279	523	T2-4	D2 gastrectomy	OS	5-year OS: 69.2%	1.03 (0.77–1.37)	.85
							vs. D2/PAND gastrectomy		vs. 70.3%		
25	1995–2003	JP	JCOG9502	NCT00149266	167	T2-4	Transhiatal approach	OS	5-year OS: 52.3%	1.36 (0.89–2.08)	.92
							vs. left transthoracic approach		vs. 37.9%		
26	2002–2009	JP	JCOG0110	NCT00147147	505	T2-4/ N0-2	Splenectomy	OS	5-year OS: 75%	0.88 (0.67–1.16)*	.025
							vs. spleen-preservation		vs. 76.4%		
27	2010–2015	JP	JCOG1001	NCT00152243	1,204	T2-4	Nonbursectomy	OS	3-year OS: 86%	1.07 (0.81–1.42)	.68
							vs. bursectomy		vs. 83.3%		
28	2008–2013	JP, KR, SIN	JCOG0705/ KGCA01 (REGATTA)	NCT03001726	175	Stage IV	Chemotherapy alone	OS	median OS 16.6	1.09 (0.78–1.52)	.70
							vs. gastrectomy, chemotherapy		vs. 14.3 months		

*Noninferiority margin < 1.21.

Abbreviations: HR; hazard ratio; CI, confidence interval; JP, Japan; PAND; para-aortic node dissection; OS, overall survival; KR; Korea; Ref, reference; SIN, Singapore.

with two modulators of 5-FU activity, 5-chloro-2,4-dihydroxypyridine and potassium oxonate in a molar ratio of 1:0.4:1.[36] The landmark phase III ACTS-GC trial was initiated in 2002, comparing D2 gastrectomy alone with surgery plus S-1 for 1 year in patients with pathologic stage II/III GC.[33] The result was remarkable; adjuvant S-1 yielded a 32% reduction of risk for 3-year OS (80.1% for S-1 vs. 70.1% for surgery alone; HR 0.68; 95% CI, 0.52–0.87; p = .003). These results dramatically changed clinical practice in Japan, where surgery had been believed to be the only effective treatment of locally advanced GC. After these findings, the majority of chemotherapy regimens have been developed in combination with S-1.

Another adjuvant study was started in 2006 in three Asian countries, South Korea, China, and Taiwan, which aimed to seek an optimal adjuvant regimen after curative D2 gastrectomy. This study was abbreviated as the CLASSIC trial, and compared surgery alone with capecitabine plus oxaliplatin (CapeOX) as adjuvant therapy.[35,37] This study was stopped in accordance with the recommendation by the data monitoring committee for reasons of benefit, unveiling the efficacy of CapeOX with a 3-year disease-free survival HR of 0.56 (95% CI, 0.44–0.72; p < .0001).

Efficacy of adjuvant chemoradiation therapy was first demonstrated by the INT0116 study in the United States.[38] However, because surgery alone has been deemed to offer good local control, radiation therapy, which also provides local control, has not become common in Japan. Most clinical trials from Japan comprise of chemotherapy alone without radiation. For that reason, adjuvant chemoradiation therapy in an Asian population was first evaluated in South Korea. This randomized phase III trial (ARTIST trial) compared adjuvant capecitabine and cisplatin (XP) with XP plus concurrent capecitabine radiotherapy (XRT) after curative D2 gastrectomy.[34,39] No additional benefit with radiation was observed in both 5-year OS (HR 1.130; 95% CI, 0.775–1.647; p = .527) and disease-free survival (HR 0.710; 95% CI, 0.520–1.050; p = .922), although the XP group showed significantly more local recurrence (XP 13% vs. XRT 7%; p = .033). However, subgroup analyses suggested some benefit for patients with positive lymph node involvement (HR 0.700; 95% CI, 0.493–0.994), motivating them to start another study (ARTIST-2 trial) in which three arms of chemotherapy or chemoradiation regimens will be compared: adjuvant S-1 and oxaliplatin (SOX) plus radiation (45 Gy) and two chemotherapy regimens (S-1 alone for 1 year and SOX for 6 months) for patients with node-positive disease after curative D2 gastrectomy.

Adjuvant S-1 has become the standard of care since 2006 when the results of the ACTS-GC trial was unveiled. The final result was published in 2011, showing a 5-year OS of 71.7% with S-1 compared with 61.1% with surgery alone (HR 0.669; 95% CI, 0.540–0.828). In contrast, patients diagnosed with a more advanced stage (stage IIIB) demonstrated unsatisfactory survival outcomes, with no significant difference in 5-year OS (50.2% for S-1 vs. 44.1% for surgery alone; HR 0.791; 95% CI, 0.520–1.205).[40] These data have provoked a discussion for another strategy to improve survival among patients with high-risk of relapse, which includes the possibility of neoadjuvant treatment and/or regimens with multiple agents.

Several clinical trials are currently being conducted in Asia. A randomized phase III trial by JCOG was initiated in 2016 comparing surgery plus adjuvant S-1 compared with preop-

erative SOX and surgery plus adjuvant S-1 in patients with cT3-4 node-positive disease (JCOG1509). Another group in Japan is evaluating the superiority of S-1 plus docetaxel compared with S-1 alone for patients with stage III disease after curative D2 gastrectomy (START-2 trial). Nivolumab, an anti–PD-1 monoclonal antibody, demonstrated a survival benefit in patients with unresectable advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer refractory

TABLE 2. Practice-Changing Randomized Phase III Trials For Neoadjuvant Therapy in Asia

Ref	Recruit Time	Country	Trial	Registry	No. of Patients	Target	Arms	Primary Endpoint	Result	HR (95% CI)	p Value
29	1988–1992	JP	JCOG8801	Not registered	573	cT1-3/ any N	Surgery alone	OS	5-year OS: 82.9%	0.738 (0.498–1.093)	.17
							vs. MMC, 5-FU IV, 5-FU PO		vs. 85.8%		
30	1993–1994	JP	JCOG9206-1	Not registered	252	cT2-3/ N1-2	Surgery alone	RFS	5-year RFS: 83.7	(77.1%–90.2%)	.13
							vs. MMC, 5-FU IV, Ara-C, 5-FU PO		vs. 88.8%	(83.2%–94.3%)	
31	1993–1998	JP	JCOG9206-2	NCT00147147	268	cT3-4/ N0-2	Surgery alone	OS	5-year OS: 60.9%	(52.6%–69.2%)	.482
							vs. cisplatin IP, cisplatin IV, 5-FU IV, UFT		vs. 62.0%	(53.7%–70.2%)	
32	1997–2001	JP	N-SAS-GC	NCT00152243	190	cT2/ N1-2	Surgery alone	OS	5-year OS: 73%	0.48 (0.26–0.89)	.017
							vs. UFT		vs. 86%		
33	2001–2004	JP	ACTS-GC	NCT00152217	1,059	Stage II/ III	Surgery alone	OS	3-year OS: 74.2%	0.68 (0.52–0.87)	.003
							vs. S-1		vs. 80.1%		
34	2004–2008	KR	ARTIST	NCT00323830	458	D2, R0	XP	DFS	3-year DFS: 74.2%	0.740 (0.520–1.050)	.0922
							vs. XPX + RT/XP		vs. 78.2%		
35	2006–2009	CH, KR, TW	CLASSIC	NCT00411229	1,035	D2, R0	Surgery alone	DFS	5-year DFS: 53%	0.58 (0.47–0.72)	<.0001
							vs. CapeOX		vs. 68%		
Ongoing Adjuvant Phase III Trials											
	2013	KR	ARTIST-II	NCT01761461	900	Stage II/ III	S-1	DFS			
							vs. SOX				
							vs. RT/SOX				
	2013	JP	START-2	UMIN 000010337	1,100	Stage III	S-1	RFS			
							vs. S-1, docetaxel				
	2016	JP	JCOG1509	UMIN 000024065	470	cT3-4/ N1-3	S-1	OS			
							vs. SOX (neoadj), S-1 (adj)				
	2017	JP, KR, CH, TW	ATTRAC-TION-5	NCT03006705	700	Stage III	Placebo, S-1, or CapeOX	RFS			
							vs. nivolumab, S-1 or CapeOX				

Abbreviations: HR, hazard ratio; CI, confidence interval; JP, Japan; MMC, mitomycin C; 5-FU, 5-fluorouracil; IV, intravenous; PO, per os; OS, overall survival; Ara-C; cytosine arabinoside; RFS, recurrence-free survival; UFT, oral fluorouracil; KR, Korea; XP-X, capecitabin/cisplatin; Ref, reference; RT, radiation therapy; CH, China; TW, Taiwan; CapeOX, capecitabin/oxaliplatin; SOX, S-1/oxaliplatin; neoadj, neoadjuvant therapy; adj, adjuvant therapy.

to or intolerant of standard therapy.[41] Based on the result, an international phase III trial will begin in 2017 in which the efficacy of nivolumab as adjuvant therapy will be investigated in patients with pathologic stage III disease who will undergo curative D2 gastrectomy.

D2 gastrectomy has long been the gold standard for locally advanced GC, which will remain unchanged in gastric cancer surgery for the time being. However, not only in Asia but also worldwide, questions of what practice is the best and which chemotherapy regimen is optimal will continue to be debated. Even though numerous chemotherapy drugs have become available worldwide during the last decade, the majority of trials in Asia are planned in combination with S-1. Hence, at least in Asian populations, S-1 will continue to be a key agent in the perioperative treatment of locally advanced GC.

MULTIDISCIPLINARY APPROACHES IN RECURRENT OR METASTATIC GC: PARADIGM SHIFT FROM CYTOTOXIC TO MOLECULARLY TARGETED THERAPY

The effect of surgical therapy for unresectable and metastatic GC has long been controversial, because it is unknown whether resection of the primary tumor provides a survival benefit. For this reason, a phase III randomized trial was conducted in Japan, Korea, and Singapore in which palliative gastrectomy plus chemotherapy was compared with chemotherapy alone for advanced GC with a single noncurable factor (JCOG0705/KGCA01, REGATTA trial).[28] OS between the two groups showed no significant difference (HR 1.09; 95% CI, 0.78–1.52; p = .70), concluding that palliative resection offered no survival benefit. However, patients with a tumor in the lower gastric body, namely who were likely to undergo distal gastrectomy, showed relatively favorable outcomes; further subgroup analyses are currently underway.

Because superiority of chemotherapy over best supportive care was demonstrated in patients with advanced GC, several phase II trials were conducted in Japan to determine the optimal regimen. However, no standard regimen for advanced GC was proposed worldwide at that time. Therefore, the 2004 Guidelines for Diagnosis and Treatment of Carcinoma of the Stomach by the Japanese Gastric Cancer Society recommended chemotherapy with a fluorinated pyrimidine (e.g., 5-FU) combined with cisplatin as a standard regimen for the treatment of GC, but a specific regimen could not be recommended based on results from clinical trials inside and outside of Japan.[42] In a randomized phase III trial by JCOG (JCOG9205), three regimens of 5-FU alone, cisplatin plus 5-FU, and UFT plus MMC were compared, and demonstrated median OS of 7.1, 7.3, and 6 months, respectively, although cisplatin plus 5-FU yielded the best response rate of 34%.[43] This study suggested that the response rate was not always correlated with survival outcomes, which also provided evidence to a growing consensus that efficacy of chemotherapy should be evaluated by survival in a phase III trial (Table 3).

In 1999, when S-1 was first launched in Japan, a large, randomized phase III noninferiority/superiority trial commenced that compared the noninferiority of S-1 alone and superiority of irinotecan plus cisplatin compared with infusion 5-FU alone for the first-line treatment of advanced GC (JCOG9912).[44] Another phase III trial was also conducted to compare S-1 alone with S-1 plus cisplatin for the same patient population in 2002 (SPIRITS trial).[45] The result from JCOG9912 was presented at the American Society of Clinical Oncology Annual Meeting in 2007, showing noninferiority of S-1 compared with 5-FU (median OS, 11.4 vs. 10.8 months, respectively; HR 0.83; 95% CI, 0.68–1.01; p = .0005). As a result, oral S-1 replaced infusion 5-FU as standard of care. Results from the SPIRITS trial were also presented, revealing superiority of S-1 plus cisplatin compared with S-1 alone with a median OS of 13.0 months and 11.0 months, respectively (HR 0.77; 95% CI, 0.61–0.98; p = .04). Since this meeting, the first-line treatment of advanced GC has been S-1 plus cisplatin until today.

A recent phase III study comparing SOX with cisplatin plus S-1 in patients with advanced GC (G-SOX trial) demonstrated noninferiority of S-1 plus oxaliplatin compared with S-1 plus cisplatin with a median progression-free survival of 5.5 months and 5.4 months, respectively (HR 1.004; 95% CI, 0.840–1.19 with a noninferiority margin of 1.30; p = .0044). As a result, SOX has become a major option as first-line chemotherapy.[46] In addition, an advantage of SOX is that it can be safely administered on an outpatient basis without any hydration, which is used for cisplatin. For such a reason, SOX has rapidly gained popularity among expert communities of GC.

Since the mid-2000s, molecular-targeted agents have become popular in the management of gastrointestinal solid tumors as well as breast cancer, exemplified by monoclonal antibodies like trastuzumab, bevacizumab, cetuximab, and so forth. An international, large phase III trial (ToGA trial) was started in 2005, in which chemotherapy (5-FU plus cisplatin or capecitabin plus cisplatin) plus trastuzumab was compared with chemotherapy alone.[47] A total of 584 patients with HER2 expression were included from 122 centers in 24 countries including Japan, South Korea, China, Taiwan, and India. The HER2-positive rate was 22.1%, which was consistent to that in breast cancer. The result demonstrated additional benefit of trastuzumab compared with chemotherapy alone (median OS, 13.8 vs. 11.1 months, respectively; HR 0.74; 95% CI, 0.60–0.91; p = .0046) with acceptable tolerance, offering a new treatment option for advanced GC. The Japanese and Korean guidelines thus recommend that trastuzumab should be added to the first-line chemotherapy regimen for HER2-positive disease.[50,51]

In contrast, the AVAGAST trial did not demonstrate a survival advantage with the addition of bevacizumab to capecitabine and cisplatin compared with placebo (median OS, 12.1 vs. 10.1 months, respectively; HR 0.87, 95% CI, 0.73–1.03; p = .1002) in patients with unresectable and/or metastatic GC.[52] One big difference between the two studies was that the ToGA trial included only patients with positive HER2

TABLE 3. Randomized Phase III Trials for Unresectable/Metastatic Gastric Cancer in Asia

Ref	Recruit Time	Country	Trial	Registry	No. of Patients	Line	Arms	Primary Endpoint	Response Rate	Median OS	p Value
43	1992–1997	JP	JCOG9205	Not registered	280	First	FU alone	OS	11%	7.1 months; 1-year 28%	-
							vs. FU, cisplatin		vs. 34%	vs. 7.3 months; 1-year 29%	.34
							vs. uracil, tegafur, MMC		vs. 9%	vs. 6.0 months; 1-year 16%	.11
44	2000–2006	JP	JCOG9912	NCT00142350	704	First	5-FU CIV	OS	9%	2.9 months	-
							vs. irinotecan, cisplatin		vs. 38%	vs. 4.8 months (HR 0.69)	.0194
							vs. S-1		vs. 28%	vs. 4.2 months (HR 0.77)	.0233
45	2002–2004	JP	SPIRITS	NCT00150670	298	First	S-1	OS	31%	11.0 months	.04
							vs. S-1, cisplatin		vs. 54%	vs. 13.0 months (HR 0.77)	
46	2010–2011	JP	G-SOX	JapicCTI	685	First	S-1, cisplatin	PFS	55.7%	5.5 months (PFS)	.0044*
				101021			vs. SOX (noninferiority)		vs. 52.2%	vs. 5.4 months (HR 1.004)	
47	2005–2008	JP, KR, CH, etc	ToGA	NCT01041404	584	First	XP or FP	OS	35%	11.0 months	.0046
							vs. XP or FP, trastuzumab		vs. 47%	vs. 13.8 months (HR 0.74)	
48	2010–2012	JP, KR, CH, etc	RAINBOW	NCT01170663	665	Second	Placebo, paclitaxel	OS	16%	7.4 months	.017
							vs. ramucirumab, paclitaxel		vs. 28%	vs. 9.6 months (HR 0.807)	
41	2014–2016	JP, KR, TW	Nivolumab (ONO-4538)	NCT02267343	493	Third	Placebo	OS	0%	4.14 months	< .0001
							vs. nivolumab		vs. 11.2%	vs. 5.32 months (HR 0.63)	
49	2011–2012	CH	Apatinib	NCT01512745	267	Third	Placebo	OS/PFS	0%	4.7 months (OS)	.0149
							vs. apatinib		vs. 1.70%	vs. 6.5 months (HR 0.709)	
Ongoing Phase III Trials											
	2013	JP	JCOG1013	UMIN 000007652	740	First	S-1, cisplatin	OS			
							vs. S-1, cisplatin, docetaxel				
	2015	JP, U.S., etc	RAINFALL	NCT02314117	616	First	Placebo, XP	PFS			
							vs. ramucirumab, XP				

Continued

TABLE 3. Randomized Phase III Trials for Unresectable/Metastatic Gastric Cancer in Asia (Cont'd)

Ref	Recruit Time	Country	Trial	Registry	No. of Patients	Line	Arms	Primary Endpoint	Response Rate	Median OS	p Value
	2013	JP, KR, CH, U.S., etc	JACOB	NCT01774786	780	First	Placebo, trastuzumab, XP, or FP	OS			
							vs. pertuzumab, trastuzumab, XP, or FP				
	2013	KR, JP, TW	ENRICH	NCT01813253	400	Second	irinotecan	OS			
							vs. nimotuzumab, irinotecan				
	From 2014	JP, KR, U.S., etc	BRIGHTER	NCT02178956	700	Second	Placebo, paclitaxel	OS			
							vs. BBI608, paclitaxel				
	From 2015	JP, KR, TW, U.S., etc	JAVELIN			Third	Oxaliplatin/5-FU doublet or BSC (100)	OS			
							Any chemotherapy/BSC or BSC alone (300)				
			-Gastric 100	NCT02625610	666		vs. avelumab				
			-Gastric 300	NCT02125610	330		vs. avelumab, BSC				
	From 2015	JP, KR, HK, SIN, TW, U.S., etc	KEYNOTE			Third	Paclitaxel (061)	OS, PFS			
							FP (062)				
			–061	NCT02370498	720		vs. pembrolizumab				
			–062	NCT02494583	750		vs. pembrolizumab, FP				
							vs. pembrolizumab alone				

*Noninferiority margin, 1.30.

Abbreviations: OS, overall survival; JP, Japan; FU, fluoropyrimidine; MMC; mitomycin C; CIV, continuous intravenous; HR, hazard ratio; PFS, progression-free survival; SOX; S-1/ oxaliplatin; KR, Korea; CH, China; FP, 5-FU/cisplatin; XP, capecitabin/cisplatin; BSC, best supportive care; Ref, reference; TW, Taiwan; US, United States; HK, Hong Kong; SIN, Singapore.

status, whereas the AVAGAST included all eligible patients without any molecular selection. A biomarker study from AVAGAST suggested that baseline plasma VEGF-A levels and tumor neuropilin-1 expression were potential predictors of bevacizumab efficacy.[53] Therefore, patient selection was unlikely to be a reason for the negative result of AVAGAST, implying that targeted molecular expression or serum levels as predictive biomarkers for efficacy must be examined before use to exploit molecularly-targeted agents.

With regard to second-line chemotherapy, there are two randomized phase III studies from Japan (WJOG4007) and Korea.[54,55] The former trial, WJOG4007, evaluated superiority of irinotecan alone compared with paclitaxel alone as a consensus regimen, resulting in a median OS of 9.5 months with paclitaxel and 8.4 months with irinotecan (HR 1.13; 95% CI, 0.86–1.49; p = .33). Although the result was negative, this study provided evidence and further treatment options for the second-line treatment of advanced GC. The latter trial compared docetaxel or irinotecan alone with best supportive care. Patients who received chemotherapy demonstrated a median OS of 5.1 months (95% CI, 4.0–6.2) compared with 3.8 months with best supportive care (95% CI, 3.0–4.6; p = .009). Based on the results of these two studies, the Japanese guideline recommends monotherapy with either docetaxel, paclitaxel, or irinotecan, whereas the Korean guideline recommends combination therapy including docetaxel, paclitaxel, platinum, and fluoropyrimidine.

Recent key global studies for the second-line treatment were the REGARD and RAINBOW trials, in which the efficacy of ramucirumab plus paclitaxel was evaluated compared with placebo plus paclitaxel in patients with previously treated advanced gastric or GEJ adenocarcinoma.[48,56] The result of the RAINBOW trial was positive (HR 0.807; 95% CI, 0.678–0.962; p = .017), providing a new option for second-line treatment. Another landmark was the ONO-4538 (nivolumab) trial conducted in Japan, South Korea, and Taiwan. The result was presented at the 2017 ASCO Gastrointestinal Cancers Symposium, which showed an OS benefit in patients with unresectable advanced or recurrent gastric or GEJ cancer refractory to or intolerant of standard therapy.[41] This is the first immunotherapy with demonstrated efficacy in terms of OS in GC. The median OS was 5.3 months with nivolumab and 4.1 months with placebo (HR 0.63; 95% CI, 0.50–0.78; p < .0001) and a 1-year OS of 26.6% and 10.9%, respectively. All patients accrued had received at least two prior treatment regimens; therefore, nivolumab will be used in the third- or subsequent-line in clinical practice. In China, a randomized phase III trial using apatinib, a tyrosine kinase inhibitor that selectively inhibits VEGFR2/KDR, was conducted among patients with chemotherapy-refractory advanced or metastatic gastric or GEJ adenocarcinomas. In this trial, apatinib alone showed a survival benefit and is thus regarded as another promising targeted agents for the third or subsequent line.[49]

Numerous potential molecularly targeted antitumor agents have been developed and tested, which are likely to alter the standard of care after completion of their phase III controlled trials. Many promising agents are currently being investigated in collaboration with Asian and Western countries. The RAINFALL trial, which is being conducted in the Americas, Europe, and Japan, is evaluating the efficacy of ramucirumab, a human IgG1 monoclonal antibody directed to the ectodomain of VEGFR2. In this global phase III trial, patients with HER2-negative, metastatic gastric or GEJ adenocarcinoma will receive ramucirumab plus cisplatin and capecitabine with placebo plus cisplatin and capecitabine as first-line treatment. Another study, named the JACOB trial, is a parallel-arm study that is evaluating the efficacy of pertuzumab in combination with trastuzumab, fluoropyrimidine, and cisplatin as first-line treatment in patients with HER2-positive metastatic gastric or GEJ adenocarcinoma. These two studies have the potential to establish combination therapy with ramucirumab or pertuzumab as an option for the first-line treatment of advanced GC.

Two studies are investigating drug candidates for second-line treatment: the ENRICH and BRIGHTER trials. The ENRICH study is a collaborative trial between Japan and Korea that is comparing nimotuzumab plus irinotecan with irinotecan monotherapy in patients with EGFR-overexpressed advanced gastric and GEJ cancer who have received previous treatment. The BRIGHTER trial will evaluate the efficacy of paclitaxel plus BBI608, an orally administered first-in-class cancer stemness inhibitor, compared with paclitaxel plus placebo in patients with pretreated, advanced gastric and GEJ cancer. Other molecularly- argeted agents, avelumab and pembrolizumab, are also being investigated in Asian and Western countries (JAVELIN-100, -300 trials and KEYNOTE-059, -061, -062 trials).

BEST PRACTICE IN A NEW ERA OF PRECISION MEDICINE: SO FAR AND HEREAFTER

We are currently at a major turning point in medical history. Until very recently, only a single landmark trial established the optimal regimen, in which most patients receive "one-size-fits-all" chemotherapy. Since the beginning of the 21st century, however, numerous molecular candidates for targeted agents have been discovered, and subsequently, a tremendous number of molecularly targeted agents are currently being tested in clinical trials. In the future, it may be almost impossible to compare the exponentially increasing combinations that will be available in the next decades. Therefore, it naturally follows that patients will receive a "bespoke" regimen based on their own gene signatures and molecular expression, which is called precision medicine.[57,58] To achieve this, new biomarkers that can predict a patient's disease status and treatment outcomes are urgently needed.[59-61]

The Cancer Genome Atlas Research Network performed comprehensive molecular characterization of gastric adenocarcinoma by analyzing 295 primary gastric adenocarcinomas. The study proposes a new classification of GC that falls into four genomic subtypes according to the following tumor profiles: positive for Epstein-Barr virus, microsatellite unstable, genomically stable, and chromosomal instability.[62]

The Asian Cancer Research Group proposed another classification based on gene expression profiles with distinct clinical outcomes: microsatellite unstable type, mesenchymal-like type, and p53-active or -inactive types.[63] Each subtype demonstrate noticeable genomic features, which can help develop molecularly-targeted drugs. Patient eligibility in future clinical trials may include such gene profiles to select for distinct populations.

In Asia, during a long period of time, we have established our own evidence that established the best practice and management strategies to treat patients with GC. In a new era of precision medicine, even though differences in history, culture, race, religion, and way of thinking continue to exist, differences in the best practice are soon disappearing, as similarly seen in the globalization of the economy. The new era has just begun. However, there remains a paucity of data. In the future, we should accumulate individual information to be analyzed, share the data, collaborate, and then establish global and comprehensive evidence for the sake of our patients with GC.

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Immunotherapy for Esophageal and Gastric Cancer

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OVERVIEW

PD-L1 upregulation occurs in approximately 40% of gastroesophageal cancers. However, unlike other solid tumors, there is minimal PD-L1 expressed on the cancer cells; rather, expression occurs predominantly on infiltrating myeloid cells. Preliminary clinical data involving single-agent PD-1/PD-L1 inhibitors in metastatic gastroesophageal cancer have reported response rates of 22%–27% for patients with PD-L1$^+$ tumors and 10%–17% for unselected patients. The phase III ONO-4538-12 (ATTRACTION 2) trial has demonstrated an improved overall survival for nivolumab compared with placebo for patients with heavily pretreated gastric cancer. In the future, we will need better biomarkers to select those most likely to respond and/or identify patients who may need combination immunotherapeutics or alternate strategies. A number of subsets of gastric cancer with different immune signatures, most notably tumors positive for Epstein-Barr virus and microsatellite instability, have been identified, with approximately 50% and 94% PD-L1$^+$ staining seen on tumor cells and immune cells in the EBV subtype and approximately 33% and 45% PD-L1$^+$ staining seen on tumor cells and immune cells in MSI high tumors. Both subtypes demonstrate PD-L1$^+$ immune cells with tumor-infiltrating patterns, unlike the more commonly seen PD-L1$^+$ immune cells at the invasive margin. PD-L2 expression has been reported in 52% of esophageal adenocarcinomas but little is known about the expression of other immune checkpoints. Additional factors that suggest gastroesophageal cancers may respond to checkpoint inhibition include the high somatic mutation burden and the link with chronic inflammation. Here we provide a comprehensive review of the checkpoint inhibitor data published to date in advanced esophagogastric cancers and rationalize how the immune microenvironment in these diverse tumors can explain response or resistance to immunotherapeutics.

Esophageal and gastric cancers have limited treatment options in the locally advanced and metastatic setting, with chemotherapy resistance limiting efficacy beyond the first- or second-line setting. With the exception of trastuzumab and ramucirumab, results of clinical trials utilizing targeted agents have been disappointing.[1-3] The Cancer Genome Atlas (TCGA) recently published comprehensive molecular characterizations of gastric and, more recently, esophageal cancer.[4,5] It was hoped that with a more complete biologic understanding of the mutational landscape underpinning upper gastrointestinal tumors, newer targeted therapeutic options would emerge. Unfortunately, this does not seem to be the case, and although basket trials investigating novel targeted agents may be useful for a small select patient population with a targetable oncogenic mutation, the majority of patients will not derive substantial therapeutic benefits.

The link between infection, chronic inflammation, and malignancy has long been recognized in esophagogastric cancer and suggests that targeting the immune system may lead to improved outcomes in tumors that are inherently resistant to systemic treatments as a result of histologic, molecular, and etiological heterogeneity.[6-8] TCGA investigators identified that the Epstein-Barr virus (EBV) subtype in gastric cancer displays recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, PD-L1, and PD-L2, and the microsatellite instability (MSI) subtype shows elevated mutation rates.[4] It is likely that the majority of patients who respond to single-agent checkpoint inhibition may have these subtypes, although this remains to be determined. Alternatively, patients with the genomically stable subtype (mutations of RhoA or fusions involving Rho-family guanosine 5′-triphosphatase–activating proteins) and the chromosomal unstable subtype (marked aneuploidy and focal amplification of receptor tyrosine kinases) may need novel combination immunotherapeutics. Recently published TCGA esophageal data also highlighted that squamous cell esophageal carcinomas show frequent genomic amplifications of *CCND1* and *SOX2* and/or *TP63*, whereas *ERBB2*, *VEGFA*, *GATA4*, and *GATA6* were more commonly amplified in adenocarcinomas. In fact, esophageal adenocarcinomas strongly resembled the chromosomally unstable variant of gastric adenocarcinoma.[5] These data, although interesting, do not help us with preselecting patients for immunotherapeutic strategies. Emerging data in other tumor types suggest that negative immune checkpoint

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proteins are usually upregulated in tumor tissues with a T cell–inflamed phenotype and that infiltration of tumors by effector T cells is necessary to drive upregulation of immune checkpoints.[9] This finding suggests that targeting the PD-1/PD-L1 axis in esophagogastric cancer may only be clinically effective in the subgroup of tumors (excluding MSI^+ or EBV^+) that contain tumor-infiltrating immune cells. The clinical relevance of other factors such as the potential contributions of myeloid-derived suppressor cells, $CD4^+CD25^+FoxP3^+$ regulatory T cells, and indoleamine 2,3-dioxygenase (IDO) must be elucidated. Given the considerable number of trials that are currently ongoing, it is hoped that improved characterization of the tumor immune microenvironment in upper gastrointestinal tumors may yield a more nuanced understanding of the interactions between $CD8^+$ T cells and immunosuppression and provide further targets for immune-based therapy.

THE IMMUNE MICROENVIRONMENT IN ESOPHAGEAL AND GASTRIC CANCER

Tumors escape immune surveillance by a number of mechanisms, but, simplistically, four groups have been proposed utilizing PD-L1 status and the presence or absence of tumor-infiltrating lymphocytes (TILs). These include type I ($PD\text{-}L1^+$ with TILs driving adaptive immune resistance), type II ($PD\text{-}L1^-$ with no TIL indicating immune ignorance), type III ($PD\text{-}L1^+$ with no TIL indicating intrinsic induction), and type IV ($PD\text{-}L1^-$ with TILs indicating the role of other suppressors in promoting immune tolerance).[10] Malignant melanoma has been extensively studied and a high proportion of type I and type II microenvironments are seen,[11] whereas this information is yet to be defined in gastric and esophageal cancers. It is clear, however, in two of the four proposed immune resistance mechanisms that PD-L1 expression appears to play a key role. The early events that lead to enhanced expression of PD-1/PD-L1 by tumor cells and/or host immune cells in esophageal and gastric cancer are not yet known. Genomic aberrations leading to enhanced PD-L1 expression have been demonstrated in both the MSI and EBV subtypes of gastric cancer.[4,12]

We currently know that there are a number of factors in the immune microenvironment that can predict whether a patient is likely to respond to single-agent PD-1 inhibition. These factors include a high tumor antigen load, loss of help by $CD4^+$ helper cells, and immune-regulatory cytokines and ligands for coinhibitory proteins expressed by tumor and stromal cells, leading to a progressive loss of the ability of effector $CD8^+$ T cells to produce proinflammatory cytokines (e.g., interleukin-2, interferon [IFN]-γ, tumor necrosis factor-α, and β-chemokines) and ultimately their ability to kill cancer cells, a state termed T-cell exhaustion. We previously demonstrated in esophagogastric cancers that more $CD8^+$ T-cell infiltration occurs in tumors and at the peritumoral interfaces of tumors that were also $PD\text{-}L1^+$ compared with those that were $PD\text{-}L1^-$. When $CD8^+$ T-cell densities were divided into low, mid-, and high categories, we found that 89% of stroma $PD\text{-}L1^+$ tumors had high $CD8^+$ densities. This highlights the linkage between $CD8^+$ T cells, mechanistically thought to be a source of cytokines such as IFN-γ, and expression of PD-L1 in esophagogastric cancer.[11,13]

PD-L1 upregulation occurs in approximately 40% of gastroesophageal cancers; however, key differences are emerging in that unlike lung cancer or melanoma, there is little PD-L1 expressed on the cancer cells of upper gastrointestinal tumors, but rather expression occurs predominantly on infiltrating myeloid cells at the invasive margin.[13-15] There are exceptions, however. In the 10% of gastric cancers that are EBV^+, approximately 50% and 94% $PD\text{-}L1^+$ staining is seen on tumor cells and immune cells, respectively.[16] MSI also affects $PD\text{-}L1^+$ status, with tumor and immune cells staining positive in 33% and 45% of cases, respectively, with both subtypes having $PD\text{-}L1^+$ immune cells with tumor-infiltrating patterns.[16] The localization of PD-L1 expression within the tumor microenvironment (infiltrating immune cells, at invasive margin or tumor core) may affect its use as a biomarker and the stromal expression rather than membranous expression may be responsible for the somewhat lower responses to single-agent PD-1 inhibitors in gastroesophageal cancer compared with other tumor types but more knowledge is needed. PD-L2 expression has been reported in 51.7% of esophageal adenocarcinomas,[14] but little is known about the expression of other checkpoints and what the impact is on the response to PD-1 inhibitors. Additional factors that warrant investigation in esophagogastric cancers and may predict response include the association with chronic inflammation and high somatic mutation burden.

KEY POINTS

- **PD-L1 is expressed in approximately 40% of esophagogastric cancers.**
- **Unlike melanoma or lung cancer, membranous PD-L1 expression is rare in esophageal and gastric cancers and occurs predominantly on infiltrating myeloid cells at the invasive margin.**
- **The EBV and MSI subtypes of gastric cancer are unique, with approximately 50% and 94% $PD\text{-}L1^+$ staining seen on tumor cells and immune cells in EBV positive tumors and approximately 33% and 45% $PD\text{-}L1^+$ staining seen on tumors cells and immune cells in MSI high tumors. Both subtypes demonstrate $PD\text{-}L1^+$ immune cells with tumor-infiltrating patterns, and preliminary data show higher response rates to PD-1 inhibitors.**
- **Phase II and phase III data show that unselected patients with metastatic esophagogastric cancer have response rates of approximately 10%-17%, whereas patients who have $PD\text{-}L1^+$ tumors (> 1% of cells) have response rates of 22%–27%. Novel combination trials are ongoing with improved efficacy but with more toxicity.**
- **The ONO-4538-12 (ATTRACTION 2) is the first phase III immunotherapy trial to date to show an improved overall survival benefit for patients with heavily pretreated metastatic gastric and esophageal cancer (5.32 months with nivolumab vs. 4.14 months with placebo; hazard ratio, 0.63; $p < .0001$).**

CHRONIC INFLAMMATORY CHANGES, HIGH SOMATIC MUTATION BURDEN, AND EBV

Esophagogastric tumors develop in part as a result of prolonged chronic gastric reflux–induced inflammation. In response to gastric reflux, the occurrence of Barrett metaplasia in the esophagus is accompanied by a change from an acute (TH1-type) immune response associated with IFN-γ expression to a TH2-type chronic inflammation with production of interleukin-4/interleukin-13, which is reported to result in an immunosuppressive, tumor-promoting microenvironment.[17,18] In addition, it is thought that high somatic mutational burden may be important in predicting response to PD-1 inhibitors and only melanoma, lung, and bladder cancers display a more mutated profile than gastroesophageal cancers.[19] Continued research on the link between mutation burden and the T cell-inflamed phenotype may be more predictive of response than the number of mutations alone.

Defective mismatch repair (MMR) genes have also been identified as being predictive of response to PD-1 inhibition, because somatic mutations have the potential to encode non-self immunogenic neoantigens.[12] Whole-exome sequencing has demonstrated a mean of 1,782 somatic mutations in MMR-deficient tumors compared with approximately 73 in MMR-proficient tumors.[12] In addition, immunologic assessment of the immune microenvironment in MMR-deficient tumors demonstrated strong expression of several immune checkpoint ligands, most notably, PD-1/PD-L1, LAG-3, IDO, and CTLA-4, which help confer resistance to immunologic attack.[20] MMR deficiency has been identified in approximately 17%–21% of gastric cancers, and very preliminary data indicate a higher response rate among these patients (on the order of approximately 50%).[15,21] Ongoing and future studies of gastroesophageal cancer are stratifying patients according to their MSI status.

EBV^+ gastric cancers occur predominantly in the gastric fundus or body and are more common among men. Gastric TCGA investigators describe a recurrent amplification at 9p24.1; this is the locus containing *JAK2* but also *CD274* and *PDCD1LG2*, which encode PD-L1 and PD-L2, respectively. These 9p amplifications occurred in 15% of EBV-driven gastric tumors and result in enhanced neoepitope

TABLE 1. Selected Ongoing Clinical Trials Involving PD-1 Targeting Therapies for Esophageal and Gastric Cancer

Clinical Trial Identifier	Phase	Study Design	Study Population	Primary Endpoints
Pembrolizumab				
NCT02443324	I	Pembrolizumab plus ramucirumab	Gastric/GEJ plus other tumor types	Safety
NCT02346955	I	Pembrolizumab plus CM-24 (anti-CEACAM1)	Gastric/GEJ plus other tumor types	RP2D, safety
NCT02268825	I	Pembrolizumab plus FOLFOX chemotherapy	Metastatic gastric/esophageal	Safety
NCT02563548	IB	Pembrolizumab plus PEGPH20	Gastric/GEJ plus other tumor types, second line	ORR, safety
NCT02689284	IB/II	Pembrolizumab plus margetuximab (anti-HER2)	Metastatic, $HER2^+$, second line	MTD, antitumor activity
NCT02730546	I/II	Pembrolizumab plus chemotherapy plus RT	Resectable GEJ/cardia	Pathologic response, PFS
NCT02452424	I/II	Pembrolizumab plus PLX3397 (CSF1R inhibitor)	Gastric plus other tumor types	Safety
NCT02318901	I/II	Pembrolizumab plus trastuzumab/emtansine/cetuximab	$HER2^+$ gastric plus other tumor types	R2PD
NCT02393248	I/II	Pembrolizumab or chemotherapy plus INCB054828 (anti-FGR)	Multiple lines, gastric/GEJ	Safety, MTD
NCT02335411	II	Pembrolizumab with or without chemotherapy (KEYNOTE-059)	Multiple lines, gastric/GEJ	Safety, ORR
NCT02830594	II	Pembrolizumab plus RT	Multiple lines, metastatic gastric/GEJ	Biomarkers
NCT02494583	III	Pembrolizumab with or without chemotherapy (cisplatin plus 5-FU/capecitabine)	Metastatic, first line	PFS, OS
NCT02370498	III	Pembrolizumab vs. paclitaxel (KEYNOTE-061)	Second-line gastric/GEJ	PFS, OS
Nivolumab				
NCT02746796	II	Nivolumab plus chemotherapy	First-line gastric/GEJ	ORR
NCT02267343	III	Nivolumab vs. placebo	Unresectable gastric/GEJ	OS

Abbreviations: CEACAM1, carcinoembryonic antigen related cell adhesion molecule 1; FOLFOX, leucovorin calcium (folinic acid)/fluorouracil/oxaliplatin; RT, radiation therapy; CSF1R, colony stimulating factor 1 receptor; FGR, fibroblast growth factor; 5-FU, fluorouracil; GEJ, gastroesophageal cancer; R2PD, recommended phase II dose; ORR, objective response rate; MTD, maximum tolerated dose; PFS, progression-free survival; OS, overall survival.

presentation.[4] Ongoing studies are evaluating checkpoint inhibitors in EBV+ gastric cancer (NCT02488759).

PD-L1 EXPRESSION IN ESOPHAGEAL AND GASTRIC CANCER

PD-L1 expression occurs in approximately 40% of gastric and gastroesophageal junction (GEJ) cancers.[22-24] The KEYNOTE-012 trial assessed single-agent pembrolizumab administration for patients with PD-L1+ advanced gastric or GEJ adenocarcinomas (with Dako 22C3 antibody staining both tumor cells and mononuclear inflammatory cells). Of the 162 patients screened, 65 (40%) were considered PD-L1+. PD-L1 positivity was defined as membrane staining in at least 1% of scorable cells or the presence of a distinctive interface pattern. The trial investigators commented that it was necessary for them to assess PD-L1 expression in the immune cells as opposed to tumor cell expression exclusively.[15] We previously reported that of 34 resected gastric or GEJ tumors stained by immunohistochemistry using the 5H1 clone, only 12% of tumors demonstrated cell membranous PD-L1 expression, whereas 44% showed expression within the immune stroma.[13] We do not yet know whether stromal versus membranous expression affects response in esophagogastric cancer; however, in a recently published first-line metastatic lung cancer study comparing pembrolizumab to chemotherapy, membranous PD-L1 expression of more than 50% was needed to demonstrate superiority of immunotherapy over cytotoxic therapy.[25]

MOVING BEYOND PD-L1: OTHER POTENTIAL BIOMARKERS IN ESOPHAGOGASTRIC CANCER

In addition to PD-L1 staining, a mononuclear inflammatory cell density score of 0–4 was assessed in the KEYNOTE-012 trial.[15] Four of 9 patients (44%) with a score of 3 or more had a partial response, compared with only four of 26 patients (15%) with a score of 2 or less. Unfortunately, these numbers are too small to make definitive conclusions, but the data are intriguing. Ongoing larger phase III studies are assessing a number of immune correlates and gene signatures, which should provide more clarity. The KEYNOTE-012 trial also investigated the use of a six-gene IFN-γ signature that was previously identified to predict response in melanoma.[26] The six genes included *CXCL9*, *CXCL10*, *IDO1*, *IFNG*, *HLA-DRA*, and *STAT-1* and were used to calculate an IFN-γ composite score. Unfortunately, the numbers of enrolled patients were small and the prespecified gene signature did not meet significance at .05, but there is a signal and the ongoing KEYNOTE studies will continue this line of investigation.

CLINICAL TRIAL DATA INVOLVING PD-1/PD-L1 INHIBITORS IN ESOPHAGOGASTRIC CANCER

Nivolumab (PD-1 Inhibitor)

ONO-12 (ATTRACTION 2) was a multicenter, double-blind, randomized phase III study of nivolumab for patients with unresectable advanced or recurrent gastric or GEJ cancer refractory to or intolerant of two or more prior chemotherapy regimens (NCT02267343; Table 1). The results were presented at the 2017 ASCO Gastrointestinal Cancers Symposium and showed for the first time that PD-1 inhibition could lead to an improvement in overall survival for patients with heavily pretreated gastric or gastroesophageal cancer.[27] Median overall survival was 5.32 months (95% CI, 4.63–6.41) with nivolumab versus 4.14 months (95% CI, 3.42–4.86) with placebo, and the 12-month overall survival rate was 26.6% (95% CI, 21.1%–32.4%) versus 10.9% (hazard ratio, 0.63; 95% CI, 6.2%–17%; $p < .0001$). In addition, median progression-free survival was 1.61 months with nivolumab versus 1.45

TABLE 2. Selected Ongoing Combination Studies Involving PD-1/PD-L1 Inhibitors Plus Targeted Therapeutics in Esophageal and Gastric Cancer

Clinical Trial Identifier	Phase	Study Design	Study Population	Primary Endpoints
Durvalumab				
NCT02572687	I	Durvalumab plus ramucirumab	Second-line/subsequent-line gastric/GEJ	Safety
NCT02734004	I/II	Durvalumab plus olaparib	Advanced ATM-negative gastric cancer	Disease control rate, safety
NCT02318277	I/II	Durvalumab plus epacadostat (IDO inhibitor)	Second-line/subsequent-line gastric/GEJ	Safety, ORR
NCT02678182	II	Durvalumab vs. capecitabine vs. trastuzumab vs. control	Locally advanced/metastatic HER2+/- gastric cancer, maintenance therapy	PFS
Avelumab				
NCT01772004	I	Avelumab monotherapy	First-line maintenance, second-line gastric/GEJ	Safety, ORR
NCT02625623	III	Avelumab vs. best supportive care	Third-line gastric/GEJ cancer	OS
NCT02625610	III	Avelumab vs. chemotherapy	Continuation first-line therapy metastatic/unresectable gastric/GEJ	PFS, OS
Ipilimumab				
NCT01585987	II	Ipilimumab vs. best supportive care	Maintenance after first-line therapy, gastric/GEJ	irPFS

Abbreviations: IDO, indoleamine 2,3-dihydrogenase; GEJ, gastroesophageal junction; ATM, ataxia telangiectasia mutated protein; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; irPFS, immune-related progression-free survival.

TABLE 3. Selected Ongoing Immune-Oncology Combination Studies in Esophageal and Gastric Cancer

Clinical Trial Identifier	Phase	Study Design	Study Population	Primary Endpoints
NCT02834013	II	Nivolumab plus ipilimumab	Metastatic gastric SCC, multiple lines, other tumor types	ORR
NCT01928394	I/II	Nivolumab with or without ipilimumab	Gastric plus other tumor types, multiple lines	ORR
NCT02488759	I/II	Nivolumab with or without ipilimumab	EBV$^+$ gastric cancer (neoadjuvant plus metastatic)	Safety, ORR
NCT02340975	IB/II	Durvalumab plus tremelimumab	Multiple lines, metastatic gastric/GEJ	Safety, ORR, PFS
NCT02658214	IB	Durvalumab plus tremelimumab plus chemotherapy	Gastric/GEJ plus other tumor types, multiple lines	Safety
NCT02735239	I/II	Durvalumab plus tremelimumab with or without oxaliplatin/capecitabine with or without RT	Multiple lines, esophageal/GEJ	Safety
NCT02935634	II	Nivolumab plus ipilimumab vs. nivolumab plus IO	Metastatic gastric or GEJ cancer	ORR, DoR, PFS

Abbreviations: RT, radiation therapy; IO, novel immune-oncology drug; SCC, squamous cell cancer; EBV, Epstein-Barr virus; GEJ, gastroesophageal junction; ORR, objective response rate; PFS, progression-free survival; DoR, duration of response.

months with placebo (hazard ratio, 0.60; p < .0001). The overall response rate was 11.2% with nivolumab versus 0% with placebo, and the median duration of response to nivolumab was 9.53 months (95% CI, 6.14–9.82 months).

CheckMate-032 was a phase I/II open-label study of the safety and activity of nivolumab alone or with ipilimumab in advanced and metastatic solid tumors (NCT01928394). This study enrolled 160 patients with advanced/metastatic gastric or gastroesophageal cancer who had progressed while receiving standard chemotherapy, most of whom received two or more prior regimens.[28] Patients were randomized to receive 3 mg/kg of nivolumab every 2 weeks (N3), 1 mg/kg of nivolumab plus 3 mg/kg of ipilimumab (N1 plus I3) or 3 mg/kg of nivolumab plus 1 mg/kg of ipilimumab (N3 plus I1) every 3 weeks for four cycles, followed by 3 mg/kg of nivolumab every 2 weeks until disease progression or treatment was no longer tolerable. Treatment toxicities (any grade) were more common in the N1 plus I3 arm (84%) than in the N3 (70%) or N3 plus I1 (75%) arms. From the preliminary data presented to date, 96% of patients (154) were evaluable for efficacy outcome reporting and the objective response rates for unselected patients were 14% (nivolumab alone), 26% (N1 plus I3), and 10% (N3 plus I1). The median overall survival was highest in the N1 plus I3 group (6.9 months; 95% CI, 3.6 or not achieved), followed by N3 (5.0 months; 95% CI, 3.4–12.4), and N3 plus I1 (4.8 months; 95% CI, 3.0–9.1). For patients with PD-L1$^+$ tumors (defined as greater than 1% of cells staining positive), the response rate for single-agent nivolumab was 27% (four of 15 patients); the response rate for the combination of the more active N1/I3 was an impressive 44%, albeit the numbers reported to date are small and we await updated information (four of nine patients). For patients with PD-L1$^-$ tumors (< 1% of cells staining positive), the response rates were 12% (three of 25 patients) for nivolumab and 21% (six of 29 patients) for N1/I3. These data highlight important points for future investigation. As with other solid tumors, we know that PD-L1 is not a perfect biomarker; however, given the relatively low response rate among patients with esophagogastric cancer whose tumors are PD-L1$^-$, it may be more appropriate to investigate combination strategies in this population.

Many of the studies performed to date have included only the adenocarcinoma histology in esophagogastric cancer. We do, however, have some data investigating nivolumab for patients with advanced esophageal squamous cell cancer. In the ONO-4538-12 study, nivolumab (3 mg/kg every 2 weeks) was administered to 65 patients in a phase II, single-arm, multicenter study in Japan, and the investigators found that 17.2% of patients achieved an objective response.[29] The median overall survival was 12.1 months and 14% of patients had serious adverse events, but no treatment-related deaths occurred. This study supports further phase III testing of nivolumab for patients with esophageal squamous cell cancer. The ongoing adjuvant study CheckMate-577 investigating nivolumab in resected stage II/III esophageal cancer is enrolling both patients with adenocarcinoma and squamous cell carcinomas.

Pembrolizumab (PD-1 Inhibitor)

In addition to nivolumab, there are a number of ongoing trials investigating the efficacy of the PD-1 inhibitor pembrolizumab in esophagogastric cancer. The KEYNOTE-012 study was a multicenter, nonrandomized, open-label, multicohort phase Ib trial evaluating single-agent pembrolizumab (10 mg/kg every 2 weeks or a 200-mg fixed dose every 3 weeks) for patients with PD-L1$^+$ recurrent or metastatic gastric/GEJ adenocarcinoma.[15] From the data published to date, 39 patients were enrolled at 13 centers based in the United States, Israel, Japan, South Korea, and Taiwan and 36 were considered evaluable. A partial response rate of 22% (8 of 36 patients; 95% CI, 10–39) was observed for this group of heavily pretreated patients, more than 75% of which had received two or more prior therapies in the metastatic setting. The regimen was well tolerated overall, with 13% of patients experiencing grade 3–4 toxicity; no patients discontinued the study because of a treatment-related adverse

TABLE 4. Summary of Selected Published and Ongoing Phase III Trials or Completed Phase I/II Trials in the Refractory Setting in Gastroesophageal Cancer

Anti–PD-1, Anti–PD-L1, or Anti–CTLA-4	Adjuvant or Neoadjuvant	First-Line Metastatic Cancer	Second-Line Metastatic Cancer	Refractory Disease	Refractory Disease (Phase I/II Trials)
Nivolumab (PD-1)	CheckMate-577 (phase III): nivolumab vs. placebo in resected stage II/III esophageal/GEJ cancer			ONO-4538-12 (ATTRACTION 2; phase III): nivolumab vs. placebo; OS, 5.32 months vs. 4.14 months; 12-month OS, 26.6% vs. 10.9%	CheckMate-032 (phase I/II): ORR, 14% PD-L1 unselected; ORR, 27% PD-L1$^+$ (> 1%)
					ONO-4538 (phase II): ORR, 17.2% (Asian patients, squamous cell esophageal)
Pembrolizumab (PD-1)		KEYNOTE-059 (phase II): pembrolizumab plus cisplatin/5-FU (cohort B) or pembrolizumab alone (cohort C)	KEYNOTE-061 (phase III): pembrolizumab vs. paclitaxel		KEYNOTE-012 (phase I): ORR, 22%
		KEYNOTE-062 (phase III): pembrolizumab vs. pembrolizumab + cisplatin/5-FU vs. placebo + cisplatin/5-FU	KEYNOTE-181 (phase III): pembrolizumab vs. paclitaxel, docetaxel, or irinotecan		KEYNOTE-028 (phase I): ORR, 30%
					KEYNOTE-180 (phase II): third-line study of single-agent pembrolizumab
Avelumab (PD-L1)		JAVELIN Gastric 100 (phase III): maintenance avelumab after FOLFOX			JAVELIN (phase I): ORR, 9.7% PD-L1 unselected; ORR, 18.2% PD-L1$^+$ (> 1%)
Nivolumab/ipilimumab		CheckMate-649 (phase III): nivolumab + ipilimumab vs. FOLFOX/XELOX			CheckMate-032 (phase I/phase II): ORR, 26% PD-L1 unselected; ORR, 44% PD-L1$^+$ (> 1%)
Durvalumab/tremelimumab					NCT02340975 (phase I/phase II) durvalumab vs. tremelimumab vs. combination

Abbreviations: GEJ, gastroesophageal junction; 5-FU, fluorouracil; FOLFOX, leucovorin calcium (folinic acid)/fluorouracil/oxaliplatin; XELOX, capecitabine (Xeloda)/oxaliplatin; OS, overall survival; ORR, objective response rate.

event. PD-L1 positivity was reported in 40% of gastric/GEJ tumors, and the authors defined positivity as membranous staining on more than 1% of scorable cells or the presence of a distinctive interface pattern using immunohistochemistry clone 22C3.[22]

The KEYNOTE-028 study evaluated the role of pembrolizumab (10 mg/kg every 2 weeks up to 2 years or until progression) in PD-L1$^+$ advanced solid tumors including esophageal/GEJ cancers (adenocarcinoma and squamous cell cancer).[30] From the data presented to date, 23 patients were enrolled, with a median follow-up duration of 31 weeks (range, 5.7–71), and 87% had received two or more prior therapies. The objective response rate was 30% (95% CI, 13.2–52.9) with 6- and 12-month progression-free survival rates of 30.4% and 21.7%, respectively. In this trial, 74% of patients had squamous histology.

Per ongoing efforts in other solid tumors, PD-1 inhibitors are being combined with cytotoxic chemotherapy in an attempt to improve response rates. The KEYNOTE-059 study is a first-line HER2$^-$ phase II study of patients with advanced

gastric/GEJ adenocarcinoma. Patients receive 200 mg of pembrolizumab plus 800 mg/m^2 of fluorouracil (5-FU; or 1,000 mg/m^2 of capecitabine in Japan) plus 80 mg/m^2 of cisplatin every 3 weeks for six cycles, followed by pembrolizumab plus 5-FU/capecitabine maintenance for up to 2 years or until progression.[31] After a median follow-up of 5.5 months (range, 4.0–7.3), 17 patients (94%) had experienced a treatment-related adverse event (any grade), including anorexia, nausea, and neutropenia; of these patients, 12 (67%) experienced grade 3–4 toxicities. These preliminary data suggest that combinatorial PD-1/chemotherapy therapy has manageable toxicity profiles for patients with advanced gastric cancer. We await the efficacy data from this study; given the positive results from a lung cancer trial of pembrolizumab plus chemotherapy, it is hoped that they will be similar in esophagogastric cancer.[32]

Important ongoing phase III studies are the KEYNOTE-061 and the KEYNOTE-062 trials. KEYNOTE-061 is an open-label trial evaluating pembrolizumab versus paclitaxel for patients with advanced gastric or GEJ cancer whose tumors have progressed after first-line therapy with a platinum/fluoropyrimidine combination.[33] Patients are randomly assigned to receive 200 mg of pembrolizumab every 3 weeks or 80 mg/m^2 of paclitaxel on days 1, 8, and 15 of a 28-day cycle. Treatment will continue until the disease progresses or the drug is no longer tolerated; the primary efficacy endpoints are progression-free survival and overall survival for patients with PD-L1$^+$ tumors. The KEYNOTE-062 trial is designed to compare the efficacy and safety of pembrolizumab alone (200 mg every 3 weeks) or in combination with cisplatin plus 5-FU (cisplatin 80 mg/m^2 every 3 weeks and 5-FU 800 mg/m^2 on days 1–5 of each 3-week cycle) with chemotherapy alone (cisplatin + 5-FU) as first-line therapy for PD-L1$^+$/HER2$^-$ advanced gastric or GEJ adenocarcinoma. Primary endpoints are overall survival and progression-free survival.

Avelumab (PD-L1 Inhibitor)

Avelumab, an anti–PD-L1 IgG1 antibody, is currently being assessed in the JAVELIN program (NCT01772004) with expansion cohorts for selected tumor types, including gastric/GEJ tumors (Table 2).[34] Patients received 10 mg/kg of avelumab every 2 weeks, and preliminary data show a 9.7% response rate in the second-line setting. For Japanese patients who had progressed while receiving prior chemotherapy, the reported overall response rate was 15% (three of 20 patients), with the proportion of patients' progression-free survival at 12 weeks being 43.3%.[35] The JAVELIN Gastric 300 trial is currently recruiting patients with recurrent, locally advanced, or metastatic gastric/GEJ tumors in an open-label study comparing avelumab to best supportive care in the third-line setting (NCT02625623). Maintenance immunotherapy is being assessed in the JAVELIN Gastric 100 study, which compares single-agent avelumab (10 mg/kg every 2 weeks) to continuation of first-line chemotherapy (5-FU/leucovorin or capecitabine plus oxaliplatin; NCT02625610).[36]

Durvalumab (PD-L1 Inhibitor)

Durvalumab is a selective, high-affinity, human IgG1κ monoclonal antibody that blocks PD-L1 binding to CD80 and PD-1. Investigators reported that 10 mg/kg of single-agent durvalumab given intravenously every 2 weeks for 12 months showed potential clinical activity in gastroesophageal cancers.[37] A small 26-patient phase II open-label study is currently investigating treatment with 1,500 mg of maintenance durvalumab given intravenously every 4 weeks to patients with persistent residual esophageal cancer after definitive surgery following concurrent chemoradiation (NCT02639065). A phase IB/II study is currently enrolling patients with GEJ or gastric adenocarcinomas in the second- and third-line metastatic settings for treatment with single-agent durvalumab, single-agent tremelimumab, or combination durvalumab and tremelimumab (anti–CTLA-4).[38]

ADJUVANT AND NEOADJUVANT STUDIES IN STAGE II/III ESOPHAGOGASTRIC CANCER

Alternative approaches to improve patient outcomes with acceptable toxicity might include substitution of immunotherapy into the adjuvant or indeed neoadjuvant setting in stage II or stage III disease (Table 3). Given the potentially harmful effects of multiple chemotherapy treatment regimens on the immune system, it is possible that application of PD-1 pathway blockade earlier in a disease course before a tumor metastasizes may significantly enhance a drug's ability to induce immune-mediated cancer regression. In addition, it is postulated that PD-L1 and other immune biomarkers may actually be induced by prior anticancer therapy including chemoradiation.[39] We have shown that after neoadjuvant therapy, there is a consistent trend for chemoradiation to induce more TILs (tumor lymphocytes), clustering of lymphocytes around tumor-associated blood vessels (perivascular lymphocytes), and clusters of lymphocytes (tertiary lymphoid structures).[13] The appearance of these microenvironment features after induction therapy suggests that a tumor will respond favorably to immune-based therapy and, in particular, to PD-1–based checkpoint blockade. This provides an intriguing possibility to study the efficacy of neoadjuvant and adjuvant PD-1 inhibition.

CheckMate-577 is a randomized phase III study of adjuvant nivolumab for patients with resected lower esophageal/gastroesophageal cancer (Table 4). Approximately 760 patients will be randomly selected in a 2:1 fashion to receive either 240 mg of nivolumab intravenously once every 2 weeks for 16 weeks and then 480 mg once every 4 weeks for a maximum of 12 months or to the current standard of care (placebo). To date, this is the largest adjuvant study of a checkpoint inhibitor performed in esophageal cancer. Primary endpoints are overall and disease-free survival. Results of this study are eagerly anticipated, as the lack of data for adjuvant chemotherapy after trimodality therapy in resected stage II/III esophageal cancer has led to confusion about the optimal treatment strategy for patients who do not achieve a pathologic complete response to neoadjuvant chemoradiation. Smaller phase I/II studies with differing

designs are currently assessing the safety and efficacy of nivolumab, pembrolizumab, and durvalumab in the neoadjuvant setting, given either concurrently or sequentially with neoadjuvant chemoradiation.

CONCLUSION

Preliminary data from clinical trials involving single-agent checkpoint inhibitors in metastatic gastroesophageal cancer have demonstrated response rates of approximately 22%–27% for the subset of patients with PD-L1$^+$ tumors (40%) and response rates of approximately 10%–17% for unselected patients. In addition, as with other solid tumors, it is likely that viral infection, mutational burden, and MSI status will be predictive of response to checkpoint inhibitors, driven in part by differences in the density of TILs and PD-L1 expression. We do, however, need a much greater understanding as to how immunosuppressive factors such as myeloid-derived suppressor cells, CD4$^+$CD25$^+$FoxP3$^+$ regulatory T cells, and IDO interact in the immune microenvironment in esophagogastric cancer. We must also determine whether tumor location plays a role, with distinctive biology emerging between esophageal, GEJ, and gastric cardia tumors. A recent TCGA publication on esophageal cancer showed that no esophageal adenocarcinomas were positive for MSI or EBV.[5] However, among GEJ adenocarcinomas that were not clearly of esophageal origin, the authors did identify MSI$^+$ and EBV$^+$ tumors.

It is also hoped that we can determine whether specific mutational changes akin to the recently described *JAK1/2* mutations leading to loss of IFN-γ signaling are present in esophageal and gastric cancer.[40] These immunotherapy-resistant mutations represent an immune-editing process that defines patients with cancer who would not be good candidates for PD-1 blockade therapy. We must ensure that the genomic data obtained from the esophageal and gastric TCGA are used in future immunotherapy trials as we look for signals for responsive or resistant disease. The efforts to identify predictive signatures to guide our treatment decisions are of crucial importance, and we must refine PD-L1 assessment so that it becomes easier to interpret. In 2017, we know that the higher the PD-L1 expression, the higher the response rate; this seems to be similar for combination strategies involving PD-1/CTLA-4 inhibitors. However, there is a substantial subset of patients with PD-L1$^-$ tumors that respond to combination strategies, with 21% of heavily pretreated patients responding to nivolumab/ipilimumab combinations. In the coming years, it is hoped that as the larger phase II/III esophagogastric immunotherapy studies mature, we will gain a more nuanced understanding of the interactions that are occurring in the immune microenvironment so that individualized tailored treatment can be prescribed for patients so that the true promise of immunotherapy can be realized in these diverse tumors.

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Pancreatic Adenocarcinoma: Improving Prevention and Survivorship

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OVERVIEW

Pancreatic cancer is a growing problem in oncology, given slowly rising incidence and continued suboptimal outcomes. A concerted effort to reverse this tide will require prevention, early diagnosis, and improved systemic therapy for curable disease. We focus on these aspects in detail in this study. Hereditary pancreatic cancer is an underappreciated area. With the growing use of genomics (both somatic and germline) in cancer care, there is increasing recognition of hereditary pancreatic cancer cases: around 10% of all pancreatic cancer may be related to familial syndromes, such as familial atypical multiple mole and melanoma (FAMMM) syndrome, hereditary breast and ovarian cancer, Lynch syndrome, and Peutz-Jeghers syndrome. Screening and surveillance guidelines by various expert groups are discussed. Management of resectable pancreatic cancer is evolving; the use of multiagent systemic therapies, in the adjuvant and neoadjuvant settings, is discussed. Current and emerging data, along with ongoing clinical trials addressing important questions in this area, are described. Surveillance recommendations based on latest ASCO guidelines are also discussed. Finally, the multimodality management of borderline resectable pancreatic cancer is discussed. The various clinicoanatomic definitions of this entity, followed by consensus definitions, are described. Then, we focus on current opinions and practices around neoadjuvant therapy, discussing chemotherapy and radiation aspects, and the role of surgical resection.

Pancreatic adenocarcinoma remains a vexing cancer. Incidence is increasing slowly, but clinical outcomes have not improved remarkably. There are 53,670 new cases expected in the United States in 2017,[1] and it is expected to be the second leading cause of cancer-related deaths by 2030.[2] Important reasons for these statistics are late diagnosis—only about 20% of cases present as resectable disease—and suboptimal efficacy of systemic therapies. Therefore, prevention, early diagnosis, and improved therapeutic approaches and agents are components of a broad strategy aimed at reducing morbidity and mortality from this cancer. Our focus is to discuss these components, highlighting state-of-the-art evidence and future directions.

BEST PRACTICES IN MANAGEMENT OF RESECTABLE PANCREATIC CANCER: EMERGING STANDARDS FOR ADJUVANT THERAPY AND SURVEILLANCE

Definition of Resectability

The terms resectable, borderline resectable, and unresectable tumor are emerging as consensus terminology to describe the feasibility of surgical resection. These are based largely on the relationship of the tumor to surrounding blood vessels. Borderline resectable cancer is discussed in detail in the final section. For resectable cancers, we focus on tumor-vessel wall interface, describing the extent of the interface in terms of geometry (degrees of circumference), instead of subjective terms such as abutment, involvement, impingement, encasement, etc. The working definition of resectable cancers is derived from the Intergroup approach[3]:

- Absence of tumor-artery (celiac artery, common hepatic artery, superior mesenteric artery, and, if present, replaced right hepatic artery) interface;
- No involvement, or < 180° tumor-vein (portal vein, superior mesenteric vein) interface, and patent portal vein/splenic vein confluence; and
- Absence of metastatic disease (including lymphadenopathy outside the surgical basin).

Based on this definition, about 15%–20% of cases of pancreatic cancer are resectable at presentation.

Standard of Care for Resectable Disease

The standard of care is upfront resection followed by adjuvant therapy (Table 1). The goal of resection is to remove all macroscopic disease; all attempts should be made

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TABLE 1. Key Published Adjuvant Therapy Trials in Pancreatic Adenocarcinoma

Study, Year First Published	Total Patients	Treatment Arms	Primary Outcome	Result*
GITSG, 1985	43	5-FU/RT × 2 years, Sx	OS	20 vs. 11 (p = .03)
EORTC, 1999	218	5-FU/RT, Sx	OS	24.5 vs. 19 (HR 0.8; p = .21)
ESPAC-1, 2004	289	4 arms, 2 × 2 design: 5-FU vs. no comparison	OS	20.1 vs. 15.5 (HR 0.71; p = .009)
ESPAC-1, 2004	289	4 arms, 2 × 2 design: RT vs. no comparison	OS	15.9 vs. 17.9 (HR 1.28; p = .05)
CONKO-001, 2007	368	Gem, Sx	DFS	13.4 vs. 6.7 (HR 0.55; p < .001)
RTOG 9704, 2008	451	5-FU with 5-FU/RT, Gem with 5-FU/RT	OS	NA (HR 0.93; p = .51)
ESPAC-4, 2017	730	Gem with capecitabine, Gem	OS	28 vs. 25.5 (HR 0.82; p = .032)

*All outcomes are shown in months.

Abbreviations: RT, radiation; Sx, surgery; Gem, gemcitabine; DFS, disease-free survival; NA, not available.

to obtain negative surgical margins. A common adjuvant approach consists of gemcitabine for 6 months, based on improved disease-free survival (primary outcome) seen in the CONKO-001 study.[4] Overall survival (OS) was marginally improved with gemcitabine in this trial. The ESPAC-1 study also suggested an improvement in OS with the addition of adjuvant 5-fluorouracil (5-FU).[5] The ESPAC-3 and RTOG-9704 trials showed no difference between gemcitabine and 5-FU, making either approach reasonable.[6,7] The role of adjuvant radiation remains controversial: there are no data clearly showing improvement in OS with the addition of radiation, other than the original GITSG study, albeit a small trial with older treatment methods.[8] In fact, later studies such as ESPAC-1 and EORTC 40891 showed no improvement in OS with adjuvant chemoradiation.[5,9] A meta-analysis of these trials of adjuvant therapy showed that 5-FU is associated with the most benefit, gemcitabine with modest benefit, and chemoradiation with no benefit.[10] Although the nuances of each study and differences between the various trials are debatable, it is clear that even with the best care standard today, surgery followed by adjuvant therapy, the median OS remains less than 2 years (Table 1).

KEY POINTS

- **Around 10% of pancreatic cancer cases may be familial.**
- **Increased genetic testing may allow early identification of persons at risk of developing pancreatic cancer, and surveillance recommendations are available to guide follow-up.**
- **For resected pancreatic cancer, adjuvant therapy standards are evolving toward multiagent chemotherapy regimens; the role of radiation is being tested.**
- **Borderline resectable pancreatic cancer is now well-recognized as an important clinical entity, and a consensus definition and management paradigms are evolving.**
- **Neoadjuvant chemotherapy is being tested for resectable tumors and chemotherapy and chemoradiation strategies for borderline resectable tumors. Results from these trials in the coming years will help refine standards of care.**

Emerging Standards for Resectable Disease

The ESPAC-4 trial results were published recently.[11] It was shown that adjuvant gemcitabine plus capecitabine, compared with gemcitabine alone, improved OS (28 vs. 25.5 months; hazard ratio [HR], 0.82; 95% CI, 0.68–0.98; p = .032). Therefore, the addition of capecitabine to adjuvant gemcitabine may become the new standard of care for adjuvant therapy. In addition, this is the first large study to report median OS of more than 2 years in this setting; it is unclear if this is the result of better patient selection with improved imaging techniques, better overall management, or both.

The growing realization, however, is that pancreatic cancer is a systemic disease from the outset.[12] The ideal approach, therefore, is to treat with systemic therapy upfront. We now have FOLFIRINOX (5-FU, irinotecan, and oxaliplatin) and gemcitabine/nab-paclitaxel as effective regimens in the metastatic setting.[13,14] It is only logical that these should be tested in the curative setting as well. The perioperative/neoadjuvant setting allows for early delivery of aggressive systemic therapy (which may not be feasible after major surgery), evaluation of chemosensitivity of cancer in vivo (potentially sparing those with chemotherapy-resistant disease major surgery), and tolerance of chemotherapy. This approach is being studied in various clinical trials (Table 2) for which results will guide future management strategies.

Role of Surveillance

After completion of adjuvant therapy, surveillance for recurrence remains undefined. The Clinical Practice Guidelines from ASCO recommend clinical evaluation every 3 to 6 months.[15,16] The use of routine imaging or serial tumor markers such as carbohydrate antigen (CA) 19.9 is not

TABLE 2. Key Ongoing Trials in Resectable Pancreatic Adenocarcinoma

Study, Clinical Trial Registry Number	Planned Duration	Planned Sample Size	Treatment Arms	Primary Outcome
RTOG 0848, NCT01013649	2009–2020	950	Adj Gem + RT, adj Gem	OS
NEOPAC, NCT01521702	2009–2014	310	Neoadj GemOx + adj Gem, adj Gem	DFS
UNICANCER, NCT01526135	2012–2020	490	Adj FOLFIRINOX, adj Gem	DFS
APACT, NCT01964430	2014–2019	846	Adj Gem/nab-P, adj Gem	DFS
NEPAFOX, NCT02172976	2014–2019	126	Periop FOLFIRINOX, adj Gem	OS
SWOG S1505, NCT02562716	2015–2018	150	Periop FOLFIRINOX, periop Gem/nab-P	OS
NEONAX, NCT02047513	2015–2019	166	Periop Gem/nab-P, adj Gem/nab-P	DFS

Abbreviations: adj, adjuvant; Gem, gemcitabine; RT, radiation; neoadj, neoadjuvant; Ox, oxaliplatin; DFS, disease-free survival; FOLFIRINOX, 5-FU, irinotecan, oxaliplatin; nab-P, nab-paclitaxel; periop, perioperative.

recommended because of lack of data showing clinical benefit of these interventions; limited data suggest that they may simply be contributing to lead-time bias, and they come at the cost of financial burden and emotional distress. Early detection of asymptomatic pancreatic cancer recurrence, unfortunately, does not translate into improved outcomes, unlike, for example, colorectal cancer, because of limited therapeutic options for pancreatic cancer.

MULTIMODALITY MANAGEMENT OF BORDERLINE RESECTABLE PANCREATIC CANCER: WHEN IS AN OPERATION APPROPRIATE?

Definition of Borderline Resectable Pancreatic Cancer

The definition of borderline resectable pancreatic cancer (BRPC) is evolving.[3,17] One approach is to evaluate this entity from three different perspectives[18]: (1) anatomic BRPC, defined based on tumor and vessel wall interface; (2) biologic BRPC, characterized by indeterminate or questionable metastatic disease; and (3) BRPC for comorbidities, including patients with poor performance status and/or major medical comorbidities.

Anatomic BRPC. Numerous definitions of anatomic BRPC have been proposed, with the greatest point of contention being related to the involvement of the superior mesenteric vein-portal vein (SMV-PV).[3,19,20] Some heterogeneity also depends on the experience of the physicians involved in the care of these patients, as the evaluation in experienced centers leads to a change in the staging and management of 20%–30% of cases.[21,22] The most common definitions are listed in Table 3. The definition of anatomic BRPC used in the Intergroup Trial A021101 relies on objective radiographic criteria to increase uniformity,[3] and it has been likewise adopted by the 2016 National Comprehensive Cancer Network (NCCN) guidelines. Anatomic BRPC often requires a vascular resection associated with pancreatectomy. A recent meta-analysis showed that, compared with patients undergoing standard pancreatectomy, those undergoing upfront surgery with SMV-PV resection had an increased risk of postoperative mortality (risk difference, 0.01) and R1/R2 resection (risk difference, 0.09) and poorer 5-year OS rates (hazard ratio, 3.18).[23] Similar results are reported for pancreatectomy with resection of superior mesenteric artery/common hepatic artery/celiac trunk. In a meta-analysis, arterial resections were associated with a significantly increased risk of perioperative mortality (odds ratio, 5.04) and of poor 3-year OS (odds ratio, 0.39) compared with patients without arterial resection.[24] In keeping with these data, involvement of the splenic artery has recently emerged as a new prognostic factor. This was not included in the formal definition of anatomic BRPC (Table 3) because pancreatic cancer involving splenic artery alone is usually technically resectable. Three studies indicate that 5-year OS was 0% for all patients with pathologic infiltration of the splenic artery, compared with 8%–32% when the splenic artery was uninvolved.[25-27] It can be postulated that the morphologic evidence of vascular infiltration represents the stigmata of more advanced disease, leading to a higher risk of incomplete (R1/R2) resection and distant metastases. Of note, R0 resections are associated with improved OS rates (18–41.6 months) when compared with R1 (14–23.4 months) or R2 resections (10–11 months).[28-30]

Biologic BRPC. In the setting of biologic BRPC, the disease is technically resectable, but there is a high likelihood of occult metastases. The proportion of patients who develop tumor recurrence and die within 1 year from surgery can be as high as 37%.[31,32] Factors associated with early recurrence after surgery include elevated CA 19.9, presence of back pain as presenting symptom, and duration of symptoms more than 40 days.[32-35] Particularly, high preoperative CA 19.9, with a cutoff ranging between 100 and 200 U/mL, has been correlated with the presence of micrometastatic disease.[32,35-38] A recent study analyzing 10,806 patients with early-stage pancreatic cancer from the National Cancer Database (NCDB) showed that those with CA 19.9 greater than 37 U/mL had significantly decreased survival at 1 and 3 years (56% vs. 68% and 15% vs. 25%, respectively) compared with patients with normal levels (< 37 U/mL).[37]

BRPC for comorbidities. Finally, some patients can be considered "borderline resectable" because of their poor performance status and/or associated comorbidities. Pancreatic resections are recognized as highly invasive procedures, with a considerable postoperative morbidity,[39] which may

preclude delivery of adjuvant therapy. As a matter of fact, only 62% of patients in the CONKO-001 trial received the planned full dose of adjuvant gemcitabine.[40] Only 54.3% of 1,144 patients who underwent pancreatectomy at Johns Hopkins University received adjuvant therapy, and these data are in keeping with adjuvant chemotherapy rates from national databases (51%–54%).[41-43] Postoperative complications and lower preoperative prognostic nutritional index were associated with failure to complete adjuvant chemotherapy in different studies.[41-44]

Management of BRPC: Neoadjuvant Treatment Strategy

Currently, there is no established standard of care for managing BRPC. Enrollment in a clinical trial is preferred. The neoadjuvant approach is widely considered as the step forward—we review extant literature and discuss possible strategies moving forward. It is worth nothing that the 2016 NCCN guidelines do not recommend upfront surgery for BRPC and suggest an initial approach involving neoadjuvant therapy, preferably at a high-volume center.

A note on semantics: Neoadjuvant treatment usually implies that resection is feasible and planned, whereas in many BRPC cases, that may not be true. In anatomic BRPC, especially, resection may not be feasible even after chemotherapy with/without radiation. The approach to allow resection in such cases may be better termed "conversion" therapy. However, as discussed further below, radiologic assessment after chemotherapy—and, especially, radiation—may not be entirely reliable, and surgical exploration may indeed be recommended. Given these uncertainties, unless unresectable, the term "neoadjuvant" continues to be in favor when applied to systemic therapy for pancreatic cancer where resection is being considered.

Several retrospective or population-based studies have been published to analyze the role of neoadjuvant treatment. The interpretation and comparison of these studies is difficult because they have used various definitions of borderline resectable, they sometimes include a combination of resectable, borderline resectable, and locally advanced tumors, and they used different neoadjuvant chemotherapy/chemoradiation regimens, with or without adjuvant treatment.[3,17] Considering these limitations, recent and growing data support the advantages of the neoadjuvant approach, with resectability rates of 60%–80% for patients with BRPC, R0 resection rate of 80%–90%, and median OS of 20–30 months in an intention-to-treat analysis for those resected, similar to survival rates of patients with up-front resectable disease.[45-49] Importantly, neoadjuvant chemotherapy/chemoradiation was not associated with increased postoperative morbidity and mortality.[45,49,50] Two recent studies analyzed a large cohort of resected patients with stage I to II pancreatic cancer from the NCDB and showed that neoadjuvant chemotherapy was associated with improved OS, lower pathologic T- and N-stage, and lower rates of positive resection margins.[45,46] Perioperative (neoadjuvant plus adjuvant) chemotherapy demonstrated a considerable OS advantage compared with adjuvant chemotherapy alone.[45] Another study identified 593 patients with stage III pancreatic cancer from the NCDB.[48] Of these, 377 (63.6%) underwent neoadjuvant treatment, and 273 (46%) had subsequent resection, in which 216 (36.4%) were in the surgery-first cohort. Intention-to-treat Kaplan-Meier analysis demonstrated superior survival for neoadjuvant compared with surgery-first strategy (median OS, 20.7 vs. 13.7 months).

Neoadjuvant Chemotherapy/Chemoradiation Regimens

Currently, given the lack of prospective randomized studies, no particular preoperative regimen can be recommended over others. Emerging clinical trials support the use of regimens most active in the treatment of systemic disease (FOLFIRINOX: gemcitabine/nab-paclitaxel).[50] There is also considerable debate regarding the role of neoadjuvant radiation in addition to chemotherapy. Chemoradiation has been considered to be particularly important to facilitate a margin-negative resection for those patients with anatomic BRPC, especially if there is an involvement of the superior mesenteric artery.[51] A recent analysis of the NCDB data failed to show a survival advantage for neoadjuvant chemoradiation over chemotherapy alone.[45] However, the quality of this analysis is limited by the lack of data on duration and intensity of radiation treatment. The choice to perform chemoradiation instead of chemotherapy alone was likely influenced by the extent of tumor and may reflect more advanced disease. Further studies are needed to clarify the role and timing of radiation therapy in the neoadjuvant setting, especially in patients with biologic BRPC without vascular involvement.

TABLE 3. Comparison of Borderline Resectable Pancreatic Cancer Definitions[3]

	AHPBA/SSAT/SSO	MDACC	NCCN	Intergroup
SMV-PV	Abutment/encasement/occlusion	Occlusion	Abutment/impingement/narrowing	Interface > 180°
SMA	Abutment	Abutment	Abutment	Interface < 180°
CHA	Abutment/short-segment encasement	Abutment/short-segment encasement	Abutment/short-segment encasement	Reconstructable short-segment interface
CA	Clear	Abutment	Clear	Interface < 180°

Abbreviations: AHPBA, American Hepato-Pancreato-Biliary Association; SSAT, Society for Surgery of the Alimentary Tract; SSO, Society of Surgical Oncology; MDACC, The University of Texas MD Anderson Cancer Center; NCCN, National Comprehensive Cancer Network; SMV-PV, superior mesenteric vein-portal vein; SMA, superior mesenteric artery; CHA, common hepatic artery; CA, celiac artery.

When Is an Operation Appropriate After Neoadjuvant Treatment?

The assessment of treatment response is critically important in patients with BRPC. In these patients, defining an appropriate treatment response can be challenging. Particularly, radiographic imaging can be inadequate to detect tumor response, as in most cases, considerable downsizing is not evident. The difficulty is likely because of the dense stromal component of pancreatic cancer, which may remain radiographically unchanged even in the presence of a noteworthy pathologic response, and the development of treatment-related fibrosis after treatment, especially chemoradiation.[52,53] Two recent studies reported a high number of pancreatic resections following neoadjuvant treatment in BRPC with a sizable proportion of R0 resection (> 60%) despite no considerable anatomic tumor downstaging.[54,55] The lack of a demonstrable radiologic response should not be considered a contraindication for surgical exploration in the absence of frank local or systemic progression. In view of these limitations, it would be useful to evaluate other (biologic) factors; currently, however, a reliable biomarker of response is lacking. Furthermore, the role of adjuvant therapy after resection of BRPC treated with neoadjuvant therapy remains to be defined.

In conclusion, in BRPC, enrollment in a clinical trial focusing on a neoadjuvant strategy should be considered strongly instead of upfront surgery. The recommended regimens of chemotherapy/chemoradiation remain to be determined. Surgical exploration after neoadjuvant therapy should be reserved for patients who have good performance status (ECOG score ≤ 1) and in whom there is absence of local and/or distant radiologic progression, even in the absence of a radiologic response.

HEREDITARY PANCREATIC CANCER: SURVEILLANCE AND MANAGEMENT

Genetic Basis

Approximately 10% of cases of pancreatic cancer are thought to have a familial basis.[56,57] Multiple studies have demonstrated that a family history of pancreatic cancer in a first-degree relative confers a significantly elevated risk,[58-63] and that risk increases with the number of first degree relatives affected. A large prospective study found that patients with one first-degree relative with pancreatic cancer had a standardized incidence ratio of 4.6, whereas those patients with three or more affected first-degree relatives had a standardized incidence ratio of 32.[64] These patients are considered to compose one broad group of hereditary pancreatic cancer, defined as familial pancreatic cancer.

Multiple hereditary syndromes also confer an elevated risk for developing pancreatic cancer. Patients with familial cancer syndromes, such as FAMMM syndrome (*p16*/*CDKN2A*), hereditary breast and ovarian cancer (*BRCA1*, *BRCA2*, and *PALB2*), Lynch syndrome (DNA-mismatch repair genes *hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*, and *hMSH6*/*GTBP*), and Peutz-Jeghers syndrome (*STK11*), have a significantly increased risk of developing pancreatic cancer.[65-67] Approximately 5%–10% of cases of hereditary pancreatic cancer are attributable to this group, broadly defined as those with pancreatic cancer–associated hereditary syndromes.[68] Next-generation sequencing and genome-wide association studies have identified additional potential susceptibility genes that may be implicated in familial pancreatic cancer.[69,70] Patients with a family history of prostate cancer, without a hereditary cancer syndrome, have an elevated risk (1.45-fold) of developing pancreatic cancer.[60] The novel capability to examine detailed gene associations will likely lead to better risk stratification and hopefully provide new opportunities for therapeutic interventions.

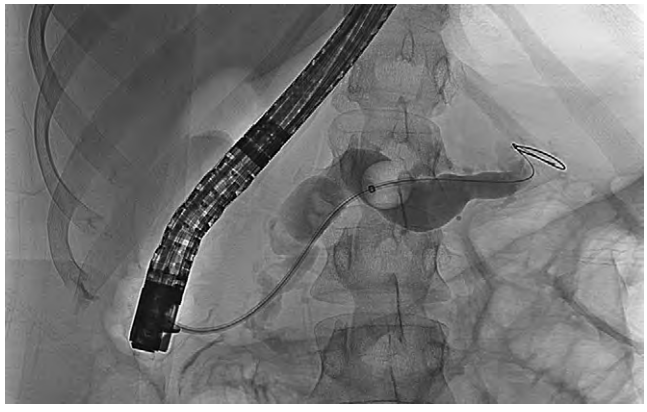
Hereditary Pancreatitis

In addition to familial pancreatic cancer and pancreatic cancer–associated hereditary syndromes, hereditary pancreatitis is a major risk factor for the development of pancreatic cancer.[67,71-73] Studies suggest that the standardized incidence ratio of patients with hereditary pancreatitis and pancreatic cancer may be as high as 87.[71,72,74] Hereditary pancreatitis is a rare cause of recurrent acute and chronic pancreatitis, often identified in patients in the first 2 decades of life, and frequently manifesting with parenchymal fibrosis and calcification, ductal distortions, and strictures (Fig. 1). Hereditary pancreatitis is attributed to defects in multiple genes, including *PRSS1*, *CFTR*, *CTRC*, and *SPINK1*.[67] One study suggested that patients with a history of both hereditary pancreatitis and cigarette smoking may develop pancreatic cancer approximately 20 years earlier than patients whose sole risk factor was cigarette smoking.[75] Given the predilection for progression to pancreatic cancer in patients with hereditary pancreatitis, screening should be considered, as described further in review of guidelines.

Clinical Features and Diagnosis

Hereditary and sporadic forms of pancreatic cancer present with similar clinical manifestations. Late presentation

FIGURE 1. Fluoroscopic Image From an ERCP in a Patient With Hereditary Pancreatitis



The patient was a 24-year-old woman with four hereditary pancreatitis mutations (one *CTRC*, one *SPINK1*, and two *CFTR* mutations) who presented with recurrent acute pancreatitis. Her pancreatogram revealed a severely dilated and ectatic pancreatic duct with side branch dilatation and stricturing in the pancreatic head and neck region.

is common.[76] The most common presenting symptoms include abdominal pain, asthenia, weight loss, and jaundice. Symptoms may vary depending on the location of the tumor; for instance, pancreatic head tumors more often present with jaundice and steatorrhea than tumors in the body or tail.[77] The initial work-up typically involves a laboratory evaluation and cross-sectional imaging. Abdominal CT has been shown to be more sensitive and specific than ultrasound for detecting pancreatic cancer.[78,79] MRI with magnetic resonance cholangiopancreatography is another option to delineate ductal anatomy and may help discriminate solid from cystic mass lesions. Endoscopic ultrasound (EUS) is the most sensitive modality for diagnosing pancreatic mass lesions, and EUS with fine needle aspiration can establish a tissue diagnosis in the vast majority of cases.[80,81] Endoscopic retrograde cholangiopancreatography (ERCP) is frequently indicated in patients with ductal obstruction, jaundice, and or ascending cholangitis. Although hereditary pancreatic cancer may present earlier than sporadic, it is still rare for hereditary pancreatic cancer to develop prior to the age of 45.[82] Hereditary pancreatic cancer is slightly more common in men than in women. A history of pancreatic cancer (especially in first-degree relatives), familial cancer syndromes, or a personal or family history of hereditary pancreatitis increases the probability of a hereditary predisposition.

Screening and Surveillance

Family members of patients with hereditary pancreatic cancer, familial cancer syndromes, or hereditary pancreatitis have a greatly increased risk of developing hereditary pancreatic cancer. The risks, benefits, and data on outcomes can allow patients and providers to make individualized decisions regarding strategies for screening and monitoring. Ideally, screening should be performed in patients who would be candidates for pancreatic surgery at an experienced center with a multidisciplinary team available to participate in their care. A validated risk-assessment model has been developed for hereditary pancreatic cancer (PancPRO), which can predict risk for the development of pancreatic cancer, based on age and mutation carrier probability.[83]

There have been several guidelines published for screening high-risk individuals for hereditary pancreatic cancer (Table 4). In 2007, the Fourth International Symposium of Inherited Diseases of the Pancreas updated recommendations for counseling people at risk for the development of pancreatic cancer. This panel recommended screening patients with a more than 10-fold increased risk for pancreatic cancer. This high risk group was defined as follows: (1) patients with three or more first-, second-, or third-degree relatives with pancreatic cancer, (2) patients who are known carriers of *BRCA1*, *BRCA2*, or *p16* with at least one first- or second-degree relative with pancreatic cancer, (3) patients who are known to be germline carriers of Peutz-Jeghers syndrome, (4) patients with two relatives in the same lineage (and one of those who is a first-degree relative) with pancreatic cancer, and (5) patients who have a diagnosis of hereditary pancreatitis. However, this group was unable to form a consensus on how or when to perform screening.[84]

In 2013, screening guidelines by the International Cancer of the Pancreas Consortium were published. Their suggested high-risk screening population was similar, but added patients who carried the hereditary breast cancer gene *PALB2* as well as patients who were known carriers of DNA-mismatch repair genes (Lynch syndrome). For the initial screening modality and subsequent surveillance, this group recommended EUS as the primary and MRI/magnetic resonance cholangiopancreatography as the secondary modality. Abdominal CT was not favored because of the use of ionizing radiation, and ERCP was not favored because of the lack of additional diagnostic yield and the risk of post-ERCP pancreatitis. The recommended screening interval was 6–12 months for a nonsuspicious cyst and 3 months for an indeterminate solid lesion or indeterminate main pancreatic duct stricture. They were unable to form a consensus on which patients should undergo surgery, recommending individualized decision making.[85]

TABLE 4. Summary of Published Guidelines for Screening for Pancreatic Cancer

		Published Guidelines		
Criterion	**Relative Risk for PC**	**4th International Symposium**	**CAPS Consortium**	**ACG 2015**
More than 3 relatives with PC	Up to 32	✔	✔	✔
Two relatives with PC, one an FDR	Up to 6	✔	✔	✔
Known carrier of PJS (*STK11* gene)	132	✔	✔	✔
Known carrier of HBOC (*BRCA1*, *BRCA2*, and *PALB2* genes)	3–10	✔	✔	✔
Known carrier of FAMMM (*p16* gene)	13–36	✔	✔	✔
Known carrier of Lynch syndrome (DNA-mismatch repair genes)	8.6		✔	✔
Known diagnosis of hereditary pancreatitis (*PRSS1*, *SPINK1*, and other genes)	50–82	✔		✔

Abbreviations: PC, pancreatic cancer; CAPS, Cancer of the Pancreas Screening; ACG, American College of Gastroenterology; FDR, first-degree relative; PJS, Peutz-Jeghers syndrome; HBOC, hereditary breast and ovarian cancer; FAMMM, familial atypical multiple mole melanoma.

The American College of Gastroenterology published their screening guidelines in 2015. They defined high-risk individuals who should be screened for pancreatic cancer similarly, but expanded their recommended screening to individuals with fivefold or higher relative risk for pancreatic cancer and added additional familial cancer syndromes (Table 4). They recommended surveillance be performed at experienced centers under research conditions and using a multidisciplinary approach. They recommended surveillance with EUS or MRI and specified that surveillance be annual, starting at age 50, or 10 years younger than the earliest age of pancreatic cancer in the family, or at age 35 in individuals with Peutz-Jeghers syndrome. No guidelines could be issued as to when surgery would be indicated and noted that this decision is best individualized after multidisciplinary assessment.[86]

Management

There are no established guidelines on the management of pancreatic lesions found during screening, which occurs up to 42% of the time during screening of individuals at risk for hereditary pancreatic cancer.[87] A conservative, individualized, stepwise approach to management, based on the type of lesion identified, and performed at an experienced center with input from a multidisciplinary team is recommended. Rarely, solid pancreatic lesions are detected during screening with EUS or MRI. These lesions can be true cancers, pancreatic neuroendocrine tumors, or low-grade pancreatic intraepithelial neoplasia.[87,88] For solid or concerning lesions, EUS-guided fine needle aspiration with on-site cytology may often be helpful in the evaluation. For suspicious solid lesions (≥ 1 cm, visualized on multiple imaging modalities) or with positive cytology, surgical resection may be indicated. For indeterminate solid lesions (subcentimeter, seen on only one imaging modality, or with negative cytology), close interval surveillance may be considered. Each case should be individualized and presentation at a multidisciplinary tumor board for a consensus recommendation is frequently beneficial.

Cystic lesions are found in approximately 60% of those screened, and the prevalence increases with increasing age.[87] The majority of these cysts are low-risk, small side-branch intraductal papillary mucinous neoplasms that remain stable throughout the surveillance period.[89,90] EUS-guided fine needle aspiration is not recommended for very small cystic lesions because of the low cytologic yield[91]; however, EUS may be indicated with larger cysts or for cysts with worrisome features (pancreatic ductal dilatation > 5 mm, lymphadenopathy, thickened or enhancing cyst walls, solid component or mural nodule, or growth on surveillance imaging).[92] Benign-appearing cystic lesions may be monitored with repeat annual imaging. Main pancreatic duct strictures should be evaluated with EUS with or without fine needle aspiration and followed with surveillance imaging to exclude an occult neoplasm.

In conclusion, genetics play an increasingly recognized role in the development of pancreatic cancer. Hereditary pancreatic cancer predisposition may be considered in three groups: familial pancreatic cancer (individuals with multiple family members with pancreatic cancer), hereditary syndromes with pancreatic cancer associations (FAMMM, hereditary breast and ovarian cancer, Lynch, and Peutz-Jeghers syndrome), and hereditary pancreatitis. With the development of next-generation genome sequencing, additional, novel mutations are being associated with pancreatic cancer. Guidelines can steer providers to screening modalities and frequency; however, there is no clear consensus, and surveillance is individualized based on the patient's wishes, risk, and suitability for surgical management if a lesion is detected. For patients who wish to be proactive and have risk factors for the development of pancreatic cancer, we may offer alternating EUS and MRI on a yearly basis. Given the poor prognosis, it is hoped that more refined genetic data combined with more powerful screening and surveillance tools may lead to early detection that can translate to improved OS.

CONCLUSION

Pancreatic cancer remains a difficult, and growing, problem in oncology. We are now better understanding the biology, especially with respect to genomic (both somatic and germline) alterations as pathogenic, predictive, and prognostic factors. Better interventional and surgical approaches are minimizing procedural morbidity and mortality. We have some improvement in overall outcomes with aggressive systemic regimens. However, the ultimate goal of considerable improvement in clinical outcomes will require continued scientific and clinical investigations, multidisciplinary care of patients, and focus on collaborative research across various institutions. We have highlighted the emerging trends in early diagnosis, especially in known or suspected cases of familial origins of pancreatic cancer, neoadjuvant and perioperative approaches for resectable and borderline resectable cases, and key ongoing clinical trials that can help us better understand the nuances of multimodality management of these cases.

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The Promise of Immunotherapy in the Treatment of Hepatocellular Carcinoma

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OVERVIEW

Advanced hepatocellular carcinoma (HCC) has presented a therapeutic challenge. Despite its heterogeneity, which is partially related to its various etiologies, it frequently arises in a background of chronic inflammation, which makes it a potentially excellent candidate for immunotherapeutic approaches. There is evidence of antitumor immunity in HCC as manifested by the cell infiltrate and its association with prognosis, the presence of tumor-associated antigens, and the reports of immune-mediated spontaneous regressions. However, both the liver itself and the tumor environment possess a diverse armamentarium of mechanisms that suppress antitumor immunity. Here, we describe the rationale for immunotherapy in HCC and discuss the emerging clinical data from various immunotherapeutic approaches including checkpoint inhibition, cell therapy, oncolytic viral therapy, and various combinatorial approaches. We also highlight the potential for various modalities to be adapted across different stages of the disease.

HCC has an incidence of over 500,000 new cases globally and is the second most frequent cause of cancer-related deaths worldwide.[1] In the United States, the incidence of HCC has increased from 4.4 per 100,000 (95% CI, 4.3–4.5) in 2000 to 6.7 per 100,000 (95% CI, 6.6–6.8) in 2012.[2] The curative treatment options of liver transplantation or liver resection are limited to patients who present with early-stage disease, typically defined as Barcelona Clinic Liver Cancer (BCLC) stage A. The treatment of more advanced disease, defined as BCLC stages B and C, has been a challenge; locoregional modalities such as transarterial chemoembolization or radioembolization for patients with BCLC stage B disease result in a median survival of about 20 months[3]; sorafenib, the multitargeted kinase inhibitor, is the only approved systemic therapy for advanced HCC (BCLC stage C) with a median survival of 10.5 months reported in the SHARP trials and 6.5 months in the Asia Pacific study.[4,5] Needless to say, there is a pressing need for more effective treatment options that would result in longer survival and expand the chance of cure to more patients.

BRIEF OVERVIEW OF THE CURRENT STATUS OF TREATMENT OF ADVANCED HCC

As noted earlier, sorafenib continues to be the only standard therapeutic option for patients with advanced HCC, commonly defined as those with extrahepatic metastases, vascular invasion, or multifocal liver-limited disease that has failed locoregional therapy. Since the approval of sorafenib, there were multiple randomized phase III trials that compared other targeted agents or a combination of targeted agents to sorafenib, all of which failed to reach their primary endpoint (Table 1).[6-10] At the time of this review's publication, a press release had recently reported that a randomized phase III study of lenvatinib versus sorafenib in patients with HCC who had not previously received systemic treatment reached its primary endpoint of noninferiority for overall survival (OS), but with superior response rates and progression-free survival compared with sorafenib. In the setting of second-line treatment (after sorafenib failure), prior to the results of the RESORCE trial, several phase III trials comparing agents such as brivanib,[7] ramucirumab,[11] and everolimus[12] to placebo had failed to show an improvement in OS. In the RESORCE study,[13] patients with documented radiologic progression on sorafenib who had tolerated a dose of 400 mg or higher of sorafenib daily for 20 of the last 28 days, were randomly selected in a 2:1 fashion to receive regorafenib versus placebo. Regorafenib resulted in superior OS (10.6 vs. 7.8 months; HR 0.62, 95% CI, 0.50–0.78) and became the first agent to show a clinically and statistically meaningful benefit after sorafenib failure.

THE RATIONALE FOR IMMUNOTHERAPY IN HCC

Evidence of Antitumor Immunity in Patients With HCC

Despite being rare, there are scattered reports in the literature of spontaneous HCC regression, which has been

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TABLE 1. The Challenge: First-Line Randomized Phase III Trials

Phase III	Target(s)	Time to Progression (Months)	Overall Survival (Months)
Sunitinib vs. sorafemb (Cheng et al[6])	VEGFRs, PDGFRs, c-kit, (Flt)3, RET	3.8 vs. 4.1; HR 1.13, 95% CI, 0.98–1.31; p = 0.16	7.9 vs. 10.2; two-sided p < .0014
Brivanib vs. sorafenib (Llovet et al[7])	VEGFR2, FGFR	4.2 vs. 4.1; HR 1.01, 95% CI, 0.88–1.16	9.5 vs. 9.9; HR. 1.06, 95% CI, 0.93–1.22; p < .373
Linifanib vs. sorafenib (Cainap et al[8])	VEGFR and PDGFR	5.4 vs. 4; HR 0.76, 95% CI, 0.64–0.89; p < .001	9.1 vs. 9.8; HR 1.04, 95% CI, 0.89–1.22; p = NS
Sorafenib + erlotinib vs. sorafenib + placebo (Zhu et al[9])	VEGFR1/2/3, Ras, Raf, EGFR	3.2 vs. 4; HR 1.13, 95% CI, 0.94–1.36; p = 0.91	9.5 vs. 8.5; 0.92, 95% CI, 0.78–1.1; p = 0.2
Doxorubicin + sorafenib vs. sorarfenib CALGB 80802 (Abou Alfa et al[10])	VEGFR1/2, PDFG, Ras, Raf	3.6 vs. 3.2; HR 0.90, 95% CI, 0.72–1.2	9.3 vs. 10.5; HR 1.06, 95% CI, 0.8–1.4

attributed to the host antitumor immune response as well as vascular events.[14,15] Patients with HCC tumors who have a marked proinflammatory T-cell infiltrate with a high CD4:CD8 ratio have a reduced risk of tumor recurrence following liver transplantation; the hypothesis behind the CD4:CD8 ratio impact is that CD8+ cytotoxic T cells rely on CD4+ helper lymphocytes for maximal effect.[16] Similarly, patients with resected HCC whose tumors contained a low intratumoral T-regulatory lymphocytes (Tregs) level in combination with high intratumoral activated CD8+ cytotoxic T cells (CTLs) had improved disease-free survival and OS.[17] The other evidence of immunogenicity in HCC comes from the presence of tumor-associated antigens recognized by CTLs in 50%–70% of patients with HCC[18,19]; the tumor-associated antigens recognized by CTLs included cyclophilin B, squamous cell carcinoma antigen recognized by T cells (SART) 2, SART3, p53, multidrug resistance-associated protein (MRP) 3, alpha-fetoprotein (AFP), and human telomerase reverse transcription (hTERT). Unfortunately, the presence of intratumoral T-cell infiltration that could inhibit tumor growth and the detectable adaptive immune responses against tumor antigens are counteracted by tolerance-inducing mechanisms that prevent a consistent effective antitumor response.[20]

KEY POINTS

- **HCC continues to represent a major therapeutic challenge.**
- **HCC is an immunogenic disease.**
- **Antitumor immunity is suppressed by various mechanisms in HCC.**
- **Checkpoint inhibition has shown consistent and promising early signals of efficacy.**
- **Combinatorial approaches of various immunotherapies or of immunotherapy with standard modalities hold great promise.**

The Immunosuppressive Environment of HCC

Both the liver itself and the tumor environment possess a diverse armamentarium of mechanisms that suppress antitumor immunity. These mechanisms of immune tolerance have been described in several elegant reviews,[21,22] and a detailed discussion of these mechanisms is beyond the scope of this article. However, we will highlight a few examples of immunosuppressive processes that represent opportunities for potentially effective immunotherapeutic interventions.

Upregulation of inhibitory molecules. CTLA-4, PD-1, TIM-3, LAG-3 (lymphocyte activation gene 3 protein), and BTLA (B and T lymphocyte attenuator) are coinhibitory molecules known as immune checkpoints that regulate the activation of T cells to prevent unchecked immune activation and collateral tissue damage.[23,24] Lower expression of levels of the PD-1 ligands, PD-L1 and PD-L2 in HCC tumor cells, is associated with superior disease-free survival and OS.[25] CD4 and CD8 lymphocytes infiltrating the tumor in hepatitis B–related HCC show expression of TIM-3 and are replicative senescent.[26] In the setting of hepatitis C infection, there is evidence of apoptosis in immune cells and spontaneous T-cell exhaustion, which are at least partially driven by upregulation of TRAIL, LAG-3, TIM-3, PD-1, and CTLA-4 in hepatitis C–primed peripheral blood mononuclear cells.[27]

Production of immunosuppressive cytokines. Interleukin-10 (IL-10), TGF-β, IDO, and arginase are among a long list of immunosuppressive molecules that HCC cells can produce to escape innate and adaptive immunity.[22] Tumor-associated macrophages in HCC produce IL-6, which in turn enhances IL-10 production by myeloid-derived suppressor cells (MDSCs); high IL-10 levels downregulate HLA class II expression by macrophages, which impairs antigen presentation, stimulates Treg cell expansion, and blocks natural killer cell activation.[28] IDO inhibits T-cell activation and proliferation, and promotes Treg cell function.[29,30] In the setting of HCC, IFN-γ production suppresses T-cell proliferation and functionality by a mechanism that is blocked upon addition of the IDO inhibitor 1-methyl-tryptophan.[31]

Shift toward an immunosuppressive environment driven by immune cell subtypes. MDSCs represent a diverse group of myeloid cells that suppress antitumor immunity and produce protumoral effects. Patients with HCC have been shown to have increased levels of CD14+ HLA-DR−/low MDSCs in the peripheral blood and in tumors. These MDSCs are unable to stimulate an allogeneic T-cell response, suppress T-cell proliferation, and induce CD4+ CD25+ Foxp3+ Treg expansion.[32] MDSCs contribute to the immunosuppressive milieu of HCC through a variety of other mechanisms that are detailed in a review by Wan et al.[33] One notable example is

the inhibition of natural killer cell cytotoxicity and cytokine release by MDSCs (CD14+ HLA-DR−/low).[34] Tumor-associated macrophages constitute another cell type with protumor effects by inducing angiogenesis and promoting tumor cell invasion and metastasis.[35] There is evidence of active dynamic interaction and communication between MDSCs, Tregs, and tumor-associated macrophages, which creates a network of immunosuppression. On one hand, tumor-associated macrophages produce chemokines such as CCL17, CCL18, and CCL22, which preferentially attract Treg and Th2 cells to the tumor and, in turn, impair CTL activation.[36] On the other hand, Treg production of IL-10, IL-4, and IL-13 can promote differentiation of monocytes into immunosuppressive tumor-associated macrophages.[37]

Impact of Tumor Immune Milieu on Patient Outcomes in HCC

There is an emerging body of literature linking the status of antitumor immunity to outcomes of patients with HCC treated with various modalities. The prognostic association of various components of the antitumor immunity with survival provides another justification for immunotherapy in this disease. In a study of 36 patients with HCC treated with hepatic intra-arterial infusion, the frequency of MDSCs was significantly lower in the group with complete or partial response to therapy compared with the group with stable disease or progressive disease ($p = .006$); furthermore, the OS of patients with a high frequency of MDSCs before treatment was significantly shorter ($p = .003$). The frequency of MDSCs remained as a prognostic marker on multivariate analysis.[38] Gao and colleagues evaluated the impact PD-L1 and PD-L2 expression in tumors in patients with resected HCC; the median disease-free survival and OS were 14.9 and 29.6 months, respectively, for PD-L1–positive patients compared with not reached and 59.4 months for PD-L–1 negative patients, respectively ($p = .047$ and $p = .029$, respectively). Similarly, there was a significant association between PD-L2 expression and OS ($p = .041$).[39] In another study, CD3+, CD4+, CD8+, Foxp3+, and granzyme B+ tumor-infiltrating lymphocytes were assessed by immunohistochemistry in tissue microarrays containing HCC from 302 patients. The presence of low intratumoral Tregs in combination with high intratumoral activated CD8+ CTLs, a balance toward CTLs, was an independent prognostic factor for both improved disease-free survival ($p = .001$) and OS ($p < .0001$). Five-year OS and disease-free survival rates were only 24.1% and 19.8%, respectively, for the group with intratumoral high Tregs and low activated CTLs, compared with 64.0% and 59.4%, respectively, for the group with intratumoral low Tregs and high activated CTLs, respectively.[17]

CHECKPOINTS AS A THERAPEUTIC TARGET IN THE CLINIC

Targeting CTLA-4

As discussed previously, the upregulation of inhibitory immune checkpoints including CTLA-4 and PD-1 has been reported in the setting of HCC and has been associated with outcome. Given the success of targeting CTLA-4 and PD-1/PD-L1 in multiple solid tumors, it became important to evaluate the efficacy of checkpoint inhibitors in HCC. Tremelimumab, an IgG2 anti–CTLA-4 monoclonal antibody, was the first checkpoint inhibitor to be evaluated in HCC by Sangro and colleagues.[40] Patients with hepatitis C–related HCC, Child-Pugh A or B, and whose disease was not amenable to curative therapy, percutaneous ablation, or locoregional therapy were enrolled. Notable baseline characteristics included a Child-Pugh B status in 43% of patients, presence of portal vein thrombosis in 29%, and extrahepatic metastases in 10%. Twenty-four percent had received prior sorafenib treatment. In the 20 patients evaluable for safety, the most common treatment-related grade 3 or higher adverse events included AST and ALT elevation in 45% and 25%, respectively, total bilirubin elevation in 10%, neutropenia in 5%, and diarrhea and rash in 5% each. Seventeen patients were evaluable for treatment response; three patients (17.6%) had a confirmed partial response lasting 3.6, 9.2, and 15.8 months. Ten patients (58.8%) had stable disease. Intent-to-treat median time to progression was 6.48 months (95% CI, 3.95–9.14) and median OS was 8.2 months (95% CI, 4.64–21.34). One of the important conclusions of this small study was the feasibility of administration of an anti–CLTA-4 antibody to patients with HCC in the setting of liver cirrhosis and hepatitis C; the adverse events appeared to be manageable and the elevation of AST and ALT were transient and not associated with overall deterioration of liver function. Another important finding of the study is the documentation of antiviral and antitumor immune responses in patients; there was a statistically significant decrease in hepatitis C viral load in 11 patients at day 120 ($p = .011$) and in six patients at day 210 ($p = .017$) along with a general trend to increased number of virus-specific IFN-c–producing lymphocytes.[40]

Targeting PD-1/PD-L1

Nivolumab, a fully human IgG4 monoclonal antibody against PD-1, has been undergoing evaluation in CheckMate 040, a phase I/II study for patients with advanced HCC. Given hypothetical concerns about the risk of inducing immune-mediated fulminant hepatitis and the overall safety of checkpoint inhibition in the setting of viral hepatitis, the phase I part of the study included a classic 3 + 3 dose escalation in parallel separate cohorts of patients with hepatitis B, hepatitis C, and noninfected patients. There was no maximum tolerated dose despite escalation up to 10 mg/Kg every 2 weeks. One dose-limiting toxicity of grade 2 hepatic decompensation was noted at 10 mg/Kg in the uninfected cohort. The adverse events were consistent with the toxicity profile of nivolumab in other tumor types. During the phase I dose escalation part of the study, grade 3 and 4 treatment-related adverse events occurred in 25% of patients (12 of 48); the most common grade 3 and 4 adverse events were asymptomatic laboratory abnormalities including lipase increase in 13%, AST and ALT increase in 10% and 6%, respectively, and amylase increase in 4%. During the phase II expansion,

214 patients were recruited into one of four parallel cohorts: (1) noninfected sorafenib naive or intolerant, (2) noninfected sorafenib progressors, (3) hepatitis C–infected, and (4) hepatitis B–infected. The safety profile for the phase II expansion was similar to the dose escalation. Baseline characteristics for the overall patient population (dose escalation and expansion combined) were notable for 67% of patients who had prior treatment with sorafenib, 76% with extrahepatic metastases, and 8% with vascular invasion. All patients (except two) had Child-Pugh scores of 5 or 6. In terms of efficacy, the objective response rate based on RECIST 1.1 was 15% (including three complete responses) during dose escalation and 20% during dose expansion. Responses were seen across all cohorts independent of etiology. During dose escalation, for which there was adequate follow-up, the median duration of response was 17 months (95% CI, 6–24) and the median OS was 15 months (95% CI, 9.6–20.2). Median OS in the uninfected sorafenib progressor cohort was 13.2 months (95% CI, 8.6–NE [not estimable]); medians were not reached in the other dose-expansion cohorts. There was no clear association between PD-L1 expression on tumor cells (< 1% vs. ≥ 1%) and the likelihood of radiologic response. Other biomarkers are being evaluated in tumor samples and peripheral blood.[41-43]

In addition to nivolumab, other studies evaluating pembrolizumab, durvalumab and other PD-1– or PD-L1–targeting agents have been ongoing for hepatocellular carcinoma. Ongoing phase III studies are critical to validate the promising signal seen in early-phase trials; such phase III studies include Keynote-240, comparing pembrolizumab to placebo in patients who had documented disease progression on sorafenib or intolerance to sorafenib (NCT02702401), and CheckMate 459, comparing nivolumab with sorafenib in patients with advanced HCC who had not received other prior systemic therapy (NCT02576509).

Other checkpoints and costimulatory receptors. As is the case with other tumors, there is a rationale to block other immune checkpoints (such as Lag-3, TIM-3, etc.) and to evaluate antibodies that agonistically bind costimulatory receptors on immune cells (OX40, GITR, CD137). Early-phase studies evaluating such agents are ongoing, and some of them allow patients with HCC. There are also emerging efforts to combine agents that targets immune checkpoints such as PD-1 and CTLA-4 as well as other combinations involving costimulatory receptors.

Other combinations involving immune checkpoint antibodies. There is a large number of preclinical and clinical studies that are evaluating multiple modalities in combination with immune checkpoint inhibitors; the unifying concept is to harness various components of the immune system or to circumvent potential resistance mechanisms. An extensive review of this field is beyond the scope of this article. However, we will highlight a few approaches that highlight the potential of such combinations. Stereotactic radiation, in which a high dose of radiation is delivered to a limited area, can induce cell death and release of tumor antigens that can be recognized by the immune system to generate a tumor-specific T-cell immune response. In a preclinical model, the administration of an anti–PD-1 antibody concurrently with SBRT resulted in superior survival and was associated with increased CD8+ CTLs in the tumor and increased expression of PD-L1 on tumor-infiltrating macrophages.[44] Studies evaluating the combination of PD-1 or PD-L1 inhibitors with SBRT are recruiting patients with a variety of solid tumors. Embolization and ablative techniques have also been shown to release tumor antigen and stimulate antitumor immunity, which may be further enhanced with the simultaneous administration of checkpoint inhibitors. The combination of the anti–CTLA-4 antibody, tremelimumab, with subtotal radiofrequency ablation or chemoablation was evaluated in 32 patients with HCC; the majority of the patients' disease had progressed on or had been intolerant to sorafenib. This pilot study established the feasibility of the combination, as there were no dose-limiting toxicities and the side effect profile was consistent with that of tremelimumab. Nineteen patients had lesions that were evaluable for response outside of the areas treated with ablation or transarterial chemoembolization; five patients (26%; 95% CI, 9.1%–51.2%) achieved confirmed partial responses. The frequency of activated CD8+ T cells in the peripheral blood was increased by twofold over baseline and was sustained for at least 12 weeks. Tumor biopsies at the time of ablation revealed an increase in tumor-infiltrating lymphocytes compared with baseline.[45] The intriguing clinical and biologic activity noted in this pilot study should be further evaluated in subsequent larger but carefully designed trials.

LEVERAGING THE IMMUNE SYSTEM BEYOND CHECKPOINT INHIBITION

Immunotherapeutic approaches beyond checkpoint inhibition have been evaluated for hepatocellular carcinoma. These include adoptive cellular therapy, vaccines, and oncolytic viruses. Below we will highlight various examples of such approaches in HCC.

Cell Therapy

There are various forms of cell therapy including cytokine-induced killer cells (CIKs), tumor-infiltrating lymphocytes, and genetically modified T cells. Adoptive cell therapy using CIKs has been evaluated in the clinic for HCC. The promise of CIKs is highlighted in the results of a multicenter, open-label, randomized phase III study that evaluated their safety and efficacy as adjuvant therapy after curative therapy for HCC; 230 patients treated by surgical resection, radiofrequency ablation, or percutaneous ethanol injection were randomly assigned to receive immunotherapy (injection of 6.4 109 autologous CIKs, 16 times over 60 weeks) or no adjuvant therapy (control). The autologous CIKs consisted of CD3+/CD56+ T cells, CD3+/CD56– T cells, and CD3–/CD56+ natural killer cells. The median recurrence-free survival (primary endpoint) was 14.0 months longer in the immunotherapy group (44.0 months) than in the control group (30.0 months). The frequency of grade 3 and 4 adverse events and of serious adverse events was comparable between the two groups.[46]

The majority of the patients in this study had hepatitis B, tumors that measured less than 3 cm, and were treated with RFA most commonly; the positive results need to be further evaluated in various populations to validate the benefit, which could offer a highly impactful option in an area of unmet need. This study also serves as a good example of the potential role of immunotherapeutic approaches in early stages of HCC, in contrast to the checkpoint inhibitors, which are now being evaluated largely in advanced disease. Another example of the emerging role of cellular therapy in various stages of HCC is highlighted in a meta-analysis of studies that evaluated transarterial chemoembolization with any form of cell therapy including CIKs, tumor-infiltrating lymphocytes, natural killer cells, and dendritic cells. Patients who underwent cell therapy had higher 6-month PFS (OR, 2.78; p = .05), 12-month PFS (OR, 3.56; p < .00001), 6-month OS (OR, 2.81; p = .0009), 12-month OS (OR, 3.05; p < .00001), and 24-month OS (OR, 3.52; p < .0001).[47]

Oncolytic Virus Therapy

Various viral constructs have been evaluated in HCC preclinical models including adenoviruses, vaccinia viruses, and listeria monocytogenes. The general idea is to use viruses to deliver specific molecules into the liver tumor.[21] JX-594 is an oncolytic and immunotherapeutic vaccinia virus expressing granulocyte-macrophage colony-stimulating factor that has cytoreductive effects and activates both innate and adaptive immune responses.[48,49] Intratumoral injections of JX-594 were shown to be safe with an early signal of efficacy[50]; however, a randomized phase IIB study failed to demonstrate improved OS in patients with advanced HCC whose disease had failed prior first-line chemotherapy, as reported by the company, and did not reach its primary endpoint improvement of OS.[51] An ongoing phase III study is comparing the combination of JX-594 (Pexa-Vec) with sorafenib versus sorafenib alone in first-line treatment of HCC (NCT02562755). In addition, a trial combining JX-594 (Pexa-vec) with anti–PD-1 therapy is pending activation.

THE FUTURE: CHALLENGES AND OPPORTUNITIES

As the body of preclinical and clinical data for immunotherapy in HCC continues to grow, it is critical to focus efforts on identifying biomarkers that would enhance patient selection for the various immune therapeutic modalities and that would allow for smarter combinations based on potential escape pathways and mechanisms of resistance. Another challenge would be to expand the clinical benefit to various patient subgroups, including those with compromised liver function (beyond Child-Pugh A) as well as patients with early- and intermediate-stage disease. Additional investigations in the area of adjuvant therapy and in combination with standard effective locoregional modalities are needed. Lastly, it is critical to account for the biologic heterogeneity of HCC and carefully evaluate the potential interplay between etiology and the oncogenic pathways in the tumor and the tumor microenvironment. The efficacy of certain immunotherapeutic interventions may vary based on such interplay and should be accounted for. In conclusion, the emerging body of evidence suggests that immunotherapeutic modalities have a real potential of bringing new hope to patients with HCC across all stages and etiologies.

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GENITOURINARY (NONPROSTATE) CANCER

Evolving Treatment Paradigm in Metastatic Renal Cell Carcinoma

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OVERVIEW

The treatment paradigm for advanced and metastatic renal cell carcinoma (mRCC) has evolved rapidly since the arrival of targeted therapies and novel immunotherapies. mRCC was previously treated only with cytokines. However, discoveries of mutations affecting the von Hippel–Lindau tumor suppressor gene (leading to increased expression of VEGF and hypoxia inducible factor/HIF-1) and of deregulations in the phosphatidylinositol-3 kinase/AKT/mTOR pathway (resulting in tumor angiogenesis, cell proliferation, and tumor growth) have led to the development of numerous targeted therapies. The U.S. Food and Drug Administration (FDA) has thus approved a total of nine targeted therapies since 2005, including VEGF tyrosine kinase inhibitors (sunitinib, pazopanib, axitinib, sorafenib, and lenvatinib), a monoclonal antibody targeting VEGF (bevacizumab), mTOR inhibitors (temsirolimus and everolimus), and a multityrosine kinase inhibitor (cabozantinib). Furthermore, the development of immune checkpoint inhibitors has again shifted the mRCC therapeutic landscape with the FDA's approval of nivolumab. Herein, we discuss the unprecedented changes in the field of clear cell histology mRCC in both the first-line and salvage settings, and we also discuss future therapies and recommend a treatment paradigm on sequencing of these agents.

Prior to 2005 when the FDA approved the first antiangiogenic agent in RCC, treatment of mRCC consisted solely of cytokines. The FDA approved high-dose interleukin-2 (HDIL-2) in 1992 for first-line treatment of mRCC, after preliminary data showed an overall response rate (ORR) of 15% as well as a 5% complete response (CR).[1] A follow-up study reported a 7% CR, with a median duration of response of at least 80 months.[2] However, given acute dose-limiting toxicities, inclusion criteria require excellent performance status and adequate organ function.[1] In an attempt to decrease toxicity, Yang et al[3] compared high- and low-dose interleukin-2 but, unfortunately, ORR was greater in the high-dose arm (21% vs. 13%, p = .048). In addition, analysis from a 2017 prospective cohort (352 patients)[4] and a 2016 retrospective cohort (391 patients)[5] suggests that the survival benefit with HDIL-2 may extend to many more patients. In addition to those with partial response and CR, stable disease (SD) as the best response to therapy was present for 39% and 32% of patients, respectively. Although SD is not historically categorized in HDIL-2 trials, the presence of SD was associated with a survival benefit in these two independent cohorts.[4,5] Interferon-α (hereafter referred to as interferon) had more modest outcomes (overall survival [OS] 2.5 months greater than placebo) without the durable responses of HDIL-2; however, interferon was better tolerated with broader eligibility criteria and therefore was the mainstay of treatment of most patients with mRCC prior to the advent of antiangiogenic therapy.[6]

FIRST-LINE THERAPY SETTING

VEGF-Targeted Therapies

VEGF-targeted therapies with tyrosine kinase inhibitors (TKIs) were developed as a result of improved understanding of von Hippel–Lindau gene mutations leading to the induction of angiogenic protein.[7] VEGF-TKIs currently approved for mRCC include sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, and lenvatinib (Fig. 1). Similarly, bevacizumab is a monoclonal antibody directed against the VEGF receptor (VEGFR). For over a decade, cytokines were the only approved treatment for mRCC. In 2005, sorafenib changed this paradigm, with the TARGET study showing improvement in progression-free survival (PFS) versus placebo in the second-line setting after cytokine therapy (5.5 vs. 2.8 months; p < .01).[8] Shortly thereafter, a landmark 2007 study by Motzer et al[9] showed improved PFS with sunitinib compared with interferon in the first-line setting (11.0 vs. 5.0 months; p < .001). In 2007, AVOREN trial investigators published a comparison of bevacizumab and interferon in combination versus interferon monotherapy. Again, the results nearly doubled the PFS of the comparator arm (10.2 vs. 5.4

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months, p = .0001).[10] In a phase III study published in 2010 (VEG105192), pazopanib was used for previously untreated patients and those who had progressed after cytokines. Compared with placebo, there was a 5-month improvement in PFS (9.2 vs. 4.2 months; p < .0001).[11] In 2009, the FDA approved both pazopanib and bevacizumab in combination with interferon (Table 1).

Since that time, no other agent has been approved for the first-line therapy setting. However, a recently published study[24] may change this. Cabozantinib is a small molecule inhibitor targeting multiple tyrosine kinases, including VEGFR-2, hepatocyte growth factor (MET), and AXL. The Alliance A031203 CABOSUN trial compared cabozantinib to sunitinib for patients with previously untreated mRCC with poor and intermediate prognosis per International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. Results showed improvement in PFS (8.2 vs. 5.6 months) and ORR (46% vs. 18%) and a 34% reduction in the rate of progression or death (adjusted hazard ratio [HR], 0.66; 95% CI, 0.46–0.95; one-sided p = .012) in the cabozantinib arm, with a similar incidence of grade 3 or 4 adverse events (AEs; 67% vs. 68%).[24] Preliminary data on OS, a secondary endpoint, revealed a 20% decrease in the rate of death with cabozantinib, although the study was not designed to show a difference in OS. An independent review for the primary endpoint of PFS is ongoing and if this confirms the findings then cabozantinib will be submitted to the FDA for consideration of approval as front-line therapy.

KEY POINTS

- **New discoveries and advances with antiangiogenic agents have changed the treatment paradigm for clear cell advanced and metastatic renal cell carcinoma.**
- **Based on improved outcomes, axitinib, nivolumab, cabozantinib, and combination lenvatinib plus everolimus are considered standard of care in the post-VEGF/TKI salvage therapy setting, with no clear consensus on how to optimally sequence these agents in the absence of head-to-head comparisons of these agents. Until validated molecular biomarkers predictive for the efficacy of specific agents are discovered, clinical decision making would be key to optimizing sequencing of these agents.**
- **Novel targeted therapies, immune checkpoint inhibitors, and immune-modulating drugs are currently under investigation, many in combination with VEGF pathway inhibitors, in the first-line setting and may replace sunitinib, pazopanib, and HDIL-2 as preferred first-line agents in the near future.**
- **Multidisciplinary input is important when considering the role of cytoreductive nephrectomies and metastatectomies in selected cases depending on overall prognosis and organ of involvement with metastatic disease.**
- **No efforts should be spared in providing access to clinical trials, facilitating approval of novel agents and combinations, and expediting validation of therapeutic biomarkers as well as exploring the optimal sequencing of the therapies.**

mTOR Inhibitors in Front-Line Therapy

Other discoveries showed that mutations in phosphatidylinositol-3 kinase, a kinase upstream of mTOR, were both common in mRCC and amenable to targeted therapy.[25] In 2007, the FDA approved an mTOR inhibitor (temsirolimus) for patients with previously untreated mRCC who were in the poor prognosis category, based on a study showing improvement in OS compared with interferon (10.9 vs. 7.3 months; p = .008) in the Global ARCC trial. Notably, although it was not the primary endpoint, there was only a modest improvement in PFS over interferon by independent radiographic assessment (5.5 vs. 3.1 months). The combination of interferon with temsirolimus was also evaluated but did not improve PFS or OS.[12] With low response rates and modest clinical benefit, temsirolimus is not a widely used therapy in front-line mRCC management.

Notable First-Line Studies Not Resulting in Changes in Regulatory Approval

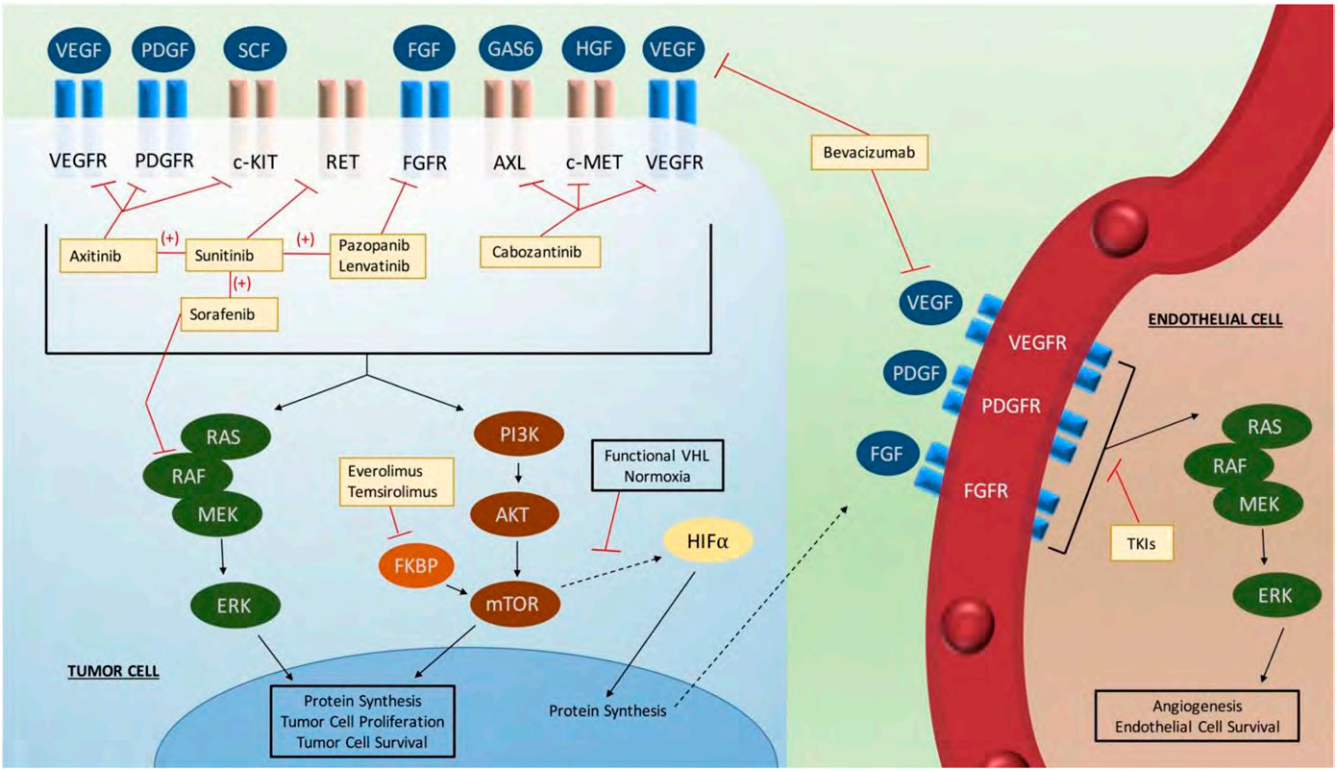
In a randomized study of sorafenib compared with interferon for previously untreated patients, there was no improvement in PFS (5.7 vs. 5.6 months).[26] Another study investigated axitinib versus sorafenib for 288 previously untreated patients. There was an improvement in ORR (32% vs. 15%) and a nonsignificant trend toward improved PFS (median 10.0 vs. 6.5 months) favoring the axitinib arm.[27] The TIVO-1 trial investigated VEGF-TKI tivozanib with sorafenib for 517 previously untreated patients. Although there was an improvement in PFS in the tivozanib arm (11.9 vs. 9.1 months; p = .042), there was a trend toward longer OS in the sorafenib arm (29.3 vs. 28.8 months; p = .105). However, this may have been complicated by notable cross-over differences in the two arms. Of 189 patients who discontinued tivozanib, only 36% received a second therapy and only 10% received another VEGF-directed therapy. Of 226 patients who discontinued sorafenib, 74% received a second-line treatment and nearly 70% received tivozanib.[28] Everolimus, an mTOR inhibitor, was compared with sunitinib for 471 previously untreated patients in the RECORD-3 study using a cross-over treatment design following disease progression. The primary endpoint was noninferiority of everolimus compared with sunitinib in the first-line therapy setting. In addition to inferior PFS in the everolimus arm (7.9 vs. 10.7 months), the combined PFS was inferior with everolimus followed by sunitinib versus sunitinib followed by everolimus (21.1 vs. 25.8 months).[29] The median OS also favored sunitinib followed by everolimus, rather than the reverse (32 vs. 22.4 months). In a 2015 trial, investigators evaluated bevacizumab in a four-arm first-line study with bevacizumab monotherapy versus bevacizumab, temsirolimus versus bevacizumab, and sorafenib versus sorafenib and temsirolimus. There was no notable improvement in the primary endpoint of PFS, but toxicity was significantly greater in the combination arms. Forty-four percent

of patients in the bevacizumab monotherapy arm had grade 3–5 AEs compared with 77%–84% of those in the combination arms.[30] After encouraging phase II results, a phase III trial studied IMA901, a vaccine of 10 tumor-associated peptides, in combination with sunitinib in previously untreated mRCC. Although the peptide vaccine was well tolerated, there was no improvement in clinical outcomes compared with sunitinib monotherapy.[31]

Preferred First-Line Agent

HDIL-2, sorafenib, sunitinib, pazopanib, and bevacizumab with interferon are currently approved agents for previously untreated mRCC. Temsirolimus is approved for patients with mRCC with three or more poor prognosis criteria. To help elucidate the preferred agent, Motzer et al[32] compared pazopanib to sunitinib in the first-line setting in the randomized COMPARZ trial. Although there was a greater ORR with pazopanib (31% vs. 25%), there was no difference in PFS (8.4 vs. 9.5 months) or OS (28.3 vs. 29.1 months). Although the rates of dose reduction and drug discontinuation because of AEs were similar in both arms, health-related quality-of-life scores were worse in the sunitinib arm and were mainly driven by fatigue, mouth and throat soreness, and hand–foot syndrome.[32] The PISCES study, an innovative double-blind randomized controlled cross-over trial assessing treatment preference for pazopanib versus sunitinib, was undertaken with the primary endpoint being patient preference for a specific treatment as determined by a questionnaire developed by mRCC clinicians administered at the end of the treatment period. Utilizing 10-week treatment courses with a 2-week washout, the study showed improvement in patient preference (70% vs. 22%) as well as clinician preference, a secondary endpoint, (61% vs. 22%) favoring pazopanib.[33] Importantly, this is a relatively small study with a high attrition rate and has been criticized for administering the questionnaire immediately prior to the sunitinib rest period.[34] Notably, there have not been any other trials comparing agents currently approved in the first-line therapy setting. Results from the CABOSUN trial may add another layer of complex decision making if they lead to the approval of cabozantinib for the first-line setting. Furthermore, the treatment landscape in the first-line therapy setting is expected to undergo major shifts with expected approval of multiple agents, based on results of numerous ongoing first-line clinical trials (Table 2).

FIGURE 1. Mechanisms of Action of Targeted Therapies in Metastatic Renal Cell Carcinoma



Ligand binding of RTKs leads to many downstream effects. Proangiogenic RTKs (VEGFR, PDGFR, and FGFR) are labeled in blue, whereas growth factor ligand binding to RTKs is colored orange. Simplified mechanisms of the MAPK pathway (left) and mTOR pathway (right) are labeled in the tumor cell. Activation of HIF-α occurs in states of hypoxia and through lack of inhibition from a nonfunctional VHL gene. It leads to synthesis of VEGF, PDGF, and FGF. This can lead to MAPK activation in endothelial cells, depicted on the left side of the diagram. Through FKBP is the site of action of mTOR inhibitors everolimus and temsirolimus and is labeled in orange. Bevacizumab is a monoclonal antibody directed against VEGF. TKIs include sorafenib, sunitinib, axitinib, pazopanib, cabozantinib, and lenvatinib. The aforementioned TKIs inhibit multiple RTKs. RTKs of importance are inhibited by the following TKIs: axitinib (VEGFR, PDGFR, c-KIT), sunitinib (VEGFR, PDGFR, RET, c-KIT), sorafenib (VEGFR, PDGFR, RET, c-KIT, Raf kinases), pazopanib (VEGFR, PDGFR, FGFR, c-KIT, RET), lenvatinib (VEGFR, PDGFR, FGFR, c-KIT, RET), and cabozantinib (VEGFR, c-MET, AXL, c-KIT, RET).

Abbreviations: ERK, extracellular signal–regulated kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FKBP, FK506-binding protein; GAS6, growth arrest-specific 6; HGF, hepatocyte growth factor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol-3 kinase; RTK, receptor tyrosine kinase; SCF, stem cell factor; TKI, tyrosine kinase inhibitor; VEGFR, VEGF receptor; VHL, von Hippel–Lindau.

TABLE 1. Trials Leading to FDA Approval for Agents in mRCC

Drug	Line of Therapy (Previous Treatment)	FDA Approval	No. of Patients	Control Arm	PFS (Months) vs. Control	OS (Months) vs. Control
Interleukin-2[1]	First	1992	255	None	15% ORR	
Temsirolimus[12]	First (at least 3 poor prognostic factors)	2007	626	Interferon	5.5 vs. 3.1	10.9 vs. 7.3*
Sunitinib[9,13]	First	2006	750	Interferon	11.0 vs. 5.0	26.4 vs. 21.8
Bevacizumab plus interferon[10,14]	First	2009	649	Interferon	10.2 vs. 5.4	23.3 vs. 21.3**
Pazopanib[11]	First/second (cytokines)	2009	435	Placebo	9.2 vs. 4.2	22.9 vs. 20.5**
Sorafenib[8]	Second (cytokines)	2005	903	Placebo	5.5 vs. 2.8	19.3 vs. 15.9*,**
Everolimus[15,16]	Second (sorafenib or sunitinib)	2009	410	Placebo	4.9 vs. 1.9	14.8 vs. 14.4**
Axitinib[17,18]	Second (systemic)	2012	723	Sorafenib	6.7 vs. 4.7	20.1 vs. 19.2**
Nivolumab[19]	Second (antiangiogenic)	2015	821	Everolimus	4.6 vs. 4.4**	25.0 vs. 19.6*
Cabozantinib[20,21]	Second (antiangiogenic)	2016	658	Everolimus	7.4 vs. 3.8	21.4 vs. 16.5
Lenvatinib plus everolimus[22,23]	Second (antiangiogenic)	2016	153	Everolimus	14.6 vs. 5.5	25.5 vs. 15.4

*OS primary outcome.

**Did not reach statistical significance.

Abbreviations: FDA, U.S. Food and Drug Administration; mRCC, advanced or metastatic renal cell carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

As we await the data from these ongoing trials, we suggest HDIL-2 as the preferred agent for patients with excellent performance status, clear cell histology, and intact organ function (regardless of prognostic risk categorization), because HDIL-2 is currently the only agent shown to be associated with durable responses for approximately 10% of patients. We prefer sunitinib or pazopanib for patients in the good and intermediate risk categories who are not candidates for HDIL-2, based on equivalent survival outcomes in a randomized controlled trial comparing these agents. Although there is no randomized trial comparing the combination of bevacizumab and interferon to pazopanib or sunitinib, this remains a reasonable regimen to consider in front-line mRCC. For patients in the poor prognosis category, temsirolimus is approved but is associated with modest survival benefits and requires weekly intravenous administration, which may not be desirable or feasible for many patients. For these patients, sunitinib or pazopanib are the preferred options, based on the results of the COMPARZ trial in which clinical outcomes were similar with both agents.[32]

SECOND-LINE THERAPY AND BEYOND

Headlined by the 2005 FDA approval of sorafenib for patients previously treated with cytokine therapy, antiangiogenic

TABLE 2. Selected Interventional Trials Investigating First-Line Therapy of Novel Agents in mRCC

Identifier	Phase	Arms	Primary Outcome	No. of Patients	Completion Date
NCT02982954	IIIB/IV	Nivolumab plus ipilimumab vs. sunitinib	irAEs	200	January 2023
NCT02420821	III	Atezolizumab plus bevacizumab vs. sunitinib	PFS, OS*	900	July 2020
NCT02853331	III	Pembrolizumab plus axitinib vs. sunitinib	PFS, OS	840	December 2019
NCT02811861	III	Lenvatinib plus everolimus vs. lenvatinib plus pembrolizumab vs. sunitinib	PFS	735	January 2020
NCT02684006	III	Avelumab plus axitinib vs. sunitinib	PFS	583	June 2018
NCT01582672	III	Sunitinib with/without AGS003 or placebo	OS	450	April 2017
NCT02996110	II	Nivolumab plus ipilimumab vs. nivolumab plus BMS-986016	ORR, DOR, PFSR	650	January 2022
NCT02959554	II	Nivolumab vs. sunitinib or pazopanib after 3 months TKI	OS	244	November 2022

*OS only calculated for those with detectable PD-L1 tumor expression.

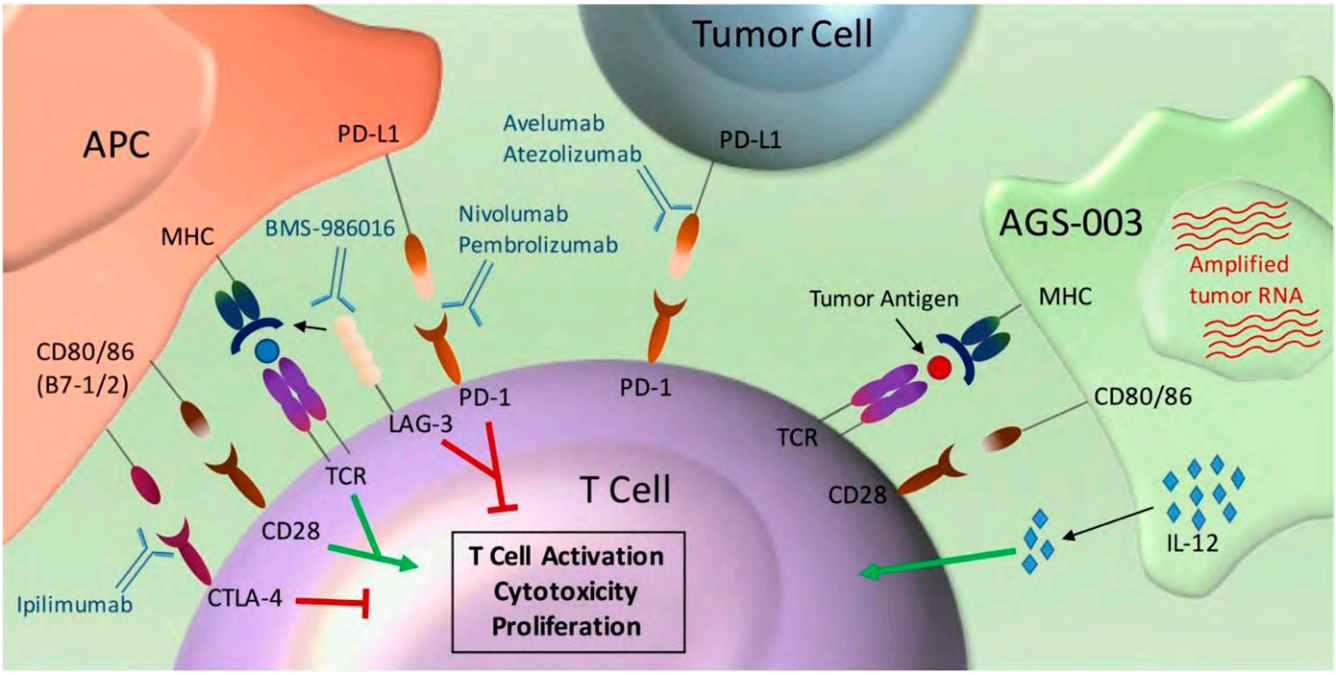
Abbreviations: DOR, duration of response; irAE, immune-related adverse event; mRCC, advanced or metastatic renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFSR, progression-free survival rate; TKI, tyrosine kinase inhibitor.

agents have transformed treatment of mRCC salvage therapy over the past decade. After the TARGET study showed improvement in PFS over placebo (5.5 vs. 2.8 months; p < .001), sorafenib became the first VEGF-TKI approved for mRCC.[8] This was followed by the RECORD-1 trial, which investigated everolimus versus placebo for patients who progressed after treatment with sunitinib or sorafenib. Patients in the everolimus-treated arm showed improved PFS (4.9 vs. 1.9 months; p < .001), but everolimus was also associated with increased rates of stomatitis, rash, and fatigue. Similar to temsirolimus studies, there was also an increase in pneumonitis.[15] In the aforementioned phase III VEG105192 study, pazopanib was also compared with placebo for patients in the first-line setting and for those who had progressed while receiving cytokine treatment and improved PFS in both subsets (9.2 vs. 4.2 months; p < .001).[11]

In 2012, the AXIS investigators published results from a study comparing axitinib to sorafenib for 723 patients with mRCC who had progressed with previous systemic therapy (35% of whom were treated with cytokines; the rest received prior treatment with sunitinib, bevacizumab plus interferon, or temsirolimus). Initial results showed that the axitinib arm had improved PFS of 2 months compared with the sorafenib arm (6.7 vs. 4.7 months; one-sided p < .0001), which improved in the updated results (8.3 vs. 5.7 months; one-sided p < .0001). There was a notable improvement in PFS among subsets of patients previously treated with cytokines (12.2 vs. 8.2 months) or those treated previously with sunitinib (6.5 vs. 4.4 months), but not among those who had prior treatment with bevacizumab and interferon or temsirolimus. Overall, ORR was also improved in the axitinib arm (23% vs. 12%), but OS was similar in both arms. AEs were also similar in both arms.[17,18] Temsirolimus was also compared with sorafenib in a study of 512 patients who had previously progressed while taking sunitinib. There was no difference in PFS, but median OS favored the sorafenib arm (16.6 vs. 12.3 months).[35]

The next paradigm shift occurred in 2015, when three novel agents showed improved outcomes in the salvage setting. Nivolumab, a monoclonal antibody directed against the PD-1 receptor, is an immune checkpoint inhibitor that works to reverse tumor-induced immune suppression and stimulate antitumor immunity. Nivolumab was first approved for use in metastatic melanoma followed by non–small cell lung cancer, when a landmark Checkmate025 study compared nivolumab to everolimus in the second-line setting for 821 patients after progression on one or two previous antiangiogenic agents. Although PFS was similar in both arms (4.6 vs. 4.4 months), the primary endpoint OS was superior in the nivolumab arm (25.0 vs. 19.6 months; HR for death, 0.73; p = .002). ORR was also greater in the nivolumab arm (25% vs. 5%) and there were significantly fewer grade 3–4 AEs (19% vs. 37%).[19] Another landmark study, the METEOR trial, investigated cabozantinib versus everolimus for 658 patients who had progressed after antiangiogenic therapy directed against VEGF. Sixty-nine percent of patients had only received one prior treatment, whereas the remaining patients had received at least two prior therapies. Cabozantinib resulted in

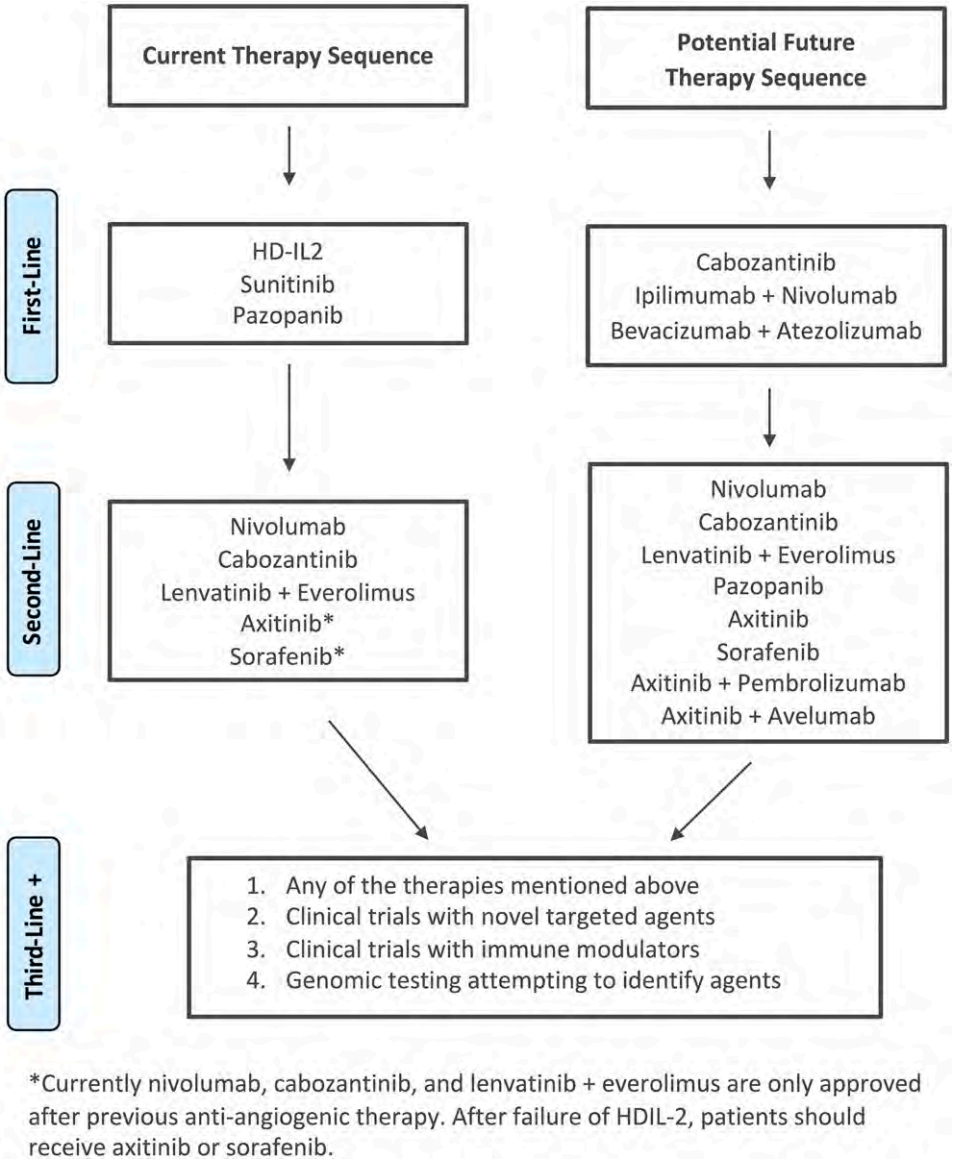
FIGURE 2. Mechanisms of Action of Immunotherapies for Metastatic Renal Cell Carcinoma



Immune checkpoint inhibitors and AGS-003 are featured. Ipilimumab is a monoclonal antibody directed against CTLA-4 on T cells. Nivolumab and pembrolizumab inhibit PD-1 on both tumor and T cells, whereas avelumab and atezolizumab inhibit its ligand, PD-L1. BMS-986016 is a novel immune agent that targets LAG-3, preventing immune inhibition by preventing LAG-3 binding to its ligand, MHC class II receptor. AGS-003 is a mature dendritic cell that has been coelectroporated with tumor DNA and human CD40 ligand. By processing and then presenting tumor antigen, it binds both the TCR and CD28. A third signal leads to with IL-12 promotes memory T-cell development.

Abbreviations: IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor.

FIGURE 3. Sequencing Paradigm of Metastatic Renal Cell Carcinoma



Asterisks indicate that nivolumab, cabozantinib, and lenvatinib plus everolimus are currently approved for use only after previous antiangiogenic therapy. After failure of HDIL-2, patients could receive axitinib or sorafenib.

Abbreviations: HDIL-2, high-dose interleukin-2.

improved in PFS (7.4 vs. 3.8 months; p < .001), ORR (17% vs. 3%; p < .001), and OS (21.4 vs. 16.5 months; HR, 0.66; p = .00026). Remarkably, treatment with cabozantinib resulted in the longest PFS in the post-VEGF/TKI salvage monotherapy setting reported to date. More than 99% of patients in both arms reported an AE of any grade, but there was a greater incidence of grade 3–4 AEs in the cabozantinib arm (68% vs. 58%). More frequent grade 3–4 AEs with cabozantinib included hand–foot syndrome, hypertension, diarrhea, nausea, and thromboembolic events.[20] Also reported in 2015, a phase II study investigated treatment with lenvatinib (a TKI of VEGFR1–VEGFR3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET and KIT) for 153 patients with mRCC who had progressed after VEGF-targeted therapy. Patients were randomized into three arms: combination lenvatinib and everolimus versus lenvatinib monotherapy versus everolimus monotherapy. Respectively, PFS (14.6 vs. 7.4 vs. 5.5 months) and OS (25.5 vs. 18.4 vs. 15.4 months) were greater in the combination arm but only met statistical significance for the primary endpoint, which was PFS for patients who received lenvatinib plus everolimus versus everolimus monotherapy. Combination therapy was more toxic than everolimus monotherapy (grade 3–4 AEs, 71% vs. 50%) with significantly greater diarrhea in the combination arm.[22] These three studies led to FDA approvals for nivolumab, cabozantinib, and lenvatinib in combination with everolimus for patients with mRCC for which an antiangiogenic agent failed previously. Notably, these agents are only approved after VEGF-directed treatment failure and are not approved

for those patients with mRCC for which immune therapy failed.

ONGOING CLINICAL TRIALS FOR UNTREATED MRCC

Although the landscape of second-line and salvage therapy is rapidly evolving, there are many clinical trials at various stages investigating first-line therapy for mRCC (Table 2).

Immunotherapy: Checkpoint Inhibitors

Numerous immunotherapy agents are under active investigation in the first-line setting for mRCC, including seven trials investigating immune checkpoint inhibitors (Fig. 2). In a phase IIIB/IV trial (NCT02982954), nivolumab is being studied in combination with ipilimumab, a checkpoint inhibitor directed against CTLA-4. Nivolumab is also being studied in two phase II trials (NCT02996110 and NCT02959554). The aforementioned trial plans to enroll 650 patients and is comparing nivolumab with ipilimumab versus nivolumab with BMS-986016, a monoclonal antibody checkpoint inhibitor directed against lymphocyte activation gene-3 (LAG-3). The latter trial is enrolling 244 patients and comparing nivolumab to sunitinib or pazopanib after treating patients for 10–12 weeks with a TKI. Pembrolizumab, another PD-1 monoclonal antibody, is currently being studied in combination with axitinib compared with sunitinib in a phase III trial of 840 patients and completion is expected in 2019 (NCT02853331). Another phase III trial of 735 patients (NCT02811861) is comparing the combination of pembrolizumab and lenvatinib against combination lenvatinib and everolimus as well as sunitinib monotherapy. Investigators are also enrolling patients for first-line studies of checkpoint inhibitors targeting PD-L1 (avelumab and atezolizumab). In a phase III trial with 583 patients (NCT02684006), avelumab is being studied in combination with axitinib versus the comparator sunitinib.

Selected Novel Agents in Development

AGS-003 is a personalized immunotherapy of mature autologous dendritic cells that are coelectroporated with both synthetic RNA and the patient's tumor RNA. AGS-003 was designed to achieve the immunomodulatory effects of HDIL-2 with a more favorable toxicity profile, and AGS-003 was studied in combination with sunitinib in a phase II study of 22 patients with low- or intermediate-risk mRCC. There were no CRs, but nine patients had a partial response and the median PFS and OS were encouraging (11.2 and 30.2 months, respectively). Notably, OS exceeded 5 years for five patients (24%), with two patients (approximately 10%) achieving durable responses for more than 5 years.[36] The phase III ADAPT trial (NCT01582672) has completed accrual and results are currently awaited. LY2510924 (X4P-001) is a novel cyclic peptide that inhibits CXCR-4, a chemokine receptor shown to be important in tumorgenesis.[37] A phase II trial (NCT01391130) comparing monotherapy with sunitinib versus sunitinib with LY2510924 is enrolling 108 patients, with completion anticipated in 2017. In a small phase I trial (NCT02035358) with 18 patients, researchers are also investigating a polyvalent immune vaccine called HyperAcute-Renal, which is composed of an allogenic renal cell carcinoma (RCC) cell that has been genetically modified to express 1,3-galactosyltransferase with the intention to augment cellular immune responses. Hypoxia-inducible factors (HIFs) are transcription factors activated in hypoxic states and by loss of von Hippel–Lindau function. HIF-1α and HIF-2α overexpression has long been known to be associated with malignant disease.[38,39] In particular, HIF has been implicated in both tumorigenesis and angiogenesis in mRCC (Fig. 1).[40] In another trial (NCT02293980), PT2385, a recently developed direct antagonist of HIF-2α, is being investigated as a monotherapy and in combination with either cabozantinib or nivolumab for patients with mRCC who have progressed while taking previous therapy. A very similar agent, PT2399, has shown antitumor activity in a mouse model.[40]

Dalantercept, an activin receptor-like kinase 1 inhibitor that targets angiogenesis, is being tested in combination with axitinib for patients who progressed despite previous VEGF/TKI treatment. Phase II results of the DART study reported no dose-limiting toxicities among the 29 patients treated, with an ORR of 25% and PFS of 8.3 months.[41] Part II of the study is a randomized trial (NCT01727336) in which this combination is being compared with axitinib alone; the study is currently enrolling 174 patients, with completion estimated in 2018. Another trial (NCT01806064) is combining a monoclonal antibody against endoglin, TRC105, with axitinib compared with axitinib monotherapy for 168 patients with mRCC. Endoglin is a glycoprotein expressed on endothelial cells and plays an important role in angiogenesis and tumorgenesis.[42]

ROLE OF SURGERY IN THE METASTATIC SETTING

Cytoreductive Nephrectomy

Most patients with mRCC who have been enrolled in systemic therapy clinical trials on mRCC have had cytoreductive nephrectomy (CN) performed. In addition to palliation of pain, hematuria, and paraneoplastic syndromes, CN, if clinically feasible, is likely to improve outcomes for carefully selected patients. CN has been a standard of care since two landmark trials showed an improvement in OS (17 vs. 7 months; HR, 0.54) for patients who underwent CN prior to therapy.[43,44] Although both studies used interferon as the systemic therapy, an updated retrospective cohort of 15,390 patients treated with antiangiogenic targeted therapies reported similar survival data for those who underwent a CN (median OS of 17.1 vs. 7.7 months; $p < .001$).[45] In a different retrospective cohort from the Surveillance, Epidemiology, and End Results database, investigators found that of 7,143 patients with reported mRCC treated with antiangiogenic targeted therapy, 37% underwent CN. Those who underwent a CN had improved 1-year OS (61% vs. 22%; HR, 0.40), which was influenced by many factors, including a greater likelihood of having localized disease and younger age.[46] In a retrospective IMDC cohort in the targeted therapy era,

investigators performed a multivariate analysis of 314 patients, 201 of whom underwent CN. Again, the IMDC investigators noted improvement in OS with CN (19.8 vs. 9.4 months; p < .01), but this benefit was greatest for those with a favorable and intermediate prognosis.[47] Given the inherent biases of these retrospective studies, a prospective study (CARMENA, NCT00930033) is investigating CN by comparing sunitinib with or without CN in previously untreated patients with mRCC. CARMENA has a planned sample size of 700 participants with eligibility including biopsy proven mRCC and an ECOG 0-1. The primary endpoint is OS.

Although prospective results are pending, it is paramount that the treatment decision for CN be based on an individual patient's performance and prognostic status and made in conjunction with multidisciplinary input. Although no specific guidelines yet exist, a reasonable approach may be to exclude those who did not benefit from CN in the IMDC study. These included those with at least four poor IMDC prognostic factors: time from diagnosis to treatment less than 1 year, Karnofsky performance score less than 80, anemia, neutrophilia, and thrombocytosis. In addition, those with anticipated OS shorter than 1 year may not benefit from CN.[47,48] It is also important to consider the probability of successfully debulking of adequate portion of the tumor.

Metastasectomy

Similar to CN, the role of metastasectomy for patients with mRCC is nuanced based on underlying patient characteristics. In a 1998 study of 278 patients with recurrent RCC, investigators found that 44% of patients were able to have long-term remission with oligometastasectomy (based on 5-year OS). Favorable features for response included a solitary metastatic organ site, the lung as the metastatic site, and age younger than 60. Those with the brain as a solitary metastatic site had inferior outcomes to oligometastasectomy than those with lung (5-year OS, 18% vs. 54%; p < .05).[49] A 2011 study of 887 patients who underwent nephrectomy for RCC who later developed lung-confined metastatic lesions also showed impressive 5-year OS with complete versus incomplete resection (73.6% vs. 19.0%; p < .001).[50] The same study also showed a survival advantage, although less robust, favoring complete over incomplete resection for patients with extrapulmonary metastatic lesions (5-year OS, 32.5% vs. 12.4%; p < .001).[50] Other studies have shown improvement for resection of symptomatic bone lesions as well as complete resection of visceral metastases to the liver, thyroid, and pancreas.[51-54] A randomized, double-blind placebo-controlled study, E2810 (NCT01575548), is currently enrolling patients to study whether pazopanib improves outcomes for individuals who successfully undergo complete resection of metastatic lesions.

Adjuvant Therapy

Thus far, adjuvant therapy results have been disappointing in RCC. A 2003 study of 69 patients with locally advanced or metastatic RCC treated with adjuvant HDIL-2 showed no benefit in disease-free survival (DFS) compared with a similar cohort of patients followed with observation.[55] Recently, the Eastern Cooperative Oncology Group (ECOG) 2805 trial investigated sunitinib or sorafenib or placebo as adjuvant therapy for 1,943 patients with resected nonmetastatic RCC. Unfortunately, results revealed that neither sorafenib or sunitinib improved DFS compared with placebo.[56] In the S-TRAC adjuvant study of 615 patients with resected nonmetastatic RCC, sunitinib significantly improved DFS compared with placebo (6.8 vs. 5.6 years; HR, 0.76); however, the duration of improvement in median DFS was similar to the duration of adjuvant therapy with sunitinib.[57] Notably, per independent central review, the magnitude of benefit was higher with adjuvant sunitinib for patients with a higher risk of recurrence, defined as those with T3 tumors, without or with undetermined nodal involvement, with Fuhrman grade 2 or higher tumors, and with a ECOG performance score of 1 or higher; or those with a T4 tumor, local nodal involvement, or both. For these patients, DFS was significantly improved with sunitinib versus placebo (6.2 vs. 4.0 years; HR, 0.74; 95% CI, 0.55–0.99; p = .04). The OS results need to mature on further follow-up to see whether systemic anti-VEGF therapy actually effects a cure for any patient with mRCC. Recently reported preliminary results of the PROTECT study (NCT01235962) with adjuvant pazopanib also failed to reveal a DFS benefit over placebo. A phase III trial through the National Clinical Trials Network, PROSPER RCC, was activated in 2017 and is comparing neoadjuvant and adjuvant nivolumab versus observation in localized RCC, with the hypothesis that prenephrectomy administration may improve T-cell response. In addition, phase III adjuvant therapy trials with atezolizumab and pembrolizumab are ongoing and continue to use placebo as the control arm.

SEQUENCING PARADIGM

To date, no randomized trials have yet established the optimal sequence of therapy in renal cancer. Most of the targeted therapies have been established in phase III trials that were conducted within the same timeframe, so very few were done with comparisons to another agent. The COMPARZ trial showed that pazopanib was noninferior to sunitinib, so either could be considered as a front-line therapy option.[32] Randomized front-line trials comparing either axitinib or tivozanib to sorafenib did not reveal an advantage in efficacy.[27,28] Of the previous trials, only COMPARZ used sunitinib for the comparator arm and others used sorafenib. Contemporary ongoing first-line studies of nivolumab and ipilimumab, atezolizumab and bevacizumab, pembrolizumab and axitinib, avelumab and axitinib, and lenvatinib and pembrolizumab are all using sunitinib as the control (Table 2). As discussed above, the CABOSUN trial also used sunitinib as the comparator against cabozantinib in the first-line setting. As the only therapy with decades of follow-up, HDIL-2 is associated with durable responses for 10% of patients and remains a treatment consideration; however, HDIL-2 requires carefully selecting patients with robust performance status and organ function, which limits its use.

Second-line therapies were also established in clinical trials that were conducted in parallel. Axitinib showed

improved PFS compared with sorafenib, and everolimus showed better efficacy than placebo for patients previously treated with VEGF-directed therapies. All recent studies for the pretreated mRCC population have used everolimus as the comparator arm. Nivolumab, cabozantinib, and lenvatinib plus everolimus each revealed superior efficacy in response rates and OS. Hence, a contemporary therapy sequence pattern has emerged of sunitinib or pazopanib followed by nivolumab or cabozantinib or axitinib. Generally, if nivolumab is used in the second line, cabozantinib or axitinib is used in the third line or later and vice versa. Given higher toxicities but relatively higher response rates and PFS of the lenvatinib plus everolimus combination, this may be reserved for patients with rapidly progressive high-volume disease in the second-line therapy setting, or after disease progression following other monotherapies. It is postulated that the therapeutic sequence will undergo a dramatic change based on the results of first-line therapy trials (Table 2). Figure 3 provides an overview of current and potential future therapeutic sequencing in mRCC.

A biomarker selection process would be a helpful tool; however, no predictive markers have been validated to date. Recent reports on BAP-1, SETD2, and PBRM-1 as potential prognostic and predictive biomarkers may foster the possibility of impacting risk profiling.[58] Even PD-L1 expression, a useful marker in other malignancies, has failed to predict the efficacy of immune therapy in mRCC. Mutation load and the neutrophil-to-lymphocyte ratio are promising biomarkers to predict response to immune therapy within mRCC.[59-61] Novel targets involving resistance pathways such as CXCR-4 (X4P-001) and HIF-2 (PT2385) and immune modulators such as LAG-3 inhibitors (BMS-986016) are under clinical investigation and therapeutic development.

CONCLUSION

The field of kidney cancer has surprisingly thrived on targeted therapy, despite the disease being notorious for its heterogeneity. New advances have improved response rates, OS, and treatment-related toxicities for patients with mRCC. Although new discoveries in targeted therapies are paralleled by those in immunotherapy, the treatment paradigm continues to evolve. Despite the FDA's approval of multiple agents, clinical trials should continue to be the mainstay of treatment in mRCC, because every advance to date can be attributed to patient participation in therapeutic studies.

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New Developments and Challenges in Rare Genitourinary Tumors: Non-Urothelial Bladder Cancers and Squamous Cell Cancers of the Penis

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OVERVIEW

The diagnosis and treatment of rare genitourinary tumors is inherently challenging. The Rare Diseases Act of 2002 initially defined a rare disorder as one that affects fewer than 200,000 Americans. The lack of widely available clinical guidelines, limited research funding, and inaccessible clinical trials often lead to difficulty with treatment decisions to guide practitioners in rendering effective care for patients with rare genitourinary cancers. This article will discuss basic tenets of diagnosis and treatment as well as recent developments and clinical trials in rare non-urothelial bladder cancers and penile squamous cell cancers.

NON-UROTHELIAL BLADDER CANCER

In 2016 alone, there were 76,960 new cases of bladder cancer, with a higher incidence among men compared with women (58,950 vs. 18,010) and 16,390 deaths (11,820 men and 4,570 women).[1] Although the majority of bladder cancers (over 90%) are urothelial in histology, variants or divergent differentiations exist, which poses a unique challenge in the diagnosis and treatment of bladder cancers. Non-urothelial bladder cancer and variants of urothelial carcinoma comprise up to 25% of all bladder cancers.[2] Pure non-urothelial bladder cancers in the aggregate comprise only 5% or fewer of all bladder neoplasms.[3] The majority (close to 90%) of non-urothelial cancers are also epithelial in nature, such as squamous cell carcinoma (SCC), adenocarcinoma, and small cell carcinoma, whereas non-epithelial tumors include extremely rare histologies in the bladder such as sarcoma, lymphoma, and melanoma. However, these rare histologies pose a substantial barrier to effective management not only because of their generally perceived aggressive nature but also because of a lack of adequately powered studies to define standards of care for treatment. This article describes the unique challenges and pitfalls in the diagnosis and treatment of and recent developments in non-urothelial bladder cancers.

2016 World Health Organization Classification of Urothelial Tumors

The 2016 World Health Organization (WHO) classification for bladder tumors mainly kept the recommendation of the 1997 International Society of Urological Pathology classification and placed strong emphasis on better defining the noninvasive entities of urothelial dysplasia and urothelial proliferation of uncertain malignant potential. A distinction was made to compare the third and fourth editions of the WHO classification, especially with regard to invasive urothelial carcinoma with divergent differentiation. The difference between the 4th and the 3rd edition of the WHO classification are as follows: the nested (including large nested) variants, microcystic, micropapillary, lymphoepithelioma-like, plasmacytoid/signet ring cell/diffuse, the sarcomatoid, giant cell, poorly differentiated, lipid-rich, and clear cell.[4] Although it is still unclear whether treatment or outcomes may differ from these divergent differentiations, pathologists are also encouraged to quantify the amount of morphologic variants seen, because as many as 33% of variants are encountered with invasive urothelial carcinoma.[5]

In addition, apart from urothelial tumors or those with divergent differentiation, non-urothelial cancers consist of the following subclassification: squamous cell neoplasms, glandular neoplasms, urachal carcinoma, tumors of Mullerian type, neuroendocrine tumors, melanocytic tumors, mesenchymal tumors, urothelial tract hematopoietic and lymphoid tumors, and miscellaneous tumors (which includes tumors arising in a bladder diverticulum; Sidebar 1).

Guidelines on Diagnosis and Management of Invasive Non-Urothelial Cancers

Bladder squamous cell carcinoma. Although SCCs account for only 3%–5% of all bladder carcinomas in the United States, SCC confers a fairly dismal prognosis.[6] In areas endemic

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SIDEBAR 1. Non-Urothelial Bladder Neoplasms

Squamous Cell Neoplasm
- Pure squamous cell carcinoma
- Verrucous carcinoma
- Squamous cell papilloma

Glandular Neoplasms
- Adenocarcinoma, not otherwise specified
- Enteric
- Mucinous
- Mixed
- Villous adenoma

Urachal Carcinoma

Tumors of Mullerian Type
- Clear cell carcinoma
- Endometrioid carcinoma

Neuroendocrine Tumors
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Well-differentiated neuroendocrine tumor
- Paraganglioma

Melanocytic Tumors
- Malignant melanoma
- Nevus
- Melanosis

Mesenchymal Tumors
- Rhabdomyosarcoma
- Leiomyosarcoma
- Angiosarcoma
- Inflammatory myofibroblastic tumor
- Perivascular epithelioid cell tumor, benign or malignant
- Solitary fibrous tumor
- Leiomyoma
- Hemangioma
- Granular cell tumor
- Neurofibroma

Urothelial Tract Hematopoietic and Lymphoid Tumors

Miscellaneous
- Tumors arising in bladder diverticulum

Adapted from the World Health Organization.

KEY POINTS

- **The most common non-urothelial bladder cancers consist of adenocarcinoma, squamous carcinoma, and neuroendocrine tumors potentially with a more aggressive course and poor response to traditional treatments.**
- **Localized penile cancers are amenable to local therapies with topical chemotherapy, surgery, or radiation, with penis-sparing options, whereas multimodal therapy incorporates chemotherapy for advanced stages.**
- **Studies show that genetic aberrations, amplifications, and protein expression may herald potential drug targets in non-urothelial bladder cancers and penile cancers.**

for schistosomiasis (the second most frequent parasitic infection next to malaria), SCCs comprise the majority of bladder cancers (upward of 75%), which are also termed bilharzial squamous bladder cancers.[7] However, in the United States and other Western countries, triggers that include chronic irritation and inflammation, such as those seen among patients with indwelling catheters, are known to be additional risk factors for nonbilharzial squamous carcinoma.[8,9] Other histopathologic features such as keratinizing squamous metaplasia or other noninvasive histologies like verrucous squamous hyperplasia are known to increase the risk of subsequent development of invasive SCCs,[10,11] although the exact mechanism and fate of these is not quite clear, precluding definitive recommendations for aggressive surgical extirpation in all cases. SCC occurs in men and women about equally. Clinicopathologic behavior is different between bilharzial versus nonbilharzial bladder cancers, with the former presenting with lower-grade or better-differentiated, high-stage, and non-papillary disease,[12] whereas both present in usually more advanced or muscle-invasive stages compared with their urothelial counterparts[13] but with lower rates of lymph node metastases or lymphovascular invasion.

Given the rarity of these cancers, no standard consensus regarding treatment has been advocated.[14] However, studies show that radical cystectomy, with the possibility of preoperative radiation in bilharzial SCC,[8,15] may improve outcomes. Although chemotherapy using cisplatin as the backbone has had relative success in treating urothelial carcinoma, this is less so with SCC. TIP (Taxol or paclitaxel, ifosfamide, and platinum or cisplatin)[16] was used in a prospective trial of patients with non-urothelial variants, which revealed a dismal median survival of 8.9 months but conversely showed complete remission in two out of eight patients with SCC. One large retrospective trial reported on 27 patients with resectable T2–T4 disease; eight patients underwent neoadjuvant therapy, although only three were able to successfully proceed with radical cystectomy.[17] Therefore, it is best to offer patients who are deemed candidates for radical cystectomy the option to undergo surgery upfront, because the therapeutic benefit of neoadjuvant chemotherapy is unclear.

Bladder adenocarcinoma. Adenocarcinomas of the bladder comprise < 2% of all bladder carcinomas. Similar to SCC, infection with schistosomiasis may be a risk factor in up to 10% of bladder cancers that occur in the form of non-urachal adenocarcinomas. Other risk factors such as bladder exstrophy and bladder augmentation can be seen. The distinction between urachal and non-urachal adenocarcinoma is important because their clinicopathologic behavior and treatment are vastly different. Primary adenocarcinomas are therefore typically subdivided into urachal carcinomas, which comprise up to 30% of all primary adenocarcinomas,[18] or non-urachal carcinomas, which comprise 70%. The urachus is a remnant of the umbilical ligament, which is typically obliterated at birth and can be a site of future adenocarcinoma. Patients with urachal carcinoma typically have adenocarcinoma features, their disease is usually advanced when they present with hematuria, and they may

TABLE 1. Differences Between the Mayo Clinic and Sheldon Staging Systems for Urachal Carcinoma

Stage	Mayo Clinic System	Sheldon Staging System
I	Tumors confined to the urachus and/or bladder	No invasion beyond the urachal mucosa
II	Tumors extending beyond the muscular layer of the urachus or the bladder	Invasion confined to the urachus
III	Tumors infiltrating the regional lymph nodes	Local extension into the:
		Bladder (IIIA)
		Abdominal wall (IIIB)
		Peritoneum (IIIC)
		Viscera other than bladder (IIID)
IV	Tumors infiltrating nonregional lymph nodes or other distant sites	Metastases to the: regional lymph nodes (IVA) and distant sites (IVB)

have a palpable mass.[19] There are different staging schema, and it should be noted that the usual TNM staging that is applicable to other primary urothelial bladder carcinomas is not applicable to urachal cancers because the tumor grows from outside of the bladder inward and, depending on the staging, may not even manifest with involvement within the bladder that can be visible via cystoscopy. The Sheldon staging system is commonly used,[20] although a more simplified staging system has also been proposed and used[21] (Table 1). Urachal carcinomas are unique in their presentation, such that presentation in the midline or dome of the bladder should raise suspicion of urachal carcinoma, given direct extension of the umbilical ligament. Urachal carcinomas are almost universally adenocarcinomas in histology, which can have mucinous differentiation. Enteric-type histology, absence of accompanying urothelial cancer or cystitis cystica or dysplasia, and lack of objective findings of involvement of another organ would support the diagnosis. Treatment of urachal carcinomas is also unique, in that they are considered invasive but do not require radical cystectomy and treatment with a partial cystectomy with en bloc resection of the urachal ligament is possible.[22,23] Similarly, given the lack of consensus regarding objective responses to chemotherapy, neoadjuvant chemotherapy is not uniformly recommended. On the other hand, non-urachal adenocarcinomas typically present in more advanced stages with high propensity for metastasis. However, it is of paramount importance to rule out other primary adenocarcinomas, particularly of the colon, gastrointestinal tract, or lung. Radical surgery has historically been the treatment of choice, which results in long-term survival in up to 40% of patients in 5 years.[24] However, few options exist for patients with advanced or unresectable cancer. Early investigations, mostly at The University of Texas MD Anderson Cancer Center, used a regimen that utilizes 5-fluorouracil (5-FU) similar to that for a colon cancer regimen[25] and yielded some promising responses as well as a 5-FU/cisplatin combination with about a 33% response rate. This led to a trial at MD Anderson utilizing gemcitabine, 5-FU, leucovorin, and cisplatin for patients with locally advanced or metastatic urachal carcinoma, suggesting a reasonable objective response rate in about one-third of patients.[26,27] Other regimens reported mostly in case reports or small series include 5-FU and oxaliplatin with leucovorin for colon cancer, single-agent chemotherapy with irinotecan,[28] cisplatin/S-1,[29] or TIP,[16] similar to the SCC bladder histology.

Neuroendocrine/small cell carcinoma. Neuroendocrine cancers or small cell cancers of the bladder are rare, making up only < 1% of all bladder tumors.[30,31] However, they represent aggressive histologic subtypes that mimic the course of other extravesical neuroendocrine tumors and usually present with locally advanced stages.[32] Neuroendocrine cancers typically consist of either small cell cancer, large cell cancer, well-differentiated neuroendocrine tumors, and paragangliomas. Given the uniformly poor prognosis, many advocate for upfront radical cystectomy, which still has dismal outcomes, especially in those with nonconfined bladder tumors.[33] Given the potential benefit of the use of preoperative chemotherapy regimens typically used for extravesical neuroendocrine tumors such as platinum with etoposide regimens,[34,35] multimodality therapy with combined preoperative chemotherapy followed by consolidative radiation,[36] or surgery for those with confined disease, yields the most reasonable response rates.[37]

Role of Genomics for Diagnosis

Bladder cancer is a neoplasm with high mutational burden and is considered the fourth highestnext to melanoma, squamous cell lung cancer, and adenocarcinomas.[38] However, although The Cancer Genome Atlas presented comprehensive analyses of muscle-invasive urothelial cancers and showcased the most common genetic mutations, pure non-urothelial cancers or urothelial carcinomas with divergent differentiation were not represented. However, several small reports show that molecular data may complement the diagnosis and prognostication of non-urothelial cancers or divergent differentiations/variants.[39] One study of sequencing showed high rates of aberrations in TP53, BRCA2, SMAD4, PTEN, KRAS, NRAS, and KIT for bladder adenocarcinoma, with amplifications in EGFR occurring in 27.3% of adenocarcinomas and ERBB2/HER2 in 16.7%.[40] PIK3CA mutations were seen, along with HRAS, BRCA1, and BRCA2, and FBXW7 in SCC with amplifications only in ERBB2 was seen. Interestingly, PD-1 in tumor infiltrating cells were seen in about 44% for both adenocarcinomas and SCCs while PD-L1 was seen in 11.1% and 22% in adenocarcinomas and SCCs, respectively, suggesting the potential utility of immune checkpoint inhibitors in this population of patients. Another study that evaluated the comprehensive genomic profiling of predominantly stage IV small cell bladder cancers found that there was genomic differences compared to urothelial bladder cancers, with higher frequencies of TP53 and RB1 genomic aberrations in small cell compared to urothelial cancers, and with very low FGFR3 and ERBB2 alterations in small cell bladder cancers.[41]

Role of Traditional Chemotherapy for Non-Urothelial Bladder Cancers

Cisplatin-based chemotherapy in the form of dose-dense or accelerated MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) or gemcitabine/cisplatin has been the cornerstone of chemotherapy use in patients with locally advanced bladder cancer.[42] However, patients with pure non-urothelial variants have varying, although usually suboptimal, responses to traditional chemotherapy and these novel entities deserve particular mention in their management. In general, if the histology is predominantly urothelial but the presence of divergent differentiation is documented, treatment still follows that of typical urothelial bladder carcinoma, understanding that the behavior may be more aggressive and warrants a careful approach.

Role of Immunotherapy and/or Targeted Therapy

Immunotherapy has played a major role in the treatment of urothelial cancers, both in noninvasive cancers (e.g., the use of the vaccine Bacille-Calmette Guerin) and in metastatic urothelial cancer; atezolizumab (an antibody against protein PD-L1) was recently approved for treatment of metastatic bladder cancer after failure of first-line platinum.[43] However, its role in non-urothelial bladder cancer or with divergent differentiation is not well defined, because most of the studies using PD-1 and PD-L1 inhibitors either excluded the non-urothelial bladder cancers or did not definitively capture the percentage of urothelial variants or divergent differentiation. Regardless, several small studies with the use of VEGF inhibitors or checkpoint inhibitors are showing promise. A small phase II trial utilizing cabozantinib, a vascular endothelial growth factor (VEGFR-2) and MET pathway inhibitor, included three cohorts of metastatic urothelial cancers, a bone-only cohort, and a third cohort with rare genitourinary tumors.[44] Responses were seen for two of six patients with small cell carcinoma, for three patients with adenocarcinoma, and for one patient with SCC. In a phase I trial utilizing cabozantinib combined with nivolumab, a PD-1 pathway inhibitor, 24 patients in cohort 1 were enrolled, with an intriguing overall response rate of 43% for the whole cohort; four patients with urachal adenocarcinoma and three with SCC exhibited a response.[45] The combination was deemed safe, with fatigue noted in 13% of patients, thromboembolic events in 13%, and decreased neutrophil count in 17%. The recommended phase II dose was 40 mg of cabozantinib with 3 mg/kg of nivolumab with part II of this expansion cohort that includes ipilimumab. In the updated reporting of this trial, four patients with urachal carcinoma and two patients with squamous cell carcinoma were enrolled, with complete response seen in one patient with squamous cell and partial response in the other patient with squamous cell carcinoma and the urachal carcinoma.[46] SWOG Trial S1609 (NCT02834013) is currently accruing patients with rare tumors and is utilizing nivolumab plus ipilimumab with the primary objective of overall response rates.

In summary, diagnosis and treatment of non-urothelial cancers, whether in pure form or with mixed histologies or divergent differentiation, poses a major diagnostic and treatment challenge for the practicing clinician. Efforts to refine molecular targets for both diagnosis and treatment may pave the way for improved outcomes in this very difficult disease state.

SQUAMOUS CELL CARCINOMA OF THE PENIS

SCC is the most common malignant primary tumor of the penis. In the United States, there are an estimated 2,000 new cases of penile cancer per year.[1] The risk of these rare tumors has been linked to lack of circumcision and exposure to human papillomavirus (HPV).[47] Incidence increases with age and peaks among men age 50–70. Despite a lack of randomized controlled trials, several treatment strategies have emerged consisting of surgery or radiotherapy for localized penile cancer, multimodal therapy for locally advanced disease, and systemic therapies for palliation of patients with distant metastasis.

Histologic Classification and Role of HPV

Histologic variants of penile SCC include the basaloid, warty, and verrucous subtypes, which are collectively termed "unusual" variants, and the remaining histology is the majority of penile cancer, which is termed "usual" type, or keratinizing SCC.[48] There may be more than one histologic pattern within a tumor. Evidence of HPV infection has been found in both the usual-type and unusual histologic variants. An estimated 31%–66% of all penile cancers are HPV related, with type 16 virus being most prevalent. The basaloid and warty subtypes are associated with HPV in 80%–100% of cases, whereas the usual type is less commonly associated and the verrucous subtype is least associated.

The viral genes E6 and E7 are expressed in HPV-transformed cells and are known to interact with the RB1 and TP53 tumor suppressor pathways.[49] These pathways are therefore implicated in penile cancer. Mutations of TP53 are found in a subset of penile cancers and are associated with a higher incidence of lymph node metastasis and lower overall survival.[50,51] It is likely that somatic mutations in the RB1 and TP53 pathway genes are more common in HPV-unrelated tumors where those pathways are not already inactivated by viral proteins. Thus, there are possibly distinct molecular mechanisms underlying HPV-related and unrelated penile cancer. HPV-related penile cancers appear to have better prognosis than those that are unrelated.

Treatment Strategies for SCC of the Penis

For patients with localized penile cancer, factors affecting the choice of treatment include tumor size, proximal or distal location, histologic grade, confinement to the foreskin, and patient preference. Topical chemotherapy such as imiquimod or 5-FU is first-line treatment in cases of carcinoma in situ.[52] Other options are laser ablation or total or partial glans resurfacing.[53,54] For Ta/T1a lesions, a glansectomy or circumcision with intraoperative assessment of surgical margins may be sufficient. Penis-sparing techniques allow better quality of life than with partial penectomy. Local

recurrence rates are generally higher with organ-sparing surgery compared with partial penectomy (5%–12% vs. 5%), but with good salvage results and a minimal effect on survival.[55] Radiotherapy is another penis-sparing option for tumors that are less than 4 cm and stage T2 or lower.[56] Higher clinical stage (T3–T4) or more proximal tumors may require total penectomy with perineal urethrostomy for adequate local control.

Patients with regional lymph node metastases are potentially curable. Lymphatic spread occurs first to unilateral or bilateral superficial and deep inguinal lymph nodes.[57] Pelvic lymph nodes are the second regional group to be involved. Radical inguinal lymphadenectomy is the mainstay of treatment. Patients with pelvic lymph node metastases are rarely cured with surgery alone, so the role of pelvic lymph node dissection remains controversial. Some authors recommend neoadjuvant chemotherapy followed by unilateral or bilateral pelvic lymph node dissections in patients with stable or responding disease.[58-60] Spread to lymph nodes above the aortic bifurcation is classified as distant metastasis and such patients are not thought to be curable with current treatment methods.

Chemoradiotherapy to the pelvis has been suggested as an alternative to pelvic lymph node dissection in patients with metastatic penile cancer.[61] There is a lack of positive evidence for this approach in penile cancer specifically. By way of extrapolation, however, successful use of radiotherapy instead of pelvic lymph node dissection for women with metastatic SCC of the vulva has generated interest in this approach for penile cancer.[62] Currently, chemoradiotherapy to the pelvis remains a valuable option for men who have metastatic penile cancer that is inoperable, refuse surgery, or do not respond to neoadjuvant chemotherapy. An upcoming international, multicenter randomized clinical trial (NCT02305654) proposes to randomize patients between upfront surgery, neoadjuvant chemotherapy, and neoadjuvant chemoradiotherapy, with a second randomization between pelvic lymph node dissection and after adjuvant radiotherapy. This will be the first randomized controlled clinical trial for this disease, using overall survival as the endpoint.

Role of Targeted Therapy

Studies of EGFR by immunohistochemistry reveal high levels of expression in the majority of penile cancers.[63] EGFR gene amplification has been identified as a potential mechanism of protein overexpression in penile cancer, although estimates vary on how commonly this occurs.[64] Activating mutations of EGFR are notably rare. Clinical experience with EGFR-targeted therapy for metastatic penile cancer has been largely anecdotal. There are case reports of chemotherapy-refractory penile cancer subsequently responding to cetuximab or pembrolizumab alone and in combinations with chemotherapy.[65-70] For example, in a retrospective series from MD Anderson,[69] 17 patients received cetuximab with or without cisplatin; there were four partial responses (24%). Patients with only lymph node involvement had significantly better overall survival than patients with visceral or bone metastases (median 49.9 weeks and 24.7 weeks, respectively). In a separate multicenter retrospective analysis of second-line systemic therapy for metastatic penile cancer, 17 of 65 men received cetuximab or a cetuximab-including regimen, with a trend for an improved overall response rate compared with other agents (odds ratio, 5.05; 95% CI, 0.84–30.37; p = .077).[71] These results suggest a palliative benefit for some patients treated with EGFR-targeted therapies owing to tumor response, but without evidence of any improvement in progression-free and overall survival. Continuing this line of investigation, a prospective study of afatinib for advanced penile SCC following systemic therapy is currently in progress (NCT02541903).

Role of Checkpoint Inhibitors

PD-1 is a coinhibitory receptor found on B cells, T cells, and natural killer cells. Interaction of PD-1 with its ligand PD-L1 results in inhibition of T-cell proliferation and cytokine production. Immunohistochemistry revealed that a subpopulation of tumor cells express PD-L1 in penile cancer, which was seen in both HPV-related and unrelated penile cancers.[72-74] A multicenter phase II trial of pembrolizumab for advanced penile SCC (T4, N3, or M1) following chemotherapy (one or more regimens) is currently in progress (NCT02837042).

In summary, penile cancer exemplifies a rare disease in which progress has been hampered by the limited ability to conduct randomized trials. Conventional treatment methods that integrate surgery, radiotherapy, and chemotherapy have been largely successful, and a new international randomized trial is aimed at defining the optimal sequence of such treatments. Recent insights regarding the biology of penile cancer have led to opportunities for prevention (HPV), immunotherapy (PD-L1), and targeted therapy (EGFR).[75] Ongoing multicenter clinical trials are essential for development of more effective treatment options.

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Systemic Therapy for Non–Clear Cell Renal Cell Carcinoma

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OVERVIEW

Treatment options for metastatic clear cell renal cell carcinoma (ccRCC) have evolved markedly over the past decade, with multiple targeted therapies approved for the disease. In contrast, little improvement has been made in the management of metastatic non–clear cell RCC (nccRCC). Non–clear cell disease is an umbrella term that encompasses multiple biologically distinct entities, including but not limited to papillary, chromophobe, and sarcomatoid RCC. To date, prospective studies have largely explored treatments for ccRCC (e.g., VEGF- and mTOR-directed therapies) in trials that aggregate non–clear cell histologies. However, the studies do not acknowledge the varying biology of each non–clear cell subtype. Emerging studies in nccRCC should examine individual histologies and apply biologically relevant therapies. An example of this is SWOG 1500, a randomized phase II study that will compare a VEGF-inhibitor to one of three MET-directed therapies in patients with metastatic papillary RCC. Until the biologic diversity of nccRCC is appreciated, outcomes are likely to remain dismal.

The treatment landscape for metastatic RCC has evolved substantially since the cytokine era, when the mainstay of therapy encompassed agents such as interleukin-2 and interferon alpha (IFN-α).[1] These agents yielded clinical benefit in a small minority of patients and came at the expense of substantial toxicities. A steady stream of targeted therapies have been approved from 2005 onward, beginning with the VEGF-directed therapies followed by inhibitors of mTOR.[2] Over the past 2 years, three new treatments have been introduced for metastatic RCC—the multikinase inhibitors lenvatinib and cabozantinib were approved, as well as the immune checkpoint inhibitor nivolumab.[3-5]

With the notable exception of temsirolimus (an mTOR inhibitor), the phase III trials culminating in the approval of the aforementioned novel therapies have primarily included patients with ccRCC. Clear–cell RCC comprises roughly 80% of all diagnoses, and it has long been known that the disease is driven by alterations in the von Hippel Lindau (*VHL*) gene.[6] Disruption of *VHL* leads to increased levels of hypoxia inducible factor-a (HIF-α) and subsequent upregulation of VEGF, thus explaining the activity of most targeted therapies for this disease. The remaining 20% of RCC has been characterized collectively as non–clear cell. This umbrella term encompasses a multitude of distinct histologies, each of which appears to have unique biology. In contrast to ccRCC, for which dramatic advances have been made in clinical outcomes for metastatic disease, relatively little is known about the optimal management for non–clear cell disease. Herein, we summarize the available literature and highlight potential future directions for the investigative community.

PAPILLARY RCC

Papillary RCC represents 10% to 15% of RCC cases. The Cancer Genome Atlas investigators recently reported genomic analyses from 161 primary papillary RCC specimens.[7] Ultimately, three subsets were characterized. Type I disease was noted to bear a higher frequency of alterations in the *MET* proto-oncogene, whereas type II tumors had *TFE3* fusions, *CDKN2A* silencing, and *SETD2* mutations. Increased expression of *NRF2-ARE* pathway elements was also noted in type II disease. A particularly aggressive subset of type II disease was discerned, bearing mutations in the fumarate hydratase (*FH*) gene.

The activity of sunitinib and sorafenib, both VEGF receptor (VEGFR) tyrosine kinase inhibitors, in papillary RCC was examined in a retrospective study by Choueiri and colleagues. The study included a total of 41 patients with metastatic papillary RCC, among whom only two patients (4.8%) achieved a partial response.[8] There have been several attempts to prospectively characterize the activity of sunitinib in patients with papillary RCC. Tannir and colleagues performed a phase II study including 57 patients with nccRCC, of whom 27 had papillary histology. No responses were observed in this experience, and median progression-free survival (PFS) among patients with papillary RCC was a meager 1.6 months. Better results with sunitinib were achieved in the phase II SUPAP trial reported by Ravaud and colleagues.[9] A total of 61 patients were enrolled, with 15 and 46 patients characterized as type I and type II, respectively. Among type I patients, two patients (13%) were noted to have a partial response and median PFS was 6.6 months. In patients with

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type II disease, five responses (11%) were observed and median PFS was 5.5 months.

As alluded to previously, the phase III evaluation of temsirolimus in metastatic RCC did include patients with non–clear cell histology.[10] In this comparison of temsirolimus compared with temsirolimus/IFN-α or IFN-α alone, temsirolimus monotherapy was noted to improve survival compared with IFN-α monotherapy (10.9 months vs. 7.3 months, p = .008). Although the benefit of temsirolimus was noted to extend across both clear and non–clear cell subsets, no distinction was made in the available data for papillary patients. Current clinical guidelines reflect this dataset and suggest mTOR inhibition as a possible first-line approach in patients with nccRCC.

Several attempts have been made to reconcile whether VEGF or mTOR inhibition should be the mainstay of treatment of patients with nccRCC. The randomized, phase II ESPN trial included a total of 68 patients with nccRCC. In the overall cohort, no significant difference in PFS was seen between sunitinib and everolimus (median PFS, 6.1 and 4.1 months, respectively; p = .6), but the trend favored sunitinib.[11] No significant difference in overall survival (OS) was observed in either treatment arm. Interpretation of these results is confounded by the multiple histologic subgroups included in this trial; specifically, 27 patients with papillary RCC, 10 patients with unclassified RCC, seven patients with translocation RCC, 12 patients with chromophobe RCC, and 12 patients with sarcomatoid RCC. Among those patients with papillary disease, no clear benefit was seen in either treatment arm. Crossover was allowed at the time of progression, but the high attrition rate observed from first- to second-line therapy makes these results challenging to interpret.

Two other studies have taken the approach of directly comparing sunitinib and everolimus in the context of non–clear cell disease. The randomized, phase II ASPEN study used an identical randomization schema, although eligibility was limited to chromophobe, papillary, and unclassified histologies.[12] With a total of 108 patients enrolled, a numerical advantage in PFS was seen with sunitinib compared with everolimus (8.3 months vs. 5.6 months; p = .16), mirroring results from ESPN. Again, with a limited number of patients with papillary histology, drawing firm conclusions from this subset is difficult. The RECORD-3 clinical trial is the third study to compare sunitinib with everolimus.[13] The study differs from ESPN and ASPEN in its inclusion of clear cell histology. Akin to ESPN, crossover was allowed at the time of progression. In the cohort of patients with nccRCC (totaling 66 patients), a trend was once again seen toward benefit with sunitinib compared with everolimus (median PFS, 7.23 vs. 5.09 months).[12] No information is available from this trial pertaining to the breakdown of clinical benefit by individual histologies.

From ESPN, ASPEN, and RECORD-3, several common themes emerge (Table 1). First, sunitinib appears to have greater activity than everolimus in non–clear cell disease. Second, each study has a diverse mix of histologies, making it challenging to infer the specific benefit of VEGF-inhibition in metastatic papillary RCC. Third, each study suggests that the benefit of sunitinib is more modest than anticipated in the context of clear cell disease. In RECORD-3, for instance, median PFS with sunitinib in the clear cell cohort was 10.84 months compared with 7.23 months in non–clear cell disease. These collective results have informed the design of an international randomized, phase II study led by the Southwest Oncology Group (SWOG; Fig. 1). In SWOG 1500, patients with metastatic papillary RCC with zero to one prior therapies (excluding VEGF-inhibitors) will be randomly assigned to receive either sunitinib (the control arm) or one of three MET-directed therapies. As noted previously, The Cancer Genome Atlas data indicate a role for *MET* in the context of type I disease. Data from the French RCC network further supports *MET* as an oncogenic driver across papillary RCC subtypes—in this large experience of samples from 220 patients, 81% and 41% of type I and type II cases, respectively, demonstrated copy number alterations in *MET*.[14]

The MET-directed therapies comprising the experimental arms are each associated with varying levels of evidence in metastatic RCC. Cabozantinib, a dual VEGFR2/MET inhibitor, has been assessed in a phase III clinical trial in metastatic ccRCC.[4] Compared with everolimus, cabozantinib was associated with improved PFS and OS in patients who had previously received first-line VEGF-directed therapy.[4] Surprisingly, little data are available pertaining to the activity of cabozantinib in non–clear cell subtypes, although an antitumor effect with cabozantinib has been observed in the ACHN cell line, derived from a patient with papillary RCC (personal communication, Jeremy Jones, PhD). Savolitinib is a distinct and more specific MET inhibitor that will be examined in SWOG 1500. This agent has been shown to have activity in multiple papillary RCC xenograft models, and results from an ongoing phase II study that included patients with papillary RCC are anticipated in the near future.[15] Crizotinib will be evaluated in the third experimental arm in SWOG 1500. Crizotinib is approved in *ALK*-rearranged non–small cell lung cancer, but the agent also appears to have affinity for MET kinase. Patients with type I metastatic

KEY POINTS

- **Non–clear cell renal cell carcinoma is an umbrella term that encompasses an array of biologically diverse diseases.**
- **Published clinical trials to date (e.g., ESPN, ASPEN) have largely taken the approach of aggregating multiple non–clear cell subtypes.**
- **Interpreting results from these studies can be challenging given the inclusion of small numbers of each subtype.**
- **Future studies should take the approach of treating a single histology using agents with biologically relevant mechanisms of action.**
- **As one example, SWOG 1500 will explore MET-directed therapies in the context of papillary renal cell carcinoma.**

TABLE 1. Selected Prospective Trials in Non–Clear Cell RCC

Trial	Treatment	Randomized?	Number Enrolled	Histology Type	Overall Response Rate	Progression-Free Survival	Overall Survival
ESPN	Sunitinib vs. everolimus	Yes	68 patients	All non-clear cell	9% vs. 3%	6.1 vs. 4.1 months	16.2 vs. 14.9 months
ASPEN	Sunitinib vs. everolimus	Yes	108 patients	All non-clear cell	18% vs. 9%	8.3 vs. 5.6 months	31.5 vs. 13.2 months
RECORD-3	Sunitinib vs. everolimus	Yes	66 patients	All non-clear cell	N/A	7.2 vs 5.1 months	N/A
SUPAP	Sunitinib	No	61 patients	Papillary	13% (type I) and 11% (type II)	6.6 months (type I) and 5.5 months (type II)	17.8 months (type I) and 12.4 months (type II)

papillary RCC were included in the CREATE trial, a basket study led by the European Organisation for Research and Treatment of Cancer in which multiple tumor types were treated with crizotinib.[16] Among a total of 23 patients enrolled, responses were observed in two of four patients bearing *MET* alteration. No responses were observed among 16 patients lacking this alteration. With the caveat of a relatively small sample size, mean treatment duration was also noted to be longer in the *MET* altered cohort (11.9 vs. 5.3 months).

This is not the first time a correlation between response and *MET* status has been observed in the context of MET-directed therapies for metastatic papillary RCC. In a phase II study examining foretinib, a dual VEGFR2/MET inhibitor, in patients with metastatic papillary RCC, responses were observed in five of 10 patients (50%) bearing germline alterations in the *MET* oncogene.[17] In the remaining 57 patients, only five responses were observed (9%). These datasets have informed the translational aims of SWOG 1500, which will perform a detailed exploration of *MET* status, including assessment of *MET* mutation and copy number alteration, as well as MET protein expression.

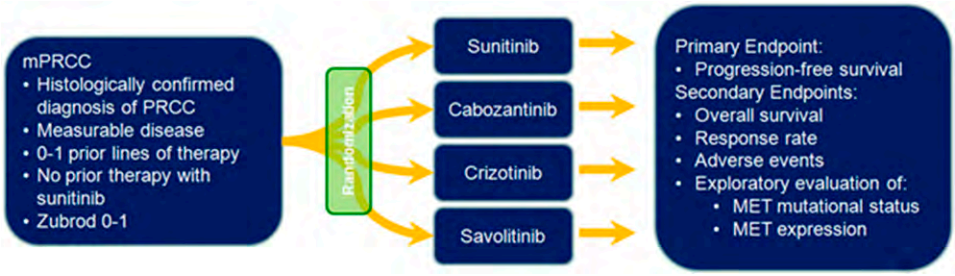
CHROMOPHOBE RCC

As with papillary RCC, the biology of chromophobe RCC, which comprises roughly 5% of RCC cases, has been characterized by The Cancer Genome Atlas investigators.[18,19] In a series of 66 cases, the major observations were alterations in mitochondrial DNA (mtDNA), underscoring the importance of oxidative phosphorylation in the pathogenesis of chromophobe RCC. Increases in TERT expression were also observed, derived through rearrangements in the *TERT* promoter region. From the standpoint of systemic management, there are scant data to address the role of targeted agents in chromophobe disease. Keizman and colleagues reported a retrospective experience including 36 patients with metastatic chromophobe RCC who received first-line sunitinib therapy.[20] Median PFS was 10 months and median OS was 26 months. When matched to similar patients with metastatic clear cell disease, no significant difference in clinical outcome was observed. Data for mTOR inhibitors in the context of chromophobe disease are more scant; several case reports suggest potential activity, though no large case series exist.[21-23]

SARCOMATOID RCC

Sarcomatoid histology rarely exists as an independent entity; rather, sarcomatoid elements are typically admixed with other RCC histologies. It is estimated that 15% to 20% of patients with RCC harbor sarcomatoid elements. Patients with RCC with sarcomatoid features often have an aggressive clinical course and poor prognosis. Recent genomic assessments of sarcomatoid RCC (sRCC) have produced varying results. Through comparison of sarcomatoid and nonsarcomatoid components in individual patients using RNA-sequencing, our group has shown increased expression of aurora kinase pathway elements and increased mTOR pathway activity in sarcomatoid disease. Karam and colleagues assessed a larger series of patients with dominant sarcomatoid histology using comprehensive genomic profiling.[24]

FIGURE 1. Schema for SWOG 1500: A Randomized, Phase II Study Comparing Sunitinib, Cabozantinib, Crizotinib, and Savolitinib in Patients With Metastatic Papillary Renal Cell Carcinoma



In 26 patients, the most frequent alterations were in *TP53* (42.3%), *VHL* (34.6%), *CDKN2A* (26.9%), and *NF2* (19.2%).

Although these studies appear to suggest that sarcomatoid histology may have a biology unique to ccRCC, the current treatment paradigms for metastatic sRCC do not reflect this. Initial approaches to sRCC centered on use of cytotoxic chemotherapy. In ECOG 8802, the regimen of doxorubicin plus gemcitabine was assessed in a series of 38 patients.[25] The degree of the sarcomatoid involvement varied: 18 patients (47%) were noted to have pure sarcomatoid disease. The response rate in this cohort was 16%, with a modest PFS of 3.5 months. A separate study assessed a regimen of doxorubicin and ifosfamide in 25 patients with metastatic sRCC.[26] No responses were observed, and PFS was a meager 2.2 months. Other studies have attempted to study the combination of cytotoxic therapy with VEGF inhibition in sRCC. One phase II study evaluated gemcitabine and sunitinib in 39 patients with sRCC. Patients with sRCC had an overall response rate of 26%.[27] Median time to progression was 5 months, and median OS was 10 months. Patients developed grade 3 or higher adverse events of neutropenia, anemia, and fatigue. There is an ongoing randomized phase II trial of sunitinib alone compared with sunitinib and gemcitabine in patients with advanced RCC with sarcomatoid features (NCT01164228).

Given the low response rates to cytotoxic therapy, additional efforts have been made to characterize the activity of VEGF- and mTOR-directed therapies in sRCC. A retrospective experience including 43 patients with metastatic sRCC treated with VEGF-directed agents showed a response rate of 19%, with a median PFS of 5.3 months.[28] The activity of everolimus has similarly been characterized in patients with sarcomatoid disease. Bastos and colleagues retrospectively assessed the activity of temsirolimus and everolimus in 29 patients; a median PFS of 3.4 months was observed with three responses (10%).[29]

With the approval of the immune checkpoint inhibitor nivolumab for metastatic ccRCC, there has been renewed interest in the activity of checkpoint inhibitors in non–clear cell histologies as well. The PD-L1 inhibitor atezolizumab was evaluated in a mixed cohort of pretreated patients with both clear cell and sarcomatoid disease.[30] Among 18 patients who demonstrated either Furhman grade 4 or sarcomatoid histology, an encouraging response rate of 22% was observed. A randomized phase III study comparing the combination of bevacizumab with atezolizumab to sunitinib in the first-line metastatic setting will include patients with sarcomatoid elements (NCT02420821). Furthermore, an ongoing adjuvant clinical trial comparing atezolizumab with placebo in patients with high-risk localized RCC will similarly allow for patients with sarcomatoid elements (NCT03024996).

RARE NON–CLEAR CELL RCC SUBTYPES

Several rare non–clear cell subtypes comprise less than a percentage point of all RCC diagnoses. These tumor types are both diagnostic and therapeutic conundrums. Collecting duct carcinoma is a particularly aggressive disease affecting a younger patient population.[31] We recently reported a genomic assessment of 17 cases of collecting duct RCC, identifying occasional alterations in *NF2, SETD2*, *SMARCB1*, and *CDKN2A*.[32] At present, these data have not been used in a prospective study to inform therapy. The one prospective study that has been conducted to date explores a combination of gemcitabine with either cisplatin or carboplatin.[33] Median PFS and OS were 7.1 and 10.5 months, respectively, with a response rate of 26%. Anecdotal reports exist documenting responses to sunitinib and sorafenib therapy.[34-36] No consensus exists regarding optimal treatment of this entity, although platinum-based chemotherapy is still frequently used in clinical practice.

Renal medullary carcinoma carries a similarly aggressive phenotype, and affects younger patients with sickle-cell trait. Loss of the tumor suppressor *SMARCB1/INI1* is the most common genetic alteration.[37-39] Shah and colleagues recently reported an experience including 52 patients with renal medullary carcinoma, the majority of whom had stage III or IV disease.[40] Of 45 patients who received chemotherapy, 13 patients (29%) had an objective response. Interestingly, among 28 patients who received targeted agents, no responses were observed. Of note, there was a recent case report of a young man with sickle-cell trait and renal medullary carcinoma who had a total nephrectomy and adjuvant chemotherapy (carboplatin, gemcitabine, paclitaxel, and bevacizumab). He then developed disease recurrence in the lymph nodes and was subsequently treated with nivolumab. Interestingly, he had a complete response that lasted more than 9 months and was ongoing at the time of publication.[41] Upon retrospective analysis of the patient's lymph node biopsy, 23% of the tumor cells had PD-L1 expression. Two percent and 5% of stromal cells expressed PD-1 and PD-L1, respectively. Tumor-infiltrating T cells accounted for 21% of the cells (10% CD8-positive and 41% CD4-positive). This case is tantalizing and suggests a potential role for immune checkpoint inhibition in patients with renal medullary carcinoma.

Xp11.2 translocation RCC is another distinct entity comprising a small fraction of all RCC cases. The translocation entails fusion of the *TFE3* gene with the alveolar soft part sarcoma locus (*ASPL*) or *PRCC,* and the fusion product appears to regulate cell cycle.[42] Two separate reports document the activity of VEGF-directed agents in Xp11.2 translocation RCC. The Juvenile RCC network reported a series of 11 patients who received sunitinib in the first-line setting with a median PFS of 8.2 months.[43] Choueiri and colleagues assessed a separate series of 15 patients with Xp11.2 RCC. In this series, three patients (20%) achieved a partial response, and median PFS was 7.1 months.[44]

Notably, the rare histologic subtypes of RCC presented herein are not intended to represent a comprehensive list. Multiple other subtypes exist, including unclassified, mucinous tubular, and spindle cell, and so on. However, the body of evidence behind specific systemic therapy regimens is scant. At present (mirroring other more common subtypes),

practitioners often extrapolate from treatment algorithms for clear cell disease.

As more interest has developed in immune checkpoint blockade, PD-L1 status has also been evaluated in several studies. In one series of 101 archival specimens of nccRCC, PD-L1 expression by tumor cells was demonstrated in only 11% of specimens and associated with poor prognosis (higher grade and stage, as well as shorter OS).[45] In contrast, 56% of samples demonstrated PD-L1 expression on tumor-infiltrating mononuclear cells. However, others have shown that PD-L1 expression by tumor cells from archival specimens is not correlated with prognosis.[46] These early correlative studies are, at best, hypothesis generating. Performed carefully in a rare disease population, though, they can be quite helpful in designing future studies. In general, clinicians need better biomarkers for response to immune checkpoint blockade.

CONCLUSION

The approach to systemic management of nccRCC has been relatively straightforward over the past several decades. Simply put, approved treatments for ccRCC have been transposed to non–clear cell histologies. In the era of VEGF- and mTOR-directed therapies, this approach has produced modest results at best, as illustrated by the numerous examples cited herein. Investigators have also made the mistake of lumping together multiple non–clear cell histologies in prospective trial designs. As seen in the ASPEN and ESPN trials, blending a heterogeneous array of histologic subtypes within a single study can confound interpretation of results.

Progress in treating nccRCC will likely be contingent upon acknowledging the unique biology of individual histologies. Trials such as SWOG 1500, which test a potentially relevant pathway in a single disease (e.g., MET inhibition in papillary RCC), are more apt to improve the current standard of care. These trials do not come without substantial challenge—randomly assigning hundreds of patients with these rare tumor types requires national, if not international, cooperation in trial conduct. It is challenging to envision any definitive studies taking place at single institutions; rather, cooperative group mechanisms must be used to band together a sufficient number of tertiary centers with experience in these rare diseases. Patient advocacy groups are also key to disseminating information pertaining to these trials. With a unified approach, the investigative community can gradually shift the treatment paradigm for nccRCC.

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GENITOURINARY (PROSTATE) CANCER

Diagnosis and Treatment of Prostate Cancer: What Americans Can Learn From International Oncologists

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OVERVIEW

The three main sections in this article illustrate a number of facets of European health care. The first section looks at the influence of NICE on treatment of metastatic castration-resistant prostate cancer. The second section explores the impact of molecular imaging on diagnosis and treatment, in particular the development and clinical implementation of ^{68}Ga PET imaging in prostate cancer. The final section of the session looks at the STAMPEDE trial and how running a trial on this scale has impacted care of prostate cancer in the United Kingdom and also at the uptake of docetaxel chemotherapy in hormone-sensitive advanced disease.

European health care systems vary enormously from country to country in terms of structure and funding models. They broadly operate, however, on the principle that the state has a duty to ensure health care is available to all members of the population. This contrasts with the situation in the United States, starkly illustrated by the recent U.S. presidential elections, with huge controversy over the Patient Protection and Affordable Care Act (also known as "Obamacare") and the idea that health care may be an individual's rather than the state's responsibility—an alien concept to most Europeans. This leads to the situation where U.S. citizens with adequate insurance enjoy some of the most technologically advanced health care in the world, while some of their fellow citizens struggle with huge financial burdens associated with uninsured health care costs. In contrast, implicit in social insurance or taxpayer-based systems is some form of centralized decision making. This may lead to restricted access to "cutting-edge" medicines but, at the same time, facilitates access for all affected to an accepted standard of care.

Within Europe, two broad subdivisions may be identified in how health care advances are funded. With new drugs, there are two levels of decision to be made: Should a drug be approved for patients—marketing authorization—and secondly, should the public health care system fund the use of the drug? In many countries (e.g., France, Germany, Italy), no distinction is made and a marketing authorization makes the drug available via the public health care system. In a second group, notably in the United Kingdom and Scandinavia, these decisions are separated so that a marketing authorization may or may not lead to broad public access. In the United Kingdom, these decisions are made by the National Institute for Health and Care Excellence (NICE), and NICE decisions are often then used as templates by other countries and hence are very influential. NICE attempts to judge the cost effectiveness as well as the clinical effectiveness of new agents. It is the former that drives the controversy often associated with some NICE decisions. However, the need to meet NICE cost-effectiveness requirements is undoubtedly a factor in driving down the costs of new medicines within the United Kingdom in particular, as compared with countries where marketing authorization and access are simultaneous.

A further feature of the U.K. system is the state supports entry into academic trials via the National Health Service (NHS). This means the public hospital system is directly financially incentivized to support trials badged as suitable by the U.K. National Cancer Research Institute. This has led to the United Kingdom having one of the highest rates in the world of cancer trial participation. This is well illustrated by the STAMPEDE trial, which has to date recruited more than 8,000 men to a trial now encompassing 10 research arms, with two further in setup, across more than 100 hospitals. With such a broad base of participation, questions are asked and answered in a very "real-world" setting, ensuring broad applicability. It also ensures relatively easy rollout of positive results (such as the docetaxel data), as centers and clinicians are familiar with the rationale and administration of the trial therapies and have also personally invested their own time and energy into the trial data set.

The three main sections in this article illustrate a number of facets of European health care. The first section looks at the influence of NICE on treatment of metastatic castration-resistant prostate cancer (mCRPC). The second section explores the impact of molecular imaging on diagnosis and treatment, in particular the development and clinical implementation

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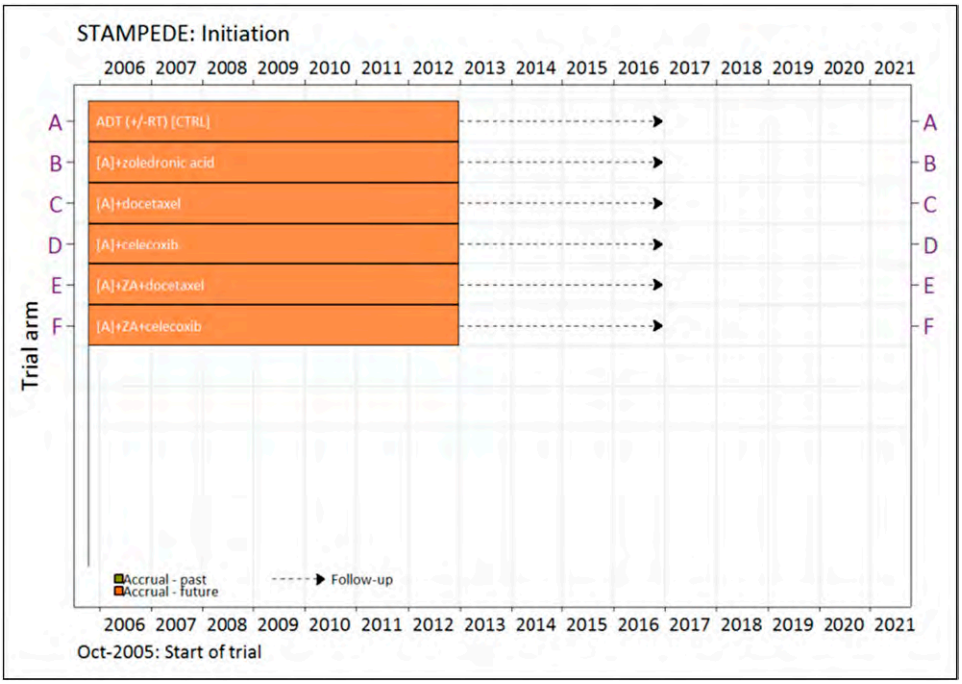
FIGURE 1. Original Trial Design



of ^{68}Ga PET imaging in prostate cancer (PCa). The final section of the session looks at the STAMPEDE trial and how running a trial on this scale has impacted care of PCa in the United Kingdom and also at the uptake of docetaxel chemotherapy in hormone-sensitive advanced disease.

HOW RANDOMIZED TRIALS OF STAMPEDE HAVE INFLUENCED TREATMENT DECISIONS IN THE UNITED KINGDOM

Background

The STAMPEDE trial was set up in 2004 and 2005 and commenced recruitment in 2005. The basic principle of the trial was to assess the addition of new treatment modalities to standard of care with the aim of improving overall survival. At the time of setup, zoledronic acid had recently been approved for mCRPC affecting bone, and docetaxel was in the final stages of phase III evaluation. Both agents seemed to be worth evaluating in the newly diagnosed, as opposed to the relapse setting. Given the large numbers of patients diagnosed with PCa, the Trial Management Group decided to seek a third agent to evaluate and eventually selected celecoxib as an agent with possible metastasis and invasion-preventing properties. The Trial Management Group also decided to look at agents both alone and in combination, giving a total of five experimental arms in original design. A second novel feature of the trial was the integration of a feasibility stage, interim efficacy stages, and a final overall survival stage to give a multiarm, multistage design. Table 1 shows the primary and secondary endpoints for the various stages. Figure 1 shows the original trial design in terms of agents being evaluated.

KEY POINTS

- **The PSMA represents a promising molecular target in PCa useful for PET imaging.**
- **In patients with relapsed PCa, PSMA PET imaging improves detection of metastatic lesions even at low PSA values.**
- **In patients with primary intermediate to high-risk PCa, PSMA PET imaging showed increased specificity and sensitivity compared with current standard imaging for detection of lymph node and bone metastases.**
- **In combination with multiparametric MRI, PSMA PET imaging might provide additional molecular information useful for intraprostatic PCa localization.**
- **Although current knowledge is still limited and derived mostly from retrospective series, PSMA-based imaging might enable improved patient-tailored PCa management in the future.**

TABLE 1. Trial Endpoints

Comparison Stage	Primary Outcome Measure	Secondary Outcome Measures
Pilot phase	Safety*	Feasibility
Activity stages	Failure-free survival**	Overall survival
		Toxicity
		Skeletal-related events
Efficacy stage	Overall survival	Quality of life
		Cost effectiveness
		Failure-free survival**
		Toxicity
		Skeletal-related events

*Based on toxicity.

**Including biochemical failure.

Setting Up and Running the STAMPEDE Trial

The aim of running what is effectively a suite of phase II and III trials is to reduce the bureaucracy associated with the opening and closing of multiple studies and linked inherent delays in the analysis, close down and set up when the traditional phase II and separate phase III model is used. We estimate that around 30% of phase III trials produce a positive result in the sense that the experimental arm is better than the control arm. By having multiple arms, we, simply put, had more chances to win and hence to change practice. Secondly, the fact that all patients contribute to all analyses overall means that fewer total patients are needed compared with separate phase II and III studies. In particular, separate phase III studies for each agent would each need a control arm, which is hence duplicated if multiple trials are recruiting in the same disease "space." This again means that, overall, fewer patients are needed to answer questions about different agents compared with multiple simultaneous trials. In addition, multiple trials would be competing with each other for resources and, very importantly, for patients, leading to likely slower overall aggregate recruitment. The effects on numbers of patients and time are illustrated in Fig. 2.

A second consequence of the multiarm, multistage model is that new arms can be added at a later stage, with the staged analyses for the new arm being frame shifted to the timetable for that arm. We first tested this approach in 2011 with the addition of arm G evaluating the upfront use of abiraterone. We have subsequently added three further arms: radiotherapy (RT) in M1 patients, combination abiraterone/enzalutamide, and metformin, with two additional new arms in setup.

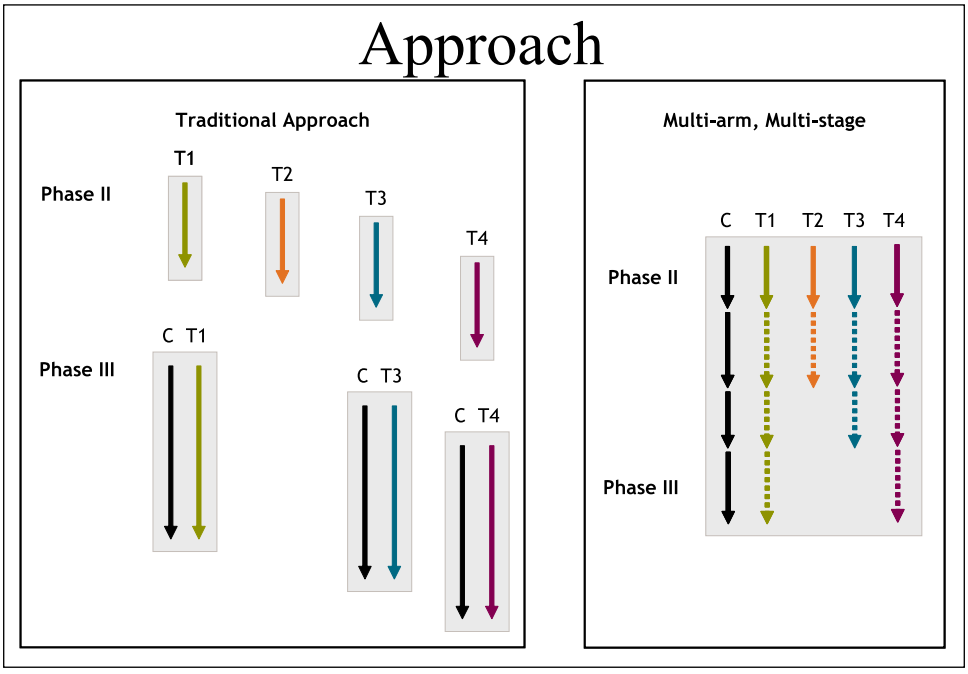
Adding an arm is extremely efficient compared with setting up a new trial, which would compete for patients with the original trial. All setup costs have to be reincurred for the new arm, and investigators' time and energy are diverted. In contrast, adding an arm by protocol amendment is simple from the administration point of view in centers and avoids competition between trials for scarce resources and patients. Figure 3 shows the time to set up the original comparisons as compared with the first three arms added.

The faster setup is also translated into faster recruitment, as, once open, the new arm benefits from the established ongoing recruitment for the parent trial. Figure 4 shows the recruitment to arm G (abiraterone) was originally projected to run from Q4 2011 to Q4 2014 with 1,500 patients. Due to very rapid recruitment, the target was expanded to 1,800, which was completed a year ahead of schedule in late 2013. Arms H (RT:M1) and J (abiraterone/enzalutamide) have similarly recruited well ahead of time and target again with expanded numbers to increase power and accelerate reporting.

To recruit patients to a trial with oncology-based therapies such as docetaxel, we needed to change referral pathways. This required buy-in from urologists and a willingness to refer patients from urology to oncology much earlier than was previously the norm. We have involved urologists in the design, setup, and implementation of the trial, and support among urologists throughout has been huge.

The U.K. system facilitates the shared financing of trials. The core resource has been funded via Cancer Research UK, with additional resources from the Medical Research Council Clinical Trials Unit. We had financial assistance from the manufacturers of the three drugs initially chosen for evaluation in terms of free or subsidized drugs and additional grant support over and above the core academic funding.

FIGURE 2. Multiarm, Multistage Trials Versus Multiple Phase II and III Trials



In addition, a key feature of the U.K. NHS is that NHS hospitals receive additional funding in return for putting patients in suitably badged studies via the National Cancer Research Institute and linked National Cancer Research Network.

In conclusion, the structure of clinical trial funding within the U.K. NHS greatly facilitates large-scale trials. The STAMPEDE multiarm, multistage model works well within this system, and the flexible approach to adding arms to an existing trial results in extremely rapid uptake and recruitment compared with starting multiple new trials.

Control Arm Data: Radiotherapy in Node-Positive Disease

With a trial as large as STAMPEDE recruiting in every major oncology center in the United Kingdom, data emerging from the control arm has immense value in telling us about patterns of care and the impact of different care patterns on outcomes. The best example to date is the impact of radiotherapy in locally advanced or node-positive, nonmetastatic disease. Radiotherapy was recommended but not mandatory from 2005 to 2011 when two randomized trials demonstrated the impact of radiotherapy in locally advanced disease. Within the trial, many patients up to 2011 did not receive RT for locally advanced disease due to differences in unit policies. The impact of RT in this group was to increase failure-free survival at three years from 62% to 87%, validating the SPCG7[1] and PR07[2] results in a real-world, high-risk setting. Additionally, and very importantly, we were able to look at the impact in TxN+M0 disease and saw an increase in three-year failure-free survival from 47% to 71%. There are no randomized trials in this setting; multivariate analysis suggested a hazard ratio for the improvement of 0.5 in favor of pelvic and prostate radiotherapy.[3]

Docetaxel Data

The first survival data from the trial were published in 2016[4] and showed an increase in survival from six cycles of docetaxel but no significant impact from zoledronic acid given at inception of hormone therapy.[4] The docetaxel results confirmed data from the U.S. CHAARTED trial in M1 disease[5] and cemented the role of upfront chemotherapy in newly diagnosed metastatic disease (Fig. 5). This was confirmed by a meta-analysis copublished with the STAMPEDE results.[6] The broad base of recruitment to STAMPEDE means that these results can be seen as broadly applicable within the NHS.

Implementing STAMPEDE Trial Results

In order for results to have impact, they must be implemented in the health care system. The NHS in the United Kingdom is actually four devolved services: England, Wales, Scotland, and Northern Ireland, with around 80% of the population living in England. Within NHS England, NICE considers medical treatments and makes guidelines to NHS hospitals. This is two edged, as it can either facilitate or block implementation. After some initial delay, NHS England and NICE decided to run a rapid evidence review and issued guidance via NICE[7] and commissioning guidance[8] supporting the use of docetaxel in this setting. This was published January 2016, the same month as *The Lancet* results publication, thus ensuring broad availability from date of publication.

The STAMPEDE trial illustrates a number of positive features of the "socialized" health care model: the ability to centrally support trials and the flexibility in trial legislation that has allowed the trial to evolve into a platform for serially evaluating many different interventions. Finally, the central control, although sometimes a tool for rationing,

FIGURE 3. Time to First Patient Into Trial Across STAMPEDE Centers by Trial Arm

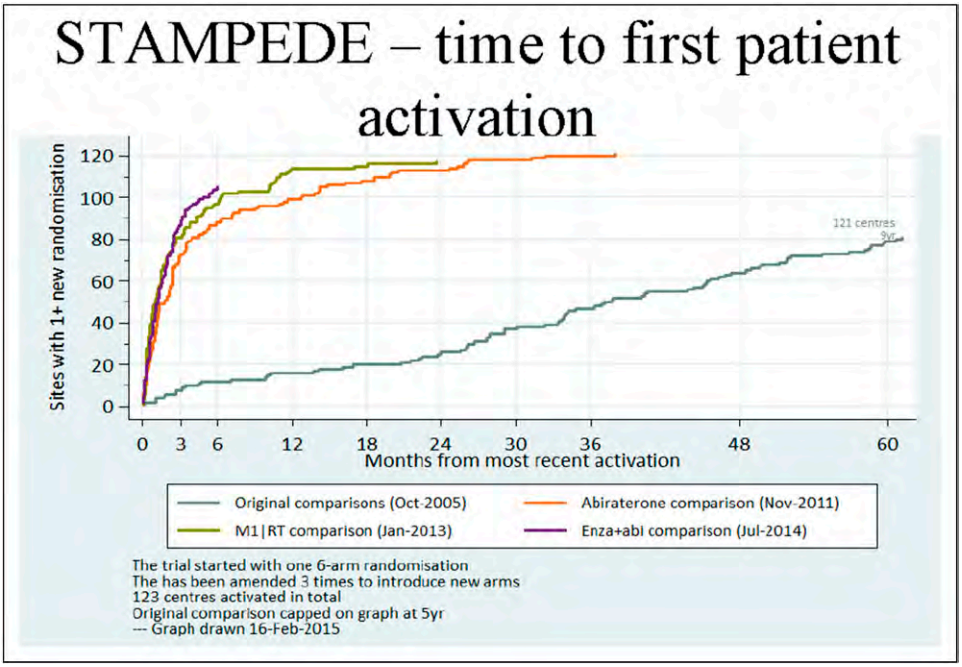
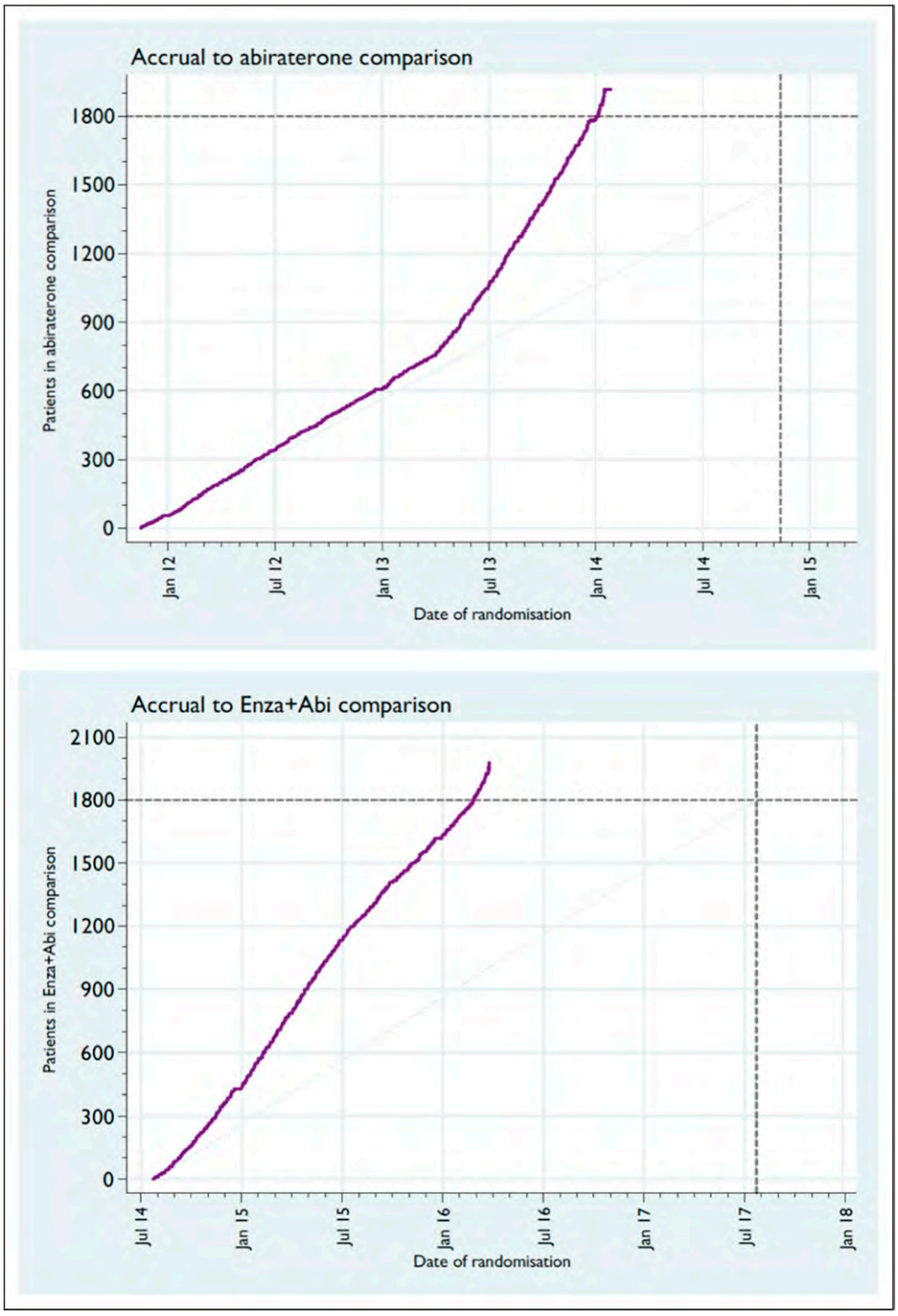


FIGURE 4. Recruitment in Arms Added After Trial Inception

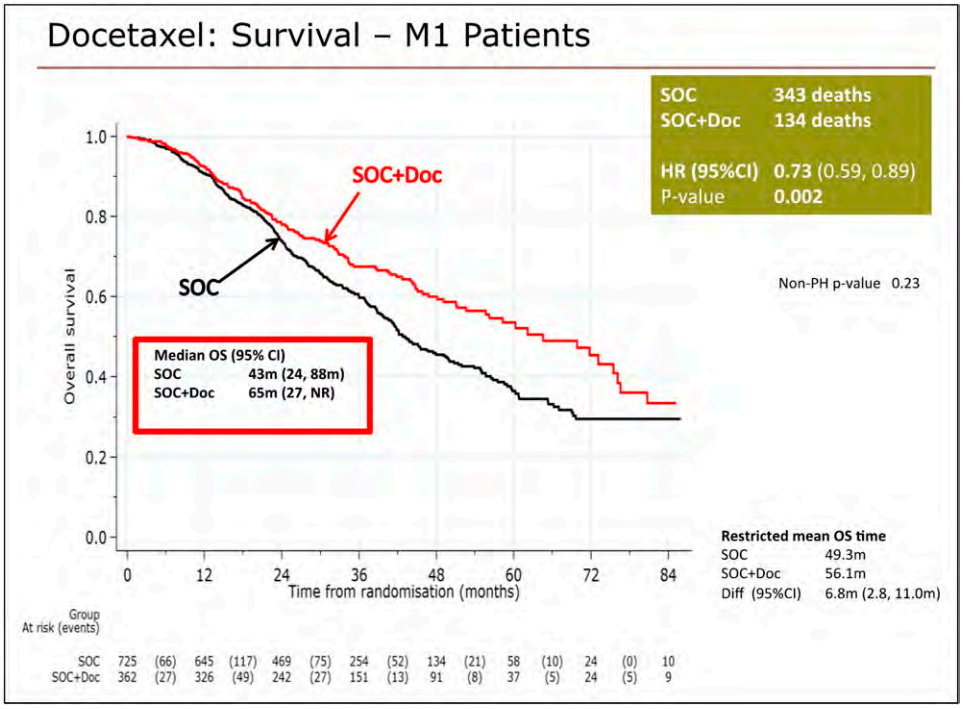


can also be a tool for enabling the rapid implementation of clinically important results.

HAVE DECISIONS BY NICE AFFECTED OUTCOMES OF BRITISH PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER?

Government-funded health care systems must ensure that taxpayers' money is being well spent. The NHS Constitution states that "it is committed to providing the most effective, fair, and sustainable use of finite resources."[9] It is generally agreed that evidence-based medical practice improves outcomes and reduces variations in care. The Cochrane ladder of evidence (efficacy, effectiveness, and cost effectiveness) puts the assessment of cost effectiveness as the optimum goal for evidence-based practice.[10] The quality-adjusted life year (QALY) is the most widely adopted method and allows cancer treatments to be compared with, for example, treatments for

FIGURE 5. Impact of Docetaxel on Overall Survival in Men With Metastatic Disease Starting Long-term Hormone Therapy for the First Time



mental illness. Inevitably, there are compromises. In the United Kingdom, NICE uses the EuroQoL EQ-5D system to measure quality-of-life benefits.[11] Compared with cancer-specific measures such as the EORTC QLQC33 or FACT-P for PCa, EQ-5D is less detailed, but it offers two key advantages. EQ-5D can be applied to different medical conditions, and it can be weighted to reflect the values that different societies place on health states. Estimated total costs and QALYs are collected over the modeled time horizon for each treatment. The total costs will include all costs associated with the treatment, follow-up, further treatment, and management. QALYs are calculated by multiplying the life years that patients spend in each health state by the associated quality-of-life weighting, which represents the patient's and society's valuation of their health state.[12] Cost effectiveness is calculated by assessing the incremental change in health utility measured by QALYs. The incremental cost-effectiveness ratio (ICER) can then be calculated using the formula shown in Figure 6.

NICE was set up in 1999 by Tony Blair's Labor Government as the National Institute for Clinical Excellence to reduce variations in availability and quality of care in the NHS in England.[13] Initially, it was run as a special health authority within the NHS, but from April 2013, it has been a nondepartmental public body outside the NHS, accountable to the Department of Health, and with a broader remit for social care as well as health care. Its name was changed to the National Institute for Health and Care Excellence, but the acronym NICE was retained.

NICE is an English body but provides some services for Scotland, Wales, and Northern Ireland. Its appraisal system for new drugs applies only to NHS England. Drugs approved through the Technology Appraisal (TA) system[14-25] have a guaranteed funding stream for the duration of the guidance. This distinguishes TAs from all other NICE guidance (clinical guidelines, diagnostic assessments), which are advisory to the various bodies that commission health and social care. The privileged financial position of NICE TAs means that they sit separately from NICE's clinical guidelines and are excluded from them. The two NICE guidelines on the management of PCa published in 2008 and 2014 have no guidance

FIGURE 6. Formula 1

$$\text{Incremental cost effectiveness ratio (ICER)} = \frac{\text{Mean cost with B} - \text{Mean cost with A}}{\text{Mean effect with B} - \text{Mean effect with A}}$$

"Incremental Costs" / "Incremental QALYs/Effects"

TABLE 2. NICE Technology Appraisals of Drugs for mCRPC

Drug	Technology Appraisal	Date	Outcome
Docetaxel	TA101[14]	June 2006	Approved
Cabazitaxel	TA255[15]	May 2012	Not recommended
Abiraterone postdocetaxel	TA259[16]	June 2012	Approved
Enzalutamide postdocetaxel	TA316[17]	July 2014	Approved
Sipuleucel-T	TA332[18]	January 2015	Not recommended
Radium-223	TA376[19]	January 2016	Approved
Enzalutamide prechemotherapy	TA377[20]	January 2016	Approved
Abiraterone prechemotherapy	TA387[21]	April 2016	Approved
Cabazitaxel	TA391[22]	May 2016	Approved

on the use of chemotherapy or radium-223 in mCRPC, other than the incorporated recommendations from the appraisal of docetaxel in 2005 (TA101).[26]

So this discussion of NICE's decisions on treatments for mCRPC will focus on the TA process for men treated by NHS England. It will also cover treatments provided by the CDF and issues relating to NICE's clinical guidelines on the management of PCa. NICE has appraised the following drugs for mCRPC: docetaxel, cabazitaxel, abiraterone, enzalutamide, sipuleucel-T, and radium-223. Table 2 shows the dates and outcomes of the appraisals.

There are two types of appraisals for new drugs, single technology assessments (STAs)[23] and multiple technology assessments.[24] Most appraisals are STAs, as was the case for all the drugs for mCRPC. The advantage of an STA is that it is generally a quicker process. The manufacturer submits a case for the clinical and cost effectiveness of their product, and this is sent to an independent academic group, the evidence review group (ERG), commissioned by NICE to review the submitted evidence. Then the manufacturer and the ERG present their findings to the TA committee that makes a decision.

In a multiple technology assessment, an independent group is commissioned to produce a health technology assessment of a product or multiple products with one or more indications. This assessment is presented to the TA committee along with evidence from selected stakeholders such as health care professionals, patients, and commissioners. The process is more complex than an STA and usually takes longer, but it can result in multiple recommendations on several products and their relationship to each other.

In its early days, NICE was criticized for the slowness of its appraisal process, resulting in a move toward more STAs. An appraisal cannot start until a drug receives U.K. marketing authorization, but NICE works closely with the licensing authorities and tries to issue a scope for the appraisal within a few months of authorization. There are problems with the STA process:

- It is restricted to a single drug for a single indication, so if several drugs are licensed for the same indication over a relatively short time, the recommendations may not reflect the way that the drugs are being used in clinical practice.
- It relies on evidence provided principally by the manufacturer (albeit with an independent review).
- Early assessment of cost effectiveness can be difficult due to a lack of evidence, particularly of downstream consequences.
- It has become less transparent as more confidential drug discounts, called patient access schemes, are being negotiated.
- It relies on the cooperation of the manufacturer.

Although an STA is an accelerated approval process, it is not exactly quick, as the timeline for the approval of enzalutamide prechemotherapy, TA377, shows (Table 3). The entire process from scoping to publication of the final decision took 2 years and 3 months. However, NICE did start the TA a year before marketing authorization for the change in license for this indication. A detailed look at this TA highlights some of the complexities in approving new drugs.

A draft scope for TA377 was developed in October 2013 by NICE. This was exactly one year ahead of the decision of the European Medicines Agency on Oct. 23, 2014, that approved a variation to the EU marketing authorization for enzalutamide for "the treatment of adult men with meta-

TABLE 3. Timeline for the Appraisal of Enzalutamide Prechemotherapy

Step	Date
Draft scope for the appraisal	October 2013
European Medicines Agency approval for EU marketing authorization	October 2014
Final scope for the appraisal	November 2014
U.K. marketing authorization	November 2014
First TA committee meeting	May 2015
Appraisal consultation document	June 2015
Second TA committee meeting	July 2015
ERG critique of Astellas' revised patient access scheme submission	November 2015
Final appraisal determination	December 2015
TA377 published	January 2016

Abbreviations: TA, technology appraisal; ERG, evidence review group.

static castration-resistant PCa who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated." The draft scope used a PICO format (P: Patient, Population, Problem; I: Intervention, prognostic factor, or exposure; C: Comparison or intervention; O: Outcome) to outline the population, comparators, and outcomes. It also posed several questions to stakeholders who were invited to comment, as were a number of invited topic experts. The final scope was published in November 2014, and an ERG at the University of Aberdeen was commissioned by NICE to appraise the manufacturers' submission.

NICE's TA Committee B met in public in May 2015 to discuss the evidence with the manufacturer, the ERG, and invited experts, including patient representatives. The committee then moved to a closed session to agree on the appraisal consultation document (ACD), which was published in June 2015. The initial recommendation was not to recommend the drug as not cost effective. There is a very detailed summary of the committee discussions in the ACD relating to the interpretation of the data from the PREVAIL trial,[27] the appropriate comparator, and other issues affecting the health economic calculations.

After public consultation on the ACD and a resubmission of evidence by the manufacturer Astellas, which included a revised patient access scheme (discounted price), the ERG produced a critique in November 2015. This resulted in a final appraisal determination that reversed the previous decision and, in January 2016, recommended approval of enzalutamide. What changed between the ACD and final appraisal determination? A decision was made to use only the comparator of enzalutamide versus best supportive care, changes were made to the downstream modeling to reflect the type of treatments NHS patients would receive after progression on enzalutamide, and Astellas offered a discount on the list price of enzalutamide. Due to the confidential nature of the patient access schemes, NICE does not publish detailed cost calculations. However, we know from the ACD[25] that the incremental cost-effectiveness ratio for enzalutamide compared with best supportive care was between £40,000 and £50,000 in the ERG's base case. In the final appraisal determination, this had fallen to below £30,000, and enzalutamide was considered a cost-effective treatment.

Cancer Drug Fund

From October 2010, patients in England have had access via the Cancer Drug Fund (CDF) to many drugs not approved by NICE. The fund was set up by the coalition government (Conservative and Liberal Democratic coalition in power from May 2010 to May 2015) "to enable patients to access the cancer drugs their doctors think will help them."[28] Initial implementation was variable because the fund was managed separately by 10 regions in NHS England, each of whom had different drugs available. From April 2013, the fund has been centrally administered with a single list for all of England. The annual budget of £200 million was exceeded in 2013 and, by 2014/2015, was overspent by 48%. A National Audit Office report in 2015 noted that it was "difficult to evaluate in a meaningful way the £733 million spent through the Cancer Drugs Fund since October 2010."[29] The fund was substantially restructured in July 2016. It is now managed by NICE, whose TA committees can recommend adding a drug to the CDF list if there is insufficient evidence to either approve or reject the treatment. Drugs will be provided via the CDF for up to two years, and NICE will reassess the drug based on data collected centrally by the systemic anticancer therapy (SACT) database (www.chemodataset.nhs.uk). The SACT data set is a mandatory collection of chemotherapy data from cancer centers in England who upload the information monthly.[30]

Have the decisions by NICE affected outcomes for men with metastatic PCa? There is no doubt that approval by NICE following market authorization takes many months, sometimes several years. However, the introduction of the CDF has significantly reduced the period between market authorization and the drug becoming available to patients in NHS England. In fact, enzalutamide prechemotherapy, the subject of the TA discussed previously, was available via the CDF before it received market authorization. Figure 7 shows the timelines of the treatments that have received marketing authorization for mCRPC since 2005: when they were licensed, when they were assessed by NICE, and when they were made available via the CDF. The only treatment not available in the United Kingdom was sipuleucel-T, which received marketing authorization in September 2013 but had it withdrawn in May 2015.

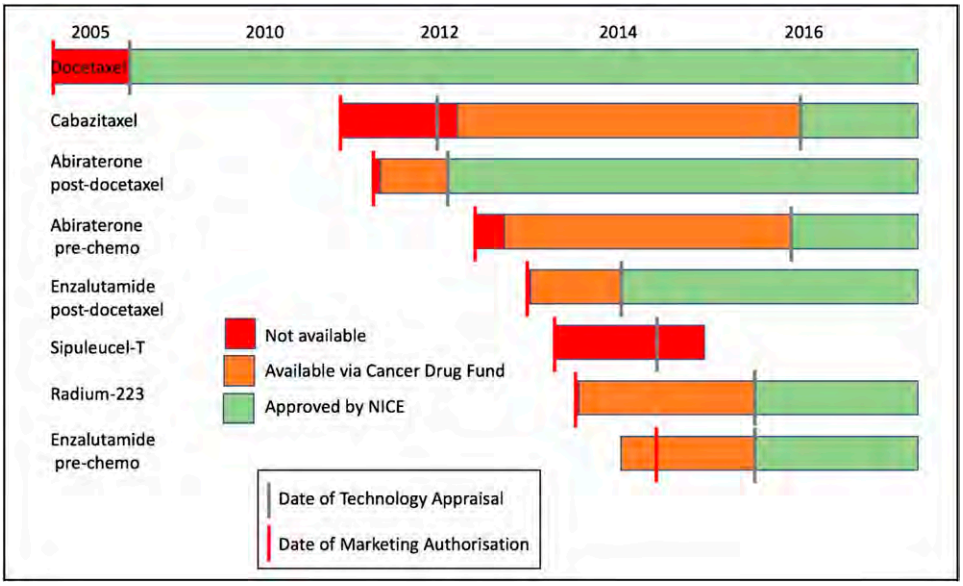
Latest cancer statistics show the mortality from PCa in England falling between 2005 and 2014, the last year for which figures are available. In 2005, the age-standardized mortality rate per 100,000 men in England was 53.92, and in 2014, it was 48.15.[31] A similar fall in PCa mortality has been seen in many developed countries over this period. To date, in the United Kingdom, we have not had enough information to determine whether treatment availability has affected outcomes. The restructuring of the CDF and the collection of chemotherapy prescribing information via SACT, which has only been available for a few years, should allow us to establish the efficacy and cost effectiveness of new anticancer treatments when used in routine clinical practice.

Approvals of treatments for men in England with mCRPC have not substantially delayed availability and are unlikely to have substantially affected outcomes. All treatments that have been licensed for mCRPC since 2005 (bar sipuleucel-T) are currently available in NHS England, most at a substantial discount to the list price.

HOW ADVANCES IN MOLECULAR IMAGING HAVE CHANGED OUR UNDERSTANDING OF STATE AND STAGE OF THE DISEASE

Currently, CT, MRI, and bone scintigraphy represent standard imaging procedures in PCa. Over the last two decades, PET evolved as novel imaging technology for detection or staging in PCa patients. For PET imaging, several tracers

FIGURE 7. Dates of Marketing Authorization, Cancer Drug Fund Approval, and NICE Technology Assessment



have been used in the past, but recently with the introduction of small molecular tracers targeting the prostate-specific membrane antigen (PSMA), PET imaging has gained increasing interest. PSMA is a transmembrane protein that shows overexpression on most PCa cells and thus represents an ideal molecular target. In biochemical recurrent PCa, PET imaging using ^{68}Ga-labeled PSMA inhibitors has been shown to increase detection of metastatic sites even at low PSA (prostate-specific antigen) values in comparison with conventional imaging or PET studies with different tracers. In primary intermediate to high-risk PCa, PSMA-based PET imaging has been reported to improve detection of metastatic disease as compared with CT or MRI, possibly rendering additional cross-sectional imaging or bone scintigraphy unnecessary. Furthermore, ^{68}Ga-PSMA PET imaging in combination with multiparametric MRI might provide additional molecular information useful for intraprostatic PCa localization. Thus, although current knowledge is still limited and derived mostly from retrospective series, PSMA-based PET imaging holds great promise to substantially influence PCa management in the future.

Until recently, imaging procedures for detection or staging of PCa depend mainly on morphology or bone metabolism and cannot always meet the diagnostic needs for clinical decision making. Consequently, imaging specialists have tried to identify specific molecular targets on PCa cells that can be used for molecular-based PET imaging.[32] Several radiotracers have been proposed, including choline, as a marker of membrane cell proliferation. For recurrent PCa, choline-based (i.e., ^{18}F-choline or ^{11}C-choline) PET/CT is currently widely used in clinical routine in Europe and is beginning to be adopted in the United States. Numerous studies reported an increased sensitivity and specificity compared with standard cross-sectional imaging; however, the diagnostic potential especially in early biochemical recurrence is still limited.[33,34] Other radiotracers evaluated for PET imaging of PCa include ^{11}C-acetate, bombesin analogs, and ^{18}F-FACBC (^{18}F-fluciclovine, a radiolabeled leucine analog).[32,35-38]

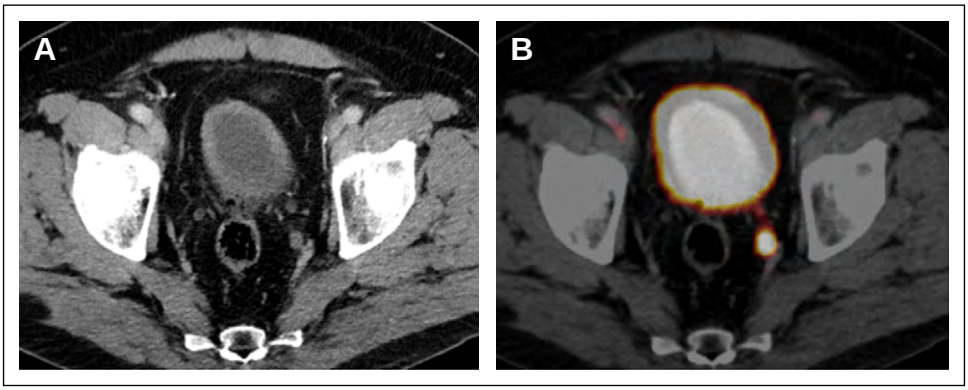
PSMA as Molecular Target in PCa

In recent years, the PSMA, a transmembrane protein that shows overexpression on most PCa cells, has gained increasing interest as a molecular target for PCa PET imaging.[39] Instead of targeting metabolism, PSMA tracers directly target PCa cells based on PSMA expression, independently of their metabolic state. So far, several small compounds directed against PSMA (also known as PSMA ligands) have been developed and are currently being investigated. The majority of data available report experience using the ^{68}Ga-labeled PSMA inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (also termed: ^{68}Ga-PSMA, ^{68}Ga-PSMA HBED-CC, ^{68}Ga-PSMA-11).[40-44] Compared with previously used PSMA antibodies for imaging, PSMA ligands seem to provide superior contrast images due to extracellular binding followed by internalization into PCa cells and fast blood clearance reducing background activity.[45-47]

PSMA PET for Staging of Recurrent PCa

A major challenge for imaging is localization of PCa lesions in patients with biochemical relapse. The differentiation between localized disease and metastatic spread is of great importance, especially at low PSA values, as it might influence further disease management (targeted radiotherapy, salvage surgery vs. systemic treatment). As mentioned above, choline-based PET examinations improve staging and show enhanced detection rates in recurrent PCa compared with conventional cross-sectional imaging.[36] However, they still lack the ability to identify smaller or less metabolic lesions, especially at low PSA velocity or PSA values below 2 ng/mL.[33,48]

FIGURE 8. Patient With PCa Relapse (PSA of 1.26 ng/mL) and Histologically Proven Lymph Node Metastasis Corresponding to ^{68}Ga-PSMA PET Imaging



(A) CT. (B) Fused ^{68}Ga-PSMA PET/CT.

In 2015, two large patient cohorts on ^{68}Ga-PSMA PET have been published evaluating the staging of recurrent PCa.[49,50] In the study by Afshar-Oromieh et al, 319 patients with recurrent PCa (226 after radical prostatectomy; median PSA value, 4.6 ng/mL) were examined.[49] The authors reported detection rates of 50% and 58% for PSA values below 0.5 ng/mL and between 0.5 and 1 ng/mL, respectively. In a subset of 42 patients, histologic confirmation of suspicious lesions could be obtained. In these patients, all ^{68}Ga-PSMA PET–positive lesions could also be histologically confirmed to contain metastatic PCa. In this study, Gleason scores as well as antiandrogen deprivation therapy did not significantly influence detection rates. Our group confirmed those results in a homogeneous consecutive cohort of 248 patients with biochemical recurrence after radical prostatectomy (mean PSA value, 1.99 ng/mL).[50] Here, ^{68}Ga-PSMA PET revealed suspicious lesions in 89.5% of the patients. Similarly, detection rates increased from 57.9%, 72.7%, 93.0%, to 96.8% for PSA values of 0.2 to less than 0.5, 0.5 to less than 1, 1 to less than 2, and above 2 ng/mL, respectively. Compared with contrast-enhanced CT, ^{68}Ga-PSMA-11 PET exclusively showed suspicious findings in 32.7% of patients and provided information about additional involved anatomic regions in 24.6%. Compared with absolute PSA value, the effects of PSA velocity and PSA doubling time were less pronounced, although they also influenced detection rates.

Most recently, Perera et al summarized data from literature for ^{68}Ga-PSMA, including 16 studies with over 1,300 patients. The predicted positivity rates in a meta-regression analysis were 58%, 76%, and 95% for PSA values of 0.2 to 1.0, 1.0 to 2.0, and over 2.0 ng/mL, respectively.[51] These values are considerably higher than reported for choline-based PET tracers.[33,48,52-54] Furthermore, two studies comparing ^{18}F-choline and ^{68}Ga-PSMA in a head-to-head analysis both show higher detection rates for PSMA-based PET imaging.[45,46]

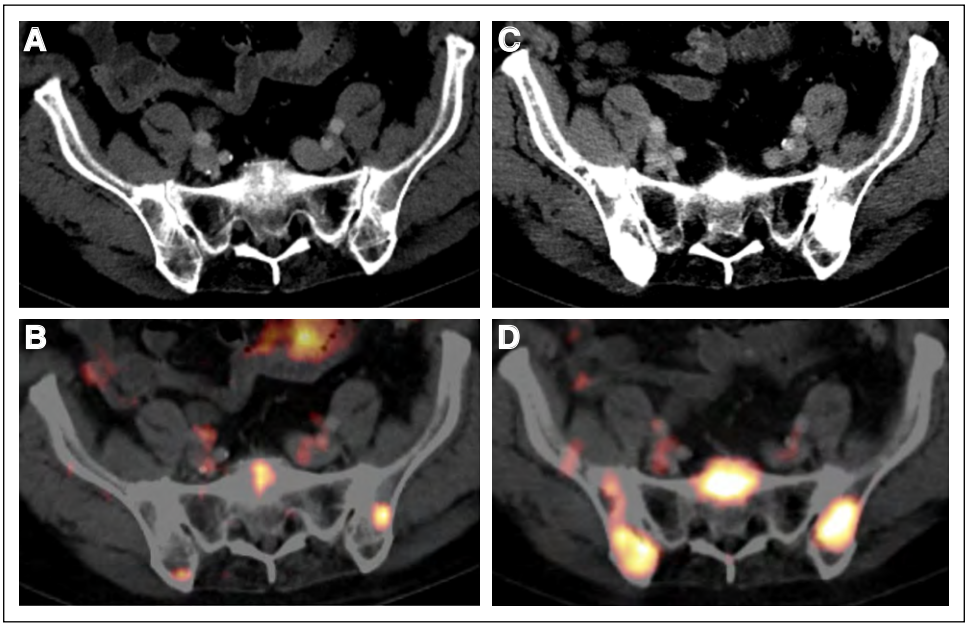
A major limitation of all the above-mentioned PET studies in patients with recurrent PCa is the lack of systematic histologic confirmation. Thus, in general, results of those imaging studies still have to be considered with caution. However, due to their high sensitivity and specificity, PSMA ligands have also been successfully applied in intraoperative tracking of metastatic PCa lesions during radioguided surgical procedures.[55,56] With the technology of PSMA-radioguided surgery, even small metastatic soft-tissue PCa deposits could be localized and successfully removed during salvage surgery procedures (Fig. 8).

PSMA PET for Primary Staging

For primary staging of PCa, evidence for ^{68}Ga-PSMA PET is still limited. The goal of primary staging is to detect metastatic spread to lymph nodes, bone, or other visceral organs. In low-risk PCa, metastatic spread is very unlikely and consequently current guidelines suggest staging examinations only for intermediate to high-risk PCa. In these patients, exact staging can have great impact on further treatment (e.g., radical prostatectomy vs. radiation therapy vs. palliative systemic treatment; extent of lymph node dissection during surgery, planning of radiation field; multimodal therapy concepts).

Conventional cross-sectional imaging almost exclusively depends on morphologic information, and metastatic lymph nodes are mainly detected by size. However, almost 80% of metastatic lymph nodes in PCa are smaller than the threshold size of 8 mm and therefore cannot be detected by anatomic imaging.[57,58] In the currently largest series of 130 patients with intermediate to high-risk PCa undergoing radical prostatectomy and template lymph node dissection, ^{68}Ga-PSMA PET imaging significantly improved lymph node metastases prediction compared with standard imaging.[59] On a patient-based analysis, the sensitivity, specificity, and accuracy of ^{68}Ga-PSMA PET were 65.9%, 98.9%, and 88.5%, respectively, compared with anatomic standard imaging with 43.9%, 85.4%, and 72.3%, respectively ($p = .002$). However, data from this study and others also showed that lymph node metastases smaller than 3 to 4 mm are also regularly missed by ^{68}Ga-PSMA.[59-61] Thus, especially in patients with high-risk disease, a negative ^{68}Ga-PSMA PET examination should not preclude a proper treatment of local lymph node drainage fields.

FIGURE 9. Patient With PCa With Metastatic Bone Lesions



Although bone lesions were hardly detectable on initial CT (A), fused ^{68}Ga-PSMA PET/CT (B) showed lesions already highly suggestive for bone metastases. Follow-up imaging clearly revealed bone metastases on CT (C) and fused ^{68}Ga-PSMA PET/CT (D).

Furthermore, bony and visceral lesions of PCa that might not be detectable by standard imaging can be visualized by ^{68}Ga-PSMA PET (Fig. 9). However, data are even more limited. In a comparative study of 126 PCa patients, ^{68}Ga-PSMA PET significantly outperformed planar bone scintigraphy for the detection of affected bone regions as well as determination of overall bone involvement.[62] Especially for identification of small metastatic bone lesions, ^{68}Ga-PSMA PET performed superior.

PSMA PET for Local Detection

In recent years, multiparametric MRI evolved as imaging of choice for local detection of PCa as well as evaluation of capsule penetration or seminal vesicle involvement.[63,64] The introduction of whole-body hybrid PET/MRI scanners with simultaneous acquisition and anatomic coregistration of PET imaging and multiparametric MRI opened the window to combine these functional MRI-derived sequences with molecular information from PET.[65,66] Although the spatial resolution of PET imaging is clearly inferior to MRI, ^{68}Ga-PSMA PET could still be of value to localized PCa by adding molecular information from PET. In a recent retrospective study on 53 patients who underwent radical prostatectomy after imaging, ^{68}Ga-PSMA PET/MRI improved the diagnostic accuracy for PCa localization both compared with multiparametric MRI as well as PET imaging alone.[67] On a sextant-based analysis, simultaneous ^{68}Ga-PSMA PET/MRI statistically outperformed multiparametric MRI (area under the curve: 0.88 vs. 0.73; $p < .001$) and sole ^{68}Ga-PSMA PET (area under the curve: 0.88 vs. 0.83; $p = .002$) for localization of PCa. Furthermore, compared with multiparametric MRI, ^{68}Ga-PSMA PET imaging was more accurate (area under the curve: 0.83 vs. 0.73; $p = .003$). It could be observed that PSMA-based PET provided a high uptake ratio between malignant versus nonmalignant tissue. However, although simultaneous ^{68}Ga-PSMA PET/MRI might improve the diagnostic accuracy for PCa localization and thus might be useful for example biopsy targeting or boost irradiation, availability of this technology as well as cost-efficiency issues might preclude ^{68}Ga-PSMA PET/MRI from widespread use (Fig. 10).

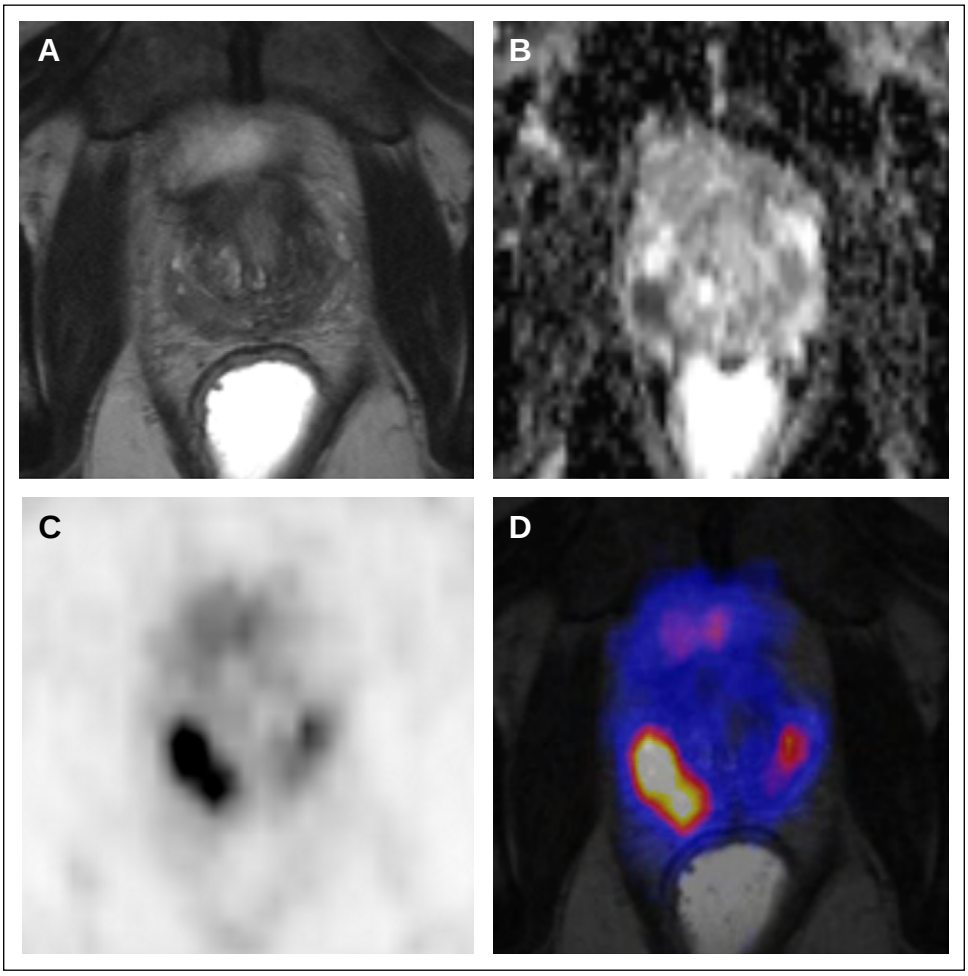
Limitations of PSMA-Based PET Imaging of PCa

Although PSMA-based PET imaging might be on its way to revolutionize PCa imaging, several limitations have to be addressed. It has to be noted that not all PCa exhibits a significant PSMA overexpression. Up to 10% of primary PCa can be negative on PSMA PET.[59,67] Thus, not only the local tumor, but also metastases might not be detectable. In addition, a variety of reports describe positive PSMA PET in several benign and malignant conditions.[47] Thus, accurate analysis of PSMA PET studies by experienced imaging specialists is mandatory.

CONCLUSION

Imaging with ^{68}Ga-PSMA PET has already achieved high potential to influence PCa management.[46] In biochemical recurrent PCa, ^{68}Ga-PSMA PET imaging has been shown to increase detection of metastatic sites even at low PSA values in comparison with conventional imaging or PET examination with different tracers. Furthermore, especially in high-risk PCa patients, ^{68}Ga-PSMA PET could enable a complete and more accurate staging of local tumors, lymph node involvement, and bone and organ metastases within

FIGURE 10. 65-Year-Old Patient With Histologic Proven Intraprostatic PCa Within the Right Basal Peripheral Zone



T2 sequence of multiparametric MRI (A) shows a hypointense area in the right prostate base with corresponding diffusion restriction (B). ^{68}Ga-PSMA PET (C) and fused ^{68}Ga-PSMA PET/MRI (D) reveal an area with increased tracer accumulation. Gleason score, 3 + 4; PSA, 10.3 ng/mL.

a single examination, thus outperforming current standard imaging. Thus, although current knowledge is still limited and derived mostly from retrospective series, PSMA-based imaging holds great promise to advance PCa management.

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Personalizing Therapy for Metastatic Prostate Cancer: The Role of Solid and Liquid Tumor Biopsies

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OVERVIEW

Although biopsies of metastatic prostate cancer are rarely undertaken in the clinical setting, there is increasing interest in developing personalized approaches to therapy by taking into account the genetic and phenotypic changes in an individual tumor. Indeed, analysis of metastatic prostate tumors can predict sensitivity to agents that inhibit DNA repair and resistance to novel hormonal agents, such as abiraterone and enzalutamide, and identify phenotypic changes, such as neuroendocrine differentiation, that have important clinical implications. Although obtaining metastatic tumor tissue is necessary for this genomic and molecular profiling, knowing when to biopsy, selecting the appropriate metastatic lesion, and interpreting the results are major challenges facing clinicians today. In this article, we discuss the rationale for obtaining metastatic tumor tissue, review the bioinformatic approach to analyzing these specimens, discuss the timing and approach to solid and liquid tumor biopsies, review the challenges associated with obtaining and acting on clinically relevant results, and discuss opportunities for the future.

Prostate cancer is characterized by a long natural history, with 10 years or longer often elapsing between the time of diagnosis and time of death in many patients. Further, prostate tumors typically acquire molecular alterations with disease progression and treatment resistance. Therefore, evaluation of the primary tumor is not often representative of what is going on when trying to make a treatment decision for a patient with metastatic castration-resistant prostate cancer (mCRPC). Hence in recent years, metastatic biopsies have become increasingly considered in clinical practice for patients for whom guidance for trial participation or next-line therapy is needed.

CHALLENGES IN TRANSLATING MOLECULAR RESULTS INTO MEANINGFUL CLINICAL USE

Genomic evaluation of cancers to guide treatment decisions is conceptually within the realm of precision oncology, an approach to match the right patient with the best systemic therapy on the basis of the underlying molecular alterations of that patient's tumor. However, in prostate cancer, precision oncology is challenged by a predominance of sclerotic bone metastases making biopsies technically challenging, few therapeutically actionable mutations, and limited guidelines to inform when and how to perform metastatic biopsies in patients and what to do with the results.

Clinical Indications

Although there are no formal guidelines outlining evidence-based indications for performing metastatic biopsies in patients with advanced prostate cancer, recent research studies have pointed to potential scenarios in which a biopsy may be considered.

Clinical trial participation. Metastatic biopsy programs, including the International Stand Up To Cancer-Prostate Cancer Foundation Dream Team, have elucidated the genomic landscape of mCRPC and have identified mutations that are enriched in advanced disease.[1-3] In addition to well-understood perturbations of androgen receptor (AR) signaling, potentially actionable and/or prognostic alterations include *TP53*, WNT pathway (e.g., *R*-spondin rearrangements and *CTNNB1* mutations), PI3K pathway (e.g., *PTEN* copy loss and *PIK3CA* and *PIK3CB* mutations), and cell cycle pathways (e.g., *RB1* and *CCND1*). These data combined with encouraging results from early-phase clinical trials have led to the initiation of several ongoing or planned biomarker-driven trials for patients with mCRPC. Therefore, repeat biopsy and genomic assessment may be indicated for patients for whom these trials are being considered.

A finding that is already influencing clinical decisions to pursue tumor genetic testing is that loss-of-function mutations in homologous recombination (HR) and mismatch DNA repair pathway genes are present in approximately 20% of metastatic prostate cancer tumors.[1,3,4] Mutations in

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HR DNA repair genes such as *BRCA1* and *BRCA2* are well-established predictors of response to PARP inhibitors and platinum-based chemotherapy in ovarian cancer.[5,6] This has led to the recent U.S. Food and Drug Administration approval of two PARP inhibitors as monotherapy for patients with ovarian cancer who harbor *BRCA1* or *BRCA2* mutations in tumor tissue (olaparib[7] and rucaparib[8]). Results from early-phase clinical trials suggest that *BRCA1*, *BRCA2*, and other HR DNA repair gene mutations will also prove to be highly predictive of PARP inhibitor response in men with metastatic prostate cancer. In the TOPARP-A phase II trial, 14 (88%) of 16 patients with metastatic prostate tumors who had HR DNA repair gene mutations predicted to inactivate both gene copies (biallelic) responded to the PARP inhibitor olaparib, compared with only two (6%) of 33 patients who did not.[9] This finding has led to a biomarker-driven phase III trial and the U.S. Food and Drug Administration granting "breakthrough status" for olaparib in men with metastatic prostate tumors who harbor biallelic *BRCA1*, *BRCA2*, or *ATM* mutations. There is also early data that suggest these mutations predict response to platinum-based chemotherapy in metastatic prostate cancer. One small case series found that three of three patients who had an exceptional response to carboplatin therapy harbored biallelic inactivating *BRCA2* mutations in their tumors.[10]

Remarkably, approximately one-half of the men with metastatic prostate cancers harboring DNA repair gene defects have a germline (inherited) mutation.[1,11] A recent multi-institutional study that evaluated 692 men across eight independent cases series of men with metastatic prostate cancer not selected for age or family history found that nearly 12% had potentially clinically significant high-penetrance germline mutations in 16 different DNA repair genes.[11] This was compared with 4.6% of men in a primary prostate cancer cohort from The Cancer Genome Atlas heavily enriched for high-risk disease (2.7% in the general population). The bulk of the mutations were in *BRCA2* (5.3%), *BRCA1* (0.9%), *ATM* (1.6%), and *CHEK2* (1.9%). Another recent study of 313 men with metastatic prostate cancer revealed similar rates of germline *BRCA2*, *BRCA1*, and *ATM* mutations (6% combined for these three genes) with fewer mutations in men with low-risk localized disease (1.4% combined for these three genes).[12] These findings not only inform treatment considerations, but also have implications for genetic testing and cancer risk for family members (i.e., breast, ovarian, pancreatic, and prostate cancers).

Somatic alterations involving PI3K/AKT pathway genes, most commonly *PTEN* deletion, occur in approximately 40% of patients with mCRPC.[1] In a phase II study by de Bono et al,[13] the combination of the AKT inhibitor ipatasertib with abiraterone improved progression-free survival and overall survival (OS) for patients with mCRPC when compared with placebo, and PTEN loss was associated with response.[13] Based on this work, a phase III trial is planned, including further investigation of PTEN as a predictive biomarker.

Recent trials in mCRPC have found that a subset of patients with mCRPC responded exceptionally well to immunotherapy with checkpoint inhibitors. Graff et al reported data from 20 patients enrolled on an ongoing phase II trial in which pembrolizumab was added at time of progression on enzalutamide.[14] Of the 11 patients who responded, profound and durable responses were observed, and in some cases, prostate-specific antigen (PSA) declined to undetectable levels. Similar to other tumor types, there is early suggestion that defects in mismatch repair and the hypermutated phenotype may predict response to immunotherapy. Although less than 5% of patients with mCRPC demonstrated loss of mismatch repair, this may nonetheless have clinical significance in selecting patients for anti–PD-1 inhibitor therapy.

When is the optimal time to test for genomic alterations involving these and other genes? Although certain alterations tend to be enriched in mCRPC, research into how they evolve during the course of therapy, including studies of matched primary metastatic tumors, has been limited. Therefore, in practice, biopsy evaluation is often recommended at the time of trial consideration.

Small cell/neuroendocrine transformation. Despite primary androgen deprivation therapy and subsequent potent AR-directed therapies, most mCRPC tumors continue to evolve as an androgen-driven disease. Therefore, a major focus of research and drug development has been to identify more effective therapeutic strategies to target the AR more potently. But a subset of tumors become less dependent on the AR and, in some cases, can lose AR expression and/or signaling altogether. This evolution from mCRPC to an AR-indifferent state is often associated with clinical, pathologic, and molecular characteristics of small cell neuroendocrine carcinoma.[15] A similar phenomenon has been observed in EGFR-mutated lung adenocarcinomas in which a subset of patients transform to small cell lung cancer at the time of resistance to EGFR-targeted therapy, with retention of the original EFGR mutation.[16] Conceptually, targeting

KEY POINTS

- **Multiple new therapeutic targets have been identified in metastatic prostate cancer; however, selecting the right therapy for an individual patient is a clinical challenge.**
- **Obtaining metastatic tissue to inform these decisions has historically been hampered by cost, morbidity of the biopsy, and concerns about low tumor yields.**
- **Recent studies show that metastatic solid tissue biopsies, including bone biopsies, are feasible and can provide clinically relevant molecular and phenotypic information.**
- **Different approaches to gene sequencing (hotspot panels, comprehensive gene panels, and whole exome/genome approaches) provide qualitatively different types of information, with important clinical implications.**
- **Additionally, liquid biopsies of circulating tumor cells and circulating tumor DNA can inform a patient's prognosis, predict response to new hormonal therapies, and serve as a discovery platform for precision medicine.**

a key driver in cancer (in prostate cancer, this is the AR) leads to an escape mechanism associated with epithelial plasticity as a way for the cancer cells to evade therapy. Once a predominantly neuroendocrine prostate cancer (NEPC) phenotype is diagnosed, patients may respond better to small cell carcinoma chemotherapy regimens than typical mCRPC therapies. When to evaluate patients with mCRPC for small cell/NEPC transformation is not well defined. Metastatic biopsies may be considered if there is clinical suspicion of NEPC, including rapid progression, often to unusual sites including parenchymal brain metastases, in the setting of a low or modestly rising serum PSA (suggesting less androgen-driven disease). Treatment regimens based on data for aggressive variant prostate cancer and applicable to mixed CRPC-adenocarcinoma tumors may include platinum (carboplatin or cisplatin) plus etoposide (extrapolated from small cell lung cancer data) or platinum plus taxane.[17] Defining the prognostic significance of mixed/hybrid tumors and non–small cell histologic variants in mCRPC is an area of active research.

Biomarker Research

Genomics in combination with clinical data have informed the development of molecular biomarkers. As these data continue to accumulate in the coming years and with prospective clinical follow-up of large patient cohorts, the predictive and/or prognostic value of common molecular alterations in mCRPC and how to test for them will continue to be defined.

The presence of AR alterations, including mutations, amplifications, and overexpression of AR splice variants (most commonly the AR-V7 variant), commonly occur in patients with mCRPC[1] and has been associated with decreased response to subsequent abiraterone or enzalutamide.[18-20] In addition to prognostic value, detection of AR alterations may also improve selection of next-line therapy such as the selection of taxane versus AR-targeted therapy for a patient with mCRPC.[21] Further, patients may be selected for trials investigating AR *N*-terminal domain inhibitors or novel drugs targeting the AR variants.

Loss of *RB1* and *TP53* occurs in 5% of primary prostate cancers and up to 40% of mCRPC and is enriched in patients with the NEPC resistance phenotype (similar to small cell lung cancer, in which losses of *RB1* and *TP53* are universal).[1,15] In preclinical studies, the combination has been associated with lineage plasticity, enzalutamide resistance, and AR independence,[22,23] and current clinical efforts are focused on further defining the prognostic and predictive role of *TP53*/*RB1* in mCRPC.

Another area of active research is understanding the prognostic role of DNA repair alterations and their association with response to other agents such as AR-targeted therapies, taxanes, and immunotherapy. Further understanding of the biologic role of other common genomic alterations such as WNT pathway alterations and other cell cycle alterations[1] and their clinical impact, particularly in the context of other common resistance pathways, may also play an appropriate biomarker role for emerging drugs and the early identification of resistance mechanisms in patients.

What and Where to Biopsy

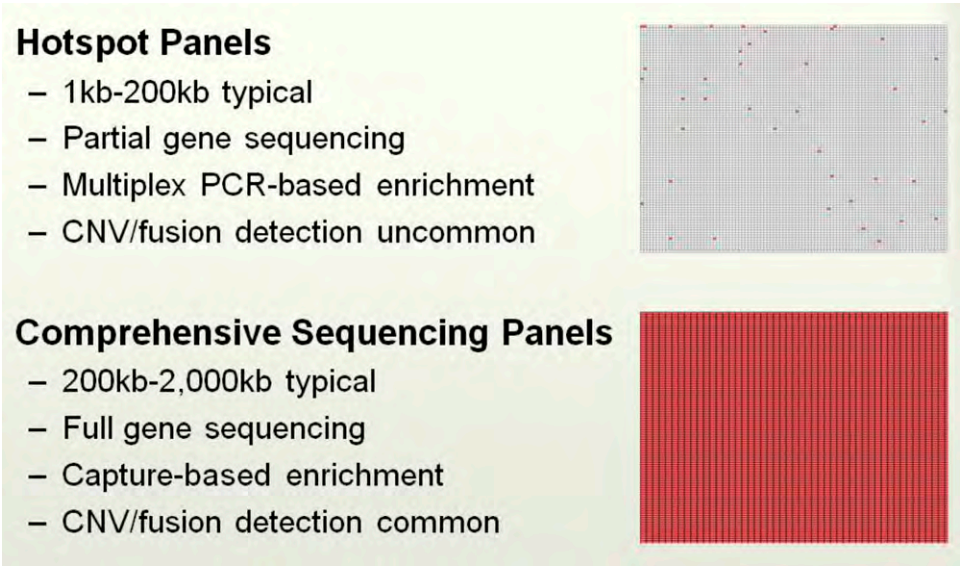
Ninety percent of patients with mCRPC have bone metastases, and up to 50% of patients have bone-only metastases. Visceral metastases develop in up to 20% of patients with mCRPC, typically arising in later stages of disease progression.[24] Nodal, visceral, or other soft tissue (i.e., nonbone) metastases are typically the biopsy lesions of choice because of higher tumor yield and technical feasibility. The location choice in patients with multiple sites is usually based on safety and accessibility for image-guided biopsies. To date, no noteworthy genomic differences have been reported between bone and nonbone lesions, although the transcriptome is likely influenced by the microenvironment.

Bone metastases in prostate cancer are most often sclerotic, rather than lytic, making bone biopsies technically challenging. Although there has been an increased focus on applying newer imaging techniques and novel tracers for patients with mCRPC, the most widely deployed modalities for identifying and monitoring bone metastases are a combination of bone scintigraphy and CT scan. These images provide limited information to guide interventional radiologists toward the most active lesion to biopsy. Recent studies focused on applying clinical and imaging criteria may improve diagnostic yield and acquisition of high-quality tissues and nucleic acids for genomic and other molecular studies.[25] Along with improvements in biopsy tools, tissue processing, and pathology evaluation, bone biopsy success rates have improved in recent years to approximately 60% to 80% at specialized centers.

What to Ask for

In the past, metastatic biopsies in mCRPC were typically performed to confirm a diagnosis of prostate cancer, and therefore limited pathologic evaluation was necessary. Biopsies in mCRPC may demonstrate poorly differentiated carcinoma. Gleason grading is not applicable for treated tumors. In a patient with suspected NEPC transformation, discussion with the pathologist regarding the morphologic characteristics may help distinguish classic adenocarcinoma, adenocarcinoma with neuroendocrine differentiation, small cell or large cell carcinoma, intermediate atypical carcinoma, mixed or hybrid tumors, or other pathologic variants.[26] Immunohistochemistry for AR signaling markers (e.g., PSA, AR, PSMA, and NKX3.1) and classic neuroendocrine markers (e.g., chromogranin, synaptophysin, and CD56) may support a diagnosis. For small cell carcinoma of unknown primary, a positive ERG break-apart fluorescence in situ hybridization test may be clinically useful to confirm prostatic origin. For patients in which immunotherapy trials are to be considered or if a hypermutated phenotype is identified by sequencing, MSI and MMR genes (i.e., MLH1 and MSH2) may be considered. Most commercial and institutional sequencing platforms incorporate a panel of genes to evaluate for copy number and somatic nucleotide variants, and both sample

FIGURE 1. Hotspot Versus Comprehensive Somatic Mutation Panels



quality and tumor content are important. These tests may or may not include germline DNA into the test/filter, which may affect the clinical interpretation (as discussed later).

Genomic Cancer Panels: Methods Matter

Translating these new genetic biomarkers into clinical use requires careful attention to who and when to test, testing methods, and the accurate interpretation of test results. In this section, we cover aspects of genomic cancer panel testing that is already clinically available and increasingly used for men with metastatic prostate cancer. Specifically, we will focus on testing methods, sample considerations related to cancer tissue and plasma circulating DNA, and reporting considerations. These are covered with an emphasis on issues most relevant to metastatic prostate cancer from the perspective of a practicing molecular pathologist.

Next-generation sequencing (NGS) technology is arguably the key driver for the rapid discovery and clinical implementation of new genetic biomarkers in prostate cancer. Compared with the older Sanger sequencing methods, NGS produces about a millionfold more data for the same cost and speed. For discovery, whole-genome and whole-exome sequencing are quite useful. For clinical use, smaller targeted gene panels that encompass only genes of interest are the current standard. Targeted NGS gene panels focus the sequencing power on just the genes of interest, allowing high depth of coverage and better assay performance compared with spreading out the same sequencing power across the whole exome or genome. Targeted panels also facilitate custom design to ensure key, clinically meaningful mutations are detected in regions that can be missed by generic exome and genome sequencing methods.

There are two general types of NGS cancer panels: hotspot panels and comprehensive panels (Fig. 1). Hotspot panels only interrogate specific sites or portions of genes that are known to be hotspots for somatic mutations. They typically sequence less than 200 kb of total DNA and use multiplex polymerase chain reaction as the method for gene enrichment (also known as amplicon-based sequencing). Hotspot panels usually do not accurately detect copy number variation, although this can be achieved with specialized bioinformatics.[27] A commonly used hotspot approach is the "AmpliSeq" panel, which has been applied to prostate cancer.[28] Advantages of hotspot approaches are that they are usually faster and cheaper, use less sample input, require less bioinformatics support for a laboratory to operate, and are easier to interpret. The primary disadvantage is that hotspot approaches may miss many of the mutations, including de novo ones, which are most important for guiding cancer care.

Comprehensive panels typically sequence between 200 to 2,000 kb of DNA, which is more than hotspot approaches but still far less than whole-exome or -genome sequences (compare with approximately 50,000 kb for exome sequencing). Although methods are variable, comprehensive panels typically use a "capture-based" approach to enrich the target genes that relies on solution hybridization with baits that pull down the genes of interest. An advantage of this approach is that it is easier to preserve gene dosage and perform accurate gene copy number assessment. DNA capture-based approaches may also detect gene fusions if the correct regions are captured and appropriate bioinformatics employed. Comprehensive NGS cancer panels have been successfully applied to metastatic prostate cancer to detect relevant events that would not be readily detected by hotspot approaches, such as *TMPRSS2-ERG* fusions, *AR* amplification, complex DNA repair gene rearrangements, and homozygous *BRCA2* copy loss.[4,29,30] Although comprehensive panels have the advantage of greater sensitivity, they are generally more expensive, require greater bioinformatics expertise, and are more challenging to interpret than hotspot approaches. Marketing can be misleading: It is important for the practicing oncologist to understand that

the number of genes sequenced often matters less than the regions of the genes sequenced. In other words, a 200-gene hotspot panel is not the same as a 200-gene comprehensive panel.

Limit of detection can be especially important in tumor panel testing, particularly in the setting of cell-free circulating tumor DNA (ctDNA) testing in which mutations may be present at very low levels. Clinical NGS assays achieve improved limit of detection through multiple means, including higher depth of coverage, specialized genomic library preparation methods that improve signal-to-noise by eliminating most polymerase chain reaction artifacts, and bioinformatics approaches that improve signal-to-noise through error suppression.[31,32] When asking about methods, it is important to understand that higher depth of coverage alone usually cannot improve the overall limit of detection below approximately 1% because of sequence error rates.[33] In other words, "What's your depth of coverage?" is only one part of the question.

Sample Considerations: Tissue or Plasma?

The specifics of the sample tested for tumor profiling are critical to the quality of the study. Metastatic prostate cancer sources used for current clinical testing can be from fresh or fresh frozen tissue, formalin-fixed, paraffin embedded tissue, or ctDNA in plasma, each with unique characteristics in terms of quality, quantity, tumor content, and the possibility of false-positive and false-negative results (Table 1). For each specimen, it is important to ask the following: (1) Is the sample appropriate for the clinical question and representative of the tumor(s) I am trying to treat? (2) What is the prostate cancer content, and is it high enough for the test being performed? (3) Is there enough quantity of sample for testing? (4) Could there be unrelated somatic "interfering" mutations that might be misinterpreted as coming from prostate cancer? It is standard practice for molecular pathology laboratories to assess sample quality and tumor content for cancer tissue–based testing for NGS panels by reviewing the histomorphology in corresponding stained slides. Tumor content can be enriched through dissection of tumor-rich areas. For ctDNA, the tumor content is just as critical to the quality of testing, but it is not possible to review a corresponding slide and not straightforward to do tumor enrichment. There are emerging techniques that can allow assessment of tumor content in plasma cell–free DNA that rely on differences in fragment length in cancer-derived ctDNA, but these techniques are not yet widely used in clinical practice.[34-36]

When testing plasma ctDNA in a patient with metastatic prostate cancer, it is critical to understand that prostate cancer may not be the only source of somatic mutations present in the plasma. Age-related and cytotoxic chemotherapy treatment–related clonal hematopoiesis is well described and quite common in older men.[37-39] Most hematopoietic clones can be subtracted out when matched white blood cell sequencing is done, although this is not always done. Further, there are likely to be additional sources of somatic clones in the plasma that are as yet not well understood. Special caution should be exercised in interpreting mutations detected in ctDNA that are not obviously derived from the prostate cancer, especially those detected at very low variant allele fractions.

TABLE 1. Sample Considerations for Cancer Next-Generation Sequencing Testing

	Fresh Tumor Tissue	Fixed Tumor Tissue	Plasma Circulating Tumor DNA
Quality	High	Moderate	Low
Quantity	High	Moderate	Very low
Tumor Content	High (usually)	High (usually)	Low (usually)
False Negatives	Less common	Less common	More common
False Positives	Less common	Fixation artifact	Somatic clones in blood misinterpreted as cancer derived

Reporting Considerations

Reporting considerations for NGS cancer panels can be divided into two aspects: analytical and clinical (Table 2). Analytical features include the types of mutations that are validated (e.g., whether or not copy number changes are detected), the limits of detection (e.g., whether or not this test has a chance of detecting the resistance mutation you are looking for), and sequencing platform–related issues that may make some types of mutations more prone to false-positive or false-negative results. Clinical features include the context for testing (e.g., post-abiraterone or post-enzalutamide treatment in which AR-V7 and other resistance clones may be present versus treatment-naive presentation of metastatic prostate cancer), the laboratory's strategies for variant classification, and the laboratory's policies on how much to report.

Somatic mutation reporting guidelines have only recently been proposed and are not well established. This year, ASCO, the Association of Molecular Pathologists, and the College of American Pathologists published a framework for somatic mutation interpretation based on four tiers that

TABLE 2. Reporting Considerations

Analytical
1. Types of mutations validated
2. Limits of detection
3. Pseudogenes
4. Platform-specific considerations
Clinical
1. Clinical context
2. Strategy for poorly characterized variants
3. Decision support
4. Incidental findings

depend on the level of evidence of a specific mutation or alteration being associated with a specific therapy.[40] Guidelines for interpretation of germline mutations, such as the joint recommendations by the American College of Medical Genetics and Genomics and the Association of Molecular Pathologists, are better established and typically rely on a five-tier system that classifies variants as either pathogenic, likely pathogenic, uncertain significance, likely benign, or benign.[41] These variant interpretation guidelines are helpful but do not adequately address the complexity of the diagnostic challenge for an individual patient with prostate cancer because the clinical history and other patient- and sample-specific factors must be understood to render an accurate interpretation of the mutation results. The challenge is equal or greater than that of other areas of diagnostic medicine, such as complex imaging studies in radiology and histopathologic diagnosis in surgical pathology. Similar to testing in radiology and surgical pathology, the performance and interpretation of these NGS studies is part of the practice of medicine. These studies require highly trained doctors who specialize in the area of medicine to render an accurate diagnosis and should not be treated simply as routine laboratory tests or medical devices in which an algorithmic approach can be applied to interpretation and reporting.

Reporting on ctDNA sequencing is especially challenging because we do not yet understand all of the factors that influence these results. Recent studies that compared clinical reporting of plasma ctDNA and tumor-based NGS results between two widely used commercial reference laboratories found that less than one-half of the reported mutations overlapped within the same patients.[42,43] More importantly, only about one-quarter of the treatment recommendations on clinical reports overlapped. Some of the discordance could be attributed to the reporting of low-level clones in ctDNA (at variant allele fraction less than 1%), with the key mutations that are most likely to be predictive of treatment more often being shared.[42] This highlights the need for expert interpretation of both tissue and ctDNA results when treatment recommendations are made.

Case Vignette

We end this section with a hypothetical case vignette to highlight the use of clinical NGS panels in metastatic prostate cancer tissue and ctDNA. A 63-year-old man diagnosed with Gleason 5 + 4 prostate cancer underwent a radical prostatectomy followed by salvage radiotherapy. After 2 years, he developed metastatic disease to bone and soft tissue, including the liver. A metastatic biopsy of his liver lesion was performed for NGS panel testing to evaluate for therapeutic options. The tumor slide was reviewed by the molecular pathologist, and tumor content was estimated at 50%. Results from a comprehensive sequencing panel revealed a BRCA2 frameshift loss-of-function mutation (c.5946delT, more commonly known as 6174delT) detected in 49% of sequencing reads and without associated loss of heterozygosity; a second complex BRCA2 frameshift loss-of-function mutation was detected in 25% of sequencing reads. Because of the pattern of the variant allele fractions of the two BRCA2 mutations, and because the 6174delT mutation is a common pathogenic germline mutation, the molecular pathologist reported back to her oncologist colleague that there was a high suspicion the 6174delT mutation was inherited in the germline. This came as a surprise to the oncologist because there was no known family history of cancer. Follow-up targeted germline testing confirmed that the BRCA2 6174delT was present in the germline. Additional at-risk family members were offered genetic counseling and targeted testing. The patient received a regimen including carboplatin chemotherapy with a complete PSA response for 18 months. Following a PSA rise, NGS panel testing of plasma ctDNA was performed to evaluate for possible resistance and showed no evidence of secondary resistance such as BRCA2 reversion mutations.[44] Based on the ctDNA results, the oncologist switched to a PARP inhibitor, which resulted in a sustained PSA response.

Challenges

Pathway crosstalk. Evolution of drug resistance in mCRPC involves a concerted interplay between multiple genes and pathways. For instance, biologic insights into the reciprocal feedback between AR signaling and PI3K/AKT pathways has led to the rational development of cotargeting strategies.[45] How genomic alterations interact and influence treatment response is an area of active research and will be essential for the identification of robust predictive molecular biomarkers and approaches for targeting pathway crosstalk.

Nongenomic pathways. Although most "precision medicine" approaches have focused on genomic alterations, epigenomic assessment, messenger RNA/pathway analysis, immune analyses, and other functional readouts will also be critical in identifying novel resistance pathways that may not be identified by genomics. The use of patient-derived preclinical models including organoids and patient-derived xenografts may accelerate this process.[46,47]

Tumor heterogeneity and evolution. Most studies evaluating tumor metastases in patients with advanced disease have supported a monoclonal origin of mCRPC,[48,49] with all metastatic lesions traceable back to a common early ancestor and mostly shared genomic driver alterations observed across metastases. The differences or heterogeneity that are also observed across metastases that occur through polyclonal subclonal seeding or other means, and the temporal evolution of cancer with disease progression and treatment resistance, are not captured well by single-site biopsies and may be better captured by circulating tumor cell (CTC) or ctDNA approaches (as described later).[50,51] This heterogeneity poses important questions for interpretation of mutation results obtained from a single metastatic site, and for results from ctDNA, which a mixture of shedding from multiple metastatic sites. Fortunately, there is evidence that there is minimal metastasis-to-metastasis heterogeneity of the key driver mutations that constitute the "trunk" of the prostate cancer rather than the "branches" and that NGS testing of a single metastatic site may be sufficient for the clinical

TABLE 3. Comparison of Solid and Liquid Biopsies

Source of Cancer Cells	Advantages	Limitations
Metastatic biopsy	Pathologic gold standard	Cost
	Histology and phenotypic changes easily assessed (pure adenocarcinoma, neuroendocrine differentiation, intermediate atypical phenotypes)	Morbidity
	Ample genomic material (DNA, RNA) and protein for analysis; deep sequencing feasible	Not all lesions amenable to biopsy
		Bone biopsies are technically challenging (approximately 70% success rate)
		Does not account for heterogeneity of different metastatic sites
Circulating tumor cells	Noninvasive	Limited cell recovery (typically < 1,000 cells)
	Serial monitoring feasible	Contamination by leukocytes, endothelial cells
	Cell counts are an established prognostic marker for survival	Inherent selection bias in most platforms, hard to recover all circulating tumor cells shed by a tumor; may not identify cells that have undergone epithelial to mesenchymal transition
	Detection of AR-V7 predictive of resistance to abiraterone/enzalutamide	Unclear origin of circulating tumor cell: primary tumor vs. metastasis
	Estimation of tumor heterogeneity; can identify multiple circulating tumor cell subsets	Genomic analysis may require DNA amplification and introduce bias; rare mutations may be missed
	Immunocytochemistry can shed light on AR localization (nuclear vs. cytoplasmic), presence of AR splice variants, and cell surface markers	Limited ability to profile RNA/gene expression
ctDNA	Noninvasive	Unable to estimate tumor heterogeneity
	Serial monitoring feasible	Most platforms only screen a limited panel of genes
	Highly sensitive detection of specific mutations	Limited ability to screen for novel mutations
	Circulating-tumor DNA burden prognostic for survival	Limited ability to profile RNA/gene expression
	Adrogen-receptor mutations and copy gain may predict resistance to abiraterone/enzalutamide	DNA by definition released from dying cells; may not accurately capture resistance mutations in living tumor cells
	Potential to identify DNA repair mutations and predict response to PARP therapy	

purposes of selecting therapy because therapies are aimed at the key oncogenic drivers.[49]

LIQUID BIOPSIES: CURRENT UTILITY AND FUTURE DIRECTIONS

Isolation and analysis of CTCs and ctDNA from patients with prostate cancer have emerged in recent years as a way to better understand molecular and genomic mechanisms that drive the disease. Although these "liquid biopsies" yield less tumor tissue than a soft tissue or bone biopsy,[1,25,52] they do offer numerous advantages: liquid biopsies are noninvasive, less morbid, faster to perform, and offer the realistic ability to monitor changes serially in the tumor over time (Table 3). Additionally, although PSA is a widely adopted biomarker across all stages of disease, it is a unidimensional measurement of disease burden, with limited prognostic and predictive capabilities, especially in the mCRPC setting.[53] Analysis of liquid biopsies in prostate cancer therefore offers the opportunity to better establish an individual patient's prognosis, to predict response to specific therapy, and to discover specific genomic alterations that may be clinically actionable. Here we will discuss some of the current utility of CTC and ctDNA analysis in men with prostate cancer, focusing on the different context in which they could be useful for the clinician and researcher and some of their potential drawbacks. We will lastly discuss opportunities for the future.

Defining and Detecting ctDNA and CTCs

ctDNA and CTCs are both thought to be shed from cancer cells into circulation, and increasingly sophisticated techniques to identify these cells and genomic fragments are being developed.[54] Broadly, analysis of ctDNA allows for the identification of multiple genomic abnormalities, including point mutations, changes in copy number, translocations, and epigenetic changes. Because these genomic changes are tumor specific, ctDNA analysis can rapidly identify these rare sequences among the large pool of shed-circulating

DNA. Additionally, although initial techniques such as real-time or digital polymerase chain reaction have focused on the identification of predefined, known oncogenic mutations,[55,56] increasingly sophisticated methods of identifying ctDNA are allowing for the detection of whole-exome and whole-genome copy aberrations and translocations.[57-59] Currently, most clinically available ctDNA platforms focus on a panel of specific DNA alterations, providing the clinician with a list of potentially actionable genomic changes present in the cancer.[60-62] Major challenges facing this field are the identification of de novo genomic changes, estimation of tumor heterogeneity, and the inability to detect genomic aberrations that occur at the transcriptional or translation level.

CTCs offer a similar ability to analyze tumor DNA; however, they also offer the ability to quantify RNA expression, fusion transcripts, and splice variants, identify expression of specific proteins, and visualize cellular and subcellular morphology and can allow for an estimation of tumor heterogeneity. Multiple technologies exist to enrich for and identify prostate cancer CTCs; although not completely comprehensive, broadly, CTCs can be identified using antibody capture techniques;[63] high-resolution imaging;[64] separation by physical properties such as size,[65] density,[66] microfluidic properties,[67] and dielectric potential;[68] or separation by specific physical characteristics such as invasive potential[69] or through secretion of known proteins.[70] Each of these techniques has advantages and disadvantages, in that platforms that require expression of a specific antigen, for example, may miss cancer cells that have downregulated the protein, although systems that aim to identify all cancer cells in circulation may suffer specificity issues from the identification of false-positives. Therefore, it should be strongly emphasized that there is no best CTC-capture technology; rather, each of these technologies should be thought of as a specific tool. In this light, an antibody-capture technique, such as the CellSearch platform, may be suitable for reliable enumeration of epithelial cell-adhesion molecules plus CTCs, whereas high-resolution imaging such as the Epic Sciences platform may be more suitable to estimate CTC heterogeneity or to identify nuclear versus cytoplasmic AR localization.

Clinical Applications of CTC and ctDNA in Prostate Cancer

Establishing prognosis. In prostate cancer, enumeration of CTCs has been investigated to establish whether their number can inform clinicians as to whether a patient will have longer or shorter survival. In this regard, the CellSearch (Veridex) platform has been perhaps the best explored. In a study of over 200 patients with mCRPC starting a new line of chemotherapy, the presence of five or more CTCs was associated with shorter overall survival (median 11.5 vs. 21.7 months; $p < .0001$).[63] Change from unfavorable counts to favorable was statistically associated with improved overall survival, and conversely, change from favorable to unfavorable was associated with worse overall survival. This work was validated in the context of a phase III study of docetaxel-based therapy,[71] and findings similar to these have been reported for patients with metastatic breast and colon cancers.[72,73]

For ctDNA, recent work has shown that the ctDNA burden is similarly prognostic for survival in a phase III study of chemotherapy.[74] Perhaps more excitingly, the detection of mutation-specific ctDNA after definitive surgery has been associated with subsequent disease recurrence in patients with colon[75] and breast[76] cancers, although it remains to be seen if this will be the case for patients with prostate cancer, and indeed, the utility of liquid biopsies for men with localized disease is under investigation.[77-79]

These studies of liquid biopsies in mCRPC are important in that they support the notion that the circulating tumor burden reflects the underlying disease burden. The major challenge is that using CTCs and ctDNA to establish prognosis, especially in the metastatic setting, has rather modest clinical utility, in that it does not inform the clinician as to whether switching therapy would be of benefit. Indeed, a randomized study of women with breast cancer failed to show a benefit to a chemotherapy switch for women with unfavorable counts after the initiation of chemotherapy.[80] That said, improving the ability to predict recurrence after definitive treatment of localized disease could prompt studies of adjuvant therapies or enhanced surveillance strategies and may be useful to add to known prognostic scores[81-84] for risk-stratifying patients in clinical trials.

Predicting response to therapy. Understanding some of the limitations of a purely prognostic biomarker, a number of investigators have sought to use liquid biopsies to inform the decision about whether to give a particular therapy. Perhaps the most research to date in prostate cancer has focused on the ability to predict response to next-generation hormonal therapy such as abiraterone acetate and enzalutamide. Although both of these agents target the AR and have impressive clinical activity, approximately 20% of patients did not respond to treatment.[85,86] Preclinical work has shown that alternative splicing of the AR messenger RNA can lead to constitutively active forms of the receptor that are unable to bind ligand and are therefore generally insensitive to AR ligand blockade or other forms of hormonal manipulation.[87,88] The detection of these AR splice variants in CTCs has been investigated in a number of contexts using multiple platforms, and the presence of a specific, relatively abundant form called AR variant 7 (AR-V7) was shown to independently predict resistance to abiraterone and enzalutamide in multiple different cohorts of men with mCRPC.[19,21,51] Importantly, in these studies and others, the presence of AR-V7 did not predict responsiveness to taxane-based chemotherapy, demonstrating its specificity as a marker for AR inhibitor resistance, rather than a marker of overall poor prognosis.[89] Multiple assays to identify AR-V7 in CTCs are currently in commercial development.

Beyond AR-V7, a number of recent efforts have sought to characterize the AR more comprehensively using liquid biopsies. In one study, investigators were able to use NGS to sequence informative regions of the AR using plasma

ctDNA in 97 men with mCRPC.[18] They detected both AR copy gain and point mutations and saw the emergence of nonsynonymous (protein-altering) mutations in 13% of patients whose disease was progressing on abiraterone. The presence of pre-existing AR gain was also associated with resistance to abiraterone and shorter overall survival. A similar study collected plasma ctDNA from 62 patients with mCRPC whose disease was progressing on therapy.[20] These investigators observed that AR amplification was more common in patients with enzalutamide-resistant disease, and detected potentially significant AR mutations in 18% of patients. Patients with these aberrations seemed to have less profound PSA declines and shorter times to radiographic progression. Other studies have described similar findings, including through the analysis of AR transcripts contained in exosomes.[90,91] Taken together, these recent studies highlight the potential for analysis of liquid biopsies to inform specific treatment decisions for patients with mCRPC.

Moving beyond the AR, recent studies have shown that PARP inhibition has activity in men with mCRPC whose tumors harbor mutations in key DNA repair genes such as *BRCA1*, *BRCA2*, *ATM*, and others.[9] Recent studies have also shown that these mutations are detectable in CTCs in men with mCRPC, and their presence appears to correlate with response to PARP inhibition.[92] If confirmed, these findings could offer clinicians a noninvasive means to identify patients for treatment and potentially monitor for the development of resistance. Indeed, serial monitoring of response to therapy using liquid biopsies has shown promise in multiple other malignancies, including in lung cancer, where a liquid biopsy can predict the development of resistance to EGFR- or ALK-targeted therapy,[93,94] and in colorectal cancer, where mutations in KRAS have been documented in the circulation well in advance of clinical resistance to EGFR-targeted therapy.[95]

Discovery of novel targets. Perhaps the most immediate use for liquid biopsies is to personalize therapy by generating an individual tumor profile to identify targets for therapy. Recent transcriptomic analysis of single cell mCRPC CTCs has highlighted the importance of noncanonical WNT signaling in resistance to hormonal therapy[96] and could spur the development of therapeutic strategies aimed at this pathway. Currently, multiple commercial assays are available that profile ctDNA and provide the clinician with list of mutated or aberrant genes.[60,93] This approach parallels what is currently underway with solid tissue biopsies, in which targeted sequencing can identify oncogenic and potentially actionable mutations.

Although generating a personalized genomic profile of a patient's tumor using a liquid biopsy represents a step forward for precision medicine, it should be emphasized that this approach comes with both costs and benefits. The clear benefit is the identification of a therapeutic target that would not otherwise be found and may provide the rationale for using "off-label" treatment for an individual patient, potentially to their benefit. The risk to this approach is that it is still not known if the vast, unbiased genetic information provided is worth the added cost and potentially serious side effects associated with assigning patients to unproven therapy without appropriate study in clinical trials.[97] Additionally, given recent evidence that only about one-half of genetic findings between matched solid and liquid biopsies were concordant, caution should be used to avoid acting on a potentially false-positive call.[42] Given that the trend toward personalized medicine is well underway, future studies must validate this approach to better understand its clinical utility.

DIRECTIONS FOR THE FUTURE

Moving beyond straightforward CTC enumeration, recent work has shown that it is possible to identify tumor heterogeneity,[50] identify a neuroendocrine phenotype,[98] profile transcriptomic changes in tumor-derived exosomes[99] (cell-derived vesicles that contain tumor protein and RNA), and use CTCs as a surrogate for survival in clinical trials.[100] Although still in early stages, these all have potential to improve our ability to better assign therapy but need validation in appropriately designed cohorts with clear clinical endpoints. As the cost of genetic sequencing continues to decline[101] and the number of actionable targets in prostate cancer increase,[102] the ability to rapidly obtain personalized genomic information about an individual patient in a minimally invasive way will be critical to delivering better care.

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Screening and Treating Prostate Cancer in the Older Patient: Decision Making Across the Clinical Spectrum

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OVERVIEW

Treatment of the growing geriatric patient population is increasingly being recognized as a necessary priority of the oncology community. As the most common cancer among men in developed countries, prostate cancer afflicts a sizable portion of elderly men. Caring for this population requires knowledge of aspects of disease presentation, screening strategies, treatment approaches, and survivorship care considerations unique to the geriatric population. In this article, we review characteristics of prostate cancer screening and treatment decision making for localized disease in elderly men, including a discussion of the biology of disease in the elderly population. We also review best practices for providing treatment for localized and recurrent disease in an elderly population, including engaging in a basic geriatric assessment to determine fitness for treatment, eliciting information about patient preferences and support systems, and balancing treatment decisions in the context of these factors using the resources of a multidisciplinary care team. We then consider complications of prostate cancer survivorship related to systemic treatment in the elderly population of men with this disease. Finally, we emphasize the importance of engaging patients in treatment decision making across the spectrum of disease to personalize treatment plans and provide optimal care.

It is expected that between 2012 to 2050 the population older than age 65 in the United States will nearly double, increasing from 43.1 to 83.7 million, making up approximately 20% of the overall population (Fig. 1).[1] Prostate cancer is the most common cancer among men in developed countries, and the incidence of prostate cancer increases with age.[2,3] Given the aging population, the incidence of prostate cancer in the United States alone is expected to climb as high as 382,000 diagnoses annually in 2030—nearly 2.5 times higher than the expected 161,360 diagnoses in 2017.[2,3] Therefore, providing expert screening, treatment, and long-term survivorship care for the aging prostate cancer population is paramount as we move into this era.

Evidence suggests that although technological advances have improved cancer survival outcomes overall, not all populations appear to experience the same degree of improvement.[4] In particular, an analysis of Surveillance, Epidemiology, and End Results (SEER) data for patients with prostate cancer by age found that although younger men had noteworthy improvements in survival during the past decade, survival has not improved significantly in men age 75 and older.[4] It is postulated that the reason for this is multifactorial, including different prescribing patterns by age group. This is compounded by a lack of clinical trial data specific to the older patient population and provider concerns about extrapolating data to elderly patients with a poorer functional status and a greater number of comorbidities. Further, patient preferences to maximize quality of life as they age may lead them to decline more toxic treatments despite a possible survival benefit. Whether because of provider decisions or patient preferences, this disparity in outcomes by age provides an opportunity to improve health outcomes among the elderly prostate cancer population.

In this article, we review aspects of screening, initial treatment, treatment of recurrence, and survivorship care specific to the elderly prostate cancer population, with a focus on risk-adapted decision strategies throughout the spectrum of disease.

PROSTATE CANCER PREVALENCE AND AGGRESSIVENESS IN ELDERLY PATIENTS: THE IMPORTANCE OF PATIENT ASSESSMENT

There is increasing evidence that older patients have a higher risk of being affected not only by prostate cancer but also by more aggressive disease as compared with their younger counterparts. In an autopsy study of men with no previous history of prostate cancer, 45% of men age 70 or older or were affected by prostate cancer, compared with 19% of men younger than age 70.[5] Furthermore, older men were

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more likely to have higher stage disease (pT3: 21% vs. 3.8%) and more poorly differentiated tumors (Gleason score ≥ 7: 42% vs. 15% in older vs. younger men, respectively).[5] The association between age and prostate cancer aggressiveness has also been confirmed in several retrospective series that demonstrated higher rates of progression and cancer specific mortality in elderly men when compared with their younger counterparts.

When determining a treatment plan for elderly men with prostate cancer, the higher rates of aggressive prostate cancer at presentation should be considered in the context of the overall patient health and comorbidity status to minimize the risk of under- or overtreatment. There is general consensus that the diagnostic and therapeutic clinical decision-making process should not be based on chronologic age, but on biologic aging and health status. To accomplish this, recently released guidelines have suggested using a stepwise process for treatment decision making that incorporates multiple patient parameters, including age, patient comorbidity profile, cognitive and neurologic function, and nutritional status.[6] Such a comprehensive assessment should be performed to properly classify elderly patients into different prognostic groups, namely healthy or fit, frail, disabled or patients with severe comorbidities, and the terminally ill.[6] This classification is key to properly selecting the most appropriate personalized treatment strategy for an individual patient.

Are Screening and Early Diagnosis Justified?

Currently, screening for prostate cancer is one of the most controversial topics in urologic literature. Based on conflicting results coming from large, randomized controlled trials, many scientific societies and groups have taken different positions.[7-11] Although the U.S. Preventive Services Task Force currently recommends against routine screening for men of any age group,[9] many medical and urologic societies suggest offering individualized risk-adapted strategies to well-informed men.[7,10] Such an approach should be multifactorial, including patient age, family history of prostate cancer, and baseline prostate-specific antigen (PSA) values, to maximize the benefit of screening while limiting the risk of over-detection. All available recommendations underline the importance of correctly informing men of the uncertainties, harms, and potential benefits associated with prostate cancer screening.

With regard to specific recommendations in the elderly population, general consensus exists against routine screening in men with a life expectancy of less than 10 to 15 years because the expected mortality benefit from screening is estimated to occur years after the initial screening.[8,10-13] The decision not to screen men with a shorter life expectancy is primarily a consequence of the long natural history of untreated localized prostate cancer and the impact of competing causes of death.[14,15]

In elderly men with a longer life expectancy, the potential benefit of prostate cancer screening remains unclear. In the recently released European Randomized Study of Screening for Prostate cancer (ERSPC) trial, there was no benefit to screening men age 70 or older, although no screening study has been specifically restricted to elderly patients only.[12] Because subgroup analyses of cohorts included in large trials cannot provide the quality of evidence needed to definitively address clinical questions, the real effect of routine screening in the elderly population remains to be proven. Therefore, although some men older than age 70 have a life expectancy of less than 10 to 15 years and may benefit from PSA screening, the quantitative evidence defining the magnitude of benefit in this age group is limited.

Given the complexity of the decision and the heterogeneity of the patient population, the life expectancy of elderly men should be estimated prior to informing them of the harms and benefits of risk-adjusted PSA screening and early detection. This is of particular importance in the context of a higher incidence of aggressive disease in this patient population. Several validated predictive models developed in community-dwelling elderly patients based on age, gender, body mass index, functional status, and comorbidities can be used to assess patient life expectancy.[16,17]

KEY POINTS

- **Older adults are much more likely to have other comorbidities and chronic conditions, which can impact the biology of their disease and influence decisions about screening and treatment of early prostate cancer.**
- **Older men must have an RLE greater than 10 to 15 years to consider screening for prostate cancer, and those with longer RLE should have an informed, shared discussion about their treatment goals with their physician.**
- **Treatment decisions for elderly patients with prostate cancer should include consideration of a patient's fitness for treatment, an estimate of RLE, a review of cancer aggressiveness, and a discussion of patient preferences and expectations.**
- **Engaging a multidisciplinary team to provide care to the elderly prostate cancer population is an ideal way to provide the medical, physical, and social supports necessary to meet the unique needs of this patient population.**
- **Systemic treatment with androgen-deprivation therapy can result in long-term complications, including osteoporosis and fracture, cardiovascular disease, diabetes, and cognitive impairment, which can increase morbidity and mortality in the elderly patient population.**

Who Are the Optimal Candidates for Treatment of the Primary Tumor?

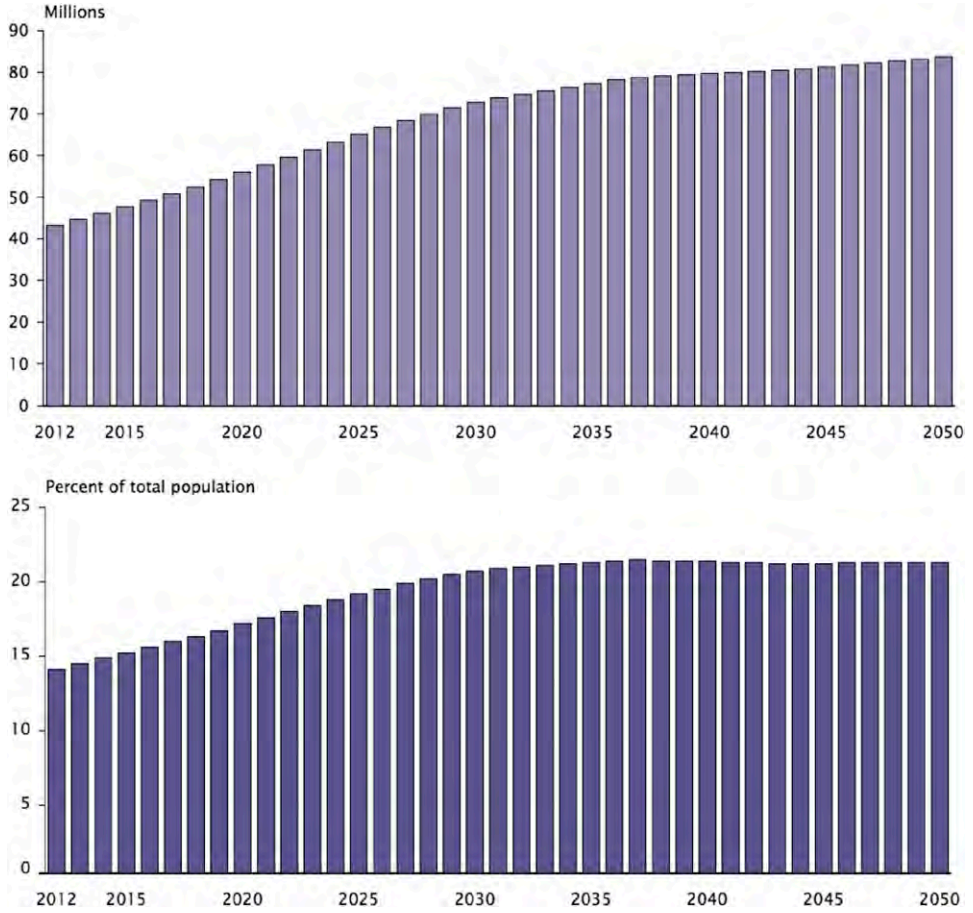
Once elderly patients diagnosed with prostate cancer are thoroughly assessed and deemed fit for treatment with a life expectancy of 10 years or longer, the standard treatment algorithm for younger patients can be followed. Although subanalyses coming from prospective randomized trials should always be interpreted with caution, it seems that the effect of treatment of the primary tumor is not significantly

affected by patient age. In the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) study, although the highest benefit of radical prostatectomy was seen in younger men, surgery was associated with reduced risk of metastases in men age 65 or older (p = .04).[18] Similar results were obtained in the subanalysis performed in older men included in the Prostate Cancer Intervention versus Observation Trial (PIVOT) using metastasis-free survival as an endpoint.[19] Furthermore, in the recent Prostate Testing for Cancer and Treatment (ProtecT) trial, the number of deaths from prostate cancer was similarly low across all age groups regardless of treatment arm.[20] Taken together, these results indirectly suggest a role for primary treatment in older men with adequate life expectancy.

In addition to considering life expectancy, the indication for primary treatment in elderly patients should be individualized according to prostate cancer features. The highest benefit of primary treatment seems to be expected in men with more aggressive prostate cancer features, even among elderly patients.[21] Results coming from studies including patients treated with noncurative intent have shown that older men with high-risk prostate cancer (i.e., PSA ≥ 20 ng/mL, biopsy Gleason score of ≥ 8, or a clinical stage ≥ T2c) have a substantial risk of dying from the disease.[7] A nationwide study in Sweden showed that among patients age 75 or older with Gleason scores 7 or higher who are treated conservatively, prostate cancer was the leading cause of death.[22] Similarly, in another population-based cohort study including men with localized prostate cancer diagnosed between 1971 and 1984, men older than age 70 with Gleason scores 8 or higher who were managed conservatively had a 64% chance of dying of their disease.[23]

However, despite these data, too few elderly men with high-risk prostate cancer receive curative treatment. An analysis of different age groups in the United States demonstrated that a minor proportion of men age 75 or older were treated with radical prostatectomy, including those with high-risk disease. Less than half of these men received any form of radical treatment, compared with 90% of patients age 74 or younger.[24] A study of the U.S. Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database reported that, of the 11,790 men included in the analysis, up to 60% of men older than age 75 were conservatively treated.[25] Regardless of their risk score, older men were more often treated with androgen-deprivation therapy (ADT) compared with their younger counterparts. Interestingly, even after accounting for confounders, older men (> age 70) with high-risk tumors receiving local therapy had

FIGURE 1. U.S. Census Projected Population Age 65 and Older From 2012 to 2050 in Millions and as Percentage of Total Population[1]



a 46% reduction in mortality compared with those treated conservatively. Similar results were reported in Europe.[25]

Taken together, these data suggest possible undertreatment among elderly men, perhaps because of the assumption that they will die of other causes than prostate cancer. This has been disproven in men with high-risk disease. Conversely, older patients with low/very low–risk disease are likely good candidates for active surveillance. Although this occurs because of the natural course of the disease and the impact of competing causes of death, increasing evidence suggests that patient age is a negative prognostic factor for men affected by prostate cancer and initially treated with active surveillance.[26] Older men undergoing active surveillance are indeed at higher risk of disease reclassification and progression over time. These findings were confirmed when a population of patients suitable for active surveillance but treated with radical prostatectomy was analyzed: patient age was a significant predictor ($p < .05$) of unfavorable prostate cancer at final pathology.[27,28] Ultimately, fit elderly men initially treated with active surveillance should be properly counseled from the beginning about their higher risk of disease reclassification and progression over time. Frank conversations about the risks and benefits of active surveillance compared with active treatment should be conducted.

Prostate cancer features in elderly patients: Lead-time bias or biology? Two possible explanations may be used to explain the more aggressive tumor characteristics and higher risk of recurrence in elderly patients. The first is lead-time bias: the onset of prostate cancer in specific categories of elderly patients may be similar to their younger counterparts, but the presence of a greater number of adverse features in the tumor can be simply related to a delayed diagnosis.[29,30]

On the other hand, the intrinsic biology of tumor cells and their relationship with cellular aging process may play a more important role. Indeed, the phenomenon of tumor senescence has been emphasized by several studies.[31] Cellular senescence is essentially an irreversible arrest of cell proliferation and growth that occurs when cells are exposed to potentially oncogenic stress. As an example, cellular senescence can be potentially induced by telomere shortening,[32,33] genomic damage,[34,35] mitogens and proliferation-associated signals,[36,37] epigenomic damage,[38,39] and activation of tumor suppressors.[38,40]

Despite the arrest of cell proliferation, an important feature of many senescent cells is the senescence-associated secretory phenotype (SASP), which includes a large number of cytokines, chemokines, growth factors, and proteases. The SASP is probably the most impressive feature of senescent cells because it has the potential to explain the role of cellular senescence in aging and hyperplastic pathologies.[41,42] Important evidence comes from xenograft studies, where co-injection of senescent, but not nonsenescent, fibroblasts significantly ($p < .05$) stimulated the proliferation of mouse and human epithelial tumor cells in immune-compromised mice. This stimulation is partially because of soluble factors produced by senescent cells.[43,44] Of particular importance are the SASP components stromelysin (MMP3),[44] which also promotes tumor cell invasion, and VEGF,[45] which promotes tumor-driven angiogenesis.

In addition to stimulating tumor growth in mice, SASP factors can stimulate malignant phenotypes in cultures. One such phenotype is the epithelial-to-mesenchymal transition, which enables transformed epithelial cells to invade and migrate through tissues and is critical in the development of metastatic cancer.[46,47] Senescent cells may also promote cancer initiation. Indeed, an important feature of the SASP is the ability to cause inflammation, stimulating the infiltration of leukocytes, which produce reactive toxic moieties that can cause DNA damage.[48,49] The picture that emerges is that senescent cells accumulate with age, creating a microenvironment that is permissive for the development and progression of cancer. This hypothesis represents one of the possible explanations for the adverse characteristics that are usually observed in elderly patients affected by prostate cancer.

CARE CONSIDERATIONS FOR OLDER MEN WITH RECURRENT PROSTATE CANCER

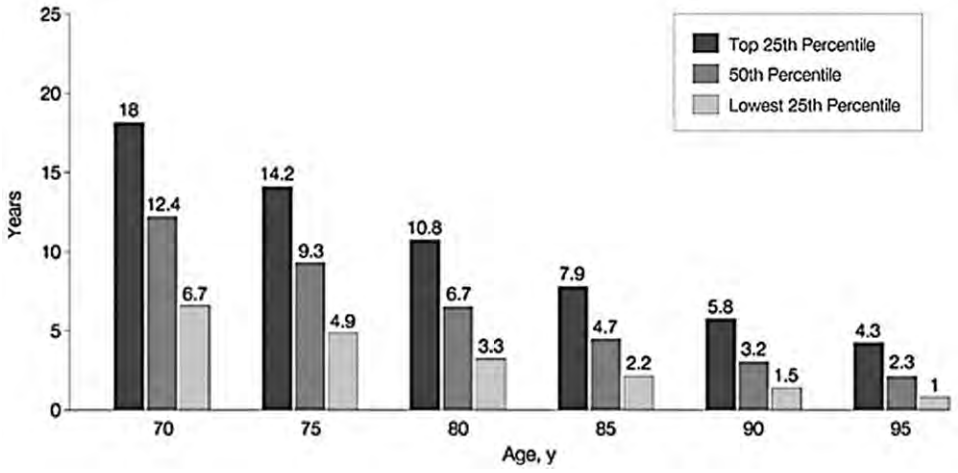
Treating older men with prostate cancer—whether early in the course of disease, after recurrence, or during the later stages—appropriately first requires staging the cancer and then "staging the aging."[50] A clinician must balance the risks from treating the disease with the risks of not treating it, weighing a patient's remaining life expectancy (RLE) against the likely progression of the cancer. This must be done while considering the impact of potential treatment options on the disease and further considering the impact of toxicities on the aging individual.[51] Individualizing care for older adults therefore uses care strategies from both oncology and geriatrics. Systematically using those strategies is the core of an integrated approach to caring for older men with prostate cancer. To illustrate this approach, this section focuses on older men with early disease recurrence.

The first evidence of disease recurrence following initial treatment is a rising PSA on a surveillance blood test in an asymptomatic patient, typically referred to as biochemical recurrence.[52] This occurs in approximately 25% to 40% of men initially treated with surgery or radiation.[53] In such a situation, clinicians often consider initiating ADT. However, there is a paucity of evidence confirming that ADT prolongs life or reduces side effects in this clinical situation.[54] Furthermore, ADT is associated with numerous side effects, including osteoporosis, sarcopenia, falls, fractures, and frailty—complications that can be detrimental both in the short and long term for elderly patients.[55] Current guidelines suggest the use of ADT for biochemical recurrence only in a small proportion of highly selected men with adequate life expectancy.[56] How should a clinician make the decision to pursue immediate treatment or to delay it in the setting of elderly patients?

Use of Geriatric Assessment

From an aging perspective, there are, broadly speaking, two important clinical considerations when making treatment

FIGURE 2. Upper, Middle, and Lower Quartiles of Life Expectancy for Elderly Men at Selected Ages



Adapted from Walter et al.[57]

choices for older patients with cancer: (1) what is the patient's RLE, independent from their cancer-based prognosis? and (2) what resources are needed to maximize functional status and quality of life?[57] (Fig. 2). Fortunately, both of these can be objectively ascertained through the use of a geriatric assessment, which then can be used to make decisions about when to offer cancer-directed therapy, as well as which referrals, interventions, and resources may optimize quality of life.

RLE can be assessed in a number of ways using elements from geriatric assessment. The primary goal is to ascertain in which of three groups a given patient belongs: fit, vulnerable, or frail. If an older patient is found to be fit, with a long RLE, then cancer treatment timing should be indistinguishable from younger adults. If found to be frail, then cancer treatment—especially treatments with high toxicity like ADT—should be started only when absolutely necessary to help improve quality of life. For those found to be vulnerable, with shorter RLE, but not fully frail, more nuanced approaches to choosing treatments are required. Fortunately, the geriatric assessment can also be used to guide this approach.

Broadly speaking, geriatric assessment is grouped into a number of health domains, including physical health (e.g., comorbidities, nutritional status), mental health (e.g., depression, cognitive impairment), functional health (e.g., instrumental activities of daily living), symptoms (e.g., pain, shortness of breath), and social health (e.g., caregiving support, social networks; Table 1).[58] Each of these domains can identify those areas in which patients are in greatest need of support. Resources can be targeted to those domains found to be in need on a geriatric assessment. Geriatric oncology experts in both the United States and Europe have agreed on which of these domains are of greatest importance to be acted on when deficits are identified.[59,60]

Putting It Together

Once an older man with recurrent prostate cancer has undergone a geriatric assessment, a treatment strategy can be devised.[61] Based on the projected risk of disease progression—using a combination of Gleason score, PSA doubling time, and time to relapse—and a geriatric assessment for assessing RLE and areas needing to be addressed, decision making about care plans can be performed. While formulating a treatment plan, it is critical to consider an individual patient's preferences for care. Even after a thorough medical assessment of the patient, shared decision making requires clear communication about the treatment options that may be medically available, as well as the integration of patient values when choosing treatment options.

In summary, a five-step process for making appropriate treatment decisions for older patients is as follows:

1. A cancer-based prognosis with and without treatment (i.e., staging the cancer)
2. An aging-based prognosis separate from cancer-based prognosis (i.e., staging the aging)
3. Identification of resources needed to maintain independence using a geriatric assessment and targeting interventions to match those needs
4. Ascertainment of the patient's preferences and values for care
5. Communication of the available options to the patient

Considering a 75-year-old man with biochemical recurrent prostate cancer, such a decision-making process might go as follows: First, an assessment of the risk of cancer reveals that he has Gleason (3 + 4; 7) disease, no evidence of bone metastases on imaging, a PSA doubling time of 8 months, and a time to recurrence of 3 years. These factors place him in a moderate-risk category when staging the cancer. Second, a geriatric assessment places him in the lowest 25% and gives him a noncancer RLE of about 6 years. Among the deficits identified are weakness based on a low score on physical performance, difficulties in managing his money and cooking, and poor social support since his wife died last year. Throughout the process, the physician investigates the patient's preferences and learns that he wishes to remain living independently at home in his apartment. His geriatric

oncologist chooses to delay the start of ADT out of concern for further loss of strength and loss of independence. She also arranges for the patient to receive physical therapy at a nearby facility and engages with social work to arrange Meals on Wheels and help with his finances. This team then identifies a daughter who lives nearby who can arrange a pillbox every week and help cook some meals. The doctor orders a dual energy x-ray absorptiometry scan to assess for osteoporosis and initiates bisphosphonate therapy in anticipation of starting ADT in the future. Thus, a multidisciplinary, integrated care plan commences that combines appropriate cancer care and a functional-centered approach compatible with the patient's preferences.

PHYSICAL AND COGNITIVE EFFECTS OF SYSTEMIC THERAPY IN ELDERLY MEN WITH PROSTATE CANCER

It is estimated that 40% to 50% of the men living with prostate cancer in the United States will received systemic treatment with ADT during the course of treating their disease.[62] In addition to hot flashes, erectile dysfunction, and loss of libido that noticeably affect patients shortly after starting ADT, this treatment causes numerous other more insidious physical and cognitive complications that negatively impact morbidity and mortality in men with prostate cancer. With an average age of diagnosis of 66 and a 5-year survival of 99% overall, many of the men exposed to ADT and its side effects are elderly. Despite the tendency for older men to have more aggressive disease, they are still more likely to die of comorbid illness rather than prostate cancer itself.[63] Considering the burden of treatment effects on men, the potential increase in mortality from comorbid conditions, such as diabetes, cardiovascular disease, and falls, and the risk of disease progression are critical aspects of treatment decision making for the elderly prostate cancer population.

Osteoporosis and Risk of Fracture

Though osteoporosis is commonly considered a disease of elderly women, one-quarter of all hip fractures occur in elderly men, and the lifetime risk of fracture in men over age 50 is 27%.[64-67] The mortality risk in the year after hip fracture is higher among men than women, ranging from 30% to 35%, compared with 17% to 22% for women.[66,68,69] This increased risk of mortality persists after the first year when individuals are compared with age-matched controls without a fracture, and the risk in men exceeds that of women at any given age.[69,70] In addition to mortality, hip fracture is a major cause of loss of mobility and independence in the elderly, and it comes with a high financial burden.[69,71,72]

ADT causes a decline in bone mineral density (BMD), eventually leading to osteoporosis and increasing the risk of fracture.[73-77] Evidence from prospective studies suggests that within the first year of treatment, BMD typically decreases by approximately 2% at the hip and 3% at the lumbar spine (range 0.7%–3.3% and 1.4%–3.3% at the hip and lumbar spine, respectively).[78-80] This decline in BMD is associated with an increased rate of fracture in several population-based studies.[76,77] In a SEER-Medicare analysis including over 50,000 men, the rate of developing a fracture in the 5 years after diagnosis of prostate cancer was

TABLE 1. Common Geriatric Assessment Tools, Based on Data From Balducci et al[58]

Tool	Description
Mini Nutritional Assessment (MNA)	A validated nutrition screening and assessment tool used to identify geriatric patients age 65 or older who are malnourished or at risk for malnutrition
Mini Mental State Examination (MMSE)	A brief, quantitative measure of cognitive status in adults that serves as a screen for cognitive impairment and to estimate the severity of cognitive impairment at a given point in time; the MMSE can be used to follow cognitive changes over time.
Geriatric Depression Scale (GDS)	A basic screening measure for depression in older adults
Activities of Daily Living (ADLs), Instrumental Activities of Daily Living (IADLs)	ADLs: Measures of a person's daily functioning, reflecting the things we normally do in daily living, including any daily activity we perform for self-care IADLs: Measures of activities that allow an individual to live independently in a community
Barthel Index	Ten items that measure a person's daily functioning, specifically ADLs and mobility; the Barthel Index can determine a baseline level of functioning and monitor improvement in ADLs over time.
Eastern Cooperative Oncology Group (ECOG) Performance Status	Criteria used to quantify how the disease affects the patient's daily living abilities
Cumulative Illness Rating Scale for Geriatrics (CIRS-G)	A tool to measure comorbidity that reflects chronic medical illness burden including the severity of chronic diseases; the CIRS-G is a revised version of the original measure that reflects common problems of elderly people, and it was validated in a geriatric residential population.
Euro-QoL 5D (EQ-5D)	A standardized instrument to measure health outcomes for a wide range of health conditions and treatments; it provides a simple descriptive profile and a single index value for health status.
Pain Visuo-Analogic Scale	An instrument that measures a continuum of pain values
Short Physical Performance Battery (SPPB)	An objective assessment tool for evaluating lower extremity functioning in older persons
Vulnerable Elders Survey (VES 13)	A function-based tool for screening community-dwelling populations to identify older persons at risk for health deterioration
Senior Adult Oncology Program (SAOP2)	A screening tool to identify elderly persons at risk for disabilities

19.4% in men treated with ADT compared with 12.6% in unexposed men.[76] A similar analysis in a random 5% sample of Medicare participants with nonmetastatic prostate cancer found a relative risk of any form of clinical fracture of 1.21 (95% CI, 1.14–1.29; p < .001) for men exposed to ADT compared with unexposed men.[77]

Guidelines suggest that men receiving treatment with ADT should initiate screening with bone density scans and treatment with osteoclast inhibitors to prevent fractures when appropriate.[81] Clinicians should consider using osteoclast-inhibiting therapy to prevent the decline of BMD for men with a 10-year probability of hip fracture 3% or greater or with a 10-year probability of major osteoporosis-related fracture 20% or greater.[81] Although bone density scans are recommended to make this assessment of fracture risk more precise, rates of screening for osteoporosis among men is low overall (14.5% of men initiating ADT in 2007–2009), and it decreases in the elderly (odds ratio [OR] 0.76% in ≥ 85 years vs. 66–69 years).[82] This is particularly concerning in the elderly prostate cancer population, which may be at risk for fracture because of systemic treatment of prostate cancer and higher risk of mechanical falls because of aging. A recent study of 363 men seen at a single academic center found that 3.3% of men age 70 or younger are at high enough risk for fracture to meet criteria for osteoclast-inhibiting treatment, whereas 76.6% of men between ages 70 and 79 and 98.8% of men over age 80 meet the criteria.[83] Though older men are at higher risk of fragility fracture, they are being screened for intervention at a lower rate.[82] Finally, it is also important to recognize that although they do not experience fractures as commonly as white men, black men experience a similar rate of BMD decline with ADT and should take similar precautions to avoid skeletal complications, particularly with long-term exposure to ADT.[84]

Obesity and Sarcopenia

Approximately 41% of American men between ages 65 and 75 meet criteria for obesity—a condition associated with excess mortality in elderly individuals.[85,86] In men with prostate cancer, 1 year of exposure to ADT was associated with increasing rates of obesity, with a 10% increase in fat body mass and a 3% decrease in lean body mass.[87,88] In particular, subcutaneous abdominal adipose tissue increases with ADT exposure, raising the risk of cardiovascular disease, diabetes, and death.[89-92] Specific guidelines describing the optimal strategy to prevent the development of obesity during treatment with ADT have not yet been developed. Despite that, it is important to discuss this complication in conjunction with information on maintaining an active lifestyle and heart-healthy diet when making treatment decisions in the elderly prostate cancer population to prevent obesity and associated diabetic and cardiovascular complications.

Impaired Insulin-Sensitivity and Diabetes

The prevalence of diabetes in the United States is 29.1 million, with 20.1 million diagnosed and 8.1 million undiagnosed.[93] Diabetes is the seventh leading cause of death in the United States, and it is likely that its impact on mortality is underreported.[93] Risk factors for developing diabetes in the general population include obesity and increasing age.[93]

ADT is associated with the development of insulin resistance, a condition that in turn increases the risk of diabetes.[92,94-96] In a small prospective study of 25 men with locally advanced or recurrent prostate cancer without diabetes initiating treatment with ADT, there was a decrease in insulin sensitivity as early as 12 weeks after starting treatment (insulin sensitivity index decreased by 12.9 +/− 7.6%; p = .02).[94] Three population-based analyses demonstrate an association between ADT and an increased rate of developing diabetes.[97-99] A SEER-Medicare analysis of 73,196 men with locoregional prostate cancer found an adjusted hazard ratio (HR) for developing diabetes of 1.44 (p < .001), suggesting that exposure to ADT increased the risk of diabetes by 44%.[97] This association was validated in a Canadian matched cohort study including 38,158 men, 50% of whom were treated with ADT.[99] The HR for men exposed to ADT was 1.16 (95% CI, 1.11–1.21).[99] In a cohort of 37,443 veterans, treatment with ADT was associated with an increased risk of incident diabetes (adjusted HR 1.48; 95% CI, 1.31–1.67).[98]

Importantly for elderly men considering treatment of prostate cancer, the risk of developing diabetes during treatment with ADT appears to increase with age. A recent study of 2,985 men without baseline diabetes enrolled in a prospective clinical trial suggests that there is a synergistic relationship between ADT and increasing age such that the risk of diabetes increases with each year in age after 76 (OR 2.1; 95% CI, 1.0–4.4).[100] The study failed to find an association between diabetes and ADT exposure in men younger than age 76.

Cardiovascular Complications

Cardiovascular disease is the leading cause of death among American men, with 25% of deaths in the United States attributable to heart disease.[101] Both increasing age and male gender increase the risk of cardiovascular complications.[102,103] Treatment with ADT has been associated with the development of cardiovascular disease in multiple studies, though others fail to find a relationship.[97,104-106]

One population-based SEER-Medicare study included 73,196 men older than age 66 with locoregional prostate cancer.[97] Treatment with ADT was associated with an increased risk of sudden cardiac death (HR 1.16; p = .04), myocardial infarction (HR 1.11; p = .03), and new diagnosis of heart disease (HR 1.11; p < .001).[97] A subsequent SEER-Medicare study of 22,816 men age 65 or older with any-stage prostate cancer found a 20% increased risk of cardiovascular morbidity associated with ADT exposure.[104]

In contrast, several other analyses failed to find an association between ADT and cardiovascular disease. A Canadian-linked administrative database compared 19,079 men older than age 66 with prostate cancer who were treated with 6 or more months of continuous ADT with age-matched controls with prostate cancer not treated with ADT.[99] There was no association between ADT and the risk of

cardiovascular disease (HR 0.91; 95% CI, 0.84–1.00). Multiple Radiation Therapy Oncology Group prospective studies have been assessed retrospectively to evaluate cardiovascular morbidity and mortality and failed to find an association between treatment with ADT and cardiovascular disease despite long-term follow-up.[105-108]

The relationship between ADT and cardiovascular disease may affect specific populations more than others, and elderly men may be at higher risk than their younger counterparts.[100,109-111] Several studies suggest that increasing age is associated with an increased risk of cardiovascular disease.[100,110,111] In one prospective study including 3,112 men with localized prostate cancer without baseline cardiovascular disease, there was a synergistic association between increasing age, ADT exposure, and cardiovascular disease, with risk of cardiovascular disease increasing at age 74 (OR 1.9; 95% CI, 1.0–3.5) and with each year of age thereafter.[100] In a population-based study of 3,262 men treated with ADT after prostatectomy, ADT was associated with increased cardiovascular disease only among men older than age 65.[110] A meta-analysis of three studies including men treated with radiation and ADT also found an association between ADT and cardiovascular disease in men older than age 65 but not in younger men.[111] In addition to age, a SEER-Medicare analysis of men with prostate cancer found an increased risk of cardiovascular disease in men treated with ADT with a history of cardiovascular disease at baseline (HR 1.09; 95% CI, 1.02–1.06).[109] This is especially important when treating elderly men with prostate cancer because of the increased risk of cardiovascular disease with increasing age.

Elderly men with pre-existing cardiovascular disease may be at the highest risk of future morbid or fatal cardiac events.[109] In practice, ADT should be avoided when its use is not supported by evidence. Additionally, engaging with other specialties to provide multidisciplinary care is critical. By including primary care physicians and cardiologists to identify and treat patients with risk factors associated with cardiovascular disease, we may reduce the chance of potentially catastrophic cardiovascular complications in the elderly prostate cancer population.[112]

Cognitive Complications

Controversy exists regarding whether ADT is associated with cognitive decline in elderly men with prostate cancer. However, several recent studies suggest that ADT is associated with cognitive decline, Alzheimer disease, and other forms of dementia. In a prospective study of 58 men with locoregional prostate cancer receiving ADT, 84 age-matched controls with prostate cancer not receiving ADT, and 88 men without cancer, ADT was associated with cognitive impairment at 12 months ($p < .001$).[113] A smaller prospective study included 29 men with biochemical recurrent prostate cancer and assessed cognitive function before, during, and after intermittent ADT.[114] Participants experienced a reversible decline in working memory and spatial abilities.[114] A recent claims-based study of men with prostate cancer demonstrated an association between ADT exposure and risk of Alzheimer disease (HR 1.88; $p = .21$).[115] Increasing age was associated with an increased risk of developing Alzheimer disease (HR 1.06; 95% CI, 1.04–1.08, $p < .001$).[115] The same group subsequently found a similar association between duration of ADT exposure and development of an array of types of dementia in a second claims-based analysis (HR 2.17; 95% CI, 1.58–2.99; $p < .001$).[116] A recent meta-analysis of 14 studies demonstrated a consistent decline in visuomotor task scores but failed to find a consistent decline in other cognitive domains across studies.[117]

Data from several other studies failed to find an association between ADT exposure and cognitive decline.[118,119] A Canadian group compared objective and subjective measures of cognitive function among 57 men with nonmetastatic prostate cancer treated with ADT and 51 healthy matched controls.[118] After a median duration of ADT of 1.8 years, there was no significant difference between groups in subjective or objective measures of cognitive function.[118] A second prospective cohort study included 77 men with nonmetastatic prostate cancer treated with ADT, 82 men with prostate cancer not receiving ADT, and 82 healthy controls over 36 months.[119] In this study with long-term follow-up, ADT was not associated with a decline in cognitive function.[119] Finally, a population-based study from the United Kingdom including a cohort of 30,903 men with non-metastatic prostate cancer failed to find an association between ADT exposure and duration of ADT exposure with dementia.[120]

The controversy regarding the association between cognitive decline and ADT is still being settled, and prospective studies that may establish a biologic rationale for cognitive change in the setting of low testosterone in the elderly prostate cancer population are necessary. One prospective study couples imaging with cognitive testing in men with metastatic castration-resistant prostate cancer randomly assigned to treatment with ADT and abiraterone acetate compared with enzalutamide in an effort to clarify a biologic rationale for the development of cognitive dysfunction in the setting of low testosterone signaling (NCT03016741). For the elderly population of men with prostate cancer, developing cognitive complications can limit independence, can lead to falls and functional decline, and may contribute to frailty. Considering whether patients may be at greater risk to experience cognitive decline should be an integral part of treatment decision making, particularly in settings in which ADT use is discretionary.

CONCLUSION

The incidence of diabetes, cardiovascular disease, osteoporosis, and dementia increase with age in the general population, and use of ADT in elderly men with prostate cancer puts them at a much higher risk than untreated men. However, clinicians must be aware of the increased risk of aggressive prostate cancer in this population and consider it in the context of the geriatric assessment or multidisciplinary team-based assessment of the patient's holistic fitness for more toxic treatments. Appropriate prevention,

screening, and referral strategies—particularly multidisciplinary strategies—are a critical part of caring for elderly men with prostate cancer receiving systemic hormonal therapy. In situations in which the use of ADT is discretionary, it is critical to consider the potential consequences of treatment when making treatment decisions. This is particularly important in the elderly population as seemingly trivial complications can be debilitating, permanently life altering, or fatal.

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GERIATRIC ONCOLOGY

Improving Quality and Value of Cancer Care for Older Adults

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OVERVIEW

The concepts of quality and value have become ubiquitous in discussions about health care, including cancer care. Despite their prominence, these concepts remain difficult to encapsulate, with multiple definitions and frameworks emerging over the past few decades. Defining quality and value for the care of older adults with cancer can be particularly challenging. Older adults are heterogeneous and often excluded from clinical trials, severely limiting generalizable data for this population. Moreover, many frameworks for quality and value focus on traditional outcomes of survival and toxicity and neglect goals that may be more meaningful for older adults, such as quality of life and functional independence. A history of quality and value standards and an evaluation of some currently available standards and frameworks elucidate the potential gaps in application to older adults with cancer. However, narrowing the focus to processes of care presents several opportunities for improving the care of older adults with cancer now, even while further work is ongoing to evaluate outcomes and efficiency. New models of care, including the patient-centered medical home, as well as new associated bundled payment models, would be advantageous for older adults with cancer, facilitating collaboration, communication, and patient-centeredness and minimizing the fragmentation that impairs the current provision of cancer care. Advances in information technology support the foundation for these models of care; these technologies facilitate communication, increase available data, support shared decision making, and increase access to multidisciplinary specialty care. Further work will be needed to define and to continue to tailor processes of care to achieve relevant outcomes for older patients with cancer to fulfill the promise of quality and value of care for this vulnerable and growing population.

Great progress has been made in advancing cancer treatment in the United States over the past decade. New drugs have come to market, mortality is declining (166.4 deaths per 100,000 in 2015 compared with 209.9 in 1995), and more people are cancer survivors (14.5 million in 2015 compared with 6.5 million to 8.3 million in 1995).[1] In 2016, momentum accelerated with the creation of the Cancer Moonshot initiative, bringing heightened awareness to the cause with the dedication of $1 billion in federal funding for cancer research. Although the needle is moving in the right direction, considerable challenges remain to ensure quality and value in cancer care for older adults. Cancer care delivery for older adults with cancer is compromised by tenuous consensus on what constitutes quality and value in cancer care (a you know it when you see it mentality), a paucity of research focused on older adults with cancer, and gaps in services for older adults largely because of an insufficient number of geriatric specialists.

A brief history of the concepts of quality and value in health care reveals ongoing debate about concise definitions, measures, and desired endpoints. These concepts are not easily reducible to straightforward standards, particularly when considering the complexity (medical, psychosocial, and otherwise) of caring for older adults with cancer. Some progress is being made toward establishing quality measures and value frameworks for the care of patients with cancer, but consensus has not been achieved, and many of the frameworks described below fail to consider elements of critical importance to older patients and their caregivers. In particular, a focus on drug costs alone, survival outcomes, and treatment toxicity neglects to account for comorbidity and competing risk, functional outcomes, indirect costs to patients and families, patient preference, and other considerations.

Quality measures often focus on care processes, whereas value attempts to measure outcomes per unit cost. Although several representative value frameworks are presented for discussion, it is premature to consider widespread application of these nascent frameworks to the care of older adults with cancer. It is not premature, however, and is in fact imperative to develop structures and care processes that optimize the care of these patients. Several concepts are known to influence quality of care at an overarching level, particularly for the growing population of patients with complex

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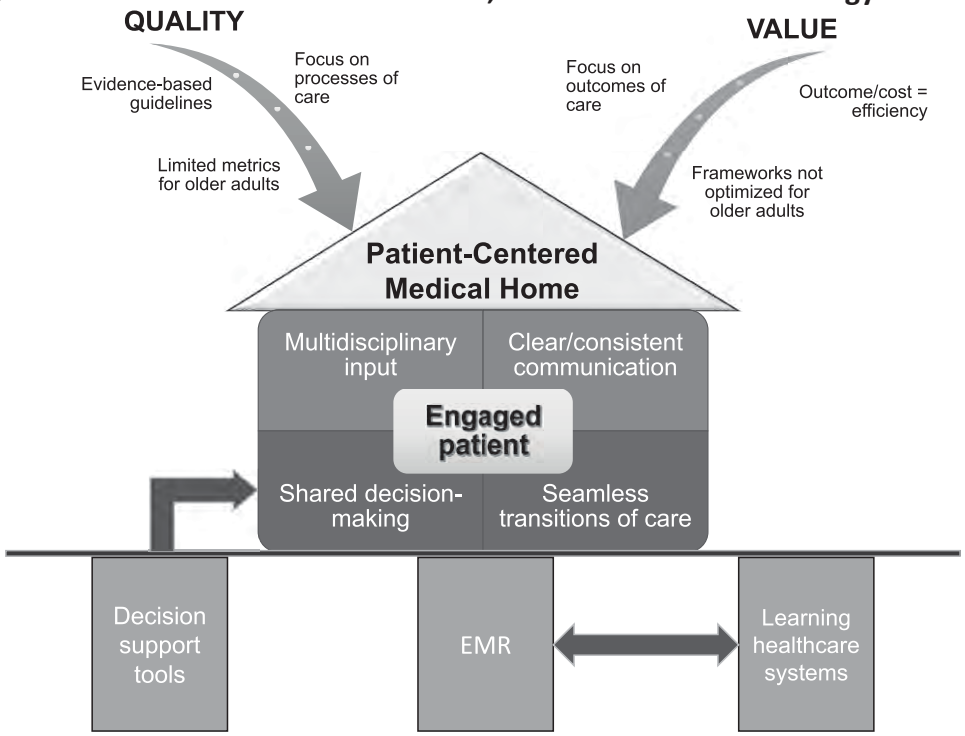
FIGURE 1. Conceptual Model for the Care of Older Adults With Cancer: Relationships Between Quality, Value, the Patient-Centered Medical Home, and Information Technology



Abbreviations: EMR, electronic medical record.

medical needs: consistent communication between providers and between providers and patients; engaged and informed patients; and seamless transitions along the care continuum (Fig. 1). These structural underpinnings can be developed as part of a paradigm of patient-centered care. The medical neighborhood is introduced as an embodiment of this paradigm. Novel payment methods are discussed that will shift the focus of care and incentivize high-quality processes of care.

KEY POINTS

- **Existing quality measures and value frameworks of cancer care fail to consider elements of critical importance to older patients and their caregivers.**
- **Quality measures often focus on care processes, whereas value attempts to measure outcomes per unit cost with outputs unfamiliar to most patients and providers.**
- **We as a nation are not prepared to meet the needs of a projected 10-fold increase in the prevalence of cancer by 2040 (compared with 1975) among adults age 75 to 84 and a 17-fold increase among those age 85 and older.**
- **The paradigm of patient-centered care in models, such as the medical home or medical neighborhood, must be applied to older adults with cancer.**
- **Considered use of information technology may provide a foundation for overcoming gaps in services and fulfilling the promise of quality and value of care for this vulnerable and growing population.**

One way for processes of care to be given structure and become ingrained within the medical neighborhood is via the use of health information technology. This technology can improve the quantification of quality and value, which has been hampered by poor documentation. Big data and machine-learning capabilities could dramatically enhance the understanding of real-world outcomes in real time; this is particularly compelling for older adults with cancer, who are generally excluded from the randomized clinical trials that form the current basis for evidence in cancer care. Finally, information technology can expand the reach of the medical neighborhood, enhancing access to specialized interdisciplinary care, which is known to improve cancer outcomes. Geriatric expertise, in particular, is a scarce resource but is highly necessary in the care of the rapidly growing population of older adults with cancer.

DEFINING QUALITY AND VALUE FOR OLDER PATIENTS WITH CANCER

A Brief History of Quality and Value Standards in Cancer Care

The search for standards and definitions of quality health care goes back decades. The movement toward quality health care can be traced to the early 20th century, when the American College of Surgeons developed "Minimum Standards for Hospitals," a one-page document. This grew to an 18-page standards manual, first printed in 1926.[2] The Joint Commission on Accreditation of Hospitals was founded 1951 as an independent, not-for-profit organization. In the

late 1970s, the name was changed to The Joint Commission on Accreditation of Healthcare Organizations (now The Joint Commission), whose current mission is "to continuously improve health care for the public, in collaboration with other stakeholders, by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value."[3] Multiple quality mandates for the Medicare and Medicaid programs have been issued since Congress passed legislation in 1965 establishing the programs as Title XVIII and Title XIX of the Social Security Act. Each variation has been intended to incrementally improve health care for the populations covered by the two programs,[4] but no clear, overarching definition of quality health care emerged.

Currently, the most cited definition of quality in health care is from a 1990 Institute of Medicine report. It states, "Quality of care is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[5] Although this has served as a working definition for many clinical populations, its foundation is particularly relevant here: "Health care implies a broad set of services, including acute, chronic, preventive, restorative, and rehabilitative care, which are delivered in many different settings by many different health care providers. This broad dimension is particularly important for the elderly, who often receive a wide range of services from different sources."[5] In 2001, the Institue of Medicine strengthened the definition, adding six specific aims: safety, effectiveness, patient-centeredness, timeliness, efficiency, and equitability.[6]

Concise definitions of quality care for patients with cancer are scarce. ASCO's working definition of quality is "the best scientific, evidence-based care delivered in the safest manner to a patient in a specific disease state, in a consistent and reproducible manner across multiple settings." ASCO has initiated the Quality Oncology Practice Initiative (or QOPI), a validated practice-based quality tool, which can be verified by voluntary Quality Oncology Practice Initiative certification review.[7] In 2016, the National Comprehensive Cancer Network published a treatise on National Comprehensive Cancer Network guidelines and quality cancer care, which states, "It is nearly impossible to arrive at a concise, comprehensive, and reproducible definition of quality medical care,"[8] and argues that the Institute of Medicine's six goals of quality are subjective and difficult to quantify. In defining safety and quality care, the Agency for Healthcare Research and Quality posits, "Safety is the foundation upon which all other aspects of quality care are built."[9] The European Society for Medical Oncology adopts Britain's National Institute for Health and Care Excellence quality standards, which are prioritized statements designed to "drive measurable improvements in the 3 dimensions of quality—safety, experience and effectiveness of care."[10] Other agencies and organizations, such as the National Institutes of Health, the National Cancer Institute, the National Coalition for Cancer Survivorship, the American Cancer Society, and others, address standards of quality care in diverse ways, but none have created a concise metric.

The Institute of Medicine definition of quality turned focus away from "a divisive issue like cost control or an evasive issue like patient satisfaction" toward measurable improvement in patient outcomes, anticipating that these would result in lower costs and greater patient satisfaction.[11] However, with the rapidly escalating costs of health care, particularly within cancer care, the concept of value has drawn increasing attention. Attempts to quantify the concept of value have been as challenging as defining the concept of quality. Although value can be defined simply as outcomes achieved per money spent, stakeholders (patients, providers, payers) may prioritize different types of outcomes. Cost reduction for its own sake, without careful attention to selecting appropriate outcomes, is self-defeating, leading to false savings and potentially limiting effective care.[12] Moreover, desired outcomes may differ between providers and patients. A focus only on traditional outcomes such as survival and toxicity may neglect the priorities and preferences of the patient. Older patients in particular prioritize other outcomes (such as functional independence and preserved cognition) over survival.[13] Multiple frameworks for assessing value have recently been proposed with varying measures and perspectives:

- The ASCO Value Framework assesses the value of new cancer therapies on the basis of clinical benefit, side effects, and improvements in patient symptoms or quality of life in the context of cost. It is intended to serve as the basis for a user-friendly software tool that doctors can use in shared decision making with patients.[14] It was initially published in 2015 and modified in 2016 following receipt of more than 400 comments from patients, patient advocates, physicians, representatives of the pharmaceutical industry, and other members of the cancer community.[15]
- The European Society for Medical Oncology has developed a validated and reproducible tool to assess the magnitude of clinical benefit for cancer medicines, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale. It can be used to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from anticancer therapies.[16] Although it is intended to "help frame the appropriate use of limited public and personal resources to deliver cost-effective and affordable cancer care," it does not include cost in the algorithm.[17]
- The National Comprehensive Cancer Network has refined its guidelines and collaborated with McKesson Specialty Health and the US Oncology Network to develop value pathways powered by National Comprehensive Cancer Network in response to the move toward value-based reimbursement. A software companion is Clear Value Plus, a tool that provides physicians evidence-based treatment options as well as clinical and financial information at the point of care.[18]
- The Institute for Clinical and Economic Review Value Assessment Framework seeks to improve the reliability

and transparency of value determinations made by insurers in the United States, to achieve greater consistency across insurers, provide greater certainty for manufacturers, and enhance the legitimacy of medical policy decisions with patients and the public.[19]

- Memorial Sloan Kettering Cancer Center DrugAbacus is designed to calculate fair prices for cancer drugs on the basis of relative weights, determined by the user, of eight value domains (efficacy, tolerability, novelty, research and development costs, rarity, population burden, unmet need, and prognosis).[20]

Definitions and Caveats for Older Patients With Cancer

Quality is a measurement of adherence to evidence-based guidelines. Moreover, quality measurement focuses largely on care processes. For example, of the 196 quality measures that are part of ASCO's Quality Oncology Practice Initiative 2016 set, the vast majority are process measures,[21] with a much smaller number focused on structure, outcome, or the patient experience. Quality is linked conceptually to value in that quality care should produce better outcomes. The challenge for older patients with cancer is that evidence is generally limited in this population. Numerous studies have shown that older individuals are underrepresented in cancer clinical trials.[22-24] A 2013 study found that two-thirds of medications relevant to geriatrics and approved by the U.S. Food and Drug Administration in the previous 10 years (143 of 214) lacked adequate prescribing information about efficacy and safety data in older populations.[25]

Value is defined by the health outcomes achieved relative to the costs and measures the efficiency of health care delivery.[12] Value is therefore a measure of the outcomes achieved, not the volume of services provided or the process of care used to achieve those outcomes.[12] Value should be defined in a patient-centric way (i.e., to and for the patient). This construct of value raises important questions for older patients with cancer, who may prefer quality of life over quantity of life, palliation over survival, or independence over longevity. Moreover, older adults often have multiple comorbid conditions that may contribute unanticipated complications and subsequent cost to the treatment of cancer, obscuring calculations of value for these patients.

Quality Indicators for Older Patients With Cancer

Although evidence is limited for older patients with cancer, efforts have increased to develop guidelines and recommendations for standards in treatment of this population.[26-31] However, there are pitfalls and limitations to the use of guidelines to create quality indicators in an older population. Older adults are heterogeneous, with variations in comorbid conditions and health status precluding simple one-size-fits-all algorithms. For example, one study in older adults showed that adherence rates to guideline-based performance quality measures were poorly associated with the quality of cancer screening. Pitfalls identified included (1) not properly considering illness severity of the sample population audited for adherence to screening, (2) not distinguishing screening from diagnostic procedures when setting achievable target screening rates, and (3) not accounting for patient preferences or clinician judgment when scoring performance measures.[32] Another limitation to accurate measurement of quality is the lack of standardization of documentation, particularly for older and/or medically complex patients. One study found that of 499 individual cases of colorectal cancer, because of a lack of documentation, only 61 could be evaluated for quality.[33] Even for data culled from electronic medical record (EMR) systems, documentation was still a problem in nearly half of the cases.[33]

Despite the challenges associated with evidence and documentation, some attempts to create quality indicators in older frail patients (including those with cancer) have been successful. For example, the RAND Corporation's Assessing Care of Vulnerable Elders (ACOVE) project developed a short questionnaire to identify noninstitutionalized vulnerable elders, those at higher risk for adverse outcomes such as disability and death. They selected 22 clinical conditions prevalent among the elderly for quality measurement and developed an evidence-based set of more than 200 quality-of-care process indicators to evaluate the care provided to these vulnerable elders. In late 2007, these indicators were reviewed and updated, with the addition of five new conditions: chronic obstructive pulmonary disease, colorectal cancer, breast cancer, sleep disorders, and benign prostatic hypertrophy. ACOVE-3 contains 392 quality indicators encompassing 26 different conditions, includes 14 different types of care processes (e.g., taking a medical history or performing a physical exam), and covers all four domains of care: screening and prevention (31% of quality indicators), diagnosis (20%), treatment (35%), and follow-up and continuity (14%).[34-36] These quality indicators are created using expert panels to define quality care, which often allows the creation of a quality indicator even when evidence is lacking or minimal. The success of the ACOVE project may provide a roadmap for the creation of further quality indicators specific to older adults with cancer.

Value Frameworks for Older Patients With Cancer

Multiple frameworks propose to appraise value of cancer care; key features of selected frameworks are summarized in Table 1.[17,37] Although value frameworks represent progress toward defining value, several aspects limit their applicability to older adults. The type of evidence used for a value framework is critical to assessing its generalizability to an older population. For example, ASCO and DrugAbacus use primarily pivotal randomized controlled trials with parameters that qualify for Food and Drug Administration registration. Most randomized controlled trials use narrow inclusion and exclusion criteria to eliminate confounders and select the participants most likely to benefit from an intervention. In a systematic sampling of randomized controlled trials published in high-impact journals, 38.5% excluded older adults, and 81.3% excluded individuals with common medical conditions.[38] Older adults and patients

TABLE 1. Selected Value Frameworks Developed for Patients With Cancer

	ASCO Value Framework	NCCN Value Pathways	ESMO MCB Scale	ICER Value Assessment	MSKCC DrugAbacus
Target Audience	Doctor, patient	Doctor, patient	Payer, policy maker	Payer, policy maker	Payer, policy maker
Evidence	Pivotal trials	Broad	Mainly phase II and III comparative trials	Broad	Pivotal trials
Efficacy	OS, PFS, RR, TFS	OS, PFS	OS, PFS	Varies; usually QALYs	OS
Indirect Loss (Productivity)	No	No	No	No	No
Toxicity	Yes	Yes	Yes	Yes	Yes
QOL/Palliation	Yes	No	Yes	Yes	No
Patient Preference	No	No	No	No	No
Cost	Displayed	Part of calculation	Displayed	No	Displayed
Patient Cost	Drug copay	No	No	Maybe	No
Medical Cost Offsets	No	No	No	Yes	No
Methodology	New	New	New	New and old	New
Outcome	Net health benefit scale (20–130), drug cost	Score 1–5 on each of five evidence blocks	Graded 1–4	Value-based price	Value-based price
Use of Real-World Data	No	Yes	No	Yes	No
Patient Perspective	No	Yes	No	Yes	No

Abbreviations: NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; MCB, magnitude of clinical benefit; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PFS, progression-free survival; RR, relative risk; QALY, quality-adjusted life-year; QOL, quality of life; TFS, treatment-free survival.

with multiple comorbidities are often a target of clinical practice guidelines but are poorly represented in the evidence-generating trials upon which clinical guidelines are based. This is especially important for the frail elderly, who fall into both categories.[39] There is more applicable evidence in phase IV, postmarketing studies, and in pragmatic trials that include older individuals.

Although value should be defined in a patient-centric way, none of the frameworks include patient preference as part of the value algorithm. The exclusive focus on traditional measures of efficacy, such as overall survival and progression-free survival, may not provide sufficient information for older patients with cancer. Although all frameworks account for the toxicity of cancer treatment, not all frameworks incorporate symptom management, palliation, and quality of life, outcomes highly prioritized by patients. None of the value frameworks incorporate outcomes specific to the preferences of older adults, such as functional independence and aging in place. A recent survey by AARP revealed that 81% of older individuals prioritize staying in their current homes and communities.[40]

Most of these value frameworks use new methodologic approaches that yield outputs unfamiliar to most patients and providers, who may be uncertain how to apply them in practice. Moreover, interpretation of the value framework in the setting of shared decision making necessitates adequate health literacy and numeracy on the part of patients. More than half of adults have difficulty understanding and acting on health information, and most health information sources available in the United States exceed the average person's reading ability.[41] Most adults, even those with adequate health literacy, struggle to understand numbers in the context of health decision making.[42] Therefore, value frameworks that generate a value output, but also require consideration of a displayed cost, might be confusing to older patients.

Last, most of these value propositions consider only drug costs. They do not consider patient costs (except the ASCO Value Framework, which includes drug copays, and Institute for Clinical and Economic Review methodology, which includes a broader cost analysis). Costs largely not considered within these frameworks include direct out-of-pocket expenses (copays and deductibles) and expenses from indirect consequences of an illness (indirect costs). However, there are also direct nonmedical expenditures, such as travel, lodging, and home services (e.g., home health aides and durable medical equipment). Last, indirect costs include the lost earnings and productivity by patients or caregivers related to a cancer diagnosis.[43]

STRUCTURAL APPROACHES TO IMPROVING QUALITY OF CARE FOR OLDER ADULTS WITH CANCER

Cancer and Aging in the United States: The Silver Oncologic Tsunami

Cancer is a disease of aging.[44] The incidence and prevalence of cancer is increasing in older adults; by 2040, it is anticipated that 73% of cancers will be diagnosed in patients older

than 65.[45] In comparison with cancer prevalence in 1975, this projection represents a 10-fold increase among adults age 75 to 84 and a 17-fold increase among those age 85 and older. Some have referred to a silver oncologic tsunami, and we, as a nation, are not prepared to meet these patients' health care needs.[46] Cancer care delivery is extremely complex, and the complexity is considerably amplified by the needs of this aging population.[47] Decisions regarding cancer screening are complicated by ambiguous evidence, particularly for older adults. The advent of personalized medicine has exponentially expanded the individual patient factors to be incorporated into treatment decision making. For older adults, these factors include not only the expanding panoply of tumor-related factors (such as molecular and genetic information) but also specifications of comorbid conditions, health status, and functional independence, among others.

Costs to deliver this complex care are unsustainable. In 2004, cancer cost the nation $72 billion, rising to $125 billion in 2010; in 2020, the cost is projected to be $173 billion.[44] As prevalence of cancer increases and people live longer with cancer, costs will continue to rise. As these costs are passed to patients, treatment becomes less accessible. The two elements cited as most concerning to patients with cancer are the cost of drugs and rising deductibles, as highlighted by a recent survey, which found that 24% of Americans have a hard time paying for prescription drugs, and 72% view the prices of prescription drugs as unreasonable.[48] For older adults, particularly those on fixed incomes, the choices become very difficult, and patient costs may play heavily in their treatment decisions.

The Paradigm of Patient-Centered Care Applied to Older Adults With Cancer

As the silver oncologic tsunami continues to rise, changes in care delivery are needed to keep pace with patient needs, while undergirding and giving structure to the quality and value of care delivered. Older adults with cancer are likely to have comorbidities with varying severity and to require a large number of medications (polypharmacy) to manage these conditions. Geriatric syndromes such as delirium and frailty are also common and may affect treatment decisions. Older adults require supportive interventions such as psychosocial support, physical rehabilitation, and caregiver support far more than their younger counterparts with cancer. Thus, older adults require an expanded and interdisciplinary care team; without intentional collaboration fragmentation of care could lead to confusion, frustration, compromised quality and safety, and a poor patient experience.[46]

The paradigm of patient-centered care offers a roadmap for the provision of high-quality care of older patients with cancer by optimizing the care processes linked to quality indicators. Extrapolating from the successful application of this paradigm to patient-centered care in geriatric oncology requires (1) multidisciplinary input, (2) clear and consistent communication between providers and between providers, patients, and caregivers, (3) informed and engaged patients, (4) shared decision making, and (5) seamless transitions along the care continuum, including into survivorship. In a patient-centered environment, the care team rallies around the patient and closely attends to his or her wants, needs, and preferences.

Together, patients and caregivers in conjunction with the health care team can determine the best course of treatment that is relevant to the patients' goals. Timely exchange of information longitudinally across all members of the health care team is paramount to the success of the care delivered. This information needs to be shared with patients and caregivers in a manner that is understandable and meaningful to them to facilitate shared decision making at every step. Considering the anticipated shortage of oncology providers and the complexity of care, meeting the needs of older patients with cancer will rely on a highly integrated, patient-centered approach.[45] Expanding, training, and empowering the workforce to care for these vulnerable patients is integral to the delivery of patient-centered care.

Structural Elements of Care Delivery: The Medical Neighborhood and Bundled Payment Models

As the needs change, so must the environment. One concept in patient-centered care is the medical neighborhood, aimed at improving systems and processes to better support coordination of care.[49] Shifting toward a patient-centered approach begins with coordination at the level of both patients and providers. Examples of initiatives focused on improving care coordination are the National Committee for Quality Assurance patient-centered medical home and patient-centered specialty practice accreditation programs. In these models, accountability is centered on the primary care provider and specialist to facilitate the coordination of all care at each point along the care continuum. The patient-centered medical home initially placed the primary care provider at the center of care. The expectation was that access to services would improve, the referral process and communication would be streamlined, duplication of testing would diminish, and fragmentation as well as unnecessary emergency department visits and hospitalizations would be reduced. But primary care providers rely on specialists to provide disease-specific care, and it quickly became evident that patient-centered care would require multidisciplinary collaboration to address the comprehensive needs of patients. To further enhance the structural framework for improving coordination, ASCO has developed the Community Oncology Medical Home model, intended to support coordinated oncology care. In a pilot across seven U.S. practices, implementation of this model was associated with a reduction in hospital admissions, readmissions, and emergency department visits. The program is now being expanded nationally. Both models serve as a framework for making changes in practice to influence coordination and support quality improvement.[50]

With the focus on care coordination and patient-centeredness in accreditation and certification programs, payment models have also begun to change. A shift from a volume- to a value-based focus is occurring, emphasizing synchronous

quality enhancement and cost reduction. Success in this environment requires joint accountability among providers on the care team. This shared stake is likely to affect referral patterns and partnerships between providers as payments are bundled and tied to performance. Adoption of bundled payment care models is increasing, with a recent survey indicating a 31% uptake already among health care providers, highlighting the need for "a comprehensive strategy and plan…to participate in these models."[51]

Providers and payers are increasingly cognizant of a shared interest in coordinating care. The Oncology Care Model, a Centers for Medicare & Medicaid Services payment model, was initiated in 2016 and incentivizes medical oncology practices (via an additional monthly reimbursement) to improve coordination of oncology care.[52] Participation in certification and value-based programs such as the Oncology Care Model is time and resource intensive but is likely to be inevitable. The Oncology Care Model has been recognized as an advanced payment model under the Medicare Access and CHIP Reauthorization Act of 2015 ruling, which will begin to affect provider payments in 2019.[53] Early engagement with these models offers an opportunity to restructure practice to be successful at capturing reimbursements in the future, as well as to enhance patient and caregiver satisfaction and further a dedication to quality, safety, and cost control that distinguish the practice.

Care coordination via models such as the medical neighborhood will require commitment of oncology practices to routine continuous practice analysis and improvement. Establishment of a culture of change through strong leadership is critical to the success of this practice transformation. Care teams will need to buy into the urgent need to change to meet the challenges that complex care delivery poses in a rapidly changing health care environment, including bundled payment models for oncology. Even under promising new models of care delivery that prioritize care coordination for medically complex patients, however, older adults remain at risk. These new models have the potential for great impact, but they are in their infancy, and it will take time to assess and analyze effectiveness. The medical neighborhood model, in conjunction with emerging value frameworks in cancer care, is beginning to form scaffolding for implementation of quality cancer treatment of patients with cancer. However, many gaps remain for older adults.

The Medical Neighborhood and the Continuum of Care

To best facilitate the highest quality cancer care during the entire trajectory of a patient's disease and survivorship, seamless transfer of information and care across all members of the care team must be maintained in a shared model of mutual investment. A considerable barrier to optimizing care into survivorship has been the lack of guidance on management of cancer survivors.[54] Perhaps the most critical element in caring for older patients with cancer will be post-treatment planning. The need for better coordination across the care continuum has led key organizations such as ASCO, the American College of Surgeons (Commission on Cancer), and the Centers for Medicare & Medicaid Services to promote the use of survivorship care plans. Survivorship care plans are implemented longitudinally to facilitate communication among oncologists, patients, caregiver(s), and primary care providers. Data on effectiveness are limited, as survivorship care plans have not been widely adopted because of the time and resources required to develop and validate them.[54] As technology gets smarter, however, survivorship care plans are likely to become a critical element in transitions of care.

Information Technology and Quality Care for Older Patients With Cancer

Information technology, the EMR, and patient-centered care. Advances in health information technology undergird and facilitate all the aims of patient-centered care, including coordinating communication among providers and patients, promoting patient engagement, enriching shared decision making, and enabling smooth transitions along the care continuum. The EMR is the foundation for information technology infrastructure in most health care settings. Far from being a mere repository of patient files analogous to paper charts, modern EMRs have extensive capabilities to support complex care. EMRs as databases can aggregate data at both the patient and population levels, providing an ongoing means for assessment of outcomes. They include multiple tools for communication and data sharing between providers. Many provide patient portals permitting patients to access their chart, communicate directly with providers, and remotely enter patient-reported data. The EMR can be programmed to trigger automated advisories or order sets, enhancing adherence to clinical guidelines and best practices.

Unfortunately, these advantages are offset by several barriers. Perhaps the most important barrier is the lack of interoperability between EMR systems, with EMR platforms offered by numerous vendors.[55] Market competition has entailed financial disincentives for supporting interoperability with other vendors' software. Consensus is building regarding a mandate for interoperability, but efforts are hampered by the lack of standards; providers, for example, have prioritized "custom and alignment with local workflow idiosyncrasies." Fragmentation of care and inconsistent communication remain issues when providers are using different EMR platforms. Moreover, the use of EMRs can actually serve as an impediment to patient-centeredness, increasing the time allocated to data entry at the expense of time spent with patients in shared decision making and elicitation of goals and preferences.[56] Surveys conducted with physicians indicate a high bureaucratic cost and low satisfaction associated with use of an EMR, with tasks such as documentation of meaningful use criteria impeding efficiency and overall care.[57] It is clear that more work needs to be done to standardize interoperability, maximize efficiency, and optimize the end user experience before the full benefits of EMRs for quality care delivery can be realized.

TABLE 2. A Selection of Online Decision-Making Tools for Older Adults With Cancer

Online Decision Tool	Website	What Is Calculated	Ages Included	Comments
ePrognosis	http://eprognosis.ucsf.edu	Overall prognosis/life expectancy; risk/benefit of cancer screening	Varies by tool	Variety of prognostic indices available: by care setting, time frame, quality of evidence; also has U.S. population life expectancy tables
CARG Chemotoxicity	http://mycarg.org/Chemo_Toxicity_Calculator	Risk for chemotherapy toxicity	≥ 65 years	Gives percentage risk of grade 3–5 chemotoxicity
ACS NSQIP Surgical Risk Calculator	http://riskcalculator.facs.org/RiskCalculator	Risks of surgical procedures	All	Built using outcomes from nearly 3 million surgical procedures, reported from 586 hospitals

Abbreviations: ACS, American Cancer Society; CARG, Cancer and Aging Research Group; NSQIP, National Surgical Quality Improvement Program.

Information technology and shared decision making. Decision making among older adults with cancer, particularly those with frailty and/or complex comorbidities, is hampered by the dearth of clinical trial data in this population. Advances in medical informatics capabilities offer another potential source of information in the form of big data from population-based databases. Machine learning and other computational methods can transform databases into learning health care systems that can dynamically adapt to changing input, potentially resulting in more immediate benefits to patients compared with traditional research, which typically yields clinically useful information only after years of data collection and analysis.[58] These systems could be applied at both the population and individual patient levels. Application at the population level (e.g., all older patients with cancer within the system) could permit providers and others to analyze trends and overall quality metrics, and application at the patient level promotes individualized decision making and personalized medicine.

In 2015, ASCO introduced the Cancer Learning Intelligence Network for Quality, a big-data platform that can aggregate and analyze data from EMRs, providing real-world and continually updated data to enhance the quality of care for patients with cancer.[59] By the end of 2016, the database contained more than 1 million distinct patient records from oncology practices across the country. This approach has the potential to increase the availability of information for patients not typically represented in clinical trials, as well as yield data for outcomes beyond traditional survival measures (such as quality of life, toxicity, and functional status).

Other web-based decision tools are currently accessible to oncology providers to assist in decision making for older adults with cancer (Table 2); unfortunately, implementation of these tools into EMR platforms has not yet been achieved. One key piece of information that helps frame discussions about cancer screening or treatment options in older adults is an estimate of life expectancy. Many older adults have competing risks of mortality because of frailty or comorbid conditions and may experience more risk than benefit from some decisions, such as decisions to screen for cancer or to administer adjuvant chemotherapy.[60,61] The ePrognosis website contains multiple brief tools for the assessment of life expectancy for older patients across health care settings, as well as population tables generated from U.S. Census data. Older adults are at higher risk for chemotherapy toxicity compared with younger peers, and a subset of items from the Comprehensive Geriatric Assessment, a set of validated instruments assessing an older person's functioning across multiple domains, has been shown to predict the risk for severe chemotherapy toxicity.[62] The prediction tool, which could be easily completed during a clinic visit, is available at the Cancer and Aging Research Group website. Older age, impaired functional status, and comorbid conditions also increase the risk for surgical procedures used to treat cancer. The American College of Surgeons maintains the National Surgical Quality Improvement Program database, as well as guidelines for the care of older surgical patients. A risk calculator, providing estimates of risk for postoperative complications, readmission, nursing home discharge, and death for a variety of surgical procedures is available. These tools and others are useful adjuncts to help guide discussions with older patients in the oncology clinic.

Information technology and access to geriatric oncology expertise. Another sizable barrier to the provision of quality multidisciplinary care to older patients with cancer is the inaccessibility of geriatric expertise, particularly in rural areas. The number of geriatricians is diminishing, with fewer physicians entering geriatrics training programs each year. Approximately 7,000 geriatricians were in practice in 2008, with a projected need for 36,000 practitioners by 2030.[63] There are insufficient numbers of other personnel with specialized geriatrics training (including physician assistants, nurses, social workers, and physical and occupational therapists) to provide the multidisciplinary care that would benefit many older patients with cancer.

Telemedicine encounters could expand access to specialty care for older adults with cancer, with limited investment in technology. All that is needed is a stable internet connection and Health Insurance Portability and Accountability Act–compliant video-conferencing software to perform a remote interview and assessment of gait, mobility, and functional status, which may adequately substitute for an in-person clinic visit. Patient-reported data could be uploaded via an EMR web-based patient portal. Telemedicine technology has successfully been used to deliver high-quality multidisciplinary care to older adults with other complex health conditions, such as Parkinson disease.[64]

Telemedicine could increase access to care for patients in the community who cannot travel to a large medical center, but the shortage of geriatric specialists remains a drawback. An alternative model, teleECHO (Extension for Community Healthcare Outcomes), partners specialist providers at academic medical centers (hub sites) with providers at satellite (spoke) sites via virtual multidisciplinary roundtables similar to tumor boards.[65] Providers at the satellite sites, often community clinics, bring complex cases for discussion. They receive recommendations accompanied by focused didactics and collaborative learning facilitated by the hub site. This model disseminates knowledge and encourages independence and self-efficacy of providers caring for patients with complex medical needs. This model has been successfully used for 29 separate indications, including geriatric mental health, hepatitis C, diabetes, and palliative care. It is a promising model to consider for geriatric oncology as well.

CONCLUSION

The populations of older patients with cancer as well as those surviving after cancer treatment are growing rapidly, outpacing the ability of the health care system to address their complex longitudinal needs. Recent quality initiatives, such as ASCO's Quality Oncology Practice Initiative, have attempted to set standards for cancer care, and value frameworks have emerged to attempt to codify and measure efficiency of cancer care, often using novel methodologies. However, quality and value remain conceptually nebulous when applied to the care of older adults with cancer, particularly those with complex comorbidities, frailty, or other vulnerabilities. Tied up in the definitions of quality and value are personal preferences about what it means to have a quality of existence and about what is valuable, and the preferences of older adults with cancer are likely to diverge from a sole focus on the traditional endpoints of survival and toxicity.

Further work is needed to address these gaps and to broaden the concepts of quality and value to encompass a patient-centered understanding of the heterogeneity of various populations. Although clinical trial data are very limited for older adults with cancer, particularly for those with comorbidities or frailty, the increasing ability to capture real-time, real-world data and refine them within large learning databases could help address gaps in our determinations of quality and value. Additionally, we can begin building other structures that support a patient-centered model of care delivery. It is already known, from studies in cancer and other complex medical conditions, that certain overarching principles greatly affect quality of care: multidisciplinary input, consistent communication, informed patients, shared decision making, and seamless transitions along the continuum of care. Models such as the medical neighborhood are emerging to integrate these principles and are highly likely to continue to shape health policy discussions and payment models. These models, additionally incorporating advances in health information technology to enhance data capture, communication, and access to care, are compelling options to increase quality of care for older adults with cancer.

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GLOBAL HEALTH

Global Health Initiatives of the International Oncology Community

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OVERVIEW

Cancer has become one of the leading causes of morbidity and mortality in low- and middle-income countries (LMICs), where 60% of the world's total new cases are diagnosed. The challenge for effective control of cancer is multifaceted. It mandates integration of effective cancer prevention, encouraging early detection, and utilization of resource-adapted therapeutic and supportive interventions. In the resource-constrained setting, it becomes challenging to deliver each service optimally, and efficient allocation of resources is the best way to improve the outcome. This concept was translated into action through development of resource-stratified guidelines, pioneered by the Breast Health Global Initiative (BHGI), and later adopted by most oncology societies in an attempt to help physicians deliver the best possible care in a limited-resource setting. Improving outcome entails collaboration between key stakeholders, including the pharmaceutical industry, local and national health authorities, the World Health Organization (WHO), and other nonprofit, patient-oriented organizations. Therefore, we started to observe global health initiatives—led by ASCO, the Union for International Cancer Control (UICC), and the WHO—to address these challenges at the international level. This article discusses some of these initiatives.

Over the past few decades, cancer has become one of the leading causes of morbidity and mortality, not only in high-income countries but also in LMICs, where 60% of the world's total new cases are diagnosed.[1] Although incidence and mortality are decreasing in high-income countries, both are escalating in LMICs because of the increase in risk factors typical of Western countries, such as smoking, excess body weight, physical inactivity, and changing reproductive patterns, with limited resources for control. The challenge for effective control of cancer is multifaceted. It mandates integration of effective cancer prevention, early detection, and comprehensive therapeutic and palliative approaches. In the resource-constrained setting, it becomes challenging to deliver each service optimally.

Governments in LMICs must make difficult decisions regarding priorities for their limited budgets. Health workforces are correspondingly small and unable to cope with the burden of disease. The WHO reports that Sub-Saharan Africa—with 11% of the world's population and 25% of the global burden of disease—accounts for less than 1% of global health expenditure. In contrast, the Americas, with 14% of the worlds' population and 10% of the global burden of disease, account for more than 50% of the global health expenditure.[2] Therefore, different international organizations and societies are working together to help improve access to cancer control worldwide.

The WHO identified the provision of access to detection and treatment of cancer as instrumental to the efforts to control noncommunicable diseases (NCDs) in 2014. This year, WHO's Executive Board agreed to put the topic of cancer resolution on the agenda of the 2017 World Health Assembly for a vote in Geneva in May—a step that highlights the importance of the contribution of cancer control to world health.

ASCO, recognizing its role as a leading oncology society, established the Global Oncology Leadership Task Force to evaluate the state of cancer care in LMICs and international efforts to address urgent needs and to identify areas where ASCO could meaningfully address the needs of international members and their practice. Details are described in the section "ASCO's Global Oncology Leadership Task Force Report on Global Health."

Indeed, resource allocation to funding medicine does not by itself improve cancer care. The issue is more complicated and entails parallel improvement in access to surgery, radiotherapy, imaging, and pathology, as well as the organization and structure of care delivery. Radiation therapy is often perceived as a complex and expensive solution. In Africa, 29 of 52 countries have no radiotherapy facilities at all, and these 29 countries comprise an estimated 198 million people.[3] The UICC convened a Global

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Task Force on Radiotherapy for Cancer Control (GTFRCC) to assess the actual demand for radiotherapy and its expected positive impact on outcome of cases diagnosed in LMICs. The outcome of their assessment and subsequent plans to improve access to radiation therapy is described below in the section "UICC Task Force for Access to Essential Radiotherapy."

When it comes to therapeutic interventions, the challenge starts by accessing and subsequently applying knowledge in low-income countries, while access to the application of knowledge is more likely to be the challenge in middle-income countries. The paradigm shift in the way we approach cancer using the concept that precision medicine translates to unaffordable medicine in the real life practice of physicians in LMICs. Once the promise of a new therapeutic hope (e.g., immunotherapy) is recognized as a new option, registration in a country brings hope, but both physicians and patients alike are struck by the unrealistic price tag.[4] A recent survey of the prices of cancer drugs in high-income countries revealed a difference of 28% and 388% between the highest priced country and the lowest priced country for the same drug.[5] This adds to the risk of countries overpaying by using external price referencing, and it further increases the divergence between price, costs, and value of new cancer medicines. Therefore, each country must have country-specific value-based pricing backed by a legally enforced health technology assessment process.[6]

Although comparison studies showed no correlation between cancer-specific expenditure, including medicines, and outcomes,[7] there is a false impression that these new pricey drugs are the major modality of cancer control and cure.[8] To further complicate this image, most guidelines worldwide include those pricey options as the standard of care. One has to wonder whether the clinical-benefit bar in clinical trials is set high enough to justify approval or at least inclusion in guidelines. The actual value of a new medicine was not addressed in guidelines until lately with the advent of the concept "resource-stratified guidelines" as discussed in this article. This step was pioneered by the BHGI and later adopted by most oncology societies in an attempt to help physicians deliver the best possible care in a limited-resource setting by efficiently allocating resources.

Improving cancer control involves prevention and encouraging early detection and utilization of resource-adapted therapeutic interventions. Implementing the new evidence to improve outcome mandates collaboration between key stakeholders including the pharmaceutical industry, local and national health authorities, the WHO, and other nonprofit, patient-oriented organizations. Improving outcomes does not always mean using the most recently approved drugs or procedures, but the most valuable tool for the option. Value remains a challenge to define in the context of different economic and cultural settings.

KEY POINTS

- **Effective control of cancer is multifaceted, involving effective cancer prevention and encouraging early detection and utilization of resource-adapted therapeutic and supportive interventions.**
- **Guidelines that consider not only evidence of efficacy and safety but also the availability of resources are necessary to optimally fulfill health care needs and maximize outcomes in LMICs and health care systems.**
- **ASCO's Global Oncology Leadership Task Force has evaluated and made specific recommendations to the Board of Directors for improving global oncology.**
- **Equity of access for patients is an imperative, as 80% of patients with cancer across the world are in LMICs but have access to only 5% of global radiotherapy resources. The associated up-front costs of developing radiotherapy services are recouped within 10 to 15 years.**
- **The key mission of the WHO's work in cancer control is to promote national cancer control policies, plans, and programs that are harmonized with strategies for noncommunicable diseases and other related health concerns.**

ASCO'S GLOBAL ONCOLOGY LEADERSHIP TASK FORCE REPORT ON GLOBAL HEALTH

NCDs include chronic illnesses of the heart and lungs, as well as diabetes and cancer. Globally, 38 million deaths from NCDs occur annually, the majority of which are in LMICs, and 42% of these are considered premature deaths because of inadequate health care. In 2011, the United Nations' High-Level Meeting on Non-Communicable Diseases declared that NCDs should be a priority for nations' disease prevention and control policies, and, in 2014, the United Nations (UN) recommended that nations set NCD target commitments. The WHO further specified the provision of basic access to detection and treatment of cancer and to palliative care as integral to these efforts. By 2016, 60% of countries had established time-bound NCD target indicators.[9]

Under the direction of the ASCO Board of Directors, the International Affairs Department developed innovative programs to address the needs of ASCO's growing international membership and the patients they care for, leading to a major expansion of ASCO's global health efforts between 2013 and 2016. To prepare for the next phase of development, the ASCO Board of Directors established the Global Oncology Leadership Task Force—comprising ASCO past presidents, board members, and ASCO members with relevant experience—to evaluate the state of cancer care in LMICs and international efforts to address urgent needs, as well as to identify areas where ASCO could meaningfully impact the trajectory of global oncology.

Key Findings

1. ASCO's efforts should be framed by its traditional focus on education and professional development, quality improvement, and promotion of research. More specifically, professional development includes training and building an adequate multidisciplinary

workforce including oncologists, pathologists, nurses, technicians, and potentially primary health care providers of cancer care. Domestically, ASCO should drive acceptance of global oncology as a recognized academic field and partner with professional societies and networks of U.S.-based ASCO members who promote oncologic development in their original countries of origin. As much as it is doing in the United States, ASCO should promote quality improvement, access to affordable care, and research in implementation science as well as clinical trials, with recognition and respect for cultural nuances.

2. Different models apply to addressing the needs of low- versus medium-income countries. Generally, medium-resourced countries are likely to have stable geopolitical environments, a favorable health care infrastructure to build on, and a growing middle class with income to support quality care. In such countries, ASCO can move quicker. Although low-income countries present a more challenging environment with more fundamental needs, with concerted effort and close collaboration with other organizations, major impacts can be achieved.
3. To achieve sustainable improvements at scale, ASCO must take a systems approach. This entails a long-term commitment to a willing health care system and a comprehensive approach that includes multidisciplinary and multi-stakeholder engagement including local and national government ministries, such as Health and Finance, as well as international organizations such as the UN, WHO, International Agency for Research on Cancer, and UICC. Within the United States, federal agencies including the National Cancer Institute's Center for Global Health, U.S. Agency for International Development, and U.S. Department of State have interests in global health efforts originating in the United States. As U.S. cancer centers develop global health in an academic environment, they will often partner with health care entities in low-income countries and provide another opportunity for ASCO collaboration.[10]

Recommendations

The following are the Global Oncology Leadership Task Force's recommendations to the ASCO Board of Directors and the initial steps now being taken in direct response to the guidance:

1. **Promote the recognition of global oncology as an academic field.** A joint task force of the International Affairs Committee and the Professional Development Committee is being formed that will identify barriers and opportunities to promoting global oncology as an academic career path. A summit meeting to gather stakeholder feedback is being contemplated.
2. **Support rigorous research in the field of global oncology.** Adding to its International Innovation Grant offerings, ASCO's Conquer Cancer Foundation will be developing early-career research awards for innovative research in global oncology.
3. **Train nonspecialists in LMICs in cancer screening and prevention services.**
4. **Develop the next generation of national oncology leaders as strong and effective ASCO members**. ASCO will continue its grants programs, such as Leadership Development Program and IDEA, and the mentoring of authors submitting papers to the *Journal of Global Oncology*.
5. **Assert ASCO's global role as an arbiter of cancer care quality**. ASCO's Quality Oncology Practice Initiative (known as "QOPI") certification program is our principal mechanism by which U.S. practices measure quality of care and are provided feedback to evaluate their performance. Prior to 2017, QOPI participation with the independent auditing that is required for certification had been available only in Greece on a pilot basis; ASCO will expand to a full certification program in Brazil, Spain, and other countries. Other previously U.S.-based quality programs such as the Quality Training Program will also undergo international expansion.
6. **Pursue a systemic approach to quality improvement**. ASCO is collaborating with the College of American Pathologists to delineate the steps toward capacity building for pathology diagnosis and prognostic/predictive characterization of malignant lesions occurring in low-income environments. ASCO is also working with the UICC on a program called the City Cancer Challenge, launched at Davos earlier this year. This initiative will support improvement in cancer care delivery in selected cities in low-income countries, working together with local city governments and partners, and with ASCO members local to those cities. ASCO will continue to expand our national efforts in Henan Province, China, Vietnam, and Honduras.

Economists assess a nation's wealth by measuring its net economic productivity divided by the number of its citizens. In theory, this ratio, the per capita income, reflects the financial resources a country can bring to address societal needs and is precisely how the World Bank categorizes countries as low income or middle income. Clearly, for these countries to advance the health of their populations, external resources are necessary. For ASCO and other organizations to succeed as a vehicle for improving global health, we must attract the financial support of like-minded donors, including high net worth individuals and their charitable foundations, and international companies that may not be in health care. To succeed, we must embrace a larger world.

RESOURCE-STRATIFIED GUIDELINES: CONTROLLING CANCER STEP BY STEP

Cancer incidence is increasing at a fast pace around the world, with a disproportionate share of cancer cases and deaths occurring in LMICs, which generally have limited resources available to treat the disease, leading to major disparities in cancer control across the world.[11,12] The ratio

between cancer deaths and the total number of cases is 47% in high-income countries and 66% in LMICs, which invest a fraction of what high-income countries do in cancer prevention and management. In one study, the economic burden from cancer in the United States, United Kingdom, and Japan varied between $183 and $460 per patient, while in South America, India, and China, the economic burden was between $0.54 and $7.92 per patient. Overall, high-income regions spend five to 10 times more per capita than LMICs.[13] In addition to a relative lack of resources, these differences exist because policy makers in LMICs do not always see cancer as an important public health issue.

Health care systems with limited resources must invest in cancer control in a cost-effective, stepwise fashion to achieve the best results in the shortest amount of time with the most rational allocation of resources. This means clinicians may need to provide less-than-ideal care to patients when diagnostic and treatment resources are lacking, despite knowing the optimal management strategy based on guidelines developed in wealthier countries. For this reason, it is important to prioritize best practices that will most effectively fill the health care needs in limited-resource regions, where patients commonly present with more advanced disease at diagnosis, and to provide resource-allocation guidance to maximize outcomes systematically.

Several groups, such as the BHGI, Asian Oncology Summit, National Comprehensive Cancer Network (NCCN), and ASCO, have taken the initiative to develop resource-stratified guidelines to help fill this gap. By collecting and interpreting evidence and categorizing it by resource availability, these guidelines provide recommendations for countries on how to improve their situation and advise physicians on how to provide the best care possible within limited-resource regions.

The Breast Health Global Initiative

Breast cancer is increasingly common in LMICs, and treatment can significantly improve survival. In 2002, in an effort to improve outcomes, BHGI created an international health alliance to develop evidence-based guidelines for countries with limited resources. BHGI serves as a program for international guideline development and as a network for clinicians, governmental health agencies, and advocacy groups to translate guidelines into feasible policy and practice. BHGI collaborated with 12 national and international health organizations, cancer societies, and nongovernmental organizations to host BHGI Global Summits. BHGI initially stratified resources in basic, limited, enhanced, and maximal levels, and then went on to develop and update resource-sensitive, culturally appropriate, evidence-based guidelines where available, during the 2002, 2005, and 2007 Global Summits. Guidelines were published in 2003 as a theoretical treatise on international breast health care, and they were expanded into a fully comprehensive and flexible framework to permit incremental improvements in health care delivery, based on outcomes, cost, cost-effectiveness, and use of health care services in 2006.

From 2007 on, the initiative has focused on the implementation of the guidelines with pilot educational projects in Asia, Latin America, and Africa known as learning laboratories. The 2010 Global Summit focused on optimizing the delivery of health care, and the 2012 Global Summit focused on palliative care and survivorship. As of 2014, authors associated with BHGI have published more than 200 related articles, and more than 500 papers from non-BHGI authors have cited the guidelines and the initiative.[14]

BHGI presents recommendations based on a four-tiered, resource-stratified system: basic, limited, enhanced, and maximum levels. Basic level indicates fundamental or core services that are necessary for any cancer system to function (e.g., mastectomy). Limited level includes second-tier services that intend to produce major improvements in outcomes and are achievable with scant financial means and modest infrastructure (e.g., tamoxifen as adjuvant therapy). Enhanced level includes third-tier services that are optional in a resource-constrained setting but are important and should produce further improvements in outcome and increase the number and quality of therapeutic options and choices for patients (e.g., aromatase inhibitors). Maximum level represents services that might be used in settings with many resources or those that might be recommended in cancer guidelines that do not account for resource constraints. These should be judged lower priority than resources or services listed in the basic, limited, or enhanced categories, based on their greater cost or impracticality for broad use in a resource-limited environment (e.g., colony-stimulating factors in adjuvant therapy). To be useful, resources at the maximum level always depend on the existence and functionality of all lower-level resources.[15-20]

Resource-Stratified Guidelines and Consensuses in Asia

Using the four-tiered, resource-based approach pioneered by BHGI, the Asian Oncology Summit, under the auspices of *Lancet Oncology*, led the development of a series of consensuses that, although based in and created for Asia, serve as an added model for use in both LMICs and high-income countries around the world. These consensuses, which range from non–small cell lung cancer and breast cancer to nasopharyngeal and gastric carcinomas to screening and palliative care, were created with preparatory work before and during the Asian Oncology Summit sessions between 2009 and 2013. Like the BHGI guidelines before them, these guidelines give individual clinicians a practical framework for treating patients and provide policymakers insight into how to plan resource-appropriate cancer control. One of the innovative aspects—of the colon cancer guidelines, in particular—was the formal use, review, and development (when none were available) of health-economics evaluations and their incorporation into consensus development using WHO cost-effectiveness criteria for the inclusion of diagnostic and treatment technologies at each resource level. A full list of the Asian Oncology Summit guidelines is included in the Sidebar.[21]

SIDEBAR. Asian Oncology Summit and *Lancet Oncology* Resource-Stratified Guidelines and Consensuses[21]

1. Management of gastric cancer in Asia: Resource-stratified guidelines
2. Management of hepatocellular carcinoma in Asia: Consensus statement from the Asian Oncology Summit 2009
3. Management of colon cancer: Resource-stratified guidelines from the Asian Oncology Summit 2012
4. Management of HER2-positive breast cancer in Asia: Consensus statement from the Asian Oncology Summit 2009
5. Management of endometrial cancer in Asia: Consensus statement from the Asian Oncology Summit 2009
6. Management of kidney cancer in Asia: Resource-stratified guidelines from the Asian Oncology Summit 2012
7. Management of prostate cancer in Asia: Resource-stratified guidelines from the Asian Oncology Summit 2013
8. Management of the neck after chemoradiotherapy for head and neck cancers in Asia: Consensus statement from the Asian Oncology Summit 2009
9. First-line systemic treatment of advanced-stage non–small cell lung cancer in Asia: Consensus statement from the Asian Oncology Summit 2009
10. Management of sarcoma in the Asia-Pacific region: Resource-stratified guidelines
11. Management of B-cell non-Hodgkin lymphoma in Asia: Resource-stratified guidelines
12. Management of adult and pediatric acute lymphoblastic leukemia in Asia: Resource-stratified guidelines from the Asian Oncology Summit 2013
13. Management of multiple myeloma in Asia: Resource-stratified guidelines
14. Management of T-cell and natural killer cell neoplasms in Asia: Consensus statement from the Asian Oncology Summit 2009
15. Cancer prevention in Asia: Resource-stratified guidelines from the Asian Oncology Summit 2013
16. Supportive, palliative, and end-of-life care for patients with cancer in Asia: Resource-stratified guidelines from the Asian Oncology Summit 2012.

NCCN Framework for Resource Stratification of NCCN Guidelines

Based on the same principles detailed above, the NCCN created a framework to guide evidence-based adaptation to available clinical treatment resources. These were also divided into four tiers—basic, core, enhanced, and NCCN guidelines—and serve as a tool for health care providers to identify treatment options that will provide the best possible outcomes given specific resource constraints.

According to the NCCN, their framework "outlines a rational approach for building cancer management systems to provide the highest achievable cancer care by applying available and affordable services in a logical sequence. Each NCCN Framework builds on the one before it, with incremental changes to the allocation of resources, providing a structure for improving cancer care. Treatment recommendations applicable to each NCCN Framework can be viewed within the context of the NCCN Guidelines."

Currently, the diseases for which the NCCN framework is available include bladder cancer, breast cancer, cervical cancer, gastric cancer, head and neck cancers, cancers of the lip and oral cavity, hepatobiliary cancers, non–small cell lung cancer, pancreatic cancer, and prostate cancer.

ASCO's Resource-Stratified Guidelines

Building on these experiences and on its own record of accomplishment in guideline development, ASCO is currently working on resource-stratified recommendations as well, starting with three examples in cervical cancer. This unified effort covered the whole spectrum of the disease, divided in three areas: primary prevention, secondary prevention/screening, and work-up and treatment, which also included survivorship, supportive care, and palliative care. Under the leadership of a Guidelines Advisory Committee, ASCO started to expand this experience into a planned series of resource-stratified guidelines continuing with palliative care and colorectal cancer.[22,23]

UICC TASK FORCE FOR ACCESS TO ESSENTIAL RADIOTHERAPY

The 2011 UN Resolution of NCDs states that they "constitute one of the major challenges for development in the 21st century, which undermines social and economic development throughout the world and threatens the achievement of internationally agreed development goals." Cancer is a significant component of the global NCD burden, with incidence estimated to rise to 24.6 million new cases by 2030.

A robust response is therefore essential, and radiotherapy is a key component but vastly under-resourced. The International Atomic Energy Agency data show that only three countries in Africa come close to the recommended standard of access to radiotherapy.

The GTFRCC Lancet Oncology Radiotherapy Commission[24] was created in 2013 as an international collaboration between oncologists, physicists, economists, and industry and global health experts to understand the global demand for radiotherapy and to quantify the investment needed to achieve global equity in access by 2035. The GTFRCC explored:

1. Future (until 2035) global burden of cancer and the demand for radiotherapy: Using a linear scale-up model, the Commission employed these estimates to calculate total life-years gained from expanding access to radiotherapy to meet 100% of global demand by

2035, as well as increases in economic productivity from this improved life expectancy.
2. The facilities, equipment, and personnel required to deliver a single radiotherapy treatment: These estimations were used to calculate the costs of creating and delivering the required global radiotherapy capacity.
3. Two different models (nominal and efficiency) were used to estimate the costs and benefits of radiotherapy investment.

The Commission's key finding is that expanding access to radiotherapy not only saves and prolongs lives but also delivers notable economic returns. The GTFRCC estimated that radiotherapy is recommended in 50% of cancer cases in LMICs, which equates to approximately 7 million patients with cancer, based on 2012 data. This need is forecasted to increase to 12 million cases warranting radiotherapy in 2035. Radiotherapy is crucial intervention for many cancers. The projected increase in cancer incidence underscores the urgency with which countries must meet the demand. The continuing disparity in access to radiotherapy is being perpetuated by the misconception that it is too costly or impractical to successfully implement in LMICs.

To explore radiotherapy costs further the commission divided them into two components: (1) capital costs to develop a new facility, such as building, equipment, and training of new staff; and (2) operating costs to deliver treatments once a facility is established. Although salaries constitute most of the costs in high-income countries, capital costs of equipment are the major cost drivers in LMICs. The up-front costs of infrastructure, equipment, and training to create a radiotherapy center and services for a LMIC was estimated at $350 per session or a one-off investment of $5 million to benefit 800 to 1,000 patients with cancer per year. Although radiotherapy requires a large initial investment, the benefits of investment are realized over 10 to 15 years. Moreover, subsequent operational costs are predictable and are comparatively low in LMICs.

The cost of scaling up radiotherapy to meet 100% of global demand by 2035 in LMICs is estimated at $184 billion. Moreover, if radiotherapy capacity were increased incrementally, 26.9 million life-years could be saved in LMICs, resulting in a net economic benefit of $278.1 billion. The models used to develop these estimates were very conservative and, as such, do not account for key efficiency savings that countries could benefit from. These efficiencies include longer operating hours for machines and price reductions through purchasing planning.

The GTFRCC also noted that, although not factored into the economic model, radiotherapy also provides immense value for patients through the provision of palliative care and pain relief, which can significantly reduce suffering and disability caused by cancer. Although a direct economic benefit is not easy to quantify, terminally ill patients, their loved ones, and society qualitatively benefit from effective control of distressing symptoms at the end of life.

Radiotherapy investment also brings with it structural benefits across the health system. The GTFRCC recognizes that the delivery of radiotherapy requires a strong enabling environment, but this investment in radiotherapy processes can help to strengthen health care delivery. For example, effective radiotherapy requires surgery and pathology services to enable correct diagnoses alongside improved public education about cancer prevention and symptoms. The organizational and operational frameworks that support the delivery of these services are central to a functioning health system. Improved regulatory systems for quality and safety assurance, along with the training required to deliver this, would be also relevant to all medical practitioners and help strengthen the system as a whole.

Technologic innovations could enable the development of distance or e-learning platforms to help meet the shortfall in skilled staff or mentoring for oncology professionals. Cloud computing could help disseminate best practices faster and facilitate diagnoses and reporting through telemedicine systems.

Environmentally friendly technologies could help reduce the burden of radiotherapy machines on local power networks. Innovative financing for radiotherapy investments, such as guarantees by development banks, could be used to mitigate investment risk. Health planners could benefit from drawing on numerous models—such as strategies used to mobilize and pool resources for AIDS, tuberculosis, and malaria—to fund radiotherapy investment.

WHO EFFORTS TO SUPPORT GLOBAL CONTROL OF CANCER

WHO has an ambitious but compelling mandate to address the growing crisis of NCDs, which formally began at the UN's 2011 High-Level Meeting on Non-Communicable Diseases, leading to the 66th World Health Assembly endorsement of the "WHO Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013–2020" (resolution WHA66.10).[25] In 2015, the UN's Sustainable Development Goals were adopted unanimously by its 193 member states. Among its 17 goals and 169 targets is target 3.4: a one-third reduction in preventable deaths from NCDs by 2030.[26]

The next high-level UN meeting on NCDs takes place in 2018, and progress on NCDs thus far has been slower than anticipated. The 2015 WHO NCD Country Capacity Survey[27] and the cancer control data presented in the Global Cancer Snapshot[28] illustrate the magnitude of the challenges in achieving cancer control targets, particularly in low- and lower-middle income countries. For example, nationwide implementation and population coverage of the HPV vaccination and cervical cancer screening remain unacceptably low, especially in the WHO African region and in countries with a high burden of HIV/AIDS—an important risk factor for cervical cancer.

The WHO has an important role to play in global cancer control, providing guidance and technical support for countries to address the growing cancer burden. With its headquarters in Geneva, as well as six regional offices and more

than 150 country offices, the WHO is uniquely positioned to help guide countries in the prevention and management of disease and to navigate an increasingly complex, interconnected, global health landscape. Among the WHO's core functions are to develop norms and standards (i.e., guidelines) and to provide technical assistance at the country level to improve the health of populations.

The newly updated WHO website's main cancer page addresses this subject[29]: "The key mission of WHO's work in cancer control is to promote national cancer control policies, plans and programs that are harmonized with strategies for noncommunicable diseases and other related health concerns. Our core functions are to set norms and standards for cancer control including the development of evidence-based prevention, early diagnosis, screening, treatment and palliative care programs as well as to promote monitoring and evaluation through registries and research that are tailored to the local disease burden and available resources."

In this context, in collaboration with the International Agency for Research on Cancer and the International Atomic Energy Agency and its Program of Action for Cancer Therapy, along with the National Cancer Institute's Center for Global Health (now a WHO Collaborating Center), the UICC, the International Cancer Control Partnership, and other civil society organizations, the WHO has risen to this challenge in leading the development and dissemination of evidence-informed guidance in cancer control. Some recent examples include the following:

- In 2015, with support from UICC, the WHO released an updated Model List of Essential Medicines with an additional 16 new cancer medicines.[30]
- UNAIDS in partnership with the WHO, the UN Interagency Task Force on NCDs, and the Global Coalition on Women and AIDS launched a new guide, "HIV, HPV, and Cervical Cancer: Leveraging Synergies to Save Women's Lives" at the 2016 International AIDS Conference in Durban, South Africa. This document highlights the need for more attention and better integration of health services for women living with HIV/AIDS who are at increased risk of developing cervical cancer, an AIDS-defining illness.[31]
- On World Cancer Day (February 4, 2017), WHO Director General Dr. Margaret Chan launched the "Guide to Cancer Early Diagnosis"[32] to provide health policy makers, planners, and managers with guidance to facilitate timely and equitable access to cancer care.

A new manual, the WHO "List of Priority Medical Devices for Cancer Management," is due for release later in 2017, and a major revision to the costing analysis for NCD interventions (known as "Appendix 3" of the WHO NCD Global Action Plan) is expected to be approved at the next World Health Assembly.

The WHO also works with its member states and international organizations to improve access to pain control and palliative care.[33] A new guideline for the management of cancer pain is in progress.

Lastly, in response to the needs expressed by member states, the WHO has partnered with the International Agency for Research on Cancer, International Atomic Energy Agency, UNAIDS, UN Population Fund, UNICEF, and UN Women in a new UN Global Joint Programme on Cervical Cancer Prevention and Control[34], under the auspices of the UN Interagency Task Force on NCDs.

CONCLUSION

Improving the outcome of patients with cancer is not guaranteed by the success of intervention in a phase III trial; it is the access to that intervention that makes the difference. This challenge can be overcome by international collaboration between key stakeholders, including the pharmaceutical industry, local and national health authorities, the WHO, and other nonprofit, patient-oriented organizations.

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Biomarker Testing for Personalized Therapy in Lung Cancer in Low- and Middle-Income Countries

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OVERVIEW

There have been many important advances in personalized therapy for patients with lung cancer, particularly for those with advanced disease. Molecular testing is crucial for implementation of personalized therapy. Although the United States and many Western countries have come far in the implementation of personalized therapy for lung cancer, there are substantial challenges for low- and middle-income countries (LMICs). Globally, the LMICs display great heterogeneity in the pattern of implementation of molecular testing and targeted therapy. The current review presents an attempt to identify the challenges and obstacles for the implementation of molecular testing and the use of targeted therapies in these areas. Lack of infrastructure, lack of technical expertise, economic factors, and lack of access to new drugs are among the substantial barriers.

Globally, lung cancer has the highest mortality rate among all cancer types. Each year, approximately 1.8 million people are diagnosed with lung cancer and 1.6 million people will die of the disease.[1,2] Approximately 58% of all global lung cancer cases occur in LMICs.[3] Although the use of tobacco is the main cause of lung cancer in the Western world, other factors, such as use of local tobacco products, pulmonary infections, and other environmental factors including asbestosis, may cause lung cancer rates to be higher in LMICs. These factors may also play a role in the varying prevalence of specific molecular drivers important for new targeted therapies. Additionally, health expenditure and the mortality-to-incidence ratios of cancers seem to be correlated in many low- to middle-income areas, including in Central and Eastern Europe.[4,5]

Much progress has occurred in the treatment of lung cancer, particularly for patients with advanced non–small cell lung cancer (NSCLC), because of the development of molecularly targeted therapies for specific markers, such as *EGFR* mutations and *ALK* and *ROS1* fusions, and immunotherapy. The life perspective has changed dramatically for the subgroups of patients whose tumors harbor these genomic rearrangements and for patients who respond to novel immunotherapeutic regimens.

In the current era of personalized medicine, advanced guidelines, sophisticated diagnostics, and tailored oncogene-driven therapy, the everyday work of oncologists, pathologists, and other health care providers treating lung cancer in countries with low- and middle-income environments face numerous challenges and require perspicacious solutions. Absence of routinely available biomarker testing and unavailability of access to new therapies make most of the acknowledged guidelines for treatment of advanced lung cancer inapplicable in the countries with limited income.

Not much scientific data have been gathered on this topic that focus on LMICs. Most recently, data were presented from a survey of oncology practices on the treatment of lung and breast cancers in India, China, Thailand, Philippines, Malaysia, Vietnam, Indonesia, Argentina, Brazil, Chile, and Mexico, among other countries.[6] Among 139 of the survey respondents, 58% claimed to always use guidelines to support their clinical decisions; however, 75% of the respondents who use international guidelines modify them in some way to treat their patients.

This article reviews problems reported in different LMICs by region and aims to provide a path to overcome the barriers to implementation of molecular tumor testing and personalized therapy for patients with lung cancer.

LATIN AMERICA

Most of the 33 Latin American/Caribbean sovereign states are categorized as middle-income countries and are home to approximately 650 million people. The region is very

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heterogeneous, ranging from the populous country of Brazil to small islands in the Caribbean.

Lung cancer diagnosis and mortality have high incidence in the area, although limited published information is available for most countries in this region. Best-of-care chemotherapy is in use in Latin America. Recently, oncologists in Mexico, Colombia, Brazil, and Argentina, among other countries, have been exerting an arduous effort to offer state-of-the art treatment to their patients. That includes fighting for local approval and access to novel agents and for implementation of molecular testing that can support the proper selection of patients who are likely to benefit from several of these particular drugs or regimens.

The frequency of molecular alterations in patients with lung cancer shows regional heterogeneity. *EGFR* mutations have been reported on average in 23% to 26% of patients with NSCLC, a frequency that is between that of Caucasian and Asian populations.[7,8] However, in individual countries, these frequencies varied largely,[7-11] ranging from the lowest levels in Bolivia (≤ 10%), Venezuela (≤ 10%), and Argentina (14%), to intermediate levels in Colombia (25%), Brazil (26%–30%), Panama (27%), Costa Rica (31%), and Mexico (34%), to the highest levels in Peru (33%–51%). This variation in frequency of *EGFR* mutations in patients in Latin American countries has been related to the heterogeneity of ethnicity and ancestry migration. In Argentina, for example, the population is predominantly Caucasian, and Peru has been a destination of Asian migration. Environmental factors have also been related to the heterogeneity of *EGFR* mutations. Conversely, frequencies of *ALK* fusions are less variable and have been reported on average in approximately 6% of patients with NSCLC, ranging from 8% in Mexico, 4%–6% in Argentina, 5% in Colombia and Costa Rica, and 4% in Brazil.[12-14] Few other molecular drivers such as *KRAS* and *BRAF* have been investigated in Latin American populations.[9,15]

Several initiatives are under way and represent important first steps toward scaling up implementation of lung cancer precision medicine in Latin America. One of these initiatives, sponsored by the International Association for Study of Lung Cancer, is examining the conditions of molecular testing in support of targeted therapies.[16] This investigation preliminarily identified that there are numerous diagnostic laboratories, mostly in academic settings in the larger cities of the most populated countries (Brazil, Argentina, Mexico, Colombia), offering a variety of molecular tests in resected or biopsied tissue. These tests mostly cover analysis of gene mutations (*EGFR*, *KRAS*, and *BRAF*) and gene fusions or overexpression (*ALK*, *ROS1*) in single assays or multiplexed panels. However, tests for immunotherapy biomarkers or analyses of liquid biopsies are only rarely available. These later assays, as well as large mutation panels, have been outsourced to the United States or countries of the European Union and are mostly covered by patients themselves.

One major complaint from practicing oncologists in Latin America is the restricted access to novel drugs that have proven efficacious in international settings and are in use in high-income countries. It is common that these new agents remain unapproved by national health regulatory agencies for long periods, largely because of complex bureaucracy or the country's inability to cover their costs in the public health systems once they are approved. Therefore, the physicians commonly cannot follow the proposed international guidelines (e.g., guidelines from the National Comprehensive Cancer Network, American Society of Clinical Oncology, etc.) and do not have national or local guidelines to follow in their place.

Consequently, the major sponsor of novel molecular testing and therapy in the Latin American region has been the pharmaceutical and biotechnological industries through clinical trials or in routine clinical practice. Although these settings may help a subset of eligible patients in the short term, they only benefit a restricted number of patients and come with substantial burdens. The liabilities include establishing potential conflicts of interest for the physicians and damaging the efforts for implementation of local testing because the companies usually outsource the testing to established, central laboratories located in high-income countries. It may also discourage and weaken the local and regional oncology leadership who will be far away from the trials' primary investigators, who are usually based in the high-income countries.

From the molecular diagnostic point of view, a high level of enthusiasm has been recognized among laboratory directors in several Latin American countries for moving to the new era and facing the new challenges. Nevertheless, few laboratories have found ways to circumvent the financial difficulties and have implemented adequate infrastructure

KEY POINTS

- **Lung cancer has high prevalence in LMICs, and the frequency of abnormal molecular drivers is largely heterogeneous among those countries.**
- **Overall, routine biomarker testing for lung cancer is confined to a few large hospitals in a few large cities. Most diagnostic laboratories offer few tests for EGFR mutations and ALK rearrangement; even fewer test for immunotherapy markers.**
- **The major challenge of implementing biomarker testing for personalized therapy for patients with lung cancer in LMICs, is the economic barrier, which affects technical infrastructure, including the training of expert personnel and the implementation of sophisticated technologies.**
- **The lack of access to new targeted therapy agents, which commonly are not approved by regulatory agencies in LMICs for many years after their full use in developed countries, is also a negative impacting factor of implementation of molecular testing in those countries.**
- **Despite peculiarities in specific countries and geographical areas, there is a substantial number of obstacles to biomarker testing for personalized therapy in lung cancer that are shared by numerous LMICs. A collaborative effort could help overcome some common barriers.**

for assay validation and competency test for technical personnel. The majority of laboratories would benefit from multiple improvement factors such as a larger professional network, better training, shared technical expertise, and access to scientific and technical advice from experts involved in the field for many years and who hold a great level of experience.

Another difficulty frequently cited by physicians in Latin America is the insufficiency of scientific and technical literature in their two prevalent native languages, Spanish and Portuguese. Nearly all information is published or presented in English, and the proficient access to this language by most health care professionals is suboptimal to understand the information, to formulate questions, and to properly troubleshoot their daily activities. In addition, it has been difficult to obtain large numbers of responses to surveys provided in English. Moreover, there is a compelling theory that results of these surveys are biased toward the personal experience of professionals with greater level of English language skills, rather than being representative of the local and regional experience.

MIDDLE EAST

According to a 2001 publication by the Middle East Consortium (MECC),[17] which includes Egypt, Cyprus, Jordan, and Israel, the age standardized rates of lung cancer in comparison with U.S. Surveillance, Epidemiology, and End Results Program (SEER) data were half the age standardized rate for Israel (Arab and Jewish populations) and almost one-third and one-fifth for Egypt, Cyprus, and Jordan. The incidence was higher in males than females. Among the male population, it was highest in the Israeli Arab population followed by the Israeli Jewish, Cypriot, and Jordanian populations, with the Egyptian population having the lowest incidence. The incidence of lung cancer among females from the MECC data was much lower than that from the SEER data. For example, lung cancer incidence was higher in the Israeli Jewish population from the MECC data, which was one-third that of females from the SEER data. In the MECC data, the incidence of lung cancer in females was half that of the Israeli Jewish population, from the Jordanian and Egyptian populations having the lowest incidence. Pathologic subtypes showed that adenocarcinoma was more frequent in females from the Cypriot population, with an incidence of almost 78%, followed by the Israeli Arab, Egyptian, Israeli Jewish, and Jordanian female populations.

In a more recent publication in 2014,[18] lung cancer was the third or fourth most commonly diagnosed cancer in Egypt, representing 5% to 7% of all cancer incidences. However, no stratification was published according to pathologic diagnosis. The combined incidence of lung cancer in both sexes was 4.2% and the incidence among females was very low.

There is a large heterogeneity of scenarios regarding molecular testing for lung cancer among Middle Eastern countries because not all of them are categorized as low- or medium-income. In Saudi Arabia, Kuwait, Oman, and Qatar, for instance, there are no difficulties in performing *EGFR* mutation testing and supplying the adequate medication. Conversely, in other countries, tests are not offered or are only offered under the sponsorship of pharmaceutical companies. This is the situation, for instance, in Egypt, where pharmaceutical companies supply the testing for *EGFR* mutation free of charge for tissue samples, but not for liquid biopsy. Initially, tumor samples are sent abroad for testing, but recently a diagnostic laboratory was accredited and now the turnaround time is 5 to 7 days instead of 2 to 3 weeks. This model, however, is only applicable to the private sector in which the patient is covered by private or employer-provided insurance. Other molecular tests are not offered, because the governments do not supply targeted drugs.

A strategy to overcome the drug approval barrier and convince the governments to support anti-*EGFR* therapy would be to perform a cost-analysis study showing the pros and cons compared with chemotherapy. The study should stress the importance of the quality of life, clinical response and outcomes, and pricing. In Egypt, for instance, the drugs are available at relatively lower costs than in other countries. However, an important variable in this cost analysis remains missing, which is the incidence and prevalence of *EGFR* mutations in NSCLC, because there are no such demographic studies in the Middle East.

For the future, a demographic data collection to detect the prevalence and incidence of *EGFR* mutations in the region, should be mandatory to properly plan future trials. Moreover, educational events regarding the importance and management of *EGFR* mutations are critical to the pulmonologists and oncologists in the region. These educational events should cover comparison with chemotherapy regarding quality of life and clinical outcomes.

SOUTHEAST EUROPE

Southeast Europe has the highest incidence and mortality of lung cancer in Europe. In many countries of the region, antismoking campaigns have had limited effects, failing to efficaciously decrease the smoking rate. Noninvasive and invasive diagnostic techniques for lung cancer are, in most cases, available but not easily accessible for the whole populations and treatment options for advanced-stage lung cancer are harshly limited.

One of the cornerstones for initiation of actions directed toward improvement of this obviously gloomy situation is to increase the knowledge of the frequency of common driver mutations in patients with lung cancer. Although scientific studies of the region are scarce, some recent reports are revealing the data on common mutation frequencies.[19-21]

In most of the Southeast European countries, biomarker testing is sponsored by the pharmaceutical industry, sometimes covering entire testing technology. These companies also commonly cover the acquisition of laboratory equipment to conduct polymerase chain reaction (PCR) and automatic immunostainers, whereas staff labor is typically reimbursed from government-held health care insurance. These technical obstacles are closely followed by the lack of approved drugs. In summary, biomarker testing for lung cancer

in the region is almost completely dependent on industry donations, and although it may be reliable and sustainable, it is dependent on global market decisions.

In the two largest countries of the region that account for more than 10 million inhabitants, Serbia and Croatia, the lung cancer biomarker testing situation is similar. In Serbia, *EGFR* testing is provided for all patients with stage IIIB and IV lung adenocarcinoma and is sponsored by pharmaceutical companies. Testing technology in Serbia is usually provided by institutions and available in only two large tertiary centers. First- and second-generation tyrosine kinase inhibitors (TKIs) are available and reimbursed as first- and second-line therapy of stage IIIB and IV *EGFR*-positive lung adenocarcinomas. T790M test kits are provided by the industry and an anti-T790M mutation agent is available through a special program. ALK immunohistochemistry (IHC) is not routinely performed outside of research and it is available in only one center, and ALK inhibitors are not reimbursed in Serbia. PD-1/PD-L1 testing is currently not available in Serbia outside of the clinical trial setting. However, because an immunotherapy program was initiated during first half of 2017, the IHC tests are registered and will be available soon. Unfortunately, PD-1/PD-L1 inhibitors for lung cancer are still not reimbursed. *ROS1*, *KRAS*, and other druggable mutation tests are not routinely performed in Serbia.

Biomarker testing conditions are similar in Croatia. First- and second-generation TKIs are available only as second-line treatment, and testing and inhibitors for the T790M mutation are available through the patient name program. ALK IHC is routinely performed in Croatia and an ALK inhibitor is reimbursed as a second-line treatment. Outside of clinical trials and patient name programs, PD-1/PD-L1 and immunotherapies are not available. Biomarker testing is even more limited in Macedonia, Bosnia and Herzegovina, and Kosovo. There are no current data on mutation frequencies and most of the therapies are not readily available.

More or less, a similar situation is apparent across the region, with smaller variations on reimbursement of both biomarker testing and targeted therapies. These huge inabilities to comply with high-income world standards frustrate both physicians and patients. The physicians are aware that they are not providing the standard-of-care for their patients and, in the internet era, patients are well-informed about diagnostic and therapeutic possibilities that their physicians are not providing them. The only solution, in an absence of financial resources and political will, is in the increase of high quality clinical trials. Nonetheless, currently the clinical trial initiation in the region is facing numerous obstacles and difficulties, mostly administrative in nature.

SOUTHEAST ASIA

Lung cancer is one of the leading causes of cancer death in Asia, as 51% of the world's lung cancer cases occur there[22] and 21% of cancer deaths in the region are due to lung cancer.[23] Of note, the diagnosis and treatment of this disease varies widely between high-income countries (Japan, Korea, Taiwan, and Singapore) and LMICs, especially those in Southeast Asia (Indonesia, Malaysia, Myanmar, the Philippines, Thailand, and Vietnam).

The molecular profiling of patients with advanced NSCLC, for known oncogenic drivers, is recommended during routine practice. However, the tests of these genes are not well established in LMICs in Asia (Table 1). Usually the tests are available in major academic centers in most countries but the cost is still high, which limits patients' access. Moreover, patients who test positive for molecular drivers are unlikely to be treated with targeted agents due to their restricted local approval.

Most local and regional laboratories perform basic IHC assays such as TTF-1, p63, and Napsin A for diagnosis, according to the 2015 World Health Organization classification.[24] Presently, several pharmaceutical companies provide financial and technical support for other molecular testing, which mainly include *EGFR* mutations and *ALK* fusions. However, despite availability of drugs such as EGFR TKIs and ALK inhibitors, many patients must pay for these agents and most patients cannot afford these expensive drugs.

In Thailand, government agencies usually obtain all of the available drugs; however, special regulations prevent reimbursement for EGFR TKIs used as first-line treatment, and are only reimbursed when used in the second- and third-line. Testing for *ALK* fusion by IHC, sometimes by fluorescence in situ hybridization or PCR, is partially reimbursed for some patients. PD-L1 testing is being introduced to the country. The tests vary because of automated platforms in use in the centers. The major obstacles in Thailand is the availability of cancer tissues after diagnosis and prioritization of testing. Rebiopsy is another issue for patients whose disease has

TABLE 1. Molecular Testing in Low- and Medium-Income Southeast Asia Countries

	Thailand	Indonesia	Myanmar	Vietnam
EGFR	IHC, RT-PCR	Direct sequencing	RT-PCR	RT-PCR
***ALK* Fusion**	IHC, FISH	NA	NA	NA
PD-L1	IHC	NA	NA	NA
Others	Ros-1 (IHC)	NA	NA	NA
Centers Available	6 (varies*)	Large cities	≥ 1	≥ 2

*Each center has its own algorithm of testing. Chiang Mai in Thailand uses reflex testing for mutation-specific *EGFR*, *ALK,* and PD-L1 followed by *EGFR* mutations or *ALK* FISH.

Abbreviations: IHC, immunohistochemistry; RT-PCR, real-time polymerase chain reaction; FISH, fluorescence in situ hybridization; NA, not available.

IHC assays for EGFR are of exon 19 deletion and exon 21 L858R. IHC assays for ALK are from Ventana D5F3 or Leica 5A4 and for ROS-1 from D4D6. FISH assays are from Abbott Molecular.

progression in an organ site where proper tissue is unlikely to be taken, such as brain or bone. Liquid biopsy is increasingly available in the major academic centers of Thailand, especially for patients with progressive NSCLC, anticipating T790M mutation, which usually is not reimbursable. *EGFR* mutation testing can only be conducted with blood. However, liquid biopsy should not replace the tissue biopsy, which contains more cells and may be used for testing more mutations.

In Indonesia, *EGFR* testing is performed in only the major cities and most tests are IHC and direct sequencing.

In Myanmar, only one laboratory can perform *EGFR* mutation testing after IHC for TTF-1 has been confirmed positive. The *EGFR* mutation testing is commercially available as a reverse transcriptase PCR assay for exons 18 to 21. The major obstacle is the limited amount of cancer tissue available after a diagnostic IHC is performed. Moreover, the test is not consistently available.

In Vietnam, only *EGFR* testing is established in Ho Chi Minh City and Hanoi, presumably within academic centers. The method is also commercially available for real-time PCR. The major obstacles are availability of tissue for testing and the lack of reimbursment fortest costs.

CONCLUSION

Implementation of molecular testing and personalized therapy for patients with lung cancer in LMICs has numerous barriers and poses many challenges. Despite peculiarities specific to countries or geographic regions, there is a substantial number of common obstacles that could be confronted by similar efforts, thus collaborative discussions may be helpful. In LMICs, the lack of, or restricted access to, molecularly targeted therapies already approved and in use in most high-income countries is a major problem. Consequently, there is no incentive to develop and conduct molecular testing in patients who will not be able to access the proper drugs.

In many LMICs, pharmaceutical companies are the major sponsors of targeted agents and lung tumor molecular testing. These countries complain of a deficient infrastructure both at local and reference hospitals, as well as at regulatory offices at the national level. Although financial aspects may be the most significant obstacle in numerous countries, the lack of strategic planning to overcome infrastructural barriers for implementation of precision therapy is also a relevant limiting factor.

Another common theme among LMICs is the insufficient level of research, education, and expertise available. Academic and professional organizations should be encouraged to gather more scientific data from those countries to support an educational strategy and facilitate the implementation of lung cancer personalized therapy and molecular testing.

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Cancer Care and Control as a Human Right: Recognizing Global Oncology as an Academic Field

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OVERVIEW

The global burden of cancer incidence and mortality is on the rise. There are major differences in cancer fatality rates due to profound disparities in the burden and resource allocation for cancer care and control in developed compared with developing countries. The right to cancer care and control should be a human right accessible to all patients with cancer, regardless of geographic or economic region, to avoid unnecessary deaths and suffering from cancer. National cancer planning should include an integrated approach that incorporates a continuum of education, prevention, cancer diagnostics, treatment, survivorship, and palliative care. Global oncology as an academic field should offer the knowledge and skills needed to efficiently assess situations and work on solutions, in close partnership. We need medical oncologists, surgical oncologists, pediatric oncologists, gynecologic oncologists, radiologists, and pathologists trained to think about well-tailored resource-stratified solutions to cancer care in the developing world. Moreover, the multidisciplinary fundamental team approach needed to treat most neoplastic diseases requires coordinated investment in several areas. Current innovative approaches have relied on partnerships between academic institutions in developed countries and local governments and ministries of health in developing countries to provide the expertise needed to implement effective cancer control programs. Global oncology is a viable and necessary field that needs to be emphasized because of its critical role in proposing not only solutions in developing countries, but also solutions that can be applied to similar challenges of access to cancer care and control faced by underserved populations in developed countries.

Globally, more people die of cancer than of tuberculosis, malaria, and HIV/AIDS combined. However, for the majority of patients with cancer who live in low- and middle-income countries (LMICs), especially in some of the poorest regions in Sub-Saharan Africa, cancer remains a neglected disease. Therefore, the economic region of the world in which a patient is diagnosed with cancer determines his or her likelihood of dying from cancer and the likelihood of a death accompanied by insufferable pain.[1]

Disparities exist in the distribution of resources allocated for cancer control globally. Developing countries have only 5% or less of the global share of resources for cancer care and control. However, these countries represent 80% of the disability-adjusted life-years lost worldwide to cancer.[2] Furthermore, disparities in cancer case fatality rate, which is the proportion of patients diagnosed with cancer who die from the disease, are driven by a growing incidence of cancer and poor survival in LMICs, whereas survival in developed countries is either steady or improving. For example, the case fatality rate for breast cancer is 23.9% in a high-income country, compared with 56.3% in a low-income country. This represents a gap of 32.4%, meaning that an excess of 32.4% of women diagnosed with breast cancer would die of their cancers just because they were diagnosed in many parts of Sub-Saharan Africa and not Boston, Massachusetts.[3] For men diagnosed with prostate cancer, the gap in case fatality rates between a country of low income and one of high income is 56.1%.[3] Similar gaps exist with regard to palliation for cancer pain, with 99.9% of patients with cancer who die in pain located in the developing world, compared with only 0.1% in developed countries.[1]

Although the disparities in cancer care and survival are more amplified between high-income countries and LMICs, disparities also exist even within high-income regions of the world. In a large retrospective analysis of 107 and 74 cancer registries for major adult and childhood cancers, respectively, in 29 European countries (EUROCARE-5), the results showed the largest improvement in survival for all cancers combined from 1999–2001 to 2005–2007. However, it was noted that despite overall improvement in survival, cancer survival in Eastern Europe (Bulgaria, the Czech Republic, Estonia, Latvia, Lithuania, Poland, Slovakia) was generally

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lower for both adult and childhood cancers compared with cancer survival in their European neighbors in Northern, Central, and Southern Europe and the United Kingdom and Ireland.[4,5]

Despite these data highlighting cancer care disparities, access to care in LMICs remains limited. The right to cancer care and control interventions should be regarded as a human right not defined by geographic or economic boundaries. There is a need to place equal value on saving lives and alleviating the suffering of patients with cancer in the developing world, as we do in the developed world. The arguments that have stalled global action on cancer are similar to the myths perpetuated decades ago early in the HIV/AIDS pandemic: that the disease is too expensive and too complex to treat. Current data show that contrary to this notion, expanded funding and access to antiretroviral therapy worldwide have led to improved outcomes and prolonged survival in individuals living with HIV globally. On the contrary, the burden of cancer morbidity and mortality is predicted to increase substantially in the coming years, and continued inaction of the global community will result in increasing numbers of avoidable deaths.[6]

The development of global cancer medicine as an academic field will greatly help in the development of approaches to increase access to quality cancer care to many who reside in parts of the world where few or no options currently exist.

EPIDEMIC OF CANCER IN LIMITED-RESOURCE COUNTRIES

The paradigm that cancer is a disease of affluent societies has completely changed in the past decade. Epidemiologists and clinicians are now aware that cancer has become a leading cause of death and disability in LMICs.[6,7] The majority of the estimated 13 million cancer deaths in 2030 will occur in limited-resource countries,[8] while a huge strain will be put on the health systems to manage an estimated 21.6 million new cases diagnosed each year by 2030. Population aging and growth, coupled with changes in lifestyle that do not seem to be efficiently counterbalanced by prevention initiatives, are the main reasons why cancer will become the leading public health issue in LMICs.

KEY POINTS

- **Cancer incidence and mortality are on the increase, with a disproportionate burden of disease mortality and morbidity borne by patients in low- and middle-income countries.**
- **Cancer care and control should be a human right accessible and affordable to all patients regardless of their geographic or economic region.**
- **The basic approach to national cancer planning should include a resource-stratified, integrated approach that includes all realms of cancer care from education, prevention, and screening to cancer diagnostics, treatment, survivorship, palliative care, and follow-up.**
- **Current innovative approaches have relied on partnerships between developed and developing countries to address the global burden of disease in low- and middle-income countries.**
- **Global oncology is a necessary academic field to train world experts who can think critically about innovative solutions to cancer care implementation in developing countries and underserved communities in developed countries.**

PREVENTION VERSUS TREATMENT

In establishing the agenda for global cancer control, the choice between preventive and therapeutic interventions is a false dichotomy, which is invoked differentially with regard to cancer care in LMICs. It is unethical to prescribe a comprehensive care approach to a patient with a potentially curable cancer in a developed country but deny these lifesaving therapies to a person living in a poor country. Poverty should not determine who lives or dies. Prominent proponents for prevention suggest that this is more feasible because one-third of cancers are preventable, which does not address the needs of the remaining two-thirds of the cancer population and the 8 million new cancer cases diagnosed in the developing world alone.[6] Children's cancers are not preventable. Yet with appropriate therapy, more than 80% of children will survive their cancer. Many adult cancers, such as Hodgkin lymphoma and testicular cancer, are not preventable but are highly curable. This also does not address the fact that prevention is a complex issue.

The reluctance to scale up comprehensive access to early detection, diagnosis, treatment, and palliation in LMICs continues to be driven by the purported cost of these interventions, not the cost of human lives lost to cancer. In the HIV era, there was an initial emphasis on prevention rather than treatment, which cost many lives. It was later realized that the combination of prevention and treatment is the most effective model for saving lives. These lessons must instruct how we address the burden of cancer in LMICs. In fact, there are growing data highlighting that an integrated system for delivering quality cancer care is feasible in LMICs, and limitations in sophisticated diagnostics and infrastructure or shortage of oncology specialists should not deter current efforts to scale up both prevention and treatment.

Sidebar 1 shows a nonexhaustive list of cancers grouped by those that are amenable to different types of interventions within an integrated care system.[2] For example, cervical cancer, which is the number one or two cause of cancer mortality and morbidity among women in LMICs, is amenable to both preventive methods through HPV vaccination and early detection and treatment. And it must be remembered that if all young girls in a country are vaccinated today, there are still many women already infected with HPV who will be at risk for developing cervical cancer in the years to come. Hepatocellular cancer, which has a high case fatality rate globally, is more appropriately targeted with a preventive approach by hepatitis B vaccination. Even in the developed world, our ability to successfully treat hepatocellular carcinoma is very limited. On the other hand, for nonpreventable cancers such as childhood acute

lymphoblastic leukemia, with a potential cure rate of at least 80%, treatment should be emphasized. Other cancers that fall within this category are Burkitt lymphoma and testicular cancer. Costing data based on treatment of patients at the Butaro Cancer Center of Excellence in Rwanda, which is a partnership between the Rwandan Ministry of Health, Partners in Health, and the Dana-Farber Cancer Institute and Brigham and Women's Hospital, estimated a cost of $1,500 to completely treat a child with Hodgkin lymphoma and $1,400 for Wilms tumor (C. Neal et al, unpublished data). Moreover, a recent publication showed improved outcomes, supporting the application of cost-effective treatment of Wilms tumor, with a high potential for cure.[9]

In 1977, the World Health Organization (WHO) proposed, and has since maintained, the Essential Medicines List (EML), which has traditionally included relatively inexpensive generic cytotoxic cancer therapy.[10] The most recent update of the WHO EML in 2015 resulted in 16 disease-related additions used to treat 26 different types of cancers in adults and children.[11] However, this update included the monoclonal antibody trastuzumab for patients with *HER2*-positive breast cancer and the tyrosine kinase inhibitor imatinib for patients with chronic myeloid leukemia (CML).[11] Both of these additions were supported by impressive survival data despite the high costs.[12-14] These additions to the WHO EML underscore the important issue of cost barriers to access but do not justify inhibiting access of these effective treatments in LMICs. Recently the chief executive officer of a pharmaceutical giant argued that "giving out free cancer drugs would not help the poorest parts of Africa." He identified the capacity for training doctors as the biggest issue in the world's poorest countries, not the cost of drugs.

On the contrary, the price of drugs is one of the biggest barriers to access, and emerging data show that when essential medicines for cancer are provided at no charge, there are clinical benefits. In the case of CML, Novartis, the manufacturer of imatinib, partnered with the Max Foundation in the Glivec International Patient Assistance Program in 2002 to expand access to imatinib at no cost to approximately 50,000 patients with CML who are uninsured and cannot afford to pay out of pocket for imatinib and live in resource-limited countries. The program expanded access to several countries in Sub-Saharan Africa and emerging economies in other countries.[15] Prior to making the free drugs available, the Glivec International Patient Assistance Program assesses the existing infrastructure to ensure that CML can be properly diagnosed and that therapy can be safely administered and monitored. A recent publication from Rwanda reported the outcomes of two public district hospitals in Rwanda, including the Butaro Cancer Center, where the Glivec International Patient Assistance Program has been implemented. The study was a retrospective analysis of 49 patients with pathologically confirmed diagnoses of CML treated between 2009 and 2014. The estimated overall survival among 43 patients included in the analysis was 94.7% (95% CI, 0.80–0.99) at 12 months.[16] In contrast, trastuzumab and biosimilars are not available for patients at Butaro, because of their high cost, and this translates into unnecessary loss of life.[17] For example, a costing scenario for medicines for locally advanced estrogen receptor–positive/*HER2*-positive breast cancer, including cyclophosphamide, doxorubicin, paclitaxel, and tamoxifen, without trastuzumab, is $273, compared with $40,767 with the inclusion of 1 year of trastuzumab (unpublished data).

Partners in Health and Dana-Farber Cancer Institute have navigated these difficulties in two LMICs, Rwanda and Haiti. Diagnostic and treatment guidelines have been developed that are similar to the WHO EML supporting documents for countries that do not have either the ability to test for *HER2* receptor status or do not have access to trastuzumab. These guidelines assist internists treating patients with cancer at Butaro Cancer Center of Excellence in Rwanda and Hospital Universite Mirebalais in Haiti. A patient with a suspected breast lump and axillary lymphadenopathy is diagnosed with support from histopathological and immunohistochemistry services offered by the Brigham and Women's Hospital. Assuming the pathology confirms clinically stage III invasive ductal carcinoma that is estrogen/progesterone receptor negative *and HER2* positive, this patient will receive

SIDEBAR 1. Cancer Amenable to Prevention, Early Detection, and Treatment in Countries of Low and Middle Income

Preventable cancers by risk factor:

- Tobacco: lung cancer, head and neck cancer, bladder cancer
- HPV infection: cervical cancer, head and neck cancer
- Hepatitis infection: hepatocellular cancer

Cancers that are potentially curable with early detection and treatment, including surgery, and sometimes systemic therapy and radiation:

- Breast cancer
- Cervical cancer
- Colorectal cancer

Cancers that are potentially curable with systemic treatment, even when presenting at advanced stage:

- Burkitt lymphoma
- Large cell lymphoma
- Hodgkin lymphoma
- Testicular cancer
- Acute lymphoblastic leukemia
- Soft tissue sarcoma
- Osteosarcoma

Cancers that are often well palliated with systemic treatment:

- Kaposi sarcoma
- Advanced breast cancer
- Ovarian cancer
- Chronic myeloid leukemia

neoadjuvant chemotherapy comprising of doxorubicin, cyclophosphamide (AC) dosed every 3 weeks for four cycles, followed by paclitaxel (T) also dosed every 3 weeks for an additional four cycles. It is important to note that in clinical practice and consistent with WHO supporting documents on advanced stage breast cancer, we do not recommend *HER2* testing if trastuzumab is not available. The complete list of the WHO essential medicinesand supporting diseased-based documents with management guidelines for related cancers is publicly accessible on the WHO website. In contrast, if the same patient presented to a cancer center in the United States, the prescribed course of therapy will be AC dosed every 2 weeks with growth factor support followed by paclitaxel plus trastuzumab and pertuzumab, both HER2-directed therapies.[18]

RATIONALE FOR GOVERNMENTS AND MINISTRIES TO TACKLE CANCER

There are substantial data supporting the rising burden of cancer globally. It is imperative therefore for governments and ministries of health to prioritize cancer care and control. As previously discussed, access to cancer care and control is a human right that should not be denied to citizens of LMICs. Tackling cancer in the context of a well-tailored cancer control program designed for a resource-limited setting will ameliorate unnecessary deaths and pain from cancer. During the HIV/AIDS epidemic, many lives were lost because of a delayed call to action. Governments must act now to avert deaths among children with curable cancers, women with cervical and breast cancers, and men with prostate cancer and to prevent suffering in the majority of patients who present with advanced-stage disease or metastatic disease that is not curable.

We realize that there are many challenges to implementing a cancer delivery program in a resource-constrained setting, including a paucity of in-country expertise, financing, and general health care infrastructure, and these should not be ignored or minimized. Nonetheless, with focus and an incremental approach, low-income countries have shown that it can be done.

An additional argument is made for the economic potential lost to premature deaths from cancer. Furthermore, shifting the burden of out-of-pocket cancer care costs onto the poor further entrenches them in a continuous cycle of poverty. Governments therefore must address cancer because of the immense potential to save and prolong lives and to positively affect economic growth.

BASIC APPROACHES TO NATIONAL CANCER PLANNING

The central tenet of national cancer planning globally, including in LMICs, is to develop an integrated approach that includes a continuum of education, prevention, screening, cancer diagnostics, treatment, survivorship, and palliative care. The goal should also include developing and strengthening in-country capacity for all aspects of care and for the full spectrum of cancer specialists, while maintaining high-quality cancer care for patients with treatable and preventable cancers.

Tackling cancer requires a framework that is integrative of all aspects of disease control and management. For example, cancer cannot be treated effectively and safely without pathologic confirmation of a specific diagnosis. Conversely, there is no ethical reason for screening or performing a biopsy and processing specimens if effective treatment is not available. Current innovative approaches to cancer control have managed to succeed despite the absence of on-site oncologists, pathologists, or hematologists by partnering with off-site specialists via electronic communication. Many countries have few or no in-country oncologists, and even with an increase in global training programs, there will not be enough trained oncologists to care for most of the world's patients with cancer for decades. Therefore, alternative models to globally expand access to care that leverage the current environment of rapid technological advancements are needed. The partnership between Partners in Health, the Dana-Farber Cancer Institute and Brigham and Women's Hospital, and the Rwandan Ministry of Health at the Butaro Cancer Center of Excellence is an example of such a model.

Another guiding principle learned from the experience in Rwanda is the structured development of priorities and standardized guidelines for cancer prevention and treatment. The WHO EML is an important guide for national cancer programs for prioritizing cost-effective therapies that should be included on national essential medicines lists. However, it is equally important to ensure that there are measures in place to guide accurate chemotherapy forecasting and procurement to ensure a reliable supply of drugs.

All aspects of cancer care should have embedded within them continuous monitoring and evaluation, surveillance, and research. The research component will ultimately improve our understanding of variations in disease biology and presentation, effectiveness and safety of cancer care delivery, drug toxicity and efficacy, and how these interact with epigenetic factors. These lessons will further guide improved innovative approaches to cancer management and future treatment strategies for delivering care globally.

Finally, health care financing for cancer is a complex issue with a rising burden worldwide. There has been considerable progress in cancer therapy over the past several decades, derived from an increased understanding of basic cancer biology, leading to a spectrum of targeted therapies for many malignancies and an evolving field of immunotherapy. Parallel to this trend has been an explosive increase in the cost of cancer therapy within this same time period. The average price of patented cancer drugs has more than doubled from a decade ago to more than $10,000 per month.[19] As much as access and cost barriers to cancer care are issues in well-funded health care systems in the developed world, they are even more so in LMICs. Despite these rising costs, it is important to highlight that care should be affordable and that poverty should not be a barrier to care. For many in the world, this will mean that care must be free. As was the case with HIV/AIDS approaches 15 years ago, a concerted

effort is needed by international organizations such as the WHO, the World Bank, private funding and donor agencies, pharmaceutical companies, nongovernmental agencies, and local governments to design and implement sustainable approaches to expand access to the world's poorest.

ADDRESSING LIMITATIONS IN ACCESS TO CARE: THE GLOBAL ONCOLOGY MANDATE

Many organizations, including ASCO, the European Society for Medical Oncology (ESMO), and other bodies, have condensed the progress being made in cancer treatment into well-written, evidence-based, "gold-standard" guidelines and recommendations, with the ultimate goal of providing education and guidance to medical professionals and helping them care for their patients throughout the world. However, every person who practices or visits oncology departments in limited-resource environments soon becomes aware that there are important barriers in guidelines' implementation as a result of many competing health priorities and financial constraints. We will briefly review the main limitations, to underline these as global oncology target areas for research, with the goal of identifying the best solution to improve cancer care. There is immense heterogeneity around the world in terms of accessing cancer care; therefore, there is no "one-size-fits-all" solution. Global oncology academic teams, developed ideally as partnerships between developed and less developed centers, are key to address the various issues. Local partners from LMICs are essential to provide insight into the issues they are facing and in partnership with specialists from affluent countries to build upon already implemented local solutions. Despite many limitations, huge numbers of patients are currently treated with the available resources, and we all can learn from this hands-on experience.

Cancer diagnosis and treatment rely on timely access to adequate pathology. Moreover, inadequate pathology hampers gaining knowledge about the true incidence of and mortality from cancer, accuracy of cancer registries, and therefore effective national cancer plans. However, despite the essential core role of pathology, many health systems struggle at various levels in ensuring good access. In certain regions, such as Sub-Saharan Africa, pathology coverage is at best 10%, with several countries having less than one pathologist per 2.5 million people or less than 4% of what is needed.[20] In other areas, lack of resources for pathology leads also to suboptimal facilities and equipment, limited access to quality assurance programs, and low availability of immunohistochemistry.

All three essential pillars of cancer care (surgery, systemic treatment, and radiotherapy) suffer from severe access limitations. A recent report revealed wide equity and economic gaps in global cancer surgery, estimating that only 5% of patients in low-income countries and approximately 20% of patients in middle-income countries have access to safe, affordable, and timely cancer surgery.[21] Although considered a basic health intervention, scaling up access to cancer surgery in LMICs proves challenging, as the health system infrastructure, human resources, and processes that together define surgical oncology are lacking in many countries.

Worldwide access to radiotherapy is unacceptably low.[22] Constant underfunding due to the high initial investment has led to a situation in which 90% of the population in LMICs lacks access to radiotherapy, with extreme situations in Sub-Saharan Africa, where most countries do not have any radiotherapy service.[23] Access to radiotherapy is further hampered by a lack of trained personnel, including medical physicists and radiation technicians. Globally, in LMICs, besides the technical aspects, issues exist relating to political commitment, social awareness, and education to reduce negative cultural beliefs related to cancer and radiotherapy. Increasing affordability and transportation options are key to increasing access to radiotherapy.

There are substantial differences in formulary availability, out-of-pocket costs, and actual availability for many cancer medications across the world, as shown by the preliminary results of a recent ESMO survey.[24] These differences are more profound in lower-medium- and low-income countries. The impact of these differences is most acute with diseases for which noncurative outcomes are dependent on the availability of expensive anticancer agents such as *EGFR*- or *ALK*-mutated non–small cell lung cancer, melanoma, renal cell cancer, or *RAS/RAF* wild-type colorectal cancer. These discrepancies are less pronounced in curative settings. This is best illustrated for trastuzumab in adjuvant breast cancer regimens, which, though expensive, in some countries may be subsidized and available, though in many it remains unaffordable for any indication. However, many cheap generic chemotherapy medicines on the WHO EML are available only at full cost in many low-income countries. A previous ESMO survey revealed that several "essential," old, and inexpensive drugs such as tamoxifen are not always available, even in Europe, mainly because of drug shortages; this is not cost related and opens a whole range of questions that must be answered from a global oncology perspective.[25]

In many LMICs, there is a huge need for trained medical oncologists, surgical oncologists, radiation oncologists, pediatric oncologists, gynecologic oncologists, pathologists, and specialized oncology nurses. Even in the United States, a survey conducted by ASCO in 2007[26] and updated in 2014[27] predicted important shortages of more than 2,000 medical oncologists by 2025. In many developed countries, organ specialists receive appropriate training to deliver systemic cancer therapy. However, in LMICs, the general lack of availability of medical staffing in all disciplines calls for innovative solutions to train nononcologists to actively participate in cancer care.[28] One such approach that has been taken in some countries where professional resources are limited, including Tanzania and South Africa, is to train physicians in both medical oncology and radiation oncology.

Only 14% of people who need palliative care receive it.[29] A global opioid availability survey revealed that in many places across Africa, Asia, the Middle East, and Latin America, governments are failing patients with cancer in the delivery of adequate pain relief, mainly because of over-regulation.[30]

INNOVATIVE SOLUTIONS: WHAT WORKS WHEN RESOURCES ARE LIMITED?

Many organizations, institutions, and groups invest great efforts in projects to improve cancer care across the globe. The concept of stratified guidelines, first proposed by the Breast Health Global Initiative, allowed the development of economically feasible guidelines that offer a framework for incremental, step-by-step resource allocation to improve cancer care in LMICs.[31] This model has been replicated beyond breast cancer in many other malignancies.[32] Recently, the National Comprehensive Cancer Network adopted this framework to adapt its guidelines to help health care systems provide optimal care for patients with cancer with varying available resources.[33]

Important progress in treating cancer comes lately at an elevated cost. Because many health care systems are underfunded and relatively fragile, cost-effectiveness, affordability, and sustainability are now critical issues. The ESMO Magnitude of Clinical Benefit Scale has been recently developed and validated as a reproducible scale that uses a rational, structured, and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anticancer treatment, helping frame the appropriate use of limited public and personal resources to deliver cost-effective and affordable cancer care.[34] The ASCO Value Framework assesses the value of new cancer therapies on the basis of clinical benefit, side effects, and improvements in patient symptoms or quality of life in the context of cost, and physicians can use it as a tool in shared decision making with patients.[35] The National Comprehensive Cancer Network guidelines now include, for certain malignancies, evidence blocks that help inform the choices of health care providers and patients when selecting systemic therapies on the basis of measures related to treatment, supporting data, and cost.[36]

GEOGRAPHY VERSUS PERSPECTIVE

We must also remember that high-income countries face many of the same issues as LMICs in cancer prevention and control for patients of lower socioeconomic status, those without health insurance or who are underinsured, and those living in rural areas. Training in global oncology can help oncologists in high-income countries better deliver care in their own countries. Task sharing for cancer-related medical care with nurses and community health workers can help expand the availability of services, as well as reach patients sometimes out of reach of cancer care. Training surgeons, family practitioners, internal medicine specialists, and pediatricians to deliver standard chemotherapy regimens and manage the expected toxicities of chemotherapy, with backup from oncologists, can help make cancer care more available in rural and other medically underserved areas. Innovative telemedicine strategies, such as Project ECHO, have been shown to improve quality of care and the expertise of medical providers in treating complex medical conditions.[37]

CONCLUSION

The average oncologist is not prepared to face and react to these global challenges. To have a comprehensive understanding of this complex reality, we believe that specific training is required. Global oncology as an academic field should offer the knowledge and skills needed to efficiently assess situations and work on solutions, in close partnership with academic institutions, local governments, and ministries of health. We need medical oncologists, surgical oncologists, pediatric oncologists, gynecologic oncologists, radiologists, and pathologists trained to think globally. Moreover, the multidisciplinary fundamental team approach needed for most neoplastic diseases requires coordinated investment in several areas; lacking a "quick-fix" solution, politicians and health authorities are frequently postponing important investments in cancer research because of the complexity of the situation. We believe that global oncology, as an academic field, should be able to propose solutions to cover the existing gaps in certain health care environments and work, in close cooperation with local professionals, toward improving cancer care outcomes globally. The world is shrinking thanks to travel expediencies and social media, emphasizing that we are all part of a greater humanity with shared social obligations.

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Thinking Differently in Global Health in Oncology Using a Diagonal Approach: Harnessing Similarities, Improving Education, and Empowering an Alternative Oncology Workforce

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OVERVIEW

Cancer is a leading global cause of death, and diverse and minority populations suffer worse outcomes compared with white people from Western societies. Within the United States, African Americans and other blacks, Hispanics, Asians, and American Indians have lower cancer survival rates than whites. In the rest of the world, those from low- and middle-income countries have the greatest disparities, but even those from non-Western high-income countries such as Oman and the United Arab Emirates are diagnosed with cancer at later stages and suffer increased mortality. Although considerable differences exist among these populations, similarities and synergies are also apparent. Challenges can be very similar in reaching these populations effectively for cancer control to improve outcomes, and innovative strategies are needed to effectively make change. In this review, the authors discuss new approaches to the prevention and early detection of cancer as well as the implementation of programs in global oncology and put in evidence cultural similarities and challenges of different populations, highlighting strategies to improve cancer survival and quality care around the world through innovations in training and education, empowerment of an alternative workforce, and a diagonal approach to cancer care using case studies drawn from the authors' work and experience.

Cancer is a leading cause of death globally, and diverse and minority populations suffer worse outcomes compared with white people from Western societies.[1] Within the United States, African Americans and other blacks, Hispanics, Asians, and American Indians have lower cancer survival rates than whites.[2] In the rest of the world, those from low- and middle-income countries have the greatest disparities, but even those from non-Western high-income countries such as Oman and the United Arab Emirates are diagnosed with cancer at later stages and suffer increased mortality.[3] Although considerable differences exist among these populations, similarities and synergies are also apparent. Challenges can be very similar in reaching these populations effectively for cancer control to improve outcomes, and innovative strategies are needed to effectively make change.

The following three sections that will be discussed are: Alternative Approaches to Prevention, Early Detection, and Implementation in Global Health. This review, and its accompanying presentations given at the 2017 ASCO Annual Meeting, will discuss cultural similarities and challenges of different populations and highlight strategies for improving cancer survival and quality care around the world through innovations in training and education, empowering an alternative oncology workforce, and a diagonal approach to cancer care using case studies drawn from the authors' work and experience.

CULTURAL SIMILARITIES, CHALLENGES, AND INNOVATIVE STRATEGIES FOR CHANGE: AN AMERICAN INDIAN AND MIDDLE EASTERN EXAMPLE

When working with any population, more similarities than differences exist. Overall, people strive for human connectedness, happiness, and quality of life. The family is the core of all societies and holds a special meaning for most people around the globe.[4] The value of interconnected generations is a component of the family focus.[5] Aside from some genetic and environmental factors, humans are also susceptible to

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the same diseases, cancer being one of the most common and one of the deadliest.

Among the cancer professional world, similarities also exist. Doctors, nurses, and other professionals strive for a cure when possible, rely on palliative care to manage deleterious symptoms that occur along the cancer trajectory, and hope for the best possible outcomes for the given population. When working and interacting with professionals from diverse populations, an immediate connection occurs based on similar experiences and a deep understanding and respect for the common ground on which they work.

Both the personal and professional similarities should be embraced when working with any diverse culture; yet, it is important to recognize the differences and the challenges that affect cancer care and outcomes. Fears and attitudes about cancer, spiritual and religious customs, and gaps within the health care systems are some of the differences.

Cancer Beliefs

Fear of cancer, avoidance of discussing illness, use of traditional medicine, and the importance of spirituality are commonalities among some American Indian and Middle Eastern people (and many others around the world) and are discussed briefly in this section. First, fear of cancer can be related to fatalism, in that low cancer survival rates reinforce the belief that cancer is not curable. Superstition is another part of the fear; some believe that even saying the word "cancer" can cause it to happen or, as one American Indian medicine man stated, "bring bad medicine to his people." For Middle Eastern cultures, not disclosing a cancer diagnosis is precipitated by the fear that it will have a negative impact on the patient.[6] Overall, cancer can be considered fearful and a cultural taboo in many cultures, making education and discussing the topic a challenge.[7] Use of traditional medicine is also common among American Indian and Middle Eastern cultures.[8] This topic commonly surfaces at professional cancer meetings. Finally, spirituality and/or religion are closely woven into the lives of American Indians and many from Middle Eastern and northeast African nations.[9] Meetings commonly open in prayer, which is different from most Western cultures, and spirituality and religion are openly discussed and integrated into care. Silbermann's book, *Cancer Care in Countries and Societies in Transition*, highlights many beliefs commonly shared in low- and middle-income countries and countries experiencing transitions in cancer care.[9]

KEY POINTS

- **Cancer is a major health problem worldwide, and there are disparities across and within nations and regions.**
- **Cultural similarities should be embraced and educational approaches adapted for adequate reach and implementation.**
- **An alternative workforce, composed of nononcologists, can be trained and monitored successfully and may provide care in areas of desperate need.**
- **A diagonal approach to global health in oncology overcomes the barriers between vertical (disease-specific) and horizontal (systemic) approaches by making full use of potential synergies between different programs and offers the opportunity to implement individual-centered, instead of disease-focused, approaches.**

Innovative Educational Strategies

Diverse cultural groups require innovative strategies that address cancer care, from diagnosis, through treatment, survivorship, and end-of-life care. Whether the audience is a patient or health care professional, teaching strategies should incorporate cultural aspects and engage the learners from their own personal lens and experiences. Although education is necessary to increase knowledge about cancer care and build capacity in any region, those working with global populations are often challenged with how to best present information and how to engage participants as active learners and change agents. One systematic review found that a combination of didactic and experiential teaching methods is effective in improving attitudes toward care of the dying.[10] Another systematic review examined effective methods of teaching communication skills in dementia care and found a combination of didactic methods, hands-on training, group discussions, and role-play improved communication skills.[11] A third systematic review explored training methods for communication strategies for cancer care professionals and found that programs delivered over a longer period of time were most effective, and a combination of didactic education, peer feedback, and small group participation was the best teaching strategy.[12] The limitation of these findings is that the majority of studies were conducted in resource-rich countries, and little is known about which methods work well in low- and middle-income countries.

Didactic Education

Didactic education is the current foundation of most learning activities. Health care professionals in particular require knowledge transfer on the management of cancer throughout the disease trajectory, strategies for pain and symptom management, ethics, end-of-life care, communication strategies, and evidence-based practice and research in cancer palliative care. This traditional didactic approach, however, has limitations. Little time is often left for group interaction and discussion, and patients and health care professionals alike may not be able to incorporate their cultural beliefs and customs into the plan of care. Although didactic education is important for some content, this author has found successful out-of-the-box strategies to address cancer care in American Indians and other diverse cultures.

Liberating Structures

Liberating structures have been used extensively in the Middle East and northeast Africa to teach health care professionals about cancer and palliative care. These interactive methods involve every participant, unleash creativity,

and engage in group problem-solving to collaboratively achieve better results than didactic education alone.[13] This upside-down approach to education does not assume that the teacher has all of the knowledge, but rather assumes that solutions exist within the participants and that by tapping into group think, cultural and community expertise can be incorporated into the learning process. Some examples of successful liberating structures used by this author (J. M. Brant) in the Middle East are included in Table 1.

Community Events

Although liberating structures can be used for patient education, other community event approaches may be more effective. Cancer walks or relays are one example of a community event that can engage patients, families, and health care professionals and build a sense of comradery among community members. Some of the successful events used by this author (J. M. Brant) for American Indians are included in Table 2. Although most events have focused on women's cancers, the events can be modified for men. Bringing food to the event is an important cultural tradition among American Indians and most cultures and can draw community members to the event. Examples of successful programs are well documented in the literature.[14-16]

Although working with diverse cultures may be challenging, the rewards are often immeasurable. Those of us who have had the privilege to work with patients and/or health care professionals from diverse cultures often think we go to speak and end up listening. We go to teach and end up learning.

EMPOWERING AN ALTERNATIVE ONCOLOGY WORKFORCE: AN EXAMPLE FROM INDIA

A major challenge in cancer care is access to treatment. Patients suspected of having cancer, or suffering from cancer, must have a medical care provider close to their residence. In India, the smallest administrative region is a district, which has a hierarchal system of primary health centers, block level health centers, and a district hospital that serves as the largest medical hub for the area. The low- and lower middle-income groups that form the majority of the population of India use these facilities for all of their health care needs. All administrative and government machinery providing support to these various schemes is located at district headquarters. District hospitals are multispecialty units that headquarter all programs run in the state/country mandated by the World Health Organization and various international commitments like programs for vaccination, mother and child care, tuberculosis, malaria, and others.

One of the coauthors of this paper (D. Pendharkar) was the leader for a project aimed at decentralizing cancer care to the peripheral level through the development of an innovative health care delivery model.[17] The issues in focus included the extension of cancer care to rural areas using existing human resources and infrastructure. The objective was to create a point of contact for cancer and a nodal cancer unit in each of these district hospitals (Fig. 1).

The model builds on similar global practices to address access challenges. In Australia, the Townsville Cancer Center, a tertiary cancer center in North Queensland, Australia, provides chemotherapy services to patients from surrounding small rural towns using the Queensland Remote Chemotherapy Supervision model. Rural-based generalist doctors and nurses administer selected chemotherapy regimens to patients in remote units under the supervision of Townsville Cancer Center–based medical oncologists and chemotherapy-competent nurses through videoconferencing.[18] Project ECHO has also demonstrated the viability of a telemedicine-based solution to hepatitis C control and mitigation by linking community care providers with specialist care teams at academic medical centers to treat patients who require complex specialty care via basic video-conferencing technology.[19]

Methodology

Government medical officers and qualified generalist physicians who typically perform all multipurpose duties were selected to undergo training at a cancer center. Two nursing personnel were also trained in various aspects of chemotherapy handling and administration.

The 1-month training included the basics of oncology, detection, diagnosis, treatment, chemotherapy administration and side effect management, and palliative care. Special emphasis was placed on communication and counseling skills pertinent to cancer. The physician was made to understand the role of documentation and various endpoints in oncology. The training was hospital-based and involved daily wards rounds, participation in outpatient clinics observing work of chemotherapy day care, and so on. The training also included a large motivational component on the importance of the role of the physician. Many of the physicians were evaluated by an independent board of oncologists, and their training was found to be adequate to initiate cancer care services at a district hospital. After the training, physicians returned to their respective district hospitals to begin seeing and registering patients with cancer. Patient cases were discussed either through WhatsApp (mobile phone–based chat), an electronic medical record software, or on the phone with a senior oncologist to finalize a course of action and treatment plan. Every evaluation of a new patient served as continued training and learning, with knowledge being further strengthened via regular continuing medical education events and participation in national and international meetings. This constant continuation of training helped consistently improve physicians' skills.

An additional component of establishing local systems and empowerment was done through the organization of local cancer counseling camps. The camps took place in district hospitals, and local patients were invited and encouraged to participate. Patients were examined and counseled. The local physician was briefed on the care of the patients who increased his/her confidence in handling the case. These types of activities form an important part of continuing education for the physician in charge of oncology care and also serves to build patients' trust and confidence in the system.

TABLE 1. Examples of Successful Liberating Structures Used for Didactic Purposes

Liberating Structure	Rationale for Use	Steps
Impromptu networking Used for participant introductions	Get people up and moving	Everyone gets up and finds someone they do not know
	Acquaint with others you do not know	Pairs
	Keep them thinking about the week	Introduce one another
		Two questions: (1) What do you hope to get from this workshop? (2) What do you hope to contribute to this workshop?
		2 min per person, three rounds
Conversation café To discuss opportunities and challenges of cancer screening, early detection, palliative care, or any other cancer-related issue	Engage everyone in making sense of profound challenges	Get into small groups
	Encourages everyone to express themselves	A talking object is passed from person to person
	Distributes conversation	Round 1: each person shares one strength and one challenge in their setting in regards to the topic, 1 minute per person
		Round 2: reflections after listening to everyone, 1 minute per person
		Round 3: open conversation 15 minutes without object
		Round 4: takeaways, 1 minute per person
Open space To develop a cancer or palliative care quality-improvement project	Participants control the agenda	Map of room drawn and taped to wall
	Allows individuals to begin teaming with others in their area of interest	Blank sticky notes in middle of room
	Allows leaders to emerge	Participants invited to propose a topic to discuss with others: write it on a sticky note and stake a place in the room (e.g., curriculum development, early breast cancer detection, pain)
	Everyone who joins the group cares about the challenge at hand	Once four to five topics proposed, individuals can wander to a group
		Lead must stay with group but others can wander in and out: bee (pollenates and moves ideas) or butterfly (goes group to group for various interests)
Fishbowl To illustrate successes and challenges of establishing cancer or palliative care services	Share knowledge gained from experience, because they have minimal experience with palliative care, we must be the experts	Three to four of us in the inner circle to talk about the good, bad, and ugly of establishing cancer or palliative care in the hospital and community
	Uses expertise of those who have established a palliative care program	Converse and share stories without engaging outer circle for 10–15 minutes
	Allows participants to ask questions and engage	Outer circle gets together in groups of four to list three questions, or can just have open questions
	Participants can jot down takeaways for their palliative care plans	Inner circle answers questions and interacts with outer circle
		Allow one to two empty seats for others to enter in and ask questions

Continued

TABLE 1. Examples of Successful Liberating Structures Used for Didactic Purposes (Cont'd)

Liberating Structure	Rationale for Use	Steps
Improv To demonstrate positive and negative communication skills	Everyone included as players or observers	Volunteers recruited to be actors (patient, family, nurse, physician); they write the scenario (e.g., patient has high anxiety [but cannot be told she has cancer] but daughter trying to support; physician/nurse talks to the Ministry of Health about opioid availability)
	Only so much about communication can be taught in a textbook; it has to be role modeled	Play out the scene according to cultural context
	Allows them to create their own context for the situation, and our team responds/communicates	Allow others to respond as to what went well and what could have been different
1-2-4-ALL Used to discuss case studies	Distributes group participation	Participants get into their breakout groups.
	Allows for individual reflection, small group interaction, and then a larger exchange of ideas	Each group is given a case study
		Individuals reflect on the study for 5 minutes and write down thoughts
		Groups of two share thoughts
		Groups of four, or could convene the whole group to share thoughts and come up with a plan
		Plan is written on the flip chart
		ALL: each group presents their case and plan to the larger group
Celebrity interviews To integrate spiritual and cultural knowledge and experiences into cancer and palliative care; engages community leaders as experts	Explores big challenges with those knowledgeable in the area	One person from each country chosen by us ahead of time; option: we give them questions the night before
	Allows participant leaders to share experiences on integrating spirituality into care	The three celebrities are seated in chairs at the front of the room
	Relies on their beliefs and customs	Interviewer introduces topic to be discussed and conducts the interviews: (1) What inspired you in this work? (2) How do you manage stress in your work? (3) What role does spirituality have in your work? (4) How do you integrate spirituality into your patient care?
	Stories emerge that bring concepts to life	Audience asks questions after the interviews

Monitoring of the program is being done by the office of the commissioner of health from the administrative side and by an oncologist from the medical side, and routine census is being generated. Patient profiles, documents, and materials related to care are being captured and stored. Data are being collected related to various aspects. Administrative reforms were undertaken to improve the storage, movement, and supply chain of anticancer drugs, and drug formularies were appropriately amended.

Program Execution and Outcome

The program was launched in February 2014 in the state of Madhya Pradesh and later initiated by the state governments of Odisha, Himachal Pradesh, and Uttar Pradesh. Physicians from 69 districts and nurses from 58 districts have completed training in various batches. The training was strengthened by six continuing medical education events related to early diagnosis, treatment, palliative care, and participation in national and international meetings by a few physicians.

In total, 63 district hospitals have started offering services (51 out of 51 districts of Madhya Pradesh, 7 out of 30 districts of Odisha, and 5 out of 12 districts of Himachal Pradesh). These districts are spread over an area of 374,420 km^2 (Madhya Pradesh, 308,245 km^2; Himachal Pradesh, 14,283 km^2; and Odisha, 51,892 km^2) and cover a population of approximately 90 million (population: Madhya Pradesh, 75 million; Himachal Pradesh, 4 million; and Odisha, 11.5 million). The rural population constitutes the majority (> 80%) and has a very high number of tribal and socially challenged families (up to 90% in several districts).

Three different WhatsApp groups, mentored by an oncology specialist, have been formed. Cloud-based electronic medical records, to store data electronically, have also been initiated, and physicians are being encouraged to capture data. Registration and physical data records with photocopies of the medical documents are being carried by the patient and are also kept in hospital records.

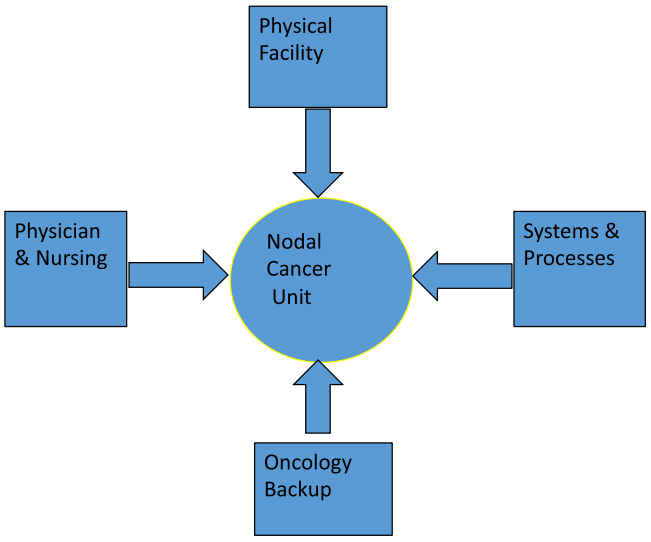
TABLE 2. Examples of Community Events

Event	Description
Pink and blue bingo nights	Separate bingo events for men and women. The evening begins with a circle conversation about breast, cervical, colorectal, and prostate cancer screening. Fecal occult blood kits are distributed to those eligible for screening. Exams can be scheduled during the meeting. Bingo follows the cancer education component.
Cancer awareness poster/photography contests	This event can engage school-aged children and adolescents in cancer awareness. The community can sponsor a poster or photography contest that features healthy behaviors to prevent cancer. Winners are awarded prizes.
Generations of wellness photos	Women of all generations can attend mammography screening together and have a professional photo taken following the mammogram. Children and those not screened can be welcome to attend. The photo is printed on site and framed for the grandmother and her children and grandchildren.
Cup art	While waiting for a mammogram or cervical cancer–screening test, women can artistically paint a mug, which is later fired in a kiln and given to the woman at a later date. An educator is present to provide information about cancer prevention and early detection for both men and women. Women are encouraged to schedule and/or bring their husbands to the clinic for cancer screening.
Dress making/beading	Ceremonial dance is important to American Indians. Women can gather to work on competition dresses and complete beadwork while a guest speaker can discuss cancer screening.
"Tough Enough to Wear Pink"	Rodeo or athletic event that encourages both men and women to wear pink in honor of breast cancer awareness month.

More than 15,000 patients have been registered and have used various services. The number of new patients being registered is increasing regularly and per month varies from district to district in the range of 5 to 30. There are more than 400 outpatient visits per month in the best performing district. The number of inpatients is also increasing. The inpatient services are being used for palliative and supportive care as well.

When a patient arrives at a unit, he/she is seen by the physician, and his/her histologic verification is confirmed. The patient is diagnosed through biopsy and appropriately staged. Diagnostic services, if not available in the hospital, are outsourced. After evaluation, the patient is brought to the group tumor board. Once the board reaches a decision, the patient is informed and counseled on the decided course of action. Chemotherapy, if needed, is started locally and offered at no cost. Surgery and radiotherapy services of the nearest cancer centers are used (Fig. 2).

FIGURE 1. Basic Drawing of a Nodal Cancer Unit



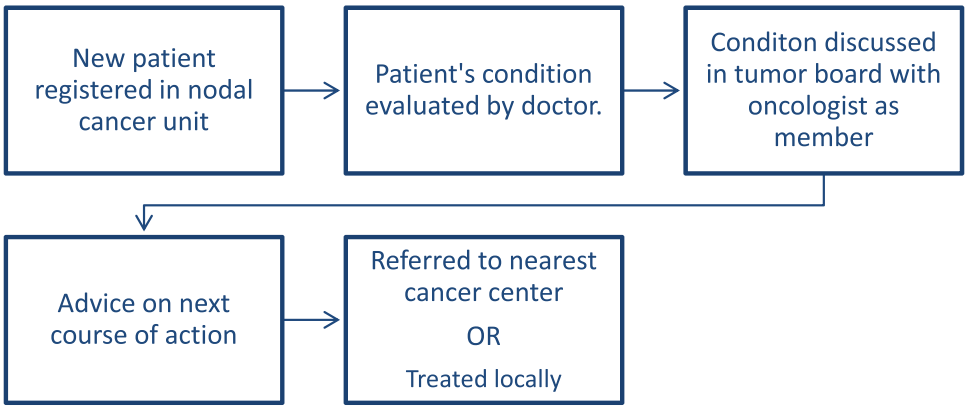
All centers have started performing chemotherapy services as per standard guidelines. The number of chemotherapy sessions ranges from 5 to 150 per month in different hospitals. All classes of drugs are being used, including those that are emetogenic or with potential of acute reactions. Initial outcomes suggest standard toxicity levels comparable to any other center. There has been only one case of mortality related to chemotherapy toxicity. Patients in advanced or terminal stages of the disease are receiving proper palliative and end-of-life care in the districts, which has come as a big relief for the families.

These units have begun serving as centers of public education on cancer and are routinely involved in various activities like rallies, public speeches, poster exhibitions, leaflet distributions, etc. Media outlets and other government machinery are being used. The units have also become centers of professional education. One of the centers is being used for hands-on training for physicians and has been incorporated in to training modules. The physicians have been designated by the state as nodal cancer officers.

Patient data are serving as a local cancer registry and enabling the studying and understanding of many small epidemiologic deviations in the districts, revealing quite striking variations in patterns across different districts. One of the best performing districts has registered 1,564 patients (790 [50.5%] males and 774 [49.5%] females). The distribution of most common cancers is listed in Tables 3 and 4, with head and neck cancer being the most common among men and breast cancer among women. Among men, lung is the second most common, whereas among women, it is head and neck cancer. Prostate cancer is commonly reported. In men, upper gastrointestinal malignancies (esophagus and stomach) are also common. In women, incidence of ovarian cancer is high, higher than cervical cancer. Incidence of hematologic malignancies including leukemia, lymphoma, and myeloma is higher.

Multiple satisfaction surveys conducted among patients attending the services have shown complete confidence in

FIGURE 2. Process of Patient Care



the system. Many patients have chosen district hospitals over tertiary centers for comparable services.

All countries with a high burden of poor, uneducated, tribal, and socially challenged populations, including India, are facing a huge problem of access to care. The problem is multiplied because of the unavailability of qualified oncology personnel or specialized cancer centers. This health care delivery model tries to find a solution to these issues. Bringing affordable care physically close to the population can only bring a positive change. This can be fit into the diagonal approach to system strengthening. More and more tertiary-level specialized cancer centers have shown confidence in districts and have started referring back local patients for intermediate care. More and more chemotherapy sessions are being performed. This proves the reproducibility of the chemotherapy facility under guidance of oncologists. The model reinforces the need for as well as the acceptance of decentralized specialized care. The program has now been running for more than 3 years and has proven its sustainability. Acceptance by other state governments, after evaluation, shows its administrative and political acceptability. Financial outcomes must be analyzed, but one thing is certain: as government services are free, patients are significantly saving out-of-pocket costs by being locally treated and not having to travel to seek care.

The extension of cancer services via a remote support system improves access to care, especially for those living in rural and underserved areas with complex health problems. With the use of electronic medical record– and WhatsApp-based interfaces, specialists are able to consult primary care providers like doctors and nurses on the care of patients with cancer, including the administration of complex chemotherapy protocols and management of side effects. Although a toxicity study is currently underway in district hospital settings, more than 3,000 patients have been treated at these centers. Many of these patients had previously been unable to receive chemotherapy because of access barriers. Those who received chemotherapy both at private or tertiary establishments and district hospitals have not reported any major differences in toxicity or clinicians' ability to manage toxicity and adverse effects. The primary goal of patients accessing treatment at the standard of care was met.

The results of this model show that it is an effective way to treat patients with cancer, administer chemotherapy, and provide palliative care in underserved areas. Implementation of this model would allow other states and nations with limited resources to treat greater numbers of patients with cancer than they are currently able to treat.

Epidemiologic data being generated appear to be different from those of the national data registry. For example, the burden of cervical cancer appears to be lower, whereas ovarian cancer is much higher. These differences are important and warrant serious thinking over causative mechanisms. If micromanagement of preventive strategies is to be planned, these data could be very helpful.

The methodology of counseling camps is turning out to be an excellent tool for the education of local physicians,

TABLE 3. Disease Pattern in Male Population (790 Patients)

Type	No. of Patients	Percent
Head and neck	353	44.7
Lung	110	14.1
Hematologic malignancy	96	12.1
Prostate	47	05.9
Upper gastrointestinal	46	05.8
Other	138	17.4

TABLE 4. Disease Pattern in Female Population (774 Patients)

Type	No. of Patients	Percent
Breast	308	39.8
Head and neck	81	10.5
Ovary	69	08.9
Hematologic malignancies	59	07.6
Cervix	41	05.3
Other	216	27.9

helping in setting local systems and processes, building confidence among the local population, and creating wide public awareness on the issue of cancer. Increasing attendance in districts is showing better participation of patients in the care continuum. The point of contact for cancer vis-a-vis nodal cancer units created are helping to drive cancer care more effectively. These physicians are now undertaking and leading all of the following activities: community-based cancer awareness, prevention, education, counseling and appropriate referrals, administering chemotherapy, conducting post-treatment surveillance, and providing palliative care.[20]

This model offers an alternative solution to managing workforce issues in oncology and establishes a new model of health care delivery in cancer care. The innovative model of empowerment using existing infrastructure and human resources touches on all proposed building blocks of an effective health system as advocated by the World Health Organization and has the potential to expand to other countries with limited resources.[21] This model can serve as an important role in expansion to universal health care. The empowerment of an alternative oncology workforce using basic level physicians can help solve many global issues of access to cancer care.

A DIAGONAL RESPONSE TO WOMEN'S CANCERS: EXAMPLES FROM THE MEXICAN HEALTH SYSTEM

Effective health systems must encompass the six overlapping components of the cancer care and control continuum by developing integrated programs for primary prevention, early detection, diagnosis, treatment, survivorship, and long-term follow-up and palliation; in other words, mapping and supporting the cancer- and patient-specific journey.[22] A diagonal approach is a strategy in which resources for disease-specific intervention priorities, like cancer, are distributed in ways that strengthen the entire health system by driving improvements in systemic areas including human resource development, financing, service provision, drug supply, and quality assurance.[23] This approach overcomes the barriers between vertical (disease-specific) and horizontal (systemic) approaches by making full use of potential synergies between different programs and offers the opportunity to implement person-centered, instead of disease-focused approaches.[24]

A diagonal approach to cancer care addresses the false dichotomy of prevention versus treatment by strengthening integration of programs along the entire continuum of care. This approach can help to link cancer care and control with many services associated with a broad range of health promotion and treatment activities and reinforce human resources and physical infrastructure in health systems in ways that avoid creation of parallel structures for service delivery.[25] A diagonal response also seeks to identify opportunities for optimal use of existing health programs or platforms, including those in other sectors, such as education, to address multiple health priorities and raise public awareness.

In this article, we discuss examples for the case of Mexico and women's cancers. Although Mexico has seen a steady decline in cervical cancer mortality, which peaked at close to 16 per 100,000 women in the late 1980s and then steadily declined to a rate of less than 8 in 2008, breast cancer mortality rose steadily, reaching over 9 per 100,000 by 1995 and has remained relatively stable since.[26,27]

One example of a diagonal approach is the inclusion of cancer in national health insurance programs. In 2003, Mexico underwent a remarkable health reform that introduced the System of Social Protection in Health that includes a publicly funded health insurance scheme, the Seguro Popular de Salud (Popular Health Insurance), to cover universal access to an essential package of services with financial protection, especially targeting the poor and informal workers.[28] As of 2012, the Seguro Popular had affiliated and covered more than 50 million previously uninsured Mexicans and by 2015 further expanded coverage to reach more than 56 million people. The number of covered diseases and interventions has steadily and considerably increased over time, including a growing list of cancers.[24] Both breast and cervical cancer treatment are included in Mexico's Seguro Popular since 2005 and 2007, respectively.

Despite the inclusion of breast cancer in Seguro Popular, access to services for early detection of breast cancer remains limited. The 2012 National Health and Nutrition Survey showed that only one in five Mexican women ages 40 to 69 reported having an annual mammogram or breast clinical exam, with large disparities across the poorest and wealthiest quintiles. The majority of hospital cases are detected at later stages, especially in poorer states and municipalities, and mortality rates are high and increasing despite better access to treatment.[24]

To address the problem of late detection, a number of innovative education, training, and awareness-building interventions have been put in place. A prominent example of the potential for applying a diagonal approach is to integrate interventions for the prevention, early detection, treatment, survivorship, and palliation of women's cancer into antipoverty or maternal and child health programs. For example, the Mexican human development and poverty alleviation program, Oportunidades (now called Prospera), is a social welfare scheme created in 1997 that offers conditional cash transfers to more than 90% of poor, urban, and rural families for the purpose of promoting education, health, and nutrition.[24] Women are the recipients of the cash transfers, and as part of the program, participate in a variety of information and educational outreach activities.[29]

Cervical cancer mortality in Mexico has concentrated among the poorest quintiles despite the fact that this is an easily preventable disease through early detection.[26] Oportunidades and now Prospera include a broad range of activities around cervical cancer. Education initiatives for cervical cancer prevention and clinic visit incentives for women to receive the Papanicolaou test have shown a positive impact on increasing the numbers of beneficiary women who are tested for cervical cancer as well as the willingness of

indigenous women to take the test and encourage other women in their communities to do so.[29] Furthermore, as of 2015, the HPV vaccination is now included in the Prospera package.

The inclusion of information on breast cancer has been much more difficult to achieve. As part of an effort to increase access to early detection of breast cancer, information was included in manuals distributed through Oportunidades, and the program was encouraged to include education and awareness-building on women's cancers in community workshops and educational outreach.[26,30] Through Oportunidades, female household heads and community health promoters throughout the country were trained with basic information about breast health and self-examination.[24] This work must be evaluated and extended as part of Prospera.

Other breast health awareness initiatives in Mexico have explored and developed various educational innovations to provide breast health education for women in their communities and to ensure a properly trained primary health workforce. A multi-institutional group, spearheaded by the civil society organization Tómatelo a Pecho, A.C., and working with the Seguro Popular, the National Institute of Public Health of Mexico, and state governments, was created to train an extensive network of community health workers, nurses, and primary care physicians on early diagnosis and the triaging of high-risk cases with family history.[31] The group worked with local organizations to develop and implement a "train-the-trainer" program to improve breast cancer knowledge among community health workers, including professional health promoters who then trained nonprofessional community health promoters. The educational strategy was designed using a competency-based approach with an emphasis on student-centered activities, innovative tools, collaborative work, and hands-on problem-solving. Training materials included manuals for physicians and nurses, educational kits and workshop development guides for health promoters, and various recreational games involving the identification of warning signs, breast self-examination techniques, treatment, and return to daily life.[32] Participants were surveyed before and after training and demonstrated improvements in understanding of breast cancer as a problem, understanding of screening, treatment, and insurance coverage issues, and knowledge of breast cancer risk factors, symptoms, and what constitutes a family history of breast cancer.[31] The training modules have since been and are now available online. More extensive training on survivorship, pain management, and palliative care is now underway.[24]

These innovative interventions to improve training, education, and awareness constitute a diagonal approach and build on overall efforts to strengthen primary care and link to specialized tertiary treatment options, instead of developing parallel systems for early detection of cancers. These examples deserve rigorous evaluation, as they suggest that diagonal strategies for early detection of breast cancer can be implemented through integration into national insurance and social security schemes and that antipoverty, maternal and child health, sexual and reproductive health, and other programs can serve as platforms for addressing early detection and prevention of cancer.[24]

CONCLUSION

The case studies presented in this article discuss different strategies for improving cancer management along the entire continuum of care. Although cultural diversity and regional idiosyncrasies across the world will always exist, and context-relevant solutions will always be needed, there are key challenges in cancer care that are universal. Improving global cancer survival requires innovative solutions for the education of both health care professionals and the public. Community empowerment through training of community health promoters and alternative workforces can ensure the uptake and sustainability of improvements in early detection and quality of care. Finally, these solutions need not be cancer specific or developed in parallel silos; health systems can be strengthened through diagonal approaches that find synergies across diseases and build off existing programs or platforms.

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Wedge Resection Versus Anatomic Resection: Extent of Surgical Resection for Stage I and II Lung Cancer

Hisao Asamura, MD, Keiju Aokage, MD, and Masaya Yotsukura, MD

OVERVIEW

Currently, surgery for lung cancer with curative intent consists of resection (removal) of the proper extent of lung parenchyma that bears the cancer lesion along with locoregional lymph nodes to assess possible cancer metastasis. Lobectomy, at least, is preferred with regard to the extent of parenchymal resection. The history of lung cancer surgery, which started around 1933 as pneumonectomy (resection of the entire lung on either side), can be characterized as an attempt to minimize the extent of parenchymal resection. In the early 1960s, pneumonectomy was replaced by lobectomy, which has long been respected as the standard surgical mode. However, the transition from lobectomy to a lesser resection, such as segmentectomy or wedge resection, was not recommended because of the results of a randomized trial performed by the North American Lung Cancer Study Group in the 1980s. As of now, the extent of parenchymal resection remains lobectomy, and lesser resection is indicated only for patients who have a compromised pulmonary reserve. Very recently, because of the advent of CT screening programs and improvements in imaging technology, fainter and smaller lung cancers are being discovered. For these smaller and earlier lung cancers, there is some uncertainty about whether lobectomy still should be indicated, as it is for larger tumors with a diameter of 3 cm or more. Therefore, several randomized trials are ongoing to compare lobectomy with lesser resections; endpoints are overall survival and postoperative pulmonary function. Until the results of these trials are available, lung cancer should still be removed by lobectomy rather than by limited resection, such as segmentectomy or wedge resection.

Surgery continues to be the mainstay in the treatment of early-stage lung cancer and may ensure the total removal of cancer cells limited to the lung parenchyma and locoregional lymph nodes to achieve a cure. The first successful en bloc left-sided pneumonectomy for lung cancer was performed by Graham and Singer[1] in 1933. Pneumonectomy is the removal of one entire lung on either side, which represents the largest amount of lung parenchyma that could be removed safely by surgery. Since then, surgeons have tried to remove tumors by removing smaller amounts of lung parenchyma while considering postoperative pulmonary function. The extent of parenchymal resection gradually was reduced from pneumonectomy to lobectomy in the early 1960s, and additional attempts to minimize the extent of resection even more, from lobectomy to sublobar resection (i.e., wedge resection and segmentectomy), were made in the 1980s. However, a smaller resection inevitably increases the risk of incomplete removal of the tumor and subsequent local tumor recurrence. In this sense, surgeons have been trying to achieve an optimal balance between the radicality of cancer surgery and a safe surgical margin.[2]

On the basis of the results of the landmark study by Ginsberg et al[3] in the 1980s, lobectomy has been considered the optimal mode of pulmonary resection for lung cancer when combined with clearance of the lymphatic route of the pulmonary hilum and mediastinum, a procedure originally described by Cahan[4] as radical lobectomy. However, because of the advent of CT screening programs and improvements in imaging technology, fainter and smaller lung cancers are being encountered in daily practice. For these smaller and earlier lung cancers, it is not quite clear whether lobectomy is an optimal surgery. Therefore, very recently, several randomized trials have been undertaken to compare lobectomy and lesser, limited resection.[5]

This article presents the technical aspects of standard and lesser, limited resections for lung cancer, a historical overview of the evolution of lung cancer surgery since the 1930s, and previous and ongoing clinical studies that aim to identify the optimal extent of the lung parenchyma to be resected in radical, curative surgery for early-stage (stages I and II) lung cancer.

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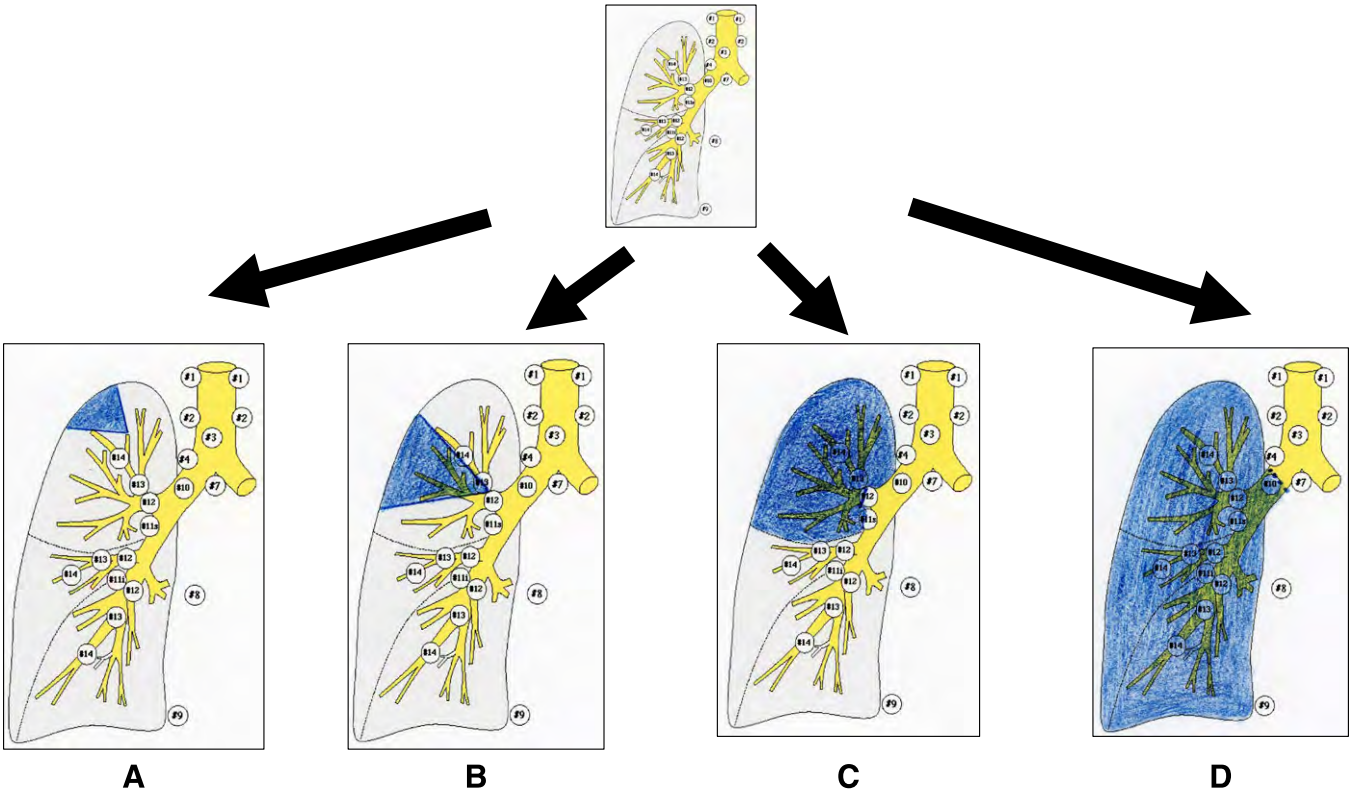
FIGURE 1. Schematic Drawing of the Extent of Pulmonary Resections



(A) Wedge resection; (B) segmentectomy; (C) lobectomy; and (D) pneumonectomy.

PARENCHYMAL PULMONARY RESECTION FOR LUNG CANCER: OPERATIVE MODES TO RESECT DIFFERENT AMOUNTS OF THE LUNG PARENCHYMA

The present-day surgery for lung cancer with curative intent consists of complete removal of the primary lesion of the lung and clearance of the locoregional lymphatic drainage route. Therefore, it involves resection (removal) of the proper extent of lung parenchyma that bears the cancer lesion together with locoregional lymph nodes to assess possible cancer metastasis.[6] For resection of the lung parenchyma, the following surgical modes technically could be selected according to the extent of the disease and its nature (Fig. 1): pneumonectomy (removal of the entire lung on either side), bilobectomy (removal of two adjacent lobes), lobectomy (removal of a single lobe), segmentectomy (removal of a single segment or adjacent segments), and wedge/partial resection (removal of wedge-shaped parenchyma regardless of the bronchovascular anatomy). If the proximal portion of the bronchus is involved by direct extension of the tumor or if there is lymph node metastasis at the hilum and neither lobectomy nor pneumonectomy could ensure that the resected end of the bronchus would be tumor free, a sleeve resection, which entails combined resection of the proximal portion of the bronchus and reconstruction, might be considered in conjunction with lobectomy (sleeve lobectomy) or pneumonectomy (sleeve pneumonectomy) to ensure a safe surgical margin. Sleeve resection enables tumor-free resection without sacrifice of uninvolved lung parenchyma.

The techniques used at the pulmonary hilum, though, can be divided into two types: anatomic (pneumonectomy, bilobectomy, lobectomy, and segmentectomy) and nonanatomic resection (wedge resection). In anatomic resection, the extent of resected parenchyma is determined according to the extent of perfusion of pulmonary vessels as well as by the extent of aeration of bronchi, which are divided at the

KEY POINTS

- **The present-day standard operative mode for the resection of lung cancer is at least lobectomy (i.e., lobectomy, pneumonectomy) with mediastinal/hilar lymph node dissection/sampling.**
- **Lesser resections, such as wedge resection and segmental resection, are referred to as limited resection or sublobar resection.**
- **Only one randomized trial to compare limited resection with lobectomy showed a higher incidence of local recurrence and a poor prognosis with limited resection.**
- **Several randomized trials are underway to determine whether limited resection can provide at least an equivalent prognosis and better postoperative pulmonary function compared with lobectomy in early-stage non–small cell lung cancer.**
- **Limited resection is routinely used for the resection of lung cancer in patients with limited pulmonary reserve or high risk of comorbidity.**

hilum. In nonanatomic resection, the extent of parenchymal resection is determined solely according to the location of the target lesion.

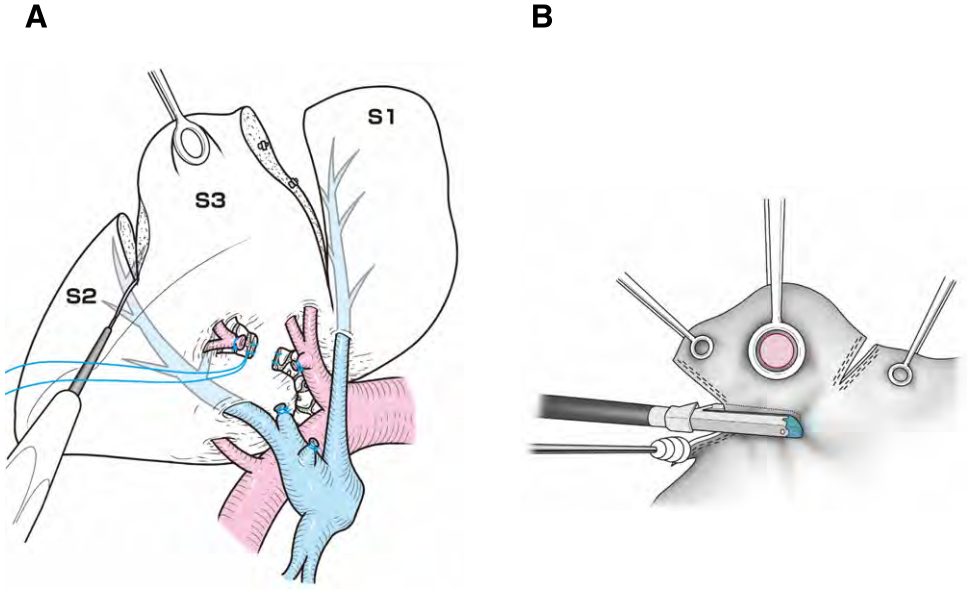
SUBLOBAR RESECTIONS

Among the modes of pulmonary resection, segmentectomy and wedge resection are both referred to as sublobar resection, because the resected parenchyma by these two modes are smaller than lobe. Despite this similar classification, their technical characteristics are quite different, especially at the hilum. In segmental resection, the hilum needs to be dissected for individual division and ligation, exactly as in lobectomy and pneumonectomy. This is why segmentectomy is considered anatomic resection (Fig. 2A). Conversely, in wedge resection, the extent of resection is determined according to what the surgeons think is appropriate, regardless of the bronchovascular anatomy. Thus, wedge resection is considered nonanatomic resection (Fig. 2B). Therefore, although they both are considered sublobar resection, these two operative modes have technical differences.

Evolution of Lung Cancer Surgery: A History of Minimization

The history of lung cancer surgery can be thought of in terms of minimization of the extent of parenchymal resection. Surgeons try to achieve an optimal balance between the radicality of cancer surgery and the preservation of postoperative lung function. The earliest report about pneumonectomy of the right side was by Kummel[7] in 1910; the patient, a 40-year-old man, died on the sixth postoperative day. After a series of early postoperative deaths after pneumonectomy in the 1920s, Evarts Graham[1] in St. Louis reported the first successful pneumonectomy, which was performed on a 48-year-old man with lung cancer by using a tourniquet technique, in 1933. After this landmark operation, successful reports of pneumonectomy for lung cancer were documented. In 1940, Overholt[8] reviewed 110 pneumonectomies, including 15 of his own patient cases, for benign and malignant lung diseases, and reported a mortality rate of 65% for the malignant group. He also stated that the operability of primary lung cancer was 25%.[8] In the 1940s, pneumonectomy was established as the standard mode of pulmonary resection for lung cancer. In 1950, Allison[9] performed pneumonectomy with intrapericardial ligation of the pulmonary vessels, and, more importantly, the addition of locoregional lymph node dissection to pneumonectomy was proposed as radical surgery for lung cancer. Cahan[10] called this procedure radical pneumonectomy, which indicated the combination of parenchymal resection and lymph node dissection. In the 1950s and 1960s, pneumonectomy gradually was replaced by lobectomy. This era was the transitional phase from pneumonectomy to lobectomy for lung cancer. In 1950, Churchill[11] reported a better 5-year survival rate with lobectomy (19%) than with pneumonectomy (12%). In 1960, Cahan[4] again defined radical lobectomy as an operation in which one or two lobes of an entire lung are excised in a block dissection along with certain of their regional hilar and mediastinal lymphatics (Fig. 3). The extent of lymph node dissection also was defined according to the primary site of the lung cancer. Cahan[4] analyzed the outcome of 48 radical lobectomies for primary and metastatic lung cancers and concluded that survival for 5 years or longer was associated in large part with more extensive lymphatic dissection and radical lobectomy. In the 1970s and 1980s, lobectomy became recognized as the standard mode of resection for primary lung

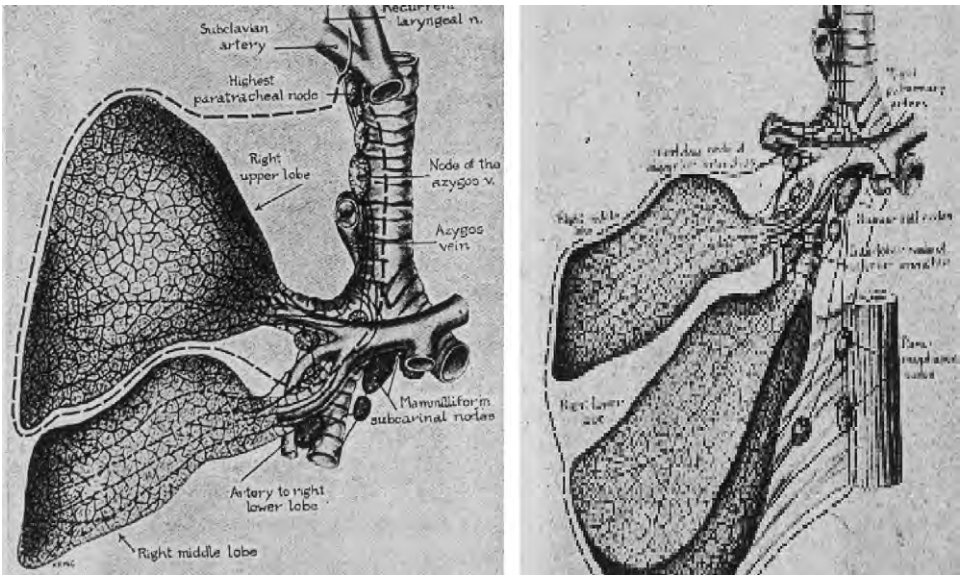
FIGURE 2. Sublobar Resections



(A) Posterior segmentectomy of the right upper lobe. Note the individual division and ligation of the pulmonary bronchovascular structures before the division of the lung parenchyma. (B) Wide wedge resection.

Abbreviations: S1, superior segment; S2, posterior segment; S3, anterior segment of the right upper lobe.

FIGURE 3. Radical Lobectomy by Cahan (1960)[4]



The extent of parenchymal resection (lobe) and lymph node dissection is determined according to the location of the primary tumor.

cancer, and pneumonectomy was no longer the standard approach.

However, lesser resections (i.e., segmentectomy and wedge resection) for peripheral lung cancer always have been reserved for compromised patients who could not tolerate more extensive procedures, such as lobectomy or pneumonectomy. Churchill and Belsey[12] originally introduced segmental resection as segmental pneumonectomy for the treatment of benign lung diseases in 1939. This technique was advocated for use later in patients with cancer who had limited pulmonary reserve and inoperable disease. In 1973, Jensik et al[13] suggested that anatomic pulmonary segmentectomy could be applied effectively to small primary lung cancers when the surgical margins were sufficient.

These reports stimulated a debate about the optimal resection technique for early-stage non–small cell lung cancer (NSCLC). The optimal technique was addressed in a prospective, randomized trial conducted by the Lung Cancer Study Group in 247 patients with stage IA NSCLC.[3] Limited pulmonary resection, including anatomic segmentectomy and nonanatomic wide-wedge resections, was compared with lobectomy to evaluate the postoperative prognosis and pulmonary function. This study showed a 39% increase in local recurrence and a nonsignificant decrease in overall survival after sublobar resection. It included patients with tumors of 3 cm or less and a significant number of nonanatomic wedge resections (i.e., one of three sublobar procedures). In retrospect, both of these parameters may have significantly limited the effectiveness of sublobar resection. In short, this study solidified lobectomy as the procedure of choice for the treatment of this disease on the basis of the inferior postoperative survival and increased locoregional recurrence in the limited-resection group. This still is the only randomized trial to compare limited resection with lobectomy directly; therefore, the gold standard for lung cancer remains lobectomy with lymph node sampling/dissection.

Recently, the results of a prospective, randomized trial (ACOSOG Z0030) to evaluate the prognostic significance of lymph node dissection in lung cancer were published.[14,15] This study compared systematic sampling and dissection for N0 or nonhilar N1, T1, or T2 NSCLC (stages I and II). This study did not show that lymph node dissection offered a prognostic advantage compared with sampling. The authors concluded that, if systematic and thorough presection sampling of the mediastinal and hilar lymph nodes is negative, mediastinal lymph node dissection does not improve survival in patients with early-stage NSCLC, but these results are not generalizable to patients whose disease was staged radiographically or those with higher-stage tumors.

On the basis of the combination of these results, it is widely accepted that the present-day gold standard should be lobectomy, at least, with lymph node sampling/dissection for stages I and II disease.

A NEW WHO CLASSIFICATION OF LUNG CANCER AND NEW CONCEPT OF EARLY FORMS OF ADENOCARCINOMA

Recently, a new classification of adenocarcinoma of the lung was published to provide uniform terminology and diagnostic criteria, with a particular focus on the classification of earlier forms of adenocarcinoma.[16] New concepts, such as adenocarcinoma in situ and minimally invasive adenocarcinoma for small solitary adenocarcinomas with either pure lepidic growth or predominant lepidic growth of less than 5 mm, were introduced to define patients who, if they were to undergo complete resection, could be expected to have 100% or near-100% disease-specific survival, respectively. However, adenocarcinomas are classified according to the predominant pattern (lepidic, acinar, papillary, or

solid) after comprehensive histologic subtyping. These earlier forms, such as adenocarcinoma in situ and minimally invasive adenocarcinoma, were recognized only after the advent of high-resolution CT scans and the dissemination of CT screening programs. In a registry study, patients with an earlier disease stage were included in a stage IA group, and the proportion of these patients might be associated with the difference in survival, especially for stage IA disease. The surgical significance of these classifications also has been analyzed.[17] Recently, the prognosis of 545 patients with radiographically determined noninvasive adenocarcinomas of the lung of ground-glass opacity was reported; a consolidation-to-tumor ratio of 0.25 or less in cT1a was used as the radiologic criteria of noninvasive cancer, and the lesion was resected by lobectomy.[18,19] The reported 5-year survival rates for noninvasive and invasive adenocarcinomas were 96.7% and 88.9%, respectively. This superb surgical outcome supports the possibility of lesser resection, such as segmentectomy and wedge resection, for patients with early lung cancers.

POSSIBILITY OF SUBLOBAR, LIMITED RESECTION FOR EARLY-STAGE LUNG CANCER

Technical and Pathologic Considerations

Several factors must be weighed in terms of the characteristics of sublobar resection, especially segmental resection, when it is considered as an option for radical resection for lung cancer, for which no tumor tissue can be left behind. In sublobar resections, the lung parenchyma must be transected and divided for completion of the procedure, whereas, in lobectomy, the fissure is divided to remove the entire lobe. In relation to the nature of these procedures, some technical limitations in sublobar resection include tumor size, location, histologic type as lung cancer, and nodal involvement. Tumor size and location, in particular, are closely related to the safe surgical margin when performed as radical resection.

Tumor size and local recurrence after sublobar resection have been extensively studied. It has been shown repeatedly that tumors larger than 2 cm have a significantly higher local recurrence rate than those smaller than 2 cm.[20-22] Another important factor is the location of the tumor in relation to the pleural surface/hilum. A fundamental, geometric understanding of a lung segment is that the segment is fan shaped with the base on the pleural surface and the apex at the pulmonary hilum. Therefore, the distance between a tumor and the resection line inevitably is closer when the tumor is located close to the hilum, even if the tumor is small. Generally, even for tumors of 2 cm or less in diameter, segmentectomy/wedge resection should be performed only when tumors are located in the outer third of the lung parenchyma. Other unfavorable factors for limited resection are an aggressive histology, such as small cell carcinoma, and lymph node involvement. These conditions indicate that there is a greater possibility of tumor spread in the lobe that contains the segment.

Very recently, the results of 164 intentional, extended segmentectomies were reported as a comparison with lobectomy.[23] The incidence of locoregional recurrence after segmentectomy was reported according to the location of the resected site. The incidences of local and locoregional recurrences, respectively, were 21.9% and 21.9% for the right upper lobe, 10.5% and 15.8% for the left upper lobe, 4.2% and 4.2% for the bilateral superior segment of the lower lobes, and 20.8% and 37.5% for the bilateral basal segments. The incidence of local or locoregional recurrence was significantly higher for segmentectomies of the right upper lobe and bilateral basal segments. These results indicated that tumors in the basal segments should be resected by lobectomy rather than by segmentectomy, even if the tumors are small. Segmentectomy could be desirable or undesirable according to on the anatomic location. This issue is related solely to the anatomic structure of the lobe and segment as a functional unit in the lung.

Oncologic Considerations

Currently, limited, sublobar resection for lung cancer could be considered for the following situations: (1) limited resection of T1N0M0 lung cancer in compromised patients who have limited cardiopulmonary reserve regardless of the type of lesion; (2) limited resection for early lung cancer with a predominantly ground-glass opaque appearance (pathologic adenocarcinoma in situ/minimally invasive adenocarcinoma); and (3) limited resection for small but invasive lung cancers located in the periphery of the lung.

As discussed in the previous section, considerable interest in sublobar resection began in the 1970s and 1980s, when the feasibility of limited resection for patients with compromised cardiopulmonary reserve was demonstrated. Then, the 5-year survival rate and the recurrence rate were considered inferior to those for lobectomy, and sublobar resection was restricted to patients who had impaired cardiac function or significant comorbidities that would preclude conventional lobectomy. Decreased survival and increased recurrence were demonstrated in 173 patients with stage I NSCLC who underwent sublobar resection or lobectomy, as reported in an early work by Warren and Faber.[24] However, recent single-institution, retrospective investigations to evaluate the equivalency of sublobar resection to lobectomy in patients who have limited cardiopulmonary reserve contradicted these earlier results and demonstrated that stage I disease has a survival advantage regardless of the extent of surgical resection or histologic subtype. Campione et al[25] found no significant difference in survival between lobectomy and anatomic segmentectomy in a series of 121 patients with stage IA disease. Other studies showed similar results with segmentectomy and lobectomy.[26-33] The surgical indication of limited resection for patients with stage IA disease who have limited cardiopulmonary reserve is respected as a reasonable treatment of choice. As discussed in the previous section, adenocarcinoma in situ and minimally invasive adenocarcinoma comprise a novel concept that refers to the noninvasive or minimally invasive nature of adenocarcinoma with a unique, ground-glass opacity. The use of limited resection for patients who have nonsolid (pure)

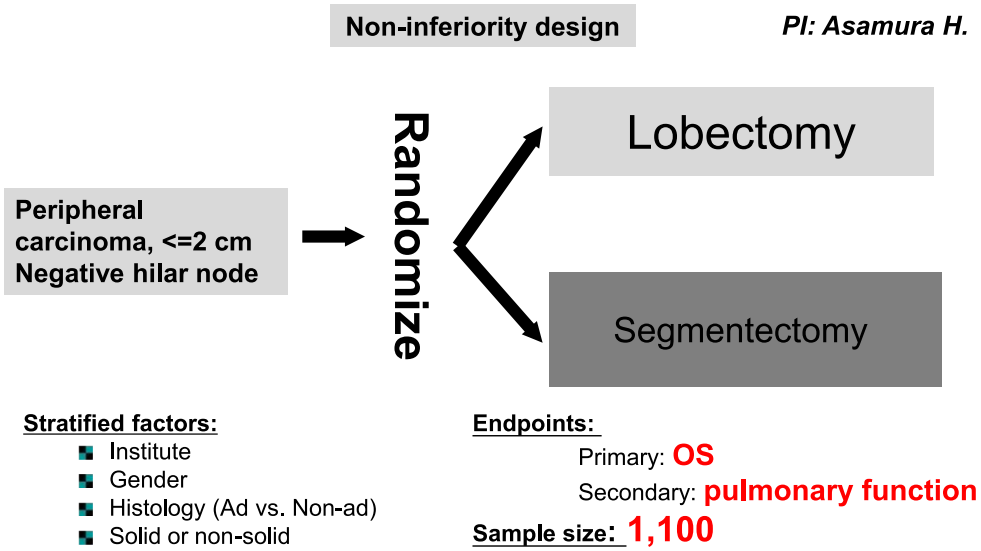
or part-solid (mixed) ground-glass opaque presentation has been assessed in a variety of retrospective Japanese studies. In each of these studies, patients with adenocarcinoma in situ or minimally invasive adenocarcinoma tumors had prolonged survival and lower recurrence after resection than those with other subtypes of NSCLC. The application of sublobar resection for these early tumors was based upon a clinicopathologic study on the correlation between the degree of invasive growth (stromal invasion) and the prognosis. Sakurai et al[34] classified 380 resected adenocarcinomas of 2 cm or less in diameter according to the degree of invasive growth (i.e., structural deformity and location in the adenocarcinoma) and showed that patients who had noninvasive or minimally invasive adenocarcinomas could achieve 100% survival despite the mode of pulmonary resection. On the basis of these clinicopathologic observations, sublobar resection for adenocarcinoma in situ/minimally invasive adenocarcinoma tumors with ground-glass opacity could be considered reasonable according to the location and size of the tumor.

The indication of sublobar resection needs to be considered from not only an oncologic but also an anatomic perspective. For occurrences in which the tumor is located deep inside the lung parenchyma, a safe surgical margin cannot be ensured in sublobar resection, because the surgical margin is close to the hilar structures. A lung segment is generally shaped like a sector, with the apex at the hilum, which indicates that there is a shorter distance between the tumor and resected margin in the area close to the hilum. The tumor diameter also affects the distance to the surgical margin. Therefore, sublobar resection should be applied only when the tumor is located in the outer third of the lung parenchyma and preferably when the tumor is 2 cm or less in diameter. For tumors located in the inner two-thirds of the lung parenchyma or for those larger than 2 cm in diameter, lobectomy still should be selected regardless of the tumor pathology.

Ongoing Trials to Compare Lobectomy and Limited Resection

For histologically invasive lung cancers that are located in the periphery of the lung as a small (2 cm or less: T1a) solitary nodule, the feasibility of limited, sublobar resection needs to be defined from a present-day perspective. This means that the Lung Cancer Study Group study in the late 1980s must be revised.[3] Indeed, the present-day routine work-up for patients with resectable lung cancer is much different than the work-up used in the 1980s. A few prospective studies are ongoing. Randomized clinical trials that enrolled patients with peripheral lung cancers of no more than 2 cm in diameter as the target lesions are underway in the United States (Cancer and Leukemia Group B study CALGB140503) and Japan (Japan Clinical Oncology Group and West Japan Oncology Group study JCOG0802/WJOG4607L).[35] As of January 2017, the targeted number of patients in the Japan Clinical Oncology Group study was registered, and data maturation is awaited. The design of the phase III Japan Clinical Oncology Group study is shown in Fig. 4. In this trial, the endpoints are overall survival (primary) and postoperative pulmonary function (secondary), and the targeted accrual is 1,100 patients. If the results show that the prognoses of patients who undergo segmentectomy is not significantly inferior to that of patients who undergo lobectomy and that the postoperative pulmonary function is significantly better for the patients who undergo segmentectomy, then we can conclude definitively that the standard surgical mode for these early tumors should be segmentectomy.

FIGURE 4. Design of JCOG0802/WJOG4607L, a Randomized Trial to Compare the Prognoses and Postoperative Function After Segmentectomy or Lobectomy for Non–Small Cell Lung Cancer ≤ 2 cm Diameter



Abbreviation: OS, overall survival.

CONCLUSION

Lobectomy with hilar and mediastinal lymph node dissection/sampling is still the present-day gold standard for the resection of lung cancer. Sublobar resection such as segmentectomy and wedge resection could be reasonably used for compromised patients at high risk. The use of sublobar resection might be justified for most early lung cancer with no or minimal inasive features located in the outer region of the lung parenchyma. The possibility of sublobar resection for lung cancer with overt invasive features is under investigation, with particular focus on tumors 2 cm or less in diameter. The results of several on-going trials are awaited. Lobectomy should be recognized as the standard mode of resection for good-risk patients.

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GYNECOLOGIC CANCER

Endometrial Cancer: Is This a New Disease?

Kathleen Moore, MD, and Molly A. Brewer, DVM, MD, MS

OVERVIEW

The incidence of endometrial cancer is increasing, and the age of onset is younger than in prior years. Although endometrial cancer still occurs more commonly in older women, for whom the mortality rate is increasing, it also is being diagnosed in younger and younger women. The underlying cause of the increase in incidence is the epidemic of obesity and the resulting hyperinsulinemia. Conservative treatment may be indicated for younger women who wish to retain their fertility. Lifestyle modifications such as diet and exercise can modulate the risk of developing endometrial cancer as well as prevent recurrence and other comorbidities associated with obesity.

In 2012, 527,600 women worldwide were diagnosed with endometrial cancer.[1] The mortality rate was 1.7 to 2.4 per 100,000 women. In 2017, there will be an estimated 61,380 cases of endometrial cancer diagnosed in the United States and more than 10,920 deaths.[2] Historically, the age of onset was typically in postmenopausal women, with a strong association with obesity. As compared with just 3 years ago, this is almost 10,000 more cases and over 2,000 more deaths as a result of endometrial cancer. However, in the past 10 years, the incidence of endometrial cancer in young women has increased dramatically as a result of earlier-onset obesity. It is the fourth most common cancer for women in the United States.

ENDOMETRIAL CANCER

Endometrial Cancer in the Older Population

The ideal management of endometrial cancer in an older population, typically defined as older than age 65, is largely unknown, despite the fact that this population is the most rapidly growing age group in the United States. Endometrial cancer, which is predominantly a disease of postmenopausal women, is expected to increase in prevalence with an increasingly older population. Whereas 25% of cases will be diagnosed in patients over age 70, 50% of deaths from endometrial cancer will occur in this same older age group. Despite the increased rates of endometrial cancer mortality seen in elderly patients, studies show these patients receive less aggressive therapy than their younger counterparts, which is presumed to be due, in part, to the physician bias that older patients cannot tolerate aggressive therapy. Prior literature supports this, showing that advanced age is an independent risk factor for perioperative morbidity, even when controlling for medical comorbidities.[3] A Surveillance, Epidemiology, and End Results (SEER) program analysis of over 37,000 women with endometrial cancer found age-related changes in management. For example, whereas 95% of women younger than age 70 underwent a hysterectomy, only 67% of women older than age 80 underwent a hysterectomy. Similar findings were reported for lymphadenectomy, with only 25% of women older than age 80 as compared with almost 50% of women age 60 to 69 undergoing full staging.[4] A multi-institutional study from France found similar trends, with declining rates of pelvic lymphadenectomy with age (85% vs. 46% in patients younger than age 65 years and older than age 80, respectively).[5]

When considering the optimal treatment approach for the older patient with endometrial cancer, there are several factors in play. One factor to consider is the mortality risk a particular cancer has for a particular patient. In other words, what type of endometrial cancer do older patients develop? What is their risk for extra-uterine spread? Can we use this information to direct the planned surgical intervention? Although not therapeutic, lymphadenectomy can direct subsequent therapy depending on findings. Identification of those patients at highest risk for extra-uterine spread of disease allows us to potentially triage our surgical approach based on these risks. Another factor to consider is the risk of surgical intervention(s) on the older patient. The intersection of these two factors can help define whether a surgical intervention is offered and, if offered, what type of surgical intervention that might be.

Disease Risk

Increasing age plays a strong role in predicting recurrence in endometrial cancer. Gynecologic Oncology Group (GOG)

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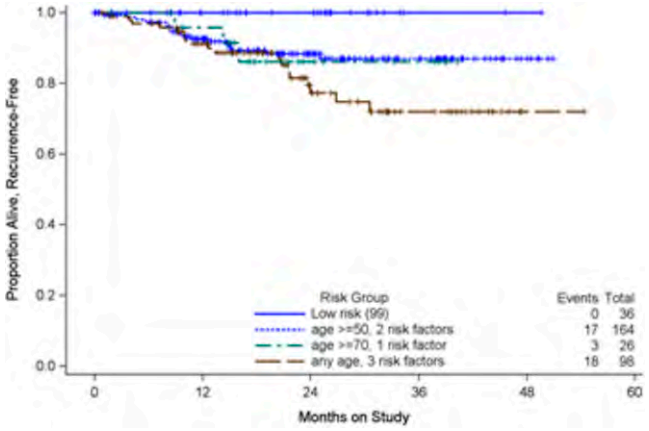
FIGURE 1. Recurrence-Free Survival Stratified by Number of Uterine Risk Factors and Age From Gynecologic Oncology Protocol 249[9]



Study 99 was designed to evaluate surgery alone, including lymphadenectomy, versus surgery and adjuvant pelvic radiotherapy in patients with intermediate-risk, stage I, and occult stage II endometrioid endometrial adenocarcinoma. A subset analysis identified a group with a 25% risk of recurrence and labeled as high intermediate risk (H-IR). H-IR patients included those older than age 70 plus one uterine factor, those age 50–70 plus two factors, or any age plus three factors. Uterine risk factors included grade 2 or 3, presence of lymph vascular space invasion, and depth of invasion to the outer one-third of the myometrium.[6] Other similar studies such as the first Post-Operative Radiotherapy in Endometrial Cancer trial also found age was associated with increased disease recurrence.[7] An ancillary data analysis of the GOG LAP2 study, which compared laparoscopic versus open hysterectomy and lymphadenectomy in clinical stage I patients, evaluated the pathologic findings and disease-related outcomes by increasing age. They reported that, of the entire LAP2 population, 37% met H-IR criteria, and 43% of those were older than age 70. Only 23% of the entire LAP2 population was older than age 70, but 55% of those patients met H-IR criteria. When looking at rates of adjuvant treatment across age groups in this H-IR subset, as age increased, significantly less radiotherapy was administered, with 60% of patients younger than age 50 receiving radiotherapy versus 24%–27% in patients age 50–79 and only 17.3% in patients age 80 or older (p = .011). Despite these differences, receipt of adjuvant radiotherapy did not impact progression-free survival (PFS) or overall survival (OS) in this subset, and the only factors that were significant for OS were grade 3 disease (p = .016; hazard ratio [HR], 1.99), nonwhite race (p = .043; HR, 1.62), age (p < .001; HR, 1.05), and body mass index (BMI; p = .008; HR, 1.03). Although age remained important in models of overall survival, it is interesting to note that of the 370 patients older than age 70 who met H-IR criteria, the majority did so by age and just one uterine risks factor, usually grade 2 or 3 disease. The recurrence risk in this group was only 3.3%, as compared with those with all three uterine factors at 20.9%.[7,8]

The idea that the GOG H-IR algorithm identifies many low-risk patients was reinforced by subset analysis of GOG 249. Here, the true discriminator of risk appears to be presence of all three uterine risk factors (Fig. 1). How increasing age modifies this risk is unknown, but these appear to be the highest-risk patients who may require adjuvant therapy to improve outcomes.

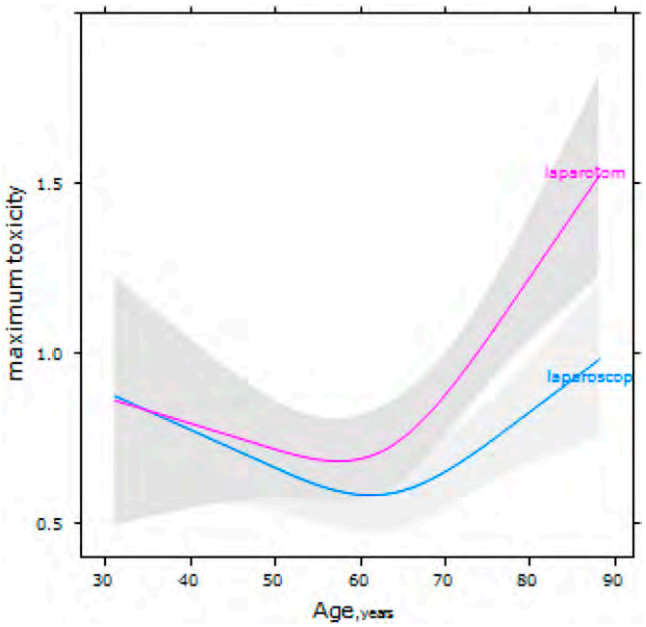
KEY POINTS

- **Obesity with a BMI greater than 30 is responsible for up to 81% of the endometrial cancer diagnosed.**
- **Older women experience increased mortality rates from both their cancer and the surgery, and risk needs to be closely balanced with benefit.**
- **Younger women also have an increase in endometrial cancer and its precursors and can be successfully treated conservatively to maintain fertility.**
- **Changing one's lifestyle, although critical, is not often successful, which may be, in part, a result of a lack of counseling from physicians as well as a long history of an unhealthy lifestyle.**

Surgical Risk

Options for primary treatment include hysterectomy alone (including vaginal hysterectomy with regional anesthesia), hysterectomy with lymph node staging, or no hysterectomy at all and treatment with primary radiation. The decision whether to plan a lymphadenectomy is a controversial topic in all endometrial cancer cases, much less in cases with older patients. From a pure morbidity standpoint, we do have data on perioperative and postoperative complications in older patients undergoing a hysterectomy with and without planned lymphadenectomy as compared with either approach in younger patients. Minimally invasive surgical management of many types of cancers is commonly used, and there is a large amount of data showing similar oncologic outcomes and decreased morbidity with minimally invasive techniques versus laparotomy.[10,11] Several small

FIGURE 2. Description of a Linear Model With Outcome of Maximum Toxicity Including Explanatory Variables



retrospective studies show decreased morbidity in older patients treated with minimally invasive techniques, but to date, we have no prospective data comparing outcomes in the elderly.[12,13]

GOG protocol GOG 2222 or LAP2 was a randomized, prospective clinical trial to compare comprehensive surgical staging by laparotomy versus laparoscopy for the treatment of patients with stage I–IIA endometrial cancer (2,616 patients). LAP2 is the largest prospective trial to date looking at minimally invasive surgical approaches in clinically early-stage endometrial cancer. This study includes 1,477 patients age 60 or older, 762 of whom are age 60–69 and 715 of whom are age 70 or older.

An ancillary data analysis was performed to look at both the operative risks of hysterectomy and lymphadenectomy in an older population and to assess histologic, tumor-related risk, and disease-specific outcome. There was noted to be a much higher rate of complications in the laparotomy group, and this difference became larger with increasing age starting at age 60. Patients younger than age 50 had the same rates of postoperative complications (laparotomy, 15.9% vs. laparoscopy, 15.7%), whereas patients age 80 or older had very different rates of complications (laparotomy, 38.9% vs. laparoscopy, 19.8%).[14]

Comparison of complications during and following laparotomy versus laparoscopy by age and controlling for race, BMI, stage, and grade found higher rates of postoperative antibiotics (odds ratio [OR], 1.63) and hospital stay longer than 2 days (OR, 12.77), as compared with patients younger than 60. Patients age 60 or older in the laparotomy group had higher rates of readmission (OR, 1.52), ileus (OR, 2.16), pneumonia (OR, 2.36), deep vein thrombosis (OR, 2.87), and arrhythmia (OR, 3.21).[14]

Figure 2 describes a linear model with outcome of maximum toxicity, including explanatory variables such as age, race, and BMI. The change in maximum toxicity before approximately age 60 is not significant, but after age 60, the toxicity appears to increase sharply, with interaction between the surgical approach and age having a moderate effect ($p = .035$). As age increases, the benefit from laparoscopy appears to increase as well, and according to this model, the benefit occurs beginning at age 60,[14] demonstrating that for older patients who are fit enough to be considered for hysterectomy and lymphadenectomy, a minimally invasive approach is favored.

There has been a shift from laparoscopic to a robotic approach, and with this shift comes potentially important changes for the older population. Robotic surgery requires a steep Trendelenberg position and potentially longer operative times, which can place patients at risk for ischemic optic neuropathy. Risk factors for this include hypertension, diabetes, known cardiovascular disease, and narrow-angle glaucoma all of which are more common with age.[15]

Despite the potential complications noted above, the data surrounding use of robotic hysterectomy with or without lymphadenectomy are similar to the laparoscopic data with less complications and acceptable surgical outcomes. Krause et al reported on 705 patients, 50 of whom were older than age 75 and underwent robotic gynecologic procedures, and found that, other than increased length of stay longer than 1 day (30.0% vs. 15%; $p < .01$) and higher incidence of postoperative arrhythmia (8.0% vs. 1.2%; $p < .01$), there were no other differences in the relatively low rate of intraoperative and postoperative complications. Of note, the arrhythmias did not result in cardioversion for any patient in the elderly group and only one patient in the younger group.[16] Similarly,

Backes et al compared open versus robotic hysterectomy with or without lymphadectomy and reinforced the safety of robotic surgery in an older population (here defined as age 70 or older). As compared with laparotomy, they report a higher incidence of pelvic lymphadenectomy completion, decreased blood loss and need for transfusion, shorter hospital stay, and no increase in intraoperative complications.[17] No incidence of ischemic optic neuropathy has been reported to date in these series of older patients.

Data also show increased risk of complications by age for patients who undergo an exploratory laparotomy for hysterectomy with or without a lymphadenectomy. A SEER analysis looked at over 25,000 women age 65 or older who underwent hysterectomy for endometrial cancer. Compared with women age 65–69, women age 85 or older were more likely to have perioperative complications (12% vs. 17%), postoperative medical complications (24% vs. 34%), a longer hospital stay (3 vs. 5 days), and require more blood transfusions (6% vs. 10%). Perioperative mortality rates were significantly higher in patients age 85 or older compared with those age 65–69 (1.6% vs. 0.4%). These results were the same when controlling for medical comorbidities.[3]

These data on postoperative complications are important to consider when selecting surgical procedures and optimal approaches in the older patient, as surgical complications can impact overall survival. Certain complications that occur within 30 days of surgery were more important than preoperative patient risk and intraoperative factors in determining survival after major surgery.[18]

Endometrial Cancer in the Premenopausal Population

The standard treatment of endometrial cancer is a hysterectomy or a bilateral salpingo-oophorectomy (BSO) with or without staging. However, with the increase in incidence in obesity that is starting at younger ages, the incidence of endometrial cancer is increasing in the premenopausal population. The worldwide prevalence of obesity more than doubled between 1980 and 2014. In 2014, more than 1.9 billion adults age 18 or older were overweight. Of these, more than 600 million adults were obese. About 13% of the world's adult population (11% of men and 15% of women) were obese in 2014, and 39% of adults age 18 or older (38% of men and 40% of women) were overweight.[19] Obesity is the single biggest risk factor for endometrial cancer.

The major precursor lesion for endometrial cancer is atypical endometrial hyperplasia (AEH). It is estimated that up to 50% of women with an endometrial biopsy with AEH will have a concomitant adenocarcinoma or will develop endometrial cancer. If there are not atypical nuclear changes, the risk of developing endometrial cancer is much lower. Many of the studies have focused on treating precursor lesions, including hyperplasia without atypia, despite a low risk for progression to cancer. Treatment of AEH or endometrial cancer in premenopausal women who wish to retain their fertility has centered around progesterone treatment to offset the unopposed estrogen created by the aromatase conversion of androgen to estrogen. Many studies have used oral progestins, either medroxyprogesterone acetate or megestrol acetate, a potent progestin. Recently, there has been an interest in the use of the levonorgestrel intrauterine device (IUD), which secretes a continuous amount of progestin and avoids the side effects of oral progestin such as increased appetite, depression, and increased venous thromboembolism risk. There is additional literature in the last several years of combining the levonorgestrel IUD with a gonadotropin-releasing hormone (GnRh) agonist to induce menopause. In addition, once menopause has been created, the use of aromatase inhibitors (AIs) is being used to offset the effect of obesity on the aromatase system.

Oral Progestin

There are numerous studies that report on the response to oral progestin. Chen et al reported that of 53 patients, 39 (74%) achieved a complete response (CR) after a median period of 6 (3–24) months on either medroxyprogesterone acetate or megestrol acetate. A CR was less frequent among obese than nonobese patients (four of 12 [33%] vs. 35 of 41 [85%]; p = .001), which suggested that obesity may reduce the risk of responding to conservative treatment. Twenty-six percent of the women with a CR recurred. Fifty-two percent of those women wishing to conceive became pregnant.[20] Simpson et al described 45 patients with AEH (19) and endometrial cancer (25) treated with oral progestin. Fifty-five percent achieved a CR, but 54% of those that responded recurred within 3 years. Five of the 53 patients achieved a pregnancy, and two delivered a live infant.[21] Ramirez et al reported on 81 patients with endometrial cancer treated with oral progestin: 76% responded to treatment, and 24% of those who responded recurred within 19 months. Twenty of the 62 patients who responded became pregnant.[22] Wang et al described six patients with endometrial cancer who underwent hysteroscopic resection of local lesions combined with oral administration of megestrol acetate for 3 to 6 months. They all had a CR, and half of them became pregnant by natural means (without assisted reproductive technology) and delivered healthy infants.[23]

Levonorgestrel IUD

Over the last 10 years, with the development of the levonorgestrel IUD, there have been several studies using the IUD in lieu of oral progestin. Scarselli et al found a 94% regression rate in 34 patients, but only 11% had AEH, and none had endometrial cancer.[24] Varma et al evaluated 105 women and found regression in 67% of women with AEH and a 90% overall regression rate.[25] Wildemeersch followed 20 patients long term with an IUD. Forty percent had AEH, none had cancer, and all women except one developed normal endometrium. One woman with AEH developed simple hyperplasia.[26] Gallos et al, in a meta-analysis, compared the response rate of oral progestin to the levonorgestrol IUD and found that the response rate of the oral progestin was lower than the IUD for complex hyperplasia (69% vs. 90%) and for AEH (60% vs. 90%).[27] Given the reasonable response

rate to the IUD, Pronin et al analyzed 70 patients with either AEH or grade 1 endometrial cancer using the IUD with a GnRH agonist for at least 6 months and found a 72% CR in the patients with endometrial cancer and 92% CR in the AEH, suggesting that adding the GnRH agonist significantly improved the relative risk (RR).[28] Minig et al also combined the IUD with a GnRH agonist and found a CR in 95% of the patients with AEH and 57% CR in women with endometrial cancer.[29] A large U.K. meta-analysis of 408 women with endometrial cancer and 151 with AEH had a live birth rate of 28% in the endometrial cancer group and 26% live birth rate in the AEH group. Treatments included oral progestin and an IUD with or without GnRH agonists.[27]

One caveat noted was the risk of conservative treatment. In one case report, a borderline ovarian cancer was found in a young woman. Review of the literature suggested that 5% of women with endometrial cancer had a synchronous ovarian cancer, so careful evaluation of the ovaries is important prior to conservative treatment of endometrial cancer.[30]

There is increasing interest in combining the progesterone releasing IUD with a GnRH agonist and AIs. Studies in patients with breast cancer comparing the use of tamoxifen with AIs found a 48% lower rate of endometrial cancer in the patients taking the AI, suggesting there may be a role for AIs in the conservative treatment of AEH or endometrial cancer, particularly in women that are obese.[31]

In conclusion, there is emerging evidence that treating young women with AEH or endometrial cancer with the combination of a levonorgestrel IUD and GnRH agonists may produce an excellent regression rate and a reasonable pregnancy rate. Addition of an AI in obese women may also have a positive impact. More evidence is needed before we have a clear picture of the best treatment of endometrial cancer or AEH in young women.

Lifestyle and Endometrial Cancer

Endometrial cancer has a strong correlation with lifestyle. Obesity with a BMI greater than 30 is responsible for up to 81% of the endometrial cancer diagnosed.[32] There is emerging literature in breast and colon cancer suggesting that obese/inactive patients have a higher mortality than those who are thinner and more physically active. Obesity may affect tumorigenesis and tumor progression through insulin resistance and hyperinsulinemia, increased bioavailability of steroid hormones, and localized inflammation.[33] Other comorbidities, in particular, cardiovascular disease, which is associated with obesity, are the cause of mortality in women with endometrial cancer at 10 years post-diagnosis, not endometrial cancer, suggesting that the obesity is associated with not only an increased risk of death from endometrial cancer, but also other comorbidities.[34]

A study by Arem et al[35] found that patients with BMIs of 25–29 had an HR of death of 1.74, compared with 1.84 and 2.39 for patients with BMIs of 30–35 and 35 and higher, respectively. Regular exercise (more than 7 hours/week) was associated with an HR of death of 0.57. In adjusted models, a woman who did moderate to vigorous physical activity and who reported more than 7 hours of moderate to vigorous physical activity per week prior to a diagnosis of endometrial cancer had a 43% lower risk of 5-year, all-cause mortality when compared with women who never/rarely exercised. The same study found more than a two-fold increased mortality risk among class II obese women (BMI > 35) when compared with women with BMIs lower than 35. BMI, physical activity, and health status all were associated with an increased risk of death from endometrial cancer (HR, 2.28) and were highly correlated.[36] Another study by Modesitt et al[37] evaluated physical fitness in obese women with and without endometrial cancer and found the patients with endometrial cancer had significantly poorer physical fitness and higher glucose levels when compared with those without endometrial cancer, even though the women had equivalent BMIs.

In the EPIC trial, a large cohort study in Europe to investigate the association between lifestyle and cancer risk, Dossus et al conducted a nested case control study of patients with endometrial cancer and evaluated four categories of characteristics to determine risk of endometrial cancer.[38] They found that insulin resistance/metabolic syndrome had an OR of 2.5 for developing endometrial cancer, the steroid factor (estradiol, dehydroepiandrosterone, androstenedione, estrone, and testosterone) had an OR of 1.68 of developing endometrial cancer, and the inflammation factor (cytokine; especially IL-6, TNF receptor, and C peptide) had an OR of 1.62 of developing endometrial cancer. Correlations with BMI and waist circumference were strongest for C-reactive protein, IL-6, IL-1 receptor antagonist, triglycerides, C peptide, and estradiol. All of these factors were statistically significantly higher in women who developed endometrial cancer compared with the controls. Although there was a significantly higher BMI and waist circumference in the patients with endometrial cancer compared with the controls, the mean BMI in the control group was 26.4 compared with 28.1, which was not enough of a difference for BMI to completely explain the increase in endometrial cancer risk.[38]

A small study investigated the impact of exercise and diet change on endometrial cancer survivors[39] and found that 84% of patients adhered to the intervention and had weight loss of 4.4 kg at 6 months and 4.0 kg at 1 year. The patients on the intervention started with a mean weight of 95.7 kg and had a mean weight of 92.7 kg at 1 year, whereas the control patients had a baseline weight of 94 kg and at 1 year were 95.4 kg. Those patients who did not participate in an intervention gained rather than lost weight. The authors concluded that patients with endometrial cancer are difficult to motivate to change their lifestyle, and only 30% of participants succeeded in the weight reduction goal. A second study by this group showed that patients with endometrial cancer had overall unhealthy lifestyles with poor eating habits and minimal physical activity as well as multiple comorbidities, and 93% had abdominal obesity.[40] A meta-analysis evaluating insulin resistance found that both fasting insulin levels and nonfasting C peptide were significantly higher in patients with endometrial cancer.[41] A Danish

study evaluated factors associated with mortality from endometrial cancer and found that education status, but not BMI, was associated with an increase in mortality from endometrial cancer. However, the majority of the patients had a BMI of less than 35, which is a different population that the current U.S. population.[42]

Insulin resistance plays an important role in endometrial cancer. High serum levels of insulin are associated with an increased risk of endometrial cancer, particularly in overweight/obese women, who also have an increase in estrogen activity.[43] Type 2 diabetes (noninsulin dependent) results in increased insulin levels for long periods both before and after the disease onset and is associated with an increased risk of atypical hyperplasia and endometrial cancer, independent of obesity.[44] Insulin reduces the liver production of sex hormone–binding globulin (SHBG), and chronically high insulin because insulin resistance is associated with high serum levels of testosterone. Insulin stimulates the ovarian and adrenal cortex production of androgens (especially androstenedione and testosterone) through the 17α-hydroxylase and 17,20-lyase activities, which are subsequently metabolized into estrogen from the aromatase enzyme in adipose tissue. Insulin also has direct proliferative effects on the endometrium, working as a growth factor, similar to insulin-like growth factor 1 as well. Epidemiologic data on postmenopausal women suggest an increased risk of endometrial cancer in nondiabetic women with hyperinsulinemia, in diabetic women with insulin resistance, and in women with metabolic syndrome.[45] Studies have shown a direct link between estrogen receptors and cell surface receptors such as insulin-like growth factor 1 receptor and EGFR, which cause the activation of kinase cascade pathways, including PI3K/AKT/mTOR and MAPK, which are directly associated with cell proliferation.[46]

In addition, the loss of tumor suppressor PTEN has been found in 40%–80% of type 1 endometrial cancers.[47] Increased insulin-like growth factor 1 levels in addition to loss of PTEN leads to the increased activation of the kinase signaling cascades. Adiponectin and insulin growth factor–binding protein help to regulate glucose levels and insulin sensitivity and therefore serve as protective factors against endometrial cancer development. Reduced levels of these protective molecules have been found in individuals with obesity and hyperinsulinemia.

The most important lifestyle change that will help correct the underlying hyperinsulin state and obesity is aerobic exercise. Limiting energy-dense foods such as carbohydrates is also an important aspect of improving the underlying metabolic abnormalities that promote endometrial pathology as well as a host of other diseases. Independent of its influence on BMI,[48] physical activity improves glucose uptake by skeletal muscles, which reduces insulin resistance and insulin levels as well as estrogen and androgen levels. The use of metformin can reduce the risk of cancer in women with diabetes or nondiabetic hyperinsulinemia. It can also be used in patients with polycystic ovarian syndrome, for whom it reduces the insulin level as well as the androgen level.[49] Metformin also reduces the proliferation of endometrial cells and may be an important aspect of treating and preventing endometrial cancer in addition to lifestyle changes.

The metabolic issues associated with obesity and hyperinsulinemia are associated with other causes of mortality. A 2012 study focusing on cardiovascular mortality used SEER registries to show that patients with endometrial cancer were more likely to die of cardiovascular disease (35.9%), followed by other causes, including other malignancies, than they were to die of their endometrial cancer.[50] In a study by Clark et al, only 29% of patients reported ever being told of the relationship between obesity and endometrial cancer. Despite this, over 50% of the patients reported attempting to lose weight through lifestyle changes after diagnosis. Those who were most likely to make lifestyle modifications were those who had received adequate counseling by a physician.[51] Thus the primary care physician, the obstetrician/gynecologist, the gynecologic oncologist, and the bariatric surgeons are extremely important factors for changing the lifestyle of these obese, hyperinsulinemic patients with such a high risk of endometrial cancer and other diseases.[52]

Moore et al published a meta-analysis in 2010 concluding that increased physical activity and decreased sedentary time were associated with a decreased risk of endometrial cancer. Women who were inactive and who sat for 9 hours per day had twice the risk of endometrial cancer compared with active women who sat fewer than 3 hours per day (RR 2.14; 95% CI, 1.48–3.10). However, if women exercised and sat for 9 or more hours per day, their reduced risk of endometrial cancer was attenuated, suggesting that prolonged inactivity is an independent risk factor for endometrial cancer.[53]

There is compelling evidence that lifestyle changes are important for both prevention and treatment of endometrial cancer. Women who have already developed endometrial cancer would benefit from structured exercise interventions, as this would decrease their obesity and insulin resistance and decrease their death from other diseases such as cardiovascular disease. In addition, their mortality from endometrial cancer would be expected to decrease. Given the obesity epidemic and the general decrease in physical activity, interventions are needed prior to the development of endometrial cancer and should be a collaboration between the pediatricians, the primary care physicians, and, once endometrial cancer develops, the gynecologic oncologist. Without these lifestyle interventions, the incidence and mortality from endometrial cancer will continue to increase along with other obesity-associated diseases. Treatment of insulin resistance is an important aspect of preventing endometrial cancer and improving outcomes and consists of exercise, dietary changes, and the use of metformin.

CONCLUSION

The incidence of and mortality from endometrial cancer is increasing primarily because of the increased incidence of obesity and the resulting hyperinsulinemia. Older women have an increase in mortality from both their cancer and the surgery, and risk needs to be closely balanced with benefit.

Minimally invasive surgery carries a lower risk of surgical complications, particularly in the older age group. Younger women are also experiencing an increase in rates of endometrial cancer and its precursors and can be successfully treated conservatively to maintain fertility. Changes in lifestyle are critical to managing this increase in risk and mortality. Weight loss and exercise are key to decreasing the hyperinsulinemia that drives the development of endometrial cancer. Changing one's lifestyle, although critical, is not often successful, which may be, in part, a result of a lack of counseling from physicians as well as a long history of an unhealthy lifestyle.

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Whence High-Grade Serous Ovarian Cancer

Elise C. Kohn, MD, and S. Percy Ivy, MD

OVERVIEW

Our understanding of epithelial ovarian cancer has blossomed, and we now recognize that it is a collection of varied histologic and molecularly different malignancies, many of which may not derive from a true ovarian anatomic precursor. High-grade serous ovarian cancer (HGSOC) is a unique type of epithelial cancer. It is characterized by nearly universal mutation in and dysfunction of p53, genomic instability rather than driver mutations, advanced stage at onset, and probable fallopian tube epithelium origin, with a serous tubal in situ carcinoma precursor. Germline deleterious mutations in *BRCA1* and *BRCA2*, as well as other less prevalent genes involved in DNA repair, such as *PALB2* and *RAD51c*, are associated with its carcinogenesis and may predict susceptibility to classes of treatment agents, including DNA-damaging agents and DNA repair inhibitors. Loss of function of these genes is associated with homologous recombination dysfunction (HRD). It is now recognized that there may be HGSOC with wild-type *BRCA1* and *BRCA2* with an identifiable HRD phenotype. Such HRD tumors also may be more susceptible to certain classes of treatments and may be phenotypically detectable with a composite molecular biomarker that has been shown to be predictive for response to PARP inhibitors. Use of this new knowledge of the anatomic and molecular background of HGSOC has led to the rational design of novel combinations of treatment classes to create an HRD-like cellular environment and thus drive treatment benefits.

The past 2 decades have brought about great progress and change in the field of ovarian cancer diagnosis, treatment, and research. "Ovarian cancer" has gone from singular to plural, and our diagnosis, treatment, and research have followed suit. Along with these changes have come new classifications, new drugs, and great opportunities to improve the quality and quantity of life for the women afflicted with this cancer. Keeping up with the frequent changes may have been daunting, although the scientific progress has also brought important answers that open viable directions to rethink screening and prevention and to target therapy more directly.

HIGH-GRADE SEROUS OVARIAN CANCER

What Is High-Grade Serous "Ovarian" Cancer?

The most common histology of malignancies of the ovary is now recognized to be an epithelial cancer emanating most commonly or most likely from the epithelium of the fimbria of the fallopian tube. This group of cancers was previously lumped together as high-grade epithelial ovarian cancer of serous or serous papillary type. An independent tumor of the fallopian tube(s) was not recognized, in part because the two organs are in such close proximity that their distinction was abrogated with tumor progression. The new World Health Organization histologic classification and grading system embraced the two-tiered grading system of low and high grades in their revision in 2014.[1] High-grade serous tumors are generally recognized by their lack of architecture and sheets of malignant cells, often enlarged and dysmorphic nuclei, and with further molecular characterization, nearly 100% *TP53* mutation frequency. These can be ascertained with relative confidence by immunohistochemistry demonstrating overexpression of nuclear p53 staining or complete lack of such staining within the tumor, the latter being the loss-of-function p53 mutations.

The World Health Organization classification recognizes the likely precursor lesion to be serous tubal in situ carcinoma lesions,[2,3] from which progression to invasive carcinoma may be found, albeit generally in small lesions. The outward-facing exposure of the tubal (and ovarian) epithelium supports early shedding and implantation. The lack of an anatomic barrier between the pelvis and the abdomen, coupled with the permissive environment of the omentum, buoys local colonization and further invasion. This is a likely reason why high-grade serous cancers present with advanced stage with abdominal involvement in more than 70% of patients.[4]

The sine qua non of high-grade serous cancers is the dysregulation of p53 and associated effects on DNA repair, leading to genomic instability and the characteristic of high copy number variability.[5] These tumors are also characterized by expression of WT-1, estrogen receptor α, and PAX8.[6-8]

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High-grade serous cancers are now being evaluated for subset analysis. Gene expression sets were found to segregate high-grade serous cancers into four descriptive groups: proliferative, mesenchymal, immune, and differentiated[5,9]; these groups have yet to be applied diagnostically or clinically. Further studies are ongoing to characterize the genomic patterns. The most validated prognostic and predictive biomarker within high-grade serous cancers is germline deleterious mutation in either *BRCA1* or *BRCA2* (*gBRCA*)[4,10] and, with somewhat less support, somatic homozygous loss of function of *BRCA1* or *BRCA2*.[11] As true suppressor genes, both copies must be disrupted or lost for the malignancy phenotype.

The proteins encoded by *BRCA1* and *BRCA2* are critical for maintenance of the high-fidelity double-stranded DNA repair pathway, homologous recombination repair.[4,12] Loss of function of these genes requires loss normal p53 regulation for cellular viability; this is consistent with the observation that p53 overexpression precedes actual serous tubal in situ carcinoma formation.[3] The Cancer Genome Atlas, which analyzed biospecimens from cases of newly diagnosed high-grade serous cancer, described 14% of HGSOC as having *gBRCA* status.[5] Another approximately 6% have somatic homozygous loss. Methylation of *BRCA1* promoter has been described as associated with loss of function; however, controversy remains if this consistently yields a homologous recombination dysfunction (HRD) phenotype, as does *gBRCA* or homozygous somatic loss.

More recently, studies have evaluated other proteins and genes within the homologous recombination pathway and validated other genes wherein germline deleterious mutations have been observed. These are found in lower frequency, accounting for about 7% additional germline heritable mutations associated with ovarian cancer.[13-16] Altogether, inclusive of *BRCA1* methylation, this describes approximately one-third of all serous cancers. *gBRCA* is prognostic of generally good outcomes, at least up to the first postdiagnosis decade,[17] and is predictive of platinum sensitivity and PARP inhibitor sensitivity. Studies are ongoing to validate prognostic and predictive utility of germline mutations in the other genes associated with familial ovarian cancer. Biomarkers to identify cancers with HRD, those that are *gBRCA*-like, have been developed,[18,19] and one such biomarker has been approved as a companion diagnostic to the PARP inhibitor rucaparib.[20]

Earlier transcription array studies also led to the identification of a subset of ovarian cancers that overexpressed cyclin E.[5,9,21-24] This has now been further supported by genomic studies such as The Cancer Genome Atlas.[5] It is estimated that disruption of the G1/S cell-cycle transition by *CCNE1* amplification (20% as estimated by The Cancer Genome Atlas), by overexpression or amplification of *CCND1* or *CCND2* (19%), or loss of regulation of the G1/S checkpoint by loss of function of pRB (10%) will account for nearly one-third to one-half of cases. Disruption of normal G1/S transitions also leads to poor DNA repair, also contributing to the classic genomic instability phenotype of ovarian cancers.[25-27]

KEY POINTS

- **HGSOC is an independent histologic and molecular set of cancers.**
- **HGSOC is genomically unstable and can be classified by molecular subgroups, the clinical application of which is yet undetermined.**
- **Biomarker tests have been developed that identify an HRD molecular phenotype, approximating *BRCA*-like drug sensitivity behavior.**
- **Optimal treatment directions may be best identified by focusing on the development of clinical synthetic lethality across high-grade serous cancer molecular types.**
- **Clinical synthetic lethality approaches may incorporate disruption of the tumor microenvironment and the immune milieu.**

What Are the Clinical Implications of a Diagnosis of HGSOC?

The preponderance of the women in clinical trials and represented in retrospective studies have HGSOC. Thus, much of the data in the literature on susceptibility to treatment, duration of response, and overall survival are driven by the behavior of this most prevalent type of ovarian cancer. Staging is used to categorize cancers for prognostic purposes, to guide therapeutic decisions, and as a classification tool for data analysis. The current 2014 International Federation of Gynecology and Obstetrics staging system,[28] the primary system used worldwide, is a four-tiered system with staging based on pathologic evaluation of surgical staging. It is thus biased by the completeness and depth of surgery. However, practically, most trials and therapeutic triage are based on disease being early stage or organ confined (stage I) or advanced disease, which includes local pelvic extension. This is pertinent to high-grade serous cancers, more than 70% of which are advanced disease at presentation. Not included in International Federation of Gynecology and Obstetrics staging but of recognized importance for decades is the role of the extent of residual disease after primary or interval debulking surgery.[4] Residual disease affects prognosis and is not specific to ovarian cancer type in its utility.

The molecular makeup of high-grade serous cancer may have the greatest implication to patient prognosis and treatment secondary to diagnosis of ovarian cancer type. The aggressive genomic instability, caused by different molecular mechanisms, may lead to selective treatment directions. How this will affect initial therapy for high-grade serous cancers is currently the subject of many clinical trials. However, the molecular makeup has already been used to define access to one class of new anticancer agents approved for use in ovarian cancer. *gBRCA*-associated ovarian cancers have been shown to be substantially more susceptible to the class of PARP inhibitors, with platinum-sensitive *gBRCA* patients responding best (range, 35%–50% or more) and the lowest response rate (7%–12%) in women with wild-type

BRCA1 and *BRCA2* whose tumors are platinum resistant.[20,29] *gBRCA* status is thus a validated predictive biomarker for use of PARP inhibitors. The drive to identify other patients whose tumors may respond to PARP inhibitors has led to a test that is used to define HRD, where biology argues susceptibility to these DNA repair inhibitors.[18-20]

Laboratory and translational science has now broadened membership in the class of DNA repair inhibitor agents beyond the PARP inhibitors.[12,30] Disruption of homologous recombination can also come from inhibition of other key events in the complex homologous recombination pathway.[30] ATR and ATM kinases are critical to this form of DNA repair, and they have been found to have deleterious cancer-associated germline mutations. Inhibitors of these kinases are now in clinical testing.[12] Another key element required for adequate DNA repair is either cell-cycle delay or sufficient time in the necessary cell-cycle phase to allow repair to proceed and complete. Block in G1/S or G2/M affects the type and extent of injury or repair, as well as potentially the type of cell death.[27,31,32] Inhibitors of cell-cycle regulatory proteins are now recognized as potential targeted agents for cancer treatment and could be included in the DNA repair inhibitor class. Example agents include inhibitors of WEE-1 kinase and CHEK1 kinase.[33-37] These kinases represent a yin-yang scenario that ultimately affect a G2/M cell-cycle halt to allow DNA repair to proceed. Dysregulation of this cell-cycle checkpoint has been shown to propagate DNA damage because of inability to repair and have been shown to drive cells into apoptosis, autophagy, and mitotic catastrophe.[38] Early clinical trials of agents targeting these kinases have had mixed results. AZ1775, a WEE-1 inhibitor, has some single-agent activity in *gBRCA* ovarian cancer and limited single-agent activity otherwise. Preclinical and early clinical data suggest that it can synergize with chemotherapy or targeted agents to greatly improve their activity. A second-generation CHEK1 inhibitor with some inhibition against CHEK2, a modulator of both G1/S and G2/M, has been reported to have clinical activity in non-*gBRCA* recurrent high-grade ovarian cancer, and study is being expanded.

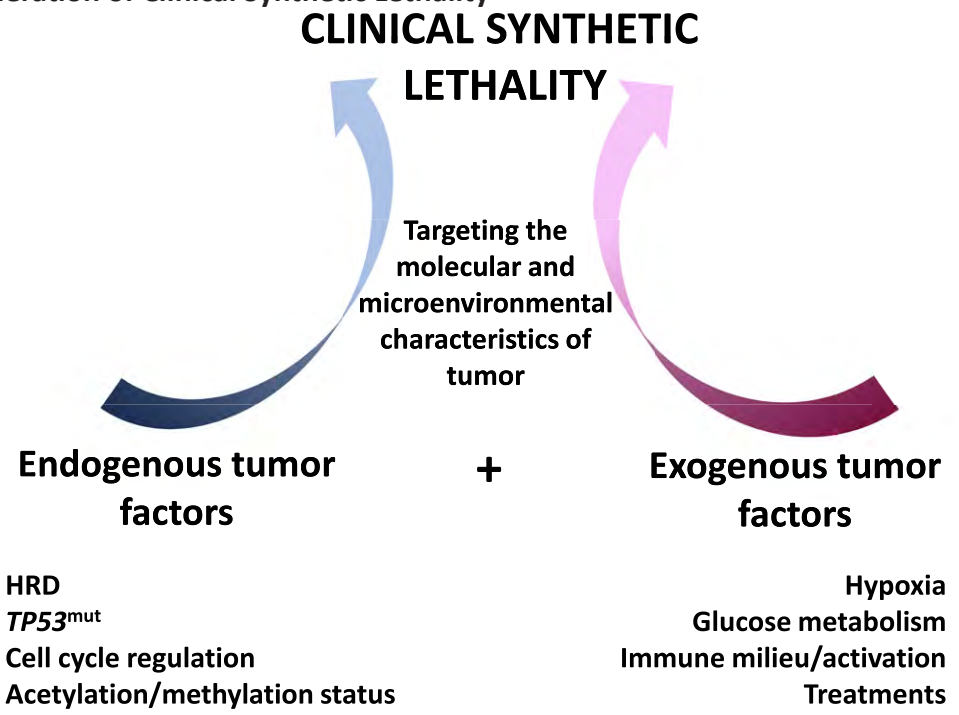
GENERATION OF CLINICAL SYNTHETIC LETHALITY

Clinical synthetic lethality may occur when a common underlying event(s) or drug causes a gain- or loss-of-function phenotype that, when combined with a drug targeted to a different pathway, collaborates to augment or create antitumor effects (Fig. 1).[30,39] For example, the targeting of PARP and its many downstream functions synergizes with existing loss of homologous repair function in tumors with homozygous loss of function of BRCA1 or BRCA2.[12] This results in greater clinical benefit in these patients than is seen in patients with wild-type and homologous recombination-intact HGSOC.[29] The latter subgroup of women do respond, albeit in a limited fashion. Investigations into creating clinical synthetic lethality to improve their outcomes to PARP inhibitors build on either contextual or chemical synthetic lethality. Chemical synthetic lethality occurs with the introduction of an additional agent(s) or modification of the microenvironment; contextual synthetic lethality leverages existing endogenous behaviors to greater benefit.[30]

Clinical Synthetic Lethality Opportunities in HGSOC

Recent reports of targeted drug combinations have introduced opportunities to examine the potential of clinical

FIGURE 1. Generation of Clinical Synthetic Lethality



synthetic lethality. For example, the combination of cediranib, a pan-VEGFR 1–3 inhibitor, and the PARP inhibitor olaparib demonstrated an unexpectedly high response rate and progression-free survival in women with HGSOC.[40,41] Greater activity was observed in women without *gBRCA* in an unplanned post hoc subset analysis of the cediranib/olaparib study, 5 versus 16.5 months for single agent versus combination.[40] Angiogenesis inhibitors have been shown to cause hypoxia and to alter local blood flow.[42-44] Hypoxia has been shown to downregulate expression of critical DNA repair enzymes.[45] Hypoxia induction, combined with chemical disruption of DNA repair with a PARP inhibitor, is an example of clinical synthetic lethality. Definitive studies are now ongoing to evaluate the benefits of this combination in platinum-sensitive (NCT02446600) and platinum-resistant (NCT02502266) HGSOC.

Our understanding of the local tumor and stromal milieu of HGSOC has opened new directions for therapeutic investigation. It has long been known that microvessel density and angiogenic profusion is more common in advanced and aggressive ovarian cancers and parses out to be more common in the high-grade serous cancers.[46,47] Not surprisingly, antiangiogenic therapies have clear benefits in newly diagnosed ovarian cancers[48,49] and in recurrent disease, as single agents as well as in combinations.[42,50-52]

The local tumor microenvironment has immune infiltration. The strong presence of tumor-infiltrating lymphocytes is prognostic of outcome in ovarian cancer.[53] This observation has been confirmed to hold fast in HGSOC.[47,54] Interestingly, it appears that highly vascularized tumors may have different immune infiltration than those not vascularized and that the combination of the immune infiltration type and vascularity may affect prognosis. Patients with high-grade serous cancers containing high regulatory T-cell infiltration and high vascularity did better than patients with T-cell infiltration without vascularity.[47] Characterization is ongoing to understand what types of immune phenotypes are within that milieu to understand how to better use immune-modulating agents.

More recently, there is evidence that the same factors that drive angiogenesis are also important in attenuating the immune response.[55] VEGF induces the accumulation of myeloid-derived suppressor cells and regulatory T cells and inhibits the migration of T lymphocytes from the vasculature into the tumor.[56] A link has been proposed between hypoxia stress and immune suppression through the HIF-1α and VEGF pathways through recruitment of regulatory T cells.[57] This microenvironmental interaction between the stromal and tumor vasculature and the peritumoral and intratumoral immune responses may help identify reasons that current immune checkpoint inhibitor approaches are not as successful as anticipated in some cancers, including ovarian cancer. It has been hypothesized that there may be additional benefits to combining angiogenesis inhibitors, stromal inhibitors, or DNA repair inhibitors with immune checkpoint modulation; both preclinical and clinical investigations are ongoing.

Propagation of poorly or unrepaired DNA in cells that do not succumb to such injury may result in mutations that, although perhaps not harmful, may create or unmask neoantigens.[58-60] Not all such neoantigens may play a role in immune stimulation. It appears that there may be select common epitopes,[58] or cancer-testis antigens, such as NYESO-1, that may activate T cell–mediated immunity more globally in patients with HGSOC. Current studies are incorporating measures of neoantigens and selective responsiveness to targeting cancer-testis antigens to test these questions. It remains unclear if these findings will be tumor-type specific, microenvironment (e.g., organ) specific, or generalizable. Clinical approaches to test these hypotheses include combinations of immune checkpoint inhibitors with angiogenesis inhibitors, some of which also incorporate DNA-damaging agents. New trials targeting immune checkpoint inhibitors with angiogenesis inhibitors have been initiated.

HRD PHENOTYPES AND BIOMARKERS

The ability to measure homologous repair defects in a semiquantitative fashion to identify and select patients for treatment with PARP inhibitors is in the early stages of phenotype analysis but appears promising. The measurement of genomic instability cannot be quantitated with a single test; the presence or absence of *gBRCA1/2* mutations is insufficient to provide a more global assessment of this highly plastic genome in HGSOC. Recently, three independent DNA-based measures (unweighted sum of scores, higher than 42) of genomic instability on the basis of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions have been described as characterizing HRD.[18,19] This has been validated prospectively for ovarian cancer in the study of niraparib presented at the 2016 Congress of the European Society for Medical Oncology. It was further investigated retrospectively using biospecimens and data from women with triple-negative breast cancer who received iniparib with cisplatin and gemcitabine. Triple-negative breast cancer tumors, including *BRCA1/2* wild-type tumors, were more likely to respond to platinum-containing therapy if they demonstrated HRD as measured by a weighted summed score of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transition.[61]

Rucaparib treatment was examined in a phase II trial for women with platinum-sensitive HGSOC, ARIEL2. The overall response rate was reported as 70%.[20] The Foundation Medicine companion diagnostic HRD test for a BRCAness signature was evaluated in this trial, in which 40% of patients with the signature and 8% without the signature demonstrated response to rucaparib. This signature may prove useful in identifying patients who will benefit from PARP inhibitor therapy.

The PARP inhibitor niraparib was examined in a randomized prospective trial of maintenance or placebo for women with high-grade ovarian cancer who have completed platinum-based therapy for recurrent disease. gBRCA patients receiving niraparib versus placebo had significantly longer median progression-free survival, 21 versus 5.5 months. The niraparib compared with placebo outcome was 12.9

versus 3.8 months in the *gBRCA* wild type cohort with HRD as measured using a composite HRD test. Among patients with platinum-sensitive, recurrent ovarian cancer, the median duration of progression-free survival was significantly longer among those receiving niraparib than among those receiving placebo, regardless of the presence or absence of *gBRCA* mutations or HRD status.

The presence of an HRD phenotype correlated with outcome for the patients in each of the settings described above. These initial steps are critically important in the development of phenotypic biomarkers that can be used to select patients with homologous DNA repair defects for treatment with PARP inhibitors and other inhibitors that interrogate the DNA damage response that is an integral part of cell replication and genomic instability.

CONCLUSION

HGSOC, now incorporating also high-grade endometrioid ovarian cancers, is a collection of relatively similar entities. They appear to originate from fimbrial fallopian tube epithelium and require p53 dysfunction to develop their characteristic genomic instability. Differential degrees of DNA repair dysfunction have been identified in different molecularly characterized subsets of HGSOC that may lead to selected future targeted clinical approaches. Leveraging the endogenous DNA repair dysfunction as identified in *gBRCA* or HRD patients with exogenously derived DNA repair dysfunction caused by induction or augmentation of local hypoxia is an example of clinical synthetic lethality that may further direct successful treatment combinations.

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HEALTH SERVICES RESEARCH, CLINICAL INFORMATICS, AND QUALITY OF CARE

More Medicine, Fewer Clicks: How Informatics Can Actually Help Your Practice

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OVERVIEW

In the information age, we expect data systems to make us more effective and efficient—not to make our lives more difficult! In this article, we discuss how we are using data systems, such as electronic health records (EHRs), to improve care delivery. We illustrate how US Oncology is beginning to use real-world evidence to facilitate trial accrual by automatic identification of eligible patients and how big data and predictive analytics will transform the field of oncology. Some information systems are already being used at the point of care and are already empowering clinicians to improve the care of their patients in real time. Telehealth platforms are being used to bridge gaps that currently exist in expertise, geography, and technical capability. Optimizing virtual collaboration, such as through virtual tumor boards, is empowering communities that are geographically disparate to coordinate care. Informatics methods can provide solutions to the challenging problems of how to manage the vast amounts of data confronting the practicing oncologist, including information about treatment regimens, side effects, and the influence of genomics on the practice of oncology. We also discuss some of the challenges of clinical documentation in the modern era, and review emerging efforts to engage patients as digital donors of their EHR data.

As cancer specialists, we have grown up in an information age in which we expect data systems to make us more effective and more efficient. There has been an unprecedented improvement in cancer death rates over the past 25 years.[1] We expect machine learning and other informatics innovations to help us advance the quality of care even faster, and not simply result in additional boxes to check in an EHR. In 2017, there are growing concerns that these expectations have not been met, to the point at which some clinicians are citing dissatisfaction with health information technology as a major driver of job dissatisfaction.[2] Despite this negativity, many tools are in development or operational for use in the clinic today to help make us better at what we do. Recently, there has been much interest in facilitating data systems to become more integrated and interoperable and to deliver care faster. These are recurring themes within the ASCO's participation in the Cancer Moonshot work and in the 21st Century Cures legislation that passed in 2016.[3] The 2016 President's Cancer Panel report, *Improving Cancer-Related Outcomes With Connected Health*, states, "We live at a most exciting and critical time of technological advances with potential to help individuals manage and improve their own health and support high-quality, patient-centered cancer care."[4]

In this article, we explore some of the success that informatics can bring to the practice of oncology. First, we review some of the currently existing informatics capabilities at one author's large integrated practice, US Oncology. Second, we discuss the topic of incorporating external knowledge into oncology practice and how informatics can provide point-of-care solutions. Third, we discuss the challenges of clinical documentation in the 21st century and how informatics tools can be used to make sense of messy real-world data. Finally, we turn toward patients and discuss how new technologies are emerging to enable digital donations to research.

CREATING AN INFORMATICS-ENABLED ONCOLOGY PRACTICE

Big Data

Over the past decade, we have seen advancements in big data systems that allow us to aggregate data in cancer beyond what has traditionally been collected by the cancer registry system. This is used across systems of care delivery to understand outcomes in various disease states outside of clinical trials in the form of real-world evidence. It remains a limitation in adult oncology that only 2% to 3% of patients enroll in prospective clinical trials, and age- and

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race-related disparities persist, yet we would like to learn from all patients with cancer.[5,6] There are also some diseases and novel molecular mechanisms in cancer that make clinical trials a challenge to open and accrue patients appropriately because of their rarity. Big data systems are a good answer to these challenges as they allow us to look for the needles within the haystacks and learn collectively. Some real-world evidence is also being used in other countries and is now even being considered by the U.S. Food and Drug Administration (FDA) for drug approval, with some caveats.[7] The FDA issued draft guidance about the use of real-world evidence to support regulatory decisions around medical devices in 2016.[8] Using real-world data systems to screen patients within care delivery systems, patients with rare diseases can be identified for clinical trials with just-in-time mechanisms including opening clinical trials at the site of care when these patients are identified. Several big data aggregators are pioneers in this new landscape: (1) CancerLinQ, ASCO's data aggregation and sharing platform among many EHR sources to enlighten outcomes and report quality in cancer care[9,10]; (2) the National Cancer Institute's Genomic Data Commons (https://gdc.cancer.gov); (3) the Oncology Research Information Exchange Network, a collaboration of many prominent North American cancer centers; (4) the American Association for Cancer Research's Project Genomics Evidence Neoplasia Information Exchange; (5) the Triangle Census Research Network at Duke University, informing data aggregation and dissemination; and (6) Project Data Sphere. Additional private entities that have invested tremendous resources in developing solutions for better use of cancer data include TriNetX, McKesson Specialty Health, Flatiron Health, and IBM Watson Health, among many others. Other systems that are internal to organizations are integrating molecular data to identify patients for selection for clinical trials. For example, Syapse is a commercial partner that works within health systems to implement precision medicine programs. US Oncology research has a just-in-time mechanism of clinical trial initiation called the STAR program to accrue patients when identified with n-of-1 tumors that would otherwise be hard to accrue in independent systems.

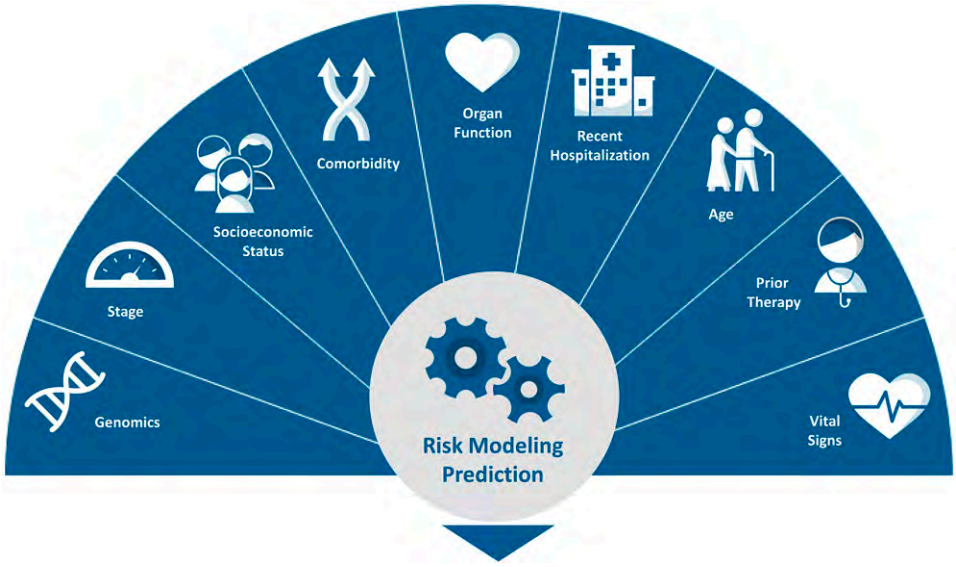
Clinical decision support systems (CDSS) have become integrated in cancer care in many ways: facilitating compliance among clinicians in prescribing therapeutic interventions within guidelines of care delivery (a quality enhancement), facilitating screening for research accrual for appropriately selected patients, and using apps and other forms of digital patient engagement to inform patients to act on, alter, or contact their providers regarding their plans of care given their individualized data. Across a large network of US Oncology community practices that vary from urban and suburban to rural and frontier in their locations, a CDSS platform called Clear Value Plus was implemented, providing an interface at the point of service for chemotherapy ordering in a value-based mechanism within nationally accepted guidelines. The implementation of this CDSS significantly improved reportable data, guideline compliance, and exception reporting, making therapy decisions easier for doctors at the point of service, in addition to enhancing guideline compliance for patients and providing the necessary data to practices to proceed with prior authorization with payers, thus enhancing quality and time efficiencies.[11] We fully acknowledge the real concerns regarding alert fatigue in the implementation of CDSS, and strongly encourage the efforts being made in the field of human-computer interaction to improve this experience.

Predictive analytics platforms are being used to improve outcomes in patients with cancer. Data from EHRs and other data sources have been used to develop models to predict the risk for hospitalization in other diseases. For example, in populations with low-socioeconomic status and heart failure, risk prediction and the interventions based upon it reduced hospitalization risk in a high-risk and difficult-to-treat population.[12] Warner et al have previously described an EHR-based predictive model for hospital-acquired complications.[13] Using such models to inform the care team about risk and facilitate appropriate interventions may be effective at reducing hospitalizations and readmissions in high-risk groups. Similar models have been developed for high-risk cancers and are being used to inform clinicians about risk and facilitate support systems and care interventions to reduce the risk for hospitalization accordingly.[14] Prediction of treatment intolerance, which can lead to nonadherence, especially in novel therapies, is also an evolving area of research, although the prior body of evidence suggests that side effects are a common reason for nonadherence and early discontinuation for traditional therapies as well.[15] Given that recent studies suggest that treatment discontinuation

KEY POINTS

- **As cancer specialists, we have grown up in an information age in which we expect data systems to make us more effective and more efficient; despite recent concerns surrounding health information technology, we are convinced that there is significant potential that is yet to be met on the large scale.**
- **US Oncology is a large integrated practice that has implemented big data, predictive analytics, and telehealth applications at the point of care.**
- **Factual and contextual knowledge, especially regarding the interpretation of genomic sequence variation in cancer, will require external knowledge support that can be integrated into clinician workflow using emerging informatics technologies.**
- **The challenges of clinical documentation in the 21st century are significant because of increasing care complexity and regulatory and billing requirements, but informatics technologies exist to facilitate documentation and its secondary use.**
- **An emerging technology called Sync for Science will be piloted in 2017, with a goal of enabling patients to become digital donors for EHR-based research such as that envisioned by the Precision Medicine Initiative's All of Us research program.**

FIGURE 1. Predictive Analytics to Understand Risk



Multiple sources of data are used to create a risk model that can predict likely outcomes for individual patients, such as the risk for hospitalization after the administration of chemotherapy.

because of intolerance is the most common reason for revolutionary drugs such as ibrutinib,[16,17] it will be critically important to identify vulnerable populations. Presently, predictive analytic platforms can come across the EHR in the form of CDSS so that they are available to clinicians at the point of care (Fig. 1).

Telehealth and virtual collaboration platforms are another way US Oncology uses data systems to enhance care delivery with efficiency. Use of these platforms is growing in scope, scale, and prevalence throughout the United States, and many states are currently considering policies that influence their implementation.[18] Innovations in platforms of interaction telehealth and virtual collaboration allow us to bridge existing gaps in geography and expertise. In the US Oncology network of oncology practices, there are sites of service that vary from urban and suburban to rural and frontier, and staffing and subspecialty expertise is also variable.

Telehealth platforms have allowed for consultation with subspecialty experts in neuro-oncology and genetic risk assessment that otherwise would have required a drive of several hours, a geographic barrier to care that frequently results in diminished utilization of subspecialty services. This has allowed patients to access subspecialty services and treatments they otherwise would not have access to and it helps us make quality care global. Our present abilities to implement telehealth include multimodal virtual collaboration (between clinicians or between clinicians and patients) and remote review of imaging and pathology, but also have become enhanced in our ability to complement the physical examination with universal serial bus attachments such as sphygmomanometers, stethoscopes, ophthalmoscopes, electrocardiographs, ultrasound probes, and cameras to make the skin examination more sensitive than to the human eye. Teledermatoscopy programs have been implemented to diagnose and follow at-risk skin lesions to detect early melanoma.[19] There are even multimodal fiber optic probes that can be used at remote sites with a clinician's assistance to interrogate cutaneous lesions and replace the need for some biopsies in skin cancer.[20] How we interact with these systems continues to change over time. These are not only technological advancements but also ways we must think differently about supporting clinical workflow to optimize the patient experience as our technological capabilities grow. Optimizing virtual collaboration with all of these platforms also allows virtual multidisciplinary planning, which can often be a critical quality measure in planning cancer care treatment. Virtual tumor boards are now in existence in many networks today, allowing geographically disparate multidisciplinary planning.[21] All of these systems are tools that close physical and mental gaps that limit care delivery today.

INTEGRATING EXTERNAL KNOWLEDGE INTO THE ONCOLOGY WORKFLOW

Generally speaking, there are four types of knowledge pertinent to the day-to-day practice of oncology: procedural, transactional, factual, and contextual. The first category, procedural knowledge, includes those factors pertinent to daily practice and is usually specific to a given location. Examples may include (1) what antibiotics and antiemetics are available in the hospital formulary, (2) the times and days laboratory technicians are available to assist with bone marrow biopsy and aspiration procedures, and (3) standard protocols decided by consensus or disease group leadership. Often, procedural knowledge is kept locally in the form of standard operating procedures.

The next category, transactional knowledge, includes those factors pertinent to the business aspects of oncology practice. This includes knowledge about what billing codes (e.g., International Classification of Diseases, 10th Revision,

Clinical Modification) are necessary and sufficient to justify a given level of professional billing, what billing codes will translate into an appropriate diagnosis-related group for a given hospitalization, and details of negotiated contracts with third-party insurers and pharmaceutical companies. As with procedural knowledge, most transactional knowledge is location specific, although some, such as information about International Classification of Diseases codes, may be amenable to external knowledge resources.

The last two categories are inter-related. Factual knowledge includes information about a disease, a prognosis, and associated treatments. One is likely to find this type of knowledge in an encyclopedia or a medical textbook. Importantly, factual knowledge is by convention limited to a representative example or a range of commonly expected examples. In other words, factual knowledge is generic and often not applicable to an individual patient. On the other hand, contextual knowledge takes into account features of an individual patient and is necessary (although not sufficient) for the practice of precision or personalized medicine.[22] In oncology practice, context includes comorbidities; performance status; treatment history, including prior drug exposures, length and depth of response, and pertinent adverse events; behavioral determinants of health such as substance abuse; psychological distress and psychosocial support systems; and belief systems (e.g., Jehovah's Witnesses will not accept blood transfusions, which may influence decisions about the intensity of cytotoxic chemotherapy).

The crux of the issue of knowledge management in oncology is what proportion of knowledge is internal as opposed to external. Internalized knowledge is that which is available to a practitioner through memory, with or without prompting. Externalized knowledge is that which is available through any type of ancillary resource. Internal knowledge is not to be taken lightly; after all, much of the 4 years of medical school and 5 to 7 years of postgraduate training are focused on the tasks of acquiring and retaining knowledge. Nevertheless, it was observed many decades ago that a practicing clinician could not possibly grasp the totality of medical knowledge.[23] We have previously determined with some back-of-the-envelope calculations that it would be necessary to read 272 articles each day, 365 days a year, just to keep up with the cancer literature.[24] So how is a practicing clinician to approach and master both facts and context?

Historically, the incorporation of external knowledge into the clinical workflow falls under CDSS. CDSS is part of the lingua franca of biomedical informatics and features prominently in recent regulations, including the meaningful-use rules and the FDA's guidance on the regulation of mobile medical applications.[25,26] Interestingly, one of the earliest CDSS, ONCOCIN,[27] was an oncology protocol management system. Indeed, the selection of chemotherapy protocols and tracking of their dosing parameters is one of the areas most amenable to external knowledge support. Although certain EHRs provide the means to build and maintain local chemotherapy regimen libraries, these are rarely comprehensive. In 2011, Dr. Peter Yang founded the site HemOnc.org, with the goal of creating a freely available, comprehensive, and accurate resource for chemotherapy regimen details.[28] The site listed more than 1,000 regimens by mid-2013, and, as of February 2017, HemOnc.org listed more than 2,000 disease-specific chemotherapy regimens across 84 distinct solid oncology, benign, and malignant hematology conditions; to our knowledge, it is the largest resource of its kind. Over time, the initial focus on capturing details of dosing and timing of chemotherapeutics has expanded to also include information on comparative efficacy and toxicity for randomized controlled trials and overall response rates for nonrandomized studies (Fig. 2).

HemOnc.org and similar resources can offer the practicing oncologist the ready means to bring external knowledge to bear, especially when prescribing obscure or infrequently used regimens. Another solution to this knowledge management problem is pathways. Pathways take into account cost, reimbursement, efficacy, and the likelihood of treatment-related complications to varying degrees. Some, such as the National Comprehensive Cancer Network guidelines, provide a fair amount of latitude in treatment selection; others, including several vendor products, enforce treatment choices with potential penalties for overrides. Zon et al[29] recently criticized the pathway approach for lacking clear processes, placing additional administrative burdens on oncology practices and not yet clearly demonstrating an impact on patient health outcomes.

The other area most in need of external knowledge support is genomically guided treatment. This is a knowledge space that is simply too large to manage without assistance. Knowledge support in this evolving area is taking several forms: (1) extensively curated somatic panel test reports, (2) molecular tumor boards that convene experts either locally or remotely, and (3) genomic knowledge bases. Although curated reports are critical, they suffer from two major flaws: (1) they are a snapshot from the time when the test was obtained and will not reflect the new genotype-phenotype knowledge that is constantly emerging, and (2) they are subject to considerable variation, as recently demonstrated by Balmaña et al.[30] Molecular tumor boards can be both clinically useful and educational but do not necessarily fall within normal clinic workflows. Genomic knowledge bases hold great promise but currently lack uniformity in format and interpretation. Recently, Ritter et al,[31] on behalf of the ClinGen Somatic Cancer Working Group, described a consensus for minimum variant level data, which is followed by knowledge bases such as My Cancer Genome[32] and ClinGen.[33] The FDA has recently issued draft guidance on the use of public human genetic variant databases to support clinical validity of next-generation sequencing panels.[34] ASCO, the Association for Molecular Pathology, and the College of American Pathologists recently issued a unified set of standards and guidelines for the interpretation and reporting of sequence variants in cancer. These efforts should eventually improve the uniformity of genomic test results.[35]

Once genomic data are integrated into the EHR, the capacity for further innovation expands.[36] In particular, a new

standard produced by Health Level Seven International, called the Fast Healthcare Interoperability Resources (FHIR) standard, increases the ability to bring external knowledge, including genomics, into the clinical workflow. Warner et al previously demonstrated a FHIR-based app, called SMART Precision Cancer Medicine, that links users to factual genomic knowledge (via Gene Wiki), contextual genomic knowledge (via My Cancer Genome), and contextual chemotherapy regimen knowledge (via HemOnc.org).[37] This app was designed to launch from a tablet device with the intent of seamless integration into the workflow of a busy clinic; it and similar apps can also easily be integrated into certain EHR environments to provide a seamless user experience.[38] ASCO is currently investigating the possibility of creating an app that will bring the results from multiple genomic knowledge bases to clinician users.

It is clear that clinical decision support, especially the invasive variety that disrupts workflow through alerts and reminders, can be perceived negatively. In anticipation of a backlash, Bates et al[39] produced the seminal article "Ten Commandments for Effective Clinical Decision Support: Making the Practice of Evidence-Based Medicine a Reality" in 2003. This group and others have also documented the frequent practice of overriding alerts, even when the result may be a fatal drug interaction.[40,41] Nevertheless, it is likely that clinical decision support and passive knowledge support will increasingly become available within the clinical workflow, ideally in the form of apps clinicians can select and customize to meet their needs.[42]

The final issue that must be addressed is the accuracy of knowledge. Although there is no shortage of studies demonstrating the fallibility and malleability of internal knowledge (the seminal paper by Tversky and Kahneman[43] is an excellent primer), the failure of accuracy of external knowledge is often treated more harshly. This is likely an issue of trust more than anything. Failure of internal knowledge banks may be attributable to a variety of factors, but it is the rare practitioner who has a fundamental lack of trust in his or her own knowledge. Conversely, external knowledge that is incorrect and provably false can raise issues of trust pertaining to the entire knowledge base. This phenomenon is well demonstrated by the ongoing skepticism of the Wikipedia resource, despite academic publications showing high levels of accuracy in certain areas of the medical domain.[44-47] Various approaches have been used to increase trust in external knowledge bases, especially those that are openly collaborative: (1) clear attribution of content to well-known experts, (2) restriction of content creation to vetted individuals, and (3) stamps of approval from specialty societies or other agencies. It remains to be seen which of these approaches, or a combination thereof, will be most successful in gaining the trust of the user community.

THE CHALLENGES OF CLINICAL DOCUMENTATION IN THE 21ST CENTURY

Clinical documentation has always served multiple purposes, including clinical (record of clinical reasoning, decisions, and clinically relevant events), billing and financial (justifying payment for services rendered), and legal (What happened? Who knew what and when?). Over time, practices and processes evolved that variably addressed all of these purposes. Some of these processes and practices were formal, but some were informal and specific to individual clinicians. With the implementation of EHRs, many of

FIGURE 2. A Portion of the Docetaxel for Non–Small Cell Lung Cancer Regimen on HemOnc.org, Showing Comparative Efficacy for 11 Randomized Controlled Trials

Docetaxel (Taxotere)

Example orders

- Example orders for Docetaxel (Taxotere) in non-small cell lung cancer

Regimen #1, 3-week docetaxel

Study	Evidence	Comparator	Efficacy
Hanna et al. 2004	Phase III	Pemetrexed	Inconclusive whether non-inferior
Chen et al. 2006	Phase III	Docetaxel 35 mg/m^2, 3 out of 4 wks	Seems not superior
		Docetaxel 40 mg/m^2, 2 out of 3 wks	Seems not superior
Kim et al. 2008 (INTEREST)	Phase III	Gefitinib	Seems non-inferior
Shaw et al. 2013	Phase III	Crizotinib	Inferior PFS
Reck et al. 2014 (LUME-Lung 1)	Phase III	Docetaxel & Nintedanib	Inferior PFS
Garon et al. 2014 (REVEL)	Phase III	Docetaxel & Ramucirumab	Seems to have inferior OS
Brahmer et al. 2015 (CheckMate 017)	Phase III	Nivolumab	Inferior OS
Borghaei et al. 2015 (CheckMate 057)	Phase III	Nivolumab	Inferior OS
Herbst et al. 2015 (KEYNOTE-010)	Phase II/III	Pembrolizumab	Inferior OS
Fehrenbacher et al. 2016 (POPLAR)	Randomized Phase II	Atezolizumab	Seems to have inferior OS
Rittmeyer et al. 2017 (OAK)	Phase III	Atezolizumab	Inferior OS

Chemotherapy

- Docetaxel (Taxotere) 75 mg/m^2 IV over 1 hour once on day 1

Hyperlinks under "Study" link to the original articles; those under "Comparator" link to other regimens on HemOnc.org.
Abbreviations: IV, intravenous; OS, overall survival; PFS, progression-free survival.

these processes were changed, either consciously or unconsciously. Although there are clear benefits of computerizing health care, there are also a number of challenges, particularly related to documentation. In this section, we discuss three challenges posed by the computerization of clinical documentation and the changing health care environment.

Structuring Inherently Messy Clinical Reality

The first challenge relates to a fundamental mismatch between our tools and what we want to accomplish. Clinical reality is difficult to define precisely. Consider this simple example: Is hypertension a disease of the blood vessels? Heart? Kidneys? Brain? Clearly all are affected and involved. However, putting hypertension into a category with well-defined necessary and sufficient conditions is challenging. Further, clinical concepts are continuously evolving. For example, the definition of a gene has changed dramatically as our understanding of molecular biology has improved. Similarly, genomically informed therapy is constantly evolving. Today's variant of unknown significance may be an actionable (targetable) variant tomorrow.

With paper records, we were not tied to specific categories. We recorded our thoughts using natural language rather than trying to express our thoughts using a predefined set of categories that are often inadequate to represent our intended meaning. Freehand drawings or diagrams could be inserted where appropriate, and shorthand was widely used. Rosenbloom et al[48] published an overview of the tensions between structured and unstructured clinical documentation.

There is no easy answer to this challenge. However, there are promising developments. First, natural language processing technology can be very useful when 100% accuracy is not required. For example, algorithms can identify specific concepts in the text even when they are not referenced with a particular name (e.g., breast cancer, brst ca, and IDC [invasive ductal carcinoma] can be recognized as synonymous). This can be very useful for a variety of purposes, including identifying cases of a particular malignancy, cancer stage, or treatment outcome in large clinical data sets and for automatically summarizing complex patient histories. A review of natural language processing in oncology was recently published in *JAMA Oncology*.[49]

Second, the field of human-computer interaction has developed into an engineering discipline with validated approaches to matching users and tasks (e.g., a clinician who has to write a note documenting an office visit) to specific tools and their characteristics. Usability experts can define existing workflow, identify areas that can be improved, and guide implementation of systems that match user needs. Professional organizations have recognized that improving the usability of clinical systems has the potential to improve clinical outcomes (e.g., by reducing errors) and have published recommendations for incorporating usability into the design of clinical systems.[50]

Competing Priorities (Business Versus Clinical Needs)

In many important ways, health care is a business. Institutions are reasonably concerned about their financial performance and must comply with an increasing regulatory burden. As a result, the decision to implement a clinical system is often driven more by business concerns rather than clinical needs, for example, the need to document compliance and streamline financial (billing) operations.

Clinical reimbursement has traditionally relied on documentation of specific services rendered. Thus, clinical notes now contain specific billing-oriented phrases such as "40 minutes spent at the bedside with greater than 50% of this time spent on counseling." This, along with the need to document in increasing detail to justify specific service levels, has led to administratively compliant but clinically less useful documentation.

Further, computerized physician order entry is a very effective way to track and influence clinical behavior. An undesirable behavior (e.g., daily laboratories) can simply be made inconvenient to order (e.g., by requiring a daily written justification). Thus, health information technology has increased the ability of the business enterprise to monitor and influence the clinical enterprise without assuming direct responsibility for clinical outcomes.

This challenge is primarily social, rather than technical. For a variety of reasons, clinicians have been reluctant advocates for clinical priorities. As a result, business priorities may outweigh clinical priorities at times simply because the clinical enterprise lacks effective representation when the relevant decisions are being made. To their credit, organizations increasingly recognize the need for clinical champions in board rooms and are hiring clinician-informaticians to lead clinical information technology efforts (e.g., chief medical information officers).

Ease of Creating Data Versus Useful Information

Current computer technology makes it very easy to generate and replicate data. For example, with a few clicks, one can copy and paste radiology reports, laboratory studies, past notes, and any other data contained in a clinical system. As a result, notes that were previously succinct have become unreadable. In contrast, it requires much more effort to summarize the clinically relevant facts. Thus, ironically, health information technology has decreased our ability to manage information. Patients who enter the hospital with hypercalcemia leave with hypercalcemia, and errors are perpetuated verbatim from note to note.

Part of the problem is that trainees are encouraged to document fully to avoid being accused of missing something important and to support billing. However, errors may creep into a long note that is assembled from pieces of other notes. Institutions struggle to develop policies that balance the need to repeatedly document the same information (e.g., often the physical exam does not change from day to day in a hospitalized patient, unless it does) and ensure that important changes are not missed. Currently, there is general agreement that cut and paste or cloning of

clinical notes is undesirable. However, there is not yet a consensus regarding best practice or how to configure clinical systems to support best practice. Clearly, the current model where by some reports clinicians are spending twice as much time documenting as they are with patients, is no longer tenable. Creative solutions such as voice-to-text systems with predictive analytic features that can autocomplete notes, scribes that can be present in a clinical encounter with disrupting workflow or rapport, and structured authoring tools will all need to be exhaustively tested in the field in order to help busy oncologists get through their clinical day.

DIGITAL DONATIONS: PATIENT CONSENT AND ENABLING TECHNOLOGIES IN THE EHR

Under the first stages of the meaningful-use EHR incentive program (2010–2015), adoption of EHR systems increased from 51% to 87% in outpatient practices[51] and from 16% to 84% in hospitals.[52] Increased availability of clinical data (including problem lists, laboratory results, prescription history, and free-text notes) presents a growing opportunity for researchers.[53] For example, combining EHR data with adverse event reporting databases has led to automated detection of previously unknown adverse drug reactions.[54] EHRs also present an opportunity for prospective research studies, as an adjunct to (and a cross-check for) data collected directly from research participants through traditional paper-based forms or recent innovations using app-based interactions.[55]

However, researcher access to EHR data has traditionally been limited to institutional settings, where data from a single clinical system or a small network of collaborating systems are available to researchers within the network. These systems expand to form wider networks with more data available to qualified researchers, as in the network of networks established by the Patient-Centered Outcomes Research Institute's Clinical Data Research Network awardees.[56] Such networks are constructed along the grain of institutional boundaries, with careful legal agreements needing to be established among entities as a prerequisite for data sharing. These institution-based studies can provide relatively easy access to EHR data by creating their own legal frameworks for intramural data sharing.

On the other hand, many research studies cut across the grain of institutional boundaries. For example, diseased-focused organizations such as the Multiple Myeloma Research Foundation create community-based registries that identify patients across the country on the basis of disease state and without regard to institutional affiliation.[57] We call these participant-based studies. We should highlight that this distinction is not a bright line; studies such as the Precision Medicine Initiative's All of Us research program pursue a hybrid approach by recruiting from in-network health care systems as well as the general population.[58]

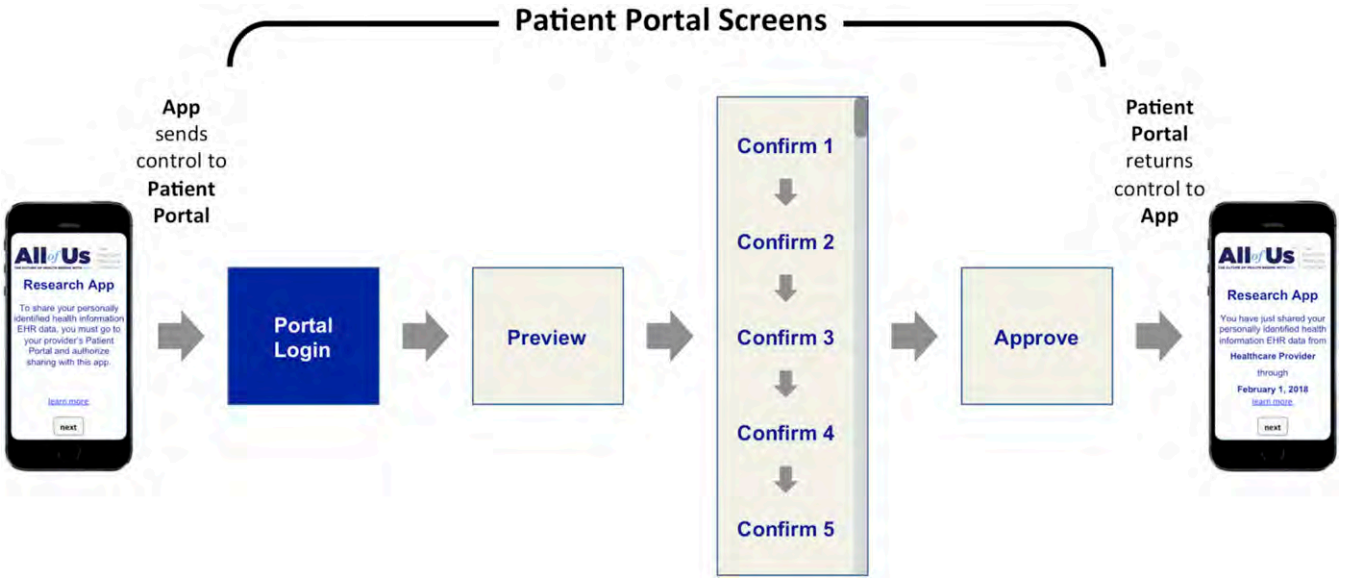
One model for sharing clinical records with participant-based studies is to engage participants to mediate the transfer. For example, after a participant completes an informed consent process, researchers might ask the patient to collect her own clinical records from the hospitals where she has received care. This model confers comprehensive access to clinical records by leveraging a patient's right under the Health Insurance Portability and Accountability Act to access a designated record set.[59] But the barriers for this model are formidable for otherwise willing participants, including driving to multiple hospitals to visit the medical records departments and filling out multiple authorization forms. In addition, data arriving from faxed or photocopied page-formatted documents instead of electronic structured data add sources of error as well as cost and time.

These shortcomings can be addressed through existing law and additional technology, in particular an application programming interface (API) that can retrieve and move data from EHRs to researchers. Three key enablers are established by federal laws and regulations: (1) The right under the Health Insurance Portability and Accountability Act for a patient to access his or her own medical records, (2) the meaningful-use stage 3 requirement that patients may access their health information with the applications they choose, and (3) the meaningful-use common clinical data set, which establishes a minimum set of data to be made available to patients through such an API, including patient demographics, allergies, immunization, medications, laboratory results, and vital signs.[60] Of note, the regulations do fall short of defining common standards for the API, which means that certified EHRs could choose to expose these data with proprietary formats and incompatible interfaces.

Through a National Institutes of Health–funded and Office of the National Coordinator for Health Information Technology–supported effort called Sync for Science, Dr. Mandel, Mr. Kreda, and colleagues are undertaking a pilot project with six commercial EHR vendors to establish and test a common, nonproprietary interface for sharing data with research. Building on open standards established through SMART on FHIR and the Argonaut Project,[38] Sync for Science has defined a focused set of APIs for EHR vendors to implement. These APIs are published alongside new functionality in each vendor's patient portal, giving patients the means to approve sharing their data with apps. Under this model, a research study can create an app that asks participants for access to their EHR data. The Sync for Science technology delivers the patient's approval in the form of an access token following the OAuth 2.0 specification[61] (Fig. 3), allowing a research app access to a participant's EHR data for a designated period of time (typically 1 year).

To support vendor implementation of the Sync for Science APIs, developer documentation (http://syncfor.science/apicalls) and a test suite that connects to each vendor's portal and provides a compatibility report have been developed. The test suite verifies the availability of sample data, validating that payloads conform to the FHIR specification and checking coded terms against a set of expected vocabularies. Although errors and warnings are produced when data fail to match expectations, the tests are permissive, allowing

FIGURE 3. Workflow for a Patient Sharing Data With a Research Study, Using an App Built Using Sync for Science Technology



researchers to obtain a richer set of real-world (if occasionally messy) data rather than a smaller set of cleaner data. Over the course of 2017, EHR vendors are working to deploy this technology at approximately 15 pilot sites around the United States. Although these APIs are designed to support any patient-selected application, the pilot deployment focuses on the Precision Medicine Initiative's *All of Us* research program as an initial testbed.

During the pilot phase, a known set of provider sites has been engaged to enable access to a single, well-respected research app, which will provide crucial experience with API-driven data sharing. That said, three impediments in scaling this technology to support a wider ecosystem of research studies are anticipated: (1) building a robust share-my-data feature requires a high-quality national provider directory that includes API endpoints for each provider, (2) connecting an app to a provider system still requires registration, a step for which not all vendors have provided an automated approach, and (3) despite regulations that empower patients to access and share their data as they choose, many health care providers are not yet comfortable enabling connections to unknown apps.

CONCLUSION

Many data systems have evolved to support improved quality of care with greater efficiencies. Despite the richness of available data and the life-threatening nature of cancer, their use throughout oncology practice remains more limited today than in other chronic diseases.

Translating innovations developed in the informatics research space into clinical practice is every bit as important as traditional bench-to-bedside translational science. To facilitate such knowledge transfer, ASCO recently launched two journals to explicitly link the cancer and informatics and bioinformatics communities together: *JCO Precision Oncology* and *JCO Clinical Cancer Informatics*. Sharing information through these and similar venues, as well as through presentation at conferences, will remain paramount in helping us all benefit from this innovation faster and ultimately allowing us to deliver more medicine with fewer clicks.

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The Oncology Care Model: Perspectives From the Centers for Medicare & Medicaid Services and Participating Oncology Practices in Academia and the Community

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OVERVIEW

Cancer care delivery in the United States is often fragmented and inefficient, imposing substantial burdens on patients. Costs of cancer care are rising more rapidly than other specialties, with substantial regional differences in quality and cost. The Centers for Medicare & Medicaid Services (CMS) Innovation Center (CMMIS) recently launched the Oncology Care Model (OCM), which uses payment incentives and practice redesign requirements toward the goal of improving quality while controlling costs. As of March 2017, 190 practices were participating, with approximately 3,200 oncologists providing care for approximately 150,000 unique beneficiaries per year (approximately 20% of the Medicare Fee-for-Service population receiving chemotherapy for cancer). This article provides an overview of the program from the CMS perspective, as well as perspectives from two practices implementing OCM: an academic health system (Yale Cancer Center) and a community practice (Hematology Oncology Associates of Central New York). Requirements of OCM, as well as implementation successes, challenges, financial implications, impact on quality, and future visions, are provided from each perspective.

Oncology is a complex and expensive medical specialty with costs rising faster than other medical specialties. The care is often fragmented and inefficient, imposing substantial burdens upon patients. Importantly, data show major differences in the cost of care in different regions of the United States without appreciable differences in outcome,[1] thus identifying opportunities for improvement. For these reasons, the CMMI recognized oncology as an important specialty for a patient-focused model emphasizing care coordination and enhanced services and worked to create the OCM.[2]

As of March 2017, 190 practices are participating in OCM, with approximately 3,200 oncologists included in the model, providing care for an estimated 150,000 unique beneficiaries (and 190,000 episodes) per year, or approximately 20% of the Medicare Fee-for-Service (FFS) population receiving chemotherapy for the treatment of cancer. The goal of OCM is to use payment incentives and required practice redesign activities to transform oncology care in the United States so that it becomes universally high quality, high value, and patient focused. In addition to usual fee-for-service payments, OCM provides a $160 per beneficiary per month (Monthly Enhanced Oncology Services [MEOS]) payment to practices to support enhanced services for Medicare beneficiaries receiving chemotherapy. A retrospective analysis is done on each 6-month episode of care to generate a performance-based payment (PBP) for practices that successfully reduce expenditures while providing high-quality care.

In addition to the payment methodology that incentivizes high-value care, there are six required practice redesign activities intended to move practices toward coordinated, patient-focused care: (1) access to a provider on a 24/7 basis with access to the patient's clinical record, (2) use of data for clinical quality improvement, (3) use of certified electronic health record (EHR) technology, (4) treatment of patients according to national guidelines, (5) provision of care navigation services, and (6) documentation of a care plan incorporating the 13 elements of the Institute of Medicine (IOM) care plan cited in the 2013 consensus report on cancer care.[3]

PERSPECTIVE FROM CMS

CMS appreciates the difficult work that practices throughout the country are undertaking to transform cancer care. Although even early objective analysis of the program's impact to date is still several months away, we are gratified by the anecdotal reports of improvements in patient-centered care. These include improved care attributed to the man-

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dated use of the IOM care plan and the creation of interdisciplinary teams formed to coordinate patient care. Our communications with participating practices often focus on the changes these practices have made to their care processes to improve quality and patient focus. In the design of OCM, such as the payment incentives and through the inclusion of other payers , our goal has always been whole-practice transformation, so we have been pleased to hear many practices report that their enhanced and newly coordinated services are offered to all of their patients, not just Medicare FFS beneficiaries.

OCM is a model test intended to transform and improve the way oncology care is delivered in the United States. The model must work across diverse geographic regions, business models, and practice types. It must function within the existing frameworks of CMS claims and ICD-10 while providing complex care to patients with a diverse array of diseases and comorbidities. Given these challenges, the model is not static; it has already adapted to address early lessons learned, and it will evolve over time as problems are identified and solutions developed.

Early Lessons

Tracking OCM beneficiaries. To be eligible for MEOS payments for a 6-month episode of care, OCM beneficiaries must have a qualifying cancer diagnosis and a qualifying chemotherapy trigger. These beneficiaries must receive the enhanced services described above, including the initial completion of the IOM care plan, with an update to the care plan during subsequent episodes if applicable. These payments and care requirements direct practices to track beneficiaries with specific diagnoses receiving specific therapies, including the dates those therapies were received. This has required practices to put in place processes that track these data to identify when claims for MEOS payments should be filed, as well as to ensure that enhanced services have been provided to OCM beneficiaries (and that these activities have been documented).

Particular attention has focused on tracking episodes for OCM beneficiaries (with Part D coverage) receiving only oral chemotherapy. The episode commences on the fill date of the chemotherapy (in association with a Part B cancer service in the previous 2 months). CMS cannot provide real-time Part D data to practices, though these data are available to practices on a several-month time lag as part of their quarterly feedback reports. To date, some practices with patients who do not fill their prescriptions in house have contacted pharmacies to obtain the fill dates of oral chemotherapy drugs for their OCM patients, though this is a manual process. We continue to work on identifying best practices and possible solutions to this challenge.

IOM care plan. One of the practice redesign activities requires practices to document a care plan that includes the 13 elements recommended by the IOM consensus committee. These elements were identified as the foundations necessary to provide comprehensive, high-quality care to the oncology patient and promote shared decision making. There has been much discussion about one of the elements—patients' out-of-pocket costs for cancer treatment—specifically how to estimate these costs. Although not traditionally an aspect of health care, increasing concerns about financial toxicity, especially in oncology, have made this an important issue. Practices are working diligently to understand not only the costs they generate specific to chemotherapy, but also costs generated from other aspects of oncology care such as radiation therapy, imaging, and laboratory diagnostics.

Adoption of EHR standards. OCM requires the entry of anatomic staging and other clinically relevant data into its data registry (e.g., molecular mutations that enable the use of targeted therapies). These data will inform the creation of subsequent payment bundles that are narrower and more clinically focused. Collection of quality measurement data is necessary for the calculation of PBPs and for practice quality improvement. The ultimate goal for reporting data to OCM is that required data elements will be seamlessly exported from practice EHRs to the OCM data registry with minimal provider burden.

CMS surveyed the EHR landscape and identified heterogeneity in capabilities, data capture fields, and electronic export standards. Several EHR vendors stated they were waiting for OCM to release such standards before building their EHRs to those specifications. CMS therefore identified the Health Level Seven (HL-7) standard for export, referred to as "Reporting to Public Health Cancer Registries from Ambulatory Healthcare Providers," to support submission of staging and clinical data. Additionally, we aligned our quality measures with nationally validated measures and existing registry reporting programs wherever possible. Given

KEY POINTS

- **The OCM was recently launched by the CMS Innovation Center.**
- **OCM uses payment incentives and practice redesign requirements toward the goal of improving quality while controlling costs.**
- **As of March 2017, 190 practices are participating, with approximately 3,200 oncologists providing care for about 150,000 unique beneficiaries per year (approximately 20% of the Medicaid Fee-for-Service population receiving chemotherapy for cancer).**
- **Key requirements for practices in OCM are to: (1) provide patients with 24/7 access to a clinician with real-time access to health records; (2) use of electronic health records certified by the Office of the National Coordinator for Health Information Technology; (3) use data for continuous quality improvement; (4) provide core functions of patient navigation; (5) document a care plan that contains the 13 components in the Institute of Medicine Care Management Plan; and (6) treat patients with therapies consistent with nationally recognized clinical practice guidelines.**

the spectrum of both practice and EHR capabilities, and the variety of existing registries, there have been some early difficulties. Accordingly, CMS decided to reduce practice reporting requirements in the first year of the model to allow time for continued practice process improvement and for EHR capabilities to further align with OCM requirements. Work continues with the data registry contractor and EHR vendors to make the data registry more user friendly and to improve the automated data export process.

Bladder and prostate cancer care. Target prices for broad cancer bundles inherently include low-cost patients for whom the cost of treatment is lower than the target price and high-cost patients for whom the cost of treatment is higher than the target price. In OCM, the target price is based on the average costs of all patients in each bundle in the historical baseline period adjusted by each practice's baseline experience. In a practice that treats a random distribution of all cancer stages and molecular subtypes, this methodology is appropriate. When separate practices consistently treats patients of different stages, then this methodology may not be appropriate.

CMS noted that, in general, urologists cared for a greater proportion of patients with low-risk bladder and prostate cancer, whereas medical oncologists cared for a greater proportion of high-risk patients. To ensure equity in the model, CMS created separate target prices for high- and low-risk bladder and prostate cancer for episodes beginning after July 1, 2017. CMS identified drugs typically used in the treatment of these different stages of cancer to generate separate target prices.

Future Directions

In the first year of OCM, participating practices have invested considerable energy and resources implementing the model, and CMS has made adaptations where necessary to respond to identified problems. We view the model test as an opportunity to learn about how care and health outcomes can be improved for Medicare beneficiaries with cancer who receive chemotherapy in diverse practice environments.

As noted above, one of the limitations of OCM, as currently designed, are its broad clinical bundles, because anatomic staging and relevant molecular markers are not a part of existing Medicare FFS claims data. By collecting detailed staging and molecular information in the data registry, we plan to link these data with claims to design more clinically refined payment bundles for different stages and molecular subtypes of cancer where meaningful cost and outcome variations exist. Part of this process will involve remaining current in clinical oncology so that molecular mutations with new targeted therapies are incorporated into the data registry as quickly as possible.

OCM also has a robust learning and diffusion component incorporated into the model. Among other activities, such as OCM's online collaboration platform, our webinars will highlight practices that develop successful approaches to practice transformation so that others may benefit from this innovative work. In addition, CMS has launched a palliative care affinity group, and future affinity groups will focus on topics such as using data for quality improvement to allow practices with specific interests or needs to learn from one another.

CMS looks forward to engaging with OCM practices and other stakeholders during the remaining 4 years of OCM to ensure that this is a successful model test that will improve the quality of cancer care in the United States.

ACADEMIC HEALTH SYSTEM OCM PARTICIPANT PERSPECTIVE (YALE CANCER CENTER)

Smilow Cancer Hospital at Yale New Haven Hospital is the clinical facility of the Yale Cancer Center. Today, we deliver care to one in four patients with cancer in the state of Connecticut. We have 10 community medical oncology and hematology practices and an academic main campus where care is delivered in multispecialty disease teams. We serve as the largest academic referral center in the state and care for the largest proportion of uninsured and underinsured patients.

Rationale for Joining OCM

The transition toward value-based care presents different challenges for a large health system compared with ambulatory oncology practices. Although reducing hospitalizations and emergency department visits represent an opportunity for savings for payers and society at large, for a health system, this savings represents a loss of revenue. For the Smilow Cancer Hospital, OCM served as a catalyst to move toward value-based payment. OCM's MEOS payments would fund clinical infrastructure that would improve oncology care, and the potential for PBPs would offset potential losses in revenue.[4]

In a best-case scenario, OCM would allow us to transform how we care for patients through implementation of new programs in care management, oncology urgent care, implementation of clinical pathways, and expansion of palliative care into the ambulatory setting, while allowing us to earn PBPs for reduced cost and higher-quality care. In a worst-case scenario, OCM would allow us to build this essential clinical infrastructure and gain experience with value-based payment, even if we did not achieve savings or PBPs. With either scenario, Smilow Cancer Hospital leadership believed OCM would enhance the quality of care while providing early experience with an alternative payment model.

Finally, as a National Cancer Institute–designated comprehensive cancer center, our mission is to improve outcomes for patients with cancer; to that end, we must participate in, learn from, and help inform new, value-oriented models for cancer care delivery. Academic centers must have a voice in national conversation that will ultimately redefine quality cancer care and inform the restructuring of our national payment system. OCM gave us this opportunity.

Steps to Prepare for and Implement OCM

Our clinical transformation and cost-saving strategy is focused on keeping patients out of the hospital by providing care management while patients are home, expanding access to urgent visits and symptom management services, and integrating palliative care earlier in the disease process. In many ways, this has meant creating the clinical infrastructure to function as an oncology medical home.

Achieving transformation in care delivery requires uniting multiple stakeholders, including the clinical arm of the school of medicine (Yale Medicine), which employs the physicians and is responsible for MEOS billing, and the hospital (Yale New Haven Health), which is funding most of the infrastructure. We created an OCM executive committee to serve as the decision-making and funding body of the program. We then organized our work into six thematic projects:

1. Patient identification and MEOS billing: We built a team that included an Epic report writer, lead pharmacist, lead physician, program manager, and billing representative to translate the detailed patient eligibility criteria into ongoing patient eligibility reports. After multiple iterations, this final patient list was translated into EHR flags and then into work queues for care management, financial counseling, and billing.
2. IOM care plan: We worked with our Epic team to centralize the 13 IOM care plan elements into one document. We made a deliberate decision not to burden our physicians and advanced practice providers with additional documentation demands. Instead, we required providers to enter patients' stage and treatment goals when ordering chemotherapy (curative vs. noncurative intent). With this documentation in place, our nurse care managers could fill out the care plan.
3. Open an oncology extended care clinic: We developed a business plan to build and staff a new extended care clinic that would be open 16 hours a day, 7 days a week. This center should open in Spring 2017.
4. Launch a care management program: The goal of this program is to improve contact with patients when they are home and identify and stabilize early symptom exacerbations before they lead to hospitalizations. We have hired four out of a total of eight OCM care managers.
5. Integrate clinical pathways into practice: We have committed to use Via Oncology clinical pathways with the goal of reducing unnecessary variation and reducing the use of high-cost drugs in situations where they do not improve efficacy.
6. Quality and registry reporting: We partnered with our tumor registrars and data analysts to define registry requirements. We created hard stops in our EHR to ensure that required documentation would be accessible in structured fields. Our tumor registry has begun abstracting in real-time, a radical change to their workflow.

Successes and Challenges

Participation in OCM requires time-intensive resources from across the organization. There is a constant tension between working to meet the reporting requirements and meaningfully transforming care. Although checklists and EHR tools may help in an audit or improve chance of PBPs, they are unlikely to change patterns of care or reduce cost. Although we are behind on completing each component of the IOM care plan for our more than 3,000 eligible patients, we have made real strides in building the infrastructure we believe will ultimately achieve clinical transformation.

Timeline challenges. Due to the complexity of eligibility requirements described below, it took more than 4 months to finalize our initial patient list; initiation of downstream services (financial counseling, IOM care plan completion, care management) and MEOS billing was delayed until this process was complete.

Barriers with patient identification and MEOS. The patient identification process was rigorous and time intensive and required an iterative report build. Because patients taking oral drugs often received multiple refills when first prescribed, we could not rely on a new prescription to trigger enrollment and instead created a candidate list of patients who received oral prescriptions in the last year. Our pharmacists manually checked disparate data systems for Medicare Part D status and prescription fill verification for thousands of patients. This resource and time-consuming process continues today. There is a critical need for CMS to make this information easily accessible to OCM sites.

We had challenges in the MEOS billing and payment process that have delayed revenue earmarked to support new clinical infrastructure. Because our hospital committed to OCM participation, we have moved forward with clinical program building despite the delayed revenue. Achieving resolution of the billing issues has been slow and labor and time intensive. Going forward, it would be helpful if there were real-time problem resolution at the OCM and CMS support lines.

IOM care plan challenges. Epic did not provide us with an out-of-the-box solution for IOM care plan. Our internal discussions have revolved around whether we should meet the program requirements by creating check boxes—such as, "I closed the referral loop," or "Treatment benefits and harms discussed with the patient"—or whether we should focus on the spirit of the program and use the care plan to facilitate meaningful discussions with patients. We have chosen the latter and believe that, in the long run, this will facilitate better prognostic understanding and influence downstream health care utilization. In the meantime, we are challenged with completing these care plans and sharing them with more than 3,000 patients.

Reporting. Reporting processes are proving to be more time intensive and manual than we had hoped. For example, classifying patients as having "very high–risk" or "high-risk" prostate cancer is challenging because the data does not exist in structured format in either our EHR or in the tumor registry. Initially, CMS reporting timeframes required

that our tumor registrar begin concurrent abstraction, a dramatic change in their workflow. However, in response to concerns from participating sites, CMS has revised reporting requirements, which has been appreciated by our tumor registrars.

Future Impact on Practice

Like other academic health centers with a strong research mission, we are challenged with balancing our role as a destination hospital for patients seeking the latest treatment options while ensuring that we elicit their true preferences, provide realistic expectations for treatment benefit, and support their quality of life.[1] We believe that OCM will serve as the catalyst to shift care from an inpatient to an outpatient setting.

Financial Feasibility

Under OCM, health systems face revenue loss from reduced inpatient services; our finance team studied the impact that success in the program would have on revenue from Medicare and private payers who would also benefit from the clinical infrastructure we sought to build. Although achieving the 4% reduction in costs required to achieve PBPs would impact the contribution margin, we found the effects would be tolerable over time.[4]

We have not formally modeled how we will fair with PBPs, which depend first on achieving a greater than 4% savings and then on performing well compared with the national average on multiple quality metrics. However, our financial justification for participation in OCM relied entirely on MEOS revenue and modeling of the impact that care transformation would have on our contribution margin. Thus, even without guarantee of PBPs, we felt the program was sustainable.

Impact on Quality

We believe that participation in OCM should improve clinical quality through better care coordination, access to urgent care services, reduction in variability of chemotherapy choice, and earlier integration of palliative care. Furthermore, OCM will ensure ongoing access to total cost of care claims data, which will allow us to provide physicians, disease teams, and community practices with detailed feedback on patterns of care, including hospital admission rates, emergency department utilization, intensive care unit use, chemotherapy near the end of life, and timeliness of hospice.

Participating in OCM has made investments in clinical infrastructure possible that were not feasible before. For 3 years, we attempted to create a workable business model for an oncology extended care clinic. Each time, the model incorporated loss of inpatient revenue and could not be financially justified. Similarly, we wanted to implement clinical pathways to diminish variation in care but had no risk-based contracts, and thus there was no financial incentive to warrant it. In the context of OCM, MEOS revenue could offset these infrastructure costs, and the potential to earn back savings as PBPs could offset some revenue losses.

COMMUNITY PRACTICE OCM PARTICIPANT PERSPECTIVE (HEMATOLOGY ONCOLOGY ASSOCIATES OF CENTRAL NEW YORK)

Hematology Oncology Associates of Central New York is a hematology/oncology practice comprised of 14 medical oncologists, three radiation oncologists, 20 midlevel providers (17 nurse practitioners and three physician assistants), and a total of 280 employees. Our main office is in East Syracuse, New York, with satellite offices in Onondaga Hill-Syracuse and Auburn. The catchment area is approximately one million. There is an infusion center at all three locations, and two sites have radiation oncology. The great majority of chemotherapy is administered in our offices, although we do have admitting privileges at three local hospitals. We have an outpatient pharmacy at our main office to provide and monitor oral oncolytic agents. We actively participate in clinical research and are a main member of the Alliance for Clinical Trials in Oncology, one of the major National Cancer Institute–sponsored cooperative groups.

Rationale for Joining OCM

Ensuring high quality of care for our patients has always been a high priority for our practice. We are Quality Oncology Practice Initiative–certified through ASCO and are one of nine Oncology Medical Homes certified by the American College of Surgeons Commission on Cancer. We have successfully participated in the CMS Meaningful Use program and continue to report quality data through the Physicians Quality Reporting System.

We decided to apply for participation in OCM for many reasons. The bottom line is that we believe that participation will help us provide better care to our patients. Our practice always strives to be progressive and up to date. We truly believe OCM is a better payment model because quality is incorporated rather than just fee-for-service. We also see participation as a way to prepare for the future.

Steps to Prepare for and Implement OCM

We began preparing for OCM in early 2015 when we hired a quality coordinator to help with the Physicians Quality Reporting System; a year later, we hired an incentive coordinator. Our EHR is regularly updated to meet quality reporting. Our chief clinical officer oversees the entire program and reports to our chief executive officer and board of directors, which is comprised of our physician partners. We also have created a quality care committee with representation from multiple departments.

We were fortunate to be accepted in the OCM program initiated in July 2016. As detailed in our application, we have completed the practice transformation plan as required by CMS:

1. Provide and attest to 24/7 patient access to an appropriate clinician who has real-time access to the practice's medical records.
2. Attest to the use of ONC-certified EHRs.
3. Use data for continuous quality improvement.
4. Provide core functions of patient navigation.

5. Document a care plan that contains the 13 components in the IOM Care Management Plan.
6. Treat patients with therapies consistent with nationally recognized clinical guidelines.

Prior to the start date of the OCM program, we had extensive training for our entire staff, including the physicians. Our EHR was updated to include OCM reporting requirements, and the health care providers had to become proficient in incorporating these changes. For example, chemotherapy could no longer be ordered without answering four questions on a dropdown bar that popped up on the screen: prognosis, goals, expected response, and advanced care plan. Pain had to be graded on a scale of 1 to 10, with a treatment plan entered. There is a tab for referral to our survivorship program.

Eligible OCM patients are identified in a number of ways, including review of health records and pharmacy ordering of chemotherapy. There have been initial challenges in identifying patients who were already receiving treatment. Patients receiving oral agents are more difficult to identify, but the EHR is monitored regularly by a dedicated information technology individual.

Once eligible patients are identified and entered into the OCM program, billing and financial services are promptly notified. A dedicated financial services advocate contacts the patient on the telephone and/or in person to explain the program and distribute the required notification from CMS.

Successes and Challenges

Internal monitoring of individual provider performance is performed regularly, and, for the most part, each individual has exceeded 90% compliance. Patients report over 90% satisfaction in monthly surveys.

Our first report to CMS was in February 2017. Five measures were reported, and these are our results from July 1 to December 31, 2016:

1. Prostate cancer (adjuvant hormonal therapy for high-risk or very high–risk disease): None of these patients were seen during the reporting period.
2. Adjuvant chemotherapy is recommended or administered within 4 months of diagnosis to patients under age 80 with stage III colon cancer: 100% compliance (35 patients).
3. Combination chemotherapy is recommended or administered within 4 months of diagnosis for women under age 70 with stage IB-III hormone receptor–negative breast cancer: 100% compliance (27 patients).
4. Trastuzumab administered to patients with stage I (T1c)-III and HER2-positive breast cancer who receive adjuvant chemotherapy: 100% compliance (34 patients).
5. Hormonal therapy for stage I-III estrogen receptor/progesterone receptor–positive breast cancer: 100% compliance (more than 800 patients).

Financial Feasibility

Enrollment in the OCM program has ranged from 311 to 755 patients. Net revenue for the first 6 months of the program was $459,958. Expenses are estimated by multiplying the salaries and benefits of the dedicated employees by the percentage of time devoted to OCM activities. Annualized expenses amount to $616,317. There are many other expenses that are more difficult to quantitate, including the many additional hours of work provided by our clinical staff and those who work in the financial services and information technology departments.

Future Impact on Practice

We will be changing to a new EHR, OncoEMR, and are working with the engineers to insure incorporation of OCM parameters and requirements into the EHR. We feel that the transition from Mosaiq should be fairly straightforward and seamless. This new EHR will be more user friendly and easier to stage new patients and document care plans, meeting the documentation requirements of CMS. We will be adding two new medical oncologists who will be trained in OCM and EHR use. Our quality committee will continue to monitor our programs. We will update and add in-house clinical pathways consistent with national guidelines.

Impact on Quality

To date, we have been very pleased with our participation in OCM. The amount of work to implement the program has been substantial, but doable, largely as a result of assembling a dedicated and competent team of individuals. They are well prepared and have been learning on the job. We believe that our first year has been a success in terms of maintaining and improving quality. The program appears to be financially viable, and although it is difficult to quantitate, we may realize a profit. In terms of the ultimate goals of CMS, we have indeed demonstrated an improvement in record keeping and compliance with the stated requirements of OCM, which should lead to better quality of care for our patients and overall less expenditure of health care dollars, as hospital admissions and emergency department visits will decrease. Alternative payment models appear to be here to stay, and we plan on continuing our participation in OCM and future programs as they become available.

CONCLUSION

OCM provides a path to improving care quality and controlling costs of care in the United States through a partnership between CMS and practices built on the backbone of the current system for reimbursement and care delivery. OCM has prompted practices to enact patient-centered delivery approaches focused on quality that are intended to improve the patient experience with care as well as measurable outcomes. This program is in its initial phase of implementation, and the ongoing experience of CMS and participating practices will provide further insights about feasibility of various aspects of the model, financial feasibility, impact on outcomes, and sustainability. CMS will be monitoring progress of OCM and a host of metrics at participating and comparator sites. Despite initial challenges at sites to implement various aspects of the model, the

aspiration of this program is to provide insights toward future approaches that optimize resources, quality, and patient centeredness in cancer care delivery.

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The views expressed in the manuscript represent the authors and not necessarily the views or policies of CMS.

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HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANSPLANT

Chronic Myeloid Leukemia: What Every Practitioner Needs to Know in 2017

Hanna Jean Khoury, MD, FACP, Loretta A. Williams, PhD, APRN, AOCN, Ehab Atallah, MD, and Rüdiger Hehlmann, MD, PhD

OVERVIEW

The prognosis of chronic phase chronic myeloid leukemia (CML) has improved so that life expectancy for patients responding to tyrosine kinase inhibitors (TKIs) is now equivalent to age-matched controls. Attention should be paid to comorbidities that impact survival. The success of TKI therapy can be easily and reliably assessed at well-accepted time points using quantitative polymerase chain reaction (PCR) standardized to the international scale. Patient-reported outcome (PRO) tools are readily available for use in the clinic and provide complementary information on the tolerance of TKIs. Effectively managing adverse events of TKIs can improve compliance and quality of life. Discontinuation of TKIs is the next frontier in CML. In select patients with sustained deep molecular remission, a discontinuation of TKI is associated with a durable treatment-free remission in approximately 50%. Patient engagement in their discontinuation can be achieved through a provider multi-team coaching, is complementary to the available guidelines, and may provide an additional safety net so that these discontinuations remain safe when applied in general practices.

Understanding the molecular pathophysiology of BCR-ABL undeniably led to a scientific breakthrough that completely transformed the landscape of CML. Indeed, in 2017, we are witnessing the dramatic effects of these discoveries with five very effective commercially available TKIs, a life expectancy that is comparable to age-matched population, and prolonged treatment-free remission in some patients, so one may even consider using the word "cure."[1] These impressive successes are broadly achievable when management is based on a set of commonly accepted treatment and monitoring guidelines—European LeukemiaNet (ELN)/National Comprehensive Center Network (NCCN). This article reviews key variables that impact outcomes of CML, provides patients' perspective on TKI tolerance, and discusses THE potential role of TKI discontinuation in daily practice.

MANAGEMENT OF CML IN PRACTICE: VARIABLES TO CONSIDER

Current Management Needs

Even with such an excellent prognosis that cure appears to be a realistic perspective,[1] more patients are currently dying of comorbidities than of their CML.[2] Thus, the skills of a general internist in addition to the expertise of the CML hematologist are needed now more than ever to effectively treat these patients. Careful monitoring of CML response is key to the success of therapy. The monitoring technology is sophisticated but also robust enough to be standardized and used by every hematologist, provided the necessary infrastructure is available.[3] A standardized and well-equipped laboratory with a turnaround time of no more than 14 days is necessary, in addition to a care facility that can reliably and regularly follow patients.[4]

Initial Testing and Monitoring

Current requirements for initial testing and follow-up are listed in Table 1. Figure 1A shows the correlation between cytogenetic and molecular findings with leukemic cell mass and response milestones as defined by ELN[5] and NCCN. The international scale was designed to make results comparable between different laboratories as illustrated in Fig. 1B.

Outcomes of Chronic Phase CML Following Treatment With Imatinib

Table 2 summarizes long-term survival of patients with chronic phase CML treated with imatinib on clinical trials.[6] The 10-year survival data are now available for imatinib, and 5-year data for the second-generation TKIs (2G-TKIs) dasatinib and nilotinib are also available.[7,8] Excellent 10- year molecular response (MR) rates are achieved with first-line imatinib: 92% for MR2 (corresponding to complete cytogenetic remission), 89% for MR3 (or major MR [MMR]), 81% for MR4 (reduction of residual BCR-ABL transcripts by ≥ 4 logs), 72% for MR4.5 (≥ 4.5 log reduction), and 59% for MR5

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TABLE 1. Evaluation of Chronic Myeloid Leukemia at Diagnosis and During Follow-up

Evaluations at Diagnosis	Follow-up
Record spleen size	Spleen size
Complete blood count (basophils, eosinophils) and basic metabolic profile	Complete blood count and basic metabolic profile
Risk score (Sokal, Euro, EUTOS, or ELTS)	
Bone marrow aspirate (blasts, karyotype)	Marrow karyotype (12 months)
Baseline molecular genetics (quantitative PCR for BCR-ABL) with transcript type	Molecular monitoring by quantitative PCR (every 3 months until MMR, then every 6 months)

Abbreviations: EUTOS, European Treatment and Outcome Study; ELTS, EUTOS Long-Term Survival score; PCR, polymerase chain reaction.

(≥ 5 log reduction).[9] Progression to blast crisis is 5% to 7% by 8 to 10 years in the randomized trial comparing imatinib with interferon/cytarabine (IRIS trial) and in the CML-study IV,[10-12] and relative survival compared with the matched general population was 92% in the CML-study IV, 96% across clinical trials in Europe (Fig. 2),[12] and around 90% in Dutch and Swedish population-based registries.[13,14]

First-Line Treatment Options

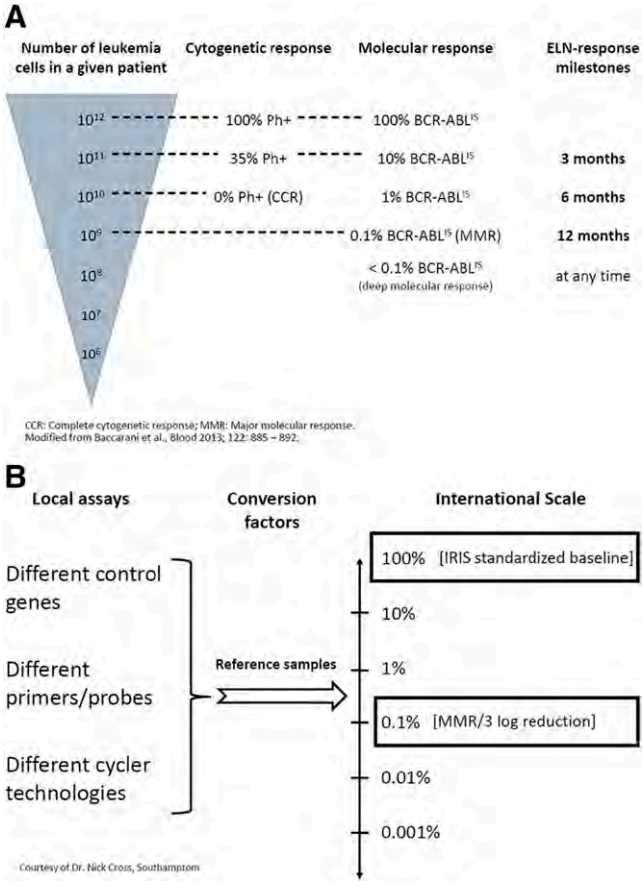
First-line treatment options include imatinib at 400 mg or higher dosages (600–800 mg), dasatinib at 100 mg, and nilotinib at 300 mg twice a day.[5] Although the second-generation TKIs dasatinib and nilotinib achieve response milestones earlier and faster than imatinib, no survival advantage has yet been reported for any TKI. In contrast to imatinib, 2G-TKIs have been associated with serious and potentially fatal adverse events. In choosing the most suitable front-line treatment in chronic phase CML, the following variables have to be considered:

1. CML risk score: Patients with high-risk disease must be monitored more closely.
2. Cytogenetics: Additional chromosomal aberrations (ACA), in particular so-called major-route ACA (+8, +Ph, i(17)(q10), +19), indicate accelerated phase and are associated with a poorer prognosis.[22,23]
3. Comorbidities: Patients with pre-existing vascular disease should not receive nilotinib, and patients with lung disease or a history of pleural effusion should not receive dasatinib. Comorbidities have been identified as the major cause of death for patients with CML in the TKI era.[2,12] They have no or little impact on progression of CML but determine survival particularly in patients with good-risk disease on stable first-line therapy.
4. Costs: Generic imatinib is now generally available at reasonable costs. In the face of the favorable efficacy and safety profile of imatinib and the increasing

KEY POINTS

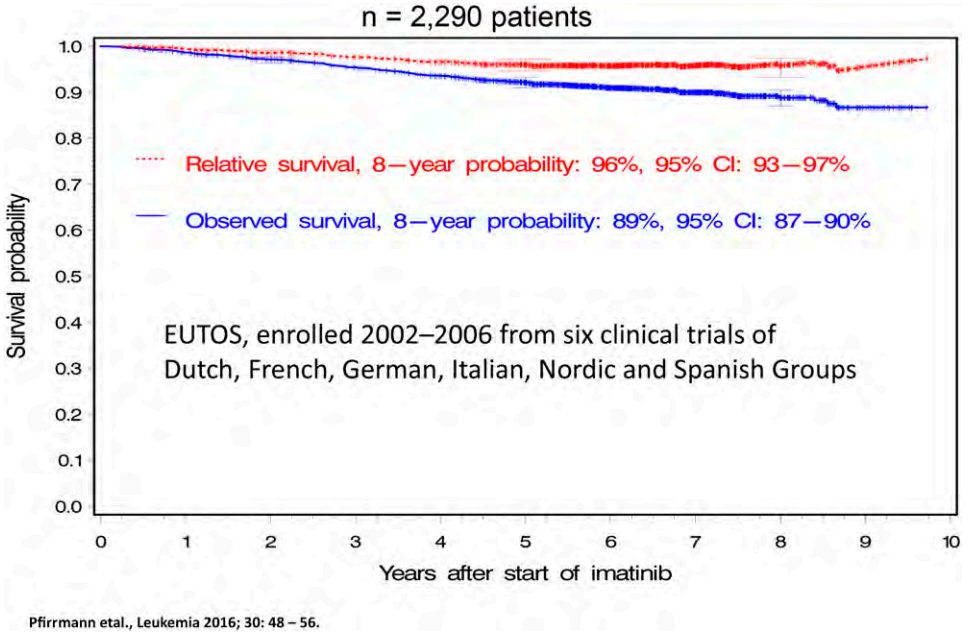
- **Current treatment of CML—if done right—results in normal, or near normal, life expectancy.**
- **Treatment choice should consider patients' comorbidities, adverse events profile of drugs, and patients' preference.**
- **PRO tools are available for use in clinical practice, can easily be completed at the time of a clinic visit, can alert clinicians to specific areas of concern, and can help clinicians follow symptom trends over time.**
- **PROs can help clinicians identify and better manage side effects of TKIs, which may lead to better adherence to therapy and improved clinical outcomes.**
- **TKI discontinuation, if done according to guidelines and in select patients, is safe and associated with a treatment-free remission of 40% to 50%.**

FIGURE 1. Correlation of Cytogenetic and Molecular Data With Leukemia Cell Mass and Response Milestones (A) and Comparability of Molecular Data Between Laboratories by Calculation of Conversion Factors (B)



Abbreviations: ELN, European LeukemiaNet; CCR, complete cytogenetic response; MMR, major molecular response.

FIGURE 2. Relative and Overall Survival in Clinical Trials



Abbreviations: CML, chronic myeloid leukemia; IFN, interferon; SCT, stem cell transplantation; HU, hydroxyurea.
Courtesy of Dr. Pfirrmann.[12]

prevalence of CML as a consequence of successful therapy (Fig. 3), generic imatinib represents a rational first-line treatment option for most patients with CML.[24]

Therefore, experts in the field consider it appropriate to start with imatinib and to switch to 2G-TKIs only in the case of intolerance or if response milestones are not reached.

TABLE 2. Long-term Survival of Patients With Chronic Phase Chronic Myeloid Leukemia Following Treatment With Imatinib on Clinical Trials

Study	IM-Dose mg	No. of Patients	Age at Diagnosis, Median, Years	5-Year Survival %	10-Year Survival %	Median Observation Time, Years
CML-IV[15]	IM 400–800	1,536	53	90	82	9.5
IRIS[10]	IM 400	553	50	89	85 (8 years)	8
GIMEMA[16]	IM 400–800	559	52	90	NA	5
Hammersmith[17]	IM 400	204	46.3	83	NA	3.2
PETHEMA[18]	IM 400	210	44	97.5	NA	4.2
TOPS[19]	IM 400	157	45	94 (4 years)	NA	3.5
	IM 800	319	48	93.4 (4 years)		3.5
MDACC[20]	IM 400	70	8.3	NR	80	9.9
	M 800	201			84	(min 8)
ILTE[21] (CCR only)	IM NR	832	51a	98 (6 years)	95 (8 years)	5.8
ENESTnd[8]	IM 400	283	46	92	NA	5
	Nilo 600	282	47	94		
	Nilo 800	281	47	96		
Dasision[7]	IM 400	260	49	90	NA	5
	Dasa 100	259	46	91		
Median (estimate)				91	82	

Abbreviations: IM, imatinib; NA, not applicable; NR, not reported; yr, year; min, minimum; CCR, complete cytogenetic response.

Second-Line Treatment

Prior to any TKI switch for secondary treatment decisions, the following variables must be considered:

1. Adherence to the prescribed drug: Poor adherence has been determined to be the most frequent cause of suboptimal response. In a review by Noens and colleagues,[25] varying degrees of nonadherence were reported in clinical trials, and nonadherence was associated with poorer event-free survival. A coordinated team approach might help to overcome problems with adherence.[26]
2. Resistance mutations dictating TKI choice: It is helpful to obtain an ABL kinase domain mutation at the time of resistance to a TKI and prior to switching to have a rational basis for choosing the appropriate TKI.
3. Clonal evolution: ACA newly arising under therapy have been defined as a sign of resistance indicating a need for a change of therapy.[5] As a rule, stem cell transplantation is considered the treatment of choice in this situation if a donor is available and the patient is suitable for transplantation.[27]
4. Intolerance: Adverse events and comorbidities predisposing adverse events must be considered when choosing the new TKI (e.g., avoid dasatinib in patients with pulmonary conditions, avoid nilotinib in patients with a history of vascular events, caution with nilotinib in the presence of liver disease or diabetes mellitus).

Safety of TKIs

Adverse drug reactions to imatinib are frequent but generally mild.[9] Most adverse drug reactions appear early and are reversible. No serious late toxicities have surfaced up to now with imatinib. Sequential analyses of glomerular filtration rates in patients receiving treatment with imatinib have indicated a reduction of filtration rates in 6% to 8% of patients, particularly in patients with preexisting renal failure.[28] These patients can be candidates for switching to nilotinib, as nilotinib has been reported beneficial for renal function.[29] Published evidence shows that approximately 2.5% of patients treated with nilotinib experience serious vascular events, which become more frequent over time.[8] Nilotinib should be avoided or used with caution in patients with vascular risk factors. Dasatinib is frequently associated with mostly benign pleural effusion and may rarely be associated with potentially fatal pulmonary arterial hypertension. Bosutinib is associated with transient diarrhea that usually resolves in the first week.[30] Lastly, ponatinib is associated with cardiovascular side effects in approximately 25% of patients.[31] An overview of adverse TKI reactions is provided in Table 3.

Impact of Health Care Setting

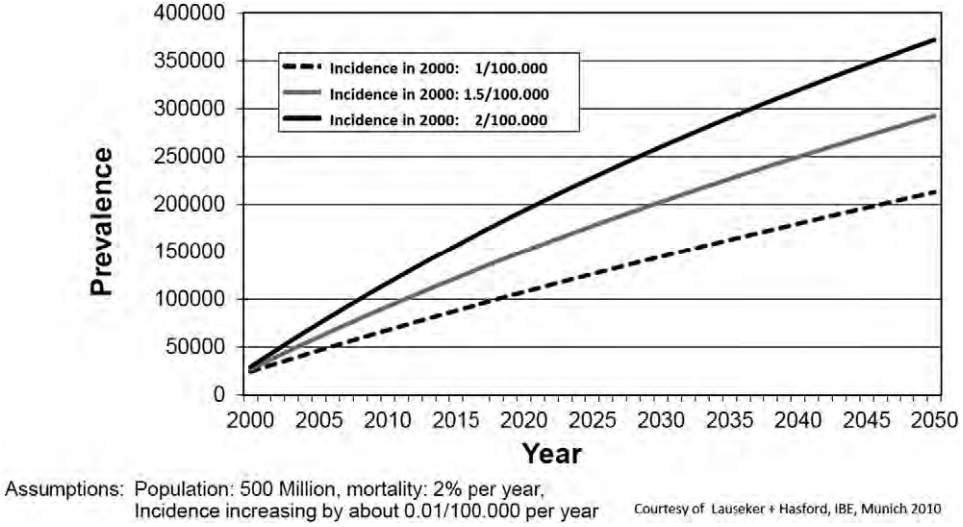
Health care infrastructure may affect quality of care and survival. Survival of patients managed at academic centers has been reported superior to office-based management or management at municipal hospitals.[36] A study on frequency of molecular monitoring in Europe and the United States has reported serious deficits, pointing to the need for standardized laboratories and better education of doctors and their patients with CML.[37]

HOW WELL ARE TKIS TOLERATED? THE PATIENT PERSPECTIVE

Patient-Reported Outcomes

Capturing patient perspectives of disease and treatment in a valid, reliable, and reproducible way is the goal of PRO measures.[38,39] PROs most often are assessed as questionnaires that measure concepts such as health-related quality of life (HRQoL), health status, symptoms, functional abilities,

FIGURE 3. Increase in Prevalence of CML in the TKI Era as Determined for Three Incidences (1, 1.5, or 2 per 100,000 per Year)



Abbreviations: CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

TABLE 3. Overview of Adverse Drug Reactions Associated With Tyrosine Kinase Inhibitors Approved for Chronic Myeloid Leukemia

	Imatinib[9]	Nilotinib[32]	Dasatinib[33]	Bosutinib[34]	Ponatinib[35]
Myelosuppression	++	+	+++	+	++
Fluid Retention	++	—	+++	—	—
Rash	+	++	—	—	++
Diarrhea	+	+	+	+++	+
Increased Glucose/Cholesterol	—	++	—	—	—
Vascular Occlusion	—	++	+	—	+++
Renal Insufficiency	+	—	(+)	?	?

treatment adherence, and satisfaction with treatment.[38] Table 4 summarizes commonly used PRO measures. Routine assessment with PROs can provide valuable information about patients' experiences of their condition to clinicians and researchers in much the same way that laboratory tests, scans, and physical findings do.[40] For clinicians, PRO assessments can be useful in improving communication with patients, making diagnoses, deciding on treatments, assessing treatment response, managing treatment toxicities to improve tolerability and compliance, and identifying targets to improve patient HRQoL.[40,41] PROs can also be useful in clinical research, in assessing quality of care, and in monitoring safety and treatment outcomes in clinical effectiveness and postmarketing registry studies.[42-44] The purpose of a PRO is to capture patients' evaluation of their experience, so by definition, PROs are subjective reports. However, the science of instrument development and psychometrics has progressed to the point that well-developed PROs can be trusted as valid and reliable measures when used for their intended purpose in their intended populations.[45] Studies in recent years have shown that PROs may be more accurate and complete measures of patient experience than clinician report and can provide complementary information to clinician assessments.[46]

Patient and Health Care Provider Perceptions

Differences between patient and health care provider perceptions of symptoms and HRQoL issues have been found in CML.[47,48] As shown in Fig. 4, patients rated the relevance of symptom issues higher than clinicians, whereas clinicians rated psychosocial issues as having more relevance than did patients.[47] Similar results were reported in another study that enrolled 422 pairs of patients with CML receiving imatinib and their treating physicians who assessed the severity of nine imatinib-specific symptoms. Patients rated individual symptoms as more severe more frequently than did their physicians. Agreement on symptom severity ranged from 34% for muscular cramps to 66% for nausea. Fifty-one percent of patients rated fatigue higher than their physicians, whereas 10% of physicians rated fatigue as more severe than their patients. Physicians rated patient health status better than the patients 67% of the time and the same as the patients 26% of the time.[48]

Clinical Use of PROs

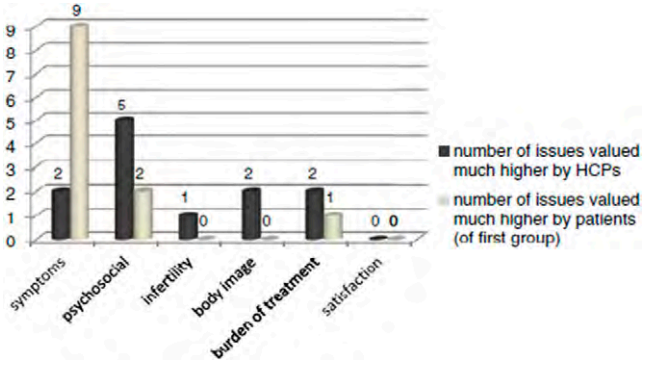
There are easy and reliable ways to capture and use PROs in the clinic. Selecting the correct PRO for clinical use is important. The health care provider should consider what information will be the most useful at a clinical visit, how easy the PRO will be for patients to understand and complete in a reasonable amount of time, and how easy the PRO will be for the clinician to review and interpret quickly. PROs that assess symptoms and functional abilities are often the most useful in clinical settings as these are simple concepts most directly related to a patient's physical condition (Fig. 5).[49]

TABLE 4. Commonly Used Patient-Reported Outcomes Measures

Type of PRO	Common PRO
Health-related quality of life	EORTC Quality of Life Questionnaire (QLQ)-C30
	Functional Assessment of Cancer Therapy (FACT)
Health status	Euro Quality of Life (QoL)-5D (EQ-5D)
	Medical Outcomes Study Short Form-12 or 36 (MOS SF-12 or 36)
Symptoms	MD Anderson Symptom Inventory (MDASI)
	Memorial Symptom Assessment Scale (MSAS)
Functional abilities	Work Productivity and Activity Impairment Questionnaire (WPAI)
Treatment adherence	Morisky Adherence Scale (MAS)
Satisfaction with treatment	Cancer Therapy Satisfaction Questionnaire (CTSQ)

Abbreviations: PRO, patient-reported outcomes; EORTC, European Organisation for Research and Treatment of Cancer.

FIGURE 4. Differences in Patients With CML and Health Care Provider Valuations of Aspects of HRQoL[47]



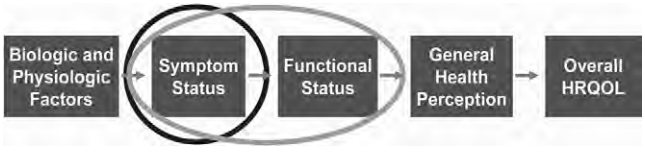
Abbreviations: CML, chronic myeloid leukemia; HRQoL, health-related quality of life; HCP, health care provider.

More complex concepts such as HRQoL require longer questionnaires, often have complicated scoring algorithms, and are better suited for research than for clinical use. However, to give clinicians an overall impression of patients' HRQoL, a single item can be valid and reliable.[50] The traditional method of PRO administration is paper and pencil. Although this is still an easy, effective, and cost-efficient method, newer technologies allow PROs to be completed electronically.[51] Computer kiosks or electronic tablets allow PRO completion in waiting area. Other methods, such as automated phone systems, mobile apps/e-diaries, and electronic medical record patient portals, allow patients to complete PROs at home prior to or in between clinic visits. Electronic applications can remind patients an assessment is due, allow direct transfer of the PRO data to the electronic medical record, provide automated scoring and reporting of results in clinician-friendly displays, and send the clinician alerts when results require follow-up.[51]

PROs for CML

Currently there are two PROs developed specifically for use by patients with CML: the MD Anderson Symptom Inventory for CML (MDASI-CML),[52] which measures the symptom burden of CML, and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CML24, which measures the HRQoL of patients with CML.[53] More general PROs can also be used in patients with CML, but they may be less sensitive to patient concerns and changes in patients' conditions. Although the use of PROs in hematologic malignancy research has lagged solid tumor research,[54] PROs have been incorporated into clinical trials and have provided insight into the tolerability of treatments for CML, including TKIs.[55] Studies have shown that most patients tolerate TKI therapy with few symptomatic effects or negative impact on HRQoL,[52,56] and some may have an improvement in some aspects of HRQoL.[57,58] However, a minority of patients will experience symptoms, such as fatigue and muscle soreness or cramping, at moderate to severe levels that impact HRQoL, and these symptoms may persist indefinitely. In one study, 25% to 30% of patients treated with imatinib reported severe fatigue, edema, musculoskeletal pain, and muscle cramps, with women being more affected than men.[56] Younger patients reported substantial role impairments because of physical and emotional problems, compared with matched normal controls.[56] In a year-long longitudinal study that assessed the symptom burden of CML using the MDASI-CML,[52] the highest severity symptoms were fatigue, muscle soreness and cramping, drowsiness, disturbed sleep, and trouble remembering things. Although these symptoms were mild (< 4 on a 0–10 scale),[52] trajectory analysis of these symptoms identified a high symptom group of 32% of patients with moderately severe symptoms (mean, 4.21, standard deviation, 1.58) that persist over time (Fig. 6).[52] Given that most patients are recommended to remain on indefinite treatment with a TKI,[5,59] tolerability of long-term therapy—especially symptoms, functional impairments, and decreased HRQoL—can be an important issue for patients. Even mild deficits that are not considered important for patients on short-term therapies can become major deterrents to treatment adherence in patients on continuous therapy[60,61] and can lead to poorer treatment outcomes.[62,63] For example, imatinib-induced nausea and muscle cramps were associated with intentional nonadherence and worse HRQoL,[64] symptoms that may not befully appreciated by treating physicians.[47,48]

FIGURE 5. Model of HRQoL



Abbreviations: HRQoL, health-related quality of life.

TKI DISCONTINUATION IN CML: IS IT READY FOR PRIME TIME?

Although the common thinking that prevailed in the CML scientific community was life-long TKIs, a team of French investigators who previously pioneered discontinuation of interferon in CML[65] launched a daring trial of TKI discontinuation in patients with sustained molecular remission and undetectable molecular residual disease.[66] Surprisingly, loss of undetectable molecular residual disease was only observed in 40% to 50% and occurred early after the TKI was stopped (6 months), whereas the other 50% to 60% enjoyed a sustained treatment-free remission. These data have since been replicated by several groups, as summarized in Table 5, with striking similarities in outcomes, despite different criteria for enrollment and/or for restarting TKI. This remarkable consistency in outcomes across all publications worldwide likely reflects the underlying biology but also the rigor and consistency with which these patients were monitored following TKI discontinuation.

Why discontinue the TKI given the excellent outcomes of patients with CML on chronic oral TKI therapy? As discussed

TABLE 5. Summary of Tyrosine Kinase Discontinuation Trials

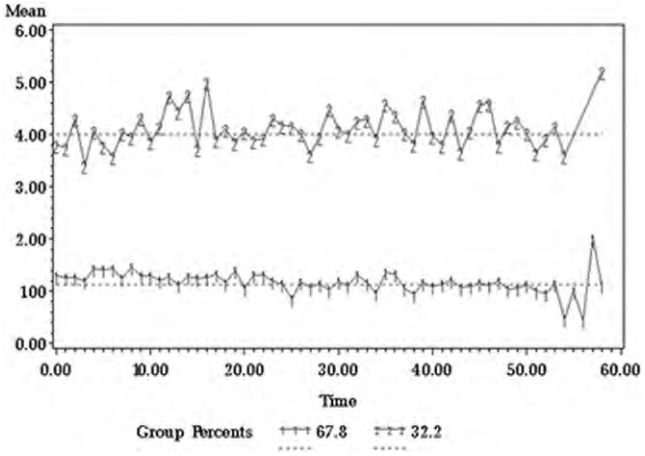
Study	TKI	Min. TKI Treatment Duration (Years)	No. of Patients	Depth of MR	Min. Duration of MR (Years)	RFS With at Least MMR
Euro-SKI[67]	IM	3	750	MR4	1	52% at 2 years
STIM[66]	IM	2	100	MR5	2	38% at 7 years
TWISTER[68]	IM	3	40	MR4.5	2	45% at 42 mos.
A-STIM[69]	IM	3	80	UMRD	2	64% at 23 mos.
KIDS[70]	IM	3	90	MR4.5	2	58% at 2 years
HOVON[71]	IM	20 mos.	18	MR4.5	2	33% at 3 years
STIM2[72]	IM	2	200	MR4.5	2	46% at 2 years
ISAV[73]	IM	2	108	UMRD	1.5	52% at 22 mos.
STOP 2G-TKI[74]	Dasa/nilo	2	60	MR4.5	2	ca. 55% at 4 years
DADI[75]	Dasa second line	1*	63	MR4	1	49% at 6 mos.
NILST[76]	Nilo	2	87	MR4.5	2	59% at 1 year
TRAD[77]	IM/dasa	3	75	MR4.5	2	58% at 6 mos.
Dasfree[78]	Dasa	2	130	MR4.5	1	63% at 1 year
ENESTop[79]	IM/nilo	3	126	MR4.5	1	58% at 4 years
STAT2[80]	IM/nilo	2	96	MR4.5	2	68% at 1 year
ENEST freedom[81]	Nilo	2	190	MR4.5	1	52% at 4 years
D-STOP[82]	IM/dasa	2*	54	MR4	2	63% at 1 year
RE-STIM[83]	(Second stop)	35 mos.	67	Mostly UMRD	31 mos	44% at 22 mos.
Total: 18			2,334			33%–68% after 0.5–7 years

*Duration of dasatinib therapy

Abbreviations: TKI, tyrosine kinase inhibitors; MR, molecular remission; RFS, relapse-free survival; MMR, major molecular remission; IM, imatinib; UMRD, undetectable molecular residual disease; nilo, nilotinib; dasa, dasatinib.

above, TKIs are overall well tolerated, but PROs have shown that 30% to 40% of patients suffer low-grade but substantial adverse drug reactions that affect quality of life and compliance[52]—not to mention the financial burden that affects both patient (i.e., copays) and the society (i.e., costs of TKI).[24,84]

FIGURE 6. Trajectory of the Five Most Severe Symptoms in the High and Low Symptom Groups Over 1 Year



This research was originally published in Williams et al.[52] © American Society of Hematology.

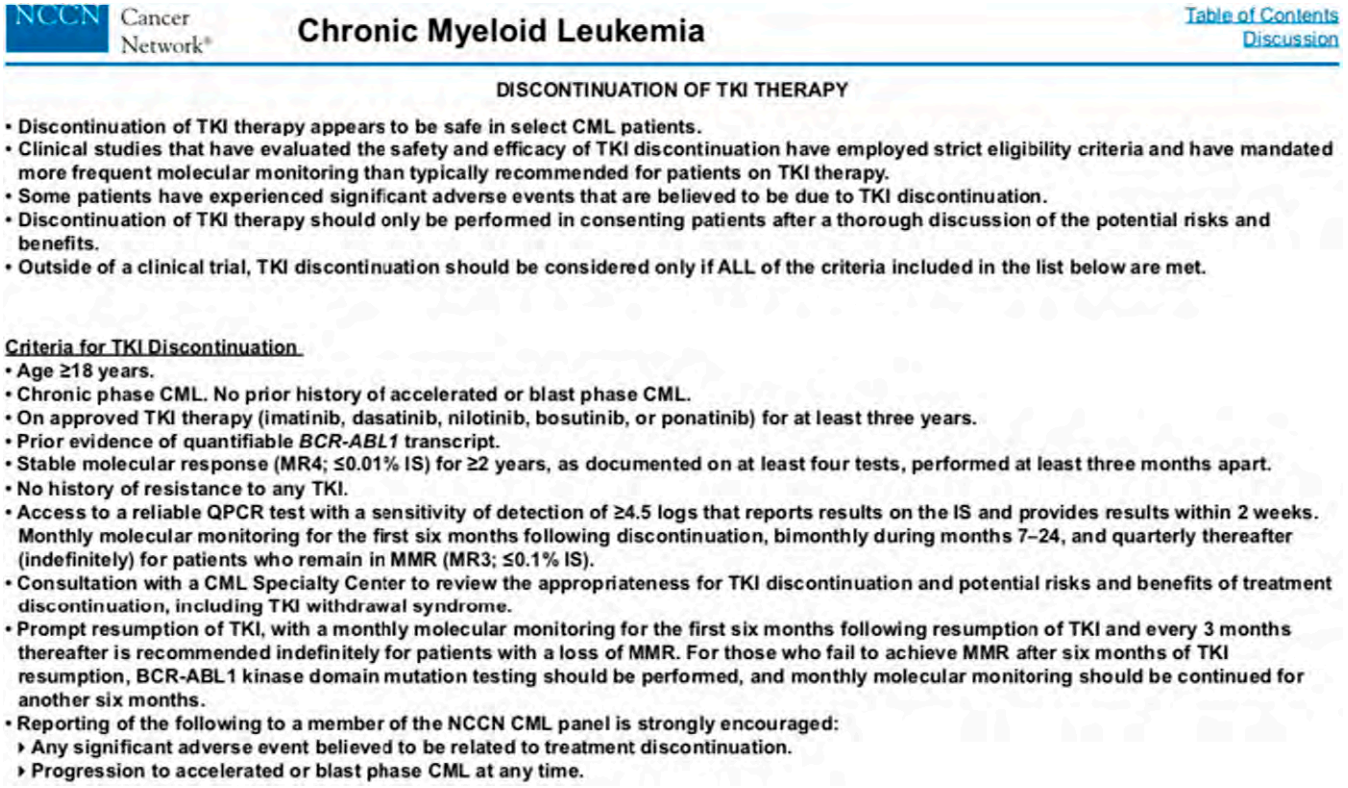
What Would It Take for TKI Discontinuation to Become Standard?

Criteria for TKI discontinuation are now part of the NCCN guidelines (Fig. 7),[59] as well as in position papers by CML experts.[4,85] In addition to the technical prerequisites that must be in place prior to considering TKI discontinuation (e.g., the availability of a molecular laboratory that quantitatively reports BCR-ABL1 levels with a reasonable turnaround time [within 2 weeks]), a key component is the CML knowledge within the practice that helps to interpret the molecular monitoring results without creating unnecessary anxiety or, on the other extreme, complaisance. An important complementary operational aspect is a multi-team approach where nonoverlapping function exists between team members who provide care, communication, and patient education—all key factors for patients' engagement in their care.[26] Indeed, such a team approach ensures patients come for their scheduled molecular monitoring and provides timely results with an interpretation on how the patient is faring with regard to the restart the TKI or not. A coordinated workforce and patients' engagement are the top two Institute of Medicine recommendations for high-quality cancer care.[86]

What Type of Patients Can Be Offered TKI Discontinuation?

Patients with chronic phase CML with no prior resistance to TKI, treated with TKI for at least 5 years with a sustained

FIGURE 7. TKI Discontinuation Guidelines



NCCN Cancer Network®

Chronic Myeloid Leukemia

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Discussion

DISCONTINUATION OF TKI THERAPY

- Discontinuation of TKI therapy appears to be safe in select CML patients.
- Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
- Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits.
- Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met.

Criteria for TKI Discontinuation

- Age ≥18 years.
- Chronic phase CML. No prior history of accelerated or blast phase CML.
- On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.
- Prior evidence of quantifiable *BCR-ABL1* transcript.
- Stable molecular response (MR4; ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.
- No history of resistance to any TKI.
- Access to a reliable QPCR test with a sensitivity of detection of ≥4.5 logs that reports results on the IS and provides results within 2 weeks. Monthly molecular monitoring for the first six months following discontinuation, bimonthly during months 7–24, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; ≤0.1% IS).
- Consultation with a CML Specialty Center to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Prompt resumption of TKI, with a monthly molecular monitoring for the first six months following resumption of TKI and every 3 months thereafter is recommended indefinitely for patients with a loss of MMR. For those who fail to achieve MMR after six months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six months.
- Reporting of the following to a member of the NCCN CML panel is strongly encouraged:
  - Any significant adverse event believed to be related to treatment discontinuation.
  - Progression to accelerated or blast phase CML at any time.

Abbreviations: CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; ALL, acute lymphoblastic leukemia; QPCR, qualitative polymerase chain reaction; IS, international scale; MMR, major molecular response; NCCN, National Comprehensive Cancer Network.

undetectable BCR-ABL1 or MR4.5 for at least 2 years appear to be the best candidates. Based on these criteria, approximately 30% to 40% of chronic phase CML treated with imatinib, nilotinib, or dasatinib achieve these landmarks.[7,8,87] So far, no reliable marker is available that helps identify those patients who will not lose MMR following TKI discontinuation. Recent studies have suggested that a higher NK-cell count at the time of TKI discontinuation[88] and a lower expression of the T-cell inhibitory receptor-ligand CD86 on plasmacytoid dendritic cells are associated with better probability of treatment-free remission.[89] The frequency with which patients must be monitored has not been established. The original STIM monitoring schedule is quite intense (monthly PCRs for 6 months, then every other month) and has been the most commonly used regimen.[66] A recent report suggests that a less intense monitoring frequency following TKI discontinuation yields comparable outcomes to current standards.[90]

Are There Risks Associated With TKI Discontinuation?

So far with current criteria and careful monitoring, TKI discontinuation appears safe with no reported blast transformations occurring off TKI. A rheumatologic syndrome commonly called "TKI-withdrawal syndrome" presenting with joint and muscle pain occurs in approximately 30% of patients in the first 4 weeks after stopping TKI.[91] These symptoms usually last 4 to 6 weeks, are managed with nonsteroidal or short-courses of steroids, and resolve in the majority of cases, but in rare cases, they require reinstitution of TKI treatment. Better identification of patients who can discontinue successfully and remain in treatment-free remission are needed and will reduce the number of patients who go through this process unsuccessfully. Additionally, if any predictor of successful treatment-free remission is identified and able to be influenced, prediscontinuation interventions may increase the pool of patients who can successfully go through a first, and perhaps a second, TKI discontinuation trial.

Is TKI Discontinuation Ready for Prime Time?

Practically speaking, this verdict will be reached by practicing physicians and patients/patient advocacy groups. Indeed, a solid enough degree of confidence from both the provider and the patient sides is needed to proceed with this intervention. To ensure that this process remains as safe as it has been so far, we need CML expert guidelines, complemented by patients and their caretakers' engagement in their discontinuation through education, communication, and technology.

CONCLUSION

TKI therapy for patients with CML has transformed cancer care and exemplifies the paradigm of precision medicine.

Previously requiring a stem cell transplantation for any hope of cure, now patients taking TKIs can expect survival similar to the general population. However, TKI therapy is not without bothersome side effects for some patients that can impair quality of life and decrease adherence to prescribed treatment. It is important for clinicians to regularly assess the patient's perspective of therapy, ideally with a routine patient-reported outcome measure, and to involve the patient in treatment decision making. The next threshold in patient care will be to define who can safely stop therapy and be cured. Evidence to date still suggests that the majority of patients will require lifelong therapy. Perhaps it is time now for CML to lead the transformation of cancer care again—setting our sights on ways to eradicate this disease and curing all patients with CML (cure defined as off therapy with no evidence of disease).

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New Insight Into the Biology, Risk Stratification, and Targeted Treatment of Myelodysplastic Syndromes

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OVERVIEW

In myelodysplastic syndromes (MDS), somatic mutations occur in five major categories: RNA splicing, DNA methylation, activated cell signaling, myeloid transcription factors, and chromatin modifiers. Although many MDS cases harbor more than one somatic mutation, in general, there is mutual exclusivity of mutated genes within a class. In addition to the prognostic significance of individual somatic mutations, more somatic mutations in MDS have been associated with poor prognosis. Prognostic assessment remains a critical component of the personalization of care for patients with MDS because treatment is highly risk adapted. Multiple methods for risk stratification are available with the revised International Prognostic Scoring System (IPSS-R), currently considered the gold standard. Increasing access to myeloid gene panels and greater evidence for the diagnostic and predictive value of somatic mutations will soon make sequencing part of the standard evaluation of patients with MDS. In the absence of formal guidelines for their prognostic use, well-validated mutations can still refine estimates of risk made with the IPSS-R. Not only are somatic gene mutations advantageous in understanding the biology of MDS and prognosis, they also offer potential as biomarkers and targets for the treatment of patients with MDS. Examples include deletion 5q, spliceosome complex gene mutations, and TP53 mutations.

MDS are bone marrow stem cell malignancies characterized by inefficient hematopoiesis, abnormal myeloid morphology, and cytopenias with risk of progression to secondary acute myeloid leukemia (AML). MDS is the most common hematopoietic myeloid cancer in adults with an average annual incidence of up to 75 per 100,000 persons 65 years or older.[1,2] The diagnosis of MDS requires persistent cytopenias in the presence of dysplasia in one or more cell lineages and/or increased myeloblasts or clonal cytogenetic abnormalities and is classified according to the World Health Organization (WHO) criteria (Table 1).[3] Over the last several years, many advances have been made in understanding the biology of MDS, most notably through the use of newer high-throughput DNA sequencing methods.

THE BIOLOGY OF MDS

Cytogenetic Findings in MDS

The earliest known molecular alterations in MDS were cytogenetic abnormalities detected by metaphase cytogenetics.[5] Approximately 45% of patients with MDS harbor a recurrent cytogenetic abnormality (Table 2).[6,7] In contrast to AML, copy number alterations including chromosomal deletions and amplifications are more common than translocations. Certain cytogenetic findings in MDS are associated with changes in prognosis and are incorporated into the IPSS-R.[8] Changes including complex karyotype (more than three cytogenetic abnormalities) and monosomal karyotype (one autosomal monosomy in the presence of a structural abnormality) have been associated with a poor prognosis.[9,10] In addition to metaphase cytogenetics, fluorescence in situ hybridization may be used to detect recurrent cytogenetic alterations, providing increased sensitivity over conventional cytogenetics and permitting more accurate monitoring of disease burden in patients with MDS undergoing treatment.

Somatic Gene Mutations in MDS

The advent of massively paralleled digital sequencing methods (often colloquially grouped as next-generation sequencing) has provided rapid growth in our understanding of the molecular biology of myeloid neoplasms.[11-13] These methods allow for the sequencing of small gene panels, the exome (the coding portion of the genome), or the entire genome with high sensitivity and at minimal cost.[14,15] Over the last 8 years, numerous studies have demonstrated the following: (1) approximately 90% of patients with MDS will harbor at least one mutation from a set of approximately

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TABLE 1. 2016 WHO Classification of MDS

Classification	Dysplastic Lineages	Cytopenias*	RS as % of Marrow Erythroid Elements	BM and PB Blasts	Cytogenetics by Conventional Karyotype Analysis
MDS with SLD	1	1 or 2	< 15%/< 5%**	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with MLD	2 or 3	1–3	< 15%/< 5%**	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS With RS					
MDS-RS with SLD	1	1 or 2	≥ 15%/≥ 5%**	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with MLD	2 or 3	1–3	≥ 15%/≥ 5%**	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1–3	1–2	None or any	BM < 5%, PB < 1%, no Auer rods	del(5q) alone or with one additional abnormality, except −7 or del (7q)
MDS-EB					
MDS-EB-1	0–3	1–3	None or any	BM 5%–9% or PB 2%–4%, no Auer rods	Any
MDS-EB-2	0–3	1–3	None or any	BM 10%–19% or PB 5%–19%, or Auer rods	Any
MDS-U					
With 1% Wood blasts	1–3	1–3	None or any	BM < 5%, PB = < 1%†, no Auer rods	Any
With SLD and pancytopenia	1	3	None or any	BM < 5%, PB < 1%, no Auer rods	Any
Based on defining cytogenetic abnormality	0	1–3	< 15%‡	BM < 5%, PB < 1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1–3	1–3	None	BM < 5%, PM < 2%	Any

*Cytopenias defined as: hemoglobin (Hb) less than 10 g/dL, platelets less than 100,000/μL, and absolute neutrophils count less than 1,800/μL. PB monocytes must be less than 1,000/μL.

**If SF3B1 mutation is present.

†1% PB blasts must be recorded on at least two separate occasions.

‡Cases with at least 15% RS by definition have significant erythroid dysplasia and are classified as MDS-RS-SLD.

Abbreviations: BM, bone marrow; EB, excess blasts; MDS, myelodysplastic syndromes; MLD, multilineage dysplasia; PB, peripheral blood; RS, ring sideroblasts; SLD, single-lineage dysplasia; U, unclassifiable.

Adopted from Arber et al.[4]

KEY POINTS

- **Over the past decade, high-throughput DNA sequencing methods have advanced the understanding of MDS biology.**
- **Somatic MDS mutations occur in five major categories: RNA splicing, DNA methylation, activated cell signaling, myeloid transcription factors, and chromatin modfication.**
- **Increasing access to myeloid gene panels and greater evidence for the diagnostic and predictive value of somatic mutations will soon make sequencing part of the standard evaluation of patients with MDS.**
- **In the absence of formal guidelines for their prognostic use, well-validated mutations can still refine estimates of risk made with the IPSS-R.**
- **Not only are somatic gene mutations advantageous in understanding the biology of MDS and prognosis, they also offer potential as biomarkers and targets for the treatment of patients with MDS.**

40 recurrently mutated MDS genes[16-18] (Table 3; Fig. 1); (2) certain somatic mutations are associated with changes in prognosis[19]; (3) somatic mutations can be used to decipher the clonal architecture of MDS; and (4) a similar spectrum of somatic mutations can be seen in older patients without dysplasia (discussed in a later section), precluding the use of sequencing-based studies to replace morphologic evaluation.[20,21] Sequencing-based "MDS gene panels" have now become commonplace in the clinical setting and can be used to better stratify patient risk and monitor clonal populations.[22]

Somatic MDS mutations occur in five major categories, including RNA splicing, DNA methylation, activated cell signaling, myeloid transcription factors, and chromatin modifiers. Although many MDS cases harbor more than one somatic mutation, in general, there is mutual exclusivity of mutated genes within a class. In addition to the prognostic significance of individual somatic mutations, more somatic mutations in MDS have been associated with poor prognosis.

Splicing mutations. Mutations involving RNA splicing are present in up to 45% of MDS; however, they appear to be rare in de novo AML.[13,24] These mutations affect 3' splice

TABLE 2. Prognostically Significant Recurrent Cytogenetic Findings in Patients With MDS

Prognostic Subgroups, % of Patients	Cytogenetic Abnormalities	Median Survival (Years)	Median AML Evolution, 25% (Years)	HRs OS/AML
Very good (3%–4%)	−Y, del(11q)	5.4	NR	0.7/0.4
Good (66%–72%)	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4	1/1
Intermediate (13%–19%)	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5	1.5/1.8
Poor (4%–5%)	−7, inv(3)/t(3q)/del(3q), double including –7/del(7q), complex: three abnormalities	1.5	1.7	2.3/2.3
Very poor (7%)	Complex: more than three abnormalities	0.7	0.7	3.8/3.6

Abbreviations: AML, acute myeloid leukemia; HR, hazard ratio; MDS, myelodysplastic syndromes; NR, not reached; OS, overall survival.
Hazard ratios are reported as overall survival/risk of AML transformation.
Adopted from Greenberg et al.[8]

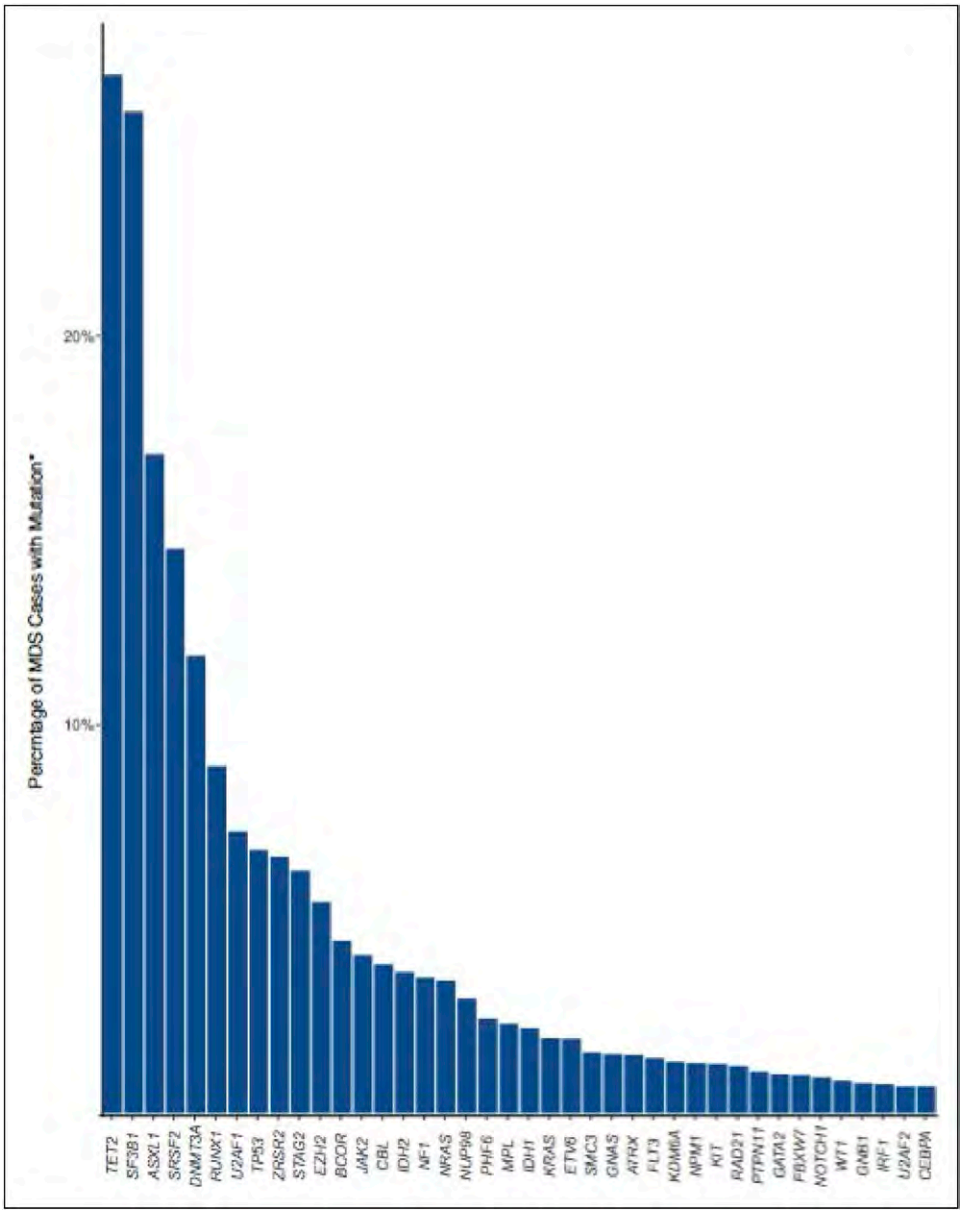
recognition sites, although the exact mechanisms by which the mutations cause dysplasia and the RNA targets of aberrant gene splicing are unknown. Mutations in the splicing factor 3b, subunit 1 (*SF3B1*) gene are present in approximately 20% of MDS and are associated with ring sideroblast morphology, lower-grade disease, and better prognosis.[25] Interestingly, mutations in *SF3B1* have also been found in patients with chronic lymphocytic leukemia (CLL) and breast cancer.[26-28] Patients with MDS with ring sideroblasts without mutated *SF3B1* (approximately 20% of patients) are thought to have an inferior prognosis compared with patients with mutated *SF3B1*.[29] Mouse models have demonstrated that mutated *SF3B1* causes an MDS phenotype and that cells carrying the mutation are sensitive to spliceosome modulator drugs.[30] SF3B1 mutations have also been associated with chronic lymphocytic leukemia.[30] Mutations in the U2 small nuclear RNA auxiliary factor 1 gene (*U2AF1* or *U2AF35*) are present in approximately 8% to 12% of MDS and are associated with a poor prognosis. *U2AF1* mutations have been shown to alter splice recognition sites and specificity of precursor messenger RNA binding, eliciting changes in thousands of RNA transcripts; however, the exact mechanism by which *U2AF1* mutations give rise to dysplasia have yet to be determined.[31] Interestingly, in vitro and animal studies have demonstrated increased sensitivity to precursor messenger RNA splicing modulator drugs.[32] Mutations in the Serine/arginine-rich

TABLE 3. Recurrently Mutated MDS Genes

Gene	Function	Chromosome	Incidence (%)	Clinical Significance
NRAS	Activated signaling	1p13.2	5–10	Associated with poor prognosis
CBL	Activated signaling	11q23.3	< 5	More frequent in CMML and JMML
JAK2	Activated signaling	9p24.1	< 5	More frequent in RARS-T
ASXL1	Chromatin modifier	20q11	15–25	Independent poor prognostic risk
EZH2	Chromatin modifier	7q35	5–10	Independent poor prognostic risk
TET2	DNA methylation	4q24	20–25	Associated with normal karotype, more frequent in CMML
DNMT3A	DNA methylation	2p23	12–18	Poor prognosis
IDH1	DNA methylation	2q33.2	< 5	More frequent in AML
IDH2	DNA methylation	15q26.1	< 5	More frequent in AML
RUNX1	Myeloid transcription factor	21q22.3	10–15	Independent poor prognostic risk
ETV6	Myeloid transcription factor	12p13.2	< 5	Independent poor prognostic risk
SF3B1	Splicesome	2q33.1	18–30	Favorable prognosis, associated with ring sideroblasts
SRSF2	Splicesome	17q25.1	10–15	Poor prognosis, more frequent in CMML
U2AF1	Splicesome	21q22.3	8–12	Poor prognosis
ZRSR2	Splicesome	Xp22.1	5–10	Poor prognosis
TP53	Tumor supressor	17p13.1	8–12	Independent poor prognostic risk, associated with complex karyotype

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; JMML, juvenile myelomonocytic leukemia; RARS-T, ring sideroblasts and thrombocytosis.
Adopted from Nybakken and Bagg.[6]

FIGURE 1. Summary of Recurrently Mutated Genes in MDS



Average reported mutation frequency for commonly mutated MDS genes from three NGS-based studies, including a total of 1,839 patients.[16,18,23] Genes were included only when evaluated in at least two of the three studies.

Abbreviations: MDS, myelodysplastic syndromes; NGS, next-generation exome sequencing.

splicing factor 2 (*SRSF2*) gene are present in approximately 10% of patients with MDS and are associated with a poor prognosis. *SRSF2* mutations are enriched in chronic myelomonocytic leukemia (CMML) and are present in up to 40% to 50% of cases.[33] Finally, mutations in zinc finger (CCCH type), RNA-binding motif, and serine/arginine rich 2 (ZRSR2) are present in 5% to 10% of patients with MDS and are associated with a poor prognosis. Mutations in *ZRSR2* lead to impaired splicing of the U12-type introns, although the downstream RNA targets are unknown.[34]

DNA methylization. Mutations involving DNA methylation including those in *TET2*, *DNMT3A*, and *IDH1/2* are common in MDS and AML as well as in the recently defined clonal hematopoiesis of indeterminate potential (CHIP), which is discussed later in this article.[35] In general, mutations of these genes are mutually exclusive within a patient. The most commonly mutated gene across MDS studies (present in over 20% of patients) is *TET2*, which encodes a protein involved in the conversion of 5-methyl-cytosine to 5-hydroxymethyl-cytosine and plays a key role in DNA demethylation.[36] Although the TET family of proteins has three members (*TET1*, *TET2*, and *TET3*), only *TET2* appears to be frequently mutated in MDS. *TET2* mutations, unlike mutations in other DNA methylation–associated genes, do not appear to have a mutational hotspot and often involve insertions and deletions, making mutations difficult to detect

outside of gene panel–based sequencing assays. *TET2* mutations are generally associated with a normal karyotype and are of unclear prognostic significance.[37] *DNMT3A* encodes a protein that catalyzes the transfer of methyl groups required for de novo methylation. Mutations in *DNMT3A* were originally described in AML and are among the most frequent mutations in AML as well as in CHIP; in MDS, *DNMT3A* is mutated in 12% to 18% of cases.[38] The exact mechanism by which *DNMT3A* mutations contribute to MDS/AML pathogenesis is unknown, but it is thought to be an early event, and mutations have been shown to act in a dominant-negative manner.[39,40] Most *DNMT3A* mutations involve the p.R882 codon. Mutations in *DNMT3A* are associated with a poor prognosis in MDS. Although *DNMT3A* mutations are an early event, they may persist during complete remission without adverse outcome.[41] Mutations in *IDH1* and *IDH2* are generally more common in AML than in MDS, where they are present in fewer than 5% of cases. Isocitrate dehydrogenases catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate; mutations in the catalytic domains of *IDH1/2* result in the accumulation of 2-hydroxyglutarate, resulting in DNA hypermethylation.[42] *IDH1* mutations occur almost exclusively in the p.R132 position, with *IDH2* mutations generally occurring in the p.R140 and p.R172 positions. *IDH1/2* mutations are also among the most common mutations in brain gliomas.[43] IDH1/2 mutations are currently of uncertain prognostic significance in MDS.

Histone modifiers. Mutations in histone-modifier genes are common in MDS and appear to be enriched in CMML. The *EZH2* gene encodes a H3K27 methyltransferase involved in histone H3 methylation leading to transcriptional repression.[44] Mutations in *EZH2* have been reported in 5% to 10% of patients with MDS and are associated with a poor prognosis independent of IPPS-R status.[45,46] The *ASXL1* gene is a member of the polycomb gene family and is involved in the epigenetic regulation of gene expression.[47] *ASXL1* is mutated in 15% to 25% of patients with MDS and is also commonly mutated in AML. Mutations in the *ASXL1* gene are associated with a poor prognosis and have also been implicated in rare cases of familial MDS.[48]

Signal transduction. Signal transduction genes as a group are less commonly mutated in MDS than in AML and myeloproliferative neoplasms. Acquisition and expansion clones containing signal transduction gene mutations have been associated with MDS progression to acute leukemia.[24,49] The *JAK2* gene is a nonreceptor tyrosine kinase that acts through the STAT signaling pathway and is also implicated in interferon receptor signaling.[50] A single mutational hotspot, p. V617F, dominates the spectrum of JAK2 mutations. Although present in nearly all cases of polycythemia vera, *JAK2* mutations are present in fewer than 5% of patients with MDS and are enriched in cases of refractory anemia with ring sideroblasts and thrombocytosis.[51] The overall prognostic significance of JAK2 mutations is uncertain. Ras family members including *NRAS*, and less commonly *KRAS*, are mutated in 5% to 10% of patients with MDS and are more frequent in patients with CMML and juvenile myelomonocytic leukemia.[52] Both *NRAS* and *KRAS* mutations occur at known hotspots, including p.G12, p.G13, and p.Q61. Mutations in NRAS confer a poor prognosis in MDS. Similar to the Ras-family members, *CBL* mutations are more common in patients with CMML and juvenile myelomonocytic leukemia and are present in less than 5% of patients with MDS.[53,54] The *CBL* gene encodes an E3 ubiquitin-protein ligase involved in protein ubiquitination. Mutations in the *CBL* gene are of unknown prognostic significance.

Transcription regulation. Commonly mutated transcriptional regulation genes in MDS include *TP53*, *RUNX1*, *GATA2*, and *MECOM*. Mutations in *TP53* have been reported in 5% to 18% of patients with MDS and are generally associated with higher-risk disease, including refractory anemia with excess blasts and therapy-related AML as well as complex cytogenetics and a subset of patients with del(5q).[55,56] *TP53* mutations are considered a poor prognostic factor in patients with MDS; however, recent studies have demonstrated that patients with MDS with *TP53* mutations show a favorable response to decitabine.[57] *RUNX1* is a transcription factor that regulates myeloid development and is mutated in approximately 10% of patients with MDS. Mutations including copy losses in the *RUNX1* gene are generally associated with a poor prognosis.[58] The *GATA2* gene encodes an important myeloid transcription factor and is mutated in approximately 1% to 2% of patients with MDS. Mutations in *GATA2* are of unknown prognostic significance but may also be seen as germline mutations in cases of familial MDS or primary immunodeficiency.[59] The *MECOM* gene (also known as *EVI1*) encodes a zinc finger protein that acts as a transcription factor. Somatic *MECOM* mutations are present in approximately 1% of patients with MDS and are generally considered to be a poor prognostic factor. Rearrangements including inv(3)(q21q26) and t(3;3)(q21;q26) also involve the *MECOM* gene and are seen rarely seen in patients with MDS and AML.[3]

The Clonal Architecture of MDS

Sequencing-based studies have demonstrated that MDS is composed of a founding clone. By analyzing the variant allele fractions (VAFs), fraction of reads containing a mutation generated by next-generation exome sequencing (NGS) methods, mutations can be assigned to clusters and can be used to determine the clonal composition of a given MDS. Most patients with MDS will harbor only 15 to 30 somatic mutations in the exome, a notably lower mutation rate than solid tumors, but similar to the number of mutations seen in AML.[60] Reconstruction of MDS clonal architecture therefore requires nonbiased sequencing approaches such as exome or whole-genome sequencing of tumor and normal germline tissue to have a sufficient number of mutations for accurate clone assignment.[61] The relationship between tumor clonality and disease progression is not well understood at present; the risk of MDS progression to AML has been associated with more subclones in at least one study.[23]

Serial sequencing of MDS bone marrow samples allows

for more accurate assessment of tumor clonality by comparing the patterns of VAF changes over time. Serial bone marrow sequencing studies have also demonstrated that somatic mutations can be detected at low levels when MDS patients are in complete remission, and the presence of detectable somatic mutations 30 days after induction chemotherapy has been associated with adverse outcome in AML.[62,63] However, the relationship between the depth of clonal clearance and recurrence has not been established. Recent studies have also shown a high concordance between blood and bone marrow samples in determining the clonal architecture of MDS, suggesting that more readily obtained peripheral blood samples could be an alternative to bone marrow–based assessment.[64]

WHAT WE NEED TO KNOW ABOUT RISK STRATIFICATION IN MDS

MDS encompass a wide spectrum of clinical phenotypes that range from largely asymptomatic patients with mild cytopenias and long life expectancy to those with profound symptoms, severe cytopenias, and a very poor prognosis. Even patients with similar clinical presentations may see their disease evolve differently over time. This variability can make it challenging for physicians to determine the optimal timing and choice of treatment of their patients and how best to counsel them about their expected prognosis. Consensus treatment guidelines for MDS rely on an accurate estimation of risk to determine optimal treatment algorithms.[65-67] Therapeutic choices for lower-risk patients share very little with the options recommended for patients of higher risk. Accurate determination of prognosis is therefore critical for individualizing risk-adapted therapy for patients.

The MDS classification system created by the WHO defines MDS subtypes comprised of patients that share disease features, genetic findings, and responses to treatment, but does not serve as a prognostic tool.[3] The criteria for WHO subtypes include the proportion of bone marrow blast cells, deletion of chromosome 5q, and, in the case of patients with few ring sideroblasts, the presence of a typical somatic mutation in the *SF3B1* gene. Other molecular and cytogenetic abnormalities are not considered, limiting the prognostic value of WHO-defined MDS subtypes. Therefore, several prognostic scoring systems have been developed that incorporate disease-related risk factors, patient features, and genetic findings to more accurately risk stratify patients with MDS. Most of these risk assessment tools do not formally incorporate somatic mutations that have been shown to carry independent prognostic associations capable of refining the prediction of disease risk. This section will review the most widely used prognostic scoring systems for MDS and summarize how somatic mutation testing can be used to more accurately assign patients to appropriate risk groups.

Prognostic Scoring Systems

WPSS. The WHO Classification-Based Prognostic Scoring System (WPSS) takes advantage of the fact that MDS subtypes are, in part, defined by several prognostic features (Table 1).[68]

The WPSS assigns risk scores to subtypes based on their bone marrow blast proportions and adds consideration of cytogenetic abnormalities and the presence of severe anemia to determine a total risk score. These scores are then translated into one of five risk groups with significant differences in median overall survival and likelihood of progression to AML. Advantages of the WPSS include its ease-of-use and that it has been validated at times other than diagnosis, making it a dynamic scoring system. Its major disadvantage is the limited number of cytogenetic abnormalities explicitly considered, which may make it less precise for certain patients.[69-71]

IPSS was the clinical standard for MDS risk assessment until the revised version was published in 2013.[72] It was derived by examining over 800 patients with MDS who never received disease-modifying therapies likely to impact overall survival. Patients with proliferative CMML and therapy-related MDS were excluded, but the IPSS included patients with 20% to 30% blasts now considered to have AML by WHO criteria. Like the WPSS, the IPSS is simple to use and considers the percentage of blasts in the bone marrow, a small number of cytogenetic abnormalities, and the presence of cytopenias as relevant risk factors. Patients are assigned to one of four risk groups. In practice (and in clinical guidelines), those with low or intermediate-1 IPSS risk are considered to have lower-risk MDS, while those with intermediate-2 or high IPSS risk are labeled higher risk. This is an important distinction, as clinical guidelines recommend very different treatment algorithms for each group.[66,67,73,74]

After its adoption, it became evident that the IPSS has some important limitations. It considers only the presence of cytopenias and not their severity, and it outweighs the impact of blast proportion compared with cytogenetic abnormalities.[75,76] This leads to an underestimation or risk in many lower-risk patients with normal blast proportions.[77]

LRPSS. The MD Anderson Lower Risk Prognostic Scoring System (LRPSS) is designed specifically to address concerns with the IPSS.[78] This model takes patients considered to have lower risk by the IPSS and restratifies them according to criteria that include age, bone marrow blast percentage, cytogenetics, and, unlike the IPSS, the severity of anemia and thrombocytopenia. Patients could be assigned to one of three risk categories. A quarter to a third of IPSS lower-risk patients fall into the highest-risk LRPSS category and have a median overall survival comparable to that of IPSS intermediate-2 patients, indicating that they should actually be considered to have higher-risk disease.[78-80] However, there are few prospective studies of approved MDS therapies demonstrating clinical benefit in patients identified as having higher-than-perceived risk in this manner.[81]

IPSS-R. The IPSS-R also addresses several limitations of the IPSS and offers other improvements that make it the clinical standard for risk assessment for patients with MDS today. Developed by studying over 7,000 untreated patients with MDS, the IPSS-R evaluates the same features as the IPSS, but does so in greater detail (Fig. 2).[8] Patients with bone marrow blasts of at least 20% are excluded, and those with

as few as 3% or 4% blasts are considered to be at increased risk. The range of cytogenetic risk scores is increased, and the number of explicitly considered karyotype abnormalities more than double (Table 2).[82] And unlike the original IPSS, the severity of each cytopenia is taken into account. This results in a broader range of risk scores and assignment of patients into one of five groups (very low, low, intermediate, high, or very high). The division between lower and higher risk is made in the middle of the intermediate risk group with an IPSS-R score of no more than 3.5 defining patients as having lower risk.

The IPSS-R has been extensively validated even in contexts for which it was not originally developed.[22] This includes cohorts of patients treated with hypomethylating agents, lenalidomide, or allogeneic stem cell transplantation.[9,83-88] It has also been examined at times other than diagnosis, where it continues to risk stratify patients well.[89,90] The IPSS-R compares favorably to other risk stratification systems, making it the current gold standard for MDS risk assessment.[70,71] However, it is important to explain to patients that survival estimates based on the IPSS-R were derived from a cohort that did not receive disease-modifying therapy. Survival estimates in treated patients may well be different, and, in practice, factors not considered by the IPSS-R should influence the final assessment of risk.

For example, patient age is not an element of the IPSS-R but figures heavily in the accurate estimation of prognosis. Age can be considered by adjusting the cutoffs for IPSS-R–defined risk groups in a model called the IPSS-RA. An online calculator (www.ipss-r.com) is available to help apply the IPSS-R and IPSS-RA.

Physicians should also consider other factors that can refine the prognosis predicted by the IPSS-R. For intermediate-risk patients near the border of lower- versus higher-risk disease, greater lactate dehydrogenase, ferritin, and bone marrow fibrosis have been shown to carry increased risk.[8,91-93] Conversely, greater time since diagnosis may portend a better-than-predicted prognosis for initially higher-risk patients.[89] Finally, comorbid conditions can impact longevity in the setting of MDS and should influence which therapeutic options are recommended for patients.[91,94-96]

Prognostic impact of somatic mutations. Studies have repeatedly demonstrated the prognostic impact of somatic mutations in patients with MDS.[17,97] These genetic events

FIGURE 2. The Revised International Prognostic Scoring System

Cytogenetic Risk Group	IPSS-R Karyotype Abnormalities
Very good	del(11q), -Y
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities
Very Poor	Complex with > 3 abnormalities

IPSS-R Parameter	Categories and Associated Scores				
Cytogenetic Risk Group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Bone Marrow Blast %	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet Count (x 109/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Absolute Neutrophil Count (x 109/L)	≥ 0.8	< 0.8			
	0	0.5			

IPSS-R Risk Group	Points	% of Patients	Median survival, years	Time to 25% with AML, years
Very low	≤ 1.5	19%	8.8	Not reached
Low	> 1.5 - 3	38%	5.3	10.8
Intermediate	> 3 - 4.5	20%	3	3.2
High	> 4.5 - 6	13%	1.6	1.4
Very High	> 6	10%	0.8	0.73

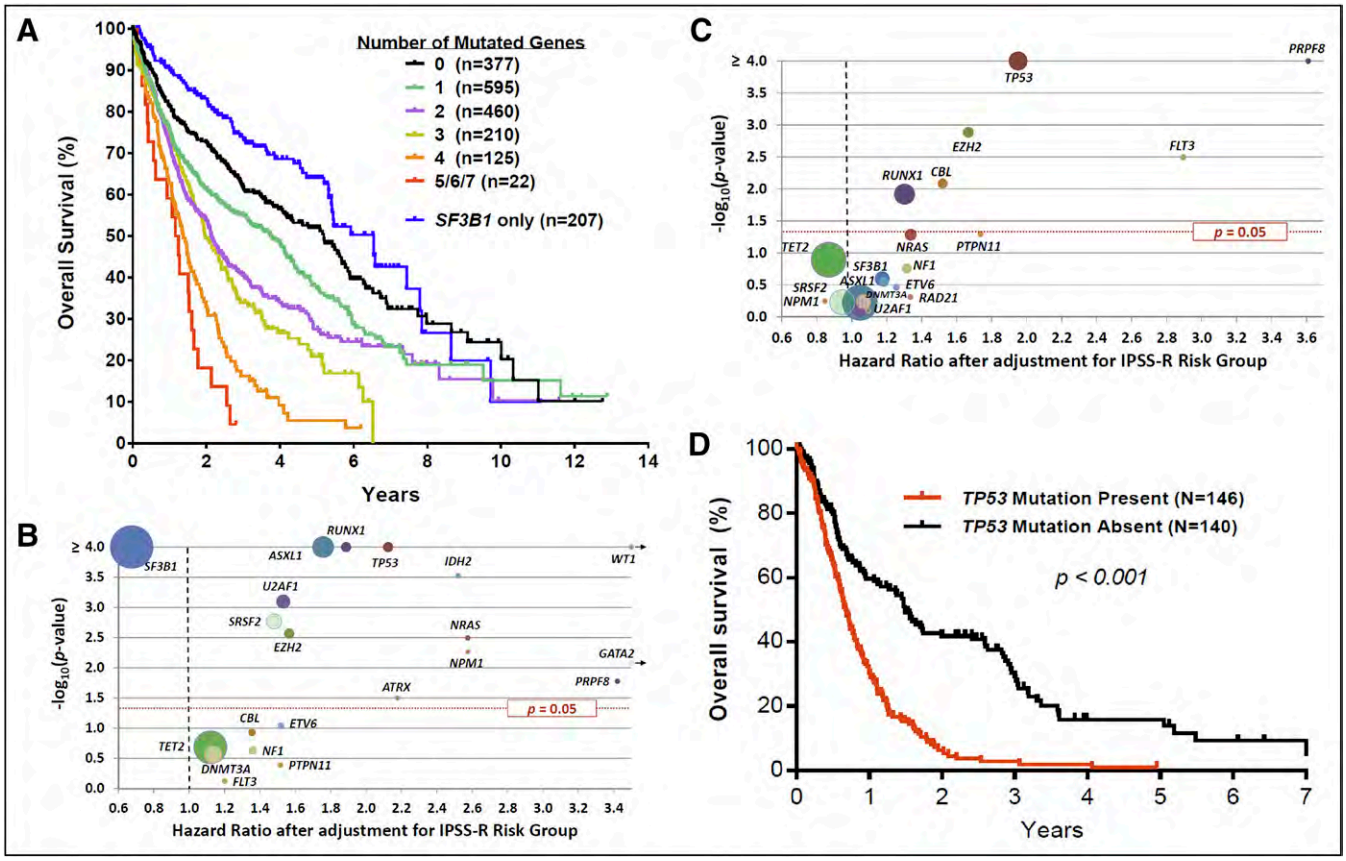
Patients with a risk score of 3.5 or below are considered to have lower risk. Patients with a score greater than 3.5 have higher-risk disease. An online calculator is available at www.ipss-r.com.

are present in nearly every patient with MDS and represent the pathophysiologic drivers of disease development and evolution (Fig. 1). This makes mutations potentially better disease biomarkers than clinical features alone. Mutations of several genes have prognostic significance independent of clinical scoring systems, including the IPSS-R.[97-100] However, mutations have not been formally incorporated into these models to date as there is no consensus of how best to consider them. This is in part because mutations can co-occur in a wide variety of patterns and can be present in either the dominant clone or smaller subclones where they might have different impacts.[17,101-103] Despite this complexity and lack of formal guidelines, somatic mutations can be used to refine the prognosis of patients with MDS today.

In general, a greater number of somatic mutations is associated with a shorter overall survival (Fig. 3A).[18,100] Yet not all mutated genes carry equal prognostic significance; their independent prognostic value may depend upon the clinical context in which they are observed. For example, the splicing factor *SF3B1* is the only recurrently mutated gene associated with a favorable prognosis.[97,104,105] *SF3B1* mutations are highly enriched in lower-risk patients, where they are associated with a longer overall survival even after adjustment for the IPSS-R (Fig. 3B).[100] However, *SF3B1* mutations lose their independent prognostic impact in those patients with rare mutated disease with higher blast proportions (Fig. 3C).

Similarly, there are several mutated genes considered prognostically adverse, primarily in patients with lower-blast proportion (Fig. 3B). These genes, which include *ASXL1*, *U2AF1*, and *SRSF2*, among others, lose their independent prognostic significance in patients with elevated blast proportions and higher-risk disease (Fig. 3C). Mutations of *RUNX1*, *EZH2*, and particularly *TP53* remain prognostically adverse across risk groups. Mutations in independently prognostic genes are not rare. About one-third of patients with MDS will carry one or more mutations associated with greater-than-perceived risk by the IPSS-R.[100] A similar fraction

FIGURE 3. Somatic Mutations and Disease Risk: Data From the International Working Group for MDS Molecular Prognosis Committee Presented at the American Society of Hematology Annual Meetings in 2014 and 2015[100,106]



(A) Overall survival in 1,996 patients with MDS sequenced for mutations in 17 genes (*ASXL1*, *CBL*, *DNMT3A*, *ETV6*, *EZH2*, *IDH1*, *IDH2*, *JAK2*, *KRAS*, *NPM1*, *NRAS*, *RUNX1*, *SRSF2*, *TET2*, *TP53*, *U2AF1*, and *SF3B1*). (B) Hazard ratio of death adjusted for IPSS-R risk group, for mutations in various genes for patients with less than 5% bone marrow blasts. The hazard ratio for each gene compares patients with a mutation in that gene to those without one in that gene. The size of the marker indicates the frequency with which the gene is mutated in this population. Genes plotted above the dotted red line show a significant association with prognosis that is independent of the IPSS-R, while those below do not reach statistical significance. Mutations in significant genes with a hazard ration of greater than 1 are adverse, while *SF3B1* is the only prognostically favorable mutated gene.[100] (C) Same as panel B but for patients with bone marrow blasts of 5% to 30%.[100] (D) Overall survival in 286 complex karyotype patients with MDS stratified by *TP53* mutation status.[106]

Abbreviations: IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes.

of lower-risk patients will carry a favorable *SF3B1* mutation. This suggests that we may be both under- and overestimating risk in a substantial proportion of patients with MDS.

This applies even in patients with complex karyotypes who typically have IPSS-R high and very high–risk disease. Approximately 50% of these patients will harbor a mutation of *TP53*, which is independently associated with a dismal prognosis even after treatment or stem cell transplantation.[84,106-109] However, complex karyotype patients without a *TP53* mutation may have substantially longer overall survival than predicted by the IPSS-R (Fig. 3D), suggesting that the adverse prognostic weight given to the complex karyotype is driven largely by its frequent association with *TP53* mutations.[17,84,106]

Summary. Prognostic assessment remains a critical component of the personalization of care for patients with MDS as treatment is highly risk adapted. Multiple methods for risk stratification are available, with the IPSS-R currently considered the gold standard. Increasing access to myeloid gene panels and greater evidence for the diagnostic and predictive value of somatic mutations will soon make sequencing part of the standard evaluation of patients with MDS. In the absence of formal guidelines for their prognostic use, well-validated mutations can still refine estimates of risk made with the IPSS-R. The impact of less-frequent mutations and how best to incorporate them in practice will await the publication of consensus guidelines based on studies of large cohorts of sequenced patients. These are in development and will improve how we assess and care for our patients with MDS.

Emergence of Molecularly Guided Therapy in MDS

The advent of NGS introduced an additional set of molecular genetic data that is now routinely applied in decision making for patients with MDS. Few mutations, such as *SF3B1*, are favorable and modify the unfavorable impact of other specific mutations such as *DNMT3A* on overall survival.[17] Not only are somatic gene mutations advantageous in understanding the biology of MDS and prognosis, they also offer potential as biomarkers and targets for the treatment of patients with MDS.

Deletion 5q and lenalidomide. The first genetic abnormality guiding management decisions in MDS were the interstitial deletion involving the long arm of chromosome 5 (del5q MDS). Lenalidomide selectively suppresses del(5q) clones by inducing ubiquitination of the haplodeficient casein kinase 1A1 (CK1α) encoded within the commonly deleted region by the E3 ubiquitin ligase CUL4-RBX1-DDB1-CRBN, resulting in CK1α degradation and erythroid growth arrest.[110] A multicenter, international U.S. registration trial evaluated 148 red blood cell transfusion–dependent patients with IPSS low/intermediate-1–risk MDS with chromosome 5q deletion.[111] Treatment with lenalidomide yielded a 50% or greater reduction in transfusions in 76% of patients, while 67% achieved transfusion independence lasting a median duration of more than 2.7 years in patients with isolated del(5q).[112] Overall, 45% of evaluable patients achieved a complete cytogenetic response and 28% a partial response, with resolution of cytologic dysplasia in 36% of patients. Interestingly, there was no significant difference in response rate between patients with isolated deletion 5q and those harboring one or more additional chromosomal abnormalities. Long-term follow-up of this study showed that patients achieving transfusion independence had a significantly longer overall survival and reduced risk of leukemia progression, suggesting that clonal suppression modifies the disease natural history.[112]

Immunosuppressive therapy. Immunosuppressive therapy (IST) in the form of antithymocyte globulin and cyclosporine can yield durable hematologic responses in a subset of lower-risk patients with MDS. The National Institutes of Health IST Response Model identifies those with the highest probability for response based upon variables that include HLA-DR15 phenotype, age, and duration of transfusion dependence.[113] The impact of somatic gene mutations in predicting response was evaluated in a retrospective study of 66 lower-risk patients with MDS treated with antithymocyte globulin plus cyclosporine.[114] The overall response rate was 42%, and among 40 patients evaluable by NGS, somatic gene mutations were not detected in 50% of patients. Those patients without mutations experienced a higher response to IST compared with those harboring gene mutations and had a longer duration of hematologic response. The presence of an *SF3B1* gene mutation was associated with a significantly lower response rate (11%) compared with wild type (68%; $p = .01$). The rate of transformation to acute leukemia was higher in patients harboring any mutation other than *SF3B1* versus patients without mutations, which was accompanied by reduced overall survival. These data demonstrate a role for consideration of somatic gene mutations in the selection of candidates for IST and further implies that immune-mediated MDS may display less genetic instability.

Molecular determinants of response to hypomethylating agents. Although azacitidine treatment improves overall survival compared with conventional care, up to 50% of patients will not respond to treatment with hypomethylating agents.[115-117] Decitabine and azacitidine inhibit DNA methyltransferases to decrease cytosine methylation, raising the question whether somatic gene mutations involving epigenetic regulators might serve as biomarkers for response to these agents. This notion was first supported by a retrospective study that found 85% of patients with *TET2* mutations responded to azacitidine, a response rate nearly twofold greater than that in the overall cohort of 86 patients.[118] In a larger retrospective study, 213 patients with MDS receiving treatment with hypomethylating agents were investigated by NGS.[119] In this larger cohort, 94% of patients carried at least one mutation, with *ASXL1* (46%) the most frequent, followed by *TET2* (27%), *RUNX1* (20%), *TP53* (18%), and *DNMT3A* (16%). Though there was a trend favoring a higher response rate in patients with *TET2* mutations, it was not significant until the analysis was limited to those patients with allele frequencies greater than 10%. At the higher variant allele frequency, *TET2* mutations were associated

with a significantly higher response rate (60%) compared with wild type (43%; p = .036). Furthermore, the presence of mutated *TET2* and wild-type *ASXL1* had the highest response rate, while those patients with mutated *ASXL1* and wild-type *TET2* had a trend toward a lower response rate (p = .051). Neither of these gene mutations impacted overall survival with azanucleoside treatment; however, *TP53* and *PTPN11* were each associated with a significantly inferior overall survival (p = .007 and .006, respectively). Of particular importance, a complex karyotype with a *TP53* mutation was associated with poor overall survival, while complex karyotypes with wild-type *TP53* had the same survival as noncomplex karyotypes. Interestingly, mutations involving *RUNX1*, *ASXL1*, *EXH2*, and *ETV6* did not significantly influence prognosis, suggesting that treatment with hypomethylating agents may modify the unfavorable impact of these mutations. More importantly, although this study identified gene mutation profiles that may impact azanucleoside response, it did not identify specific mutations linked to primary resistance, thereby limiting their usefulness for treatment selection.

Interestingly, another retrospective study of NGS gene mutations from 134 patients with higher-risk MDS treated with azacitidine revealed a significant association between karyotype and mutation profile with overall survival.[120] High-risk IPSS cytogenetics were negatively associated with survival (p < .001), while mutations involving histone modifiers, including *ASXL1*, *EZH2*, and *MLL*, were positively associated with prolonged survival (p = .001). Specifically, patients with mutations in histone modifiers without high-risk cytogenetics had a response rate of 79% and median survival of 29 months compared with a response rate of 49% and 10-month median survival in the same patients with high-risk cytogenetics (p < .001). *TP53* mutations were again a significant unfavorable covariate for overall survival (p = .001).

SRSF2 and spliceosome inhibitors. Spliceosome complex gene mutations, including *SRSF2*, *U2AF1*, and *SF3B1*, are the most commonly identified mutations in MDS and occur almost exclusively in a heterozygous state. Murine models indicate that these mutations promote the expansion of hematopoietic stem and progenitor cells and alter messenger RNA splicing and stability.[121] Mouse models show that *SRSF2*-mutated cells survive only in the presence of a wild-type allele, while pharmacologic inhibition of the wild-type protein with the spliceosome inhibitor E7107 fosters selective clonal suppression by virtue of synthetic lethality. Treatment of human AML xenografts with mutant *SRSF2* in nonobese diabetic (NOD) scid gamma mice with E7107 demonstrated significant reduction in leukemia burden compared with wild-type xenografts. A phase I/II study is currently underway to evaluate the splicing inhibitor H3B-8800 in patients with splicing gene–mutant MDS and AML (NCT02841540).

SF3B1 and luspatercept. The transforming growth factor-β (TGF-β) superfamily are potent regulators of erythropoiesis with a pathobiologic role in the ineffective erythropoiesis of MDS. TGF-β ligands trigger receptor-mediated phosphorylation and activation of the inhibitory Smad2/3 transcription factors that lead to suppression of terminal erythroid differentiation. Therapeutic agents that act as ligand traps by competitively binding several TGF-β superfamily ligands can diminish the effects of this inhibitory pathway.[122] Sotatercept is a recombinant human fusion protein that contains the extracellular domain of the human activin receptor IIA (ACRIIA) that recognizes and neutralizes multiple TGF-β ligands such as activin-A and growth-and-development factor (GDF)-11. Phase I trials demonstrated sustained increases in hemoglobin in healthy volunteers, whereas treatment of mice with the murine analog RAP-011 demonstrated inhibition of ACRIIA/SMAD signaling with rapid and significant rise in hemoglobin as a result of derepression of late-stage erythroid precursor maturation.[123,124] In a murine thalassemia intermedia model, RAP-536, a murine fusion protein including a site-specific mutated extracellular binding domain of the ActRIIB receptor, promoted erythroid differentiation while reducing hemolysis.[122] Luspatercept is the recombinant human counterpart that contains the modified extracellular domain of the activin receptor IIB, which interacts with several cognate TGF-β ligands, including GDF11, GDF8, activin-B, and bone morphogenic protein (BMP)-6 and BMP10. The luspatercept PACE-MDS trial was a phase I/II multicenter, open-label, dose-finding study of 58 patients with IPSS low/intermediate-1 MDS (27 in dose escalation and 31 in expansion phase). In the dose-escalation phase, transfusion independence was achieved in 35% of patients receiving higher doses of treatment (0.75 to 1.75 mg/kg subcutaneously every 21 days). Notably, there was a higher erythroid response rate in patients with ring sideroblasts (55% vs. 29% in ring sideroblasts–negative) and 60% of those with a *SF3B1* gene mutation.[125] This has led to a phase III, randomized, double-blind study comparing luspatercept to placebo in transfusion-dependent, low/intermediate-risk patients with MDS with ring sideroblasts, referred to as the MEDALIST trial (NCT02631070).

TP53. Although *TP53* mutations are uncommon in patients with MDS, they nevertheless represent one of the most unfavorable mutations impacting outcome.[126] Although more often associated with complex, monosomal karyotypes and del(5q) chromosome abnormalities, the clone size as measured by VAF is critical to guiding prognostic implications.[101] NGS performed on specimens of 219 patients with MDS and secondary AML showed that patients with a *TP53* mutation VAF greater than 40% had a median overall survival of 124 days, while it was not reached in those with a *TP53* VAF less than 20%, which was indistinguishable from that for wild-type cases. Two recent studies suggest that *TP53*-mutant MDS/AML may be more susceptible to clonal suppression by decitabine. In a retrospective study evaluating 109 patients with MDS treated with decitabine, *TP53* mutations were identified in 13.8% of patients.[127] *TP53* was the only somatic gene mutation predictive for complete response (CR), with 10 of 15 patients with *TP53* mutations (66.7%) achieving CR versus 20 (21%) of 94 with wild type (p = .001). Of those with monosomies, 80% achieved CR.

Median overall survival remained disappointing at 14 months. Similar results were reported in a study of 116 patients with MDS/AML treated with a 10-day course of decitabine every 28 days.[57] Patients with a *TP53* mutations had a significantly higher overall response rate compared with wild type (21 [100%] of 21 patients vs. 32 [41%] of 78 patients; p < .001) and higher rate of complete remission/incomplete marrow recovery (CR/CRi; 13 [62%] of 21 patients vs. 26 [33%] of 78 patients; p = .04). Gene sequencing at sequential time points revealed selective suppression of the *TP53* mutant clone; however, there was no discernible relationship between response and changes in cytosine methylation.

Whether *TP53* mutant clones display exclusive sensitivity to decitabine compared with azacitidine is not clear. A retrospective analysis of a 54-patient cohort suggests differential sensitivity of mutant *TP53* cases compared with wild type; however, this merits further investigation in larger numbers of patients.[128]

Allogeneic hematopoietic stem cell transplantation. Allogeneic hematopoietic stem cell transplantation remains the only curative treatment strategy for patients with MDS. Recent investigations show that somatic gene mutations also influence the probability of relapse post-transplantation.[84] In a study of 401 patients with MDS or secondary AML who underwent allogeneic hematopoietic stem cell transplantation, the number of somatic mutations and specific gene mutations significantly affected outcome.[109] Mutations involving *RUNX1*, *ASXL1*, or *TP53* were independent covariates for relapse after transplantation. Patients with *TP53* mutations had a particularly poor outcome and should be considered for novel investigational studies to mitigate the relapse risk.

CONCLUSION

With the increase in understanding of genetic mutations specific to MDS, molecular data is being utilized in clinical practice for risk stratification and in some cases, to guide treatment recomendations. Specifically, data support the use of lenalidomide in deletion 5q, wth other mutations requiring further confirmation for thier impact on treatment selection. With ongoing investigation, this set of information can evolve and offer more personalized treatment options for patients with MDS.

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Novel Therapeutics in Acute Myeloid Leukemia

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OVERVIEW

In this review, we focus on three key areas in acute myeloid leukemia (AML) developmental therapeutics: FLT3 inhibitors, IDH inhibitors, and drugs that may be particularly beneficial in secondary AML.

AML is a therapeutically challenging, heterogeneous disease in need of improved therapy, particularly for older adults. The natural history of younger adults with AML has improved over successive decades, possibly in large part because of better anti-infective agents and reduced mortality associated with allogeneic stem cell transplantation. Unfortunately, results in older adults, who have a less than 10% chance of long-term survival, have changed little in the recent past.

However, thanks to improvements in the understanding of AML biology, in great measure as a result of the recent annotation of the genomic basis for this disease, a multiplicity of so-called targeted therapies and therapies based on differential pathophysiology of leukemic stem cells compared with normal counterparts have emerged. Although the time from targeted identification to therapeutic development and approval has been much longer than hoped, at least two agents, midostaurin and CPX-351, are expected to be approved for use in AML during 2017. Small-molecule inhibitors of the isocitrate dehydrogenase (IDH) 1 and IDH2 mutant enzymes seem to be tolerable and effective as single agents and may also be added to the therapeutic armamentarium in the next few years. This review details the disease biology and developmental therapeutic history relevant to each of these classes of drugs, which represent a small subset of promising agents in AML.

FLT3 INHIBITORS

Mutant FLT3 Biology

A key focus in developmental therapeutics in AML over the past 15 years has been on inhibiting the transmembrane tyrosine kinase mutant *FLT3*, because of its prevalence, possible relevance to pathophysiology, and gain-of-function nature.[1] Two types of *FLT3* mutations occur in myeloblasts. Internal tandem duplication (ITD) or length mutations are found in approximately 25% of patients with AML (a duplication of between three and more than 300 base pairs in the region of the gene encoding the juxtamembrane domain).[2] Approximately 10% of patients with AML harbor point mutations in the tyrosine kinase domain (TKD).[2] Both mutations lead to activation of the gene by spontaneous dimerization in the absence of ligand binding.[3] Patients with AML harboring *FLT3 ITD* mutations (and possibly TKD mutations) have an inferior prognosis compared with patients with wild-type *FLT3* because of an increased rate of relapse after initial remission.[4-6] *FLT3* mutations are generally not "founder mutations" but rather are disease-promotion mutations that, although important to the biologic behavior of the AML, may not be central to its inception and even long-term persistence.[2]

FLT3 Inhibition: A Brief History

Early trials with single-agent FLT3 inhibitors, such as midostaurin, lestaurtinib, and tandutinib, and in patients with advanced mutant *FLT3* AML at best evidenced modest reductions in peripheral blood blasts.[7-9] The potential reasons for the relative lack of efficacy included disease biology—*FLT3* mutations are not intrinsically required for disease maintenance. Some patients with mutant *FLT3* leukemia experience disease relapse with *FLT3* wild-type disease, suggesting the dispensability of this mutation for leukemia persistence. Second, the small-molecule FLT3 inhibitors that first came to the clinic were highly protein bound and lacked potency and specificity.[1]

Currently, there are two major streams in FLT3 inhibitor clinical development: (1) the use of relatively specific and higher potency, often termed second-generation, FLT3 inhibitors, as single agents in advanced disease, and (2) the use of less specific, first-generation inhibitors in combination with chemotherapy in newly diagnosed mutant *FLT3* AML. Two potent and specific FLT3 inhibitors, quizartinib and gilteritinib, are currently being evaluated in comparison with standard of care chemotherapy in relapsed mutant *FLT3* AML in the context of large phase III trials in

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which survival is the primary endpoint. These phase III trials were based on earlier studies[10,11] showing a significant single-agent overall response rate (ORR) in advanced mutant *FLT3* AML. Quizartinib, which specifically inhibits the FLT3 ITD mutant protein and can select for resistance via the emergence of mutant *FLT3* TKD clones,[12] was associated with a 36% ORR but with few true complete remissions (CRs).[10] Nonetheless, an agent that profoundly reduces the blast count could serve as an effective "bridge to potentially curative transplantation." Quizartinib's ability to potently inhibit KIT, an enzyme thought to be important in early stem cell function,[10] has been proposed as a potential reason why full count recovery was not frequently observed. Similarly, gilteritinib, which inhibits proteins with either FLT3-ITD or TKD mutations, also produces a relatively high ORR with few CRs.[11] Specific FLT3 inhibitors could be relatively effective in the relapsed or refractory disease setting, in which a mutant *FLT3* clone may predominate, as opposed to the more polyclonal upfront setting.

FLT3 Inhibitors in Combination With Chemotherapy

A frequent reduction in circulating blasts, in combination with preclinical data showing synergy or at least additivity between FLT3 inhibitors and standard chemotherapy, prompted the generation of several trials in which FLT3 inhibitors were combined with standard chemotherapy. Although one randomized trial was conducted in patients with relapsed mutant *FLT3* AML, most of these studies were performed in newly diagnosed patients. Second, each of the randomized trials was conducted with relatively nonspecific multikinase FLT3 inhibitors, including sorafenib, lestaurtinib, and midostaurin.

Patients with relapsed mutant *FLT3* AML were randomly assigned to receive chemotherapy (mitoxantrone/etoposide/cytarabine) for relapses that occurred with a shorter degree for interval, and high-dose cytosine arabinoside (ara-C) for those who relapsed after a longer disease-free interval, with or without lestaurtinib, at 80 mg daily given with chemotherapy until remission or progression occurred.[13] The addition of lestaurtinib failed to improve CR rate, event-free survival, or overall survival. However, fewer than half the patients were found to have sufficient levels of *FLT3*-inhibiting activity in their plasma to expect to cause target inhibition. An ongoing trial of high-dose ara-C/mitoxantrone, with or without the more specific agent crenolanib, represents another test of the ability of FLT3 inhibitors to potentiate chemotherapy effect in patients with more advanced *FLT3* AML.

Sorafenib is a multitargeted kinase inhibitor approved for renal cell carcinoma and hepatocellular carcinoma presumptively because of inhibitory activity against vascular endothelial growth factor receptor.[14] Therapy at effective sorafenib doses can produce many problematic adverse effects, including hand-foot syndrome, liver test abnormalities, and myelosuppression.[15] At least four trials have combined sorafenib with chemotherapy in the upfront setting, but only one such trial, a nonrandomized effort conducted in older adults, restricted enrollment to patients with mutant *FLT3* AML. The Alliance for Clinical Trials in Oncology led a U.S. intergroup trial in which patients over age 60 with newly diagnosed mutant *FLT3* AML received 7 + 3 induction chemotherapy and modified high-dose ara-C–based postremission therapy plus sorafenib.[16] Patients age 60 to 69 appeared to achieve superior outcomes compared with historical controls. A prospective randomized trial of standard chemotherapy with or without sorafenib in older adults with any *FLT3* status not only failed to demonstrate an event-free or overall survival benefit to the addition of the inhibitor but documented very poor tolerance of the combination in this age group.[17] Investigators at MD Anderson Cancer Center showed the feasibility of combining sorafenib with standard induction therapy.[18] The SORAML trial randomly assigned patients ages 18 to 60 to receive standard induction and postremission chemotherapy with or without sorafenib at a dose of 400 mg twice a day beginning on day 2 until remission.[19] The trial demonstrated an event-free but no overall survival benefit with the addition of sorafenib. This trial was not restricted to those with mutant *FLT3* AML, who constituted only 17% of the total population. In this subgroup, no benefit could be discerned, but the trial was not powered to detect such a difference.

An issue that inevitably complicates the interpretation of any trial of a FLT3 inhibitor in intensely treated patients with AML is the use of stem cell transplantation in the postremission setting; transplantation as consolidation in first remission could potentially ablate any survival advantage.[20] Although power is lost when doing so, one method to isolate the effect of a FLT3 inhibitor in upfront AML would be to perform a censored analysis that does not "follow" patients after they have undergone transplantation. The "censored for transplantation" analysis performed in the SORAML trial[19] failed to demonstrate a benefit for the addition of sorafenib. Whether an improvement in event-free survival in AML without a survival benefit should justify approval of a drug or change in clinical practice remains highly controversial. There may be an intrinsic benefit to living life without relapse, but the overall impact on disease natural history might be relatively low.

KEY POINTS

- **Annotation of the genomic landscape of AML has promulgated the development of targeted therapies.**
- **Midostaurin plus chemotherapy is superior to chemotherapy alone in newly diagnosed mutant FLT3 AML.**
- **Specific and potent FLT3 inhibitors are being to compared with standard therapy in advanced mutant FLT3 AML.**
- **IDH inhibitors have significant activity, sometimes via differentiation, in IDH mutant AML.**
- **CPX-351 is more effective than 3 + 7 chemotherapy in older adults with secondary AML.**

Two recently reported randomized trials involved the addition of a relatively nonspecific FLT3 inhibitor in younger adults receiving intensive chemotherapy. Knapper et al[21] performed an analysis of two trials conducted in the United Kingdom in which patients with mutant *FLT3* AML were allocated to chemotherapy with or without lestaurtinib. Each of these two trials also included a number other randomizations designed to answer pertinent "non-*FLT3*" AML questions. This analysis failed to demonstrate an event-free or overall survival benefit for the addition of lestaurtinib. A post hoc analysis revealed that those patients who received gemtuzumab ozogamicin plus an azole, or those who had high levels of FLT3 inhibition activity in plasma, presumptively leading to higher lestaurtinib levels, did experience benefit, suggesting that the trial may have been negative primarily because of poor lestaurtinib pharmacologic availability in many patients.

In contrast to the results in the upfront lestaurtinib experience, the CALGB 10603/RATIFY trial[22] demonstrated the ability of midostaurin to improve the natural history of mutant *FLT3* AML in patients age 18 to 59 receiving standard chemotherapy. This prospective, double-blind, randomized, placebo-controlled trial enrolled patients with mutant *FLT3* AML (with either *ITD* or *TKD* mutations) documented at a central laboratory that yielded results in about 2 days. Up to 5 days of hydroxyurea was allowed while waiting for the results before full enrollment. Patients received standard daunorubicin at 60 mg/m^2 per day for 3 days plus continuous infusion cytarabine at 200 mg/m^2 per day for 7 days, with a second course permitted in the event of persistent leukemia at day 21. Four cycles of high-dose ara-C were to be given in the postremission setting plus midostaurin or placebo according to the original random assignment on days 8 through 21 at a dose of 50 mg twice daily. Patients also received 12 28-day cycles of maintenance with midostaurin or placebo after recovery from the final cycle of consolidation chemotherapy. Transplantation was not mandated but was carried out in 27% of patients in first remission and approximately 57% overall. The primary endpoint of the study was met—overall survival uncensored for transplantation; there was 22% reduction in the risk for death for patients randomly assigned to receive midostaurin ($p = .007$). Although the protocol CR rate (remission by day 60) was not statistically superior for those randomly assigned to receive midostaurin, event-free survival was significantly improved. All subgroups of patients with *FLT3* mutations benefitted (those with a high or low allelic burden *ITD* and those with *TKD* mutations). Other notable findings from this study were as follows: (1) the censored-for-transplantation analysis also showed a benefit for midostaurin; (2) patients who underwent transplantation in first remission significantly benefited from midostaurin, suggesting that midostaurin early in the course of the disease might actually lower the disease burden; and (3) midostaurin was not associated with any significant toxicity issues compared with placebo. This trial may lead to the approval of midostaurin as an adjunct to chemotherapy in patients with newly diagnosed mutant *FLT3* AML. Second, the research may spur the testing of midostaurin in combination with chemotherapy for patients with *FLT3* wild-type disease. Such an effort makes sense because of the multikinase inhibitory activity of this drug as well as the clinical benefit in those with low allelic ratio of mutant *FLT3* to wild-type *FLT3*, a situation in which the dependence on FLT3 signaling might be relatively low.

ROLE OF IDH MUTATIONS IN AML: A VALID THERAPEUTIC TARGET?

IDH1 and IDH2 Mutations in AML

Mutations within the IDH family of metabolic enzymes, specifically *IDH1* and *IDH2*, were first identified in 2009 and are now well recognized as recurrent somatic mutations within myeloid malignancies, T-cell lymphomas, and certain solid tumors such as cholangiocarcinoma, sarcoma, and brain glioma.[23] Approximately 20% of patients with AML will have *IDH1* or *IDH2* mutations, which occur specifically within the conserved IDH enzymatic active site, at the arginine residues IDH1-R132, IDH2-R140, and IDH2-R172.[24]

Under normal physiology, IDH enzymes catalyze the conversion of isocitrate to alpha-ketoglutarate (αKG); the IDH2 enzyme is located in the mitochondria and operates within the citric acid cycle, and the IDH1 enzyme catalyzes the same reaction within the cytoplasm.[25] Cancer-associated somatic mutations within IDH1 or IDH2, however, promote a reverse reaction that reduces αKG to the oncometabolite D-2-hydroxyglutarate (D-2HG). Serum D-2HG levels, as typically measured by mass spectrometry, are often 10 to 100 times greater (or more) than in patients who lack these mutations.[26,27] Available evidence suggests that the pathogenicity of *IDH* mutations is related to 2HG-induced competitive inhibition of myriad αKG-dependent enzymatic activities; leading to alterations in TET2-dependent DNA hydroxymethylation, chromatin modification, activation of the hypoxic response, and inhibition of cytochrome C oxidase within the electron transport chain, leading to increased BCL2 dependence.[28] Consistent with this altered epigenetic state, *IDH1*- and *IDH2*-mutant AML is characterized by a distinct and globally hypermethylated DNA signature.[29] Additionally, mutations in *IDH1*, *IDH2*, *WT1*, and *TET2* are nearly mutually exclusive in AML, indicating a unique epigenetic mutational class leading to impaired hematopoietic differentiation via altered methylation.

Together, *IDH* mutations occur in approximately 20% of patients with AML, with approximately 5% to 13% having *IDH1* and 8% to 17% *IDH2* mutations.[30] *IDH* mutations are more frequently identified in older patients, those with diploid or other intermediate-risk cytogenetics, sustained or higher platelet counts, and elevated bone marrow blast counts and frequently co-occur with *FLT3-ITD* and *NPM1* mutations.[31-33] Although less common in patients with lower risk myelodysplastic syndrome (MDS) and myeloproliferative neoplasm (MPN) at diagnosis, the frequency of *IDH1* or *IDH2* mutations increases to 10% to 20% at the time of leukemic transformation and are

frequently characterized by *DNMT3A*, *ASXL1*, and *SRSF2* comutations.[34,35]

Several retrospective analyses have evaluated the significance of *IDH1/2* mutations on overall AML prognosis. In general, the response rates and survival for patients with IDH1/2-mutated AML appears comparable to those with wild-type IDH AML when treated with standard cytarabine-based chemotherapy or hypomethylating agent–based therapy; in addition, prognosis is dependent on the presence of *NPM1*, *FLT3*, and other comutations.[31-33] Although the overall prognostic impact of *IDH* mutations in AML remains unclear, *IDH2-R172* mutations have been recently ascribed to a distinct subgroup of AML with fewer comutations, a unique gene expression profile with more profound metabolic aberrations, and a particularly favorable prognosis with intensive cytarabine-based chemotherapy.[36]

Targeting IDH1 and IDH2 Mutations

A noteworthy advance within the past 5 years has been the development of small-molecule mutant IDH selective inhibitors. This new class of targeted IDH inhibitors bind within the mutant IDH1 and/or IDH2 catalytic active site, preventing the oncogenic reduction reaction of αKG to the oncometabolite D-2HG.[37] In preclinical studies of IDH inhibitors, reduction of D-2HG to normal, healthy levels in the setting of progressive reversal of histone and DNA hypermethylation and evidence of cellular differentiation was observed over the course of several weeks.[38] These preclinical observations have been substantiated in early clinical studies, in which evidence of clinical activity via myeloid maturation has been demonstrated. Speaking to the distinct differentiating mechanism of action of IDH inhibitors, a unique side effect of targeted IDH therapy, termed "IDH differentiation syndrome," consisting of nonspecific clinical symptoms including culture-negative fever, edema, hypotension, and pleural and/or pericardial effusions, often in the setting of neutrophil-predominant leukocytosis, has been described in approximately 5% to 10% of patients across IDH inhibitor clinical trials.[39]

Enasidenib (AG-221/CC-90007). Previously referred to as AG-221, enasidenib is an oral mutant IDH2 inhibitor with activity against both the IDH2-R140 and IDH2-R172 mutations. Enasidenib was the first of the targeted small-molecule mutant IDH inhibitors to reach the clinic, with the first patient treated in September 2013. The maximum tolerated dose was not reached at up to 650 mg/day in the phase I dose escalation, and a 100 mg daily dose was determined as the recommended phase II dose on the basis of pharmacokinetic data including robust plasma 2HG inhibition and pharmacodynamic and clinical activity. The last interim results of this phase I dose escalation and expansion study was presented at the 2015 annual meeting of the American Society of Hematology, with 181 patients with advanced myeloid malignancies treated, including 128 patients with relapsed or refractory AML.[40] Single-agent enasidenib was well tolerated and led to an ORR of 41% with a CR rate of 18%, with responses observed in patients with both R140 and R172 mutations. Notable adverse events included indirect hyperbilirubinemia due to inhibition of the UGT1A1 enzyme, similar to Gilbert syndrome, and IDH differentiation syndrome. The phase II expansion component of this study specifically for relapsed or refractory AML has recently completed enrollment, and updated results from this AG221-001 study (NCT01915498) are anticipated at the 2017 ASCO Annual Meeting. Currently, a phase III randomized study of enasidenib versus investigator choice (NCT02577406, referred to as the IDHentify study), is enrolling patients with AML age 60 and older with *IDH2* mutation and relapsed or refractory to second- or third-line AML therapy. In addition, frontline combination phase I and II studies of enasidenib are enrolling, with 7 + 3 for newly diagnosed AML induction-appropriate patients (NCT02632708) and in combination with azacitidine versus azacitidine alone (2:1 random assignment, NCT02677922) for patients not appropriate for induction therapy.

AG-120. AG-120 is a first-in-class mutant IDH1 inhibitor with activity against the IDH1-R132 mutation. Dose expansion arms of the original phase I study (NCT02074839), including a planned expansion arm (125 patients) for relapsed or refractory AML, continue to accrue at the time of writing. The phase I dose escalation portion has completed, with 78 patients treated at doses ranging from 300 to 1,200 mg daily. The maximum tolerated dose was not reached, and the recommended phase II dose has been determined to be 500 mg daily on the basis of pharmacokinetic, pharmacodynamic, and efficacy data, including effective 2HG suppression. The ORR in the dose escalation cohort was 39%, with a CR rate of 18% and a rate of CR or CR with incomplete hematologic recovery of 28%. Of interest, data presented at the 2016 American Society of Hematology Annual Meeting suggest that a subset of responding patients (specifically, 36% of patients attaining CR) attained *IDH1* mutational clearance as assessed by next-generation sequencing analysis, which may correlate with duration of response.[41] In addition to the ongoing AG-120-001 study, frontline combination phase I and II studies of AG-120 are enrolling, with 7 + 3 for newly diagnosed AML induction-appropriate patients (NCT02632708) and in combination with azacitidine (NCT02677922) for newly diagnosed patients not appropriate for induction therapy. A phase III, double-blind, randomized, placebo-controlled study of azacitidine with or without AG-120 is planned.

AG-881. AG-881 is the only IDH inhibitor in the clinic with activity against both mutant IDH1 and IDH2. It has been characterized in preclinical studies as demonstrating improved penetration of the blood-brain barrier. Phase I dose escalation studies of AG-881 are open both in glioma and nonglioma solid tumors, as well as in patients with advanced hematologic malignancies that have progressed during prior IDH1 or IDH2 targeted therapies. At the time of this writing, no clinical data with AG-881 have been reported.

IDH305. IDH305 is a mutant-specific and brain-penetrant IDH1 inhibitor with activity against the IDH1-R132 mutation. The phase I first-in-human IDH305 dose escalation

and expansion study (NCT02381886) is notably designed in that it opened simultaneously for three broad disease areas (glioma, MDS/AML, and non–central nervous system solid tumors), with dose expansions in disease-specific cohorts to further characterize safety and explore efficacy. Preliminary results from this phase I trial were presented at the 2016 American Society of Hematology meeting,[41] with three patients with MDS and 31 with AML treated at doses of 75 to 900 mg twice daily, with evidence of antitumor activity including an ORR of 33% in the patients with MDS/AML.

Two additional mutant-selective IDH1 inhibitors, FT-2102 and BAY 1436032, are also in clinical development, FT-2102 in a phase I/IB study of FT-2102 monotherapy and in combination with azacitidine in patients with myeloid malignancies and BAY 1436032 in a phase I study of *IDH1* mutant solid tumors. No clinical data with either compound have been reported to date.

Venetoclax. Outside of targeted IDH inhibitor therapy, oral small-molecule BCL-2 inhibitors such as venetoclax (formerly ABT-199) may have enriched activity in IDH mutant AML. Preclinical data have demonstrated that cell lines and patient-derived samples with *IDH* mutations are particularly sensitive to BCL-2 inhibition, because of the elevated levels of D-2HG, which inhibits cytochrome C oxidase within the electron transport chain.[42] These preclinical findings were initially supported by results from a phase II study of venetoclax in relapsed or refractory AML, with a rate of CR or CR with incomplete hematologic recovery of 27% in patients with mutant IDH, compared with less than 15% in those with IDH wild-type.[43] Combination approaches of frontline AML therapy with venetoclax, such as with hypomethylating agents (NCT02993523) or low-dose cytarabine (NCT02287233), are under way and demonstrate encouraging activity, notably leading to a U.S. Food and Drug Administration breakthrough designation for the combination of venetoclax and hypomethylating agent therapy for untreated, elderly patients with AML; outcomes based on IDH mutations have not yet been reported and are of considerable interest.

BIOLOGY AND THERAPY OF SECONDARY AML: ANY PROGRESS?

In the revised 2016 World Health Organization classification of myeloid neoplasms, secondary AML (sAML) is included under the category of AML with myelodysplasia-related changes and is defined as AML diagnosed after a history of MDS or MDS/MPN.[44] For the purposes of this review, therapy-related AML, a category often grouped with sAML, will be excluded from the discussion. sAML accounts for 20% to 25% of cases of AML, and it is most commonly diagnosed in older adults (median age at diagnosis of 73), with three-quarters of patients older than age 65 at diagnosis.[45-47] Prior diagnoses of MDS are present in 60% to 65% of patients with sAML.[45,47] The latency time between diagnosis of prior hematologic disorder and sAML ranges from 1 to 1.5 years (for prior MDS) and from 3.5 to 7 years (for prior MPNs).

Data on the distribution of cytogenetic abnormalities in patients with sAML are limited and may be hampered by selection and/or exclusion of patients with sAML from clinical trial participation. Two population-based studies have demonstrated that adverse-risk cytogenetic abnormalities are disproportionally overrepresented in patients with sAML compared with de novo AML. In addition, favorable-risk reciprocal translocations were rarely observed in patients with sAML.[45,47]

The genomic basis of AML transformation from antecedent hematologic malignancy has been the focus of intense research in recent years. It is now well defined that most cases of sAML are oligoclonal with substantial interpatient clonal diversity at the time of diagnosis.[48] In addition, genomic studies assessing the clonal architecture of sAML have demonstrated evidence of subclonal disease progression with persistence of the founding MDS clone at the time of sAML transformation, an event marked by the serial acquisition of at least one new driver gene mutational event. Not surprisingly, no single genomic event is uniformly present at the time of transformation to sAML, and a substantial number of somatic genetic alterations with considerable combinatorial diversity can drive transformation to sAML. In routine practice, however, clinical characterization of sAML may not be straightforward, especially in older patients or those without identifiable clinical prodromes. To address this clinical dilemma, recent studies designed to elucidate the genetic basis of AML have demonstrated that sAML ontogeny could be reliably predicted by the presence of somatic mutations in one of eight genes (*SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR,* or *STAG2*).[49] The presence of these secondary-type mutations were identified in earlier (founder) malignant myeloid clones, persisted at high levels in patients in complete morphologic remission following aggressive induction chemotherapy, and were associated with worse outcomes.[49] In addition, these observations complemented earlier next-generation sequencing studies by demonstrating that these secondary-type mutations occur earlier in the development of the clonal hematopoiesis, that is, "founding mutational event" or malignant myeloid clone that with additional genomic insults can evolve into ineffective hematopoiesis and dysplasia features. Moreover, this study highlighted the transformative consequences of de novo or pan-AML mutations in disease progression of sAML.[49]

Clinically defined sAML is an independent prognostic factor associated with adverse outcomes, regardless of the treatment approach chosen.[45] Using recent data from the Danish National Acute Leukemia Registry database, 1-year overall survival of patients with sAML was compared with that among patients with de novo AML and stratified according to treatment intensity; nonintensive therapy was defined as no therapy (including hydroxyurea and supportive care) or low-intensity therapy (low-dose cytarabine or hypomethylating agents); intensive therapy consisted of remission induction therapy with a backbone of cytarabine in combination with an anthracycline or anthracycline-like

TABLE 1. Selected Randomized Studies Comparing Different Interventions for Patients With Secondary Acute Myeloid Leukemia

Reference	Comparison	CR Rates	OS	EFS
[53]	SD vs. HD ara-C (< age 45)	59% vs. 94% (OR, 5.99; p = .03)	6 years: 29% vs. 76% (HR, 0.23; p = .005)	6 years: 25% vs. 76% (HR, 0.23; p = .002)
[53]	SD vs. HD ara-C (> age 46)	53% vs. 83% (OR, 3.75; p = .002)	6 years: 29% vs. 37% (HR, 0.82; p = .50)	6 years: 21% vs. 27% (HR, 0.79; p = .38)
[54]	Aza-7 + 3 vs. 7 + 3	NA	33% vs. 50% (HR, 2.03; p = .048)	17% vs. 22% (HR, 1.15; p = .62)
[55]	GO + 7 + 3 vs. 7 + 3	47% vs. 41% (OR, 1.28, p = .30)	22% vs. 18% (HR, 1.11; p = .08)	DFS: 33% vs. 41% (HR, 1.29; p = .01)
[56]	IDA vs. DAUNO (age 50–70)	NS (OR, NA; p = .56)	NS (HR, NA; p = .65)	DFS: NS (HR, NA; p = .15) NRM: NS (HR, NA; p = .54)

Abbreviations: Ara-C, cytosine arabinoside; Aza, azacitidine; CR, complete remission; DAUNO, daunorubicin; DFS, disease-free survival; EFS, event-free survival; GO, gemtuzumab ozogamicin; HD, high-dose; HR, hazard ratio; IDA, idarubicin; NA, not available; NRM, nonrelapse mortality; NS, not stated; OR, odds ratio; OS, overall survival; 7 + 3, cytosine arabinoside plus anthracycline (idarubicin or daunorubicin); SD, standard-dose.

compound. Two important observations were reached from this study. First, independent of intensity of therapy, sAML was associated with worse 1-year survival compared with de novo AML. Second, these data suggest that patients with sAML can be further grouped into two distinct prognostic categories, including those with AML following antecedent MDS and those with prior diagnosis of MPN or MDS/MPN (non–MDS-sAML), whereas cases of non–MDS-sAML are associated with significantly worse outcomes than cases of MDS-sAML. Finally, cytogenetic risk group (intermediate versus adverse risk cytogenetics) and older age (older than age 60) are associated with adverse outcomes with the cohort of patients with sAML.[45]

To better define the contribution of these independent prognostic variables in patients with sAML, investigators from the Study Alliance Leukemia study group developed and validated a prognostic score in these high-risk patients following treatment with intensive induction therapy.[46] The following dichotomized prognostic factors were demonstrated to be independently associated with worse outcomes: age older than 60, adverse risk karyotype, wild-type NPM1 status, and platelet count less than $50 \times 10^3/\mu L$. A prognostic scoring system was created, allowing patients with sAML to be grouped into three separate cohorts (zero or one risk factor in the favorable group, two risk factors in the intermediate group, and three or four risk factors in the high-risk group) that were associated with significant differences in 2-year overall survival rates (2-year overall survival of 52% to 58% for patients in the low-risk group, 21% to 28% in the intermediate-risk group, and 7% to 9% in the high-risk group; p < .001).[46]

The adverse outcomes associated with sAML reflect an increased resistance to conventional chemotherapy, and sAML has been recently shown to be one of the strongest independent predictors of treatment resistance in patients with AML.[50] A number of randomized clinical trials and population-based studies have consistently demonstrated lower CR rates and shorter long-term survival in patients with sAML.[30,45,47,51,52] In addition, some, but not all, studies have shown a higher rate of early death in sAML.[47,51] Assessment of efficacy in patients with sAML is restricted by frequent exclusion of these patients from randomized trials, limited size of sAML cohorts, scarcity of dedicated statistical analyses in this cohort of patients, and lack of differentiation between sAML and therapy-related AML. In prospective AML studies, no intervention has consistently improved outcomes in patients with sAML (Table 1). Similar to de novo AML, karyotypic abnormalities are independently associated with prognosis in sAML.[45]

Given the worse outcomes associated with sAML, after adjustments for age and performance status, patients with sAML are frequently not offered treatment with intensive regimens.[47,51] In addition, novel agents have been developed to overcome the known mechanisms of resistance described in cases of sAML. Amonafide, a DNA intercalator that evades drug resistance mechanisms in sAML, was combined with cytarabine and compared with standard intensive induction therapy in patients with untreated sAML. Although study results were not completely reported, the combination of amonafide and cytarabine did not improve CR rates or early mortality rates.[57]

Recently, CPX-351, a liposomal formulation of cytarabine plus daunorubicin, the advantage of which may be delivery of the two agents in a fixed molar ratio as well as superior marrow penetrance, was compared with conventional induction chemotherapy (7 + 3 arm) in patients between the ages of 60 and 75 with untreated high-risk AML.[58] Patients randomly assigned to the CPX-351 arm experienced improved CR rates (37% vs. 26%, p = .04), ORRs (48% vs. 33%, p = .02), numerically inferior early mortality rates (60-day mortality, 14% vs. 21%), and improved median overall survival (9.6 vs. 5.9 months; p = .005; hazard ratio [HR], 0.69). Exploratory post hoc analyses suggest that a significant benefit was observed in those patients randomly assigned to receive CPX-351 who eventually underwent allogeneic hematopoietic stem cell transplantation (alloHSCT; median overall survival: not reached for CPX-351 vs. 10.2 months for the 7 + 3 arm; p = .005; HR, 0.46). In addition, these improvements in outcomes favoring patients randomly assigned to receive CPX-5351 were independent of age at diagnosis.[59]

Although properly controlled studies are missing for patients with sAML, previous studies have shown that alloHSCT is the most effective curative modality for sAML.[60] Population-based studies suggest that approximately 20% to 30% of patients with sAML underwent alloHSCT (most in first CR and following intensive induction chemotherapy),[45,61] and these values are expected to increase in coming years with the increased use of reduced-intensity conditioning regimens, alternative donor transplantation, and advancing age of alloHSCT in older adults. Recently, somatic mutations in *ASXL1, RUNX1, or TP53* were independently associated with unfavorable outcomes and shorter survival after alloHSCT in patients with sAML.[62]

A sizable proportion of patients with sAML are not eligible or able to undergo alloHSCT. For these patients, curative treatment strategies remain limited. AML-001, a large, international collaboration, compared azacitidine with conventional care regimens in older (older than age 65) previously untreated patients with AML who were ineligible for alloHSCT.[63] Treatment with azacitidine was associated with a nonsignificant improvement in median overall survival (10.4 vs. 6.5 months; HR, 0.85; stratified log-rank p = .10) and 1-year survival rates (46.5% vs. 34.2%). Overall, 15% to 20% of patients enrolled in the AML-001 study had histories of MDS (sAML). In these patients, univariate analysis demonstrated a similar survival trend observed for the entire cohort (HR, 0.71; 95% CI, 0.44–1.14; stratified log-rank p = .16). A comparison between decitabine and a conventional care regimen demonstrated similar results with decitabine.[64] These data suggest that treatment with hypomethylating agents may be preferred to a conventional care regimen in patients with sAML who are not eligible for alloHSCT, but since this was a subset analysis, this recommendation must be considered provisional.

In conclusion, preclinical research and clinical trial results have led to unprecedented advances in the understanding of biologic properties, designing of prognostic models, and development of promising novel treatment strategies for patients with sAML. Remaining questions in sAML persist, and future studies should focus on a better understanding of the role of minimal residual disease monitoring (molecular and immunophenotypic) as well as the incorporation of novel agents in future therapeutic strategies.

CONCLUSION

The AML world is a bit brighter thanks to the basic research that has led to the development of successful targeting of the gain-of-function mutations in the *FLT3* tyrosine kinase and in each of two IDH enzymes. The first FLT3 inhibitor to be approved, midostaurin, will be used in combination with standard chemotherapy in newly diagnosed patients with AML. IDH inhibitors may be approved in patients with advanced AML with respective mutations. Finally, old drugs in new clothing (liposomal-encapsulated daunorubicin/cytarabine delivered in a 5:1 fixed molar ratio) may be more useful than standard chemotherapy in patients with AML following a myelodysplastic prodrome or with myelodysplastic-type morphologic or cytogenetic changes. Although none of these therapies will be curative on its own, the road to a better natural history for patients with AML has its first coat of pavement.

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HEMATOLOGIC MALIGNANCIES—LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

Age and Sex in Non-Hodgkin Lymphoma Therapy: It's Not All Created Equal, or Is It?

Michael Pfreundschuh, MD

OVERVIEW

Age is the most prominent factor for survival in all patients diagnosed with lymphoma, and male sex implies an increased and independent risk for a worse progression-free survival (PFS) and overall survival (OS) in most lymphomas, possibly with the exception of mantle cell lymphoma (MCL). The worse outcome for elderly patients is only partially explained by decreased tolerance to treatment regimens associated with the increasing number and severity of comorbidities. Little is known about specific differences in lymphoma biology with respect to age and sex, and this is changing only slowly despite the recent rise in interest about these issues. To better understand the differences and their underlying mechanisms, questions of age- and sex-specific outcomes, their correlation with pharmacokinetic data, and planned and received doses, must be addressed and reported in prospective clinical trials. Such studies must be accompanied by translational research that investigates biologic differences of lymphomas between old and young and male and female patients by addressing the microenvironment, cytogenetics including next-generation sequencing and systems biology of lymphomas, and correlation of these findings with treatment results. This knowledge will enable us to adjust lymphoma treatment to the necessities of more personalized medicine.

Age is the most prominent factor for survival of patients after the diagnosis of cancer. Similarly, studies in the United States,[1] Canada,[2] Europe,[3] and Asia[4] have recently confirmed that women have a longer cancer-specific survival than men. In the Canadian study,[2] the differences in relative survival rates and model-based estimation of the relative excess risk were most pronounced for melanoma, cancer of the oral cavity and pharynx, and non-Hodgkin lymphomas (NHLs). The only exception to this was bladder cancer, for which women had a substantial disadvantage with a relative risk excess of 1.23.[2] Reasons for the survival advantage of women with cancer compared with men and the underlying mechanisms are largely unknown, and the roles of sex hormones, women's better immune system, and their healthier behaviors underlying this phenomenon have been discussed.

In the following, we will review the studies addressing the age and sex issues in hematologic malignancies, in particular lymphomas, and discuss strategies to elucidate the reasons for these age- and sex-dependent differences in lymphoma survival.

AGE

Age is a strong negative prognostic factor in all lymphoma subtypes and has been recognized in prognostic scores such as the International Prognostic Index (IPI)[5] for diffuse large B-cell lymphomas (DLBCLs), the Follicular Lymphoma (FL) IPI 2 (FLIPI-2),[6] and the MCL IPI (MIPI).[7] Though 60 years is the cutoff point in IPI, FLIPI, and MIPI, the cutoff point between young and elderly patients in prospective trials is usually between age 60 and 65, even though the more clinically relevant breakpoint is closer to age 75, where comorbidity, dependency, and geriatric symptoms become more prevalent.

Severity of frank pathologic dysfunction or comorbidity increases with age. The association between comorbidity and survival was demonstrated by Charlson[8] who showed that comorbidities are independent predictors of survival. Comorbidities and polymedication for the treatment thereof can further compromise the tolerability of therapy. The hematopoietic reserve is often reduced, and a decrease in liver function can alter the metabolism of many drugs in elderly patients. Many older patients have a decreased glomerular filtration rate and a delay in drug excretion, necessitating adaption of cytotoxic drugs to creatinine clearance. The physiologic increase of body fat and reduction in lean body mass also contribute to an increased toxicity. Many elderly patients have a reduced emotional tolerance to stress and need closer guidance to maintain treatment compliance, in particular with oral anticancer drugs.[8] All

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these facts explain why many chemotherapies cannot be given to elderly patients at doses and treatment intervals for young patients thus compromising the responses of elderly patients to treatment and worsening the outcome of these patients.

However, therapeutic compromises alone do not account for the worse outcome of elderly patients. For example, in the RICOVER-60 trial for patients with DLBCL age 61 to 80,[9] the overall relative dose intensity of six courses of R-CHOP-14 was 98% in a randomized prospective trial with more than 200 participating institutions, with no significant differences between patients younger and older than age 75. Similarly, the bone marrow reserve of these two age groups—as determined by neutropenia, thrombocytopenia, and anemia—was not significantly worse either. Nevertheless, rates of infections and treatment-related deaths were significantly higher in patients older than age 75 ($p = 0.01$), indicating that factors other than hematologic reserve determine the tolerability of a given chemotherapy regimen in elderly patients. A restriction of the outcome analysis to patients older than age 75 without treatment-related deaths who maintained a high relative dose intensity comparable to the one observed in patients younger than age 75 revealed that the older population had, nonetheless, a worse outcome with less complete responses, more progressions, and more relapses, resulting in a significantly worse OS.

The biologic factors underlying the mechanisms responsible for the worse prognosis of elderly patients other than treatment tolerability are poorly understood. Most age-related biologic differences have been described for DLBCL. Elderly patients have a higher frequency of DLBCL and less frequently anaplastic large cell lymphomas, while primary mediastinal B-cell lymphomas are rare. The morphologically defined immunoblastic variant, which is associated with a poor prognosis, is also more frequent in elderly patients,[10] as are the prognostically inferior DLBCL cases derived from activated B-cells (ABC subtype) in contrast to the germinal center cell–derived DLBCL.[11] Moreover, *BCL2* expression, and cytogenetic complexity increase with age at diagnosis. Similarly, various genetic features, such as IRF4 translocations; gains in 1q21, 18q21, 7p22 and 7g21; changes in 3q27; and gains and translocations affecting the BCL6 locus, are significantly associated with patient age, with p values ranging from $p > 0.001$ to $p = 0.04$, even though no cutoffs between age groups could be defined.[12] Finally, Epstein-Barr virus (EBV)–positive DLBCL of the elderly—an EBV-positive clonal B-cell lymphoid proliferation—occurs rarely in patients younger than age 50. It is usually associated with a poor-prognosis IPI and has an aggressive course with a median survival of only 2 years.[13,14] However, the fact that biologic differences between DLBCL developing in young and elderly patients cannot be explained by a single or a few parameters is shown by the fact that there is consensus that double-hit and triple-hit lymphomas are prognostically relevant in elderly patients, but conflicting data exist on the prognostic value of these chromosomal changes in young patients where breaks of the *BCL2* gene have been reported to confer a worse prognosis.[15] Chromosomal changes and mutations in DLBCL entertain complex interactions that are difficult to elucidate because of the large number of players involved who eventually shape the biologic landscape of a given case of DLBCL.

In MCL and FL, there is irrelevant or limited information of age-related biologic differences, and it is not known whether the differences in outcome of young and elderly patients with FL is because of differences in host characteristics, treatment protocols, or tumor biology, including the presence of chromosomal aberrations. However, the genetic landscape of pediatric FL suggests that *TNFRSF14* mutations accompanied by CNN-LOH of the 1p36 locus in over 70% of mutated cases might play a key role in the pathogenesis of this disease. The genetic profiles of pediatric FL and the t(14;18) translocations in adult FL in adults indicate that these are two different disorders.[16]

Epidemiologic studies suggest four different forms of Hodgkin lymphoma: two distinct pediatric forms (childhood Hodgkin lymphoma and adolescent/young adult), an adult form, and an older-adult form.[17] Childhood Hodgkin lymphoma is defined as affecting those age 14 and younger and has a clear male predominance (2-3:1) with an increased proportion of mixed cellularity and EBV-associated cases. Adolescent/young adult Hodgkin lymphoma occurs in individuals age 15 to 35 with no clear sex predilection and nodular sclerosis in 65% to 80% of the cases. With respect to clinical presentation and EBV status, adult Hodgkin lymphoma in patients older than age 35 is very similar to adolescent/young adult Hodgkin lymphoma; however, older adults (older than age 55) with Hodgkin lymphoma often present with advanced disease and have a worse prognosis. Apart from

KEY POINTS

- **Age and sex are major prognostic factors determining the outcome of patients with malignant lymphomas.**
- **Diminishing organ functions and increasing comorbidities are key factors for worse tolerance to cytotoxic drugs, which might be complicated by interference caused by polymedication in elderly patients.**
- **Other factors that contribute to sex differences in outcome among patients with lymphoma are less well understood. Subtypes with poor prognosis accumulate in the elderly population with DLBCL. Genetic differences FL and Hodgkin lymphoma also suggest that they are different diseases in young and elderly patients.**
- **Analyses contrasting results between old and young and between male and female patients with respect to planned and received doses and dose intensities of cytotoxic drugs and immunotherapies are also warranted.**
- **Translational research must define the molecular mechanisms underlying the different biology within a lymphoma subtype according to age and sex as a basis for a more personalized medicine approach for the treatment of lymphomas.**

differences in clinical presentation and association with EBV, there is little information on genetic or molecular mechanisms that coin the particular characteristics of the four forms of Hodgkin lymphoma.

SEX

Diffuse Large B-Cell Lymphoma

There is ample evidence that female patients with DLBCL have a better prognosis and survival. A recent study of more than 7,000 patients in a Swedish population-based study found male sex to be an adverse risk factor only in young patients with DLBCL.[18] This is in contrast to other studies that observed a female survival advantage also in elderly patients (age 61 to 80),[9] and in very elderly patients (older than age 80).[19] Epidemiologic studies suggest that the sex difference in DLBCL is more pronounced when premenopausal women are compared with men of the same age.[2,20] In contrast, in young children treated according to the pediatric BFM-NHL protocol, female patients had a worse prognosis than male patients.[21] This was also observed in children with DLBCL in the 2016 German Childhood Cancer Registry,[22] lending support to the hypothesis that the survival advantage of female patients requires the hormonal changes of puberty.[2]

The outcome advantage for female patients with DLBCL was also observed in a study using Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data for primary and salvage treatment and irrespective of aggressive, conventional, or palliative treatment.[23] The seemingly contradictory observation that high body mass index in 1,386 elderly patients with DLBCL treated with rituximab-containing therapy compensated for the negative impact of male sex is more likely because of a relatively higher dosing of cytotoxic drugs for these patients rather than a rituximab effect, as increased weight is associated with a fastened rituximab clearance[24] also in male patients.

PD-L1 expression in patients with EBV-negative DLBCL was more pronounced in male patients and associated with worse outcome.[25] In a systems biology approach examining global transcriptome DLBCL data from The Cancer Genome Atlas, female sex was associated with decreased interferon signaling, transcription, cell cycle, and PD-1 signaling, and JUN and CYCX signaling were the most critical factors associated with tumor progression in older and male patients.[26]

Follicular Lymphoma

The unbiased estimates of long-term net survival of patients with FL[20] also show a survival advantage for females compared with male patients. The differences in 10-year survival decreased from 4% in patients younger than age 45 to 1% in patients age 55 to 60, but then increased again, with a difference of 3% in patients older than age 75, probably reflecting the higher all-cause deaths of male patients in the latter age group. Similar observations were made in two prospective analyses of U.S. patients with FL utilizing the National LymphoCare Study registry, both in the general FL population[27] and in elderly patients with FL in particular, despite the fact that the latter patients received anthracyclines less often and rituximab monotherapy more often.[28] In a Swedish study, a nationwide improved survival was observed in the rituximab era, particularly in elderly women, and male sex emerged as an adverse factor with increasing rituximab use.[29] This was confirmed in a randomized study comparing maintenance anti-CD20 antibody with observation after induction therapy,[30] even though maintenance rituximab was not associated with increased OS. However, a better outcome for female patients was not observed in a German study[31] nor in a U.S. study of patients treated with rituximab alone or combined rituximab chemotherapy followed by rituximab maintenance. This suggests that rituximab levels reached with weekly rituximab and/or prolonged exposure achieved with maintenance therapy exceed the therapeutic threshold, even with fast clearance, which nullifies the negative effect of higher weight and male sex.[32]

Mantle Cell Lymphoma

The prognostic role of sex is less pronounced in MCL, which has a male preponderance. In the MIPI, sex, stage, B-symptoms, number of extranodal sites, number of nodal areas, platelet count, and hemoglobin lost their prognostic relevance in multiple Cox regression analyses with backward variable selection on the dataset of 409 complete cases. Age, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase, and white blood cell counts were identified as the four independent prognostic factors for OS.[7] Nevertheless, in a retrospective analysis using the SEER database of 5,376 patients identified from 1992 to 2007, the proportion of patients with advanced disease at diagnosis, male sex, and advanced age increased over time, and these were all associated with increased mortality.[33] Although the OS of the entire MCL population did not improve over time, the adjusted model showed an improvement in predicted survival time in patients with advanced disease. In contrast, when therapy was deferred, it was associated with an improved survival in patients with newly diagnosed MCL. Among patients with deferred therapy, predictors of improved OS included male sex, younger age, and lack of comorbidities,[34] indicating that the peculiar biology of relatively indolent MCLs that allow for the deferral of treatment reverses the sex-specific survival differences.

T-Cell NHL

A SEER-based analysis of 7,662 patients[35] with T-cell NHL (T-NHL) revealed that male sex and increasing age were independent predictors of worse OS ($p < .001$). Ten-year net survival of mature peripheral T-NHL in the French registry[20] also showed a better 5-year survival for female compared with male patients, which was more pronounced in patients younger than age 55. A very strong sex effect was observed in a randomized German study of patients with peripheral T-NHL that compared CHOP to CHOP plus alemtuzumab, an anti-CD52 antibody. Similar to the observations with rituximab in DLBCL, the advantage for female patients was most pronounced in the group receiving combined immunochemotherapy with alemtuzumab and CHOP.[36]

Hodgkin Lymphoma

Age (older than age 45) and male sex are well-established risk factors in Hodgkin lymphoma and, because of their independent role in multivariable analyses, constitute the prognostic parameters in the Hodgkin lymphoma International Prognostic Score (IPS), besides low albumin, advanced stage, leukocytosis greater than 15,000/mm^3, and lymphocytopenia. Even though the range of outcome differences between the IPS risk groups has narrowed since its implementation in 1998,[37] the IPS remains prognostic for advanced-stage Hodgkin lymphoma. Male sex had a worse 10-year net survival rate in all age groups older than age 15, except for patients older than age 75 in the French registry.[20]

Biologic studies addressing the age effect in Hodgkin lymphoma are rare. A meta-analysis of the prevalence and prognostic significance of EBV infection in classic Hodgkin lymphoma revealed that EBV-positive Hodgkin lymphoma was significantly related to male sex, mixed cellularity, and advanced clinical stages.[38] Also, peripheral regulatory T-cell levels were found to be correlated with male sex, IPS, C reactive protein, and lactate dehydrogenase and negatively correlated with albumin and absolute lymphocyte count.[39] Interestingly, an analysis of the microRNA profile in Hodgkin lymphoma showed no association with age, sex, stage, response to treatment, disease-free survival, and OS.[40]

Sex-Specific Treatment Responses

There is little information on sex specific responses to cytotoxic drugs, because the results of phase I and phase II trials are rarely reported according to sex, and very few pharmacokinetic studies report results specific for male and female patients. Similarly, there are no reports in the lymphoma literature on differences on planned and actually received absolute doses and relative dose intensities comparing male and female patients. One exception is a recent U.K. study among patients with relapsed/refractory MCL that showed a significant correlation ($p = .02$) between sex and response to lenalidomide, suggesting that female patients with MCL are more sensitive to lenalidomide than male patients.[41]

In Hodgkin lymphoma, part of the worse outcome for male patients may be because of the fact that the lower hematologic toxicity in male patients was an independent prognostic factor associated with a worse outcome in Hodgkin lymphoma,[42] and similar observations have been made in DLBCL. Hematotoxicity is consistently higher in female patients compared with male patients, indicating higher serum levels that might be associated with greater efficacy of cytotoxic drugs in female patients. Increasing the doses of cytotoxic drugs for male patients to equitoxicity with female patients could be an interesting approach for closing the gap of treatment responses between male and female patients.

Interestingly, different treatment strategies with identical drugs and doses might also have differential effects for female and male DLBCL. Although elderly female patients with DLBCL benefitted more from the addition of rituximab in the RICOVER-60 trial,[9] male patients had more benefit from dose densification of the CHOP regimen by reducing the treatment intervals from 3 to 2 weeks (CHOP-14 vs. CHOP-2; event-free survival, $p = .003$) than female patients (CHOP-14 vs. CHOP-21; event-free survival, $p = .53$) in the NHL-B2 trial of the Deutsche Studiengruppe Hochmaligne Non-Hodgkin Lymphome (DSHNHL).[43]

The sex-specific differences in elderly patients with DLBCL appear to have increased with the introduction of the monoclonal CD20 antibody rituximab into the therapeutic armamentarium. This was confirmed in a meta-analysis of 5,635 patients from 20 studies,[44] and the recently increased interest in sex effects of lymphoma treatment has been fueled by the observation in the RICOVER-60 study of elderly patients with DLBCL, where the male hazard ratio for PFS increased from 1.1 for patients treated with CHOP-14 only to 1.6 ($p < .004$) for patients treated with R-CHOP-14. Pharmacokinetic studies revealed significantly higher rituximab serum levels and longer exposure times in elderly female patients compared with elderly male patients.[45] This was because of a rituximab clearance rate that remained relatively unchanged in male patients over age 20 to 80, while female patients who have a slightly faster rituximab clearance (and hence somewhat lower rituximab serum levels and shorter exposure times) than male patients when young, but experience a sharp decrease in rituximab clearance associated with increasing age,[46] resulting in higher rituximab serum levels and exposure times in elderly female patients compared with male patients. As a result of these pharmacokinetic studies, the DSHNHL performed several phase II studies in elderly patients with DLBCL pursuing different rituximab doses and schedules. Increasing the serum levels by early dose-densification (four additional applications of rituximab in the first 3 weeks of treatment) was associated with higher rituximab serum levels but identical exposure times in the DENSE-R-CHOP-14 study and did not affect outcome.[47] In contrast, longer rituximab exposure times achieved by greater intervals between eight applications of rituximab resulted in a better PFS and OS in elderly patients with high-risk DLBCL in the SMARTE-R-CHOP-14 study in a similar population.[48] The importance of rituximab exposure time is also supported by the results of two studies on maintenance treatment.[49,50] While young female patients (with their faster rituximab clearance) benefitted somewhat more from rituximab maintenance treatment after high-dose chemotherapy and stem cell transplantation, in the randomized CORAL study of patients with DLBCL after high-dose chemotherapy rituximab maintenance improved only the outcome of male patients in two randomized studies of first-line treatment in older patients with DLBCL.[49,50]

If a minimum rituximab exposure time is crucial for its efficacy in DLBCL, this would also explain why CHOP-14 was superior to CHOP-21 in the NHL-B2 trial of the DSHNHL,[43] while there were no outcome differences between these two CHOP schedules when they were combined with rituximab[51,52]: the advantages of the more efficacious chemotherapy regimen CHOP-14 could have been offset by the shorter rituximab exposure time when chemotherapy and rituximab application are synchronized (last rituximab

application in 8 × R-CHOP-21 day 148, 6 × CHOP-14: day 71). Finally, increasing the dose of rituximab by one-third to 500 mg/mm^2 in elderly male patients compared with 375 mg/m^2 in female patients resulted in slightly higher serum levels, but significantly longer rituximab exposure times in male patients. This was associated with a better PFS and OS for male patients compared with female patients in the SEXIE-R-CHOP-14 study[53] and reversed the sex hazard observed in the RICOVER-60 study where male and female patients had received identical rituximab treatment and schedules. The ability of sex-specific adaptation of rituximab treatment to improve the outcome of elderly male patients with DLBCL is also suggested by the results of a planned historic comparison of the outcome of elderly male patients in the RICOVER-60 study, where they had received eight applications with 375 mg/m^2, and the SEXIE-R-CHOP-14 study (500 mg/m^2) in combination with CHOP-14: the increased dose for male patients resulted in a significantly better PFS ($p = 0.04$) with a strong trend in OS ($p = 0.07$).

The fact that rituximab treatment strategies are influenced by more than pharmacokinetics is demonstrated by the observation that the efficacy of rituximab is compromised by low vitamin D serum levels,[54] likely because of a decreased rituximab-dependent cellular cytotoxicity, the major effector mechanism of rituximab. The rituximab-dependent cellular cytotoxicity against DLBCL cell lines can be improved by substituting otherwise healthy controls with vitamin D deficiency with vitamin D to optimal levels in the midnormal range of 65 ng/mL; however, although this addition of vitamin improves the rituximab-mediated cellular cytotoxicity by vitamin D substitution in female patients significantly, it has only minor beneficial effects in male patients (unpublished observations).

CONCLUSION

Despite the recently increased interest in age and sex issues in lymphomas, our respective knowledge is still rather limited. Although large prospective and epidemiologic studies have shown that age is always, and male sex is nearly always, an indicator for worse survival, the underlying reasons are not well understood. That female hormonal status plays a role is suggested by the observation that male children fare better than female children and that the female advantage grows until menopause and then declines again.[20] However, this does not preclude a role of female lifestyle and attitude to health. We are only about to begin to learn about sex-specific pharmacokinetics and their influence on outcomes, and we know even less about sex-specific differences in lymphoma biology. We have similar knowledge deficits with respect to age-specific differences in lymphoma biology. In clinical research, we need sex-specific information with respect to planned and received doses and dose intensities for individual drugs correlated to the reports of sex-specific outcome. In translational research, age and sex-specific investigations of cytogenetics, whole-genome sequencing, and systems biology approaches as pursued in a recent study[26] should enable us to better master the challenges of personalized medicine, which starts with the most obvious personal items of age and sex.

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Current Approaches to Mantle Cell Lymphoma: Diagnosis, Prognosis, and Therapies

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OVERVIEW

Mantle cell lymphoma (MCL) is a unique lymphoma subtype, both biologically and clinically. Virtually all cases are characterized by a common genetic lesion, t(11;14), resulting in overexpression of cyclin D1. The clinical course is moderately aggressive, and the disease is considered incurable. Considerable biologic and clinical heterogeneity exists, with some patients experiencing a rapidly progressive course, while others have disease that is readily managed. New tools exist for risk stratification and may allow for a more personalized approach in the future. Landmark studies have been completed in recent years and outcomes appear to be improving. Randomized clinical trials have clarified the role of high-dose cytarabine (Ara-C) for younger patients and have demonstrated a role for maintenance rituximab therapy. Multiple areas of uncertainty remain, however, and are the focus of ongoing research. This review focuses on (1) strategies to differentiate between aggressive and less aggressive cases, (2) understanding who should receive hematopoietic stem cell transplantation, and (3) the role for maintenance therapy in MCL.

MCL comprises less than 10% of all cases of non-Hodgkin lymphoma and has heterogeneous clinical behavior ranging from indolent to very aggressive. The disease is characterized by the presence of t(11;14) and frequently presents at an advanced stage with a male predominance and median age of 64.[1] There is currently no standard of care for patients with newly diagnosed MCL, although many fit patients are considered for intensive, Ara-C–containing, induction therapy followed by autologous stem cell transplantation (ASCT). This approach has resulted in a median time to treatment failure of up to 9 years in studies such as the recently reported MCL Younger study, and similar impressive results have been reported in other studies incorporating Ara-C–containing induction regimens with ASCT.[2-5] In addition, currently available novel therapies and those still under investigation have markedly improved outcomes for patients with relapsed disease, resulting in prolonged overall survival (OS) for most patients with MCL, including those who cannot undergo ASCT in first remission.[6-11] However, despite recent advances, most patients with MCL will ultimately die of their disease, and very few patients are cured outside of an allogeneic stem cell transplant (alloSCT).[12] This review summarizes the currently available data regarding identification of indolent compared with aggressive disease, the role of ASCT in first remission, and the appropriate scenarios in which to use maintenance therapies.

DIFFERENTIATING BETWEEN AGGRESSIVE AND LESS AGGRESSIVE MCL

Risk Stratification in MCL

Identification of low-risk disease and consideration of a watchful waiting approach. Although most patients with MCL will initiate therapy at the time of diagnosis, a subset of patients with indolent disease can be safely observed (Fig. 1). Martin et al first described a cohort of deferred patients at Cornell, where 31 patients who delayed treatment of at least 3 months could be safely monitored for a median of 12 months (range, 4-128 months) without a negative impact on OS.[13] In this series, patients with a good performance status and low International Prognostic Index (IPI) score were more likely to receive deferred therapy.

Similar series have been presented in abstracts from British Columbia (74 patients), Memorial Sloan Kettering Cancer Center (91 patients), and an Emory University–led multicenter cohort (71 patients) describing patients deferring therapy for at least 3 months.[14-16] In these series, 17% to 29% of patients have pursued deferred therapy with a median time to treatment of 8–35.6 months. Consistent predictors of deferred therapy include good performance status, lack of B-symptoms, and normal lactate dehydrogenase (LDH). Additional pathologic factors including Ki67 less than 30% and lack of blastoid morphology have been associated with deferred therapy in some series. Finally, patients with early-stage disease and those with a leukemic

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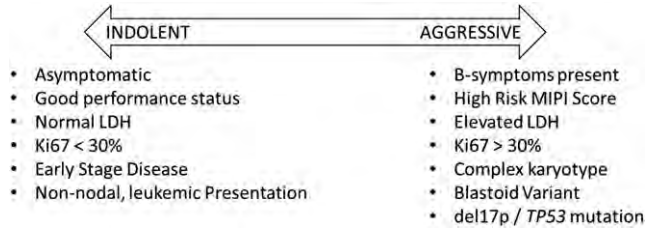
FIGURE 1. Predictors of Indolent Versus Aggressive Disease Behavior for Patients With Newly Diagnosed Mantle Cell Lymphoma



Abbreviations: MIPI, Mantle Cell Lymphoma International Prognostic Index; LDH, lactate dehydrogenase.

presentation (i.e., non-nodal with disease primarily limited to the peripheral blood) are also more likely to be observed.[17] Interestingly, the MCL IPI (MIPI) has not been associated with selection of deferred therapy in any of the previously reported series, suggesting that this index may not adequately identify the subset of patients with indolent disease who are candidates for this approach. Patients with high-risk MIPI have been safely observed in all previously reported series.

A national cohort analysis from the National Cancer Database has also evaluated the role of deferred therapy throughout the United States.[18] In this series, 492 of 8,029 (6%) patients received deferred therapy with a median time to treatment of 121 days (range, 91–1,152), and deferred therapy was associated with an improved OS (hazard ratio [HR] 0.79;) in this larger cohort. In a multivariable model, lack of B-symptoms was the strongest variable associated with receipt of deferred therapy, while extranodal presentation, Hispanic race, and residence outside of the Midwest or Southern regions were also associated with deferred therapy.

In the absence of randomized, prospective studies evaluating the role of deferred therapy, it appears that patients without symptoms, with low tumor burden, and without high-risk pathologic features can be safely observed, often for several years. In addition to the clinical and pathologic features mentioned above, SOX11 expression by immunohistochemistry (IHC) has been evaluated for its potential to identify low-risk, indolent cases. In a review of SOX11 IHC expression from the Nordic group for patients enrolled on the Nordic MCL 2 and 3 protocols, the high-expression group had a 10-year OS of 69% and patients with SOX11^{HIGH} disease had improved OS in a multivariable model.[19] A population-based series of 173 cases included 160 patients with SOX11 expression by IHC, and the median OS was 3.2 years for patients with SOX11-positive disease compared with 1.5 years for those with SOX11-negative disease.[20] However, additional series have suggested that patients with SOX11-negative disease may in fact be predisposed to a leukemic, non-nodal presentation and indolent disease behavior, and this is reflected in the updated World Health Organization criteria, which identify leukemic, non-nodal MCL as a distinct entity that is SOX11-negative.[21] Although its use in the right clinical scenario can provide useful prognostic information, SOX11 expression alone should not be used to identify indolent compared with aggressive disease without considering the clinical situation in a particular patient.

Prospective identification of high-risk patients and aggressive disease. Early identification of high-risk patients may allow providers to pursue alternative therapies and consider enrollment on clinical trials. Current approaches to identification of high-risk patients include MIPI risk score, Ki67 proliferative index, cytogenetics/fluorescent in situ hybridization, identification of genomic aberrations, and/or evaluation of gene expression profiling. Unfortunately, outcomes for patients with identified high-risk features remain poor, even with currently available Ara-C–containing induction, consolidation, and maintenance approaches.[22,23]

Although patients with low- and intermediate-risk MIPI scores have improved outcomes with currently available therapies, patients with high-risk MIPI scores enrolled in the European MCL Younger and MCL Elderly studies had a median OS of less than 3 years in a pooled analysis, and the median OS for high-risk patients in the MCL Younger cohort alone was only 3.8 years (Table 1).[22] The median OS rates for the low- and intermediate-risk subsets were not reached in either study. The impact of MIPI has also been evaluated for the Nordic MCL2 study, in which the low-risk patients have a median OS not reached after 15 years of follow-up, the intermediate-risk patients have a median OS of 11 years, and the high-risk patients have a median OS of 4 years.[24] Similar findings have been described by Damon et al with CALGB 59909, in which 67% of patients with high risk MIPI died within the median follow-up of 4.7 years.[5]

KEY POINTS

- **The MIPI integrates four clinical parameters with the Ki-67 proliferation index to identify patients with low- and high-risk disease.**
- **The best outcomes for younger patients with MCL have been achieved by incorporating high-dose Ara-C into induction therapy, followed by ASCT.**
- **AlloSCT strategies are most appropriate in the relapsed MCL setting.**
- **In older patients with MCL, maintenance rituximab has proven benefit after R-CHOP induction therapy, but its role after BR is controversial.**
- **In younger patients with MCL, maintenance rituximab administered after ASCT improves OS.**

Ki67 proliferative index and pretreatment cytogenetic assessments have been evaluated alone and in combination with MIPI to better define high-risk subgroups. Work by Katzenberger et al and Hsi et al identified Ki67 as a marker of disease activity although the optimal cutoff for high- versus low-risk disease was not described.[28,29] In recent years, 30% positivity has been frequently accepted as a cutoff for high- compared with low- Ki67 expression.[30,31] Hoster and colleagues have evaluated the role of Ki67 in conjunction with MIPI in patients treated on the MCL Younger and MCL Elderly studies and identified a significantly worse 5-year OS of 41% for patients with Ki67 30% or greater when compared with patients with Ki67 less than 30%, whose 5-year OS was 73% to 75%.[32] The impact of Ki67 was independent of MIPI risk score, and in a new model (MIPI-c) combining Ki67 and MIPI, patients were divided into four groups ranging from low risk (5-year OS: 85%) to high risk (5-year OS: 17%). In this analysis, blastoid growth identified pathologically was not prognostic for OS or progression-free survival (PFS) when Ki67 was included in a multivariable model.

Pretreatment cytogenetics has been used frequently in many hematologic malignancies to aid in risk stratification and therapy selection. In MCL, initial descriptions of outcomes for patients with a complex karyotype suggested inferior survival.[33,34] A single-center study conducted at The Ohio State University of 80 patients with untreated MCL found that 32 patients (41% of the cohort) had a complex karyotype (defined as ≥ 3 chromosomal abnormalities) identified in involved bone marrow samples.[35] Patients with a complex karyotype in this series were more likely to have an elevated leukocyte count, increased LDH, splenomegaly, and be high-risk by MIPI. Two-year OS for the complex karyotype group was 58% compared with 85% for the noncomplex group. However, in this analysis, the presence of a complex karyotype was not predictive of OS independent of MIPI and other clinical variables. Sarkozy et al evaluated the role of cytogenetics in a series of 125 patients from France, where nodal tissue, bone marrow, or peripheral blood were used for cytogenetic evaluation.[36] Fifty-nine percent of patients had a complex karyotype, and these patients were more likely to have a shortened time to initial therapy and an inferior OS in a multivariable model (HR 2.37); independent of high-risk MIPI score. This series also evaluated the prognostic impact of specific cytogenetic abnormalities, but none of the identified recurrent abnormalities were independently associated with OS. A larger cohort of patients with MCL from five centers evaluated the role of cytogenetics in untreated MCL and confirmed an association of a complex karyotype with inferior OS (median 4.5 years vs. 11.6 years for noncomplex karyotype;). A multivariable model for OS confirmed that complex karyotype and elevated LDH were independently associated with decreased OS, while MIPI risk group was not.[37]

Attempts to integrate prognostic markers into more comprehensive models have been challenging. Hoster and colleagues have combined Ki67 with MIPI to form the biologic MIPI (MIPI-b) and the MIPI-c.[32] However, additional pathologic features in this series, such as blastoid variant histology, were not independently associated with outcome. Staton et al presented the results of a multicenter analysis of 92 patients with untreated MCL who had pretreatment Ki67, MIPI, and cytogenetics reports available for review.[23] Within this series, a multivariable model indicated that Ki67 greater than 30% and complex karyotype were both independently associated with inferior PFS, while MIPI risk score was not. As a result, assessing the relative contribution of each described prognostic marker remains elusive, and many current projects are limited by modest sample sizes and heterogeneously treated patient populations. However, a number of currently available prognostic markers reliably identify high-risk patients, many of whom do not respond optimally to currently available therapy, and these patients should be considered for investigational therapies when available.

Novel approaches to risk stratification. Currently available approaches to identification of high-risk patients adequately identify patients at risk for early progression, but alternative methods are needed to better understand the biology of high-risk disease and to aid in the development of targeted therapies. Next-generation sequencing and assessment of gene expression offers the potential benefit of more specific identification of risk factors and potential therapeutic targets. Several projects have identified recurrent mutations in MCL, including *ATM, CCND1, MLL2, WHSC1, TP53, NOTCH1*, and others that occur at a lower frequency.[38,39] In two larger series that included 56[38] and 29[39] patients, there were limited clinical data associated with the presence of the mutations. However, additional projects have identified specific mutations or alterations associated with high-risk disease behavior, including *NOTCH1*,[40] *CDKN2A*,[41] and *TP53*.[41]

Prior attempts to characterize a proliferative signature in MCL through gene expression profiling have also successfully identified high- versus low-risk patients.[42] However, this

TABLE 1. Estimated Survival for Patients With MCL Based on MIPI Risk Group

Study	No. of Patients	Low Risk	Intermediate Risk	High Risk
Hoster et al, 2008[25]	409	5-year OS: 60%	Median 51 months	Median 29 months
Hoster et al, 2014[22]	958	5-year OS: 83%	5-year OS: 63%	5-year OS: 34%
Budde et al, 2011[26]	118	2.5-year OS: 93%	2.5-year OS: 60%	2.5-year OS: 32%
Eskelund et al, 2016[24]	157	Median NR	Median 11 years	Median 4 years
Chihara et al, 2015[27]	501	5-year OS: 74%	5-year OS: 70%	5-year OS: 35%

Abbreviation: MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; NR, not reached.

assay historically required fresh tissue, making its use limited to centers equipped to perform these analyses in real time. As a result, assessment of proliferation by Ki67 has been used as a surrogate. In recent years, investigators with the Lymphoma/Leukemia Molecular Profiling Project have reliably assessed gene expression using extracted RNA from formalin-fixed, paraffin-embedded archival tissue to identify cell-of-origin in diffuse large B-cell lymphoma.[43] Using this same technology, Scott and colleagues developed a 35-gene panel to identify three risk groups of patients with MCL, where high-risk patients have a median OS of 1.1 years and low-risk patients have a median OS of 8.6 years.[44] This association remained significant ($p < .05$) when controlling for Ki67 proliferative index as well as MIPI risk score. This assay is prognostic but does not currently guide therapy selection. However, the ability to perform genomic assessments on preserved tissues may provide physicians with better tools to use when counseling patients and selecting therapies in the future.

UNDERSTANDING WHO SHOULD RECEIVE A HEMATOPOIETIC CELL TRANSPLANT FOR MCL

Patients requiring therapy are evaluated based on their ability to tolerate a stem cell transplant as most guidelines include an up-front ASCT as part of therapy.[45] Besides biologic factors about the disease, the patient must be physiologically fit for high-dose therapy, ASCT, and possible complications associated with the conditioning regimen. Institutional limits to a minimum cardiovascular function, pulmonary reserve, and renal function are required for this procedure, and physiologic age and comorbidity index are increasingly being used to determine eligibility for transplant.[46] The source of stem cells is another important factor in determining eligibility of transplantation. For ASCT, it requires the patient's bone marrow is healthy enough for mobilization of stem cells, and for alloSCT, there needs to be a suitable donor (i.e., sibling, matched unrelated donor, cord blood, or a haplo-identical donor).

Up-Front Therapies Including ASCT

Initial attempts to treat MCL with regimens similar to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) produced inadequate results with most patients relapsing within 2 to 3 years.[47,48] Improved responses were noted when rituximab was combined with various chemotherapy regimens including fludarabine, cyclophosphamide, and rituximab (FCR)[49] and CHOP[50] without significantly affecting time to treatment failure or OS. Following this, multiple aggressive approaches were developed to improve the outcome of younger patients with MCL as listed in Table 2. These studies typically exclude elderly frail patients most include patients with stage II to IV MCL who are considered transplant eligible. ASCT is performed only in patients with chemotherapy-sensitive disease.

One approach pioneered at The University of Texas MD Anderson Cancer Center consisted of alternating cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone with high-dose Arc-C and methotrexate (hyper-CVAD) and produced a response rate of 93% in previously untreated patients.[58] Responding patients were taken to ASCT and experienced an impressive 3-year OS of 92% and event-free survival (EFS) of 72%. However, significant toxicity was noted. A phase II study of 97 patients treated with four cycles of rituximab and hyper-CVAD (R-hyper-CVAD) without ASCT resulted in a 3-year OS of 82%, with 64% of patients still in remission.[51] A 15-year follow-up of this patient cohort shows that the median failure-free survival is 4.8 years and median OS is 10 years, with a plateau for FFS at 10 years. Toxicity consisted of myelodysplastic syndrome/acute myeloid leukemia of 6.2% at 10 years.[59] Gruppo Italiano Studio Linfomi and Southwest Oncology Group have evaluated this regimen in a multicenter setting but found the toxicity to be too high even though outcomes were promising.[52,53]

Major groups in Europe have developed approaches to incorporate ASCT in up-front therapy. Dexamethasone, cisplatin, and high-dose Ara-C (DHAP) and then R-DHAP was added to CHOP/R-CHOP–based regimens to improve up-front response rates so that more patients could move to ASCT.[3,60] A randomized trial between up-front ASCT after induction compared with interferon (IFN)-alpha confirmed higher response rates after ASCT and an improved EFS of 39 months compared with 17 months with IFN.[54] Effect on OS was not demonstrated with the short follow-up. A dose-intensified Maxi-CHOP regimen with rituximab and high-dose Ara-C followed by ASCT[55] (Nordic 2) has reported the best outcome to date with a median OS of 12.7 and PFS of 8.2 years.[55] The European MCL Network (MCL Younger) has shown that the use of high-dose Ara-C in the up-front treatment of MCL with ASCT results in deeper remissions as indicated by negative minimal residual disease (MRD) status by nested polymerase chain reaction as well as increased PFS.[2] In this study, 497 patients were randomly assigned to differing induction arms and ASCT where the experimental arm contained higher doses of Ara-C (14 mg/m^2 compared with 800 mg/m^2) as part of DHAP as well as the conditioning regimen of ASCT. Complete responses (CRs) were higher in the Ara-C group (95% vs. 55%), but the objective response rate (ORR) was the same after ASCT in both arms. MRD negativity after induction was higher in the Ara-C group (79% vs. 47%) in the peripheral blood, and this difference was maintained in the bone marrow even after ASCT. At a median follow-up of 6.1 years, time to treatment failure was 9.1 years in the Ara-C group compared with 3.9 years, and OS was 76% at 5 years compared with 69% in the control group. The toxicity of multiagent chemotherapy has prompted investigators to evaluate other regimens that can still incorporate high-dose Ara-C. Armand et al[57] evaluated 23 patients with MCL with three cycles of bendamustine plus rituximab (BR) followed by three cycles of high-dose Ara-C and rituximab followed by ASCT. Follow-up is short but the results are promising, as MRD-negative status was reached in 96% of cases after induction. Similarly, the LyMa trial is evaluating four cycles of R-DHAP prior to ASCT, reserving R-CHOP therapy only for patients who have a partial response to R-DHAP.[56] Upcoming

TABLE 2. Studies of Aggressive Induction Regimens Including ASCT

Treatment Regimen	Reference	No. of Patients	Planned Consolidation ASCT	Median Follow-up	CR	Median OS	Median DFS	TRM	Comments
R-CHOP vs. CHOP	Lenz et al, 2005[50]	122	Yes, for younger patients		34% vs. 7%	TTF 21 months vs. 14 months; NS	No diff. in OS and PFS		Rituximab improved initial response rates
R-hyper-CVAD with alternating MTX/Ara-C 6-8 cycles	Romaguera et al, 2005[51]	97	No	15 years	87	82%; median OS is 4.8 years	64%; median FFS 8.8 years	5 died of toxicity; 4 developed MDS/AML; TRM 8%	EFS was 73% if < age 65
R-hyper-CVAD x 4	Merli et al, 2012[52]	60	Yes, only if PR	46 months	72	Median OS 73% at 5 years	5-year PFS 61%	Only 22% completed 4 cycles; 3 patients died; TRM 6.5%	
R-hyper-CVAD x 8	Bernstein et al, 2013[53]	49	No	4.8 years	55	6.8 years, 86%	Median PFS 4.8 years; 5.5 years if < age 55	39% did not complete due to toxicity; TRM 2%	Too toxic
CHOP + R x 3 + R-DHAP x 3 (multicenter)	Delarue et al, 2013[3]	60	Yes, in responding patients; TBI-based or BEAM	67 months	96; CR 12% after R-CHOP; 57% after R-DHAP	5 years, 75%	Median EFS 83 months; 5-year OS 75%	1.5%; secondary tumors 18%	Addition of rituximab improved EFS
CHOP or CHOP + R	Dreyling et al, 2005[54]	122	Up-front randomization of IFN-alpha or ASCT; TBI based		After R-CHOP 35%; after ASCT 81%	83% at 3 years vs. 77%	PFS: 39 months for ASCT vs. 17 months for IFN	0	Randomized trial that showed the efficacy of up-front ASCT for MCL
R-Maxi CHOP + HD Ara-C	Geisler et al, 2012[55]	160	ASCT; BEAM/BEAC	6.5 years		Median OS 10 years	Median EFS 7.4 years	Late relapses after 5 years	MRD evaluation and preemptive rituximab therapy offered to eligible patients
R-CHOP x 6 + DexaBEAM + ASCT (TBI + Ara-C + Mel)	Hermine et al, 2016[2]	497	Yes	6.1 years	95% in Ara-C vs. 55%	5 yr. OS 76% in Ara-C group vs. 69%	TTF 9.1 years in Ara-C group vs. 3.9 years	4%	MRD negativity after induction was higher in the Ara-C group 79% vs. 47%; MRD negativity strongest prognostic factor
R-DHAP x 4 +ASCT maintenance rituximab vs. observation after transplant	Le Gouill et al, 2016[56]	299	Yes; if CR, ASCT; PR, R-CHOP x 4 ASCT	29.3 months		3 years 83%; no difference in 2 arms	3-year PFS 74%; 2-year EFS 93% in maintenance arm vs. 81%		Omission of anthracycline; rituximab maintenance improves EFS and OS

Continued

TABLE 2. Studies of Aggressive Induction Regimens Including ASCT (Cont'd)

Treatment Regimen	Reference	No. of Patients	Planned Consolidation ASCT	Median Follow-up	CR	Median OS	Median DFS	TRM	Comments
R + bendamustine x 3 + R-HiDAC	Armand et al, 2016[57]	23	Yes	13 months	CR 96% with induction; 93% MRD negative		PFS 96%		Novel up-front regimen

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; OS, overall survival; DFS, disease-free survival; TRM, treatment-related mortality; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TTF, time to treatment failure; NS, not significant; PFS, progression-free survival; R-Hyper-CVAD, rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MTX, methotrexate; Ara-C, cytarabine; FFS, failure-free survival; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; EFS, event-free survival; PR, partial response; TBI, total body irradiation; BEAM, carmustine, etoposide, cytarabine, and melphalan; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; IFN, interferon; HD, high dose; MCL, mantle cell lymphoma; BEAC, carmustine, etoposide, cytarabine, and cyclophosphamide; MRD, minimal residual disease; Dexa, dexamethasone; Mel, melphalan; R-HiDAC, rituximab and high-dose cytarabine.

trials are likely to incorporate more targeted agents, such as ibrutinib, in the up-front regimens challenging the paradigms listed above.

There is no consensus on conditioning regimens for ASCT. Earlier studies used total body irradiation (TBI)–based regimens and a benefit in MCL was suggested by a retrospective analysis (PFS after 4 years: 71% vs. 0%, p < .0001; OS 89% vs. 60%, p = .07)[61] with some indication that it may lead to improve outcomes, but this approach has been associated with an increased incidence of second malignancies and other toxicities, and the field has moved away from it. Single agents ^{90}Y-ibritumomab-tiuxetan and ^{131}I- tositumumab have shown activity both in up-front therapy of MCL and in relapsed MCL and are an attractive means of delivering radiation to the malignant cells without the toxicity of radiation therapy.[62,63] Both agents had been safely combined with high-dose chemotherapy as conditioning for ASCT with no increased toxicity.[64,65] In the Nordic MCL-3,[66] ^{90}Y-ibritumomab-tiuxetan was used in an attempt to overcome the inherent chemotherapy resistance of a suboptimal response to up-front chemoimmunotherapy treated on the MCL-2 regimen. The ORR was 97%, and 4-year OS and PFS was 78% and 71%, respectively, similar to patients in the Nordic MCL-2 group. Use of ^{90}Y-ibritumomab-tiuxetan in patients as consolidation after hyper-CVAD has demonstrated unacceptable toxicity with 20% of the patients dying because of second malignancies.[67]

Predictors of response after ASCT. Despite high response rates, the approaches described above are challenging and there is significant risk of toxicity and second malignancies. In addition, 10% to 30% of patients undergoing aggressive induction never make it to ASCT either because of chemotherapy resistance or complications such as infections or cardiac events. A careful evaluation of some of the larger series has pointed to a few prognostic factors that can be used to predict outcomes particularly after ASCT, including MIPI/MIPI-b, MRD status, and PET scan response prior to transplant. The Nordic 2 trial demonstrated that the MIPI-b was a prognostic factor with 70% of low intermediate patients alive at 10 years compared with only 23% with a high MIPI-b.[55] In the MCL-3 trial, a positive PET before transplant as well as MRD-positive status predicted for a poor outcome.[66] Pott et al[68] reported on 27 patients post-ASCT who underwent MRD evaluation. Median PFS was 92 months if MRD-negative compared with 21 months in patients with MRD-positive disease. This was further confirmed in the larger European MCL Network study where 56% of patients achieved MRD after initial chemoimmunotherapy, and this predicted for a prolonged response duration at 2 years: 94% if MRD-negative compared with 71% if MRD-positive. ASCT increased the proportion of MRD from 55% to 72%, and a sustained MRD negativity predicted for improved outcome at 2 years (100% vs. 65% for MRD-positive). Thus, patients with poor prognostic factors, including positive MRD after induction therapy, may benefit from alternative approaches for long-term outcome.

Relapsed Setting

ASCT in MCL is less effective when offered to patients in the relapsed disease with median PFS of 1 to 2 years. Outcomes of patients undergoing ASCT was better in first complete remission when compared with transplants performed later in the disease, even when chemotherapy sensitivity was demonstrated.[58,69,70] The use of radio-immunotherapy (RIT) in conditioning regimens may be a way to improve outcomes, and this approach has been reported.[64,71] In a nonrandomized trial of RIT-containing conditioning regimens compared with conventional regimens for patients with chemoresistant disease from a single institution, the use of RIT was associated with improvements in both PFS and OS following ASCT.

Allogeneic Stem Cell Transplant for MCL

In spite of improved outcomes seen in MCL with the above described approaches, nearly all patients with MCL will relapse. The median OS of patients who relapse after ASCT is reported at 19 months,[72] though this may change with the approval of newer targeted agents. AlloSCT remains an option for suitable patients and can lead to long-term remissions and potential cures. The use of an alloSCT in relapsed lymphoma elicits a graft-versus-lymphoma effect allowing for long-term remissions, albeit at a risk of graft-versus-host disease, infections, and organ dysfunction that can lead to a risk of transplant-related mortality. The use of a reduced intensity-conditioning regimen relies on graft-versus-lymphoma effect and reduced acute toxicity allowing its use in elderly and frail patients or in patients who have failed an earlier myeloablative ASCT.

Early case reports of alloSCT in MCL performed in the 1990s demonstrated long-term remission in patients with chemo-refractory disease.[73,74] Several centers have reported the outcome of patients with MCL undergoing alloSCT as listed in Table 3 over the past 15 years. There is variability in patient selection, conditioning regimens, and supportive measures. The longest follow-up is 5 years with reported PFS of approximately 30% and OS of up to 50% in some of the newer series. Of note, even patients with refractory disease prior to transplant can achieve long-term remission. Hamadani et al[75] reported a 5-year survival of 25% in patients with refractory disease; however, transplant-related mortality was one of the highest in this series. Magnusson et al[76] have reported that even patients with PET-positive disease could undergo salvage alloSCT. The 5-year disease-free survival and relapse rates after allogeneic hematopoietic cell transplantation were 34% and 25% for all patients and 40% and 33% for residual disease recipients, respectively, suggesting that active disease at the time of allograft does not preclude long-term remissions in advanced MCL. EBMT Registry data show that patients who relapsed more than 1 year after ASCT and had a salvage alloSCT had a better outcome with a 5-year OS of 60%.[77] There appears to be no difference between myeloablative and reduced intensity-conditioning regimens in terms of outcomes even though there are no studies of direct comparisons. The use of donor lymphocyte infusion to induce remissions in patients with relapsed disease after an alloSCT indicate that there is a graft-versus-lymphoma effect in MCL. The use of RIT with ^{90}Y-ibritumomab tiuxetan as part of reduced intensity-conditioning conditioning has been evaluated by Fred Hutchinson Cancer Research Center with no clear advantage to its use.

The use of alloSCT has been studied in first remission in comparison with ASCT as reported by Fenske et al,[83] and even though the 5-year relapse was lower in the alloSCT arm (15% vs. 32%, respectively), there was increased transplant-related mortality of 25% at 1 year after the alloSCT resulting in no difference in the 5-year PFS and OS of both arms. Evens et al used an intensive induction regimen of high-dose Ara-C and randomly assigned young patients to sibling alloSCT or ASCT, but only four patients completed the alloSCT.[85] A German group reported on alloSCT in first remission compared with the relapsed setting with no difference between the two arms, thus failing to demonstrate an advantage for an earlier alloSCT.[83] In the series from Cruz et al, there were 21 patients who had an alloSCT in first complete remission and showed a 5-year PFS and OS of 80% but with a transplant-related mortality of 19%.[80] Hence, at this time, it cannot be recommended that an alloSCT be performed in first complete remission except in clinical trials.

IS THERE A ROLE FOR MAINTENANCE THERAPY IN MCL?

Maintenance therapy with rituximab has been tested in a variety of settings, with most, but not all, studies indicating clinical benefit. Two randomized clinical trials have demonstrated an OS benefit when maintenance rituximab was used as part of initial management of MCL. Many areas of uncertainty remain, however, including the optimal rituximab dose and schedule and the impact of different induction strategies maintenance rituximab efficacy. For example, one study suggested no benefit for maintenance rituximab after a BR induction. This section will review the data around maintenance rituximab in MCL and consider other maintenance strategies that may find their way into practice.

Early Studies of Maintenance Rituximab in MCL

Given the significant durable PFS benefit, maintenance rituximab has demonstrated in follicular lymphoma, it was natural to speculate that maintenance rituximab might be beneficial in MCL.[86,87] MCL was considered an incurable entity with a relatively poor prognosis. Response rates to initial therapy were high, but remissions tended to be short lived. Finally, there was a paucity of good options for management in the relapsed setting. Hence, any strategy that could prolong remission was attractive. The first trial to evaluate maintenance rituximab formally came from the Swiss Group for Clinical Cancer Research.[88] Both untreated and previously treated patients were enrolled and assigned to receive four weekly doses of rituximab. Patients without progression were then randomly assigned to receive maintenance rituximab (four more doses over 8 months) or no further therapy. There was no obvious benefit for the maintenance rituximab using this strategy. The following year, the German Low-Grade Lymphoma Study Group published a study demonstrating a significant ($p = .049$) response duration benefit for maintenance rituximab in relapsed MCL.[89] The first study of maintenance rituximab focusing on the frontline setting came from the Wisconsin Oncology Network, who reported on a single-arm, phase II study evaluating maintenance rituximab for 2 years after a chemoimmunotherapy induction.[90] The 3-year PFS of 50% was substantially better than historical controls using R-CHOP–like induction therapy and strongly suggested a benefit for maintenance rituximab. Patients only achieving a partial remission to the induction did not appear to benefit from maintenance rituximab, suggesting a complete remission may be necessary for maintenance rituximab to provide additional benefit. No worrisome safety signals were noted. Long-term follow-up of this cohort revealed that 30% remained progression-free beyond 5 years, again suggesting a potential for long-term benefit after maintenance rituximab.[91] A follow-up study by the Wisconsin Oncology Network tested the use of maintenance rituximab for 5 years after a chemoimmunotherapy induction.[92] The patient population was similar to the previous trial: untreated MCL of any age, requiring therapy. In this follow-up study, the 3-year PFS was 63%, and 50% of patients remained progression-free after 5 years.[93] In fact, no relapses beyond 5 years have been observed in this cohort, again suggesting significant benefit for maintenance rituximab. However, 5 years of maintenance rituximab did appear to translate into more infectious complications,

TABLE 3. Series of Allogeneic Stem Cell Transplants in MCL

Study	No. of Patients	Sites	Disease Status	Prior ASCT	OS	PFS	TRM acGVHD chGVHD	Comments
Khouri et al, 2003[78]	18	Single center	89% chemo-sensitive	28%	3 years 85.5%	3-year EFS 82%	TRM 11%; chGVHD 36%	DLI induced remission in 1/3 relapses
Maris et al, 2004[79]	33	Single center		42%	2 years 64%	2 years 60%	2 years 24% acGVHD 57% chGVHD 64%	
Cruz et al, 2011[80]	21	Multicenter GELTAMO	71% CR, median 2 therapies	14%	5 years 80%	5 years 80%	3 years 19.5% acGVHD 15% chGVHD 78%	OS 43% in patients > age 60 vs. 100% in younger patients
Le Gouill et al, 2012[81]	70	Multicenter		67%	2 years 53%	2 years 50%	2 years 32% acGVHD 25% chGVHD 17%	Disease status at transplant significant for EFS/OS: CR, 62%, 62%; PR, 53%; SD/PD, 11%, 31%
Kruger et al, 2014[82]	33/39 planned	East German Study Group	First consolidation		5 years 73%	5 years 67%	TRM 24% acGVHD 15%	Younger patients had better outcome
Fenske et al, 2014[83]	88	CIBMTR			5 years 31%	5 years 24%	1 year 17%	
Hamadani et al, 2013[75]	128 RIC; 74 MA	Multicenter CIBMTR	Refractory		3 years 30%	3 years 25%	3 years 47% for both RIC and MA	T-cell depleted transplant associated with increased risk of NRM; no difference between MA or RIC
Cook et al, 2010[84]	70	Multicenter		34%	5 years 37%	5 years 14%	5 years 21% acGVHD 10% chGVHD 61%	DLI induced remission in 15/18 relapsed patients; age and < 2 regimens correlated with OS and PFS
Magnusson et al, 2014[76]	28				5 years 53%	5 years 34%	2 years 15%	Allograft had favorable results even if PET+ prior to transplant
Dietrich et al, 2014[72]	80	Multicenter EBMTR	All relapsed after ASCT		2 years 46%	2 years 33%	2 years 30%	Remission duration of > 12 months after ASCT was associated with a poor outcome

Abbreviations: MCL, mantle cell lymphoma; ASCT, autologous stem cell transplantation; PFS, progression-free survival; OS, overall survival; TRM, treatment-related mortality; acGVHD, acute cutaneous graft-versus-host disease; chGVHD, chronic graft-versus-host disease; EFS, event-free survival; DLI, donor lymphocyte infusion; CR, complete response; PR, partial response; SD, stable disease; PD, partial disease; CIBMTR, Center for International Blood and Marrow Transplant Research; RIC, reduced intensity conditioning; MA, myeloablative; NRM, nonrelapse mortality; EBMTR, European Bone Marrow Transplantation Registry.

with only 20% of the group able to complete all 5 years of the planned treatment. The Eastern Cooperative Oncology Group confirmed these promising results in E1405.[94] In this trial, after a moderately intensive induction strategy, patients could be assigned to either maintenance rituximab or ASCT at the investigators' discretion. Despite the fact that the patients assigned to maintenance rituximab were generally older with higher MIPI scores, maintenance rituximab performed as well as ASCT for PFS and OS. However, until 2012, the use of maintenance rituximab remained sporadic as definitive evidence of benefit was lacking.

Evidence supporting maintenance rituximab in older patients with MCL. The use of maintenance rituximab in MCL began to gain widespread acceptance with the landmark publication by the European MCL Consortium.[95] Patients with MCL age 60 and older were randomly assigned to six cycles of FCR or to eight cycles of R-CHOP. Responding patients underwent a second randomization to receive maintenance rituximab or IFN-alpha, each given until progression. Treatment until progression was a unique feature as all previous trials of maintenance rituximab in MCL had selected arbitrary stopping points of 8 months, 2 years, or 5 years. Analysis of the trial is complicated because of the use of two different induction strategies and the 2 × 2 factorial design. When combining the two induction arms and comparing maintenance rituximab to IFN-alpha, there was a significant ($p < .001$) improvement in remission duration, favoring maintenance rituximab with a 45% reduction in the risk of progression or death. At 4 years, 58% of the patients in the maintenance rituximab arm were still in remission, compared with 29% of those receiving IFN-alpha. When analyzing the impact of maintenance rituximab according to induction therapy received, one can see that the induction therapy matters. The remission duration benefit of maintenance rituximab was limited to the patient assigned to R-CHOP and was not apparent in patients

assigned to FCR. There is precedent for such a differential effect following induction. In E1496, a frontline follicular lymphoma trial, patients were randomly assigned to receive to cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy or FC chemotherapy, with patients whose disease did not progress being randomly assigned to maintenance rituximab for 2 years or observation. A substantial remission duration benefit was observed after CVP chemotherapy, but no benefit was seen after FC chemotherapy. Why maintenance rituximab would be beneficial after one type of induction therapy and not another is not precisely known. It is possible that the profoundly immunosuppressive effects of fludarabine-based therapy negate critical effector cell functions necessary for optimal rituximab effectiveness.

The impact of maintenance rituximab on the patients treated with R-CHOP was strong enough to translate into an OS benefit. Based on these striking results, maintenance rituximab gained rapid and widespread adoption in the frontline management of older patients with MCL. An important caveat, however, centers on current induction strategies and whether maintenance rituximab confers the same benefit irrespective of the induction. Two small randomized clinical trials have indicated that BR is a superior induction strategy compared with R-CHOP.[96,97] As a result, BR as the induction strategy has gained widespread adoption in North America and Europe. Whether maintenance rituximab still confers benefit in patients receiving BR induction was the subject of a recent analysis presented at the 2016 ASCO Annual Meeting.[98] The frontline StiL NHL7-2008 study in indolent lymphoma was conducted in Germany and Austria and included a subgroup of patients with MCL. These 168 patients were considered ineligible for high-dose therapy and their median age was 71. They received six cycles of BR induction therapy, and patients whose disease responded were randomly assigned to maintenance rituximab for 2 years or to observation. Just 122 patients ultimately were randomly assigned—60 to observation and 62 to maintenance. The median PFS was 54.7 months for observation compared with 72.3 months for maintenance, but this difference was not statistically different (HR 0.71; p = .223). These results are not yet published, but the presentation did garner significant attention and has caused many to question whether maintenance rituximab after BR induction is warranted.

Evidence supporting maintenance rituximab in younger patients with MCL. In general, outcomes with initial therapy are much better for younger patients with MCL than they are for older patients with MCL. Younger patients typically have lower-risk disease, as measured by the MIPI. They are also more suitable candidates for intensive induction strategies, which tend to produce more durable remissions. One would predict it would be more difficult to show benefit from any sort of maintenance strategy in this population. The first publication to suggest benefit for maintenance rituximab in young patients with MCL who received an intensive frontline treatment came from investigators at the Fred Hutchinson Cancer Research Center.[99] In this retrospective study, the investigators examined a cohort of consecutive patients with MCL that underwent ASCT for MCL and then evaluated outcomes according to whether the patient received maintenance rituximab after ASCT (50 patients) or did not (107 patients). The decision on whether to administer maintenance rituximab was made by the treating physician, and a variety of schedules were used. With a median follow-up of 5 years, maintenance rituximab was associated with an improved PFS (HR 0.44; p = .007) and OS (HR 0.46; p = .03). Grade 4 neutropenia was more common in the maintenance rituximab group (34% vs. 18%, respectively) but this did not translate into increased mortality. Although provocative, this retrospective analysis could not be viewed as definitive as there were some key differences in the two populations. Patients receiving maintenance rituximab were more likely to have received high-dose Ara-C during induction and more likely to be in CR at the time of ASCT. The investigators acknowledge that the strategy of maintenance rituximab after ASCT would require confirmation in a prospective randomized controlled trial.

Such confirmation was presented at the 2016 American Society of Hematology Meeting, where the final results of the LyMa trial (NCT00921414) were presented.[56] The trial was limited to patients with MCL age 65 and younger, and all patients received induction therapy with four cycles of R-DHAP followed by ASCT using rituximab, carmustine, etoposide, Ara-C, and melphalan (R-BEAM) conditioning. Randomization to maintenance rituximab, consisting of a single dose every 2 months for 3 years or to observation, occurred post-ASCT. The median age was 57, and over half of the patients were low risk by MIPI, which is typical for this patient population. Two hundred ninety-nine patients were enrolled, and 240 patients were randomly selected (120 in each arm). The primary endpoint was EFS with events defined as progression, death, or severe infection after randomization. The final analysis demonstrated that maintenance rituximab after ASCT significantly prolonged EFS (78.9% vs. 61.4%, respectively) at 4 years (HR = 0.46; p = .0016). Maintenance rituximab also prolonged OS at 4 years (88.7% vs. 81.4%, respectively; HR = 0.5; p = .045). There was no difference in the rate of severe infections between maintenance rituximab and observation. Given the OS advantage noted, these results strongly support the use of maintenance rituximab after ASCT in younger patients with MCL. Randomized clinical trials evaluating maintenance rituximab are summarized in Table 4.

Other Maintenance Strategies Under Investigation

Ongoing studies yet to be analyzed, but which could impact the standard of care, are summarized in Table 5. Lenalidomide has demonstrated single-agent activity in MCL and, for mechanistic reasons, has been combined with rituximab in both induction and maintenance strategies, with promising early results.[6,100] The U.S. Intergroup trial E1411 (NCT01415752) is focused on older patients with MCL and

TABLE 4. Randomized Trials of Maintenance Rituximab in MCL

Trial Group	No. of Patients	Population	Induction Regimen	Rituximab Versus	Rituximab Schedule	Outcome
SAKK[88]	104	Untreated or previously treated	Rituximab	Observation	Single dose every 2 months x 4	No difference
GLSG[89]	176	Previously treated	R-FCM or FCM	Observation	4 weekly doses at 3 and 9 months post-induction	PFS benefit, favoring MR
European MCL Network[95]	316	Older MCL and untreated	R-CHOP or FCR	Interferon-alpha	Single dose every 2 months until PD	PFS and OS benefit after R-CHOP, no benefit after FCR
StiL[98]	122	Older MCL and untreated	BR	Observation	Single dose every 2 months x 2 years	No difference
LYSA[56]	240	Younger MCL and untreated	R-DHAP + ASCT	Observation	Single dose every 2 months x 3 years	PFS and OS benefit for MR

Abbreviations: MCL, mantle cell lymphoma; SAKK, Swiss Group for Clinical Cancer Research; GLSG, German Low-Grade Lymphoma Study Group; R-FCM, rituximab, fludarabine, cyclophosphamide, and mitoxantrone; PFS, progression-free survival; MR, maintenance rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; FCR, fludarabine, cyclophosphamide, and rituximab; PD, partial disease; OS, overall survival; StiL, Study Group Indolent Lymphomas; BR, bendamustine and rituximab; LYSA, Lymphoma Study Association; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; ASCT, autologous stem cell transplantation.

is testing 2 years of single-agent rituximab against 2 years of rituximab plus lenalidomide. The primary endpoint is PFS. This trial completed enrollment in September of 2016 (372 patients) and is expected to read out for the primary endpoint in 2019. The Bruton tyrosine kinase inhibitor ibrutinib has impressive single-agent activity in MCL, and the SHINE trial (NCT01776840) has enrolled 520 older patients with MCL. Following induction therapy with BR or BR plus ibrutinib, patients receive either maintenance rituximab for 2 years or maintenance rituximab for 2 years plus ibrutinib administered indefinitely. The results of SHINE are expected in 2018 or 2019. Ibrutinib is also being tested in combination with intensive strategies as part of the European MCL Consortium TRIANGLE study (NCT02858258). This three-arm study will compare ASCT alone, ibrutinib maintenance alone, and ASCT plus ibrutinib maintenance. Finally, the U.S. Intergroup trial EA4151 will also compare maintenance rituximab with ASCT plus maintenance rituximab in patients who have achieved an MRD-negative CR to induction therapy. This trial is scheduled to begin enrollment in 2017.

CONCLUSION

Maintenance rituximab has been shown to improve OS in both older and younger patients with MCL. However, important questions remain regarding the optimal dose and schedule. Should maintenance be administered for 2 years, 3 years, or indefinitely? In addition, it remains unclear whether the induction strategy impacts the efficacy of maintenance. In the trial supporting maintenance rituximab in older patients, the benefit was seen only after R-CHOP induction. However, a small study evaluating maintenance rituximab for 2 years after a bendamustine-based induction did not find any benefit. More study of maintenance rituximab after BR induction is warranted so that remaining discrepancies can be resolved. Maintenance rituximab for 3 years after ASCT in younger patients with MCL was shown to favorably impact OS and represents a new standard of care. Ongoing trials in Europe (TRIANGLE) and in North America (EA4151) will test whether alternative maintenance strategies can replace ASCT or whether such strategies should be an adjunct to ASCT.

TABLE 5. Trials in Progress Testing Novel Maintenance Strategies in MCL

Trial Name	Population	Status	No. of Patients	Maintenance Question
E1411 (NCT01415752)	Older MCL; frontline regimen	Fully enrolled	372	Rituximab vs. rituximab + lenalidomide
SHINE (NCT01776840)	Older MCL; frontline regimen	Fully enrolled	520	Rituximab vs. rituximab + ibrutinib
TRIANGLE (NCT02858258)	Younger MCL; frontline regimen	Enrollment started 2016	870	ASCT vs. ASCT + ibrutinib vs. ibrutinib
EA4151 (NCT pending)	Younger MCL; frontline regimen	Enrollment to begin 2017	412	Rituximab vs. rituximab + ASCT in MRD negative first remission

Abbreviations: MCL, mantle cell lymphoma; ASCT, autologous stem cell transplantation; MRD, minimal residual disease.

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Health Disparities and the Global Landscape of Lymphoma Care Today

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OVERVIEW

Lymphoma encompass a wide variety of distinct disease entities, including, but not limited to, subtypes of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). In the last 3 decades, therapeutic advancements have resulted in substantial improvements in lymphoma outcome. In most high-income regions, HL is a largely curable disease and for patients with two frequent subtypes of NHL, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), survival has dramatically improved with the incorporation of rituximab as a standard treatment approach. Despite these advances, outcomes vary between and across populations. This review will provide updated information about health disparities in lymphoma in the United States and across the globe.

The World Health Organization (WHO) classification of lymphoid neoplasms continues to evolve, recognizing distinct entities that can be broadly characterized as not only NHL and HL, but also plasma cell neoplasm and lymphoid leukemia.[1] According to 2012 estimates, there were almost 566,000 new cases of lymphoma worldwide and about 305,000 deaths.[2] When the main entities (HL, NHL, and multiple myeloma) are examined separately, the incidences of the respective cancer types do not rank highly, yet in combination, lymphoma was the seventh most frequent cancer diagnosis in the world.[2]

Focusing on NHL and HL, the last several decades have seen a dramatic improvement in survival outcomes. New treatment options and supportive care measures have resulted in unprecedented rates of long-term cure for HL with less toxic treatment approaches.[3] For patients with two frequent subtypes of NHL, DLBCL and FL, survival has also substantially improved as a result of the incorporation of rituximab into standard treatment regimens.[4-6] Survival of patients with other subtypes of NHL (e.g., peripheral T-cell lymphoma [PTCL]) has not kept the same pace; however, a number of new agents are now available.[7,8] Despite these improvements, differences in lymphoma outcome within and between populations are observed.

The National Institute on Minority Health and Health Disparities defines health disparities as "differences in incidence, prevalence, morbidity, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups."[9] Race and gender are the most frequently studied health disparities that may impact outcomes for some cancers; however, other factors such as socioeconomic status (SES), access to and type of health insurance, distance to the health care facility, cultural factors, and health literacy have been found to be relevant as well.[10-13] Middle-income countries are also particularly prone to health disparities.[14] This review will summarize the global landscape of lymphoma and identify health disparities that have been investigated in subtypes of NHL and HL, primarily in U.S. populations.

GLOBAL BURDEN OF NON-HODGKIN AND HODGKIN LYMPHOMA

GLOBOCAN, a project of the International Agency for Research on Cancer, provides contemporary estimates of cancer incidence and mortality rates in each country of the world using different methods depending on accuracy and availability of data.[15] The 2012 estimates and 2035 projections that summarize the burden of NHL and HL worldwide are shown in Table 1. GLOBOCAN estimates that there were over 385,000 NHL and nearly 66,000 HL incident cases and nearly 200,000 NHL and over 25,000 HL deaths globally in 2012.[15] For NHL, new cases occurred equally in high- and middle- to lower-income regions; however, deaths occurred more frequently in middle- to lower-income countries (62%). In the same year for HL, the vast majority of new cases and deaths (56% and 75%, respectively) occurred in middle- to lower-income regions of the world. High-income regions include all regions in Europe, Northern America, Australia/New Zealand, and Japan. Middle- to lower-income regions include all regions of Africa, Asia (excluding Japan),

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TABLE 1. Estimated World Incidence and Mortality for NHL and HL, All Ages, and Both Sexes: GLOBOCAN 2012 Estimates and 2035 Projections[15]

	Incidence (2012)		Mortality (2012)		Incidence (2035)		Mortality (2035)	
	Number	Rate*	Number	Rate*	Number	% Increase	Number	% Increase
NHL	385,741	5.0	199,670	2.5	635,144	65%	344,099	72%
Higher income	190,403 (49%)	8.6	75,128 (38%)	2.7	-			
Lower income	195,338 (50%)	3.6	124,542 (62%)	2.3				
HL	65,950	0.9	25,469	0.3	88,390	34%	38,797	52%
Higher income	28,852 (44%)	2.1	6,293 (25%)	0.3				
Lower income	37,098 (56%)	0.6	19,176 (75%)	0.3				
Total	451,691	5.9	225,139	2.9	723,534	60%	382,896	70%

*Age-standardized rate per 100,000 person-years.
Abbreviations: NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma.
Adapted from Ferlay et al with permission from the publisher.[15]

Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia. Projections suggest that both incidence and mortality rates for NHL and HL will increase by 2035, possibly because of improved diagnostic techniques, industrialization, aging populations, and rising HIV infection in certain regions.[16,17]

Estimated worldwide age-standardized incidence and mortality rates for both NHL and HL are presented in Fig. 1.[15] NHL is more common in high-income regions, with the highest incidence rates found in Australia, Western and Northern Europe, and Northern America. Lower rates are found in Asia, Eastern Europe, and Africa, with the exception of certain areas where Burkitt lymphoma is endemic (Fig. 1A). East Asian countries such as South Korea and Singapore, which have experienced dramatic economic progress over the last three decades, have shown the largest increase in NHL in Asia.[18] Epidemiologic studies analyzing the distribution of NHL subtypes across the world are challenged by the evolving classification systems, coding, and ability to confirm diagnoses; however, substantial differences in the relative frequencies of NHL subtypes exist. Asian populations typically have higher proportions of mature natural killer (NK)/T-cell lymphomas and mucosa-associated lymphoid tissue lymphoma, and lower proportions of FL and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) than Western populations.[19,20] The higher proportions of mucosa-associated lymphoid tissue lymphoma in Asia and mature NK/T-cell neoplasms in the southeastern parts of Japan are attributed to the high prevalence of *Helicobacter pylori* and human T-lymphotropic virus 1 (HTLV-1), respectively. Although the disparity between East and West suggests the influence of ethnicity, the disparity between identical or similar ethnic populations residing in different regions indicates a possible environmental influence.[21] In a study of lymphoma in Asian populations living in the United States from the Surveillance, Epidemiology, and End Results (SEER) program conducted from 1988 to 2004, Clark et al reported that incidence rates of FL, CLL/SLL, and nodular sclerosis HL were significantly higher in U.S.-born Asian populations (second generation immigrants or beyond) compared with foreign-born Asian populations (first generation immigrants), supporting the role of environmental factors in lymphomagenesis.[22]

HL accounts for no more than 0.5% of the total cancer burden worldwide in 2012; however, its unusual biology, epidemiology, and positive response to treatment draws ample attention.[15] The overall incidence of HL varies greatly throughout the world (Fig. 1C) and the pathogenesis of this geographic discrepancy is not known; however, environmental and lifestyle factors have been theorized as potential factors. Unlike NHL, which shows an exponential increase in age-specific incidence, age-specific incidence rates of HL are bimodal, with the first peak occurring during ages 15 to 34 and the second after age 60 in European, American, Hispanic, and Australian populations.[23] In middle-income countries, the incidence of HL is characteristically high in early childhood and among the oldest age groups. Affluent standards of living during childhood have been associated with

KEY POINTS

- **Lymphoma is the seventh most frequent cancer diagnosis in the world, and there is substantial variation in epidemiologic trends for individual subtypes.**
- **Recent therapeutic advancements have improved our ability to treat patients with many lymphoma subtypes, particularly DLBCL and HL, which are now curable in many instances.**
- **In the United States, the characteristics, incidence rates, and survival rates for NHL and HL vary between racial groups.**
- **Although lymphoma is less commonly diagnosed among black populations, these populations fare worse than white populations for a number of lymphoma subtypes.**
- **Health disparities are complex associations between social, environmental, biologic, and patient-centered factors that may help explain differences in lymphoma outcomes in vulnerable patient populations.**

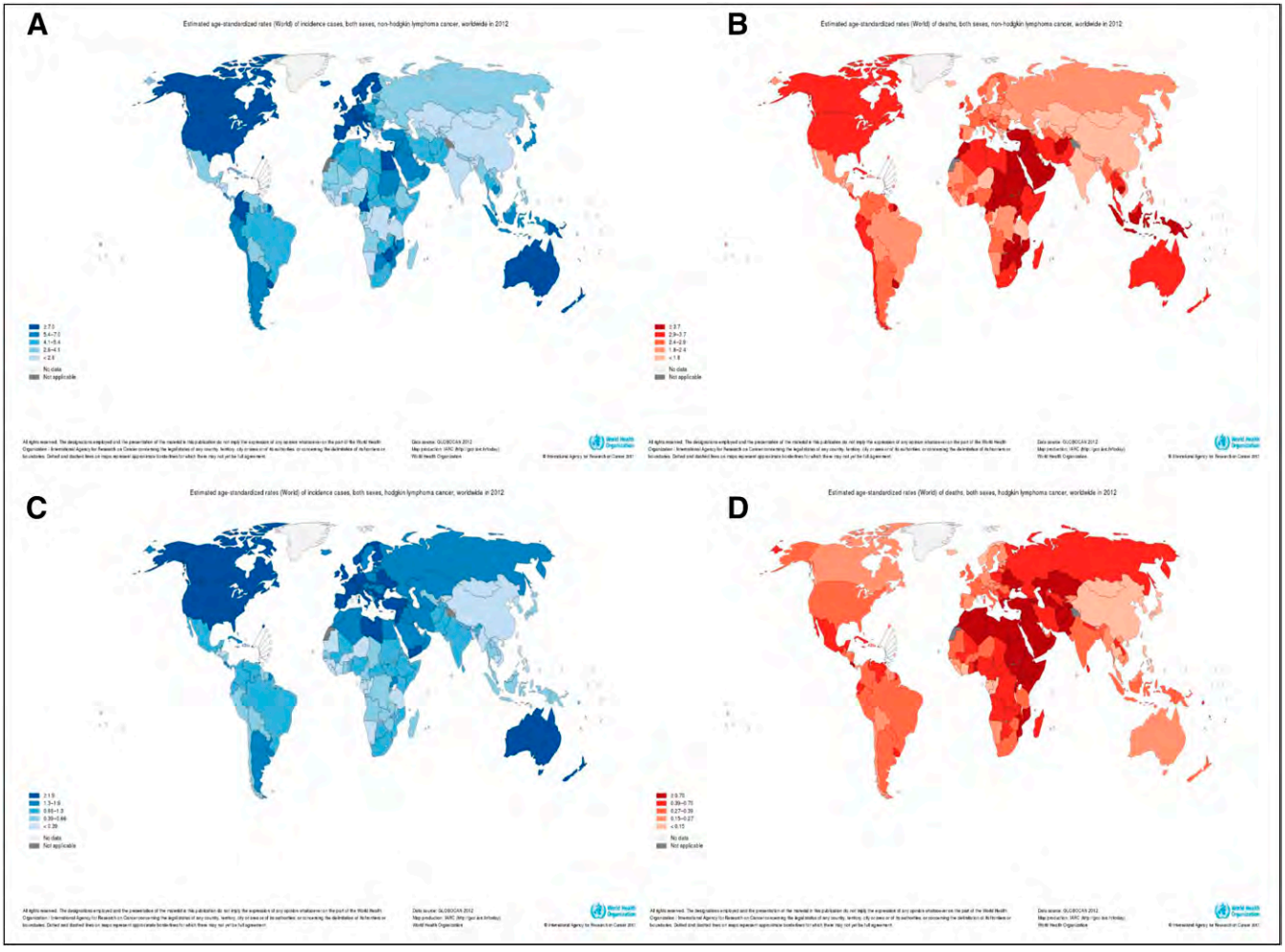
an increased risk of young-adult HL, suggesting a delayed exposure to a common infectious agent, whereas the opposite is true for children living in less favorable living conditions.[24] Therapeutic advancements, improved diagnostic ability, and health care access and management have made HL a largely curable disease in many areas of the world. Declines in mortality by more than 75% in North America, Western Europe, and Japan are reported.[6,25] Appreciable declines in HL mortality were also observed in most of Latin America, with the exception of Cuba, Costa Rica, Mexico, and Venezuela.[24,26]

U.S. LYMPHOMA TRENDS

In 2016, there were an expected 81,080 new cases of lymphoma diagnosed in the United States (8,500 cases of HL, 72,580 cases of NHL).[27] The 5-year relative survival rate for HL more than doubled from 40% in white patients from 1960 to 1963 (only data available) to 88.3% for all races between 2005 and 2011.[27] The 5-year relative survival rate is 94.1% for patients with HL who are younger than 45 at diagnosis.[27] The 5-year relative survival rate for NHL rose from 31% in white patients from 1960 to 1963 (only data available) to 71.9% for all races between 2005 and 2011.[27]

Incidence rates of NHL in the United States nearly doubled between 1970 and 1990, but have stabilized since the late 1990s.[28] NHL has been associated with broadly categorized immune-related conditions including immunodeficiency, autoimmune disease, infection, and allergy.[29-32] Although the incidence of NHL is somewhat lower among the black population compared with the white population, the black population has higher rates of extranodal NHL subtypes, PTCL and mycosis fungoides.[33] These disparities coupled with findings that associations between immune system–related gene polymorphisms and NHL vary by race have suggested that genetic predisposition may play a role in immune-related NHL.[34] In a study of over 4 million U.S. veterans, infection, autoimmune, and allergic conditions were all associated with increased risk of NHL.[35] The black population had a slightly higher risk of NHL associated with infections than the white population (likelihood ratio test p = .002), with a notable exception of risk associated with HIV, which was twofold higher in the white population.[35]

FIGURE 1. Estimated Age-Standardized Rates of Incidence Cases and Deaths of Non-Hodgkin Lymphoma (A and B) and Hodgkin Lymphoma (C and D), Both Sexes



Allergies also tended to be more strongly associated with risk of NHL in the black population than the white population (likelihood ratio test, p = .05), whereas risks associated with autoimmune conditions were similar by race (likelihood ratio test, p = .5).[35] The authors hypothesized that these patterns could reflect underlying genetic differences in immune response between racial groups.

DLBCL, FL, and CLL/SLL account for the majority of all NHL in the United States. In a SEER study of these three subtypes diagnosed between 1992 and 2010, racial differences in patient characteristics, incidence, and survival were detected.[36] The non-Hispanic white population had the highest incidence rates for all three subtypes, followed by the Hispanic white and black populations.[36] Overall, CLL/SLL had the highest age at diagnosis. For all three subtypes, however, age distribution was substantially different across races. For DLBCL, the non-Hispanic white population tended to be older than the other races.[36] For FL and CLL/SL, the non-Hispanic whites and Asian/Pacific Islander populations were older than the Hispanic white and black populations.[36] For DLBCL, the black population had the highest rate of extranodal involvement (70.52%), whereas for CLL/SLL, the Asian and Pacific Islander populations had the highest rate (92.22%).[36] For all three subtypes, the non-Hispanic white population had the highest 5-year relative survival rates, followed by the Hispanic white population. When stratified by stage, the racial difference was substantial.[36]

HEALTH DISPARITIES BY LYMPHOMA SUBTYPE

Diffuse Large B-Cell Lymphoma

DLBCL is the most common subtype of NHL in the world, accounting for approximately 30% to 40% of all newly diagnosed cases.[15] In the United States, there is a male predominance and incidence rates vary by ethnicity with the white population demonstrating higher rates than the black, Asians, American Indian, and Alaskan native populations, in decreasing order.[37] Without treatment, over 50% of patients with DLBCL survive less than 1 year; however, with the introduction of rituximab in approximately 2002, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)–based therapies increased the 5-year overall survival from approximately 45% with CHOP alone to 60% to 70%.[38] Clinical prognostic models have identified age, stage, extranodal sites, performance status, and serum lactate dehydrogenase as independentpredictors of clinical outcome with intensive chemotherapy and comprise the International Prognostic Index.[39,40]

Black patients with DLBCL have a risk of death that is 10% to 20% higher than the non-Hispanic white population in numerous studies, with survival differences persisting after the introduction of rituximab.[12,41-44] Wang et al studied 13,321 patients diagnosed with NHL between 1992 and 1999 in a linked SEER-Medicare dataset.[12] Although the black cohort was less likely to receive lymphoma therapy (odds ratio 0.68; 95% CI, 0.56–0.83) and had inferior all-cause mortality when compared with the white cohort, these differences were no longer significant after controlling for other factors and were best explained by differences in SES.[12] In that study, 72% of the black cohort was in the poorest quartile of SES compared with 22% of the white cohort.[12] The authors concluded that delayed therapy or SES (specifically poverty, education, and family income) partially explained their finding. In a retrospective analysis of a population-based dataset within the California cancer registry, Tao and colleagues considered the relationship between neighborhood SES and race/ethnicity.[45] In 33,032 patients diagnosed with DLBCL in California from 1988 to 2009, patients living in lower SES neighborhoods had increased risks of all-cause and lymphoma-specific death compared with patients in higher SES neighborhoods.[45] Neighborhood SES was determined using an index derived from principal components of seven indicator variables of SES (education level, proportion unemployed and with a blue collar job, proportion < 200% poverty line, and median household income, rent, and home value). Interestingly, the magnitude of disparity in survival associated with neighborhood SES was more pronounced in the modern era (post-rituximab adoption), in patients younger than age 65, and in patients who were married. In addition, uninsured and government-assisted insured patients experienced a 1.5-fold increased risk of death. Though notable disparities by race/ethnic groups existed, these differences were attenuated by neighborhood SES disparities.[45] Place of residence was also studied by the Nebraska Lymphoma Study Group, which found that rural patients with lymphoma treated by community-based providers had inferior overall survival compared with urban residents treated by university-based providers, urban residents treated by community-based providers, and rural residents treated by university-based providers.[46]

Other studies have described insurance-related disparities among younger patients with NHL; however, these studies lacked important confounders of survival such as performance/comorbidity score, HIV status, international prognostic index, and chemotherapy use.[47] Using the National Cancer Database to explore these insurance-related disparities, adjustment for these confounders resulted in an adjusted hazard ratio of 1.26 for patients who were uninsured and 1.52 for patients with Medicaid, indicating that insurance-related disparities are partly mediated by prevalence of known prognostic factors in DLBCL and/or by patients' pre-existing medical conditions that determine eligibility for specific health insurance.[48]

Biologic differences have also been investigated in DLBCL health disparities. Gene expression profiling has identified at least two biologically distinct and prognostically meaningful molecular subgroups of DLBCL. Germinal center B-cell type (GCB) resembles a normal germinal center B cell and has a superior 5-year survival rate with standard R-CHOP therapy, whereas activated B-cell type (ABC) resembles an activated B cell and has inferior 5-year survival rates following standard R-CHOP compared with GCB tumors.[49,50] Ethnic and racial differences in the frequency of ABC and GCB subtypes were identified in studies of patients with DLBCL

from Malaysia, Japan, Turkey, China, Germany, and North America.[51-54] A preliminary report of differences in GCB and ABC subtypes in the white and black populations, however, suggests there may not be the same effect on prognosis.[55]

Hematopoietic cell transplantation is a complex, highly specialized and resource-intensive procedure indicated for relapsed DLBCL and other types of lymphoma. In a retrospective study of 687 autologous stem cell transplant recipients with lymphoma, there was no significant impact of race on transplant outcomes; however, there was an association between SES and outcomes. Patients from areas of low median income had lower overall survival after autologous stem cell transplant compared with those of high median income, including patients who had survived without evidence of disease progression for 1 year after transplantation. The authors concluded that patients with low SES with lymphoma are a high-risk population that may need additional support through autologous stem cell transplant.[56]

Follicular and Other Indolent Non-Hodgkin Lymphomas

Although FL is the second most common NHL in western countries, incidence elsewhere, particularly in Asia, is lower.[15] The t(14;18) translocation leading to *BCL2* rearrangement is present in 90% of FLs in Western populations, but occurs in only about 60% of FLs in Asian populations.[57] Tumors without *BCL2* rearrangements tend to have *BCL6* rearrangements and grade IIIB morphology and can be associated with DLBCL.[58] Hence, FLs in Asian populations are morphologically and phenotypically similar to those in Western populations, although a subset might have different pathogenic pathways.[57]

FL survival has improved since the mid-1970s, possibly because of the introduction of new therapies such as rituximab. In a population-based study of nearly 16,000 patients in California with FL, overall and FL-specific survival improved 22% and 37%, respectively, from 1988 to 1997 and 1998 to 2005, and were observed in all racial and ethnic groups.[59] The Asian/Pacific Islander populations had better survival than the non-Hispanic white, Hispanic, and black populations who had similar outcomes. Lower neighborhood SES was associated with worse survival in patients across all stages of disease (p for trend < .01). Patients with the lowest SES quintile had a 49% increased risk of death from all causes and 31% increased risk of death from FL compared with patients with the highest SES.[59]

In 2,744 enrolled patients in the National LymphoCare Study, the largest prospective cohort to date of FL in the United States, only 3% and 5% of patients were black or Hispanic, respectively, and 90% of patients were white.[60] Compared with the white cohort, more patients in the black and Hispanic cohorts were diagnosed younger than age 45 and patients from the black cohort tended to have higher FLIPI scores at the time of presentation compared with the white or Hispanic cohorts, although the difference was not significant.[60] Patients from the Hispanic cohort were more commonly diagnosed with grade 3 FL compared with patients from the black and white cohorts (29%, 13%, and 18%, respectively) and more commonly received rituximab plus chemotherapy as initial therapy compared with the white cohort (66% vs. 50%), whereas the black cohort less commonly received anthracyclines (49% vs. 64%).[60] At a median follow-up of 52 months, progression-free survival was similar between the black and white cohorts, but was longer in the Hispanic cohort, and there was no difference in overall survival.[60] In a study of over 18,000 patients with FL from the SEER database between 1992 and 2009, 5-year overall survival improved across most races/ethnicities after the introduction of chemoimmunotherapy.[61] Interestingly, the Asian/Pacific Islanders populations did not demonstrate much improvement, perhaps because of relative superior outcomes prior to the introduction of rituximab.[61]

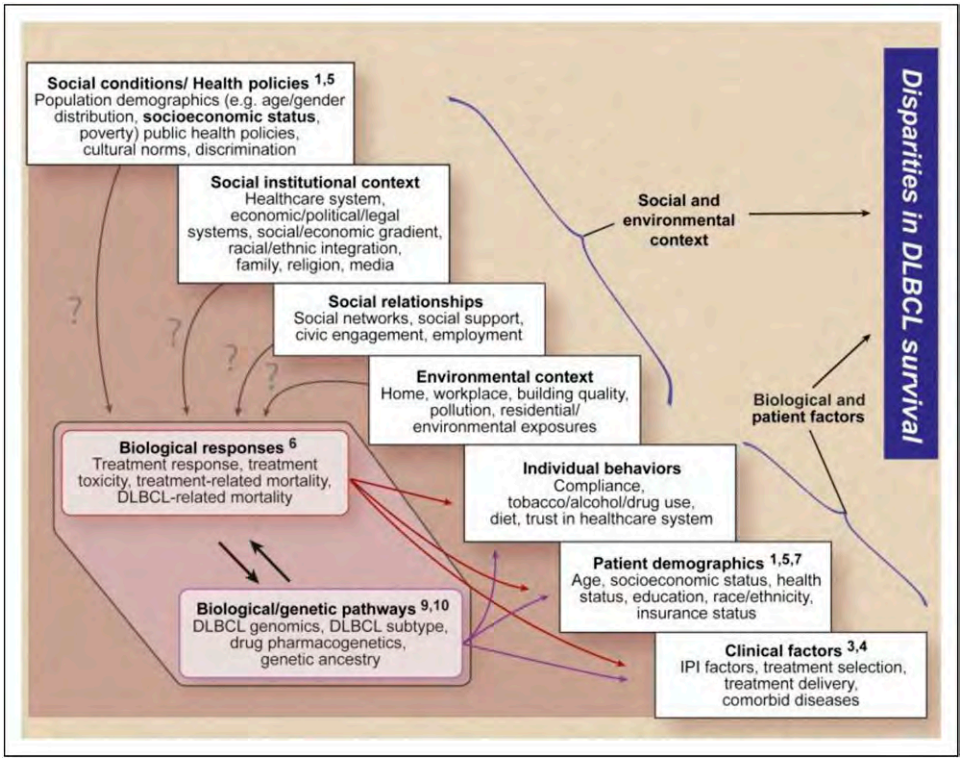
CLL is the most common form of adult leukemia in the United States and is grouped with SLL in the WHO classification.[1] Incidence rates are higher among males than females and highest among the white population, intermediate among the black population, and lowest among the Asian/Pacific Islander populations.[62] The black population with CLL/SLL present at a younger age (67 vs. 70) and had worse survival than the white population in a large SEER study.[63] The etiology of the survival disparity has not been adequately studied; however, in a study from the Mayo Clinic CLL database, outcomes between the white and black populations were comparable, suggesting differences may be due to disparities in access to care and management rather than differences in disease biology.[64]

Peripheral T-Cell Lymphoma

PTCLs are uncommon malignancies, accounting for 10% to 15% of all NHLs. Ethnic and geographic variations account for differences in prevalence; however, with rates ranging from 24% in Asia to 4% in North America.[20] The reason behind this variation is not entirely clear, but may relate to exposure or genetic susceptibility to pathogenic agents in Asian countries, notably HTLV-1 infection in adult T-cell leukemia/lymphoma and Epstein-Barr virus infection in NK/T-cell lymphoma.[20]

In a study of over 13,000 patients with PTCL identified from 2000 to 2012 in the SEER registry, compared with the non-Hispanic white cohort, the black cohort had a higher incidence of PTCL not otherwise specified, anaplastic large-cell lymphoma, and adult T-cell leukemia/lymphoma and a lower incidence of angioimmunoblastic T-cell lymphoma.[65] The Asians/Pacific Islander cohort had a higher incidence of angioimmunoblastic T-cell lymphoma, extranodal nasal-type NK/T-cell lymphoma and NK-cell leukemia, and adult T-cell leukemia/lymphoma and a lower incidence of anaplastic large-cell lymphoma. The Hispanic cohort had a higher incidence of angioimmunoblastic T-cell lymphoma and extranodal nasal-type NK/T-cell lymphoma and NK-cell leukemia, whereas the Native American cohort had a lower incidence of PTCL not otherwise specified.[65] Survival varied significantly by race/ethnicity with the black cohort in particular experiencing shorter survival for most subtypes,

FIGURE 2. A Framework for Understanding the Relationships Between Social, Environmental, Biologic, and Patient-Related Factors and Disparities in DLBCL Survival



Numbers indicate example publications from the references that address specific factors.
Professional illustration by Debra T. Dartez.[1]

highlighting the need for stronger recruitment of patients from the black population to clinical trials of PTCL.[65] Future studies of SES factors and biologic differences in PTCL may help better understand these disparities.

Hodgkin Lymphoma

HL is classified into two major types: classic HL and nodular lymphocyte predominant HL, accounting for 95% and 5% of all HL cases, respectively.[1] The incidence of HL overall has decreased by approximately 16% in the 1970s through 1997 in the United States.[66] The reasons are unclear with only a small proportion of the decrease attributed to the shift in classification and misdiagnosis.[66] Interestingly, an increase in HL incidence was observed in many female populations, including from the white and black populations.[67] The upward trend in women has been associated with decreasing parity, implicating childbearing as a possible protective factor against HL.[68]

Racial and ethnic disparities in HL rates have been reported in the United States.[69] In a retrospective study of over 16,000 cases in SEER from 1992 and 2007, a bimodal age distribution for the white and Asian/Pacific Islander populations exist, but not for the black or Hispanic populations.[69] Further, HL was more common in the Hispanic population compared with the white population above age 65.[69] Clinicopathologic racial differences included less common frequency of nodular sclerosis histology, more frequent presence of B symptoms, and more common advanced-stage disease for the Hispanic and black populations compared with the white population.[69] The etiology of these differences is not known, although several factors have been hypothesized. SES has been shown to affect incidence, because individuals living with a higher SES have a higher risk of HL. Underscoring the etiologic complexity of HL, SES differences varied by age, race, histology, and gender in a California cohort, as did Epstein-Barr virus–positive cases in a smaller sample with uniformly reviewed pathology.[70,71]

Racial disparities in survival that persist after adjustment for SES have also been detected in HL.[72,73] A possible explanation for these disparities is variation in initial treatment and management. Keegan et al have found that the black and Hispanic populations were more likely to receive chemotherapy alone (as compared with combined modality therapy) than the non-Hispanic white or Asian/Pacific Islander populations.[73] A population-based study also showed that patients from the black and Hispanics populations, and patients residing in lower SES neighborhoods, had lower utilization of radiotherapy.[74] In addition, inadequate health insurance is associated with later stage at diagnosis and undertreatment of HL.[75-77]

The incidence of nodular lymphocyte predominant HL is higher among the black population than other races.[78] In a retrospective study of patients with nodular lymphocyte predominant HL using the National Cancer Database, patients

from the black population were on average younger than patients from the white population (median age 42 vs. 45), more often female (49% vs. 29%), and more likely to have axillary lymph nodes as the primary site of disease (25% vs. 17%).[78] They also had unfavorable SES characteristics, a higher rate of no treatment in patients with early-stage disease, and a longer time to therapy initiation (median, 53.5 vs. 47 days).[78] Despite this, there was no significant difference between races with regard to stage distribution or survival. Overall survival at 7 years was 90.1% in patients with early-stage and 79.4% in patients with advanced-stage disease.[76]

CONCLUSION

The epidemiology of NHL and HL vary within and between geographic regions. In the United States, a number of studies indicate that the characteristics, incidence rates, and survival rates of various subtypes of lymphoma for certain racial groups are different from others. Although our ability to treat patients with NHL and HL has improved dramatically during the last 3 decades, health disparities exist, including for DLBCL and HL, the most curable lymphoma subtypes. Eliminating health disparities is a formidable and multifaceted task, which must address complex associations between social, environmental, biologic, and patient-centered factors. A framework developed by the National Institutes of Health Centers for Population Health and Health Disparities designed and proposed for DLBCL can be applied to other lymphoma subtypes (Fig. 2).[79,80] A better understanding of these factors will be important to identifying modifiable barriers in treatment and facilitate steps to improve outcomes for all patients.

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Understanding the New WHO Classification of Lymphoid Malignancies: Why It's Important and How It Will Affect Practice

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OVERVIEW

Improved delineation of lymphoid malignancy biology has prompted refinement of the 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors with a new framework introduced in 2016. This knowledge has provided valuable insights regarding management. Early clonal proliferations have been set apart given their limited potential for malignant dissemination. Increasing knowledge of molecular drivers of aggressive lymphomas has allowed subclassification and opportunity for clinical investigations to personalize therapy. New insights into T-cell pathophysiology has allowed grouping based on shared molecular and cellular features. This article will summarize the key changes in terms of diagnosis and histopathologic definitions, the impact of these changes on clinical management, and the challenges of future research in this field.

The Revised European American Lymphoma classification was based on the building of consensus, and it recognized that a comprehensive classification system was beyond the experience of any one individual.[1] The 19 members of the International Lymphoma Study Group contributed their diverse perspectives to achieve a unified point of view. In addition, the International Lymphoma Study Group made the decision to base its classification exclusively on published data; thus, for an entity to be included in the Revised European American Lymphoma classification, it had to be validated in more than one publication.

Recognition that the development of classification systems should be a cooperative effort was expanded with the third edition of the WHO classification.[2] It represented the first true worldwide consensus classification of hematologic malignancies and was the culmination of the efforts of a seven-member steering committee, 11 pathology committee chairs, 75 author contributors, and 44 clinician participants in a clinical advisory committee meeting.[3] In 2008, the fourth edition of the WHO classification involved the efforts of 138 authors and two clinical advisory committees comprising 62 clinical specialists with expertise in lymphoid and myeloid disorders.[4] The clinical advisory committee meetings were organized around a series of issues, including disease definitions, nomenclature, grading, and clinical relevance.[5] As with the third edition, the effort was coordinated by the European Association for Haematopathology and the Society for Hematopathology, led by the eight editors who served as a steering committee.

This model was maintained for the revision of the fourth edition, with a clinical advisory committee meeting held in 2014 to address newly emerging issues related to the definition of specific entities. The resultant revised fourth edition of the WHO classification was summarized in a review article published in *Blood* in 2016,[6] with publication of the complete monograph expected in the spring of 2017. It is being published as the revised fourth edition (not fifth edition) because fourth edition monographs for other organ systems are still in preparation, and preparation of a fifth edition must await the start of the next cycle.

The WHO classification embraces the principles of modern taxonomy by building a biomedical information network to promote disease discovery and pathogenetic insights, and to provide a framework for precision medicine.[7] The use of a common language internationally facilitates clinical trials and improves the standard of diagnosis and treatment in the general community. This article will highlight the revised classification and how it impacts clinical practice.

EARLY EVENTS IN LYMPHOID NEOPLASIA: BORDERLANDS OF MALIGNANCY

The multistep pathway of tumorigenesis is evident in the malignancies that develop in most organ systems. Additionally, histologic progression is a well-recognized feature

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of many lymphoid neoplasms, but the earliest events in lymphoid neoplasia are difficult to recognize. In fact, the lymphoid system historically has had no recognized "benign neoplasms," a fact that may be related to the propensity of lymphoid cells to circulate and not remain confined to a single anatomic site.[8] The current WHO classification addresses the problem of clonal expansions of B cells or, less often, T cells that appear to have limited potential for histologic or clinical progression. The expanded knowledge of disease-specific genetic and phenotypic alterations has resulted in the detection of clonal lymphoid lesions sharing genetic and/or phenotypic aberrations with well-defined neoplasms such as chronic lymphocytic leukemia/small lymphocytic lymphoma, multiple myeloma, follicular lymphoma (FL), and mantle cell lymphoma (MCL) without fulfilling diagnostic criteria for overt malignancy. These include monoclonal B-lymphocytosis (MBL), in situ follicular neoplasia, in situ mantle cell neoplasia, and monoclonal gammopathy of undetermined significance. Duodenal FL shares most phenotypic and genetic features with in situ follicular neoplasia, but interestingly also has some characteristics of extranodal marginal zone lymphoma.[9,10] New guidelines have been created for the diagnosis and management of these early lesions, which in general require no therapeutic intervention.

Some "indolent" and indeterminate clonal lymphoid proliferations appear to have a limited potential for progression, but they lack counterparts among the currently recognized subtypes of lymphoma. Some of these are of T-cell derivation and include indolent T-cell lymphoproliferative disorder of the gastrointestinal tract and primary cutaneous acral CD8-positive T-cell lymphoma, recognized as provisional entities in the revised WHO classification.[11,12] Pediatric-type FL falls into a similar category.[13,14] This clonal B-cell proliferation appears to have very limited capacity for aggressive clinical behavior, with little risk for progression following simple surgical excision of the affected node. However, its neoplastic nature is confirmed by the presence of clonal genetic alterations.[15-17] Recognition of these indeterminate clonal proliferations is important to avoid overtreatment of these patients. For example, some cases of pediatric-type FL might be incorrectly categorized as FL grade 3 A/B, resulting in inappropriate aggressive therapy.

KEY POINTS

- **The WHO Classification of Lymphoid Malignancies was updated in 2016, and there several key changes on pathologic and clinical perspectives.**
- **The updated guidelines provide an increased description of precursor and early lesions that may not need aggressive treatment.**
- **Patients with aggressive B-cell lymphomas are heterogeneous, and treatment is evolving.**
- **Clinical trials will need to focus on biologic lymphoma subtypes to move toward personalized therapy.**

Small B-Cell Neoplasms

Refinements have occurred in the understanding of small B-cell lymphomas. A long-standing problem had been the differential diagnosis of lymphoplasmacytic lymphoma and marginal zone lymphoma because both are usually associated with plasmacytic differentiation in the neoplastic cells. The identification of the *MYD88* L265P mutation in most cases of lymphoplasmacytic lymphoma, but only rarely in marginal zone lymphoma, has provided new tools for diagnosis.[18] The association of *MYD88* L265P and mutations in *CXCR4* has segregated immunoglobulin M monoclonal gammopathy of undetermined significance from other forms, placing it as closely related to lymphoplasmacytic lymphoma and Waldenstrom macroglobulinemia.[19-21]

MCL has been recognized as showing greater heterogeneity in clinical behavior and phenotype than previously appreciated. Leukemic non-nodal MCL has been delineated as a distinct variant associated with frequent splenomegaly, bone marrow and peripheral blood involvement, infrequent peripheral lymphadenopathy, and an indolent clinical course.[22,23] This variant is negative for SOX11, in contrast to classic MCL, and is usually derived from immunoglobulin heavy chain variable–mutated B cells. These cases had often been mistaken for chronic lymphocytic leukemia previously. SOX11 immunohistochemistry (IHC) has also proven to be useful in recognizing rare cases of classic MCL that are negative for cyclin D1.[24]

The basic approach to grading of FL remains unchanged. However, there is improved understanding of some FL variants, such as FL negative for CD10 (often positive for IRF4/MUM1) and cases of FL negative for t(14;18).[25] There have been new insights in the genetic heterogeneity of FL, with the possibility that analysis of the mutational profile will be incorporated in the future for assessment of clinical risk and protocol assignment.[26] Additionally, there is more formal recognition that FL grade 3B is biologically and clinically related to diffuse large B-cell lymphoma (DLBCL).[27]

Aggressive B-Cell Neoplasms

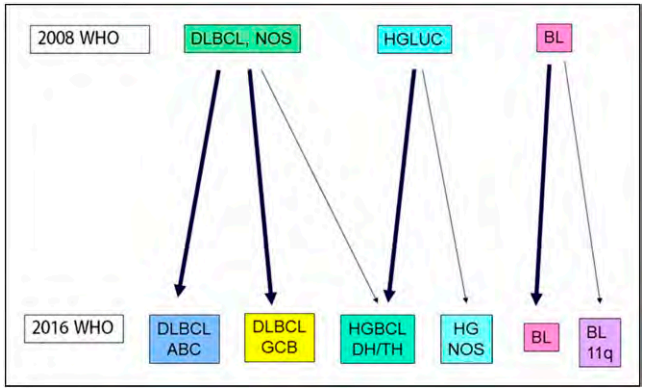
A major change in the classification of DLBCL is the recommendation that routine practice should recognize tumors belonging to the germinal center B-cell (GCB) and activated B-cell (ABC) subsets using either IHC surrogates or other means, as they may become available.[6,28,29] This subdivision has proven prognostic value and also correlates with considerable differences in the molecular pathogenesis of the tumors. Recent studies also have shown that ABC compared with GCB lymphomas exhibit differential sensitivity to certain drugs, which may direct patient management in the near future.[30] Finally, it has become clear that most double-hit lymphomas (DHLs) fall within the GCB subgroup; thus, determination of cell of origin (COO) can facilitate identification of those tumors that should undergo fluorescence in situ hybridization for *MYC* rearrangement.[31]

The 2008 WHO classification included a borderline category termed "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BL),"

often referred to informally as "high-grade lymphoma unclassifiable" or HGLUC (Fig. 1). This group, admittedly heterogeneous, was used to designate high-grade B-cell neoplasms that had intermediate cytologic features between DLBCL and BL. Many cases diagnosed as HGLUC were so-called DHL or more rarely triple-hit lymphoma, carrying translocations involving *MYC* and either or both *BCL2* and *BCL6*.[32,33] Moreover, clinical studies indicated that most of these DHLs were clinically aggressive with a poor outcome when treated with conventional chemotherapy, such as R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). However, it also became apparent that DHLs were morphologically heterogeneous, such that some were diagnosed as DLBCL, whereas others, based on intermediate cytology, were classified as HGLUC.[34] The division of what appeared to be a genetically homogeneous group of tumors into two different diagnostic categories led to difficulties in evaluating this subgroup in clinical trials and evaluating current and evolving therapeutic regimens. Thus, the clinical advisory committee agreed on the creation of a unifying category designated as "high-grade B-cell lymphoma, with rearrangements of *MYC* and *BCL2* and/or *BCL6*." Notably, this category excludes cases of B-lymphoblastic lymphoma/leukemia, which may be double hit as a consequence of progression from FL.[35-37]

Importantly, the WHO classification distinguishes between DHLs and tumors that have increased protein expression for BCL2 and MYC in the absence of dual translocations, often termed "double expressor" tumors. Double-expressor lymphomas are enriched in DLBCL of the ABC subtype of DLBCL.[31,38,39] Dual expression of MYC and BCL2 is an adverse prognostic factor, but this may be based, at least in part, on factors related to the ABC designation.

FIGURE 1. Navigating Changes in the Classification of Aggressive B-Cell Lymphomas, 2008 to 2016



This diagram illustrates changes in the classification of diffuse large B-cell lymphomas (DLBCL), Burkitt lymphoma (BL), and high-grade B-cell lymphoma unclassified (HGLUC). DLBCL NOS is now further subclassified into the germinal center B-cell (GCB) and activated B-cell (ABC) subtypes. In addition, a small subset of DLBCL NOS with both *MYC* and *BCL2* and/or *BCL6* translocations are included in the category of high-grade B-cell lymphoma with double-hit (DH)/triple-hit (TH). Other cases in this category are derived from the 2008 category of HGLUC. The definition of BL is essentially unchanged, but there are rare BL-like lymphomas that lack MYC rearrangements and have aberrations at 11q. The density of the arrows indicates the relative frequency of cases reassigned to a different group.

There remains a small group of tumors that are perceived to be cytologically "high grade," perhaps requiring more aggressive therapy. These are designated as "high-grade, not otherwise specified (NOS)" and by definition exclude DHLs and BL. This designation should be used sparingly and is not simply based on a high proliferation fraction with Ki-67.[6] However, such cases may show overlapping features with BL.

The definition of BL is essentially unchanged in the revised classification. However, there is a rare variant of high-grade B-cell lymphoma that closely resembles BL but lacks the *MYC* translocation and instead has frequent aberrations involving the 11q region. These cases occur mainly in children and are more often nodal than extranodal, in contrast to BL.[40] They are clinically aggressive but have a good response to therapy.

"Epstein-Barr virus (EBV)–positive DLBCL of the elderly" was a provisional entity in the 2008 WHO classification.[4] Since then, greater insight has been achieved regarding the epidemiology and prognostic significance of EBV in DLBCL. For one, the age distribution of EBV-positive DLBCL is much broader than originally thought and is not restricted based on age.[41,42] Interestingly, although EBV is an adverse prognostic factor in older patients,[43,44] younger patients appear to have a better prognosis.

The WHO classification newly recognizes EBV-positive mucocutaneous ulcer (EBV-MCU) as a localized lesion with a good prognosis and low risk of progression or dissemination.[45,46] EBV-MCU presents in patients with decreased immune surveillance for EBV, either related to advanced age or iatrogenic immunosuppression. The most common site of presentation is the oral cavity, including gingiva, but skin and intestinal mucosa also can be involved. Distinction from EBV-positive DLBCL is important because of very different treatment implications. Most patients with EBV-MCU can be treated conservatively.[47]

Peripheral T-Cell Lymphomas

There has been progress in illuminating the genetic landscape and classification of mature T-cell lymphomas. Genetic studies have shown recurrent mutations that affect a considerable proportion of cases of angioimmunoblastic T-cell lymphoma. Importantly, many of same genetic changes are observed in cases of peripheral T-cell lymphoma (PTCL) NOS that manifest a T follicular helper (TFH) phenotype.[48-50] For this designation, the neoplastic cells should express at least two or three TFH-related antigens among PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5. These observations have led to follicular T-cell lymphoma, angioimmunoblastic T-cell lymphoma, and nodal PTCL with a TFH phenotype being unified under a common heading.

Genomic approaches also have provided insights into the spectrum of CD30-expressing T-cell lymphomas and have facilitated the distinction of PTCL with high CD30 expression and ALK-negative anaplastic large cell lymphoma (ALCL), the latter having a superior prognosis.[51] Studies have further elucidated the genetic complexity of ALK-negative ALCL,

which is no longer a provisional category. Additionally, this genetic complexity provides important prognostic information; for example, cases of ALK-negative ALCL with DUSP22 translocation have an excellent prognosis, whereas cases with TP63 rearrangements have a very poor outcome.[52] Newly incorporated into the revised WHO classification is "breast implant–associated ALCL," which morphologically and phenotypically resembles other forms of ALCL but has very different clinical behavior. If neoplastic cells are confined to the seroma fluid surrounding the implant, patients can be managed conservatively with implant removal but no further therapy.[53]

Recent data also have led to changes in the categorization of intestinal T-cell lymphomas. It has become apparent that the two subtypes of enteropathy-associated T-cell lymphoma (EATL) are distinct, now clearly distinguished in the revised WHO classification. EATL, type I—now simply designated as "EATL"—is closely linked to celiac disease and is primarily a disease of individuals of northern European origin. EATL, type II—now formally designated as "monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)"—shows no association with celiac disease and has an increased incidence in Asian and Hispanic populations.[54,55] There remains a small group of intestinal T-cell lymphomas that do not meet criteria for EATL or MEITL as currently defined. These should be designated as intestinal T-cell lymphoma NOS.

THE APPLICATION OF WHO CLASSIFICATION FOR LYMPHOID MALIGNANCIES ON CLINICAL PRACTICE

Here we will review the changes within the 2016 revision most pertinent to practicing hematologists and medical oncologists focusing on (1) the indolent B-cell and T-cell proliferations where early recognition is important given the opportunity to avoid aggressive therapy and (2) the aggressive lymphomas where risk factor identification is critical for accurate prognostication and for consideration of intensive therapy or focused clinical trials.

The new entities have critical implications for the treating physician (Table 1). Optimal diagnosis requires adequate tissue to accurately apply the classification. In most circumstances, a fine needle aspirate and even needle core biopsies are inadequate. When possible, consideration should be given to obtaining a surgical specimen. Furthermore, accurate staging remains essential for patient care. Bone marrow biopsy is still required for most of the non-Hodgkin lymphomas (NHLs), especially when confirmation of localized disease is warranted. These steps will facilitate an active conversation between the pathologist and treating physician, guiding subsequent management. Clinical applications of the new and modified entities are reviewed below.

Early Lymphoproliferative Disorders

B-cell and T-cell clonal expansions. MBL is now understood to be the precursor to chronic lymphocytic leukemia, preceding the disease is most cases.[56] However, only a minority of patients with a peripheral blood B-cell clone will progress to an overt lymphoid malignancy. As such, the 2016 update now differentiates "low-count MBL" from "high-count MBL" with a peripheral blood clonal B-cell count of 0.5×10^9/L. Patients with high-count MBL require periodic evaluation given the genetic similarities to chronic lymphocytic leukemia and predisposition for progression over time.[57,58] Low-count MBL does not appear to have the same degree of B-cell receptor stereotypy or a similar potential for progression. As such, no specific follow-up is recommended for these patients at the current time.

TABLE 1. 2016 WHO Classification Changes for B-Cell and T-Cell Neoplasms Affecting Clinical Practice*

Entity	Clinical Practice Implications
Monoclonal B-cell lymphocytosis	Distinguish low-count from high-count MBL
	Clinical follow-up not required for low-count MBL
In situ follicular neoplasia	Low risk of progression to lymphoma
In situ mantle cell neoplasia	Low clinical risk
CD8+ T-cell proliferations	Conservative management
Pediatric-type follicular lymphoma	Conservative therapeutic approach; must differentiate from high-grade follicular lymphoma
Duodenal-type follicular lymphoma	Low risk of dissemination
EBV+ mucocutaneous ulcer	New entity associated with immunosuppression
Diffuse large B-cell lymphoma NOS	Distinction of GCB vs. ABC/non-GC type required
	Coexpression of MYC and BCL2 recognized as new prognostic marker
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* translocations	New category for double- and triple-hit lymphomas
	Consideration of dose-intensive therapy
ALK– anaplastic large cell lymphoma	Now a recognized entity; prognosis intermediate between ALK+ ALCL and PTCL

*Adapted from Swerdlow et al.[6]

Abbreviations: MBL, monoclonal B-cell lymphocytosis; NOS, not otherwise specified; GCB, germinal center B cell; ABC, activated B cell; GC, germinal center; ALCL, anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma.

In situ follicular neoplasia is used to describe a pattern of BCL2-overexpressing centrocytes and centroblasts in otherwise architecturally normal lymph nodes. A full staging work-up is needed to differentiate this entity from partial involvement by FL. In addition, larger biopsies are needed as flow cytometry of fine needle aspirations can be identical to FL because of similar cell surface markers.[11] Few patients appear to progress to disseminated FL.[59] As such, conservative management such as observation should be recommended in most cases.

Somewhat analogous to in situ follicular neoplasia, cyclin D1-positive B cells have been observed within the mantle zone of reactive lymphoid follicles.[60] The cells may be SOX11-positive and have been associated with other small B-cell lymphomas. Although uncommon, in situ mantle cell neoplasia also appears to behave in an indolent manner, rarely developing into overt lymphoma.[61]

Indolent T-cell proliferations have also been identified, warranting the addition of "indolent T-cell lymphoproliferative disorder of the gastrointestinal tract" and "primary cutaneous acral CD8-positive T-cell lymphoma" as provisional entities. Presenting within the gastrointestinal tract or the outer ear, respectively, these disorders can be mistaken for more aggressive T-cell lymphomas.[11,59] As such, identification is important to avoid overtreatment.

Small B-cell lymphoma variants. FL remains incurable but with a median survival approaching 2 decades when presenting with grade 1 to 2 histology.[62] For patients with stage I disease, localized radiation has historically been recommend predominantly based on retrospective studies demonstrating tolerance of therapy and excellent long-term outcomes.[63] Analysis of the National LymphoCare database demonstrated wide variations in management, with chemoimmunotherapy being the most commonly used approach for patients with stage I disease.[60] The WHO classification now recognizes FL variants distinct from FL often presenting as an isolated lesion and having an excellent prognosis. Recognition is critical so that appropriate conservative management strategies can be used.

Despite the proliferative appearance, pediatric-type FL is most often localized and appears to behave in an indolent manner. It presents most often in children but can be diagnosed in young adults as well. A case series including 21 pediatric patients with stage I disease reported that when treated with excision only, none had progressed with a median follow-up of 57 months.[14] In addition, disease characterized by *BCL2* negativity and a proliferation index of greater than 30% predicted for similarly indolent behavior in adult patients presenting with stage I disease as well. As grade 3 conventional FL can present with a high proliferative index and lack of a *BCL2* rearrangement, discussion between the pathologist and treating physician is needed to differentiate high-grade FL from the pediatric-type disease.

Duodenal-type FL was originally named primary intestinal FL in the 2008 classification and was described as localized intestinal involvement, most often involving mucosa/submucosa in the second portion of the duodenum. Morphology, immunophenotype, and genetic features are similar to nodal FL. The lesions demonstrate indolent behavior, rarely progressing to nodal involvement and undergoing spontaneous regression in some cases.[9] As such, observation is the recommended management strategy for this entity as well.

The heterogeneous nature of MCL is well recognized, at times demonstrating relatively slow disease progression. For such cases, observation remains a reasonable management strategy.[61] Reports have suggested that the clinical phenotype of peripheral blood, bone marrow, and splenic involvement without lymphadenopathy may often demonstrate such indolent behavior. Two subtypes of MCL are now recognized in the 2016 update. Consistent with the distinct clinical course, leukemic nonnodal MCL has a distinct pathogenesis, being SOX11-negative and having mutated immunoglobulin heavy chain variable region genes.[64] Although initial observation is appropriate for patients with this subtype, additional high-risk aberrations can be acquired resulting in a more aggressive clinical course.

EBV-positive MCU. Differentiated from EBV-positive DLBCL, EBV-positive MCU is a provisional entity in the 2016 classification. Based on the viral pathogenesis, these lesions may present in elderly patients or in the setting of immunodeficiency.[45] Presenting as an ulcerative lesion of the skin, oropharynx, or gastrointestinal tract, these lesions have an indolent clinical course, typically not requiring systemic therapy. If clinically appropriate, reduction of immunosuppression can lead to regression.[43]

DLBCL and Other Aggressive B-Cell Neoplasms

Perhaps the WHO modifications affecting the largest number of patients with lymphoma are the changes for aggressive NHL subtypes. An improved understanding of DLBCL biologic heterogeneity has led to the identification of highly prognostic molecular markers and new drug targets, paving the way for clinical trials focused on disease subsets aiming to personalize therapy.

COO: GCB and ABC subgroups. Following the identification of two distinct molecular subgroups reflective of COO, multiple groups have confirmed the biologic and prognostic differences of the GCB and ABC types of DLBCL.[62] As such, the 2008 WHO classification recognized these subsets of DLBCL. IHC emerged as a surrogate for gene expression as investigators attempted to extend COO determination to the clinic. The initially developed Hans algorithm used expression of CD10, BCL6, and IRF4/MUM1 to divide patients into GCB and non-GCB groups.[63] Eight subsequent algorithms attempted to improve the concordance with gene expression. Despite their limitations, the 2016 classification of "DLBCL NOS" now requires the identification of the COO subtype as determined by published ICH surrogates until gene-expression technology can be implemented in clinical practice.[65]

Clinical trials targeting COO. Attempting to target the NF-kB signaling pathway, early-phase clinical trials demonstrated single-agent efficacy for targeted agents including bortezomib,[66] lenalidomide,[67] and ibrutinib,[68] predominantly in the ABC subset of DLBCL. After confirming safety in combi-

nation with R-CHOP, these early signals led to randomized studies evaluating the addition of the agents. Two randomized phase II studies evaluated R-CHOP with or without bortezomib in non-GCB DLBCL, replacing vincristine in the experimental arm of one trial.[69,70] No statistical difference in response rates, progression-free survival (PFS), or overall survival (OS) were observed between control and bortezomib arms in either trial. Ongoing randomized studies similarly evaluating the addition of lenalidomide or ibrutinib to R-CHOP are ongoing. Until these results are available, it would be premature to consider combining one of the agents with R-CHOP outside of a clinical trial. However, for patients without curative options or available clinical trials, single-agent lenalidomide may provide benefit in some patients with non-GCB DLBCL.[71]

These initial results give pause to how clinical trials are conducted in this population. The outcomes for the R-CHOP control arms appear better than expected, suggesting selection bias may be impacting the results. Rigorous inclusion criteria and the time needed to confirm COO may have led to the exclusion of patients with the most aggressive disease behavior, potentially explaining the low number of events observed in these studies. Additionally, relying on IHC may also limit the number of true patients with ABC included, reducing those most likely to benefit from a strategy targeting the NF-κB pathway. Future studies must streamline accrual and incorporate carefully written eligibility criteria so as to enroll the population intending to be studied. In the meantime, treating physicians must consider clinical trial options early in the disease course and understand limitations of the published literature so as to accurately counsel patients.

Double-hit lymphoma. In addition to COO distinctions, alterations of *MYC* and those of *BCL2* and *BCL6* have clinical importance for large B-cell lymphomas. As described above, the prognostic significance of these aberrations has led to a new category in the WHO classification known as "high-grade B-cell lymphoma, with and without *MYC* and *BCL2* or *BCL6* translocations." *MYC* rearrangements as detected by fluorescence in situ hybridization have been demonstrated in up to 15% of patients with large-cell lymphoma. An additional *BCL2* or *BCL6* translocation will be observed in a proportion of these patients, resulting in approximately 5% of patients with newly diagnosed DLBCL having double-hit genetics. The majority of reports have conferred a dismal prognosis for DHL after treatment with CHOP-based therapy.[72] The BC Cancer Agency reported a 5-year OS of 27% for those with concurrent *MYC* and *BCL2* translocations.[73] Subsequent retrospective series have described similarly poor outcomes, including a median OS of approximately 1.5 years.[72] This recognition not only has prompted the development of clinical trials focused on the high-risk subgroups but also may have immediate treatment implications.

Dose-intensive therapy for DHL. Large retrospective analyses have suggested some benefit for using intensive induction regimens in DHL. A multicenter series of 311 patients with double-hit rearrangements reported an 8-month PFS for patients treated with R-CHOP compared with 22 months for those who received R-hyperCVAD, R-CODOX-M/IVAC, and DA-EPOCH-R.[74] Only in an exploratory analysis was a survival benefit suggested for patients with certain adverse prognostic factors. A second meta-analysis incorporating 394 patients from 11 retrospective studies compared outcomes for R-CHOP, DA-EPOCH-R, and R-hyperCVAD and again demonstrated a PFS advantage for the dose-intensive regimens without an OS difference.[75]

The only prospective data in this population has been reported in a preliminary analysis of a multicenter phase II trial evaluating DA-EPOCH-R in 52 patients with *MYC*-rearranged DLBCL and unclassified aggressive B-cell lymphoma.[76] Roughly half of patients tested also had a *BCL2* rearrangement. At median follow-up of 14 months, the PFS was 79% for the cohort and 87% for those with double-hit genetics. On the basis of this signal and the markedly inferior prognosis following R-CHOP, some investigators have advocated for first-line use of DA-EPOCH-R for patients with DHL.

Stem cell transplantation. Retrospective series have also focused on outcomes following autologous stem cell transplantation for patients with DHL. As a whole, a survival benefit has not been appreciated with this consolidative strategy. One limitation is that patients with DHL exhibit high rates of early treatment failure. A subanalysis of the CORAL trial found that only half of patients with relapsed disease with a *MYC* rearrangement responded to salvage therapy resulting in a 4-year PFS of 18%.[77] The SWOG-9704 trial suggested a PFS benefit for patients with high-intermediate and high-risk International Prognostic Index scores.[78] However, further analysis demonstrated that none of the patients with DHL enrolled survived 6 months.[79] A retrospective analysis of post-transplant outcomes from two centers demonstrated that patients with DHL who are able to undergo autologous stem cell transplantation continue to have inferior outcomes with a 4-year OS of 25% compared with 70% for those without the aberrations.[80] Together, these results suggest that high-dose chemotherapy and autologous stem cell rescue does not overcome the high-risk biology of DHL. The incorporation of novel targeted agents with up-front treatment will ultimately be needed to better address the genetic complexity and refractory nature of this disease.

Double-expressor lymphoma. As MYC and BCL2 can be activated through mechanisms other than translocation, several groups have evaluated protein overexpression. Compared with DHL, a larger proportion of patients overexpress MYC and BCL2, ranging from 20% to 44% of patients in retrospectively analyzed cohorts. Retrospective series have reported somewhat poor outcomes for this group of patients with an OS of 30% at 5 years following R-CHOP therapy.[38]

As with DHL, there is retrospective evidence that DA-EPOCH-R may be able to overcome the poor prognosis associated with MYC and BCL2 overexpression.[81] However, 5-year outcomes for the randomized CALGB 50303 trial comparing R-CHOP and DA-EPOCH-R found no difference in PFS and OS in a large group of unselected patients with DLBCL.[82] Additionally, higher rates of febrile neutropenia, thrombocytopenia, and neuropathy were observed among those treated

with DA-EPOCH-R. Given the available prospective data as well as the observation that patients with double-expressor large cell lymphoma do not uniformly have poor outcomes, the optimal treatment of this group is in the context of a clinical trial. Otherwise, R-CHOP remains the standard of care for this population at the current time.

Mature T-Cell Neoplasms

The progress made in identifying genetic drivers of PTCL has provided valuable insights into disease biology and new targets for study. However, most of this knowledge has yet to translate into the clinical arena. One exception is the CD30-positive T-cell lymphomas. Gene expression studies have demonstrated distinct profiles for the CD30-expressing PTCLs as compared with ALK-negative ALCL.[83] As such, ALK-negative ALCL has been moved from a provisional to a recognized entity in the 2016 update. The CD30 immunoconjugate brentuximab vedotin does appear to be active in PTCL.[84] Consistent with differences in disease biology, the responses in the relapsed/refractory setting, however, appear less frequent and less durable compared with ALCL.

THE IMPACT OF WHO CLASSIFICATION OF LYMPHOID MALIGNANCES ON CLINICAL TRIAL DEVELOPMENT

The previous two sections have outlined the key updates to the WHO classification of lymphoid malignancies based on new and increased emphasis on the role of biologic factors in the natural disease course and response to standard treatment. Although some of the shifts in classification are subtle, others are more overt, and they affect both the interpretation of existing literature and the design of studies moving forward. The two areas of clinical research most affected by these changes are aggressive B-cell lymphomas and mature T-cell lymphomas.

Aggressive B-Cell Lymphomas

There are four major changes in the classification of aggressive B-cell lymphomas, eloquently discussed above, that may affect clinical investigation: (1) the elimination of the category "B-cell lymphoma, unclassifiable, intermediate between DLBCL and BL" (also known as "BCLU" or "B-cell lymphoma, unclassifiable"), which was based on morphology; (2) the transition to combining these entities using shared genetic features of dual *MYC* and *BCL2* or *BCL6* rearrangements (double-hit/triple-hit lymphoma); (3) the requirement for COO testing in all aggressive B-cell lymphomas to distinguish GC and ABC DLBCL; and (4) the recognition of dual MYC and BCL2 protein overexpression (double-expressor lymphoma) as an adverse prognostic feature.

Although the clinical impact is clearly important, the newly recognized variants and prognostic features complicate the interpretation of existing trials. For example, the intergroup study CALGB 50303 was designed over a decade ago to compare standard R-CHOP with DA-EPOCH-R in treatment-naive DLBCL. With a primary endpoint of event-free survival (EFS), 524 patients were randomly assigned 1:1 to R-CHOP or DA-EPOCH-R. There was no difference in overall or complete response rate and no difference in the primary endpoint of EFS at either 3- or 5-year time points.[82] Similarly, the GOYA trial was designed to test the efficacy of the second-generation anti-CD20 obinutuzumab (G) compared with rituximab when added to a CHOP backbone.[85] GOYA was a large trial with 712 patients on R-CHOP and 706 patients on G-CHOP; again, there was no difference in the primary endpoint of PFS. On first glance, the conclusion from both these trials is that R-CHOP remains the standard of care for DLBCL. However, it is critical to acknowledge that there are a number of WHO-defined subsets mixed together in both of these trials, including some DHL, some double-expressor lymphoma, and of course the major dichotomy based on COO. Furthermore, many of these groups overlap; for example, the majority of DHL occurs in GC-DLBCL, whereas the majority of double-expressor lymphoma occurs in non-GC/ABC DLBCL.[38,86] Targeting what we currently consider one subset may be much more complex and thus confound the results of well-intentioned trials.

A second observation from ongoing trials is the surprisingly excellent outcome for patients treated with R-CHOP. For example, the CALGB 50303 statistical design was based on an assumed 55% EFS in the R-CHOP arm; surprisingly, patients receiving R-CHOP had an impressive 3-year EFS of 81% and 5-year EFS of 69%. The recently published PRELUDE trial also found very few events in the R-CHOP arm followed by the placebo arm; this study tested the concept of postinduction consolidation with enzastaurin compared with placebo in patients with International Prognostic Index scores of 3 to 5.[87] There was no difference between the arms, and 4-year EFS was unexpectedly excellent at 70% in patients with high-risk disease.

Similarly, retrospective and large database reports suggest that ABC DLBCL via gene-expression profiling has an estimated PFS of 40% and OS of 50% to 60% following standard R-CHOP.[88] Similar reports using IHC-defined non-GC/ABC phenotype show 2-year estimated PFS and OS of 28% and 46%, respectively.[89] By comparison, the outcomes for non-GC/ABC DLBCL on the standard R-CHOP arms of both the PYRAMID and German randomized phase II trials evaluating bortezomib in treatment-naive DLBCL showed 2-year PFS over 77% and OS 80% to 90% for this subgroup.[69,70] One explanation for discrepant outcomes between retrospective and prospective datasets is that the retrospective series includes all available patients, whereas prospective trials have inherent selection bias of only including patients fit enough to meet the trial inclusion criteria and with access to an academic center with the trial. The lesson here may be that, if we are to study high-risk and ill patients, there has to be a mechanism to enroll all patients in a more timely manner or to include flexibility regarding prephase therapy or even a full cycle of therapy while registration and regulatory processes proceed, pathology is being reviewed, biology is being confirmed, and logistics are settled.

The issues raised above make the need for adequate biopsy specimens, efficient diagnostics, and expert pathology

review more imperative than ever. One lesson learned from ECOG 1412 is the need for timely and expert review. This trial is an important U.S. intergroup randomized phase II study prospectively testing the addition of lenalidomide to an R-CHOP backbone in DLBCL, with the hypothesis being that the immunomodulatory agent will overcome the negative prognosis of ABC-DLBCL (NCT01856192). Although the study has been actively accruing, an interim evaluation found an approximate 30% ineligibility rate based on central pathology review (personal communication, G. Nowakowski, Mayo Clinic). Given these findings, the protocol was amended to expedite central review; although the high rate of ineligibility persisted, and patients were identified in several business days instead of several months, facilitating targeted enrollment.

A related issue is the ability to define molecular subsets quickly and accurately. The original definition of GC compared with ABC subtype was based on gene-expression profiling in frozen specimens.[62] However, gene-expression profiling via the original assay is not commercially available, and frozen biopsies are not commonly performed. These limitations gave rise to a series of IHC algorithms that assign COO based on protein expression of CD10, MUM1, BCL6, and LMO2, among others.[90] The IHC panels are widely used and easily accessible, and the WHO 2016 classification allows these algorithms to be used for COO designation without specifying a preferred approach. Unfortunately, each of the IHC algorithms has an approximate 20% to 30% error rate when compared with the gold standard of gene-expression profiling. There can also be discrepancy among hematopathologists as to cases that are positive compared with negative for any given marker, leading to potential inconsistency for clinical trial purposes.

There are tools in development that might change this aspect of quickly defining aggressive B-cell lymphoma subsets. The assay that is furthest along uses NanoString technology and evaluates 20 genes (Lymph2Cx).[29] When compared with either the Hans or Choi IHC algorithms, Lymph2Cx was superior and much more aligned with the original gene-expression profiling. This assay is being used in a number of trials and touts a quick turnaround time from receipt of 36 hours. However, this rapid turnaround time does not include the time for biopsy specimens to be collected by the clinical trial center, reviewed locally, and then shipped to the company for analysis. These are just some of the logistic challenges that may hamper or delay biologic stratification in real time at study entry.

Overall, the new WHO update emphasizes that subsets in aggressive B-cell lymphomas exist and are likely to influence clinical trial design and interpretation. One suggested division for future trial design is to consider trials powered for the following groups: high-grade B-cell lymphoma with *MYC* and *BCL2* or *BCL6* rearrangements (independent of histology), DLBCL NOS with standardized assessment for COO and double-expressor phenotype, and DLBCL NOS without double-expressor or double-hit phenotype. These subsets are smaller than the overall population of DLBCL, and the need for community and academic centers alike to participate in large cooperative group trials or have a seamless referral process is critical if we are to move the bar higher for this disease with personalized therapy for each subtype of aggressive lymphoma.

Peripheral T-Cell Lymphoma

Outside of aggressive B-cell malignancies, the WHO update most significantly impacts the study of systemic aggressive T-cell lymphomas (T-NHL). PTCLs have historically been grouped by their main shared phenotype of T-cell derivation but are clinically and biologically distinct. Given their rarity, the overwhelming majority of trials lump all mature T-cell lymphomas together, often including the more indolent cutaneous T-cell lymphoma alongside aggressive systemic variants.

Analogous to the studies discussed above in DLBCL, pooling all mature T-NHL has likely led to the lack of data that moves the field forward significantly. One example is the continued use of CHOP for front-line therapy. Compared with B-cell histologies, CHOP has PFS rates of only 20% to 30% in T-NHL.[91,92] Attempts to improve on CHOP have taken several approaches: adding new agents to a CHOP backbone, consolidating with autologous stem cell transplantation, or using a non-CHOP regimen. Studies of a non-CHOP backbone are relatively uncommon and have been essentially single-arm, phase II, negative trials. The use of consolidative transplant (reviewed in Moskowitz et al[93]) improves outcomes for some patients, but ineligibility for transplant because of chemoresistance or comorbidities means this treatment is only applicable to the minority of patients. Building on CHOP despite the identification of rational targets has also proven to be difficult, with many trials failing to show a significant advantage to date.[94] There are several ongoing trials that are based on an integral marker (i.e., the use of brentuximab vedotin in CD30-positive malignancies) that may change this pattern, and results are eagerly awaited.

The identification of the TFH cell as the COO of angioimmunoblastic T-cell lymphoma and the subsequent recognition of a similar etiology in one-third of PTCL NOS is a new finding.[95,96] As outlined in the first section, these T-NHL will now be grouped together under a common heading, which should facilitate clinical trials based on shared biology. Of note, angioimmunoblastic T-cell lymphoma and a number of related T-NHL appear highly dependent on epigenetic deregulation, which can and should be further studied with existing and emerging agents. For example, romidepsin is a histone deacetylase inhibitor already approved for relapsed/refractory T-NHL. Based on promising phase IB/II data,[97] there is an ongoing trial of CHOP with or without romidepsin (NCT01796002). However, this trial was designed prior to identification of the TFH phenotype and includes several histologies, possibly muting differences between the two arms. Similar to the discussion in DLBCL above, it will be necessary to power trials for subsets in the future.

CONCLUSION

The development of a universally accepted classification system has been of tremendous benefit to the field of hematologic malignancies. The 2016 WHO classification update of lymphoid malignancies includes several new entities and additional modifications that affect current treatment paradigms and provide a framework for future clinical trials. It is incumbent on treating physicians to understand the relevant changes. Doing so will facilitate dialogue with the pathologist so that an accurate diagnosis may be made, patients can be appropriately counseled, and state-of-the-art patient care can be delivered.

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HEMATOLOGIC MALIGNANCIES—PLASMA CELL DYSCRASIA

Established and Novel Prognostic Biomarkers in Multiple Myeloma

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OVERVIEW

Multiple myeloma (MM) is an incurable plasma cell malignancy characterized by notable interpatient heterogeneity. There have been important advances in therapy and overall survival, but some patients with high-risk features still have poor survival rates. Therefore, accurate identification of this subset of patients has been integral to improvement of patient outcome. During the last few years, cytogenetics, gene expression profiling, MRI and PET/CT, as well as serum free light chain assays have been used as accurate biomarkers to better characterize the diverse course and outcome of the disease. With the recent advances of massive parallel sequencing techniques, the development of new models that better stratify high-risk groups are beginning to be developed. The use of multiparameter flow cytometry and next-generation sequencing have paved the way for assessment of minimal residual disease and better prognostication of post-therapeutic outcomes. Circulating tumor cells and circulating tumor DNA are promising potential biomarkers that demonstrate the spatial and temporal heterogeneity of MM. Finally, more prognostic markers are being developed that are specific to immunotherapeutic agents. In this review, we discuss these traditional and novel biomarkers that have been developed for MM and also those that can predict disease progression from precursor stages. Together, these biomarkers will help improve our understanding of the intrapatient and interpatient variabilities and help develop precision medicine for patients with high-risk MM.

Biomarkers have been integral tools for diagnosis, prognosis, and management of different malignancies. A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1] Biomarkers could be diagnostic, in which their detection indicates the presence of disease, such as M protein in plasma cell dyscrasias, and subsequently can be used to screen patients. Prognostic biomarkers are used for estimating the likely course of a disease and, hence, the most appropriate management strategy. Another type are predictive biomarkers, in which the presence of certain molecular targets helps identify the appropriate targeted therapy and thus predict the response to these agents; somatic mutations in *BRAF* and *EGFR* genes are examples. Biomarkers also could be beneficial to identify patients with high susceptibility to certain cancers through detection of germline mutations, such as *BRCA* or somatic mutations, as in the case of clonal hematopoiesis of indeterminate potential.[2,3]

MM is a clonal plasma cell malignancy that accounts for 10% of all hematologic malignancies; there is notable inter- and intrapatient heterogeneity.[4] Biomarkers have had a pivotal role in its diagnosis and management. The first biomarker in MM was the Bence Jones protein,[5] which was followed by others, such as M protein, plasmacytosis of the bone marrow, and β2 microglobulin. The 5-year survival rate of patients with MM is 48.5%,[6] and, despite the introduction of immunomodulatory drugs (IMIDs) and proteasome inhibitors (PIs), many patients with high-risk features still have low progression-free survival (PFS) rates and poor overall survival (OS).

MM usually progresses from asymptomatic precursor stages, namely monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).[7,8] MGUS can progress into MM at a rate of 1% per year, whereas SMM carries a higher chance of progression—approximately 10% per year.[9] Some patients experience rapid progression from MGUS/SMM to MM, whereas others have disease that remains indolent, with minimal progression during their lifetimes. Several prognostic models have been used to stratify patients with high-risk SMM who are likely to experience rapid progression to overt MM. Unfortunately, these biomarkers are dependent on tumor burden measurements, and additional studies are needed to better stratify these patients.

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Standard prognostic classifications used in newly diagnosed MM, such as the Durie-Salmon classification and International Staging System (ISS), have been put in place for the purpose of risk stratification and have served to evaluate the overall clinical outcome of patients. However, they do not account for the genomic complexity of the disease that leads to a heterogeneous clinical course. Thus, it is imperative to devise new biomarkers that stratify the disease at an individual level and allow tailored therapy to achieve the optimal outcome.

This review describes traditional biomarkers used in MM, including the Durie-Salmon staging system and the ISS classification, as well as cytogenetics, fluorescence in situ hybridization (FISH), and gene expression profiling (GEP) methods that have been used to stratify patients at high risk for many years. The review also defines markers (Fig. 1) used to identify patients with high risk for disease progression in SMM and those used to define high risk for progression after therapy with evaluation of minimal residual disease (MRD) as well as imaging modalities. Finally, novel biomarkers that use next-generation sequencing (NGS) and blood biopsies are described; these options can be used in the future to additionally improve the prognostic classification of patients with MM.

CURRENT STAGING SYSTEMS

Durie-Salmon Staging System

The Durie-Salmon staging system is one of the earliest standardized systems for staging MM.[10] It classifies patient diseases into whole-body tumor burden stages of I (low), II (intermediate), and III (high), along with subclassifications of A and B that are based on renal function (Table 1). This system assesses the levels of hemoglobin, M protein, serum calcium, and creatinine, and it examples lytic lesions via x-ray imaging. However, the Durie-Salmon staging has some limitations to prediction of prognosis and survival, because bone disease interpretation is observer dependent, which decreases its precision.

KEY POINTS

- **Traditional prognostic markers include the Durie-Salmon staging system and the International staging system. Additional advances in the use of cytogenetics, interphase FISH, and gene expression profiling have improved our understanding of the heterogeneous tumor biology of MM.**
- **Newer prognostic markers of disease response and progression after therapy have emerged and include the serum free light chain assay and MRD assessment by multiparameter flow cytometry or next-generation sequencing as well as novel imaging modalities.**
- **Next-generation sequencing could help with more accurate classification of patients and their responses to therapy.**
- **Novel methods using blood biopsies with circulating tumor cells and cell-free DNA are promising future noninvasive biomarkers for detecting the mutational landscape of MM and tracking response to therapy.**
- **Biomarkers for new immunotherapies could predict their efficacy in MM and define patients who would benefit from them.**

ISS and Revised ISS

Unlike the Durie-Salmon staging system, the ISS is a convenient and more accurate method to assess prognosis in MM on the basis of serum β2 microglobulin and albumin levels as prognostic biomarkers. Even though it is independent of imaging criteria, the ISS was developed from the multivariable analyses of 3,060 patients and has proved to be a simple yet important prognostic determinant.[11] The ISS classifies newly diagnosed patients into three stages according to their prognoses. Although the ISS is more reproducible than the Durie-Salmon staging, its accuracy depends on albumin level, which is not a disease-specific marker; both albumin and β2-microglobulin could be affected by patient factors, such as renal failure and other comorbidities. However, neither system considers the biologic determinants of MM. To account for that, and with the development of more biomarkers in MM, a revised version of the ISS was set in place to include lactate dehydrogenase level and cytogenetics (Table 1).[12] The revised ISS has become the gold-standard staging system in newly diagnosed symptomatic patients[12-14]; however, these staging systems are not used in SMM. Prognostic models identifying the risk of progression in SMM have been proposed to stratify patients at higher risk of developing active disease (Table 2).

HEAVY AND LIGHT CHAINS AS PROGNOSTIC MARKERS

For years, serum free light chain (FLC) assays have been developed to aid the diagnosis of MM and to monitor treatment response and disease progression.[16-18] Current treatment plans are guided by measuring serum FLC levels and the FLC ratio to define a complete response or progressive disease in oligosecretory myeloma.[16,17]

An abnormal involved/uninvolved FLC ratio has proved an accurate predictor of progression for patients with SMM[19,20] and of survival and therapeutic response in patients with MM, whereby nonresponders initially would have a significantly higher FLC ratio than responders.[21] Furthermore, an abnormal FLC assessment before autologous stem cell transplantation predicted early progression thereafter,[22] and a one-third reduction in FLC levels within 30 or 60 days predicted a favorable prognosis.[22,23] Interestingly, the prognostic value of FLC was independent of high-risk translocations like t(4;14) and t(14;16), although they were positively correlated.[24]

Intraclonal heterogeneity is a hallmark of MM[25,26] and is believed to be the culprit behind disease relapse or progression. Thus, determination of both M protein and FLC is representative of treatment efficacy of the different clones and can have prognostic significance in treatment outcome.[27] In one study, an increase in FLC levels, irrespective of M-protein level, predicted an aggressive myeloma course.

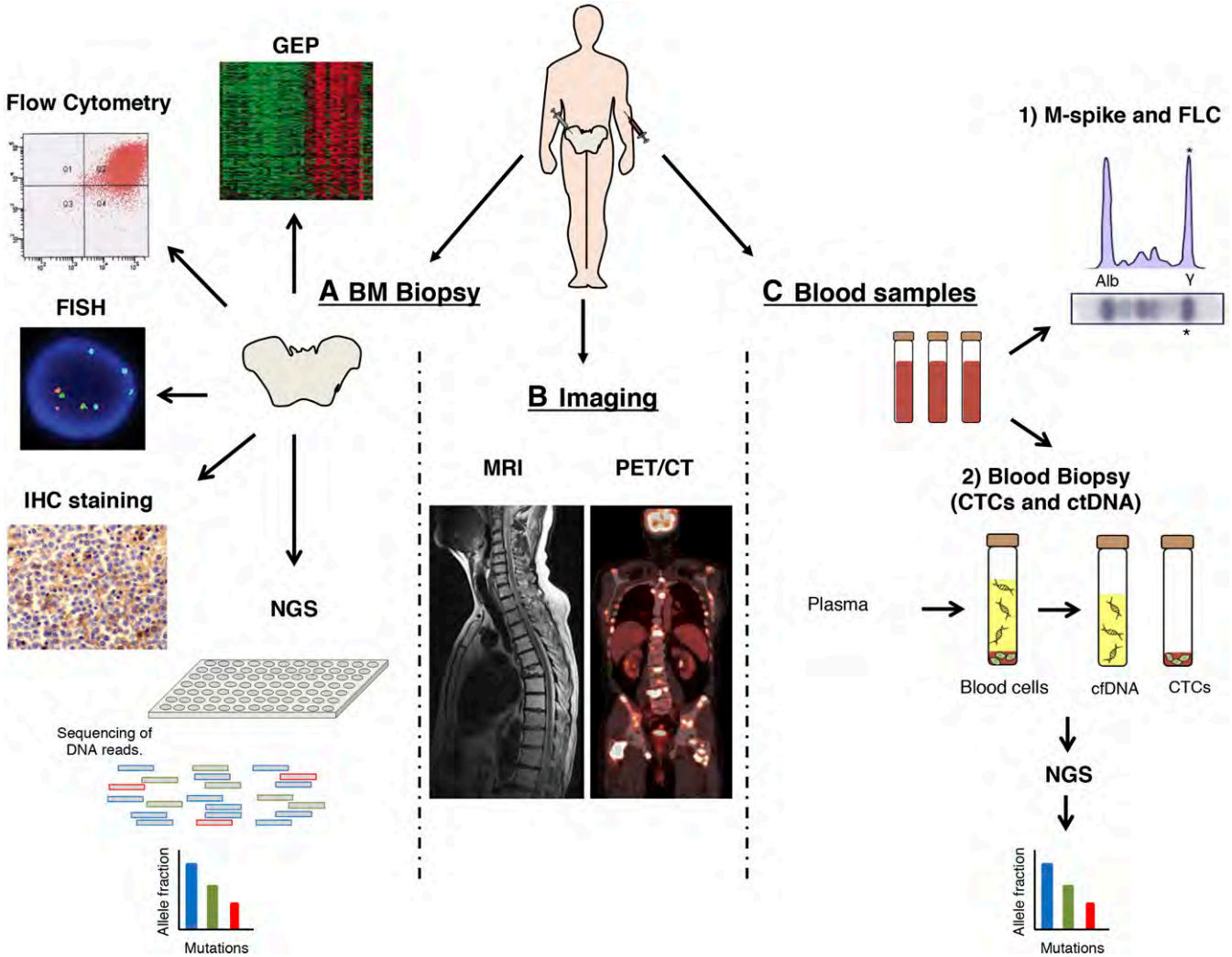
When compared with a myeloma relapse associated with an increase in M protein only, relapse defined by an increase in FLC alone predicted a shorter time to second-line therapy, a twofold increase in risk for second progression, and a threefold increase in mortality risk.[28] Thus, serial FLC measurements, starting from the time of diagnosis, could provide an accurate tool to monitor disease relapse and progression as well as treatment response.

IMAGING AS PROGNOSTIC TOOLS

Myeloma staging is dependent largely on biochemical measurements, bone marrow sampling, and flow cytometry or molecular studies assessment for MRD, all of which do not take into account the spatial heterogeneity of the disease. For a long time, radiographic findings, specifically x-rays, were used for better staging of MM via the Durie-Salmon staging system. However, with the development of new whole-body imaging modalities (CT, MRI, and ^{18}F-fluorodeoxyglucose PET/CT) of superior sensitivity,[29-31] it seemed pertinent to include them into routine anatomic and functional staging of MM. Some actually were incorporated into a new staging system, called the Durie-Salmon Plus.[32,33]

The CT is an ideal tool for detecting early bone destruction but not for detecting myeloma activity in areas of prior destruction.[31] Conversely, MRI is sensitive enough to detect early marrow infiltration, is specific enough to distinguish benign from malignant osteolytic lesions,[34] and is otherwise helpful to visualize the pattern and degree of marrow involvement. When MRI was used in asymptomatic MM, identification of at least one lesion, a diffuse infiltration pattern, and a 20% or more marrow infiltration predicted progression to symptomatic MM.[35] Furthermore, new trends in MRI

FIGURE 1. Overview of Standard and Next-Generation Biomarkers in Multiple Myeloma



(A) Current bone marrow (BM) biopsy–dependent methods used in diagnosis of multiple myeloma (MM), in addition to new emerging methods, like gene expression profiling (GEP) and next-generation sequencing (NGS). (B) Current imaging modalities in MM: PET/CT, multiparameter flow cytometry (MFC), and NGS techniques also are used to detect minimal residual disease (MRD) after therapy. (C1) Standard serum biomarkers such as M protein and free light chains (FLCs). (C2) Potential future biomarkers, such as blood biopsy, which imply detection of recurrent mutations in blood samples through circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). Blood samples from patients are collected, and free DNA is extracted from plasma, whereas CTCs are sorted by MFC. The isolated CTCs or ctDNA are then used for library preparation and sequencing for mutation calling and allele fraction (AF) calculation. AF is the number of mutatnt reads over the total reads obtained for a genomic locus. Comparison of AF in consecutive samples could provide valuable information about the response to therapy. These methods also can detect new emerging clones that could drive relapse in certain patients.

TABLE 1. Current Standardized Staging Systems in Newly Diagnosed Symptomatic MM

Stage	Durie-Salmon Staging	International Staging System	Revised International Staging System
I	Hemoglobin > 10.5g/dL Calcium ≤ 12mg/dL IgG < 5g/dL; IgA < 3g/dL Bence Jones < 4g/24hrs Bone x-ray: normal or solitary bone plasmacytoma	β2 microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL	β2-microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL plus normal LDH and no high-risk cytogenetics
II	Neither I or III A: Creatinine ≤ 2mg/dL B: Creatinine > 2mg/dL	Neither I or III	Neither I or III
III	Hemoglobin < 8.5g/dL Calcium > 12mg/dL IgG > 7g/dL; IgA > 5g/dL Bence Jones > 12g/24hrs Bone x-ray > lytic lesions	β2-microglobulin ≥ 5.5 mg/L	β2-microglobulin ≥ 5.5 mg/L and elevated LDH or high-risk cytogenetics [t(4;14), t(14;16), or del(17p)]

Abbreviations: LDH, lactate dehydrogenase; MM, multiple myeloma.

techniques, including contrast-enhanced, diffusion-weighted imaging and fat-water imaging, have made their way into clinical practice. CE is helpful to detect vascular changes after treatment[36]; diffusion-weighted imaging can accurately measure bone marrow cellularity and changes in apparent diffusion coefficient[37]; and fat-water imaging can detect fat and hematopoietic marrow alterations.[38] FDG-PET has a similar advantage to MRI but provides the results in a more reasonable time frame,[30] and CT shows early bone destruction, so PET/CT seems to be the ideal imaging modality for disease staging and follow-up.[39-41] In fact, the metabolic response and number of focal lesions found on PET/CT in patients with newly diagnosed MM after treatment proved to have independent prognostic value.[42,43] Thus, new modalities of imaging are capable of accurately differentiating early-stage MM from MGUS and SMM, for which x-rays usually are negative, and are better at discriminating among the three stages of MM and predicting progression.[32,40]

GENOMIC BIOMARKERS

During the past decades, genetic aberrations detected by interphase FISH, have been used extensively as diagnostic and prognostic biomarkers in MM.[44-46] Copy number variations (CNVs), including hyperdiploidy (trisomies or tetrasomies of odd numbered chromosomes) and focal or chromosome arm gain or loss, along with translocations involving the

TABLE 2. Risk Stratification of Patients With Smoldering Myeloma According to Mayo Clinic and Spanish Models and the Proposed New Criteria of High-Risk SMM

	Risk Factors	No. of Risk Factors	5-Year Progression (%)
Mayo Clinic Model	M protein ≥ 3 g/dL	1	25
	≥ 10% BM plasma cells	2	51
	FLC ratio < 0.125 or > 8	3	76
		Total	51
Spanish Model	≥ 95% aPC	0	4
	Immunoparesis	1	46
		2	72
		Total	46
Proposed New Criteria for High-Risk SMM[15]	Clonal BMPCs 10% and any one or more of the following: • Serum M protein > 30 g/L • IgA SMM • Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes • Serum involved/uninvolved FLC ratio > 8 but < 100 • Clonal BMPCs 50% to 60% • t(4;14) or del(17p) or 1q gain • aPC immunophenotype (95% of BM plasma cells are clonal) and reduction of one or more uninvolved Ig isotypes • MRI with diffuse abnormalities or one focal lesion • PET/CT with focal lesion with increased uptake without underlying osteolytic bone destruction		

Abbreviations: aPC, abnormal plasma cells; BM, bone marrow; BMPCs, bone marrow peripheral cells; FLC, free light chain; Ig, immunoglobulin; SMM, smoldering multiple myeloma.

immunoglobulin heavy chain locus on chromosome 14, are hallmarks of MM pathogenesis.[45] Hyperdiploidy and chromosomal translocations are the most common genetic aberrations in MM, and both are considered primary events in MM.[47] Isolated hyperdiploidy has a favorable prognosis compared with nonhyperdiploid and hypohaploidy (a range of 24 to 34 chromosomes), which have poorer prognoses.[48] Chromosomal translocations result in a fusion product, in which the partner genes become under the control of the immunoglobulin heavy chain enhancer. This leads to the overexpression of oncogenes, which as *MMSET*/*FGFR3*, *CCND3*, *CCND1*, *MAF*, and *MAFB*, in translocations t(4;14), t(6;14), t(11;14), t(14;16), and t(14;20), respectively.[49-54] These aberrations provide a survival advantage and increase the proliferative capacity of the clones that harbor them. Nonetheless, they vary in their prognostic outcomes and in their impacts on the progression of SMM to MM (Table 3). For example, t(4:14) has been associated with a poor prognosis in previous studies; however, survival outcome with this translocation has improved significantly with the introduction of PIs.[50,55] Conversely, patients who harbor high-risk cytogenetics like the 17p loss, which affects *TP53*, t(14;20), and t(14;16), continue to have poor prognoses despite advances in therapeutic options of MM.[50,56] Moreover, MAF protein, which is the fusion product of t(14;16) and its paralogue, MAFB, in t(14;20), have conferred innate resistance to PIs, which indirectly increase the stability of MAF protein.[56] Interestingly, despite their association with adverse prognoses in MM, these two aberrations are associated with a standard risk of progression in MGUS and SMM.[56-58]

Translocations activating the *MYC* oncogene are considered secondary events that occur with disease progression. These translocations are present in 15% of patients with MM and result in lower PFS and OS rates; however, their prevalence in MGUS and SMM is only 3% to 4%, and their impact on progression to MM is unknown.[59,62,63] Overexpression of *MYC* occurs through the juxtaposition of superenhancers that surround the partner gene to the *MYC* locus, but, unlike the other translocations, only 30% of *MYC* translocations in MM involve the Ig locus.[49,63] Moreover, they are positively associated with hyperdiploidy but inversely correlated with t(4;14).[64] Interestingly, the presence of *MYC* translocations alone, or with 1q amplification, defines a poor prognostic subtype in hyperdiploid MM.[49,65] The recent introduction of the *BET*-bromodomain inhibitors, which act by disrupting the superenhancers, indicates that patients with *MYC* overexpression could benefit from this targeted therapy.[66]

Cytogenetics have been a key prognostic biomarker in risk stratification of patients; however, they can render the disease course unpredictable when two markers that predict opposing outcomes coexist in the same patient.[67] They also modestly assist in determination of the appropriate regimens, so there exists a need to discover new biomarkers for targeted therapy.

GEP

Several studies have resorted to GEP to assess the molecular heterogeneity of MM and to investigate the expression level of a set of genes and associate them with clinical outcome. An early study introduced the University of Arkansas for Medical Sciences model, which stemmed from one of the most common genetic abnormalities in MM, chromosome 1 mutations.[68-70] An expression profile of 70 genes, 30% of which were on chromosome 1 (1p and 1q), in $CD138^+$ plasma cells isolated from newly diagnosed patients, revealed 51 upregulated genes and 19 downregulated genes. This 70-gene model score was able to accurately predict disease-free survival in the majority of patients and correlated well with myeloma staging, cytogenetic abnormalities, and serum levels of β2 microglobulin, along with lactate dehydrogenase and C-reactive protein. This model was reduced into a 17-gene model that had the same prognostic power.

Moreover, the Intergroupe Francophone du Myélome developed another 15-gene model that complemented the University of Arkansas for Medical Sciences model and

TABLE 3. Common Cytogenetic Aberrations in MM and SMM and Their Prognostic Outcomes

Cytogenetic Abnormality	Genes/Chromosomes Affected	% in MM	Prognostic Value in MM	% in SMM	Significance in SMM
Trisomies	Odd-numbered chromosomes	50	Good prognosis		Standard risk of progression
t(11;14)	*CCND1*	15	Good prognosis	30	Standard risk of progression
t(6;14)	*CCND3*	5	Good prognosis	NA	Standard risk of progression
t(4;14)	*FGFR-3* and *MMSET*	15	Adverse/neutral	10	High risk of progression
t(14;16)	*c-MAF*	5	Adverse prognosis	3	Standard risk of progression
t(14;20)	*MAFB*	1	Adverse prognosis		Standard risk of progression
1q gain	*CKS1B* and others	35–40	Adverse prognosis	40	High risk of progression
17p del	*TP53*	10	Adverse prognosis	NA	High risk of progression
1p del	*FAM46C*, *CDKN2C*, and *FAF1*	30	Adverse prognosis	NA	ND
Monosomy 13	*RB1*	45–50	Neutral	NA	ND
MYC 8q24	*MYC*	15-20	Adverse prognosis	3–4	ND

Abbreviations: MM, multiple myeloma; NA, not available; ND, not defined; SMM, smoldering multiple myeloma.

The above data on cytogenetic abnormalities is based on large comprehensive studies on the frequency and impact of these abnormalities on patients with MM and SMM.[49,58-61]

predicted the survival of patients with newly diagnosed MM and relapsed disease.[71] This model correlated well with known cytogenetic abnormalities and their prognoses; when combined with β2 microglobulin levels and t(4;14), it was developed into a tool with the three independent prognostic entities that accurately identified the high-risk group of patients with myeloma. Interestingly, the 15-gene model mostly included genes that pertained to the cell cycle, specifically regulators of chromosomal segregation, which suggests that these mutations maintain a state of chromosomal instability and aneuploidy, a hallmark of MM.[72]

Given that MM exhibits an increasing proliferation rate as it progresses from MGUS to overt early- and late-stage myeloma,[73] a third study was developed to construct the gene expression-based proliferation indices model, in which proliferation genes differentially expressed between proliferating malignant myeloma cell lines and nonmalignant plasmablastic cells, as well as nonproliferating normal plasma and memory B cells, were selected.[74] This index of proliferation genes turned out to be a useful prognostic tool of event-free and overall survivals in patients with myeloma who were treated with high-dose chemotherapy and autologous stem cell transplantation, and the index was independent of the most prominent clinical risk factors of MM. Many GEP studies of various myeloma cohorts followed suit through the years and concluded that GEP could be a potential method for risk assessment in MM.[75-79]

NEXT-GENERATION BIOMARKERS

NGS in MM

With the advent of NGS technologies, it became possible to examine the molecular state of the genome in the cell of a patient and detect mutations, even those that occurred at very low frequencies. These technologies have been exploited in MM to discover recurrent mutations that drive its progression. Indeed, three large studies identified 15 commonly mutated genes in MM and their prognostic value (Table 4).[64,80,81] Results of these studies revealed that the mitogen-activated protein kinase (MAPK) pathway, which includes *KRAS*, *NRAS*, and *BRAF* genes, is the most commonly mutated in MM. Mutations activating the nuclear factor κB pathway, which is commonly deregulated in B-lymphoid malignancies, are also found in MM; however, the range of these mutations varies among these malignancies.[64] Interestingly, mutations in *IRF4* and *EGR1*, which are plasma cell survival genes and targets of IMIDs, exhibit a favorable survival outcome.[82-84] Conversely, mutations in DNA repair pathway genes (*TP53*, *ATM*, and *ATR*) are considered poor prognostic markers.

A new prognostic model was developed by combining the ISS with Myeloma XI clinical trial data along with mutations that affect *TP53*, *ATM*, or *ATR*—and *ZFH4* or *CCND1*; CNVs, including del(17p) and amp(1q); and translocations involving t(4;14) and *MYC*.[64] This model showed better sensitivity than ISS alone in the early detection of disease progression and prediction of mortality risk in patients with high-risk myeloma. This may represent one of the first prognostic models that encompasses the ISS staging system along with next-generation genomic classifications to better define the prognostic markers of patients with MM (Table 2).

These prognostic findings not only improve knowledge about detection of patients with high risk and predict their outcomes but also may help identify patients who would benefit from specific therapies. Indeed, recent studies reported that two patients who harbored the *BRAF*-V600E mutation had achieved durable response with the *BRAF*

TABLE 4. Common Somatic Mutations in Symptomatic MM and Their Prognostic Outcomes

Pathway	% With Affected Pathway	Gene Name	Frequency (%)	Prognosis
MAPK	40	*KRAS*	23	Neutral
		NRAS	20	
		BRAF	8	
NF-κB	20	*TRAF*	3	Neutral
		CYLD	2	
		LTB	3	
DNA repair	10	*TP53*	9	Poor
		ATM	3	
		ATR	1	
RNA metabolism	15	*FAM46C*	9	Neutral
		DIS3	7	
Plasma cell differentiation	10	*IRF4*	3	Favorable
		EGR1	5	

Abbreviations: MAPK, mitogen-activated protein kinase; MM, multiple myeloma; NF-κB, nuclear factor κB.

These data are based on the three largest studies that examined the recurrent somatic mutations in MM and their prognoses.[64,80,81] The percentages are calculated according to the mutated occurrences of these cohorts.[85]

inhibitor vemurafenib.[86,87] This observation was supported by similar findings in cell lines that expressed mutant *BRAF* compared with controls.[81] However, paradoxical upregulation of the MAPK pathway was observed in wild-type *BRAF* cell lines and in patients with melanoma.[81,88] Notably, this upregulation was more pronounced in *KRAS* and *NRAS* mutant cell lines.[81] Target sequencing panels would be valuable tools to implement in clinical settings, given their decreasing cost and their accuracy. They can provide a more comprehensive view of the genomic landscape of MM by detecting both the common translocations and CNVs and recurrent point mutations. They also have the advantage of identifying mutations that not detected by interphase FISH but that confer a poor prognosis, such as the mutations in *TP53* and *CCND1* genes.[64,85] Somatic mutations could be valuable biomarkers that predict response to therapy and guide the decisions of adding specific target agents to standard therapies to achieve a better response. Indeed, clinical trials to target *KRAS*, *NRAS*, *BRAF*, and other actionable mutations are taking place now.[85]

MRD

MRD has emerged as one of the most relevant prognostic factors in MM. Most, but not all, MM relapses can be attributed to the persistence of MRD. Thus, a complete response definition that is based solely on protein analysis and conventional cytologic techniques is insufficient. Current data suggest that MRD could be used as a biomarker to evaluate treatment efficacy, direct the therapeutic decisions, and act as predictor of PFS and OS.[89] However, the role of MRD in MM is still a matter of debate. The standard methods to detect MRD status in patients with MM are multiparameter flow cytometry (MFC) and allele-specific oligonucleotide quantitative PCR (ASO-qPCR). MFC can detect one clonal plasma cell in 10^4 normal cells with the seven-color MFC, and this sensitivity increases to 1 clonal cell in 10^5 with the eight-color MFC.[90] However, the sensitivity of MFC for detection of MRD is dependent on the quality of the specimen, the number of cells analyzed, and the capability of the antibody panel to distinguish abnormal from normal plasma cells.[91] ASO-qPCR of variable diverse joining (VDJ) heavy chain rearrangements is another approach to detect MRD. ASO-qPCR is more sensitive than MFC, but less applicablebecause it requires production of patient-specific probes.[92] One of the limitations of both techniques is that they rely on bone marrow samples, which could vary as a result of the patchy nature of the disease; the variance, thus, can lead to false negative results. NGS was introduced to allow the detection of clonal immunoglobulin VDJ gene rearrangements with very high sensitivity (1 clonal cell in 10^6 normal cells) in patients with ALL and CLL patients; furthermore, this technique has the advantage of not being restricted to bone marrow samples like the other methods are.[93-95] In MM, similar results were seen in a study of 133 patients,[96] which suggests that VDJ sequencing could be more sensitive and specific than MFC and ASO-PCR to detect MRD in MM. However, recent advances in flow technologies indicate that next-generation flow sensitivity would be similar to that of NGS; therefore, both methods could be used efficiently to detect MRD. In addition, imaging tools, specifically PET/CT, could play an important role in monitoring MRD. A specific advantage of PET imaging relies on its ability to detect extramedullary disease and early tumor activity. MRD would be an important biomarker and endpoint to evaluate therapeutic approaches in MM; however, standardization is necessary to eliminate or correct the relative differences between MRD negativity assessment and response rates across laboratories. Recently, the International Myeloma Working Group defined new response categories of MRD negativity to allow uniform reporting (Table 5).

Potential Next-Generation Biomarkers in MM

Blood biopsy. Blood biopsy includes the detection of circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) in the peripheral blood of patients. It has emerged as a promising noninvasive tool in the era of precision medicine. In MM, bone marrow (BM) biopsy is the gold standard for diagnosis; however, it is an invasive and painful procedure. It is also limited to initial diagnosis and is less likely to be used to confirm progression. Furthermore, given that MM is a multifocal disease with patchy BM infiltration and notable clonal heterogeneity, BM biopsy is unlikely to represent the spatial or temporal mutational landscape of the disease. A blood biopsy can be a feasible noninvasive alternative that depends only on routine blood samples. Indeed, several studies have been conducted in different types of malignancies to assess the validity of this approach. The results have shown that ctDNA and CTCs can accurately detect the mutational landscape of different cancers compared with standard methods. Moreover, they can serve as prognostic and predictive biomarkers for disease relapse and response to therapy.[97-101] However, in MM, the mutational analysis of CTCs and the role of ctDNA were not described until recently.

CTCs. CTCs are released from the primary tumor or metastatic sites into the bloodstream. Whether the release of CTCs into the bloodstream is a random process or is part of the tumor biology is still unclear. Myeloma CTCs are detectable by flow cytometry and may serve as a predictor for survival in patients with newly diagnosed and relapsed disease.[102-104] In patients with newly diagnosed disease, the presence of more than 400 CTCs was associated with higher proliferation, adverse cytogenetics, lower OS, and shorter time to next treatment.[105] Another study attempted to define the prognostic value of CTCs in relapsed disease, and the presence of more than 100 CTCs predicted worse survival in patients with active disease relapse.[102] Moreover, high levels of CTCs in SMM were associated with an elevated risk of progression to MM in the first 2 to 3 years (Table 2).[106] Nevertheless, the sensitivity of standard flow cytometry is insufficient to detect myeloma CTCs in nearly 25% of patients, even among those with a high tumor burden.[103] Recently, a study demonstrated the feasibility of detecting CTCs by using multiparameter flow cytometry and interrogating them

TABLE 5. International Myeloma Working Group MRD Criteria

Result	Criteria Definition*
Sustained MRD negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to additionally specify the duration of negativity (e.g., MRD negative at 5 years).
Flow MRD negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the Euro-Flow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 or greater nucleated cells.
Sequencing MRD negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as fewer than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates with the LymphoSIGHT platform (or validated equivalent method), with a minimum sensitivity of 1 in 10^5 or greater nucleated cells.
Imaging plus MRD negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.

*These criteria require achieving complete response on the basis of the standard International Myeloma Working Group response criteria.[89]
Abbreviations: MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; SUV, standardized uptake value.

for MM-recurrent mutations.[107] In a cohort of eight patients, 93% of BM mutations were present in CTC samples, whereas only 90% of CTC mutations were present in BM. Furthermore, 100% of clonal mutations in BM were confirmed in CTC samples, and 99% of clonal mutations in CTC were present in BM specimens. Another study reported similar findings but on a single-cell level in a group of six patients. Results of tests from three of those patients showed that 100% of the mutations were concordant in both a single CTC and a BM cell. Interestingly, in the other three patients, the proportion of CTCs that harbored mutations was significantly higher than that observed in single cells from BM samples.[108] Taken together, these results illustrate the extensive genetic heterogeneity of MM and the limited ability of standard focal biopsies to reveal such a critical feature. Despite the small number of the cohorts, these findings prove the validity of CTCs as a surrogate to evaluate the clonal architecture and evolution of MM and open the door for more systematic studies.

ctDNA. ctDNA can be found in more than one form; either in tumor cells or present as cell-free DNA (cfDNA). However, cfDNA is a general term that involves both ctDNA and non-tumor DNA.[109] ctDNA is released by the tumor cells into the blood and thus harbors the mutations of the original tumor. Serial studies suggest that use of ctDNA as a biomarker may significantly improve current systems of cancer diagnosis and facilitate the detection of the tumor in early stages and of disease progression.[98-101,110,111]

In MM, two recent studies examined the significance of ctDNA as a biomarker. In a cohort of 10 patients with matched blood and bone marrow samples,[112] genetic abnormalities, including CNVs and somatic mutations, were concordant between ctDNA and BM samples. The sensitivity rates of ctDNA in harboring clonal and subclonal mutations present in the bone marrow were 100% and 96%, respectively. Furthermore, the utility of ctDNA in monitoring disease progression and response to therapy was tested by measuring the allele fraction in serial samples of seven patients.[113] It coincided with the changes in serological biomarkers and reflected a true disease status in three patients. In the other four patients, the allete fraction appeared to be a better prognostic and predictive biomarker: early changes in AF occurred before notable shifts in the standard markers. Strikingly, AF showed discordance, but a better prediction of therapeutic response, in two patients.

ctDNA could be a more promising biomarker, given the technical challenges involved in isolating and characterizing CTCs by conventional flow cytometry methods. Recently, it has been reported that NGS of clonal immunoglobulin VDJ gene rearrangements could be performed on cfDNA for MRD detection.[93-95] In addition, recent sequencing methods, like cancer personalized profiling by deep sequencing, have been highly sensitive and specific in quantifying ctDNA; in this method, probe panels are designed to target recurrently mutated regions in the cancer of interest.[114] Importantly, unlike other protein markers, the half-life of ctDNA is less than 2 hours,[115,116] which indicates that it can reflect a real-time tumor burden in patients receiving therapy and can also detect changes in tumor dynamics before conventional protein biomarkers and imaging techniques.[117,118] Indeed, several studies reported that ctDNA was more sensitive and specific than CTCs and standard protein biomarkers in various malignancies.[97,117]

Predictive biomarkers for immunotherapy. Immunotherapy is a cornerstone in MM treatment; starting with the introduction of IMIDs, which significantly improved survival outcomes, to the new monoclonal antibodies that target specific antigens, like daratumumab and elotuzumab. Recently, new therapies with antibodies that target PD-1 and its ligand PDL-1, together with those that target CTLA-4, have been associated with remarkable response rates in melanoma, non–small cell lung cancer, Hodgkin lymphoma, and bladder cancers.[119-123] The role that immune checkpoints play in mediating immune evasion and the subsequent efficacy of immune blockade have emerged as interesting topics and have warranted examination of these agents in MM. Previous studies demonstrated that PD-L1 is expressed on plasma cells isolated from different stages of MM and

is highly expressed in relapsed disease.[124-127] Moreover, PD-1 expression is reportedly upregulated in natural killer or T cells in patients with MM.[125,128] Indeed, growth of MM cells was inhibited completely in PD-1–deficient mice and transiently with administration of anti–PD-L1 antibody.[129] The role of CTLA-4 inhibitors in MM is under examination. However, early clinical results of single-agent anti–PD-1 in relapsed myeloma were underwhelming.[130] This suboptimal outcome probably is due in part to the complex network of immunosuppressive pathways in MM, which justifies the need for combination therapies to achieve a better response.[131,132] Indeed, studies that include multiple drug combinations show promising preliminary results,[133] which indicates that the role of checkpoint inhibitors is yet to be delineated in MM. On the basis of previous observations in other malignancies, the following biomarkers might play a major role in predicting the efficacy and response to these agents in MM:

1. Tumor neoantigens (mutation load): Neoantigens are nonsynonymous mutations that are transcribed and translated into a polypeptide and that possibly generate a neoepitope. These neoantigens are presented on class I major histocompatibility complex molecules on tumor cells and consequently are recognized by the adaptive immune system. Several studies in melanoma and non–small cell lung cancer identified a positive correlation between the mutation load and clinical response to CTLA-4 and PD-1 inhibitors.[134-136] Although the mutational load in MM is not as high as in those malignancies, future studies are needed to elucidate the role of neoantigens in predicting the response to immune checkpoint inhibitors in MM.
2. Tumor-infiltrating lymphocytes: Lymphocyte infiltration in the tumor microenvironment has been associated with improved survival in several malignancies and might serve as prognostic and predictive biomarker to checkpoint inhibitors.[137,138] Indeed, the clonal $CD8^+$ T-cell infiltration into the tumor and its invasive margin were positively correlated with response in patients with melanoma.[139] These observations support the need for accurate immune profiling at baseline to try to identify ideal candidates and immune monitoring to identify those who would benefit the most from these agents. Other factors, such as the ability of neoantigens not only to bind class I major histocompatibility complex molecules but also to generate an immune response that can be recognized by the T-cell repertoire, can contribute to prediction of the response to these therapies.[140] Moreover, mutations in major histocompatibility complex class I molecules and *JAK*/*STAT* pathway signaling can alter the presentation of neoantigens on tumor cells and eventually alter resistance to immune checkpoints.[141,142]

Note that it is unlikely that a single biomarker will be sufficient to predict clinical outcomes in response to immune-targeted therapy. Rather, integration of multiple tumor and immune response parameters, such as protein expression, genomics, and transcriptomics, may be necessary for accurate prediction of clinical benefit in MM.

CONCLUSION

During the past decades, biomarkers such as M protein and β2 microglobulin have shaped the knowledge about MM. Later, cytogenetic biomarkers and FLC have provided more information about the diverse course and outcome of the disease. They also enabled, with other biomarkers, prediction about the risk of progression in patients with SMM. More recently, massive parallel sequencing techniques have made it possible to detect the recurrent mutations in MM, which allowed the development of new models that better stratify high-risk groups and early precursor stages. These markers are beginning to guide clinicians about appropriate therapy for a particular patient. The blood biopsy technologies also will enable physicians to monitor the tumor progression and the response to different therapies. These promising approaches will provide valuable opportunities for early intervention before clonal expansion renders the disease refractory to treatment. However, for a biomarker to be standardized, it needs to be developed in the context of clinical trials and to be tested before its routine use in clinical practice.

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Hematologic Malignancies: Plasma Cell Disorders

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OVERVIEW

Multiple myeloma (MM) is a plasma cell malignancy characterized by the growth of tumor cells in the bone marrow. Properties of the tumor microenvironment provide both potential tumor-promoting and tumor-restricting properties. Targeting underlying immune triggers for evolution of tumors as well as direct attack of malignant plasma cells is an emerging focus of therapy for MM. The monoclonal antibodies daratumumab and elotuzumab, which target the plasma cell surface proteins CD38 and SLAMF7/CS1, respectively, particularly when used in combination with immunomodulatory agents and proteasome inhibitors, have resulted in high response rates and improved survival for patients with relapsed and refractory MM. A number of other monoclonal antibodies are in various stages of clinical development, including those targeting MM cell surface antigens, the bone marrow microenvironment, and immune effector T cells such as antiprogrammed cell death protein 1 antibodies. Bispecific preparations seek to simultaneously target MM cells and activate endogenous T cells to enhance efficacy. Cellular immunotherapy seeks to overcome the limitations of the endogenous antimyeloma immune response through adoptive transfer of immune effector cells with MM specificity. Allogeneic donor lymphocyte infusion can be effective but can cause graft-versus-host disease. The most promising approach appears to be genetically modified cellular therapy, in which T cells are given novel antigen specificity through expression of transgenic T-cell receptors (TCRs) or chimeric antigen receptors (CARs). CAR T cells against several different targets are under investigation in MM. Infusion of CD19-targeted CAR T cells following salvage autologous stem cell transplantation (SCT) was safe and extended remission duration in a subset of patients with relapsed/refractory MM. CAR T cells targeting B-cell maturation antigen (BCMA) appear most promising, with dramatic remissions seen in patients with highly refractory disease in three ongoing trials. Responses are associated with degree of CAR T-cell expansion/persistence and often toxicity, including cytokine release syndrome (CRS) and neurotoxicity. Ongoing and future studies are exploring correlates of response, ways to mitigate toxicity, and "universal" CAR T cells.

MM is a plasma cell malignancy characterized by the growth of tumor cells predominantly in the bone marrow. It is now well established that nearly all cases of MM originate from an underlying precursor state. Several lines of evidence support the notion that as with other tumors, properties of the tumor microenvironment provide both potential tumor-promoting and tumor-restricting properties. However, MM represents a relatively unique situation from the perspective of tumor-immune interactions, as it is a malignancy that directly involves an immune cell (plasma cell), and bone marrow represents a specialized tissue for survival of immune cells. Therefore, it is expected that immune cells in the MM tumor microenvironment will have the capacity for direct interactions with MM cells, essentially representing extension of normal physiology. Aspects of normal plasma cell physiology (such as the importance of protein homeostasis and unfolded protein response) will impact MM biology, and mechanisms of antibody diversification such as cytidine deaminases may play a role in mediating genomic instability. The growth of MM cells in the bone marrow also has important implications for tumor immunity in that it suggests a potential role for interactions with bone cells in regulating immunity.

The concept that most monoclonal gammopathy of undetermined significance (MGUS) lesions exhibit clinical stability in spite of advanced genomic complexity and intraclonal evolution of the tumor clone suggests that changes in growth rate, and therefore malignant transformation, may depend in part on interactions of tumor cells with the microenvironment. Recent studies have shown that MGUS cells mediate progressive growth upon xenotransplantation in humanized mice.[1] In this model, genetic humanization of mice is achieved by the expression of several human genes in mice that are essential for the growth of human cells and that mediate species-specific effects. This observation provides direct support to the concept that the observed clinical stability of MGUS lesions may indeed depend predominantly on tumor-extrinsic growth controls. In other

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TABLE 1. Diversity of Immune Effectors

	Adaptive Immunity	Innate Immunity	Unconventional T cells
Major Contributors	CD4, CD8 T cells	NK cells, Macs	Diverse; non-MHC restricted
Antigen Specificity	Yes	No	Nonpeptide
Memory	Yes	No (except some NK)	?
Tissue Distribution	Lymphoid and NLT	Lymphoid and NLT	Mostly NLT
Antitumor Effectors	CD8+ T cells, Th 1	NK cells, macrophages	iNKT
Protumor	Tregs, ? Th2, Th17 TFH (? for lymphoid tumors)	MDSCs, M2 macrophages, DCs	Type II NKT-TFH

Abbreviations: NK, natural killer; MHC, major histocompatibility complex; NLT, non-lymphoid tissue; iNKT, invariant natural killer T cells; TFH, T follicular helper cells; MDSCs, myeloid-deprived suppressor cells; DCs, dendritic cells.

words, the process of "malignant transformation" may depend more on how the tumor cells modify the host-mediated growth control. MGUS or MM cells grow primarily in the bone marrow and interact with several cells in this complex microenvironment, including immune cells, bone cells, endothelial cells, stromal cells, and noncellular matrix.[2]

Immune cells infiltrating tumors can be broadly divided into innate and adaptive immunity (Table 1). Adaptive immunity is characterized by antigen specificity and immunologic memory. In contrast, innate immune cells are typically thought to lack immunologic memory, with the exception of some subsets of natural killer (NK) cells. More recently, new subsets of unconventional T cells that recognize nonpeptide ligands have been identified. Perhaps the best studied in this setting are NKT cells that recognize lipid antigens in the context of CD1d. All three types of immune cells can have subsets that can mediate both pro- and antitumor effects. For example, cytotoxic CD8+ T cells and Th1 cells mediate tumor protection, while regulatory T cells, Th2 cells, or T follicular helper (TFH) cells can promote tumor growth. Similarly, among innate immune cells, NK cells and macrophages mediate protective immunity, but myeloid suppressor cells, alternatively activated or M2 macrophages, or dendritic cells (DCs) can promote tumor growth. Therefore, the tumor immune interactions in MM represent a balance of pro- and antitumor interactions.

KEY POINTS

- **There is a diversity of immune effectors cells in patients with MM.**
- **CD38- and SLAMF7-directed monoclonal antibodies have shown remarkable clinical activity in MM either as single agents or in combinations with thalidomide analogues or proteasome inhibitors.**
- **Cellular immunotherapy for MM, including DC vaccines, genetically modified T-cells with CARs, and enhanced T-cell receptors, have demonstrated remarkable clinical responses in early pilot studies and hold great promise for the treatment of MM.**
- **Bispecific antibodies targeting malignant plasma cells, while activating and attracting cytotoxic T cells, may allow for off-the-shelf enhanced immunotherapy for MM.**

MM tumors are infiltrated with DCs and macrophages,[2] and interactions of either myeloid or plasmacytoid DCs with MM cells can promote tumor growth.[3-6] Tumor–DC interactions may also promote cell fusion via CD47-thrombospondin-1 interactions and lead to formation of osteoclasts,[7,8] as well as genetic instability by inducing the expression of cytidine deaminases.[9] The importance of TFH cells in the generation of long-lived plasma cells is well established.[10] Interactions of tumor cells with TFH cells may also promote malignant B-cell differentiation.[11] Several studies have demonstrated the capacity of both innate and adaptive immune cells to recognize MM/MGUS cells and potentially mediate growth control.[12] Tumor-specific CD4 and CD8+ T cells can be identified in the bone marrow of patients with MGUS.[13] Much of this response is specific to individual tumors.[13] However, search for shared antigens have identified distinct targets of immunity in MGUS, such as SOX2 embryonal stem cell antigen.[14] In a recent prospective study, the presence of SOX2-specific T cells and the expression of PD-L1 on tumor cells and T cells at baseline correlated with risk of progression to clinical MM requiring therapy.[15] Progression to clinical MM is associated with a loss of effector function in several immune effectors including T, NK, and NKT cells.[16,17] However, even in the setting of clinical MM, the bone marrow contains antimyeloma T cells that may be harnessed for immune therapy.[17,18] Several mechanisms have been proposed to help explain the loss of tumor immunity with malignant progression. These include shedding of suppressive factors such as NKG2D ligands[19] and immune suppressive cytokines; suppression mediated by regulatory T cells[20,21] or myeloid-derived suppressor cells[22-24]; and induction of a senescent phenotype in T cells. It is notable that clinical MM is associated with a switch to interleukin (IL)-17–producing Th17 cells, which correlate with MM bone disease.[25-27] Several recent studies have demonstrated the expression of inhibitory immune checkpoints such as PD-L1 on tumor cells,[15,28] although a role for other checkpoints such as CD226[29] and induction of T-cell senescence[30] has also been implicated.

In addition to conventional T cells, other subsets of innate immune cells may also play a role in immune surveillance. In particular, importance of NK cells in MM control has been demonstrated in mouse models,[29,31] and human NK cells can kill MM targets.[32-35] Mechanisms underlying altered

immune surveillance by NK and other innate immune cells may therefore also regulate myelomagenesis. Another common feature of evolution to MM appears to be an increase in biochemical features of chronic inflammation including bioactive lipids.[36] Recent studies have identified subsets of human CD1d-restricted type II NKT cells against these lipids that are enriched in human MM and promote plasma cell differentiation.[37,38] Altered balance of type I compared with II NKT cells may therefore also be an important immune-regulatory axis in evolution of MM[36,39] and is further supported by loss of CD1d expression with disease progression of MM.[40] These studies also raise the possibility that targeting the underlying triggers for antigenic stimulation could alter the evolution of tumors. Together, these studies paint a complex picture, with a potential role for several immune cells, and likely create redundancy that may impact immune-mediated growth control.[41,42] They also suggest that combination approaches may be desirable for immune-based prevention or therapy of MM.

MONOCLONAL ANTIBODIES

Monoclonal antibodies are very attractive therapeutic agents for cancer due to their high specificity and acceptable side effect profile. SLAMF7 is a cell surface glycoprotein receptor highly expressed on MM cells mediating adhesion to BM stromal cells. It is selectively expressed on plasma and NK cells and lacks expression on other tissues.[43] Elotuzumab, an anti-SLAMF7 monoclonal antibody, appears to both induce direct cell killing of MM cells and enhance NK cytotoxitiy through upregulation of EAT-226 (adaptor protein present on NK cells).[44] In a phase III trial comparing elotuzumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone (Rd), the former (elotuzumab, lenalidomide, and dexamethasone) showed an overall response rate of 79% versus 66% and progression-free survival of 41% versus 27%, respectively.[45]

CD38 is a transmembrane receptor protein highly expressed on malignant plasma cells and on normal B cells during different stages of their maturation.[46] The intracellular presence of this molecule has been reported in normal tissues including brain, smooth muscle, and osteoclasts. Nevertheless, daratumumab is the first U.S. Food and Drug Administration–approved anti-CD38 antibody. Single-agent daratumumab given to 106 heavily pretreated patients showed a dose dependent efficacy with 29% to 46% response rates at 16 mg/kg and an acceptable toxicity profile: mostly with adverse events associated to drug infusion and few serious adverse events that mainly consisted of cytopenias. The median duration of response was 7.4 months, and the estimated 1-year OS was 65%.[47] In a phase III trial with lenalidomide and dexamethasone (DRd), daratumumab increased the overall response rate to 93% versus 76% with Rd, with a complete response or better (43% vs. 19%). Median progression-free survival showed a 63% reduction in the risk of disease progression or death (hazard ratio, 0.37). Patients had a median of one prior therapy with 55% of patients having received prior immunomodulatory drug therapy.[48] Similarly, a randomized phase III trial of daratumumab with bortezomib and dexamethasone (DVd) versus Vd also showed an overall response rate of 83%, with DVd of 63% with an associated improvement in progression-free survival. The greatest benefit was seen in patients who had received one prior line of treatment, indicating that earlier treatment might provide the most benefit for patients with RRMM.[49]

CARS AND BEYOND: CELLULAR IMMUNOTHERAPIES IN MM

Rationale for Cellular Immunotherapy

Harnessing endogenous anti-MM immunity for clinical responses has been challenging, likely because of low frequencies and avidity of T cells specific for tumor antigens, as well as tolerance and/or exhaustion induced by immunosuppressive factors within the MM tumor environment, such as inhibitory cells and checkpoint molecules (e.g., PD-L1).[50] Many of these limitations can be overcome through cellular therapy, in which autologous or allogeneic T or NK cells are expanded and activated ex vivo and then infused back into patients, often after high-dose melphalan (in conjunction with autologous SCT), or other lymphodepleting chemotherapy. This lymphodepletion helps to remove suppressor cells and facilitate expansion of infused cells.[51] Two general approaches have been explored: (1) infusion of unmodified cells, in which the response depends on the endogenous anti-MM immune repertoire; and (2) infusion of genetically modified cells in which anti-MM specificity has been conferred through expression of a novel antigen receptor. This review will focus on T cells and summarize clinical results to date.

UNMODIFIED CELLULAR THERAPY STRATEGIES

Allogeneic Cells

Traditional donor lymphocyte infusion, alone or in combination with immunomodulatory drugs, have activity in MM relapsing after allogeneic SCT, but responses are inconsistent and risk of acute graft-versus-host disease remains high.[52-54] Recently, Koehne and colleagues identified an association between frequency of Wilms tumor 1 (WT1)–specific T cells and response to donor lymphocyte infusion in patients with MM. These cells could be expanded ex vivo and could lyse MM cells.[55] This has led to an ongoing phase I study of donor-derived, WT1-specific T cells in high-risk patients with MM following T cell–depleted allogeneic SCT (NCT01758328).

Autologous Cells

Several studies have explored using autologous lymphocyte infusions in conjunction with autologous SCT to generate anti-MM immunity. Autologous peripheral blood lymphocytes are typically collected pre-SCT, after initial exposure to a tumor vaccine, then expanded ex vivo using anti-CD3/CD28 beads, and then reinfused a few days after SCT, followed by several booster vaccinations, in an effort to take advantage of the lymphopenic period post-SCT to expand

the infused T cells. Rapoport and colleagues first tested this concept using a pneumococcal conjugate vaccine,[56] and subsequent studies have shown that robust antibody and T-cell responses can be generated even against poorly immunogenic self/tumor-antigens such as hTERT, survivin, MAGE-A3, and idiotype.[57-59] A more recent study using this platform in conjunction with a MAGE-A3 vaccine found cellular immunity could be generated even without the ex vivo expansion, suggesting that this labor-intensive step may not be necessary.[60] Despite these immune responses, however, the progression-free survival in these studies was not appreciably different than that expected from autologous SCT alone, suggesting a limited clinical impact from targeting these particular antigens.

Borrello and colleagues recently tested a novel variation on this strategy using marrow-infiltrating lymphocytes (MIL) as the source of the autologous lymphocyte infusion. MIL harbor a greater proportion of activated, MM-specific T cells and show greater ex vivo antimyeloma activity, than peripheral blood lymphocytes.[18] Twenty-two patients with MM (45% relapsed/refractory) received a median of 9.5 × 108 ex vivo–activated MIL on day 3 following autologous SCT. No vaccine was given. Immune responses against MM cells were substantially greater after MIL infusion, and stronger immune activity correlated with deeper clinical responses.[61] Overall response rate (54%) and median progression-free survival (18 months) were modest, though a larger study with a more homogenous population is currently underway to examine clinical outcomes.

GENETICALLY MODIFIED CELLULAR THERAPY STRATEGIES

Rather than relying on the endogenous T-cell repertoire, genetically modified approaches confer novel, heritable specificity to a large population of T cells through forced expression of a new antigen receptor. In addition, genes can be inserted for coreceptors or regulatory elements that enhance T-cell activation or persistence.[62] Retroviral vectors, based either on gamma-retroviruses or lentiviruses, are most commonly used to deliver the new genetic material to the T cells.[63] To date, two main approaches have been explored in MM: transgenic TCRs and CARs.

TABLE 2. CAR T-Cell Targets in MM

Target	References
CD19*	Garfall et al, 2015[70] and 2016[71]
BCMA*	Carpenter et al, 2013[72]; Cohen et al, 2016[76]
Kappa LC*	Ramos et al, 2016[78]
CD138*	Jiang et al, 2014[79]
Lewis Y*	Peinert et al, 2010[80]
NKG2D ligands*	Barber et al, 2011[81]; Nikiforow et al, 2016[82]
CD38	Drent et al, 2016[83]; Mihara et al, 2012[84]
CS1/SLAMF7	Chu et al, 2014[85,86]
CD44v6	Casucci et al, 2013[87]

*In clinical trials as of March 1, 2017.

Abbreviations: CAR, chimeric antigen receptor; MM, multiple myeloma; BCMA, B-cell maturation antigen.

Transgenic T-Cell Receptors

This strategy involves transducing autologous T cells to express a new TCR specific for a tumor antigen peptide-major histocompatibility complex (MHC). This approach has shown activity in solid tumors[64,65] and can target either extracellular or intracellular antigens. A recent study explored infusion of autologous T cells transduced to express an affinity-enhanced transgenic TCR specific for NY-ESO1 peptide in patients with MM undergoing autologous SCT. NY-ESO1 is a cancer-testis antigen expressed variably in patients with MM, with greater expression in relapsed disease.[66] Twenty NY-ESO1+, HLA-A0201+ patients received T cells on day 2 post-SCT. Infusions were well tolerated, with three cases of self-limited autologous graft-versus-host disease. T cells expanded and homed to bone marrow and persisted in some patients for over 1 year. The near complete response/complete response rate was 70%, with a median progression-free survival of 19.1 months. Relapse was associated with loss of NYESO1 expression in some patients, suggesting immune-mediated selective pressure.[67] A follow-up study using T cells alone without SCT is ongoing.

Although promising, the transgenic TCR approach is limited by applicability to specific HLA types, potential recombination with endogenous TCR chains to generate unwanted specificity, and potential off-target toxicity because of recognition of peptides with unexpected homology to the chosen tumor antigen peptide, as described.[68] Thus, extensive in silico and in vitro testing for cross-reactivity to normal tissue epitopes is necessary for this approach.

Chimeric Antigen Receptors

In this approach, T cells are transduced with a chimeric receptor comprising a target-binding extracellular portion—typically derived from the variable regions of a mAb—and a T-cell activating intracellular portion, typically consisting of CD3-zeta signaling domain along with costimulatory domains such as CD28 or 4-1BB. Unlike transgenic TCRs, CARs are not HLA-restricted but generally can only target cell-surface proteins.

CD19-specific CAR T cells (CART19) have shown the greatest success to date, inducing frequent and durable responses in refractory chronic lymphocytic leukemia, acute lymphoblastic leukemia, and B-cell non-Hodgkin lymphoma.[69] Garfall et al explored CART19 infusion in patients with relapsed MM following salvage autologous SCT, with the hypothesis that CART19 may target CD19+ MM precursor cells. All patients had relapsed less than 1 year after a previous SCT. Infusions were well tolerated. Two of 10 patients had clear benefit, with remissions more durable than after their first SCT, despite lower doses of melphalan.[70,71] A follow-up study in high-risk patients undergoing up-front autologous SCT is ongoing, as are correlative efforts to identify which patients are likely to benefit from a CD19-targeted approach.

Multiple other proteins are now being explored as potential targets for CAR T-cell therapy in MM (Table 2). Most promising to date is BCMA, a receptor expressed almost universally on MM cells, though intensity of expression can vary.[72,73] Korchenderfer and colleagues first demonstrated preclinical activity of BCMA-directed CAR T cells,[72] leading to a dose-escalation study in 12 patients with relapsed/refractory disease, with cyclophosphamide and fludarabine (Cy/Flu) conditioning given prior to infusion. Four responded, particularly at higher doses, including a stringent complete response lasting 17 weeks and an ongoing very good partial response at 26 weeks. Responses were associated with CAR T-cell expansion and toxicity, including severe CRS and delirium.[74] Two additional BCMA CAR T-cell trials have reported preliminary results. Although the prior study uses a CAR with CD3/CD28 signaling domains, these studies both use CARs with CD3/41BB signaling domains, thought to potentially provide greater persistence of transduced T cells.[75] Cohen et al described nine patients with refractory MM who received up to 5 × 108 BCMA CAR T cells alone, without prior lymphodepletion, with responses seen in four, including an ongoing stringent complete response at 12 months with continued detectable CAR T cells. As in the prior trial, responses were associated with CAR T-cell expansion, and toxicity included severe CRS and neurotoxicity.[76] Subsequent cohorts are receiving CAR T cells after cyclophosphamide lymphodepletion. Berdeja et al reported data from nine patients treated with Cy/Flu followed by escalating doses of BCMA CAR T cells using a different CAR construct. Responses were seen in seven patients, with six ongoing at the time of reporting, and no severe CRS or neurotoxicity was yet seen.[77] Together, these studies demonstrate proof-of-principle validating BCMA as a promising target in MM, as well as feasibility of manufacturing biologically active CAR T cells from patients with heavily pretreated MM.

Challenges of Genetically Modified T Cells

Despite these early successes, multiple challenges remain. Optimal constructs and costimulatory domains, transduction methods, dosing, and lymphodepletion continue to be debated. Currently, manufacturing is only done at specialized sites and takes 2–4 weeks; this leads to difficulties in maintaining disease control in patients with rapidly progressing disease and to logistic challenges in making this therapy more widely available. T cells collected from patients with highly refractory disease are often more exhausted and terminally differentiated, which may limit persistence of manufactured CAR T cells.[88] Toxicity remains a major issue as well. CRS—in which IL-6 and other inflammatory cytokines are released during widespread T-cell activation—is usually manageable with aggressive supportive care and, if needed, the anti-IL-6-receptor antibody tocilizumab, but can still lead to hemodynamic instability, hypoxia, and a hemophagocytic lymphohistiocytosis–like syndrome in some patients.[89] Neurotoxicity, which has been described in up to 50% of patients treated with CART-19,[90] remains poorly understood and can range from mild confusion to seizures, encephalopathy, and obtundation. It typically resolves spontaneously within days to a couple weeks, though one case of posterior reversible encephalopathy syndrome treated with steroids and cyclophosphamide has been described with CART-BCMA,[91] and fatal cerebral edema has been seen with CART-19.[92] Better understanding of risk factors, as well as relevant animal models,[93] will hopefully help mitigate these toxicities.

CONCLUSION AND FUTURE DIRECTIONS

These challenges notwithstanding, cellular therapies continue to show great promise, with the potential for persistent immune surveillance that can maintain durable remissions. The genetically modified therapies remain in their infancy in MM, and next steps after pilot studies are completed will likely involve larger trials in patients with less-refractory disease, exploring serial retreatments, and combination studies (e.g., with other MM therapies, cytokines, checkpoint inhibitors). Additional approaches include novel CAR constructs and vectors that offer more efficient transduction,[94] as well as inclusion of suicide genes and safety domains to allow for rapid cytoreduction for toxicity. The most interesting approach may be new gene editing techniques such as TALEN or CRISPR/Cas9, which allow for precise knockout of specific genes within targeted cells. Potential applications include universal, “off-the-shelf” CAR T cells that lack MHC molecules and endogenous TCRs (to avoid immune-mediated rejection and graft-versus-host disease), as well as knockout of immune checkpoint molecules such as PD-1.[95-97] All of these are moving to the clinic and will help define the next era of cellular therapies in MM.

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Integration of Genomics Into Treatment: Are We There Yet?

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OVERVIEW

Using advances in genetic analysis to segment and direct treatment of multiple myeloma (MM) represents a way of maintaining therapeutic progress. Recent genetic analyses have opened the possibility of enhancing risk stratification approaches and of using different risk and biologic strata as part of clinical trials. The Myeloma Genome Project is a collaborative project that has compiled the largest set of cases with sequencing and have outcome data that are available for stratification purposes. Mutation-targeted treatment of the Ras pathway has been shown to be active in MM, but is compromised by the presence of the subclonal genetic variation typical of myeloma. Going forward, risk and biologically stratified therapy for MM looks to be a promising way of maintaining therapeutic progress, as does precision immunotherapy directed by the cellular context of the bone marrow.

The last decade has seen an unprecedented improvement in the outcome of cases with MM following the sequential introduction of new agents with differing modes of action. Despite this improvement in outcomes, there remains a substantial proportion of patients, approaching 30%, who have poor clinical outcomes even with optimal current therapy. A substantial proportion of patients relapse and are more likely to have aggressive disease that is refractory to therapy. Therefore, the current challenges in MM are to identify high-risk patients at presentation and to implement therapeutic strategies that can overcome resistance, induce responses, and improve long-term outcome. This will require a change in approach from what is currently used to one with a focus on segmentation into risk and biological strata where therapies with distinct modes of action can be focused. Such a change will have important implications for trial design, which can be smaller and involve less follow-up than would otherwise be required if long-term survivors with a good prognosis were included. However, this approach will require a greater understanding of disease biology and the use of molecular diagnostic strategies suitable for use in targeted- and precision-immunotherapy approaches.

Understanding the evolutionary processes leading to high risk MM is of crucial importance in understanding how to effectively treat it. It has been shown that the final stages of disease emerge from earlier, more benign stages based on the transition from a normal plasma cell to a cell with the features of plasma cell leukemia that coevolves with the bone microenvironment to generate a high risk state. The MM ecosystem develops after initiating events lead to the immortalization of a normal plasma cell, the fate of which would normally be to generate a long-lived plasma cell, differentiation to a memory B cell, or to undergo programmed cell death.[1] We have shown that intraclonal heterogeneity is present even at the monoclonal gammopathy of undetermined significance phase of disease[2,3] and is the essential substrate for Darwinian-type evolution. Within their niche, normal, long-lived plasma cells engage with supporting stromal cells to facilitate autocrine and paracrine loops, keeping them out of the cell cycle and mediating their long-term survival. After its initiation, MM develops to generate a complex spatiotemporal ecosystem, which, in a Darwinian view, can be considered the end result of subclonal competition for access to the bone marrow niche.[1,4]

GENETIC DRIVERS OF MYELOMA

Progression of MM is driven by acquired "genetic hits" that alter the biology of the MM propagating cell to facilitate its survival and eventual domination via successive clonal sweeps.

Initiating Lesions

Lesions initiating the myeloma clone have been shown to be present at the monoclonal gammopathy of undetermined significance stage and to be present in all clonal cells; these features include translocations involving the immunoglobulin gene loci or the acquisition of hyperdiploidy, each in roughly half of patients. The primary translocations result from aberrant class-switch recombination, abnormal V(D)J rearrangement, or receptor revision. The end result is to place various oncogenes—t(4;14): *MMSET*

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and *FGFR3*; t(6;14): *CCND3*; t(11;14): *CCND1*; t(14;16): *MAF*; and t(14;20): *MAFB*—under the influence of the strong enhancer region of the immunoglobulin genes.[1] The other major group of initiating events are the hyperdiploid chromosomes,which based on theoretical considerations are likely to contain a range of low penetrance oncogenes, which leads to their selection. The hyperdiploid group tends to have a favorable prognosis and respond well to immunomodulatory drugs (IMiDs)

Key Genetic Lesions Associated With Progression

A restricted number of key genetic lesions drive progression to more aggressive clinical behavior and are potential targets for therapy. The 1q+ abnormality is seen in 40% of cases at diagnosis and is a key prognostic factor with the number of copies being critical. Amplification of 1q (amp1q; defined as greater than four copies) is present in 10% of newly diagnosed MM cases and is tightly linked to high-risk disease. Amp1q arises via multiple cycles of break-fusion-bridge leading to the amplification of a transcriptional unit at 1q21 comprising a number of key genes including *CKS1B*, *MCL1*, and *ANP32E*. The exact gene driving the high-risk disease association has proven difficult to define, possibly reflecting the importance of the unit as a whole, which contains many interesting genes. The basis of amplification of 1q has been investigated in other malignancies and may be due to hypoxia and the expression of *KDM4A*.[5]

Loss of 1p32 is associated with high-risk disease and the deletion of the cyclin-dependent kinase inhibitor *CDKN2C*.[6-8] Loss of this cell cycle inhibitor deregulates the G1/S cell cycle checkpoint. Another important region of deletion is located at 1p12, which contains *FAM46C,* which is also frequently mutated.

Deletions of 17p, which contains the coding region for *TP53,* is seen in about 5% of patients at diagnosis, but is more frequent at relapse and in high-risk disease.[9] Small *TP53* mutated subclones occurring in up to 20% to 30% of clonal cells with monoallelic inactivation do not necessarily affect outcome and may be eradicated by therapy. However, biallelic inactivation, by copy number loss and/or mutation, is a very poor prognostic feature and is associated with high-risk disease.[6]

Deletions of chromosome 13 are a feature of approximately 40% of myeloma cases. Loss of chromosome 13 is important because, although not prognostically important itself, it likely contains a number of tumor suppressor genes, which if biallelically inactivated are pathologically important. These genes include *RB1* and *DIS3*.

There is a limited set of genes with recurrent single nucleotide mutations associated with MM, some with rare mutations. Important genes with mutations that were identified include *KRAS* (mutated in 21% of patients), *NRAS* (19%), *DIS3* (9%), *BRAF* (7%), *FAM46C* (6%), *TRAF3* (4%), *HIST1H1E* (3%), *TP53* (3%), *LTB* (3%), *CYLD* (3%), and *RB1* (2%).[10-12] These mutations deregulate a limited number of pathways including RTK/Ras signaling, p53, NFκB, and RB1.[12] Proliferation is a key feature of high-risk states and is driven by biallelic inactivation of *TP53*, *RB1*, and *CDKN2C*, as well as amp1q, and amplification of and secondary translocations to *MYC* at 8q24.[13-16] Deregulation of MYC is very frequent, as it is present in up to 50% of cases and is more frequent in hyperdiploid cases

Genetic instability is a feature of high-risk states and this is often seen as structural and whole arm chromosome changes. The best example of these variants is jumping translocations of 1q (JT1q).

KEY POINTS

- **Myeloma develops via Darwinian principals to give rise to a complex spatiotemporal ecosystem characterized by subclonal heterogeneity and regional differences in mutation content.**
- **The novel agents currently used to treat myeloma are targeted in the sense that they inhibit a specific mechanism that has major downstream consequences, such as IMiDs that target cereblon, proteasome inhibitors that target degradation in the proteosome, and anti-CD38 targets a membrane marker; however, they do not require the use of a diagnostic to identify mutation or activation state.**
- **Risk-stratified treatment is currently clinically relevant and high-risk cases can be prevented from early relapse by avoiding treatment holidays and using dose-dense regimens, and is a group in which novel therapies can be readily introduced as part of clinical trials.**
- **Etiologic genetic drivers are present in close to 100% of clonal cells and constitute good therapeutic targets; in contrast, mutations acquired late during progression, present only in minor subclones, do not constitute good targets.**
- **The development of new segmentation strategies based on mutational and immunologic data will facilitate therapeutic development by identifying subgroups with specific clinical behavior.**

CHANGES IN THE MYELOMA NICHE DURING PROGRESSION

Clonal cells alter the bone marrow niche to favor their survival, and these changes offer interesting novel targets for therapy. In this context, important cells in the endosteal niche are derived from mesenchymal stem cells, a key cellular component of the bone marrow. Together with their more differentiated progeny—the osteoblasts, osteocytes, pericytes, and adipocytes—mediate the behavior of the microenvironment. Osteoclasts and osteoblasts have opposing effects on MM growth[17-19] and mediate high-risk states directly by affecting dormancy and growth of MM propagating cells.[19,20]

An "angiogenic switch" based on increased neoangiogenesis has been proposed to explain rapid changes in MM clinical behavior and to contribute to the transition of smoldering disease to MM.[21-24] Neoangiogenesis along with mesenchymal stem cell–derived pericyte abnormalities may directly affect the endosteal and perivascular niches

leading to vascular leak and alteration in the immune content of the bone marrow. The changes in the microenvironment can be mediated directly by integrins, such as ITGB7,[25] or by secreted factors that generate paracrine loops, upregulating cytokines via the stromal cells and favor MM survival, such as interleukin (IL)-6.[26] In addition, secreted exosomes with their cargo of microRNA may be important.[27,28]

Cells of the immune system, including regulatory and effector T cells, natural killer (NK) cells, and others play a critical role in the microenvironment. Myeloid-derived suppressor cells and tumor-infiltrating cells, lymphocytes, and myeloid cells contribute to generating the immunosuppression typical of the MM bone marrow microenvironment. T-regulatory cells are reduced and there is a reciprocal increase in IL-17–producing T cells, which increases MM tumor cell growth and inhibits immune function.[29,30] NK and dendritic cells also have altered differentiation and impaired function.[31-33] Understanding these interactions and determining the effect treatment has on the complex microenvironment will be important as we optimize therapy for high-risk MM.

Novel Agents and Their Mechanisms of Action

Although not considered to be truly targeted therapy, which requires a diagnostic test to detect either a mutation or activation of a pathway, the novel therapeutic agents used to treat MM are, in a sense, targeted because they affect a specific molecular feature that has broad downstream effects. The IMiDs bind to cereblon and target downstream molecules to the proteasome for degradation.[34] This is an exciting mechanism by which lenalidomide modulates Ikaros and Aiolos to directly kill plasma cells by down-regulating IRF4 and MYC.[35] Simultaneously, it also enhances the activity of NK cells, explaining its immune-modulatory activity. This mechanism has highlighted the concept of the degrasome, whereby specific molecular targets can be targeted for degradation by adjusting the molecular shape of the IMiD molecules and, by so doing, affecting cereblon function.

The proteasome inhibitors are also targeted by inhibiting the enzymatic function of the proteasome and causing the degradation of specific subsets of proteins. This approach can be developed further by targeting ubiquitin ligases for targeting additional subsets of proteins.

Risk-Stratified Treatment

In evolutionary terms, treatment can be considered as an evolutionary selective pressure that can be manipulated to improve outcomes. Intraclonal heterogeneity (ICH) and genetic diversity are key features of myeloma and explain the fitness of the clone, its capacity to adapt to its environment, regional genetic variation, and the development of drug resistance. It is clearly important to take account of this disease feature when designing treatment strategies, and this is best addressed using drug combinations that are broadly active at presentation, aiming to overcome and eradicate potentially resistant clones and to achieve minimal residual disease states. Alternating combinations of drugs with different modes of action, which offer different selective pressures, is also key in this respect.

To date, in contrast to acute myeloid leukemia, there has generally been few truly risk-stratified trials in MM with a few notable exceptions. The IFM group carried out a trial based on interphase fluorescent in situ hybridization (iFISH) data, but subsequently dropped this approach.[36,37] The group from Arkansas has carried out a number of trials based on risk and have pursued an approach where high-risk is identified using a gene expression–based classifier, the gene expression profile (GEP) 70, which has been approved by the U.S. Food and Drug Administration for this purpose.[38-40] The results of these trials have been informative and identified a group of newly diagnosed cases that did not benefit much from the introduction of the novel antimyeloma therapies. They also identified distinct clinical patterns in these cases, characterized by early relapse during "inter-therapy" periods during early maintenance. This early relapse can be prevented using high-dose sequential therapy, in which combination chemotherapy is given at doses comparable to a greater dose density than would be achieved by the very high doses used in autologous stem cell transplantation. Segmentation into risk strata is likely to become increasingly important over the next years as the median survivals of low-risk patients increase to the point where randomized studies with adequate power to detect significant clinical improvements will require very large numbers of cases with long median follow-up such that they become impractical to fund.

Mutation-Directed Therapy

The mutational spectrum of MM is now well-understood with only a limited number of common recurrent mutations observed.[12,15,41] Using the presence of mutations to direct the use of a specific agent has been done in other cancers and clearly could work in MM with the targeting of the RAS/MAPK pathway being the optimal target with which to explore this approach further. Taken together, mutations in KRAS, NRAS, and, BRAF account for 50% of all cases at presentation and these numbers increase at relapse. Inhibition of MEK, located downstream of RAF in the MAPK pathway, has emerged as a potential strategy to treat these patients. We have shown that trametinib shows promise as a myeloma therapeutic based on responses seen in a heavily pretreated population.[42] Targeting BRAF using vemurafenib has also shown to the result in responses. However, we have also shown that subclonal genetic heterogeneity and spatial heterogeneity are more or less ubiquitous in MM and pose a threat to the effectiveness of mutation-directed therapies. Thus, if such strategies are to be pursued, it is crucial to understand the percentage of the clonal cells carrying a variant and to distinguish between subclonal eradication and lack of effect. This will require changes to the way response is assessed, with markers directed to the subclone being treated becoming important.

Targeting the trunk of the mutational tree, present in 100% of clonal cells, is clearly a better strategy than targeting

subclonal lesions, such as is the case with mutations in the RAS/MAPK pathway. In this respect, the -group cyclins are ubiquitously deregulated in MM and should constitute an important target for therapy. However, despite the availability of CDK inhibitors, a strategy to target this pathway has proven to be elusive. MMSET deregulated by the t(4;14) is another key etiologic lesion that constitutes a key potential target, but, despite this, the molecule has proven to be a very difficult to inhibit. Until new inhibitors are found, targeting this group will rely upon the use of effective proteasome inhibitors, which seem to be particularly effective in this type of disease. Targeting survival pathways also has potential in MM, and venetoclax, a BCL-2 inhibitor licensed for chronic lymphocytic leukemia, has been shown to result in therapeutic responses in MM. There has been a large amount of work carried out to refine the subgroup of MM in which this drug is most active, and the t(11;14) group characterized by upregulation of *CCND1* has the highest response rates, which could be enhanced further by looking at the ratio of pro- and antiapoptotic protein expression. In terms of targeted therapy while it is clear that we are not there yet, there is now enough evidence to support continued efforts to move forward in this direction.

Precision Immunotherapy

The development of monoclonal antibody therapies, such as anti-CD38 antibodies, provides the opportunity to use agents that are potentially agnostic to a molecular subgroup or risk group. Novel approaches to targeting the myeloma niche include the use of T-cell checkpoint blockade, including targeting PD-L1 and CTLA-4. An increase in mutation burden predicts for better responses[43-45] and could be due to an increase in neoantigen presentation.[46] The mutational burden per unit DNA in myeloma lies in the middle of the distribution for mutations seen in cancer overall. Although there is a range of mutations from 0.1 to 10 per mB, even the upper outliers within this distribution are not at the level of the mutational burden seen in the more complex cancers.

Molecular Segmentation Strategies

In newly diagnosed MM, risk was first assessed using the Durie-Salmon and later the International Staging System. Although the International Staging System can be applied to patient series, it does not predict risk well for an individual.[47,48] iFISH can be used to identify specific lesions associated with high-risk disease, but lacks specificity, as not all tumors carrying each lesion alone will be high-risk. However, if more than one adverse lesion is present, the prediction of poor outcome is more secure.[47] It is also important that cut points for the number of positive cells are chosen to reflect clinical outcome rather than laboratory values for positivity over background. A good example of this is 17p-, in which cut points of 40% to 60% are required to predict poor outcome.

Gene expression studies outperform iFISH for risk stratification and a key example is the GEP70. GEP70 identifies 15% of patients at presentation, with a median progression-free survival of 1.8 years and overall survival of 2.6 years.[38] These high-risk cases are not evenly distributed between molecular subgroups with the majority being seen in the MMSET, MAF, and proliferation subgroups. This suggests that these molecular subgroups are not intrinsically high risk, but rather have a greater likelihood of being high risk. Although the GEP70 is specific, it does not pick up all of the cases with poor outcome, having a sensitivity of only 40% to 50%. As a consequence, 15% of GEP70-defined low-risk cases behave as high risk and relapse within 2 years of diagnosis.

The Myeloma Genome Project (MGP) collaboration is trying to develop and enhance risk satisfaction by defining new genetic markers able to detect aggressive disease that is associated with early relapse. In this respect the Revised-ISS has only utilized t(4;14), t(14;16) as markers of genetic risk, and, to improve this situation, the MGP investigators are defining additional copy number biologic and mutational data that can enhance the sensitivity and specificity of tools that can form the basis for future clinical trials.

Imaging studies can be used to improve the predictive risk value by identifying focal lesions in the bone marrow with the number of focal lesions and their intensity on PET predicting shortened survival.[49,50] These lesions have a distinct set of genetic abnormalities from that seen in the bone marrow and their microenvironment is also distinct. Importantly, if a focal lesion has a high-risk GEP70 score, the outcome is poor irrespective of the random bone marrow aspirate status.

CONCLUSION

We stand at a point in time where a number of clinical and trial practices have come together that will lead to a rapid change in practice. To date we have been very successful in improving the outcomes of patients with MM by using novel agents; however, this will become increasingly difficult, and the MM field will have to borrow approaches from other tumor areas and introduce both risk-stratified and molecular-targeted therapy into mainstream practice.

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Myeloma in Elderly Patients: When Less Is More and More Is More

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OVERVIEW

Multiple myeloma (MM) is a plasma cell malignancy that occurs among older adults and accounts for 15% of all hematologic malignancies in the United States. Thirty-five percent of patients are diagnosed at age 75 or older. Novel therapeutics and routine use of autologous stem cell transplantation (ASCT) have led to substantial improvements in patient survival, although improvements have been more impressive among patients younger than age 65. Finding the balance between under- and overtreating elderly patients is one of the biggest challenges specific to them as a subgroup of patients with MM. Decision making about which therapies and their dose intensity and duration should be influenced by a patient's functional status, personal preferences, disease characteristics, and ability to tolerate therapy. ASCT should be considered for all patients younger than age 80, assuming that they are not frail. The attainment of a stringent complete response and minimal residual disease negativity is associated with improved progression-free and overall survival. Again, consideration of quality of life for these patients is paramount. Although there is a growing list of tools to sort through these issues, a fully integrated approach has not yet been finely tuned, leaving additional work to be done for the treatment of elderly patients with MM.

MM is a plasma cell malignancy that occurs among older adults and accounts for 15% of all hematologic malignancies in the United States.[1] The median age of diagnosis is 69 years; in the next 15 years, MM incidence is expected to double.[2,3] Thirty-five percent of patients are diagnosed at age 75 or older, including 10% at age 85 older.[4] Novel therapeutics and routine use of ASCT have led to substantial improvements in patient survival. The median overall survival (OS) improved from approximately 2 years in the era of conventional agents[5] (e.g., melphalan and prednisone) to 5 years in the main large phase III randomized trials that incorporated novel agents.[6,7] There is a disparity in survival, however, between the young and old.[8,9] Recent data demonstrate that patients with MM who are younger than age 65 have improved 10-year relative survival rates (19.6% vs. 35%; $p < .001$), yet patients age 75 or older have not shared the same survival advantages (relative survival rate, 7.8% vs. 9.3%; $p = .3$).[10] MM-related deaths overall are highest among patients age 75 or older, and early mortality is most common among those age 70 or older.[8,10] Survival disparities for older adults with MM are multifactorial, and factors that play a role include treatment allocation differences, therapy toxicity, drug discontinuation, and physiologic reserve or patient fitness. Herein, we review these factors, the role of ASCT, and the goal of achieving minimal residual disease (MRD) to improve outcomes for older patients with MM.

RESPECTING FRAILTY OR AGE: HOW DO WE DECIDE TREATMENT INTENSITY?

Treatment intensity and clinical decision making for patients with MM relies on chronologic age, comorbidities, and performance status.[10-12] These factors oversimplify the complexity of caring for older adults and are often unable to identify the heterogeneity associated with aging. Treatment stratification for MM has been age based, in which clinical trials of transplant versus nontransplant strategies are conducted for those younger or older than age 65, respectively. ASCT is considered the standard of care; however, transplantation is less frequently performed for adults age 65–74 and rarely in those age 75 or older.[13] Balancing the toxicities of transplantation with survival advantages is challenging for the older adult. ASCT recipients report variable improvement in health-related quality of life (HRQoL)[14] and substantial short- and long-term morbidity,[15,16] and they can develop nonmalignant late effects that negatively affect overall health and functional status.[17] Older adults with MM are vulnerable to adverse events associated with multidrug combinations, which can lead to dose reductions or cessation of therapy and are associated with poorer outcomes.[18]

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TABLE 1. Clinical Examples of Geriatric Assessment Metrics

Domain	Metric Example	Clinical Conclusion
Function	SPPB[26]	Impaired SPPB is associated with a twofold higher risk of death compared with those with a normal physical performance among populations with leukemia[27]
	TUG	Poor mobility by TUG predicts early mortality among cancer populations
	Handgrip strength[28]	Grip strength is an accurate and consistent predictor of all causes of mortality in middle-aged and elderly persons (RR, 0.89)[29]
	Brief Fatigue Inventory[30]	Fatigue strongly correlates with depression and is highly variable post-transplant[39]
	ADL/IADL	Deficits in ADL, combined with age and comorbidities among patients with MM, resulted in notable survival differences in patients[21]
Psychiatric	HADS[31]	Psychiatric morbidity results in a significantly longer length of hospital stay and influences recovery post-transplant[32]
Social	MOS Social Support Survey[31]	Social isolation and loneliness predict disease outcome and results in substantial impairment in psychologic and physical well-being[33]
		Social support structure impacts clinical outcomes and quality of life post-transplant.[34,35]
	3MS	Cognitive impairment demonstrates the greatest likelihood for mortality among older adults with leukemia[27]
		Attention deficits persist for up to a year following myeloma transplant[36]
Nutrition	MNA	Impaired nutritional status independently predicts early death in patients with newly diagnosed cancer at age 65 or older (OR, 2.77).
Comorbidities	Comorbidity calculator[38]	HCT-CI predicts nonrelapse mortality and survival in MM[37,38]

Abbreviations: SPPB, Short Physical Performance Battery; TUG, Timed Up and Go Test; ADL, activities of daily living; IADL, instrumental activities of daily living; HADS, Hospital Anxiety and Depression Scale; MOS, Medical Outcomes Study; 3MS, Modified Mini Mental State; MNA, Mini-Nutritional Assessment; RR, relative risk; MM, multiple myeloma; OR, odds ratio; HCT-CI, hematopoietic cell transplantation comorbidity index.

Elderly age and frailty are not synonymous. Identifying factors that contribute to poor physiologic reserve and make patients vulnerable to treatment toxicity are under active investigation in MM. Frailty is a clinical syndrome, distinct from disability and comorbidities, in which cumulative factors of unintentional weight loss, self-report of exhaustion, weakness, slow walking speed, and/or low physical activity confer worse survival when present.[19] Some MM studies suggest frailty as patients older than age 75 or younger patients with abnormal organ function[20]; others have suggested treatment strategies with dose-level reductions based on risk factors of age 75 or older, help with activities of daily living (ADLs), and/or end organ dysfunction.[21] Understanding risk stratification and physiologic age is critical to reducing disparities when treating older adults with MM.

A geriatric assessment (GA) is a valuable tool to identify frailty and resolve occult health factors among older adults with MM. A GA is a global evaluation of the health of an older adult, defined as an interdisciplinary diagnostic process to identify age-related medical, psychosocial, and functional limitations that results in a coordinated treatment plan.[22] A GA is a multidimensional evaluation of functional status, fall history, social support, cognitive and psychological status, sensory loss, nutritional status, and comorbidities. A GA can predict chemotherapy toxicity and survival for patients with cancer[23-25]; however, data on GA outcomes specifically among patients with hematologic malignancies are limited. Emerging data suggest that use of a GA aids in clinical decision making for patients with cancer. Table 1 depicts a set of tools often used in a cancer-specific GA.[21,26-38]

Each of these evaluations aims to identify occult factors, unique to aging, that contribute to adverse events for patients with cancer. GA tools are comprehensive metrics to accurately assess risk of morbidity and mortality among cancer populations, independent of performance status and age among patients with solid tumors.[40-42] GA tools are established to identify vulnerable patients at risk for drug discontinuation and grade 2 to 3 nonhematologic toxicity among cancer populations,[43] and both factors are associated with inferior outcomes in MM populations.

Given multiple treatment options for MM and concerns for frailty and tolerance among older adults, a GA is a valuable prognostic tool. The International Myeloma Working Group (IMWG) used a simplified GA tool based on age, comorbidities (Charlson comorbidity index), ADLs, and instrumental ADLs for newly diagnosed older adults enrolled into nontransplant frontline clinical trials.[21] The IMWG de-

KEY POINTS

- **Overall survival for elderly patients with MM is gradually improving, but at a slower rate than for younger patients.**
- **Assessment of frailty and geriatric assessments should play a role in treatment decisions.**
- **ASCT is a viable treatment option for nonfrail patients.**
- **Targeting minimal residual disease may be appropriate for the elderly patient population with MM, but the optimal balance between longevity and quality of life has not yet been established.**
- **Further clinical trials will be required to optimize decision making for this complex patient population.**

veloped a frailty score that classified patients as fit (score = 0; 39%), intermediately fit (score = 1; 31%), and frail (score ≥ 2; 30%), based on data from 869 elderly individuals with newly diagnosed MM registered in three prospective trials. Scores were predictive of death, progression, treatment discontinuation, and nonhematologic toxicities. Three-year OS was 84% for fit patients, 76% for patients with intermediate fitness, and 57% for frail patients. The cumulative incidence of grade 3 or higher nonhematologic adverse events at 12 months was 22% for fit patients, 26% for patients with intermediate fitness, and 34% for frail patients. The IMWG frailty score profiles were independent of treatment, cytogenetics, or stage in the MM population. In addition, the IMWG frailty profiles were recently validated and confirmed in an older real-world MM population.[44] Personalizing therapy based on patient fitness or frailty may improve patient outcomes among older adults. Another example includes the Freiburg comorbidity index, a frailty assessment tool based on Karnofsky performance status, lung disease, and renal disease by using the estimated glomerular filtration rate.[45] The Freiburg comorbidity index is predictive of survival independent of MM stage, therapy, and age ($p < .0015$).[46] Efforts to streamline GA tools for clinical use and the multidisciplinary process to guide treatment decisions are ongoing.[47] Therapy intensity can also be guided by the effect of treatment on HRQoL for older adults.

HRQoL is of critical importance in the MM population and HRQoL instruments are used to capture physical and mental health from a patient's perspective. Older adults are risk averse when it comes to cancer treatment and do not choose quantity of life over quality.[48] Older patients with MM experience different HRQoL burdens than age-matched controls, with more deficits in social, physical, role functions, fatigue, pain, and dyspnea.[49] Disease-focused endpoints such as response rates and progression-free survival (PFS) remain central to clinical trials; however, HRQoL can be complementary to such endpoints and the US Food and Drug Administration has increasingly recognized HRQoL as an important endpoint for approval of new cancer therapy.[50] Quality-of-life tools can be difficult to interpret and clinical significance is centered on the minimal importance difference, a nonuniversal standard that varies based on the clinical context and population of interest.[51] Older adults with MM report some of the worst HRQoL symptoms compared with other cancers.[52] In the FIRST study, patients had baseline HRQoL evaluated using MM-specific tools (QLQ-MY20) and global health tools (QLQ-C30 and EQ-5D).[53] Both lenalidomide/dexamethasone and melphalan/prednisone/thalidomide showed improvement in pain and fatigue; however, lenalidomide/dexamethasone reached the minimal importance difference for pain, whereas melphalan/prednisone/thalidomide did not. HRQoL decreased at progression and continuous lenalidomide/dexamethasone treatment was associated with improved PFS. Similarly, among older adults treated with melphalan/prednisone/lenalidomide-R, melphalan/prednisone/lenalidomide, or melphalan/prednisone, patients treated with melphalan/prednisone/lenalidomide-R had better PFS and clinically meaningful improvements in HRQoL but no improvement in OS compared with those treated with melphalan/prednisone/lenalidomide. Declines in HRQoL have also been reported with onset of therapy, which can be attributable to treatment toxicity, as reported in both the VISTA[54] and UPFRONT[54] studies. These results demonstrate that disease response is imperative, not only for survival but also for maintaining quality of life. HRQoL instruments and data are invaluable assessments of patient well-being and are increasingly being used in MM clinical trial evaluations.[55]

Development of a peripheral blood test to mark physiologic frailty would be a powerful tool for the field of MM, allowing for vulnerable individuals to be rapidly identified and treatment intensity ascribed accordingly. Biomarkers can be defined in many ways in MM and are used to describe disease biology, staging, or treatment response.[56] Many candidate biomarkers are also being explored in cancer care to estimate physiologic reserve and risk for chemotherapy and/or transplant toxicity.[57,58] Recently, N-terminal natriuretic peptide type B in combination with Charlson comorbidity index scores and ADLs were explored as predictive of survival for patients with newly diagnosed MM.[59] Patients were scored 0–3 based on frailty metrics and reported median OS from diagnosis was not reached (stage I, score 0), 58 months (stage II, score 1), 28 months (stage III, score 2), and 18 months (stage IV, score 3; $p < .0001$). Use of N-terminal natriuretic peptide type B as a novel biomarker was independent of revised International Staging System (ISS) stage, age, and traditional Eastern Cooperative Oncology Group (ECOG) performance status.[59] Other aging biomarkers of interest include measuring $p16^{INK4A}$ (p16), one of the most robust and validated aging biomarkers for patients with cancer.[60] *p16* inhibits cell cycle progression when cells are exposed to internal and external stressors[61-65] and prolonged expression leads to irreversible cell cycle arrest, termed cellular senescence. *p16* accumulates with age in a variety of human tissue types and increases more than 16-fold in peripheral blood T cells over the human lifespan.[66,67] Cytotoxic chemotherapy of MM ASCT is associated with molecular aging of peripheral blood T cells and the relationship with frailty is being explored.[58,68] The need for objective biomarkers of physiologic age is especially important in the MM population due to the age of affected individuals, heterogeneity of fitness in older adults, and diverse treatment strategies available.

In summary, chronologic age is not a limiting factor for determining treatment of MM. Assessing patient fitness can be reconciled with use of a GA, a tool to identify frailty or vulnerabilities of treatment toxicity. However, comprehensive GA tools are underutilized in MM clinical trial design and in routine care, impeding personalized care for the older adult. HRQoL matters for older adults and clinicians must provide accurate interpretations of the patient experience with the data available to them. GA tools, in combination with novel peripheral blood aging biomarkers, are compelling and may standardize our approach to recognize the nuances of aging in the MM population.

TABLE 2. Large Registry Studies of Outcomes of ASCT for Older Patients With Myeloma

Study	Year	Age (Years)	No. of Patients	Conditioning	NRM	OS at 2 Years
Auner et al[77]	1991–1996	60–64	383	Melphalan	3.9	62.5
		65–69	75		8.0	55.3
		> 70	2		NA	NA
	1996–2000	60–64	1,835		3.6	77.6
		65–70	718		4.1	71.9
		> 70	100		4.0	70.8
	2001–2005	60–64	4,253		2.4	81.1
		65–69	2,478		2.7	79.3
		> 70	497		2.4	72.7
	2006–2010	60–64	6,518		1.8	86.3
		65–69	3,860		2.1	82.9
		> 70	740		2.0	80.2
Sharma et al[78]	2008–2011	60–64	2,617	Melphalan	2.0	85
		65–69	2,049			83
		> 70	946			

Abbreviations: ASCT, autologous stem cell transplantation; NRM, non-relapse mortality; NA, not available; OS, overall survival.

ASCT FOR OLDER PATIENTS WITH MM: WHO IS NOT ASCT ELIGIBLE?

MM is the most common indication for ASCT in North America today. Although randomized trials have shown the benefit of high-dose melphalan for patients younger than age 65, this procedure is now routinely performed for patients up to age 80,[69,70] owing to recent advances in supportive care and the use of filgrastim-mobilized peripheral blood. However, fewer than 20% of all patients age 65 or older are undergoing the procedure.[13]

Rationale for Exploring ASCT for Older Patients With MM

In 2015, at age 65, the average man would be expected to live 17.9 more years on average, compared with 18 more years for a woman; at age 70, a man would be expected to live 14.1 more years on average, compared with 16.3 more years for a woman.[5] The depth of response is shown to increase survival both in the frontline and salvage settings and among both transplant-eligible and transplant-ineligible patients; this is particularly true for complete remissions and is now being shown for attainment of an MRD state.[71-76] Thus, pursuing high-dose melphalan with ASCT as a strategy that will allow for a deeper response for older patients is appropriate as long as the expected morbidity and mortality of the transplant process is acceptable. The major challenge is to identify a priori which older patients have the highest likelihood of developing severe complications and thus will not benefit from the procedure

Outcomes of Hematopoietic ASCT for Older Patients

ASCT is being performed more frequently for patients older than age 60, with improvements in NRM and overall outcomes. Table 2 summarizes the largest registry series published to date. These reports, together with multiple single-center reports, demonstrate that autologous ASCT is feasible for older patients with MM, that NRM is routinely less than 5%, and that results are comparable or only slightly inferior to those of younger patients.[77,78]

The number of autografts for older patients with MM has also increased dramatically in the last 10 years. Using data from the European Bone Marrow Transplant Registry, Auner et al[77] reported that from 1991 to 1996, a total of 381 patients with MM underwent autografting in Europe versus 6,518 in the 5-year period from 2006 through 2010. Even more dramatic is the increased activity among patients older than age 70, of which only two were reported to the European Bone Marrow Transplant Registry from 1991 to 1996, in contrast with 2,617 from 2006 to 2010. Of note, many of the patients older than age 65 received 200 mg/m^2 of melphalan without worse outcomes than younger patients.[77,78]

Complications of High-Dose Melphalan and Autologous ASCT for Older Patients

Table 3 summarizes the most common complications seen after administration of high-dose melphalan and the potential effects on older patients. Of note, atrial arrhythmias and supraventricular tachycardias are more common with high-dose melphalan than other conditioning regimens, and retrospective analysis has shown that increasing age is a predictor of this complication.[79]

Mucositis and gastrointestinal toxicities are the most common nonhematologic toxicities seen after high-dose melphalan and are not increased among the older population but relate directly to melphalan exposure. Nath et al[80]

TABLE 3. Complications of High-Dose Melphalan

Complication	Incidence	Implications for the Older Patient
Myelosuppression	Universal, with the exception of truly nonablative regimens	Prolonged myelosuppression increases risks of life-threatening infections; thus, strategies that may accelerate neutrophil recovery in older patients could be beneficial.
		Filgrastim is beneficial in shortening the duration of neutropenia.
Mucositis	10%–20% with high-dose melphalan	Severe mucositis may require opioid analgesia for pain control, which is less well tolerated by older patients. Risk of aspiration from severe mucositis may be more frequent for older patients.
		Cryotherapy (ice chips) has been shown to reduce the risk of severe mucositis. Palifermin has not.
Infections	> 50% of patients will have some infectious complication. The most common is neutropenic fever or Gram-positive sepsis.	For older patients, the ability to recover from infectious complications may be affected by prior comorbid states and ability to tolerate anti-infective therapies such as foscarnet or amphotericin B.
		Older patients require the same infectious prophylaxis as younger patients; zoster prophylaxis is required until immunity is documented and may be required for life.
Gastrointestinal toxicities	Loss of appetite is almost universal	Gastrointestinal toxicities can be more common and more severe for older patients.
	Severe nausea and emesis are rare with current antiemetic regimens	It is essential to maintain good hydration and adequate electrolyte replacement.
	Severe diarrhea can be seen with melphalan	Nutritional intervention may need to be considered earlier.
Pulmonary toxicities	Pneumonitis and diffuse alveolar hemorrhage rare after high-dose melphalan	Patients with pre-ASCT pulmonary comorbidities are at higher risk for pulmonary toxicities.
Hepatic toxicities	SOS/VOD rare with high-dose melphalan	Similar risk as younger patients
Cardiac toxicities	Arrhythmias	Atrial fibrillation is a common occurrence after high-dose melphalan.
	Congestive heart failure	
Engraftment syndrome	Rash, fever, and occasionally diarrhea and renal dysfunction	Early institution of steroid therapy is important to prevent DAH.
Graft failure	Rare	Older patients collect a lower cell dose.

Abbreviations: SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease; ASCT, autologous stem cell transplantation; DAH, diffuse alveolar hemorrhage.

measured the melphalan area under the curve for 114 patients as part of a multivariate analysis; only a higher melphalan area under the curve predicted a higher rate of grade 3 and 4 mucositis, but it was also associated with improved survival. Although many centers reduce the dose of melphalan to 140 mg/m^2 for patients older than age 70, there are currently no data to suggest that this improves outcomes in this patient population.

How to Identify the ASCT-Ineligible Patient

In general, the criteria for ASCT candidates have been well defined.[81,82] However, which characteristics identify patients who should not be considered for this procedure have not been as well documented. In principle, older patients who should not be considered for high-dose melphalan and autologous ASCT consolidation would fall into one of four categories, as described below.

Patients in the first category may have performance status or comorbidities that may make it highly unlikely that they could benefit from high-dose melphalan consolidation. In 1992, Reuben et al[83] reported on the value of functional status in predicting mortality by conducting a 4-year prospective longitudinal follow-up study of functionally impaired community-dwelling elderly persons. A total of 282 elderly patients (age 64 or older) were included. Using scales from the functional status questionnaire, patients were assessed at baseline and at an average of 51 months later. In the multivariate model, the following baseline characteristics were independently predictive of death: greater dysfunction on a scale of intermediate ADLs, male sex, living alone, white race, better quality of social interactions, and age. Of note, patients unable to perform one of the ADLs had a 2-year mortality rate of 27%.

Based on the IMWG frailty criteria, a frail patient has a 34% chance of developing severe toxicity to regular induction chemotherapy[21]; this type of patient is unlikely to benefit from high-dose melphalan and should not be considered for that treatment modality.

The hematopoietic cell transplantation comorbidity index (HCT-CI) was developed by Dr. Mohamed Sorror to predict survival and NRM in the allogeneic setting. However, this index is also shown to also predict NRM risk after autografts. Saad et al[84] studied 1,156 autograft recipients after they received high-dose melphalan, using data reported to the Center for International Blood and Marrow Transplant Research. Participants were stratified into three risk groups: HCT-CI of 0 (42%) versus HCT-CI of 1–2 (32%) versus HCT-CI of more than 2 (26%). One-year NRM was low at 2% and did

not correlate with HCT-CI score. On multivariate analysis, OS was inferior in groups with an HCT-CI of 1–2 or more than 2.[21] For younger patients, the Karnofsky performance status predicts for higher NRM and worse HCT outcomes.[21] Thus, our current recommendation is not to pursue high-dose melphalan for older patients with poor performance status (Karnofsky performance status of 80 or less).

Patients in the second category have such a good risk disease category that high-dose melphalan consolidation is unlikely to positively impact long-term outcomes, thus making short-term side effects and negative impact on quality of life unacceptable. Patients with revised ISS stage 1 have an expected 5-year survival of more than 60%; thus, a 79-year-old patient with standard risk cytogenetics and revised ISS stage 1 who achieves a complete remission to induction therapy will not likely benefit from high-dose melphalan. Conversely, a 79-year-old patient with high-risk cytogenetics who has not achieved a PR to induction would benefit from this procedure.[85]

Patients in the third category have substantial socioeconomic or cultural barriers to safely undergoing high-dose melphalan treatment. Successful ASCT requires social and family support.[86] Thus, a thorough socioeconomic assessment should be done prior to proceeding to high-dose melphalan for older patients (particularly caregiver availability and whether the patient is the caregiver of an elderly spouse).

Patients in the final category do not desire to proceed to high-dose melphalan consolidation. Many older patients simply do not want to go through the time and effort required to undergo an ASCT. Obviously, this decision must be respected but should be preceded by a frank discussion of the risks and benefits of the procedure for each individual patient.

Future Directions for ASCT for Elderly Patients

High-dose melphalan and ASCT remain the standard of care for transplant-eligible patients around the world. However, the definition of transplant eligibility has changed. ASCT was initially limited to younger patients with normal or almost normal organ function, but it is now routinely performed for individuals up to age 80 (even those with substantial comorbidities, including end-stage renal disease).

However, high-dose melphalan with autologous ASCT is still associated with notable morbidity and a mortality rate that can be as high as 10% at 1 year for older and debilitated patients with a poor performance status. Considering that many alternative therapies exist for MM today, deciding whether to proceed to ASCT must be done carefully for an older patient in close collaboration with the patient, family members, and other health care professionals. Pretransplant GA has been shown to be helpful in deciding which patients have the highest likelihood of severe complications, but it is not definitive.

Aging biomarkers that can provide a reproducible measure of physiologic fitness are currently being explored. Such biomarkers include molecular markers, inflammatory markers, immunosenescence panels, serum and hematologic parameters, and hormones. Only large prospective trials will allow us to determine whether a specific biomarker panel will be sensitive enough to determine who will tolerate high-dose melphalan well and who will not. Likewise, for the older population that proceeds to ASCT, all efforts must be made to prevent untoward toxicity. These strategies, such as pharmacokinetically directed melphalan, pre-ASCT rehabilitation and exercise training, as well as specific agents to ameliorate gastrointestinal and other toxicities, must be assessed prospectively.

In summary, high-dose melphalan can be successfully used for older patients with MM to increase their quantity and quality of life; however, its use should be determined by carefully assessing the risk/benefit ratio for each individual patient.

AIMING FOR A COMPLETE RESPONSE IRRESPECTIVE OF AGE

With a change in the treatment landscape for elderly patients, the goals for them have also been modified, with prolongation of disease-free survival and OS as important goals. The depth of response has emerged as a surrogate marker that is highly correlated with PFS and OS, and a large meta-analysis including 14 studies and 1,273 patients provided quantitative evidence to support the integration of MRD assessment as an endpoint in clinical trials of MM.[87] However, some patients that reach suboptimal response after therapy are relapse free at 10 years, raising an important question about whether a complete response (CR) is actually needed to achieve long-term survival. Indeed, biologically well-defined patient subgroups with monoclonal gammopathy of undetermined significance–like baseline profiles or specific molecular subtypes can present long-term survival without achieving a CR.[88] However, these patients represent only 10% of patients with MM. Thus, for the majority of patients, higher CR rates are needed to increase survival rates and responses of high quality are becoming optimal short-term endpoints that might potentially contribute to accelerating the approval of new agents.

The role of the conventional CR was evaluated in a retrospective analysis including 1,175 patients with newly diagnosed MM, enrolled in three multicenter trials, who were treated with melphalan/prednisone (332 patients), melphalan/prednisone/thalidomide (332 patients), bortezomib/melphalan/prednisone (VMP; 257 patients), or bortezomib/melphalan/prednisone/thalidomide (254 patients). After a median follow-up of 29 months, 3-year PFS and OS were 67% and 27% (hazard ratio [HR], 0.16; $p < .001$), and 91% and 70% (HR, 0.15; $p < .001$) for patients who obtained CR and in those who achieved very good partial response, respectively. Similar results were observed for patients older than age 75, and multivariate analysis confirmed that the achievement of a CR was an independent predictor of longer PFS and OS, regardless of age, ISS stage, and treatment.[89] In spite of these results, approximately 40% of the patients who achieved CR will relapse and 20% will die

within 4 years after initial therapy; these data reflect that the definition of conventional CR (e.g., negative immunofixation in serum and urine, disappearance of any soft tissue plasmacytomas, and less than 5% plasma cells in bone marrow) failed to detect such differences. As a result, the stringent CR was added in 2006, based on the normalization of serum free light chains and absence of clonal plasma cells in bone marrow biopsies by immunohistochemistry and/or immunofluorescence; in 2016, new CR criteria have been defined, introducing the MRD evaluation by flow cytometry, next-generation sequencing (NGS), and imaging.[90] The question now is whether MRD evaluation is ready for prime time for elderly patients with MM.

Molecular assessments include the use of allele-specific oligonucleotide quantitative polymerase chain reaction or NGS of VDJ sequences. Puig et al[91] demonstrated that among newly diagnosed patients treated according to the PETHEMA/GEM2005MAS65 protocol (including VMP or VTP as induction followed by VT or VP as maintenance), those with a molecular CR after induction had a PFS not yet reached, whereas patients with MRD positivity had a significantly shorter PFS (median 31 months; p = .03). MRD levels were measured by allele-specific oligonucleotide polymerase chain reaction, and there was a good correlation with NGS-based approaches, Martinez-Lopez et al[92] established the prognostic significance of achieving MRD negativity by deep sequencing for the same series of patients. In this study, among the patients with a CR, the MRD-negative group had a significantly longer time to progression compared with the MRD-positive group (median 131 vs. 35 months; p = .0009). Although a good correlation was reported between both molecular techniques, more than one-half of patients in clinical practice will not be evaluated by allele-specific oligonucleotide quantitative polymerase chain reaction because of the inability to detect a clone, unsuccessful sequencing, or suboptimal performance; however, the NGS approach will be applicable to more than 90% of patients and is thus the optimal molecular technique to be used considering 10^{-5} as the target cutoff level for the definition of MRD negativity.

Using multiparametric flow cytometry, only a few patients (15%) in the Medical Research Consortium Myeloma IX protocol for elderly patients achieved flow MRD negativity after induction regimens without proteasome inhibitors, and these individuals showed nonsignificantly superior PFS.[93] However, results of the Medical Research Consortium Myeloma XI protocol were recently reported and the flow MRD-negative rate was 14%, with no differences between cyclophosphamide, thalidomide, and dexamethasone and CRD. Patients achieving MRD-negative status had a significantly longer PFS but no differences were reported in terms of OS.[94] In contrast, in the PETHEMA/GEM2005MAS65 study, patients were monitored after six induction cycles; within a subset of 102 patients with a CR/very good partial response, 30% attained flow MRD negativity with PFS and OS rates at 3 years of 90% and 94%, respectively. These results were recently updated after a median follow-up of more than 5 years and show median PFS and OS rates not yet reached for patients with flow MRD negativity status after induction with VMP, but not after VTP.[95] Because patients with flow MRD negativity after two different regimens should experience similar outcomes, this study also revealed that the four-color multiparametric flow cytometry assay originally performed in these studies was underpowered for ultrasensitive detection of MRD. In recent years, the sensitivity has increased because of the simultaneous assessment of eight or more markers and evaluation of a greater number of cells, resulting in one of the most relevant prognostic factors, including among elderly patients with MM. Next-generation multiparametric flow cytometry was used to monitor MRD for 162 patients enrolled in the PETHEMA/GEM2010MAS65 study and treated with VMP and lenalidomide/dexamethasone during 18 months in a sequential (nine plus nine cycles) or alternating way (VMP, lenalidomide/dexamethasone, VMP, and so on). MRD status was an independent prognostic factor for time to progression (HR, 2.7; p = .007) and OS (HR, 3.1; p = .04), with a significant benefit for patients with flow MRD negativity (median time to progression not reached, 70% OS at 3 years), and similar poorer outcomes for patients with MRD levels, also considering the optimal cutoff level between 10^{-4} and 10^{-5}. Of note, flow MRD-negative status significantly improved time to progression for patients older than age 75, as well as for those with high-risk cytogenetics.[96] Table 4 provides a summary of the most relevant studies establishing a relation between CR or MRD negativity and outcome.

The aim of achieving CR in the bone marrow after treatment has an additional challenge because it is possible to have a patchy bone marrow infiltration or extramedullary involvement with flow or NGS MRD negativity in single bone marrow aspirates. New criteria adopted that ^{18}F-fluorodeoxyglucose PET-CT is a powerful tool to assess tumor metabolic activity and the effect of therapy on tumor-cell metabolism.[90] Multiple studies support the notion that the detection of PET-positive lesions has prognostic value for patients with MM at diagnosis. However, all studies have been conducted thus far among young patients before and after transplantation and will be prospectively evaluated in the new trials with elderly patients.

In summary, MRD clearance into and also likely outside the bone marrow is achievable for elderly patients with MM in the era of novel agents because it is predictive of superior outcomes, and this concept has been shown to also apply to patients older than age 75. Achievement of MRD negativity for patients with high-risk cytogenetic abnormalities is relevant because their outcome is similar to that of standard risk.

TYING IT ALL TOGETHER FOR ELDERLY PATIENTS WITH MM

Decision making for the elderly patient with MM is not simple. Although attainment of MRD negativity is possible for a subset of elderly patients with MM, the group of elderly patients elderly is very heterogeneous and treatment remains challenging because of specific clinical and biologic

TABLE 4. Summary of the Most Relevant Studies Establishing a Relation Between CR or MRD Negativity and Outcomes

Method	LOD	No. of Patients	CR Rate	MRD− Status (%)	PFS (MRD− vs. MRD+)	p Value	OS (MRD− vs. MRD+)	p Value	Reference
Classic CR		1,175	17	—	67% vs. 27% (at 3 years)*	< .001	91% vs. 70% (at 3 years)*	< .001	Gay et al[89]
ASO-qPCR	10^{-5}	103		46	NR vs. 31 months	.002	NR vs. 60 months	.008	Puig et al[91]
NGS	10^{-5}	133**		27	80 months vs. 31 months	< .001	NR vs. 81 months	.019	Martín-ez-López et al[92]
6-color MFC	10^{-4}	245		15	10.5 months vs. 7.4 months	.1	NA	NA	Rawstron et al[93]
6-color MFC	10^{-4}	297		14	34 months vs. 18 months	< .0001	54 months vs. 50 months	.12	de Tute et al[94]
4-color MFC	10^{-4}	102		43	90% vs. 35% (at 3 years)	< .001	94% vs. 70% (at 3 years)	.08	Paiva et al[97]
8-color MFC	10^{-5}	162		34	NR vs. 15 months	.007	70% vs. 60% (at 3 years)	.04	Paiva et al[96]

*For the classic CR method, the PFS comparison was done between CR and very good partial response.

**This study included also patients who were transplant candidates but the results were similar for both groups of patients.

Abbreviations: CR, complete response; MRD, minimal residual disease; ASO-qPCR, allele-specific oligonucleotide quantitative polymerase chain reaction; NGS, next-generation sequencing; MFC, multiparametric flow cytometry; LOD, limit of sensitivity; PFS, progression-free survival; NR, not reached; OS, overall survival; NA, not available.

features not withstanding frailty, comorbidities, and financial and psychosocial factors.[98] Is striving for CR or MRD negativity appropriate for all elderly patients with MM? Which regimens are best for this population?

Options for treatment of elderly patients abound. Current favorites, depending on region and drug availability, include lenalidomide/dexamethasone,[7] VRd,[99] VMP,[6] and ASCT. Triplet therapy including a proteasome inhibitor and an immune-modulating drug and ASCT is associated with the deepest responses and, in most instances, with better PFS and OS. Careful analyses of the combination of carfilzomib plus an immune-modulating drug have not yet been performed for elderly or frail patients. Although prolongation of disease-free and OS has historically been the ultimate goal, achieving prolonged treatment-free intervals, absence of treatment-related toxicity, and good quality of life have also become important aims for elderly patients. Recent developments in MM have focused on identifying these vulnerable patients through GA, including frailty, disability, and comorbidities.[21]

We are approaching an era in which we should be able to provide individualized treatment strategies and drug doses to improve tolerability and optimize efficacy and ultimately survival. Some studies have shown the value of MRD for evaluation of the efficacy and potential treatment decisions. Emerging work on immune profiling[96] in addition to MRD assessment may be a means to identify patients with poor, intermediate, and favorable outcomes and to guide us in decision making regarding the optimal type and duration of treatment for individual patients. All of these approaches are extremely relevant in the treatment of elderly patients with MM, and a frailty-adapted therapy together with a sensitive response assessment, including immune profiling, could help to deliver the appropriate regimen with the optimal duration avoiding under- or over-treatment. This will require a cooperative effort toward new clinical trial designs in which patients are accurately stratified and assessed according to all of these important parameters.

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LUNG CANCER

Caring for the Older Population With Advanced Lung Cancer

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OVERVIEW

The management of advanced lung cancer is changing rapidly, with new drug approvals occurring almost monthly. The average age of a newly diagnosed patient with advanced lung cancer remains around age 70. Caring for the older adult with advanced cancer differs from the care of younger adults. Chronologic age often does not accurately reflect the physiologic and functional status of older adults. Selecting treatment based on age alone results in undertreatment and overtreatment of many older adults. Addressing issues such as multiple chronic conditions, polypharmacy, geriatric syndromes, and heterogeneity in functional status among an expanding menu of treatment options for advanced disease is increasingly difficult, particularly among older adults historically underrepresented in clinical trials. In this article, we highlight key issues in caring for the older adult with advanced non–small cell lung cancer and the continued need for data supporting current and emerging treatment options. Key issues include the unique challenges of managing advanced lung cancer and a summary of the current treatment evidence as they apply to the elderly lung cancer population including supportive care strategies, risk stratification, and patient-reported outcomes.

Lung cancer is a disease of the older adult. More than 50% of patients with lung cancer are diagnosed after the age of 65, and 30% are older than age 70.[1] In addition, lung cancer is responsible for more deaths than colon, breast, and prostate cancer combined.[2] Over the next several decades, the aging demographic, particularly octogenarians, will increase exponentially.[3] Real-world evidence is needed to deliver the best-quality cancer care for older adults. The evidence base for the treatment of older adults with advanced lung cancer is improving, but large knowledge gaps exist regarding efficacy and toxicity outcomes among older adults with multiple chronic conditions (MCCs), polypharmacy, geriatric syndromes, and impaired functional status. For decades, less than 10% of patients who were age 75 or older have been included in phase II and III oncology clinical trials.[4] Under-representation of older adults in cancer treatment clinical trials perpetuates uncertainty regarding toxicity and survival outcomes when data for younger clinical trial participants is inevitably extrapolated to an older population.

THE OLDER ADULT WITH ADVANCED LUNG CANCER: UNIQUE CHALLENGES

Improving the Evidence Base to Avoid Overtreatment and Undertreatment

Generating evidence among older adults with advanced-stage lung cancer will mitigate both undertreatment and overtreatment. Undertreatment is described as withholding cancer treatment shown to improve symptoms and survival. Historically, Medicare beneficiaries have largely experienced undertreatment with less than one-half of older adults receiving any antineoplastic for advanced lung cancer.[5,6] Overtreatment can lead to excessive toxicity, complications, treatment burden, and premature death due to aggressive or novel treatments understudied among older adults. Older adults experience greater toxicity rates with chemotherapy as compared with younger adults.[7] Including a higher percentage of older adults in clinical trials is essential to improve toxicity and survival outcomes in an aging global population. This requires a paradigm shift among clinical trial design, recruitment, and implementation strategies.

Multiple Chronic Conditions and Polypharmacy

MCCs are an increasingly important consideration for the oncology care provider. In 2011, 67.3% of Medicare beneficiaries had two or more chronic conditions and 14% had six or more chronic conditions.[8] MCCs among older adults with cancer can influence survival and treatment complications.[9] Cancer treatment can also worsen or exacerbate MCCs. This is possible through several mechanisms. The first is direct toxicity on an already impaired organ such as pneumonitis in a patient with chronic obstructive pulmonary disease, acute kidney injury in a patient with chronic renal insufficiency, or hematologic toxicity in a patient with a weakened or suppressed bone marrow. The second is indirect toxicity

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on an already impaired organ such as fluid retention in an older adult with congestive heart failure. The third is the relationship between polypharmacy and MCCs. This occurs when seemingly small or standard changes or modifications to medications accompany a new cancer treatment. For example, the routine addition of pretreatment steroids before taxanes or other agents can worsen glucose control for patients with diabetes or fluid retention in a patient with congestive heart failure. In addition, the recognition of drug-drug interactions among patients on warfarin, novel oral anticoagulants, or even aspirin can prevent bleeding or clotting complications. Increasing awareness of how cancer treatment can adversely affect MCCs and polypharmacy is required in an aging population, even among older adults with a limited life expectancy due to advanced disease. Simple interventions such as a review of comorbid conditions by a medical assistant or nurse or a medication review by a pharmacist could result in improved outcomes among older adults with MCCs and advanced cancer.[10]

Geriatric Syndromes

As we age, one may develop geriatric syndromes (Table 1).[11] Geriatric syndromes such as frailty, falls, cognitive impairment, and incontinence are extremely complicated because they defy the reductionist approach to modern medicine.[11] Geriatric syndromes cross over traditional organ-based disease categories and require a systems perspective. Though modern medicine is often considered systems-oriented, the science of clinical medicine is increasingly reductionist.[12] Unlike some types of lung cancer, geriatric syndromes are not explained by a single driver mutation. Geriatric syndromes are important because they have a substantial impact on quality of life and the development of disability.[11] They are known to increase risk for hospitalization, mortality, and functional decline.[13] Older adults with cancer also have a higher prevalence of geriatric syndromes as compared with older adults without cancer.[13] Not surprisingly, geriatric syndromes can affect the success of cancer treatment, and cancer treatment can worsen geriatric syndromes.[14] Frailty in particular has been associated with an increased incidence of chemotherapy toxicity.[15] Tools for assessing geriatric syndromes, interventions, and care management strategies to prevent or worsen pre-existing geriatric syndromes, exist in the geriatrics literature but will need to become mainstream among cancer clinicians caring for an aging cancer population.

KEY POINTS

- **Older patients with lung cancer are continually under-represented in cancer clinical trials.**
- **Geriatric assessment-derived risk stratification tools can greatly improve both prognostic and toxicity outcomes among older patients receiving chemotherapy.**
- **Novel antineoplastic agents require additional research among older adults.**
- **Supportive care is a mandatory component of a comprehensive care plan for older adults.**
- **The treatment of older adults with advanced lung cancer requires a personalized, whole-person approach to care.**

TABLE 1. Geriatric Definitions

Domains of Comprehensive Geriatric Assessment	Geriatric Syndromes
Functional status	Frailty
Comorbidity	Dementia
Cognitive function	Delirium
Nutrition	Falls
Psychological state and social support	Dizziness
Medication review/polypharmacy	Syncope
Balance and gait	Pressure ulcers
Hearing and visual impairment	Incontinence
Economic assessment	Elder mistreatment
Advanced directives	

Functional Status

Significant heterogeneity in functional status exists in the last year of life among cancer decedents. Gill et al described 20.3% of decedents with no disability, 33.8% with catastrophic disability, 21.6% with accelerated disability, 20.3% with progressive disability, and 4.1% with persistently severe disability.[16] Maintaining independence and preventing disability are major health priorities for older adults with and without cancer.[17,18] Functional status needs to be assessed independently from age and the number of comorbidities.[9] Factors associated with early functional decline among older patients receiving chemotherapy include depression, cognition, mobility, nutrition, and impaired independent activities of daily living.[19] Understanding functional decline in older adults with advanced lung cancer has not been rigorously evaluated. Further research on how an older adult's prediagnosis functional status affects postdiagnosis outcomes such as toxicity, survival, and patient-reported outcomes among adults with advanced lung cancer is needed.

TREATMENT OPTIONS FOR PATIENTS WITH ADVANCED NON–SMALL CELL LUNG CANCER: A SHIFTING LANDSCAPE

Chemotherapy

Although there have been several elderly-specific chemotherapy clinical trials in advanced non–small cell lung cancer (NSCLC), much of the data derives from secondary analyses of larger studies that did not focus on elderly patients (Table 2). Clearly, more evidence is required, particularly among octogenarians and patients with MCCs (Table 1). Older patients may tolerate chemotherapy poorly because of comorbidity and organ failure, but they also have an opportunity to benefit from appropriate treatment selection. Vinorelbine, in the phase III randomized Elderly Lung Cancer Vinorelbine Italian Study (ELVIS), improved survival and quality of life in patients who were age 70 and older with advanced NSCLC, compared with best supportive care.[20]

TABLE 2. Results From Prospective and Subset Analyses of Chemotherapy Use in the Treatment of Patients Older Than Age 70 With Advanced NSCLC

Study	Regimen	Number of Patients > Age 70	Median Survival	1-Year Survival	p Value Median Survival
ELVIS[20]; Gridelli, 1999	Best supportive care	78	21 weeks	14%	.03
	Vinorelbine + best supportive care	76	28 weeks	32%	
Frasci[22] 2000	Vinorelbine + gemcitabine	60	29 weeks	30%	< .01
	Vinorelbine	60	18 weeks	13%	
MILES[21]; Gridelli, 2003	Vinorelbine + gemcitabine	232	30 weeks	0.3*	NS
	Vinorelbine	233	36 weeks	0.38	
	Gemcitabine	233	28 weeks	0.28	
ECOG 5592[23]; Langer, 2002	Cisplatin + etoposide	22	6.34 months	31.8%**	NS
	Cisplatin + high-dose paclitaxel	32	9.2 months	40.3%	
	Cisplatin + low-dose paclitaxel	32 (86 total)	9.2 months (8.53 months overall)	37.4%	
CALGB 9730[24]; Lilenbaum, 2005	Carboplatin + paclitaxel	77	8 months	35%	NS
	Paclitaxel	78	5.8 months	31%	
WJTOG9904[25]; Kudoh, 2006	Docetaxel	88	14.3 months	58.6%	NS
	Vinorelbine	91	9.9 months	36.7%	
NVALT-3[26]; Biesma, 2010	Carboplatin + gemcitabine	90	8.6 months	NR	NS
	Carboplatin + paclitaxel	91	6.9 months		
IFCT-050[27]; Quoix, 2010	Carboplatin + paclitaxel	225	10.3 months	44.5%	< .0001
	Gemcitabine or vinorelbine	226	6.2 months	25.4%	
Socinski[28] 2012	Carboplatin + paclitaxel	82	10.4 months	NR	.009
	Carboplatin + weekly nab-paclitaxel	74	19.9 months		
Zukin[29] 2013	Carboplatin + pemetrexed	38	9.9 months	40.1%	.006
	Pemetrexed	36	5.3 months	21.9%	
Ramalingam[30] ECOG 4599, 2008	Carboplatin + paclitaxel + bevacizumab	113	12.1 months	NR	.4
	Carboplatin + paclitaxel	111	11.3 months		

*One-year probability of survival.

**Entire cohort, not elderly-specific OS.

Abbreviations: NR, not reported; NS, not significant.

To improve upon results obtained with monochemotherapy, the investigation of combination chemotherapy has been an ongoing issue in the treatment of elderly patients with advanced NSCLC. In fact, the possibility of having active and well-tolerated chemotherapy, while preserving patient quality of life, is a critical concern in the treatment of elderly patients. The most-studied non–platinum-based regimen is the combination of gemcitabine plus vinorelbine, which proved active and well tolerated in several phase II trials. However, in a large phase III randomized Multicenter Italian Lung Cancer in the Elderly Study (MILES), which enrolled approximately 700 patients, combination chemotherapy with gemcitabine and vinorelbine failed to improve any outcome parameters (response rate, time to progression, survival, or quality of life) compared with single-agent chemotherapy with either vinorelbine or gemcitabine.[21] Based on these trials, for many years single-agent chemotherapy was considered the standard of care in elderly patients with advanced NSCLC and a performance status (PS) of 0 to 2.

However, over the past 2 decades, retrospective analyses of randomized phase III trials and multiple phase II studies have confirmed the activity and tolerability of cisplatin-based and carboplatin-based chemotherapy in fit elderly patients.[31,32] A randomized phase III trial led by Quoix and colleagues in patients with advanced NSCLC between the ages of 70 and 90 showed superiority in all outcome parameters for carboplatin and weekly paclitaxel versus either single-agent gemcitabine or vinorelbine.[33] Response rate was nearly triple at 29% versus 11% ($p < .0001$) with progression-free survival (PFS) of 6.1 versus 3.0 months ($p < .0001$), median survival of 10.3 versus 6.2 months ($p = .00004$), and a 1-year overall survival rate of 45% versus 26% ($p < .001$).

Quality of life was preserved or improved with the combination regimen. Survival benefit was observed in those age 80 and older (114 patients; hazard ratio [HR] 0.56; 95% CI, 0.37–0.85; p = .0067) and in individuals with PS 2 (122 patients; HR 0.65; 95% CI, 0.44–0.95; p = .027). More recently, in a retrospective subset analysis of elderly patients enrolled on a phase III study of carboplatin plus either conventional solvent-based paclitaxel administered every 3 weeks or albumin-bound paclitaxel given weekly, the latter regimen resulted in a significant improvement in overall survival at 19.9 versus 10.4 months (p = .009).[34] To date, there has been no formal, prospective phase III comparison of weekly solvent-based versus nab-paclitaxel in combination with carboplatin in elderly patients with advanced NSCLC or any other population. At the 2017 ASCO Annual Meeting, the results of the randomized phase II ABOUND 70+ trial will be unveiled; this carboplatin combination in elderly patients with advanced NSCLC compares a weekly, uninterrupted schedule of nab-paclitaxel to an interrupted schedule featuring 3 consecutive weeks of treatment followed by a 1-week break; safety and tolerability are the primary outcome measures, with response rates, PFS, and overall survival as the secondary endpoints.

The feasibility of cisplatin-based chemotherapy has been investigated. Results are pending from two separate phase III randomized trials (MILES 3 and 4) comparing single-agent gemcitabine to cisplatin plus gemcitabine in patients with squamous cell histology or single-agent pemetrexed to cisplatin plus pemetrexed in patients with NSCLC. In clinical practice, nonplatinum monotherapy remains the standard treatment of unfit elderly patients with advanced NSCLC.

Bevacizumab and Targeted Therapies

ECOG 4599 showed a survival advantage for combination bevacizumab and paclitaxel/carboplatin (PCB) versus chemotherapy with paclitaxel/carboplatin (PC) alone,[33] although a subsequent analysis of participants over age 70 suggested that this benefit was diluted in older patients. More nuanced analyses by Wakelee et al[35] and Ramalingam et al[30] suggested that males of any age sustained a survival benefit, while women up to the age of 60 also realized an overall survival advantage. It was only women age 60 or older for whom this benefit appeared to be lost, in part because the control arm performed better in this group. A more recent joint analysis pooling the data from the experimental arm of E4599 and the control arm of POINT BREAK, both featuring combination PCB, and comparing these data to PC alone, showed that the survival benefit was sustained up to age 75, with median survival of 13.4 versus 10.2 months (HR 0.78; 95% CI, 0.68–0.89).[36] For patients older than 75 in a limited cohort of 157 patients, combination PCB posed no advantage (9.6 vs. 13.0 months; HR 1.05; 95% CI, 0.70–1.57).

As for tyrosine kinase inhibitors (TKIs), a retrospective analysis of elderly patients enrolled in BR 21, which compared erlotinib to placebo in the second- and third-line setting in advanced NSCLC, showed a consistent overall response rate, PFS, and overall survival benefit, albeit older participants experienced a bit more toxicity.[37] More recently, in patients with actionable mutations or translocations, phase III trials have demonstrated a consistent overall response rate and PFS advantage for erlotinib, afatinib, and crizotinib compared with standard front-line or second-line chemotherapy regardless of age. Subanalyses using age 65 to 75 as cut points consistently show similar benefits, although the individual comparisons for elderly patients have been frequently underpowered to demonstrate statistical significance. In the EURTAC trial comparing erlotinib to platinum-based chemotherapy in patients with epidermal growth factor receptor (*EGFR*) exon 19 or 21 mutations, the magnitude of PFS benefit for the TKI was similar in those patients older than and younger than age 65; among 88 participants older than age 65, the HR was 0.26 (95% CI, 0.16–0.51), although the HR was 0.49 for 85 participants younger than age 65 (95% CI, 0.25–0.75).[38] In Lux Lung 3, which compared afatinib to cisplatin/pemetrexed in patients with advanced, treatment-naive *EGFR* mutations, PFS favored afatinib over chemotherapy in 135 patients age 65 and older (HR 0.64; 95% CI, 0.39–1.03), not too different than the benefit seen in 211 patients younger than age 65 (HR 0.53; 95% CI, 0.36–0.79).[39] Recently, the J-ALEX trial demonstrated a statistically significant and clinically meaningful PFS advantage for alectinib versus standard crizotinib in TKI-naive patients with *ALK*-positive NSCLC.[40] Among 207 enrolled participants, 22 patients were age 75 and older; the HR for alectinib's PFS benefit in this small population was impressive at 0.28, but because of small numbers and an underpowered comparison, the 95% CIs overlapped unity (0.06–1.19), and so the putative difference was not statistically significant.

Immunotherapy

Novel immunotherapy with checkpoint inhibitors nivolumab and pembrolizumab have yielded an overall survival benefit compared with standard docetaxel in second-line settings of advanced NSCLC with less toxicity.[41,42] As of 2017, PD-1 inhibitors have effectively replaced chemotherapy in the second-line setting independent of histology. In these trials, the benefits have been confirmed consistently in subgroup analysis of elderly participants, particularly in those between age 65 and 75. Representation of those older than age 75 in these studies, unfortunately, has been relatively sparse (Table 3). In some series, there is no indication of older patients experiencing increased toxicity from nivolumab.[41] To date, there are no ongoing elderly-specific trials evaluating immunotherapy in advanced NSCLC.

SUPPORTIVE AND PALLIATIVE CARE

In the early days of the palliative care/hospice movement, palliative care was considered an alternative to aggressive medical care aimed at the underlying diagnosis. Oncology patients were typically offered the choice of chemotherapy or palliative/hospice care, but not the combination of both. Palliative care was usually reserved for patients who had exhausted reasonable therapeutic options and now wished

TABLE 3. Hazard Ratios and Confidence Intervals in Various Age Cohorts in Phase III Trials of PD-1 Inhibitors Versus Docetaxel in Second-Line NSCLC

Trial and Age Cohort	No. of Patients	HR	95% CI
Checkmate 017: nivolumab vs. docetaxel in squamous histology			
≤ 65	152	0.52	0.35–0.75
> 65 to 75	91	0.56	0.34–0.91
> 75	29	1.85	0.76–4.51
Checkmate 057: nivolumab vs. docetaxel in nonsquamous histology			
≤ 65	339	0.81	0.62–1.04
> 65 to 75	200	0.63	0.45–0.89
≥ 75	43	0.90	0.43–1.87
Keynote 10: pembrolizumab vs. docetaxel in PD-L1 > 1%			
< 65	317	0.68	0.50–0.79
> 65	204	0.76	0.57–1.07

to be treated primarily supportively. There was a widespread belief among health care providers and the wider community that medications used to alleviate symptoms might hasten death in hospice patients.[43] Indeed, an early analysis of Medicare patients after enrollment in hospice programs showed a median survival of only 36 days.[44] In that study, lung cancer was the most common diagnosis, accounting for 21.4% of cases. A later retrospective analysis of survival in terminally ill Medicare patients showed improved survival in patients enrolled in hospice compared with those not enrolled.[43] This included significantly longer survival for patients with lung cancer enrolled in hospice. Saito et al conducted a retrospective analysis of the Surveillance, Epidemiology, and Results database.[45] They reviewed 7,879 Medicare beneficiaries who died between 1991 and 1999 of advanced NSCLC after surviving at least 3 months. One-year survival favored those enrolled in hospice (25.7% vs. 20.7%) as did 2-year survival (6.9% vs. 5.5%, $p < .001$). Hospice patients were more likely to be white, have higher socioeconomic status, and reside in urban areas.

There is now evidence that early use of appropriate palliative/supportive care in addition to, rather than instead of, standard oncology care improves outcomes. In 2010, Temel et al[46] published the results of a single-institution randomized trial that demonstrated the benefit of early palliative care when integrated with standard oncology care in the treatment of newly diagnosed metastatic NSCLC. In this study, patients with newly diagnosed metastatic NSCLC were randomly selected to receive either standard oncology care alone or standard oncology care plus proactive palliative care. Palliative care included initial evaluation by a palliative care team (physicians and advanced-practice nurses) and monthly palliative care visits (Tables 4 and 5).[47] Patients assigned to palliative care had better quality of life as assessed by the American Thoracic Society's Functional Assessment of Cancer Therapy-Lung questionnaire, had fewer depressive symptoms, and received less aggressive care near the end of life. Fifty-four percent of patients in the control arm received aggressive end-of-life care, compared with 33% in the palliative care arm ($p = .05$). Despite this difference, patients in the palliative care arm enjoyed longer survival (11.6 vs. 8.9 months, $p = .02$). It should be noted that this difference in survival is similar to that seen in the randomized trials of nivolumab versus docetaxel for patients with relapsed nonsquamous NSCLC.[48]

However, the results of this single-institution trial cannot be easily extrapolated to general practice. Most community oncology programs do not have the personnel to form dedicated palliative care teams, and it is unclear that the benefits of this early palliative intervention can be achieved in the absence of a dedicated team approach as used in the Temel et al study. In 2010, only 59% of National Cancer Institute–designated comprehensive cancer programs and 22% of community cancer programs had outpatient palliative care programs.[49] A more recent study of hospitals in California with inpatient palliative care programs found that only one-fifth provided outpatient palliative services, and around-the-clock services were available only in one-quarter of those.[50] In addition, rural Medicare beneficiaries and those with lower socio-economic status are less likely to be enrolled in hospice/palliative care programs and more likely to use the emergency department near the end of life.[51]

Patients with advanced NSCLC often receive chemotherapy in the last month of life. A 2001 review of Medicare patients found that 11% received chemotherapy in the last month of life.[52] An Italian study found that 33% of patients received chemotherapy in the last month of life; 15% of patients suffered grade 3–4 toxicity in the last month of life, and they noted two treatment-related deaths.[53] Clinical benefit of chemotherapy was seen in 10% of patients. A retrospective chart review of 10 community oncology practices found

TABLE 4. Palliative Care TEAM Acronym: Common Attributes of Successful Palliative Care Used in Clinical Trials

T.E.A.M.	Attribute
Time	At least an extra hour a month with the patient and family
Education	About prognosis, options, advance care planning, use of hospice
Assessments	Formal symptoms, spiritual, distress assessments
Management	By an interdisciplinary team

TABLE 5. Palliative Care Organizations With Relevant Assessment Tools

Palliative Care Resource	Website
Palliative Care Research Cooperative Group	http://palliativecareresearch.org/
National Consensus Project	www.nationalconsensusproject.org/
National Palliative Care Research Center	www.npcrc.org/content/25/measurement-and-evaluation-tools.aspx
Center to Advance Palliative Care	www.capc.org/
Patient-Reported Outcomes Measurement Information System	https://commonfund.nih.gov/promis/index
ASCO Palliative Care Guidelines	www.asco.org/palliative-care-guideline

chemotherapy was given to 43% of patients with advanced NSCLC in the last month of life and to 20% in the last 2 weeks of life.[54] Early palliative care in patients with lung cancer reduced the incidence of chemotherapy in the last month of life.[55] Interestingly, patients in both groups (oncology care alone or same and early palliative care) received similar numbers of chemotherapy regimens, but patients in the palliative care cohort had a longer treatment-free interval prior to death and an earlier and more sustained transition to hospice.

At least some of the benefit of early palliative care may be related to patient education about realistic expectations regarding outcomes in advanced NSCLC. In the Temel et al study, one-third of patients with advanced lung cancer thought their disease was curable at the time of enrollment in the study, and a majority endorsed getting rid of all cancer as a goal of therapy.[56] They found that a greater number of patients in the early palliative care arm maintained or developed an accurate perception of their prognosis versus those receiving standard care alone (82.5% vs. 59.6%, p = .02). Patients in the palliative-care arm with accurate perceptions regarding prognosis were much less likely to receive intravenous chemotherapy near the end of life (9.4% vs. 50%, p = .02). Several subsequent reports suggest that formal, advanced care planning can reduce the likelihood of futile interventions and utilization of hospice services.[57]

These data suggest that early palliative care with proper patient education about prognosis and realistic expectations can improve outcomes and reduce the utilization of expensive and futile care. Incorporating palliative care and early, advanced care planning into treatment algorithms for elderly patients with advanced NSCLC should be a goal of all centers treating these patients. This should optimize the benefits of chemotherapy in appropriate patients as well avoiding its use in patients unlikely to benefit.

GERIATRIC ASSESSMENT, RISK STRATIFICATION, AND PATIENT-REPORTED OUTCOMES

Knowing the majority of older adults with advanced NSCLC and no actionable driver mutation will experience a shortened life expectancy, a comprehensive approach to management of advanced lung cancer among older adults is necessary. The use of a comprehensive geriatric assessment (CGA) and the development of risk stratification tools are an important part of a comprehensive management approach. Karnofsky was one of the first to attempt to quantify a patients' physical functioning and ability to perform ordinary tasks,[58] yet a CGA has been shown to predict cancer outcomes such as toxicity better than a physician-rated Karnofsky PS.[59] A CGA has also been shown to add substantial information regarding functional status, even among patients with a good Eastern Cooperative Oncology Group (ECOG) PS.[60]

A CGA-directed approach has been shown to improve toxicities in older patients with advanced lung cancer. This was most recently demonstrated in the ESOGIA trial, a phase III randomized trial incorporating a modified geriatric assessment tool.[61] Patients who were at least age 70 were randomly selected to receive either carboplatin-based doublet chemotherapy or monotherapy on the basis of age and PS alone versus an experimental arm incorporating a CGA. There was a significant difference in treatment allocation between the two arms. Among the patients treated within the CGA arm, 23% of patients with frailty received best supportive care and were spared chemotherapy, thereby reducing overtreatment. In addition, a higher percentage of fit patients received a carboplatin-based doublet (45.7% vs. 35.1% in the control arm), reducing undertreatment. Although all patients in the control arm received treatment and 23% received best supportive care in the experimental arm, there was no difference in survival between the two arms because more patients in the experimental arm received appropriate treatment based on risk stratification. Due to risk stratification and appropriate treatment allocation, patients treated on the CGA-directed arm experienced less all-grade toxicity compared with the control arm (85.6% vs. 93.5%, respectively; p = .015). There were also fewer treatment failures due to toxicity: 4.8% in the CGA-directed arm compared with 11.8% in the control arm (p = .007). One reason survival differences were not seen between the two groups is due to all vulnerable patients receiving docetaxel vs. platinum-based doublet in the CGA-directed group, perpetuating undertreatment. Another reason may be due to the fact that all patients older than age 75, and all patients with a PS of 2, were required to receive a single agent, biasing the study towards healthier patients. In fact, 80% of patients in both arms were ECOG PS 0-1 while a minority were ECOG PS2.

Risk stratification tools developed from a CGA have largely addressed toxicity due to chemotherapy. Before the ESOGIA trial performed in Europe, the CALGB in the United States validated the Cancer and Aging Research Group (CARG)

TABLE 6. Four Validated Risk Stratification Tools for Older Patients With Lung Cancer

CARG[59]	CRASH[63]	ESOGIA[61]	SIOG1[64]
Age ≥ 72	ECOG PS	ECOG PS	ECOG PS 4
Number of chemotherapy drugs	Diastolic blood pressure	ADL	ADL
Chemotherapy dosing, standard dose	IADL	IADL	IADL
Hemoglobin < 11 g/dL (male) and < 10 g/dL (female)	LDH	MMSE	Comorbidities
Creatinine clearance < 34 mL/min	MMS	Geriatric syndrome	Malnutrition
Hearing, fair or worse	MNA	Charlson's comorbidity index	
Number of falls in last six months, ≥ 1	Chemotox	GDS 5	
IADLS: taking medications with some help or unable			
MOS: walking one block somewhat limited			
MOS: decreased social activity because of physical/emotional health			

Abbreviations: ADL, activities of daily living; Chemotox, toxicity of the chemotherapy regimen (see reference for values); GDS 5, geriatric depression scale; IADLS, instrumental activities of daily living[65]; LDH, lactate dehydrogenase; MMS, mini-mental health status; MMSE, mini-mental status examination; MNA, mini-nutritional assessment; MOS, medical outcomes study.[66]

chemotherapy toxicity tool to predict chemotherapy toxicity more accurately than a physician-rated Karnofsky PS.[62] The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score predicts grade 4 hematologic or grade 3/4 nonhematologic toxicity from chemotherapy.[63] Using either the CARG or CRASH tool, older patients with a lower score have a significantly lower incidence of experiencing toxicity. The components of four CGA-derived risk stratification tools are listed in Table 6. Similarly, CGA-derived risk stratification tools are needed for the use of immunotherapy and targeted oral agents but have not yet been developed. More recently, four risk stratification tools to classify older adults as fit, vulnerable, or frail were compared with SIOG1, demonstrating the best discrimination for 1-year mortality.[64] Among older adults with advanced lung cancer, there is a need to develop a consensus regarding which patients with advanced disease should receive best supportive care without concurrent antineoplastic agents.

In the evolving era of quality payment programs and an increasing number of available treatment options, patient-reported outcomes are increasingly important. Although survival is often referred to as the ultimate patient-reported outcome, older adults highly value preservation of function, cognition, and independence.[18] Eliciting health outcome prioritization in terms of survival, versus maintaining independence, versus reducing pain or other distressing symptoms could help patients and providers choose from an ever-expanding menu of treatment options. The International Consortium for Health Outcomes Measurement defined an international consensus recommendation on the most important outcomes for patients with lung cancer.[67] The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and EORTC QLQ-LC13 along with the Modified Self-Administered Comorbidity Questionnaire were recommended measures to track pain, symptoms, patient-reported health status, and comorbidities. There are significant age-related differences in responses on the QLQ-30, along with the burden of answering over 43 items.[68-70] Additional research is needed to determine if the specific needs of older patients with advanced lung cancer are adequately addressed in the currently recommended patient-reported outcome tools.

Currently, there is no consensus on the use of patient-reported outcomes among older patients with advanced lung cancer. The EORTC QLQ-ELD14 was validated as a supplement to the EORTC QLQ-C30 for measuring health-related quality of life.[31] Although this 44-item scale does address some geriatric issues such as activities of daily living, mobility, burden of illness, and mental and physical health, it fails to address important geriatric-specific patient outcomes such as falls, independence, and cognition. The patient-reported outcome measure for sarcopenia is an example of a geriatric oncology patient-reported outcome measure specifically designed for older adults.[32] This 13-item questionnaire developed for multiple cancer types (19% lung cancer) was shown to be associated with limitations in instrumental activities of daily living and limitations in physical performance. Additional geriatric oncology patient-reported outcome measures are needed to address functional decline, changes in cognition, and other geriatric syndromes in older patients with advanced lung cancer.

CONCLUSION

Caring for the older adult with advanced lung cancer requires a personalized, whole-person approach. Personalized care for older adults requires an integrated, multidisciplinary team. Finding the right drug for the right patient or precision medicine is required but not sufficient. Eliciting patient preferences, risk stratification, and shared decision making are key components of a treatment selection algorithm.[71] In an era of ever-expanding treatment options such as immunotherapeutics and oral-targeted treatments, the treatment approach for an older adult requires an understanding of both oncologic and geriatric principles, as well as a firm grounding in a rapidly expanding and complex literature based on recent phase III trials. Older adults with

advanced lung cancer pose unique challenges to care, including multiple chronic condition, polypharmacy, and geriatric syndromes. Fit individuals clearly benefit from standard treatment, and although current treatment evidence is improving, there still remain large gaps in our understanding of toxicity and survival outcomes for older adults. Supportive care strategies, risk stratification, and patient-reported outcomes are important care components to consider in an aging lung cancer population, both in clinical trials and in clinical practice.

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Clinical Pathways and the Patient Perspective in the Pursuit of Value-Based Oncology Care

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OVERVIEW

The art of practicing oncology has evolved substantially in the past 5 years. As more and more diagnostic tests, biomarker-directed therapies, and immunotherapies make their way to the oncology marketplace, oncologists will find it increasingly difficult to keep up with the many therapeutic options. Additionally, the cost of cancer care seems to be increasing. Clinical pathways are a systematic way to organize and display detailed, evidence-based treatment options and assist the practitioner with best practice. When selecting which treatment regimens to include on a clinical pathway, considerations must include the efficacy and safety, as well as costs, of the therapy. Pathway treatment regimens must be continually assessed and modified to ensure that the most up-to-date, high-quality options are incorporated. Value-based models, such as the ASCO Value Framework, can assist providers in presenting economic evaluations of clinical pathway treatment options to patients, thus allowing the patient to decide the overall value of each treatment regimen. Although oncologists and pathway developers can decide which treatment regimens to include on a clinical pathway based on the efficacy of the treatment, assessment of the value of that treatment regimen ultimately lies with the patient. Patient definitions of value will be an important component to enhancing current value-based oncology care models and incorporating new, high-quality, value-based therapeutics into oncology clinical pathways.

The health care environment and the practice of oncology is rapidly changing. The traditional approach of prescribing chemotherapy for most patients with advanced or metastatic tumors is decreasing as the number of biomarker-driven treatments and immunotherapy drugs is increasing. With many cancers, multiple treatment options now exist, from traditional chemotherapy to biomarker-driven targeted therapies to immunotherapy. Oncologists today face the challenge of keeping up with novel therapeutics as they are approved. At the same time, oncologists much consider the pros and cons of various treatment regimens across many domains (e.g., efficacy, safety, cost) and weigh the options carefully with their patients, to select the regimen with the most value for the patient.

As precision medicine has dramatically increased over the last decade, providers must find ways to assimilate all of the information available. As a result, clinical guideline and pathway tools have been developed and used to inform providers on available treatment options. The Institute of Medicine[1] defines clinical guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care." Clinical pathways are detailed, evidence-based treatment protocols within guideline sets that consist of the most efficacious and cost-effective regimens that minimize toxicity. Clinical pathways are typically disease and stage specific and list the drug names, dose, and administration schedule.[2-4] Development and utilization of high-quality clinical pathways is important to reducing errors and variation in care, improving clinical outcomes, and controlling cost. Providers must be cognizant in evaluating the clinical pathways they use, because different groups and methods may be used (e.g., professional organizations, other physician groups, payers) with varying intent. For example, oncology clinical pathways were recently produced by Eviti, New Century Health, P4 Pathways, US Oncology, Via Oncology, and other practice/payer collaborations.[4,5]

The care and treatment of patients with cancer is at a crossroads, and oncologists require tools to assist them in selecting the most appropriate treatment for each individual patient. In this review, we will address the role that clinical pathways and value-based models play in aiding oncologists' evaluation of available treatment options considering modern drug costs and value considerations, most notably patient-defined value.

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THE ROLE OF CLINICAL PATHWAYS IN INTEGRATING NEW DRUGS INTO PRACTICE

Clinical Pathways Best Practices

Many organizations have produced statements highlighting the importance of oncology clinical pathways and have provided guidance for producing quality pathways, as well as best practices for incorporating new drugs into existing pathways for use in the clinic.[1,2,5] In 2016, ASCO[2] published a policy statement, "ASCO Criteria for High-Quality Oncology Pathways Programs" (referred to hereafter as the ASCO criteria), on the development, implementation, utilization, and assessment of clinical pathways. A common theme throughout the ASCO criteria statement highlights the importance of delivering high-quality, value-based care through pathways, across the development to the assessment pathway production continuum. Perhaps the most important recommendation within the statement pertains to the need for continuous assessment to ensure that pathways represent the most up-to-date scientific knowledge that also incorporates clinical experience and patient outcomes.[2] A new drug that substantially improves response in the clinical research setting but is only tolerable by 5% of patients in the real-world setting may not be appropriate as the preferred regimen on a clinical pathway. Table 1 presents a checklist of key recommendations presented in the ASCO criteria, along with questions for consideration.

As a result of the growth and use of clinical pathways in the clinic, the *Journal of Clinical Pathways* was initiated in 2015 and is dedicated to publishing articles relevant to clinical pathways development, best practices, and research, and an annual meeting (Clinical Pathways Congress) was also subsequently established.[7,8] These resources provide oncologists with a place to obtain peer-reviewed, evidence-based information on the use of clinical pathways in practice.

KEY POINTS

- **The practice of medicine is evolving rapidly and providers must work together to keep up with the pace of new knowledge and the adoption of novel, value-based, efficacious cancer therapeutics into standard care.**
- **Clinical pathways can be used as tools to help providers stay updated on new cancer therapies and to choose only the highest-quality treatments for patients.**
- **Stakeholders, including providers and patients, must consider cost of care when deciding on a treatment regimen.**
- **Value-based models, such as the ASCO Value Framework, are available to help providers facilitate shared decision-making discussions with their patients on the efficacy, toxicities, and costs of treatments presented on clinical pathways.**
- **Although cost of treatment is important, it should not be the primary factor when assessing a treatment regimen.**

Developing and Implementing Clinical Pathways

Successful development and implementation of clinical pathways in a practice is driven by multidisciplinary team contribution. In addition to oncologists and practice administrators, the team should consist of nursing, research, supportive care, information services, pharmacy, and administrative staff. Another critical, yet often overlooked, member of the clinical pathway development team is the patient. Inclusion of patient advocates in discussions of clinical pathways and value-based care is imperative.

At the Carolinas HealthCare System's Levine Cancer Institute (LCI), oncologists and other critical team members have developed and implemented an electronic clinical pathways system, Electronically Accessible Pathways (EAPathways), to meet the institute's goal of providing consistent, evidence-based oncology care across their more than 25 locations throughout the Carolinas. The EAPathways system includes all of the major components of high-quality clinical pathways and the system is continually evaluated and enhanced. First initiated in 2012, the institute's clinical pathways program has grown from a handful of clinical pathways representing the most common solid tumors (e.g., lung, breast, colon) to more than 40 cancer-related pathways, including hematologic malignancies, supportive care, genomics, imaging, and rare tumors. In addition, EAPathways is now integrated into the institute's electronic medical records system. When comparing the EAPathways system components to the ASCO criteria, EAPathways currently meets the majority of the criteria. In areas where EAPathways does not meet ASCO criteria (e.g., reporting of provider adherence), the institute's EAPathways team is working to fulfill the criteria.

A transparent process for initial development and revisions of the clinical pathway must be established for the members of the multidisciplinary pathways team to work through. At LCI, disease-specific section teams review drugs, supporting clinical research, and real-world experience, while also considering quality and cost. Members from LCI's pharmacy and therapeutics committee participate to assist with value assessment for the drugs under review. A key component to EAPathways is the incorporation of clinical trial options in addition to approved therapeutic options. Disease section leaders consider and incorporate input from all of the team members prior to approving a new clinical pathway, an edit to an existing pathway, or a new trial option. The disease section teams meet regularly and on an as-needed basis, to rapidly update clinical pathways when new treatment options, supportive care initiatives, or genomic advances become available. Importantly, within each clinical pathway, there must be an option for oncologists to opt out of all pathways or trials for a patient, because not all patients will fall into a recommended treatment regimen or have a clinical trial option available to them.

As a result of local, multidisciplinary input to each clinical pathway, the content of each clinical pathway may differ by institution. However, the structure and components of clinical pathway systems are similar. If the clinical pathways

system is electronic (because of the constant evolution of clinical pathways, it is suggested that they be), the systems may gain from having online security features built in, such as secure logins and data storage behind a firewall. Navigation within the pathway system, such as a table of contents and linkable pages, may be useful to help guide users to the appropriate clinical pathways. Supportive documents, such as printable instructions or within-tool help features, are also useful. Completed clinical pathways are often visualized nicely in a flowchart format, with preferred drug regimens listed first. Clinical pathway users benefit from having clinic materials incorporated into the program, such as electronic order sets or drug information sheets, the ability to make clinical trial inquiries through the system, and patient education and media documents. An example of an EAPathways clinical pathway for metastatic, non–small cell lung cancer is presented in Figure 1.

Once the institution's clinical pathways are created, vetted, approved, and ready for use, the institution must inform and convince physicians to use it. Several approaches are useful. First and foremost, oncologists must see the value in using the clinical pathways system and must understand the expectations of using the program. If possible, incorporating the clinical pathways system into the electronic medical records system may be helpful. In addition, providing multiple access platforms (e.g., desktop, various mobile/tablet operating systems) facilitates regular use. Importantly, using the clinical pathways system should not disrupt the provider's normal workflow or add substantial time to ordering treatment for a patient.

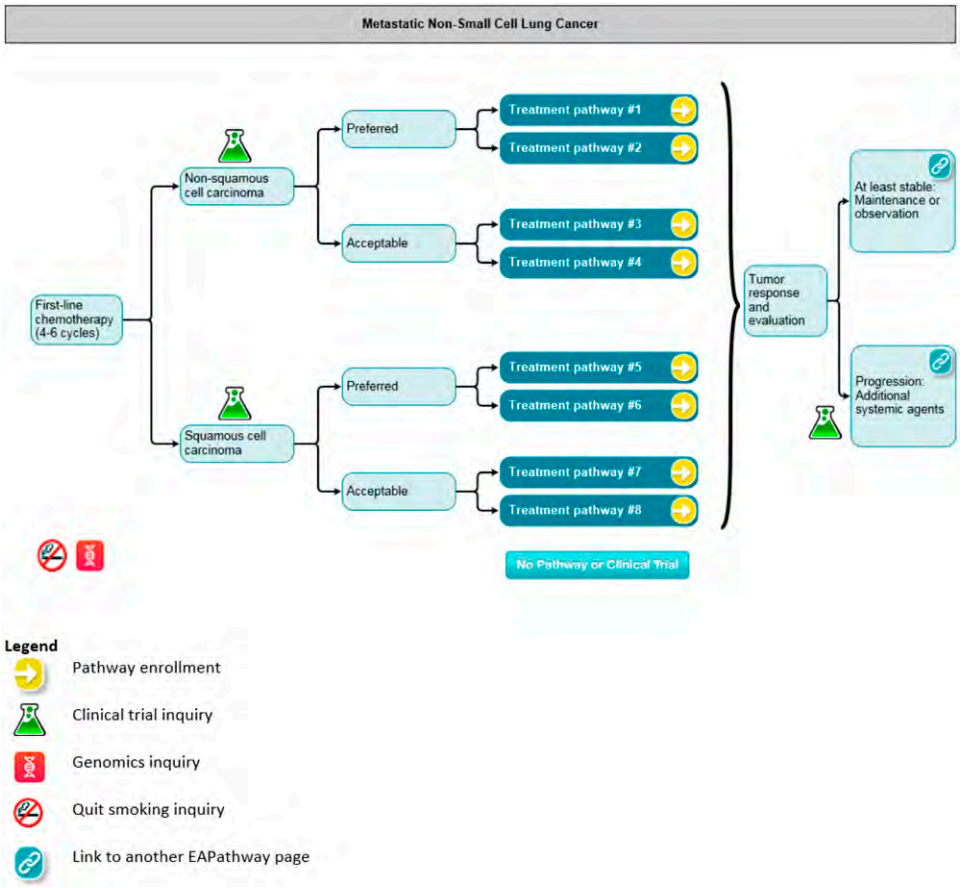
The institution may also decide to evaluate physician compliance of clinical pathway use though evaluation or clinical pathway analytics. Although LCI does not currently provide usage reports at regular intervals, EAPathways has the capability of producing usage reports as needed. Clinical pathway enrollment reports, clinical trial inquiries, and other activities are documented and queries can be conducted on demand. It is also pertinent for providers to record reasons for nonenrollment in clinical pathways and to have that information documented. Tracking this information may help in identifying treatment needs and conducting outcomes research and may assist with drug ordering. Using clinical pathways analytics may also help to identify which patient services, such as supportive care or financial counseling programs, are useful.

TABLE 1. ASCO Checklist of Criteria for High-Quality Oncology Pathway Programs

Criterion	Key Questions
Pathway Development	
Expert driven	Are practicing physicians with relevant disease specialty central to pathway development?
Reflects stakeholder input	Can patients, payers, and other stakeholders provide input in the development process?
Transparent	Is there a clear, consistent pathway development process that is transparent to all pathway users?
Evidence based	Are pathways based on the best available scientific evidence?
Patient focused	Are there options that account for patient differences, such as comorbidities, prior diagnoses, or preferences?
Clinically driven	Are stakeholder assessment and pathway analysis used for pathway revision?
Up to date	How rapidly are new, practice-changing data incorporated into recommendations?
Comprehensive	Do pathways address the full spectrum of cancer care (diagnoses, first-line therapy and beyond, supportive care, post-treatment surveillance, survivorship, end-of-life care)?
Promotes participation in clinical trials	Are available clinical trials (including phase I/II options) incorporated into the pathway?
Implementation and Use	
Clear and achievable expected outcomes	Is it clear to providers what constitutes treatment on pathway and within recommendations?
Integrated, cost-effective technology and decision support	Do pathways offer support and integration into other resources, such as electronic medical records, billing, or order sets?
Efficient process for communication and adjudication	Do pathways provide references/links to support materials?
Analytics	
Efficient and public reporting of performance metrics	Are regular reports provided to providers that demonstrate pathway performance?
Outcomes-driven results	Do pathways have analytics in place to enable a movement from adherence-driven compliance to outcome-driven results?
Promotes research and continuous quality improvement	Do pathways show commitment to research aimed at assessing and improving the impact of pathways on patient and provider experience?

Adapted from ASCO.[6]

FIGURE 1. EAPathways: Metastatic Non–Small Cell Lung Cancer



To keep up with the rapid pace of change in the health care environment, delivery of health care, and rising health care costs, oncologists must work together, adapt, and use new models to treat their patients. Utilization of clinical pathways is one way in which oncologists can come together to provide consistent, evidence-based recommendations and incorporate the use of value-based models, such as the ASCO Value Framework,[9,10] into recommendations to improve the quality of care for their patients.

Challenges to Developing and Implementing Clinical Pathways

The purpose of clinical pathways is to support best practice patient carewhile considering efficacy, safety, and cost. However, the development and implementation of clinical pathways is highly variable and reliant on the intent of the clinical pathways developer. Those who oppose the use of clinical pathways argue that their use dictates patient care and leads to cookbook medicine. Some feel that pathways are nothing more than visual displays of preferred drug formularies. Those who are in favor of clinical pathways view them as resources to guide best practice and reduce variation in care while taking efficacy, safety, and cost into consideration. Those in favor also view clinical pathways as a resource to empower physicians, along with their patients, to choose the most appropriate care plan. It is important to expand the development and use of clinical pathways beyond guiding treatment selection alone. Clinical pathways are useful in guiding physicians across the cancer care continuum, from prevention to survivorship. Until consensus on the purpose, intent, and scope of clinical pathways is reached, variability across pathways and ongoing dialogue on the challenges of clinical pathway development, implementation, and management will persist.

Considering Value-Based Care Frameworks

An important component to any clinical pathway program should be an assessment of the value of a treatment regimen. Since 2007, ASCO has been committed to educating providers on the importance of including cost discussions alongside treatment discussions and developing a framework to assist with these discussions. In 2015, the ASCO Value Framework was published, with the intent that the framework be used to facilitate a shared decision making (SDM) visit (between a physician and a patient) about the benefits and costs of a particular treatment regimen.[9] The framework was revised in 2016 to include feedback provided by more than 400 physicians, scientists, pharmaceutical industry members, and, most importantly, patients.[10]

The ASCO Value Framework is a tool that can be used by oncologists to compare treatment regimens that have been

evaluated head to head in a prospective clinical trial (e.g., erlotinib vs. cisplatin plus docetaxel or cisplatin plus gemcitabine).[9] The main components to the framework include an assessment of a regimen's clinical benefit (based on the hazard ratio for death, median overall survival, hazard ratio for progression, median progression-free survival, or response rate based on what is available), toxicity, and bonus points (an assessment of a regimen's percent amount of outcome improvement, statistically significant improvement in cancer-related symptoms, quality of life [QOL], and treatment-free interval). Each section is scored and the net health benefit is calculated by adding the scores of each section. The net health benefit is then presented, along with the drug acquisition cost and the patient cost, to the patient.[9]

There are some limitations to the ASCO Value Framework. In the current framework, only drugs that have been compared in a clinical trial can be evaluated. Additionally, and very importantly, patient-reported outcomes are not incorporated into the framework, as a result of the lack of data on these measures obtained from clinical trials, and QOL has been incorporated only in the bonus-point component of the framework.[9,10] It is hoped that in the future, inclusion of patient-reported outcomes and QOL endpoints in clinical trials will increase, and the framework could be revised to include these measures and better represent the patient perspective.

Other oncology value assessment tools have been proposed in the United States, such as the National Comprehensive Cancer Network's Evidence Blocks,[11,12] and in Europe,[13] with varying definitions of value and methodologies. Selected value assessment tools that can be used by physicians and patients are summarized in Table 2. These tools also suffer from a lack of patient-defined value measures. Oncologists must be aware of the strengths and limitations of each tool when assessing value.

WHY ARE CANCER DRUGS PRICED SO HIGH AND ARE PHYSICIANS' VALUATIONS OF ONCOLOGY THERAPEUTICS ONE OF THE REASONS?

Cancer currently costs the world more than any other disease, and that amount continues to rise. In the United States, cancer care costs are projected to rise to $157.7 billion by 2020.[16] Of all of the cost drivers of cancer treatment, the greatest determinant of inflationary growth has been drug outlay and costs fueled by new chemotherapeutic agents and biologic cancer drugs. A 2015 study by the U.S. Bureau of Economic Research[17] demonstrated that the rate of inflationary pricing of cancer therapeutics was maintained at 10% per year between 1995 and 2013. Such patterns of growth have led health policy experts and physicians to question the etiology of this perpetual inflation as well as the system's overall sustainability.

Why Are Cancer Drugs Priced So High?

There are two unique aspects of the oncology therapeutic market that may shed some light on pricing developments. The first aspect comprises the specific practice patterns and drug utilization inherent within oncology itself. Cardiologists have a variety of lipid-lowering agents within their therapeutic pharmacopeia. Psychiatrists can consider a number of selective serotonin reuptake inhibitor modulators used to treat mood and anxiety. The oncology drug market is unique, in that traditional assumptions of price competition between multiple drugs do not often apply to cancer therapeutics.

A few reasons for this near monopolist pricing mechanism have been articulated by Siqqiqui and Rajkumar,[18] who describe one of the many fundamental tenants of oncology practice. For those patients with incurable disease, oncologists usually initiate treatment with one therapy (or regimen) until progression and then move to the next line of therapy with a subsequent agent or regimen. As oncologists offer sequential agents at the time of progression, the majority of potential agents proven to be efficacious will be used in a patient's clinical course as long as patient willingness and performance status remains intact. Furthermore, in the treatment of most of oncologic diseases, there exist few circumstances in which two biosimilar agents are directly competing in the same therapeutic space. In fact, even when a particular pathway is being modulated by drug therapy (e.g., EGFR, VEGF, mTOR), there are often a variety of different types of therapeutic agents than may be used and each has a specific mechanism of action and distinct role (e.g., monoclonal antibody, tyrosine kinase inhibitor, multitargeted agent). Taken together, such forces make it difficult for two agents to be direct competitors. This lack of direct competition between biologically similar agents is one of the challenges in oncology pricing and limits pricing competition in this space. There are very few examples in oncology in which two similar agents are both approved and competing for market share within the same line of therapy and same disease. Interestingly, the emerging field of immunotherapy is one of the few instances in which such pricing competition may develop as we have multiple agents with U.S. Food and Drug Administration approvals in similar practice situations.

Given this lack of direct competition, Howard et al[17] discuss the specific mechanisms of initial drug pricing and inflation within the oncology sphere. They argue that pharmacology manufacturers base the price of their new drugs on recently approved treatments within oncology itself. As we argued above, because few clinical scenarios exist in which a novel drug is directly competing with a me-too agent in the same disease for the same indication, traditional price competition following the initial release price fails to materialize. One popularized quote from 120 of our chronic myeloid leukemia oncology colleagues in *Blood* regarding such pricing mechanisms stipulated, "How are the prices of cancer drugs decided? Of the many complex factors involved, price often seems to follow a simple formula: start with the price for the most recent similar drug on the market and price the new one

TABLE 2. Selected Value Assessment Tools for Oncology Providers and Patients

Name	Country, Year Introduced	Main Value Metrics	Setting	Strengths	Limitations	Who Should Use This Tool?	References
ASCO Value Framework	United States, 2015	Clinical benefit, toxicity, cost	Medical oncology, adjuvant, metastatic	Bonus points awarded for improved QOL	Can only be used with drugs evaluated head to head in a prospective clinical trial	Physicians, along with their patients	[9,10]
				Planned software application that can be used in SDM discussions	No incorporation of PRO or QOL measures in main components		
NCCN Evidence Blocks	United States, 2015	Efficacy, toxicity, evidence quality and quantity, evidence consistency, affordability	All NCCN guidelines	Presented in a graphic format to ease use	Only OS is considered for efficacy	Physicians and patients	[11,12,14]
			Systemic therapies	Affordability considers drug itself, infusions, supportive care, toxicity monitoring, and chance and management of hospital care	Limited to systemic therapies		
				Easily accessible by patients			
ESMO Magnitude of Clinical Benefit Scale	Europe, 2015	Efficacy, toxicity, QOL, survival	Solid tumors, curative, noncurative	Can be used with drugs evaluated in randomized phase II/III studies or comparative cohort designs or meta-analyses	Cannot accommodate single-arm studies	Physicians and policymakers	[13,15]
				Can be used in various therapeutic approaches (surgery, radiotherapy)	Thresholds for clinically meaningful HRs and absolute gains can be subjective		

Abbreviations: ESMO, European Society of Medical Oncology; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; OS, overall survival; PRO, patient-reported outcome; QOL, quality of life; SDM, shared decision making.

within 10–20 percent of that price (usually higher)."[19] Oncology drugs are priced at high initial prices, yet they rarely have associated price decreases with expansion of their market share or other market forces. For example, if left to true market forces, one would expect that if a drug is initially approved by the U.S. Food and Drug Administration and priced in a limited market space (i.e., a metastatic cancer with 5,000 U.S. patients/year), gaining a new indication in another cancer type with an additional 100,000 U.S. patients/year would cause this price to fall. Clearly, true market forces for both drug-drug price competition and alterations of drug price based on size of market have broken down, but have oncologists (and their valuations) played a role in this perturbation?

Unfortunately, for oncologists, the answer is yes. In 2006, Nadler et al[20] published a survey of academic oncologists in Boston, Massachusetts, inquiring about their attitudes regarding the value of oncologic therapies, as well as the cost-effectiveness ratios. Although 30% of respondents agreed that the cost of new cancer drugs influenced their treatment recommendations, the median implied cost-effectiveness ratio was $280,000/quality-adjusted life-year (QALY). Interestingly, the figure was $230,741/QALY for the physicians who agreed that the cost of new cancer drugs influenced their treatment decisions and it was $374,078/QALY for those who disagreed with that statement. In each instance, the dollar sum oncologists were willing to pay for one additional QALY was staggering. Yet an overwhelming percentage of oncologists were clear that patient out-of-pocket costs would influence their decision (81.1%). The study was replicated among ASCO physician members (1,355 respondents; two-thirds in community setting), as well as 238 Canadian medical oncologists who worked within a very different health care system.[21] The majority of oncologists felt that cost-effectiveness ratios less than $100,000/QALY were a reasonable definition of good value for money. However, when queried about a similar hypothetical drug scenario as the Boston group, its costs, and the benefits it provided, the average oncologist (in both the United States and Canada) endorsed its usage up to approximately $250,000/QALY or nearly the same as the Boston academic group. Similarly, more than 80% of oncologists in the United States and Canada were influenced by patients out-of-pocket costs. In fact, what was most startling in these studies was that academic oncologists in Boston, community oncologists within ASCO's membership, and oncologists in the single-payer system of Canada all had nearly superimposable views regarding value and cost.

Oncologists are the gatekeepers and prescribers of oncologic treatment. For all intents and purposes, they function solely as the demand curve for oncology therapy and these studies would argue that this demand curve is relatively inelastic throughout most prices in regard to their valuations and utilization. The elasticity of a demand curve is the change in utilization of a product as its price increases or decreases. These data suggest that as long as patient out-of-pocket costs are not burdensome, oncologists have been relatively unaffected by the inflation of drug prices. As much as oncology's U.S. Food and Drug Administration approval process and the field's treatment paradigms make true price competition challenging, our valuations of these drugs when dealing with actual patients create nearly the same unusual economic perturbations in normal market forces.

COST BENEFIT FROM A PATIENT PERSPECTIVE: INCREMENTAL BENEFIT IS WORTH IT

The Missing Element in Assessing Value-Based Care: Patient-Defined Value

The primary aim of health care is to keep people healthy and, if possible, to return them to good health when circumstances negatively affect their health. Alas, this aim is difficult to achieve in cancer care. Some cancers do not yet have any effective treatments. Few advanced cancers have clear-cut best treatments. Some cancer treatments are not effective for the majority of patients and/or have a substantial effect on QOL. Some patients cannot access the treatments that are available. In addition, cancer care is expensive, generating substantial financial burdens for patients. Given that few patients are aware of these issues when they receive a cancer diagnosis (and most are in such a state of shock that they could not process the information immediately if it were given to them), how might we enable patients to obtain the best cancer care?

Clinical pathways and value assessments in oncology are tools created for health care providers and payers that aim to provide the best possible cancer care given available treatments, evidence, and resource constraints. The ASCO criteria statement says these tools should be patient focused and should include evidence-based options to account for differences in patient characteristics and/or preferences (i.e., patient comorbidities, prior diagnoses and treatments, risks of treatment-related toxicities, treatment schedule and/or financial toxicity)?[22] This approach is a good start, because it acknowledges that patient characteristics and preferences are important for assessing the best evidence-based care options. However, this approach omits a key ingredient necessary for a high-quality cancer care delivery system: patient-defined value.

The first component of the Institute of Medicine's vision for a high-quality cancer care delivery system is "engaged patients: a system that supports all patients in making informed medical decisions consistent with their needs, values, and preferences in consultation with clinicians who have expertise in patient-centered communication and shared decision making."[23] The patient's needs, values, and preferences comprise patient-defined value. Yet none of the four cancer care value frameworks analyzed by FasterCures in 2016 (ASCO Value Framework, Institute for Clinical and Economic Review Value Assessment Framework, Memorial Sloan Kettering Cancer Center DrugAbacus, or National

Comprehensive Cancer Network Evidence Blocks) include factors based on patient-defined value.[24] Where are the criteria, methodology, and incentives to address patient-defined value? How exactly are patients engaged in developing their own care plan?

Patient-defined value requires engaged patients. It cannot be measured by typical patient engagement metrics such as the number of clicks on a cancer clinic's website or willingness to accept informational materials. Engaged patients are identified by their participation as equal members of their care teams, including participation in decisions about managing their treatment path, especially when their illness is life threatening and has no obvious best treatment. Engaged patients evolve through goals of care discussions and SDM processes. Ironically, these are components conspicuously missing from clinical pathways and economic analyses currently used to measure value in cancer care.

An Institute of Medicine survey of more than 1,000 U.S. adults in 2016 reported that most patients strongly agreed that they should be actively involved in understanding and making decisions about their care.[23] A global Pfizer study in 2015 found that patients with metastatic breast cancer would like holistic, individualized, compassionate, and culturally sensitive dialogue with their health care professionals, which can support SDM.[25] Other studies have determined that approximately 70% of patients faced with critical health care decisions preferred participating in SDM.[26,27]

Goals of care discussions are essential to helping both patients and providers identify what matters most for a given individual. The American College of Physicians High Value Care Task Force states that consistent, diverse evidence demonstrates that early discussions of serious illness care goals are associated with beneficial patient outcomes, with no harmful adverse effects, and with possible cost savings.[28] Patients want to be involved in understanding evidence and SDM. More than 75% of patients want their providers to listen to them and to tell them the truth about their diagnosis, even though it may cause discomfort, and less than 20% want to only be offered options that their provider feels are the best options.[23]

The Case for Incremental Benefit: Providing Patient-Defined Value

Most of us pursue everyday dreams, needs, and values while remaining blissfully oblivious to the fact that we will eventually die. When a health event such as a respiratory infection or broken bone disrupts our lives, health care providers are expected to reasonably and promptly return us to the best possible state of health so we can continue our pursuits.

Patients with cancer also pursue dreams, needs, and values. They are just more acutely aware of their mortality and may feel compelled to accelerate or modify their pursuits to accommodate their illness—especially in the case of patients with metastatic disease. The fact that a patient's health event is a potentially terminal illness should not mean that health care providers are less willing to return the patient reasonably promptly to the best possible state of health. The patient and health care providers just need time to come to terms with what best possible state of health means, given what matters to the patient and what evidence-based treatments can be offered by the provider based on effectiveness, side effects, projected survival, and cost.

One reason so many patients and providers struggle with decisions about the most appropriate cancer treatments, as well as transitions to palliative-only care, is that the effectiveness of treatments in clinical trials is measured primarily by survival without adequate consideration of QOL, which is defined differently by each patient. Clinical pathways alone cannot ensure that patient-defined value is fulfilled when goals of care discussions and SDM are not integrated into our cancer care system.

The success of precision medicine and its associated targeted therapy cancer drugs provides many dramatic illustrations of how evidence-based clinical pathways can contribute to patient-defined value. As an example, National Cancer Institute Surveillance, Epidemiology, and End Results Program data have shown for many years that one-half of patients with lung cancer die within 12 months after diagnosis. Physicians could offer patients with metastatic disease only intravenous chemotherapy, which had about a 20% chance of working; if it did work, it might extend life by only months, with substantial side effects in many cases. Today, if a patient with lung cancer has a positive test result for the right biomarker (e.g., EGFR, ALK, ROS1), he or she can take an oral targeted therapy that works for 60% of patients and can have a good chance of gaining a year or more of good QOL with fewer side effects than if the patient were receiving chemotherapy. Those who have a positive test result for the PD-L1 biomarker have a similar chance of success with immunotherapy, with the additional hope of enduring benefit.

Through online patient communities, news outlets, and social media networks, we know how some patients with lung cancer who take precision medicine therapies have used their bonus months of life. Andy Hill entered politics, won a state senate seat, and guided his state's budget process. Neurosurgeon Paul Kalanithi wrote a *New York Times* best seller on what makes life worth living.[29] Others got married, traveled cross country, started families, or snuggled new grandchildren they thought they would never meet. Dozens have become bloggers and advocates who share their cancer experience and encourage other patients to become engaged in their own care. What a life-changing gift those months became!

Because targeted therapies and immunotherapies are expensive, analyses based on value frameworks and QALYs may find that these therapies do not offer sufficient value for the survival benefits they offer. However, such analyses fail to consider patient-defined measures of value, such

as the QOL a patient has receiving one therapy versus the QOL they would have receiving another therapy or even no therapy at all.[30] Anecdotes from patients with metastatic lung cancer in online patient groups and blogs indicate that many of these patients who had received chemotherapy and subsequent precision medicine therapies thought they had a better QOL from targeted therapies and immunotherapies. This improved QOL manifested itself in several ways, including the reduction of serious side effects and associated medical costs, ability to continue employment, increased energy and ability to enjoy leisure activities, and ability to commit to life changes, such as marriage. Although most all patients who received targeted therapies saw their cancer progress eventually, many lived until a new breakthrough drug became available to treat their mutation and give them yet more months of life. None of these factors are currently captured in any value frameworks or economic models.

Of course, not all patients with cancer are eligible or able to access precision medicine therapies. Sometimes traditional chemotherapy is the only evidence-based treatment option, and it may offer only a few extra months of life with substantial side effects. Again, goals of care discussions and SDM are essential to making treatment choices. The patient and provider must discuss the patient's definition of value, along with evidence-based information on effectiveness, survival, side effects, and, importantly, cost. Even patients who want their doctor to choose the best treatment for them can participate by sharing what matters most to them. Being an engaged patient can assist providers using clinical pathways to select the treatment pathway most appropriate for their patient.

Only the patient can decide what defines value and acceptable QOL for him or her. A young parent might choose an aggressive therapy that offers only a few additional months of survival and might be happy to tolerate fatigue and discomfort so great she must view life from the sofa, in hopes of having just a little more time to make memories with her small child. Another individual with the same disease, demographics, and treatment options might choose palliative-only care because she feels life would not be worth living if she could not go for a walk in the woods every day. These might not be choices their provider would make if they were the patient, or that a health care system would make based on value metrics and pathways. Regardless, ethically the final choice of what matters most rests with the patient.

A clinical pathway or economic analysis should factor into the conversation, but it must not provide the final word on what gives meaning to the foreshortened life of a patient with cancer. No health care provider or system should make the QOL versus quantity-of-days decision for a patient unless the patient (or their representative) is unable or unwilling to provide their definition of value. Goals of care discussions and SDM can support both providers and patients in capturing patient-defined value, as well as choosing wisely and reducing health care costs.

CONCLUSION AND FUTURE DIRECTIONS

Precision medicine is revolutionizing oncology care for patients. Many more patients have the opportunity for treatment with biomarker-directed therapies and can avoid receiving the same cytotoxic therapy as every other patient. Immunotherapy is changing the paradigm of cancer therapeutics, especially in lung cancer, where multiple drug approvals were granted in 2016 for therapies with similar indications, both with and without companion diagnostics. With so many treatment options available to patients, how do oncologists choose the treatment with the best value?

The introduction of processes and tools to reduce variation in care and provide oncologists with the most up-to-date care is essential. Clinical pathways can deliver information on current, value-based options quickly, allowing generalists to be knowledgeable about changes to standard care and to practice more specialized medicine. As practice standards evolve, oncologists and patients must be cognizant of the associated costs and limitations. Not every newly approved drug will have good value for every patient. Much discussion has focused on which outcomes should be considered clinically meaningful, how much improvement in the outcome is needed to be clinically meaningful,[31] the definition of value, and whether we have the tools to determine whether a treatment has value.[32] Discussions about value have focused mainly on survival outcomes, such as overall survival and progression-free survival.[31] It is important to realize that although the current value-based models do incorporate survival outcomes, survival is not the only clinically meaningful endpoint to patients. All of the value assessment models have limitations with regard to incorporation of patient-defined value, which is an extremely difficult concept to quantify. Future attempts at quantifying patient-defined value could include incorporation of patient-reported outcomes and QOL measures in research studies so that these measures can be better incorporated directly into value assessment models. Future considerations may includeincorporation of SDM discussions into clinical pathways to help assess patient-defined value.

Patients have different beliefs and understandings of their disease, so their definitions of value may differ and may evolve over time. It is important to engage patients early on and continually in discussions about care goals to deliver the most individualized, comprehensive care. Goals of care discussions and SDM can support both providers and patients in capturing and understanding each individual's definition of value. Presenting options on clinical pathways and using value assessment tools can help oncologists work with their patients to identify the treatment approach that they believe is best for each individual, but ultimately, the decision lies with the patient.

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Managing Resistance to EFGR- and ALK-Targeted Therapies

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OVERVIEW

Targeted therapies have transformed the management of non–small cell lung cancer (NSCLC) and placed an increased emphasis on stratifying patients on the basis of genetic alterations in oncogenic drivers. To date, the best characterized molecular targets in NSCLC are the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Despite steady advances in targeted therapies within these molecular subsets, however, acquired resistance to therapy is near universal. Recent preclinical models and translational efforts have provided critical insights into the molecular mechanisms of resistance to EGFR and ALK inhibitors. In this review, we present a framework for understanding resistance to targeted therapies. We also provide overviews of the molecular mechanisms of resistance and strategies to overcome resistance among *EGFR*-mutant and *ALK*-rearranged lung cancers. To date, these strategies have centered on the development of novel next-generation inhibitors, rationale combinations, and use of local ablative therapies, such as radiotherapy.

Treatment strategies for advanced NSCLC have evolved in recent years because of an improved understanding of the genetic underpinnings of the disease. Indeed, the identification of genetic alterations in key oncogenic drivers (critical mediators of cancer initiation, growth, and maintenance) has informed the development of various small-molecule tyrosine kinase inhibitors (TKIs) aimed at disrupting dysregulated signaling networks in select patient populations. To date, the best characterized examples of this treatment paradigm are lung cancers that harbor genetic alterations in the *EGFR* and *ALK* genes. Each defines a distinct molecular subset of NSCLC, marked by exquisite sensitivity to treatment with genotype-specific TKIs.[1-3] In randomized phase III trials, EGFR and ALK TKIs have consistently demonstrated greater efficacy than cytotoxic chemotherapy,[4-7] which effectively established targeted therapy as the standard of care in each respective patient population.

On the basis of the success of targeted therapies in patients with *EGFR*-mutant and *ALK*-positive disease, molecular profiling of lung cancers now is routine.[8,9] Furthermore, efforts to identify and therapeutically exploit additional molecular targets are ongoing. Despite the impact of targeted therapies in NSCLC, however, resistance is ubiquitous and represents a major clinical challenge.[10] This review, therefore, provides a clinical overview of resistance to targeted therapies in NSCLC and emphasizes therapeutic strategies aimed at overcoming resistance.

FRAMEWORK FOR EVALUATING RESISTANCE TO TARGETED THERAPIES

Intrinsic Versus Acquired Resistance

Resistance to targeted therapies can be classified as either intrinsic (i.e., primary) or acquired (i.e., secondary). Intrinsic resistance implies a de novo lack of response to a given therapy, whereas acquired resistance refers to disease progression after a period of initial clinical benefit.[11] In general, intrinsic resistance to targeted therapies among *EGFR*-mutant and *ALK*-positive NSCLCs is uncommon, and insights into the mechanisms underlying intrinsic resistance are limited.[12] Recent examples include the following: (1) differential TKI sensitivities among specific *EGFR* mutations (e.g., exon 20 insertions)[13] or *EML4-ALK* variants,[14,15] (2) the presence of pre-existing, drug-resistant subclones (e.g., de novo *EGFR* T790M; see EGFR TKI Resistance),[16,17] (3) defects in apoptotic machinery (e.g., Bcl-2-like protein 11 [BIM]),[18,19] (4) phenotypic changes (e.g., epithelial-mesenchymal transition [EMT]),[20] and (5) false-positive genotyping, among others. Because of limited clinical data on intrinsic resistance, the remainder of this review will focus on acquired resistance to targeted therapies.

Overview of Molecular Mechanisms of Acquired Resistance

Molecular mechanisms of acquired resistance to targeted therapies can be characterized broadly as either on target or off target. The former refers to the development of additional genetic alterations in the primary oncogenic target (e.g., *EGFR*, *ALK*) that enable continued downstream

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signaling. Typically, this occurs via secondary point mutations and/or gene amplification of the target. Secondary point mutations generally confer resistance through steric interference or via conformational changes that alter drug binding, whereas target amplification likely mediates resistance by shifting the equilibrium back in favor of the kinase.

Beyond genetic alterations in the target, resistance also may be mediated by target-independent, or off-target, mechanisms. To date, the best described examples of off-target mechanisms of resistance involve the upregulation of bypass signaling pathways—commonly through activation of alternative receptor tyrosine kinases.[21] Ultimately, bypass tracts allow reactivation of downstream mediators of growth and survival despite continued target engagement. In addition to bypass tract activation, other off-target mechanisms of resistance include changes in tumor histology (i.e., lineage changes); increased growth factor production; and overexpression of drug efflux pumps.[11,22-24]

Oligoprogression Versus Multisite Progression

When resistance to targeted therapies in NSCLC is evaluated, other important considerations are the site and nature of progression. Patients frequently experience diffuse or multisite progression, which generally requires that clinicians consider a change in systemic therapies. However, resistance to targeted agents also may be heterogeneous,[25] which results in more limited sites of progression. For example, the term "oligoprogression" refers to isolated progression in one or two anatomic sites, with continued clinical response or stability elsewhere. Most notably, oligoprogression in the central nervous system (CNS) is a relatively frequent complication in *EGFR*-mutant and *ALK*-positive NSCLC—often because of limited penetration of TKIs beyond the blood-brain barrier.[26,27] Distinguishing oligoprogression from multisite progression may have important implications for the use of local ablative therapies, such as radiotherapy.

KEY POINTS

- **Acquired drug resistance remains a critical barrier in the effort to maximize the efficacy of targeted therapies in lung cancer.**
- **Mechanisms of acquired drug resistance include target-dependent alterations, including acquired mutations or amplification of the drug target, and target-independent mechanisms, including activation of bypass signaling pathways and histologic transformation.**
- **Second- and third-generation EGFR and ALK TKIs have been developed to overcome target-dependent mechanisms of acquired drug resistance. These drugs have increased on-target potency; however, acquired resistance remains a significant problem, even with more potent inhibitors.**
- **Rational combination therapeutic approaches to overcome drug resistance, such as the addition of MEK blockade to EGFR and ALK inhibition, have been developed on the basis of preclinical modeling of the disease states.**
- **Treatment of oligoprogressive disease with local therapies may significantly improve outcomes in patients treated with targeted therapies.**

EGFR TKI RESISTANCE: MECHANISMS AND THERAPEUTIC APPROACHES

Therapeutic Targeting of EGFR Mutations in Lung Cancer

Recurrent activating mutations in the exons that encode the tyrosine kinase domain of *EGFR* are found in 10% to 15% of patients with NSCLC in the United States and in up to 30% of occurrences in Asian populations.[1,2,28] In the United States, approximately 20,000 patients die as a result of *EGFR*-mutant lung cancer each year. *EGFR* mutations, most commonly small in-frame deletions in exon 19 (exon 19 del), which eliminate an LREA motif in the protein, and a point mutation in exon 21, which leads to substitution of an arginine for a leucine at position 858 (L858R), are associated with sensitivity to EGFR TKIs. To date, three generations of EGFR TKIs have entered the clinic. First-generation TKIs are competitive inhibitors of EGFR, while second-generation TKIs irreversibly bind to EGFR and other erbB family members. Multiple phase III trials have shown that patients with *EGFR*-mutant tumors display greater than 70% objective response rates (ORRs) and a statistically significant improved progression-free survival (PFS) when treated with first-generation (erlotinib, gefitinib) or second-generation (afatinib) EGFR TKIs (Table 1) compared with standard platinum-based chemotherapy for NSCLC.[29-32] As a result of these studies, prospective tumor genotyping for *EGFR* mutations is now the standard of clinical care, and erlotinib, gefitinib, and afatinib are approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic *EGFR*-mutant NSCLC.

Acquired Resistance to Wild-Type EGFR TKIs: Erlotinib, Gefitinib, and Afatinib

Unfortunately, despite these markedly improved outcomes, patients whose tumors initially respond to erlotinib, gefitinib, and afatinib eventually display disease progression, typically within a year of starting treatment.[4,31,32] The most common mechanisms of acquired resistance—occurring in approximately 60% of tumors resistant to erlotinib/gefitinib/afatinib—is acquisition of the T790M second-site mutation in the *EGFR* kinase domain.[22,33-35] The T790M gatekeeper mutation confers drug resistance through steric hindrance, which interferes with drug binding and through alterations in the ATP affinity of the kinases.[36] Target-independent (i.e., independent of the driver kinase, *EGFR*) resistance mechanisms also have been described; these include *MET* amplification[35]; *HER2* amplification[37]; *PIK3CA* mutations[22]; autocrine hepatocyte growth factor (HGF) production[17]; EMT[22,38,39]; and transformation to small cell lung cancer.[22,40]

Overcoming T790M-Mediated Resistance With Mutant-Selective EGFR TKIs

Recently, a new class of drugs that irreversibly inhibit mutant *EGFR* has been developed. These mutant-selective, or third-generation, EGFR TKIs were designed to overcome

TABLE 1. EGFR TKIs Currently in Clinical Use for Patients With *EGFR*-Mutant NSCLC

EGFR TKI	Selectivity	Reversible/ Irreversible	Status in Lung Cancer	Select Clinical Trials
First Generation				
Erlotinib	Wild-type *EGFR*	Reversible	FDA approved	
Gefitinib	Wild-type *EGFR*	Reversible	FDA approved	
Second Generation				
Afatinib	Wild-type *EGFR*	Irreversible	FDA approved	
Third Generation				
Osimertinib (AZD9291)	Mutant *EGFR*	Irreversible	FDA approved; T790M-positive only	NCT02296125 (phase III first line)
				NCT02511106 (phase III adjuvant)
Rociletinib (CO-1686)	Mutant *EGFR*	Irreversible	No longer in development	NCT02147990 (phase II)
Nazartinib (EGF816)	Mutant *EGFR*	Irreversible	Investigational	NCT02335944 (phase IB/II)
				NCT02108964 (phase IB/II)
Olmutinib (BI1482694/ HM61713)	Mutant *EGFR*	Irreversible	Investigational	NCT02485652 (phase II)
				NCT02444819 (phase II)
ASP8273	Mutant *EGFR*	Irreversible	Investigational	NCT02500927 (phase II)
				NCT02588261 (phase III first line)

Abbreviations: FDA, U.S Food and Drug Administration; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

the effects of the T790M resistance mutation but relatively spare wild-type EGFR. These agents also are highly potent against the original *EGFR* activating mutations (del 19 and L858R). There are several such mutant-selective EGFR inhibitors (Table 1), including osimertinib (AZD9291),[41] rociletinib,[42] and nazartinib.[43] Preclinically, these drugs potently inhibit signaling pathways and cellular growth in *EGFR*-mutant cell lines, xenografts, and transgenic mouse models.

Clinically, mutant-selective EGFR TKIs induce high ORRs and, often, durable responses in patients with *EGFR*-mutant lung cancer. The most well-studied mutant-selective EGFR TKI to date is osimertinib. In the phase I trial of this agent, the ORR was 61% and the median PFS was 9.6 months in patients with *EGFR* T790M–positive disease[44] who had experienced progression during treatment with prior erlotinib, gefitinib, or afatinib. On the basis of these results, osimertinib was approved by the FDA in November 2015 for the treatment of patients with metastatic *EGFR* T790M mutation–positive NSCLC. Osimertinib also has proven more effective than platinum-based chemotherapy for second-line treatment. In an international phase III trial (AURA 3), 419 patients with T790M-positive advanced *EGFR*-mutant lung cancer who experienced disease progression after first-line EGFR TKI therapy were randomly assigned to receive osimertinib or cisplatin/carboplatin plus pemetrexed.[45] The median PFS was 10.1 months in the osimertinib group versus 4.4 months in the platinum/pemetrexed group. The ORR also favored osimertinib (71% for osimertinib vs. 31% for chemotherapy). Notably, osimertinib also has demonstrated efficacy against CNS metastases. In the AURA 3 study, among 144 patients with CNS metastases, the median PFS was 8.5 months for patients who received osimertinib compared with 4.2 months for patients who received platinum chemotherapy.

Notably, osimertinib has shown promising results when used as first-line therapy—that is, in patients who are EGFR TKI naive, before the acquisition of T790M. In the AURA trial (NCT01802632), the ORR was 77% and the median PFS was 19.3 months for osimertinib therapy in treatment-naive patients with *EGFR*-mutant lung cancer.[46] The ongoing, global, phase III FLAURA trial (NCT02296125) is directly comparing first-line osimertinib with typical first-line therapy of erlotinib/gefitinib. Results from this trial are eagerly awaited.

Several other *EGFR*-mutant specific TKIs are being evaluated in clinical trials (Table 1), including rociletinib (CO-1686), olmutinib (BI1482694/HM61713), nazartinib (EGF816), and ASP8273. Preliminary results with olmutinib were presented recently[47]; the ORR was 54% and the median duration of response was 8.3 months in patients with *EGFR* T790M–containing tumors after progression on first- or second-generation EGFR TKIs. In a phase II trial of rociletinib, the ORR in patients with T790M-positive disease was 59%,[48] but this agent is no longer being developed.

Acquired Resistance to Mutant-Selective EGFR TKIs

As with the first- and second-generation wild-type–specific EGFR TKIs, the magnitude and duration of response to osimertinib and other third-generation EGFR TKIs are variable, and resistance inevitably develops. Mechanisms of acquired resistance to mutant-selective EGFR TKIs are only beginning to be defined. Analogous to resistance to the wild-type EGFR TKIs, resistance to mutant-selective TKIs can be

TABLE 2. Acquired Resistance Across the Spectrum of EGFR and ALK Inhibitors

TKI	Target-Dependent Mechanisms	Target-Independent Mechanisms
EGFR TKIs		
Wild-type selective EGFR TKIs	Acquisition of a secondary mutation, most commonly T790M	*HER2* amplification
		MET amplification
		PIK3CA mutation
		EMT
		Small cell transformation
Mutant-selective EGFR TKIs	Acquisition of a tertiary mutation, such as C797S or L718Q	*HER2* amplification
	Loss of T790M allele	*MET* amplification
	EGFR amplification	*KRAS* mutation
		Small cell transformation
ALK TKIs		
First-generation ALK TKIs (crizotinib)	Acquisition of secondary mutations (> 10 reported), most commonly L1196M and G1269A	EGFR activation
	ALK fusion gene amplification	MAPK pathway activation
		c-KIT amplification and SCF overexpression
		SRC activation
		IGF-1R activation
		Ligand-mediated HER2/3 activation
		Protein kinase C activation
		Small cell transformation (rare)
Second-generation ALK TKIs (ceritinib, alectinib, and brigatinib)	Acquisition of secondary mutations, most commonly *ALK* G1202R	MAPK reactivation
		SRC activation
		PIK3CA mutations
		MET amplification
		EMT

Abbreviations: ALK, anaplastic lymphoma kinase; EMT, epithelial-mesenchymal transition; IGF-1R, insulin-like growth factor 1 receptor; MAPK, mitogen-activated protein kinase; SCF, stem cell factor; SRC, SRC proto-oncogene, non-receptor tyrosine kinase; TKIs, tyrosine kinase inhibitors.

mediated through target-dependent and target-independent mechanisms (Table 2). For example, acquisition of a tertiary *EGFR* mutation, C797S, has been reported in patients with acquired resistance to osimertinib.[49,50] This cysteine residue is the site where the mutant specific inhibitors covalently bind to the EGFR ATP binding pocket. In addition, an additional tertiary mutation, *EGFR* L718Q, has been detected in a patient with osimertinib resistance.[51] To date, the frequency of these tertiary *EGFR* mutations (C797S and L718Q) has not been clearly defined. Other studies have reported loss of the *EGFR* T790M mutation or *EGFR* amplification at the time of resistance to the mutant-selective EGFR TKI rociletinib.[25] Target-independent resistance mechanisms have been described, including *HER2* or *MET* amplification and *KRAS* mutation, at the time of osimertinib resistance.[52,53] *KRAS* mutations have been identified in preclinical models of osimertinib resistance.[54] Finally, small cell transformation has been identified in patients with rociletinib resistance.[25] Overall, the data that have been reported to date for resistance to mutant-selective EGFR TKIs have come from case reports or small case series. Additional studies are needed to expand the knowledge about resistance to this novel class of EGFR TKIs.

Overcoming Acquired Resistance to Mutant-Selective EGFR TKIs

At present, there are no FDA-approved targeted therapies for patients who experience disease progression on a mutant-selective EGFR TKI, and the current standard of care is cytotoxic chemotherapy. However, several clinical trials currently are exploring novel therapeutic options for this cohort of patients. For example, preclinical evidence supports the idea of vertical EGFR and MAPK inhibition in *EGFR*-mutant lung cancer,[54,55] and the phase IB TATTON trial (NCT02143466) currently is investigating osimertinib plus the MEK inhibitor selumetinib in patients who have experienced progression during treatment with osimertinib monotherapy.[56] The TATTON trial also includes an arm to evaluate the combination of osimertinib plus the MET inhibitor savolitinib. Other studies are looking at the combination of osimertinib plus the EGFR monoclonal antibody necitumumab (NCT02496663, NCT02789345) to attempt to

prolong the initial response to osimertinib monotherapy. In addition, the combination of osimertinib with a Bcl-2 (B-cell lymphoma 2) inhibitor, navitoclax, is being tested in a phase I clinical trial. This combination stems from preclinical work showing that the Bcl-2 inhibitor restored sensitivity to EGFR TKIs in vitro.[57] Finally, a fourth generation of mutant-selective EGFR allosteric inhibitors, such as EAI045,[58] are being developed. EAI045 in combination with the EGFR monoclonal antibody cetuximab is effective in mouse models of lung cancer driven by *EGFR* (L858R/T790M) and by *EGFR* (L858R/T790M/C797S). Future studies are anticipated to bring EAI045 or similar EGFR allosteric inhibitors into the clinic, driving home the paradigm that patients can and will be treated with multiple lines of EGFR-directed therapies.

ALK TKI RESISTANCE: MECHANISMS AND THERAPEUTIC APPROACHES

Therapeutic Targeting of ALK Rearrangements in Lung Cancer

ALK rearrangements are present in 3% to 5% of patients with NSCLC and define an important molecular subgroup of the disease.[59] Shortly after the discovery of *ALK* rearrangements in NSCLC in 2007,[60] it was recognized that *ALK* rearrangements confer exquisite sensitivity to ALK inhibition.[3] Crizotinib is a first-in-class ALK/ROS1/MET inhibitor that was approved initially by the FDA in 2011 for the treatment of advanced, *ALK*-positive NSCLC. In two randomized phase III trials (PROFILE 1014 and 1007), crizotinib produced significant improvements in ORR, PFS, and quality of life compared with first- and second-line cytotoxic chemotherapy.[6,7] On the basis of these studies, crizotinib emerged as a standard first-line therapy for advanced ALK-positive NSCLC. Although crizotinib has transformed the management of *ALK*-positive NSCLC, patients ultimately still experience progression during therapy—commonly within 1 to 2 years.[6,7]

Acquired Resistance to Crizotinib

Efforts to identify molecular mechanisms of resistance to crizotinib initially focused upon on-target resistance mechanisms. In one early report, Katayama et al[61] identified secondary resistance mutations in the *ALK* kinase domain in four (22%) of 18 patients with *ALK*-positive disease who experienced progression during treatment with crizotinib. In addition, one (6.7%) of 15 patients in this series had high-level amplification of the *ALK* fusion gene without concurrent resistance mutations, which suggests that amplification alone was sufficient to confer resistance. In a separate report, Doebele and colleagues[62] found *ALK* resistance mutations and *ALK* copy number gains in four (36%) and two (18%) of 11 patients, respectively. Collectively, across all series, the most common crizotinib resistance mutations have been *ALK* G1269A and the gatekeeper mutation *ALK* L1196M, which is analogous to *EGFR* T790M.[61-63] However, in contrast to the experience with *EGFR*-mutant NSCLC, in which T790M is the lone dominant resistant mutation to first- and second-generation inhibitors, various different *ALK* resistance mutations have been described. Furthermore, these mutations are distributed throughout the kinase domain.[61-65]

Although secondary *ALK* mutations are well-established mediators of resistance to crizotinib, most patients lack these alterations. In such cases, bypass signaling pathways have been implicated frequently in resistance. To date, various bypass signaling pathways have been identified. One of the earliest examples was EGFR pathway activation via upregulation of EGFR ligands and/or the receptor itself—independent of *EGFR* mutations or genomic amplification.[61,65,66] More recently, Wilson and colleagues[67] identified ligand-mediated HER2/3 activation and protein kinase C activation (via P2Y receptors) as drivers of crizotinib resistance by using an open-reading frame library screen. In addition, *cKIT* amplification, insulin-like growth factor 1 receptor (IGF-1R) activation, and upregulation of SRC proto-oncogene, non-receptor tyrosine kinase (SRC) signaling all have been identified separately as mediators of crizotinib resistance in patient-derived specimens.[61,68,69] In addition, patients treated with crizotinib may progress in the CNS as a result of limited blood-brain barrier penetration (i.e., pharmacokinetic failure) rather than true biological resistance.

Overcoming Acquired Resistance to Crizotinib

To address the clinical challenge of crizotinib resistance, multiple second-generation ALK inhibitors have been developed (Table 3). These agents generally have greater selectivity, potency, and CNS penetration than crizotinib. Second-generation ALK inhibitors also are generally able to overcome common crizotinib-resistant *ALK* mutations (e.g., L1196M).[70] To date, two second-generation ALK inhibitors, ceritinib and alectinib, have received regulatory approval in the United States for the management of crizotinib-resistant or -intolerant, ALK-positive NSCLC. Ceritinib was approved on the basis of ASCEND-1, a single-arm, phase I study that demonstrated an ORR of 56% and a median PFS of 6.9 months among 163 patients pretreated with crizotinib.[71,72] The activity of alectinib in the crizotinib-resistant setting has been evaluated in two single-arm studies (NP28673 and NP28761), which demonstrated ORRs of 48% to 50% and median PFS times of 8.1 to 8.9 months.[73,74] In addition to ceritinib and alectinib, brigatinib, another second-generation ALK inhibitor, recently received breakthrough therapy designation by the FDA for the treatment of crizotinib-resistant or -intolerant, *ALK*-positive NSCLC. In a preliminary phase I/II study and randomized phase II trial (ALTA), brigatinib was highly active (ORRs, 45% to 62%; median PFS times, 8.8 to 15.6 months) in previously treated patients with *ALK*-positive disease.[75,76]

Given the activity and enhanced CNS penetration of second-generation ALK inhibitors, there has been a growing interest in moving these agents to the first-line setting. In one recent study (ASCEND-4), patients with *ALK*-positive disease who received first-line ceritinib experienced a prolonged median PFS of 16.6 months; however, the control arm in this study was platinum/pemetrexed rather than the current standard, crizotinib.[77] Several other randomized studies

TABLE 3. Select ALK TKIs Currently in Clinical Use and/or Under Investigation for Patients With *ALK*-Rearranged NSCLC

		Select Trial Details				
ALK TKIs	**Status in Lung Cancer**	**Trial/Name**	**Phase**	**No. of Patients***	**ORR (%)**	**Median PFS (Months)**
First Generation						
Crizotinib	FDA approved	PROFILE 1014	III	343	74	10.9
		PROFILE 1007	III	347	65	7.7
Second Generation						
Ceritinib	FDA approved	ASCEND-1	I	163	56	6.9
		ASCEND-2	II	140	38.6	5.7
		ASCEND-4**	III	376	72.5	16.6
Alectinib	FDA approved	NP28673	II	138	50	8.9
		NP28761	II	87	48	8.1
		J-ALEX**	III	207	85.4	NR (95% CI, 20.3 to NR)
Brigatinib	Breakthrough therapy designation	NCT01449461	I/II	79	62	13.2
		ALTA	II	222†	45-55	8.8-15.6
Ensartinib (X-396)	Investigational	NCT01625234	I/II	27‡	70	N/A
Third Generation						
Lorlatinib	Investigational	NCT01970865	I/II	41§	46	11.4

*Number of participants in the overall study population.

**Enrolled ALK inhibitor–naive patients.

†Participants were randomly assigned to either 90 or 180 mg of brigatinib.

‡Includes eight crizotinib-naive patients.

§Includes 26 patients previously treated with two or more ALK TKIs.

Abbreviations: ALK, anaplastic lymphoma kinase; NR, not reached; NSCLC, non–small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

comparing second-generation ALK inhibitors with crizotinib in the treatment-naive setting are ongoing. For example, in a preliminary report from the phase III J-ALEX study, alectinib demonstrated impressive improvements in ORR and PFS compared with crizotinib among 207 ALK inhibitor–naive Japanese patients.[78] A parallel global study to evaluate alectinib versus crizotinib (ALEX; NCT02075840) is ongoing. A central question, however, is whether upfront use of more potent second-generation ALK inhibitors will translate into long-term survival benefits that surpass the combined benefit of use of crizotinib and second-generation ALK inhibitors sequentially.

Acquired Resistance to Second-Generation ALK Inhibitors: Ceritinib, Alectinib, and Brigatinib

Like the experience with crizotinib in *ALK*-positive NSCLC, resistance almost invariably develops after treatment with second-generation ALK inhibitors. Interestingly, the frequency of *ALK* resistance mutations in this setting is actually higher than after crizotinib, which likely reflects the greater potency of second-generation ALK inhibitors.[63,70] Indeed, in a recent analysis of 48 biopsies from patients with *ALK*-positive disease who experienced progression during treatment with second-generation ALK inhibitors (ceritinib, n = 24; alectinib, n = 17; brigatinib, n = 7), *ALK* resistance mutations were found in 56% of patients (ceritinib, 54%; alectinib, 53%; brigatinib, 71%),[63] and each ALK inhibitor had a distinct spectrum of *ALK* resistance mutations, which likely reflected structural differences between agents. Notably, the frequency of one particular resistance mutation, *ALK* G1202R, increased significantly after treatment with all second-generation ALK inhibitors. Although *ALK* G1202R was found in only 2% of crizotinib-resistant specimens, it was detected in 21% to 43% of biopsies from patients who experienced progression during treatment with second-generation ALK inhibitors.[64] This alteration confers high-level resistance to available first- and second-generation ALK inhibitors via steric hindrance.[61,70,79]

In addition to *ALK* resistance mutations, target-independent mechanisms of resistance to second-generation ALK inhibitors have been described (Table 2). These include MAPK pathway reactivation,[69] SRC activation,[63,69] *PIK3CA* mutations,[63,69] and *MET* amplification.[80] Of note, *MET* amplification has not been reported in crizotinib-resistant specimens to date, likely because crizotinib inhibits both ALK and MET. By contrast, second-generation ALK inhibitors do not have anti-MET activity. In addition to bypass signaling pathways, several isolated cases of small cell transformation among patients with *ALK*-positive disease who experienced disease progression during treatment with crizotinib and alectinib also have been reported.[81-83] However, the frequency of this lineage change is less clear. In a large series of 103 repeat biopsies from patients with *ALK*-positive disease who experienced progression during treatment with first- and

second-generation ALK inhibitors, no occurrences of SCLC were observed, which suggests that this is a rare event.[63] In this same series, however, five (42%) of 12 post-ceritinib biopsies showed phenotypic changes consistent with EMT, such as loss of E-cadherin staining and gain of vimentin expression. It should be noted, however, that three of five patients with EMT also had concomitant *ALK* resistance mutations; thus, the role of EMT in driving clinical resistance warrants additional investigation.

Overcoming Acquired Resistance to Second-Generation ALK Inhibitors

On the basis of the success of second-generation ALK inhibitors in overcoming resistance to crizotinib, recent efforts have centered on developing additional novel ALK inhibitors (Table 3). For example, lorlatinib is a potent, third-generation ALK inhibitor that has demonstrated in vitro activity against all known *ALK* resistance mutations, including G1202R.[79] In preliminary results from an ongoing phase I/II study (NCT01970865), lorlatinib demonstrated significant activity; ORRs were 57% and 42% among patients with *ALK*-positive disease previously treated with one or with two or more ALK TKIs, respectively.[84] Furthermore, responses also were seen in patients with baseline CNS metastases (intracranial ORR, 39%) and patients with *ALK* G1202R. The phase II portion of this study is ongoing.

Because each ALK inhibitor is associated with a different spectrum of *ALK* resistance mutations,[63] another emerging strategy to combat resistance is to administer ALK inhibitors sequentially on the basis of resistance profiles. One proof-of-principle example of this approach involved the case of a patient with *ALK*-positive disease who had a dual *ALK* mutation (C1156Y and L1198F) after sequential treatment with crizotinib, ceritinib, and lorlatinib. Interestingly, this compound mutation paradoxically resensitized cells to crizotinib, which resulted in another clinical response to crizotinib.[85]

In addition to the discussed strategies, cytotoxic chemotherapy continues to play a role in the management of *ALK*-positive patients progressing on second-generation inhibitors. Additionally, ALK inhibitor combinations also are being explored in an effort to overcome potential bypass signaling pathways. For example, Hrustanovic and colleagues[86] recently found that upfront polytherapy with ALK and MEK inhibitors improved responses and eliminated the emergence of resistance in preclinical models, forming the basis for clinical trials of similar combinations. Currently, clinical trials evaluating ALK inhibitors in combination with CDK4/6 inhibitors (NCT02292550), mTOR inhibitors (NCT02321501), and antiangiogenesis agents (NCT02521051) also are ongoing. In addition, given the broad success of immune checkpoint inhibitors in NSCLC, several trials combining ALK and PD-1/PD-L1 inhibitors have been launched (e.g., NCT01998126, NCT02511184, NCT02393625), though preclinical data to support such combinations are lacking.[87] Ultimately, additional insights into the molecular mechanisms of resistance to second-generation ALK inhibitors are needed, which may in turn inform more rationale combination approaches.

ROLE OF RADIATION IN METASTATIC NSCLC

Thus far, this review has focused on multisite progression and switching to other systemic agents at the time of disease progression. However, consideration also should be given to the use of local therapy, potentially in the form of stereotactic ablative radiotherapy (SABR), as a means of controlling disease that has progressed in salvage settings or to spur the immune system action on distant sites in an abscopal mechanism. Both of these efforts could permit patients to remain on systemic agents that appear to be working in a predominant number of disease sites, aided by the use of local therapy in the resistant areas of disease. SABR is a refined radiation treatment approach, also referred to as stereotactic body radiation therapy (SBRT), that is able to deliver ablative doses of radiation using a highly conformal approach with image guidance. SABR is delivered in five or fewer treatments, providing a short course regimen that is effective in controlling local disease, noninvasive, and safely able to reach disease in most anatomical locations.

Currently, the major arguments for aggressive local treatment of metastatic disease include a general lack of ability of systemic therapy to cure solid tumors, failures most often presenting in original sites of gross disease, heterogeneity in response to systemic therapy secondary to disease biology, and reduced effectiveness of subsequent lines of systemic agents. All of these points collectively support the notion that local therapy might enhance overall tumor control, because local therapies are more effective at reducing tumor bulk, are less likely to be rendered ineffective by multidrug resistance mutations, and may reduce additional metastases by successful gross tumor control.

Reports of long-term survival of patients after surgical resection of metastases began to surface as early as the 1930s in patients with limited metastases.[88,89] In general with respect to solid tumors and particularly lung cancer metastases, intracranial disease was one of the earliest sites in which SABR/SBRT based radiosurgery technologies was utilized with a local therapy approach. The state of limited metastatic disease without widespread progression, however, ultimately was termed oligometastasis in 1995.[90] Oligometastasis now is recognized as a unique clinical entity in which aggressive, ablative therapies can result in long-term cure, primarily identified in patients with sarcoma, with colorectal cancer, and with limited brain metastases treated with surgery or radiation.[88,89] It is in this setting of oligometastases that one would expect salvage local therapy to have the potential to help systemic therapy the most with respect to PFS.

There are no prospective studies to compare surgical resection to radiation therapy for the salvage treatment of oligometastatic disease. Indeed, nonoperative approaches may be preferred for some patients with oligometastasis because of the risks of surgical morbidity and mortality as well as comorbid conditions common in patients with

NSCLC, which may increase such surgical risks. Furthermore, patients with metastatic disease generally are treated with systemic therapy for long periods of time; therefore, any local therapy that prevents or delays patients from receiving subsequent systemic therapy would be detrimental. SABR adapts the techniques of stereotactic radiosurgery for intracranial disease to the delivery of highly conformal radiation to extracranial targets, which increasingly is used to treat oligometastasis.[91]

With the current knowledge, one can argue that there is really no role for the use of radiation in widely metastatic disease states of progression except for palliation. Radiation in oligoprogression is most likely to show some benefit, especially because first failures occur in sites of original gross disease. The concept of radiation eliciting an abscopal response in unirradiated disease is still in its infancy for NSCLC and, therefore, will elicit no additional discussion in this narrative. Should salvage be given in the form of SABR without systemic therapy afterward? Should we continue the targeted therapy that may have been working for microscopic disease or for a majority of original lesions? With new generations of targeted agents, should patients switch to the new generation before local therapy is considered? Evidence is provided for some rationalizations about treatment paradigms for targeted therapy–resistant NSCLC, with a focus on extra cranial progression that may benefit from radiation.

Oligoprogression

Radiation to treat oligoprogression in NSCLC treated with targeted therapies has come to the forefront only recently after the more widespread use of targeted therapies themselves. The University of Colorado Cancer Center has published its experience with local therapies combined with targeted agents in the management of *EGFR*- and *ALK*-positive NSCLC. In one retrospective evaluation, 65 patients with either *ALK*-positive or *EGFR*-mutated tumors were identified.[92] Of these patients who received the appropriate kinase inhibitors, 51 experienced progression. Twenty-five of these 51 patients received local therapy, primarily in the form of SABR. Thereafter, patients were maintained on their original targeted therapy. The median PFS was 6.2 months after local therapy. Nineteen of 25 patients experienced progression again and required a reconsideration of this treatment approach. The authors concluded that the local therapy, which added no notable toxicity, permitted continued benefit and use of predominantly effective systemic therapies. In a second study from this same group, 38 patients with *ALK*-positive NSCLC were treated with crizotinib.[93] Thirty-three experienced disease progression during crizotinib treatment; 14 of them had extracranial oligoprogressive disease treated with SABR. There was no notable toxicity associated with SABR. All patients treated with radiation continued to receive crizotinib. Those patients who were eligible to receive SABR remained treated with crizotinib for a median of 28 months, compared with 10.1 months for those patients who did not fit the profile to receive SABR. When patients were treated with crizotinib for greater than 12 months, their 2-year overall survival was 72%; overall survival was 12% for those who were not. These data suggest a synergy between SABR and continuation of targeted therapy, though the findings could have been simply secondary to a difference in biology between patients with oligoprogressive versus widely progressive disease states.

In 2013, Yu and colleagues[94] from Memorial Sloan Kettering Cancer Center identified 18 patients with NSCLC who had been treated with extracranial local therapy in the form of surgery, SABR, or radiofrequency ablation for *EGFR*-mutant tumors that had developed resistance to EGFR TKIs. These patients had been identified from prospective tissue biopsy trials. There were no notable complications from local treatments, and 85% of patients restarted either erlotinib or gefitinib within 1 month of completion of local therapy. From completion of local therapy, the median PFS was 10 months, the time to change of systemic therapy was 22 months, and the median overall survival was 41 months. Ultimately, it appeared that the local therapy was well tolerated, allowed treatment to be maintained on targeted agents that were probably active against a majority of gross and microscopic disease, and helped these patients with respect to survival.

A single arm, prospective, phase II trial subsequently was conducted jointly at The University of Texas Southwestern Medical Center and the University of Colorado to test the contribution of SABR to targeted therapies to enhance survival and allow patients to remain on effective systemic therapies.[95] Iyengar and colleagues[95] prospectively tested the use of SABR and concurrent erlotinib in 24 patients with 52 extracranial metastases from NSCLC who had experienced progression through at least one systemic regimen, including targeted therapies, in a limited metastatic fashion. SABR was delivered as salvage to all sites of oligoprogressive disease. The median survival and PFS were 20.4 months and 14.7 months, respectively. Only three local failures of 47 evaluable lesions were observed, and 10 patients experienced progression at distant sites. The use of SABR allowed patients to remain on one targeted therapy for longer periods of time than historical standards, changed/shifted the pattern of failure from local to distant sites first, and led to prolonged overall survival and PFS (when compared with historical outcomes). Interestingly, of the 12 patients who had marker evaluation, none harbored *EGFR* or *ALK* activating mutations.

In nonrandomized, prospective approaches, there is always a question of whether oligoprogressive disease represents a biologic entity with a more indolent disease course (i.e., fewer sites of progression or metastasis, resulting in improved survival independent of treatment management). To address this caveat, a multi-institutional Canadian phase II trial will assess local therapy in the form of SBRT for oligoprogression in a randomized setting (NCT02756793) with PFS as primary endpoint. Patients with targetable mutations will be eligible.

Ultimately, the limited data to date suggest that local therapies in the form of SABR can be completed quickly, are effective for local control, cause limited toxicity, and allow patients to continue to receive the same systemic therapy that probably is working to treat a majority of the disease. Survival parameters also may be extended with local treatment, though these paradigms are actively being clarified in randomized studies. In oligoprogressive states, it appears best to combine SABR with systemic agents, not to use SABR alone. This thought comes from the evidence that suggests it is best to use the local therapy for the most resistant areas of disease but to use the systemic therapy for microscopic disease (i.e., disease that is not obvious on imaging), because it is accessible by all tissues. Finally, we should view and treat oligoprogressive NSCLC with targetable mutations potentially in the same fashion as limited metastatic colorectal cancer. Once metastasized, colorectal cancer is treated with a pragmatic approach that consists of intermittent aggressive local therapy and continued use of systemic therapies for as long as some benefit is manifest.

CONCLUSION

In summary, targeted therapies continue to reshape the management of NSCLC, particularly among patients with *EGFR* mutations and *ALK* rearrangements. Despite steady improvements in targeted therapies within these molecular subsets, however, acquired resistance to therapy is ever present. Recent preclinical models and translational efforts have provided critical insights into the molecular mechanisms of resistance. Such work has been complemented by recent advances in noninvasive tools, such as circulating free DNA assays, which have permitted additional insights into the temporal dynamics and heterogeneity of resistance. Collectively, these insights have helped inform strategies to overcome resistance. To date, these strategies have centered on the development of novel next-generation inhibitors, rationale combinations, and use of local ablative therapies. It is hoped that such approaches will continue to improve outcomes among patients who have NSCLC with targetable alterations.

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Pathology Issues in Thoracic Oncology: Histologic Characterization and Tissue/Plasma Genotyping May Resolve Diagnostic Dilemmas

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OVERVIEW

Lung cancer is a heterogeneous diagnosis that encompasses a spectrum of histologic and molecular subgroups. A paradigm shift favoring selection of treatment based on histologic and molecular makeup has positively affected prognosis for patients with metastatic lung cancer, with select patients experiencing durable responses to treatment. However, prognosis remains poor for the majority of patients. Furthermore, oncologists are increasingly faced with challenging dilemmas related to histopathologic and molecular characterization of tumors, both at diagnosis and during treatment. In this review, we focus on three particular challenges: (1) management of mixed histology tumors, a particularly aggressive group of lung cancers, (2) distinguishing multiple primary lung tumors from intrapulmonary metastases, and (3) incorporation of liquid biopsies into the diagnostic algorithm and subsequent follow-up of patients with advanced lung cancer. This review will summarize the existing literature and highlight the potential for molecular genotyping to help refine approaches to each of these challenges.

Lung cancer, the leading cause of cancer-related mortality worldwide, accounts for one-quarter of deaths from cancer.[1] In 2017, it is estimated that 222,500 people will be diagnosed with and 155,870 people will die of lung cancer in the United States.[1] Despite significantly improved prognosis for all-comers with cancer in the past 2 decades, the 5-year survival rate for lung cancer has been stagnant at 18%.[1,2] Over the years, adoption of newer chemotherapy combinations and optimization of supportive care has modestly improved outlook for patients diagnosed with metastatic lung cancer.[3] However, the greatest impact on outcome is likely to come with the recent shift from uniform prescriptions of chemotherapy to use of molecular and pathologic features to tailor treatments in the metastatic setting.

The diagnosis of lung cancer encompasses a spectrum of histologic subtypes, most notably non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[4] Although the disparate biologic behavior of these two major subtypes of lung cancer has long been recognized, the demonstration that NSCLC histologic subtype (i.e., adenocarcinoma, squamous, and large cell carcinoma) dictates outcomes to treatment is a more recent finding.[5] Indeed, the realization that histology is an independent predictor of response provided strong rationale for using pathology to guide treatment and reset the standard of care for NSCLC.[5,6] However, in a subset of patients, presence of more than one histologic subtype poses a challenge for histology-guided treatment strategies, as the optimal management of these mixed-histology tumors remains to be established. In addition, another challenge often encountered in clinical practice is the presence of multiple lung nodules. Although the histopathology of these nodules can sometimes distinguish metastatic lung cancer from multiple synchronous primaries, other testing modalities may be required, including molecular profiling of separate lesions and additional imaging studies.

Characterization of recurring molecular alterations has been instrumental in cementing the understanding of NSCLC as a heterogeneous disease comprised of distinct molecular subgroups with unique clinical features and prognostic outcomes.[7-12] Remarkably, patients belonging to select molecular subgroups are now expected to survive 3 to 4 years after diagnosis.[12-14] As such, it is now recommended that diagnostic biopsy specimens from all newly diagnosed patients with metastatic nonsquamous NSCLC undergo molecular testing for *EGFR* mutations and *ALK* and *ROS1* rearrangements, preferentially within the context of broad molecular panels.[15] Although the superior efficacy of treatment strategies that rely on defining biologic features (e.g., high PD-L1 expression or presence of molecular drivers) has shifted some focus away from histology, it should be noted that histology

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is still highly relevant because roughly one-half of patients will not have tumors bearing these markers.[9,12,16]

It is now widely accepted that histologic and molecular characterization offers greater insight into the biologic behavior of metastatic NSCLC than imaging features. Despite this consensus, molecular profiling is most often an isolated event that occurs at diagnosis with subsequent clinical decisions predicated on serial imaging. Imaging, however, can be an imprecise biomarker. Given the limitations of imaging as a barometer of underlying biology, several studies have advocated for repeat biopsy of progressive or suspicious sites and demonstrated its utility in refining treatment and improving understanding of the biology of resistance.[17-20] Based on these studies, repeat biopsy is now becoming a fundamental part of routine clinical practice for oncogene-driven NSCLC (e.g., EGFR-mutant and ALK-positive NSCLC). Serial tissue sampling, however, is not always feasible or informative.[21] Thus, there is growing interest in developing noninvasive technologies, particularly plasma genotyping assays, that establish molecular genotype at diagnosis and facilitate serial and comprehensive molecular profiling.

Although prioritizing pathology and molecular findings has rapidly transformed clinical practice and allowed for standardization of treatment approaches by molecular subtype, treatment of NSCLC is far from algorithmic. Incorporation of plasma genotyping into management strategies is likely to add another layer of complexity. In this review, we will summarize the existing literature and describe our approach to several diagnostic and therapeutic conundrums, namely optimal treatment of mixed histology tumors, differentiating between intrathoracic metastasis and second primary tumors, and interpreting plasma genotyping results within the context of current clinical practice.

KEY POINTS

- **Lung cancer is a heterogeneous disease comprised of distinct histologies and unique molecular subgroups, each with characteristic clinical features and prognostic outcomes.**
- **Mixed histology lung cancers, accounting for 5% of lung cancers, are associated with aggressive biology and poor outcomes.**
- **Comprehensive assessment that integrates radiographic, immunohistochemical, morphologic, and molecular findings may improve accuracy when attempting to distinguish multiple primary lung cancers from intrathoracic metastasis.**
- **Liquid biopsies are a promising method for detecting clinically relevant and novel molecular alterations, improving understanding of molecular response dynamics, and elucidating genetic determinants of resistance.**
- **The sensitivity of current liquid biopsy platforms is not sufficient to discount a molecular alteration if it is not present in plasma, but high specificity supports initiating treatment based on plasma-detected alterations.**

APPROACH TO MIXED-HISTOLOGY TUMORS

Although the vast majority of lung cancers can be classified into four major histologies (adenocarcinoma, squamous, large cell, or small cell carcinoma), there are a wide variety of histologic subtypes and considerable heterogeneity among less common histologies.[4] Mixed-histology tumors comprise approximately 5% of lung cancers.[22-25] Due to the rareness of these tumors and exclusion of patients with mixed-histology tumors from many of the clinical trials that have shaped the treatment landscape, these cases present unique diagnostic and therapeutic challenges.

Combined Small Cell Lung Cancer

Combined SCLC (c-SCLC) is defined by World Health Organization classification as a subtype of SCLC characterized by an admixture of elements of SCLC with NSCLC.[4] These combined tumors are believed to arise from a pluripotent stem cell capable of differentiating into either SCLC or NSCLC. This theory is supported by the identification of SCLC transformation as a mechanism of resistance to EGFR inhibition in tumors that were initially characterized as EGFR-mutant NSCLC.[18] Estimates of the incidence of c-SCLC are based on a limited number of studies and range from under 5% to as many as 30% of cases of SCLC.[26-28] Tumors that contain any component of SCLC should be classified as c-SCLC. Clinical characteristics and presentation do not differ significantly among patients with c-SCLC and those with pure SCLC.[29] Given the aggressive biology of SCLC, c-SCLCs are typically treated with SCLC regimens. Standard-of-care treatment involves doublet chemotherapy with platinum plus etoposide for patients with extensive-stage cancer and this doublet combined with radiotherapy in limited-stage disease. As in SCLC, surgery is reserved for select patients with very early-stage c-NSCLC who do not have nodal involvement. The prognosis for c-SCLC is generally comparable to pure SCLC, although there have been conflicting reports.[29-31]

Other Mixed Neuroendocrine Tumors

The spectrum of neuroendocrine differentiation includes carcinoid tumors, large cell carcinoma, and small cell carcinoma. Mixed neuroendocrine tumors with components of large cell carcinoma or carcinoid are rare and, consequently, not well described. In one large retrospective study featuring 2,501 patients, mixed neuroendocrine tumors were identified in less than 1% of cases.[32] Data are limited regarding optimal management and prognosis for patients with these mixed neuroendocrine tumors. However, tumors with carcinoid components are expected to have a more indolent course than those harboring higher-grade small cell or large cell components.[33] For localized disease, particularly tumors with a low-grade neuroendocrine component, surgery is the mainstay of treatment and may be helpful for definitive grading.[32,34]

Adenosquamous Carcinoma

Adenosquamous carcinomas are defined as NSCLCs that have at least 10% histologic components of both adenocarcinoma and squamous carcinoma.[4] Although relatively uncommon,

they represent 2% to 4% of lung cancers and often present at a more advanced stage. A study of stage I and II NSCLCs found that adenosquamous lung cancer has a worse prognosis (5-year overall survival 59.4%) than that of pure adenocarcinoma (5-year overall survival 71.7%) or pure squamous carcinoma (5-year overall survival 66.1%),[35] an association that has been observed in other published series.[25,36] Although these observations might suggest that adjuvant therapies should be used for treatment of this subtype of lung cancer, in the absence of confirmation of this hypothesis, adenosquamous carcinomas are typically treated using standard NSCLC treatment regimens. Recently, molecular profiling of these tumors has demonstrated a high incidence of driver mutations, including *EGFR* mutations and activating mutations involving the phosphoinositide 3-kinase signaling pathway.[37] Interestingly, these mutations are often present in both the adenocarcinoma and squamous components of the tumor, suggesting that these tumors may respond to treatment with molecularly targeted agents.[38] As identification of actionable alterations may allow patients to access additional therapies, we recommend molecular profiling for all metastatic adenosquamous carcinomas.

Biphasic Tumors

By definition, biphasic pulmonary tumors contain mixed epithelial and mesenchymal components. The most common examples include carcinosarcoma (0.2%–0.3% of all lung cancers) and pulmonary blastoma (0.25%–0.5% of all lung cancers), both of which are subtypes of pulmonary sarcomatoid carcinoma.[4,39,40] Carcinosarcoma is defined as a combination of a typical lung carcinoma with a sarcomatous element and is most frequently observed in middle-aged patients with extensive tobacco exposure. Pulmonary blastomas have an adenocarcinoma component with fetal features as well as a primitive mesenchymal stroma. The average age at diagnosis of pulmonary blastoma is 40 years, and occurrence is more frequent in males. Both carcinosarcomas and pulmonary blastomas are aggressive tumors that frequently exhibit rapid growth and locoregional and distant spread. Not surprisingly given these biologic characteristics, prognosis of these tumors is poorer than that of more common NSCLC histologies.[39,40]

Treatment of these tumors is a challenge, as systemic therapies do not produce robust responses. Given the poor efficacy of systemic treatments, surgical resection is recommended when feasible. Adjuvant radiation therapy has been shown to reduce the rate of local recurrence by 15% in some cases.[39] As these tumors are characterized by a poor response to chemotherapy, there is interest in exploring targeted therapy and immunotherapy for these patients. Interestingly, mutations leading to MET exon 14 skipping, an alteration that confers sensitivity to MET inhibitors, have been detected in 8% to 31% of sarcomatoid carcinomas in three published series.[41-43] In addition, high-level expression of PD-L1 was identified by quantitative immunofluorescence in 9 of 13 (69.2%) sarcomatoid carcinomas in a small study.[44] There is limited experience using checkpoint inhibitors in this patient population, and, as such, efficacy is unknown. As carcinosarcomas and blastomas have been excluded from genotyping studies, little is known about the molecular makeup of these tumors. As these tumors are also poorly differentiated, it is possible that they might share molecular features with sarcomatoid carcinomas.

DIFFERENTIATING METASTASIS IN THE CHEST FROM SECOND PRIMARIES

Identification of multiple malignant lesions within the lungs presents an increasingly common clinical challenge. Published series have estimated an incidence of multiple synchronous tumors of up to 15% among cases of NSCLC.[45,46] Several studies analyzing these cases have concluded that, whereas a majority of tumors represent metastatic lesions, approximately one-third may represent distinct primary tumors.[46,47] The high incidence of second primary lung cancers may be explained by a field effect in smokers.[48] Despite the therapeutic and prognostic ramifications, reaching a definitive conclusion regarding the origins of the lung lesions (i.e., metastatic disease or multiple primary cancers) is often difficult for pathologists and clinicians. There are several published criteria to aid in distinguishing intrathoracic metastasis from second primary tumors. The Martini-Melamed criteria (Sidebar 1), which use anatomic and histologic features to classify tumors, have traditionally been used in these cases.[49] However, these criteria were developed prior to the advent of modern imaging and molecular diagnostic technologies. In addition, these criteria may not be sufficient in situations in which the cancers are histologically indistinguishable. Indeed, several recent studies have shown that, even among histologically similar NSCLCs, approximately one-third of cases exhibit distinct molecular and/or genetic profiles.[45,50,51]

Histologic and Molecular Assessment

As reliably differentiating between these two entities requires adequate tissue for downstream analyses, biopsy of multiple suspicious lesions is essential. Notably, updated criteria have been published that incorporate detailed histologic subtyping and molecular and genetic signatures to improve accuracy when assessing clonality of separate tumors (Sidebar 1).[44,52] Comprehensive histologic assessment involves meticulous characterization of specimens, including identification and quantification of histologic subtypes and analysis of cytologic features such as grade, necrosis, and stromal appearance. Although time-intensive, the depth of analysis allows for more accurate classification of multiple tumors than the Martini-Melamed criteria.[52] Current guidelines also champion a multipronged approach to resolving this clinical conundrum. For example, the 7th edition of the *AJCC Cancer Staging Manual* recommends classifying tumors as synchronous primaries "based on features such as differences in morphology, immunohistochemistry and/or molecular studies" and absence of "evidence of mediastinal nodal metastases or of nodal metastases within a common nodal drainage."[53] Multidimensional assessment that integrates imaging, histologic, and molecular features not only increases accuracy but also decreases the potential that interobserver variation may bias conclusions.

SIDEBAR 1. Summary of Published Criteria for Definitions of Distinct Primary Lung Cancer

Martini and Melamed[49]

Synchronous Tumors:
A. Tumors physically distinct and separate
B. Histologic type
    1. Different
    2. Same, but in different segment, lobe, or lung if:
        a. Origin from carcinoma in situ
        b. No carcinoma in common lymphatics
        c. No extrapulmonary metastases

Metachronous Tumors:
A. Histologic type different, or
B. Histologic type same if:
    1. Interval between cancers ≥ 2 years, or
    2. Origin from carcinoma in situ, or
    3. In different lobe or lung, so long as:
        a. No carcinoma in common lymphatics
        b. No extrapulmonary metastases

Girard et al[52]

A. Histologic type different, or
B. For squamous carcinomas:
    1. Cytologic/stromal features different
C. For adenocarcinomas:
    1. Major histologic subtype different, or
    2. Major histologic subtype same, but:
        a. Other histologic subtype percentages different, and
        b. Cytologic/stromal features different

Detterbeck et al[45]

A. Histologic type different unless:
    1. Clearly different by comprehensive histologic assessment, or
    2. Both squamous carcinoma arising from carcinoma in situ
B. Comparative genomic hybridization, if performed, should not identify matching breakpoints
C. Relative arguments favoring separate tumors:
    1. Different radiographic appearance or metabolic uptake
    2. Different pattern of biomarkers (e.g., driver mutations)
    3. Different rates of growth (if prior imaging available)
    4. Absence of nodal or systemic metastases
D. Relative arguments favoring a single tumor source:
    1. Same radiographic appearance
    2. Similar growth patterns
    3. Significant nodal or systemic metastases
    4. Same biomarker pattern
    5. Matching appearance on comprehensive histologic assessment

As molecular profiling is now a fundamental component of the diagnostic paradigm for NSCLC, routine molecular testing results alone may adequately discriminate between metastatic tumors and second primaries. Indeed, several studies have reported discordant driver mutation status in separate lesions.[46,54] As it is possible that tumors may not contain well-characterized lung cancer alterations or that synchronous tumors of distinct origin may still share a common driver mutation, next-generation sequencing (NGS) panels that enable simultaneous interrogation of multiple genes may be the most ideal platform for establishing the molecular footprint of spatially separated lesions. In addition to these standard molecular profiling strategies, several studies have used alternative approaches, specifically microsatellite analysis and assessment of loss of heterozygosity, to distinguish metastatic foci from second primary cancers.[46,47,51]

Treatment Approach and Prognosis

When synchronous primary tumors are confirmed, the individual tumors should be staged independently and treated as distinct cancers. If the distinction between metastasis and second primary is unclear, surgical resection of both tumors is encouraged whenever appropriate, based on tumor staging and the patient's cardiopulmonary reserve. Surgical resection offers the best survival outcome and ensures sufficient tissue for comprehensive histologic assessment and molecular profiling, which might not be possible with a limited biopsy specimen.[55] For metachronous lung tumors, a biopsy or resection is recommended. Similar methods to those described above can be used to distinguish local recurrence from a second primary.[55] As synchronous and metachronous lesions with discordant *EGFR* mutation status have been observed, molecular characterization of multiple lesions is encouraged prior to pursuing investigational targeted approaches.[54] Survival estimates for multiple primary lung cancer are considerably better than that of intrapulmonary metastasis. For example, a recent meta-analysis of stage I and II tumors reported 5-year overall survival rates for multiple primary lung cancer ranging from 15% to 81%.[56] Although survival rates are comparable between synchronous and metachronous lesions, survival after a diagnosis of multiple primary lung cancer is significantly longer than that observed for patients with intrapulmonary metastasis (hazard ratio 2.66).

LIQUID BIOPSIES: A COMPLEMENTARY APPROACH TO TISSUE BIOPSIES FOR GENOTYPING NSCLC

Rationale for Liquid Biopsies

Biopsy of a suspected involved site, the longstanding gold standard for confirming a lung cancer diagnosis, allows for histologic and molecular characterization of tumors and provides invaluable guidance for designing rational therapeutic approaches.[12] However, up to one in four patients will not have sufficient tissue for molecular testing and, as such, cannot access potentially effective therapies.[57] Moreover, increasing appreciation of the evolution of lung cancers under therapeutic selective pressure suggests that serial molecular profiling may be more advantageous than a single diagnostic biopsy.[17-20] Repeat tissue sampling, however, has considerable limitations, including patient-specific factors (e.g., risk and discomfort) and lesion-specific factors (e.g., inaccessible sites and intrapatient tumor heterogeneity).[21,58,59] Recognition of the inadequacy of an isolated diagnostic biopsy as a blueprint for clinical decision making has generated broad interest in developing reliable, noninvasive methods for molecular surveillance. Several studies have shown that profiling tumor-derived free-floating nucleic acids in plasma or molecular material contained in circulating tumor cells or exosomes can provide valuable insight into a cancer's dynamic molecular trajectory.[60-66] Regardless of the analytic platform or source of genetic material, molecular profiling of plasma contents is collectively referred to as a liquid biopsy.

Of the liquid biopsy options that have been explored to date, analysis of plasma cell-free tumor-derived deoxyribonucleic acid (ctDNA) has had the most clinical impact. Notably, the initial description of circulating cell-free DNA in plasma and the realization that cell-free DNA was more abundant in patients with malignancies occurred more than half a century before the approval of the first liquid biopsy by the U.S. Food and Drug Administration.[67,68] The predominance of non–tumor-derived DNA in plasma relative to tumor-derived DNA posed the greatest hindrance to tapping into the potential of plasma profiling and likely accounted for much of the delay in translating these early observations into a robust, clinically relevant technology.[69] Groundbreaking molecular diagnostic and analytical advances in the past decade, however, have facilitated the development and incorporation of liquid biopsies into clinical practice.

Performance Characteristics of Available Liquid Biopsy Technologies

With optimization of diagnostics to suppress input from the wild-type allele and benign cells, the sensitivity of current platforms approaches 80%. Sensitivity is highest for ubiquitously present molecular alterations, particularly base substitutions or short insertions/deletions (e.g., *EGFR* exon 19 deletion and *EGFR* L858R).[63,64,70-78] For example, one study observed that plasma genotyping using allele-specific polymerase chain reaction (PCR) technology (Table 1) had a sensitivity approaching 90% for detecting sensitizing *EGFR* mutations compared with sensitivity of approximately 40% for the *EGFR* T790M resistance mutation (Table 2).[70] The performance of this Cobas allele-specific plasma genotyping assay in patients with sensitizing *EGFR* mutations ultimately led to approval of the first liquid biopsy by the U.S. Food and Drug Administration in 2016.[79] Subsequent studies have demonstrated that assays that use emulsion-based digital PCR techniques (Table 1) that enrich for tumor DNA relative to background DNA produce superior results when compared with allele-specific PCR.[63,70,74]

Although the performance characteristics of digital PCR-based liquid biopsies have been encouraging, these assays are still prone to false-negative results. In addition, these assays are not optimally equipped to detect complex alterations (e.g., fusions) and can only interrogate hot spots in a handful of genes at a given time. These shortcomings are particularly relevant, as identification of certain gene fusions (e.g., *ALK* or *ROS1* rearrangements) is of critical prognostic and therapeutic consequence.[80,81] The migration toward comprehensive molecular profiling of diagnostic biopsy specimens using multiplex or NGS panels and away from testing for individual alterations suggests that NGS-based liquid biopsy platforms may be the most optimal surrogate for tissue genotyping. Indeed, the handful of studies published to date using NGS-based plasma assays demonstrates that this method can identify a broad range of clinically relevant alterations in multiple genes with comparable sensitivity to digital PCR in patients with NSCLC.[62,64] Although only a small number of patients with fusion-driven NSCLC

TABLE 1. Techniques for Genotyping Plasma DNA

Assay Technique	Method of Detecting Mutant Variants	Detected Alterations
Allele-specific PCR (Cobas *EGFR* assays)	Uses PCR primers that selectively target and amplify the mutant variant	Insertions/deletions and base substitutions
Digital/emulsion PCR (digital droplet PCR, BEAMing)	Employs surfactant technology to partition DNA into thousands of individual PCR reactions contained in droplets; this technique allows for quantification of the number of mutant and wild-type variants and permits detection of variants present at very low levels.	Insertions/deletions and base substitutions
Amplicon-based NGS	Multiplexed detection of a broad range of alterations involving multiple genes using sequence-specific PCR primers designed to selectively target and simultaneously amplify genomic regions of interest	Insertions/deletions, base substitutions, copy number gains
Capture-based NGS	Simultaneous detection of a broad range of alterations involving multiple genes using DNA oligonucleotides complementary to sequences of interests in exons and introns	Insertions/deletions, base substitutions, copy number gains, gene fusions

Abbreviation: PCR, polymerase chain reaction; BEAM, beads, emulsification, amplification, and magnetics; NGS, next-generation sequencing.

were included in these studies, one study demonstrated high sensitivity for detecting *ALK* fusions using a hybrid capture–based NGS assay (Tables 1 and 2).[77]

INCORPORATING LIQUID BIOPSIES INTO CLINICAL PRACTICE

Utility of Liquid Biopsy for Identifying Clinically Relevant Targets at Diagnosis or Relapse

Multiple studies have established high concordance between tissue and plasma genotyping using various techniques (Table 2). Although the PCR-based Cobas assays are the only U.S. Food and Drug Administration–approved liquid biopsies, NGS-based genotyping reliably identifies established drivers of resistance in plasma, including *ALK* resistance mutations in crizotinib-resistant plasma specimens and *EGFR* T790M and *MET* amplification in plasma samples from patients with lung cancers that are resistant to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs).[64] In addition, NGS-based plasma profiling successfully captures relevant molecular alterations in cases with inadequate diagnostic biopsies, suggesting that it may be a powerful tool for guiding initial management.[62] For example, in a single-center study, plasma genotyping by NGS was successful for 50 patients with an insufficient tissue sample or an inaccessible site for biopsy, including eight cases with *EGFR* T790M.[62]

Plasma genotyping with digital PCR yields quicker results relative to tissue genotyping using comprehensive panels.[63] Use of NGS-based assays for plasma genotyping may eliminate this advantage. However, the reporting delays that arise from the increased complexity of input material may be offset by the potential to simultaneously query multiple actionable genes and types of alterations using NGS. Moreover, with the exception of the U.S. Food and

TABLE 2. Concordance Between Tissue and Plasma NSCLC Genotyping in Published Studies

Alteration	Technique	Sensitivity (%)	Specificity (%)	References
Allele-Specific PCR				
EGFR T790M	Allele-specific PCR	41	100	[70]
EGFR L858R or exon 19 deletion	Allele-specific PCR	46–90	97–100	[70-73]
Digital PCR				
EGFR T790M	BEAMing	70 to 71	67–69	[70,74]
EGFR L858R or exon 19 deletion	BEAMing	82.3–100	96.5–100	[70,74]
EGFR T790M	Digital droplet PCR	77	63	[63]
EGFR L858R or exon 19 deletion	Digital droplet PCR	74–82	100	[63]
KRAS G12X	Digital droplet PCR	64	100	[63]
NGS				
EGFR mutations	Amplicon-based	87–100	94–100	[75]
Multiple (no fusions)	Amplicon-based	58	87	[76]
ALK rearrangement	Capture-based	79.2	100	[77]
Multiple	Capture-based	72–85	96–100	[64,78]

Abbreviation: NSCLC, non–small cell lung cancer; PCR, ploymerase chain reaction; BEAM, beads, emulsification, amplification, and magnetics; NGS, next-generation sequencing.

Drug Administration–approved plasma *EGFR* assays, using ctDNA as a sole determinant of tumor genotype without attempting tissue confirmation is not supported by current guidelines and should ideally only be done within the context of a clinical trial. As targeted therapies can result in rapid clinical improvement, the authors of this review, however, acknowledge that in urgent situations, it may be in a patient's best interest to initiate treatment based on plasma results alone. If such measures are undertaken, we recommend close surveillance and expedited response assessment if tissue results are not aligned with plasma results.

The current performance of ctDNA platforms is not sufficient to discount an alteration if it is not detected in plasma. Rather, if suspicion remains high for a potentially actionable alteration (e.g., molecular testing in a never-smoker) after an insufficient tissue biopsy and negative plasma results, repeat tissue biopsy should be attempted if feasible (Fig. 1). The high specificity of available plasma assays, however, supports selection of treatment based on alterations identified in plasma. Indeed, two recent studies observed comparable outcomes to treatment with third-generation EGFR TKIs when patients with plasma-detected *EGFR* T790M mutation were compared with those with tissue-detected T790M.[74,82] These studies highlight the clinical utility of plasma biomarkers and provide the rationale for studies exploring efficacy of targeted agents in plasma biomarker-selected patients. Encouragingly, in a recent study in which plasma was exclusively used to direct patients who did not undergo repeat biopsies toward treatment with osimertinib, the reported response rate for plasma-positive patients was consistent with the studies in which dual genotyping was performed.[83] Notably, a phase II clinical trial using digital droplet PCR to identify *EGFR* mutations and enable initiation of treatment with erlotinib prior to confirmation of tissue genotype opened to enrollment in early 2017 (NCT02770014).

Serial Plasma Sampling as a Tool for Monitoring Response and Resistance

As a noninvasive, low-risk technology, liquid biopsy is ideally suited for longitudinal analysis and detection of genetic mechanisms of resistance. Indeed, using plasma assays to improve understanding of response and resistance to molecularly targeted therapies is an active area of research. As an example of the potential for liquid biopsies to uncover resistance mechanisms, serial analysis of ctDNA from patients with *EGFR*-mutant NSCLC treated with third-generation EGFR T790M-specific TKIs was instrumental in identifying novel resistance mechanisms that were subsequently confirmed in tissue specimens. These mechanisms include the tertiary *EGFR* C797S mutation as well as "loss" of T790M.[19,66] Additionally, liquid biopsies identified *MET* amplification, an alteration previously implicated in resistance to first- and second-generation EGFR TKIs, as a prevalent acquired event among patients who develop resistance to third-generation TKIs.[65] Similarly, several studies have confirmed the ability of plasma genotyping to identify acquisition of well-characterized alterations conferring resistance to targeted agents, including secondary *ALK* resistance mutations in crizotinib-resistant plasma specimens and the *EGFR* T790M resistance mutation, amplification of *MET* or *HER2*, and *PIK3CA* mutations in plasma samples collected at resistance to first- and second-generation EGFR TKIs.[63,65,77]

Several studies have demonstrated that plasma indicators of progression may predate radiographic or clinical progression by weeks to months.[84,85] However, it is unclear whether molecular relapse, defined as appearance of resistance alterations in plasma or increase in the plasma allelic frequency of pretreatment alterations, should trigger therapeutic decisions. As isolated plasma progression may become a common occurrence with widespread use of commercially available liquid biopsies, it is essential to interpret findings within the context of the current treatment landscape. Specifically, the precedent for continuing treatment beyond radiographic progression and availability of effective agents for treating relapsed or resistant NSCLC should be considered. Although the prognostic implications of resistance mutations that emerge in plasma or increase in plasma mutant allele frequency have not been systematically explored, small studies have shown that clearance of oncogenic alterations from plasma may correlate with depth of response to treatment.[63,85] Due to the lack of evidence to support discontinuing therapy for plasma progression, we advise against using plasma dynamics as a primary determinant of progression. Instead, we recommend that the decision to terminate a therapy be based on supporting radiographic and/or clinical signs.

Management Strategies for Cases With Tissue-Plasma Discordance

As liquid biopsies become integrated into clinical practice, it is conceivable that tissue-plasma discordance may be encountered in cases in which paired genotyping is used (Fig. 1). Because tissue is the accepted gold standard for genotyping and liquid biopsies are an investigational technology in most situations, we anticipate that tissue-only alterations (i.e., failure to detect a known tissue alteration in plasma) will not create diagnostic or therapeutic uncertainty. Although tissue-only alterations may limit the role of longitudinal plasma profiling in molecular surveillance, several factors affect the yield of ctDNA, including metastatic burden and location of metastases.[63,74,82] The opposite scenario (i.e., plasma-only detection), however, can be more perplexing, as findings may potentially represent false positives, and indiscriminate use of targeted agents can be detrimental in patients who do not actually harbor the target.[86] Reassuringly, in a recent study, confirmatory plasma testing with an alternative assay was able to validate plasma findings for most patients with isolated plasma alterations.[74] Durable responses to osimertinib in some patients positive for *EGFR* T790M by plasma alone support the notion that these alterations are not false positives but, rather, true mutations present at a subclonal fraction in lesions or areas not sampled.[74]

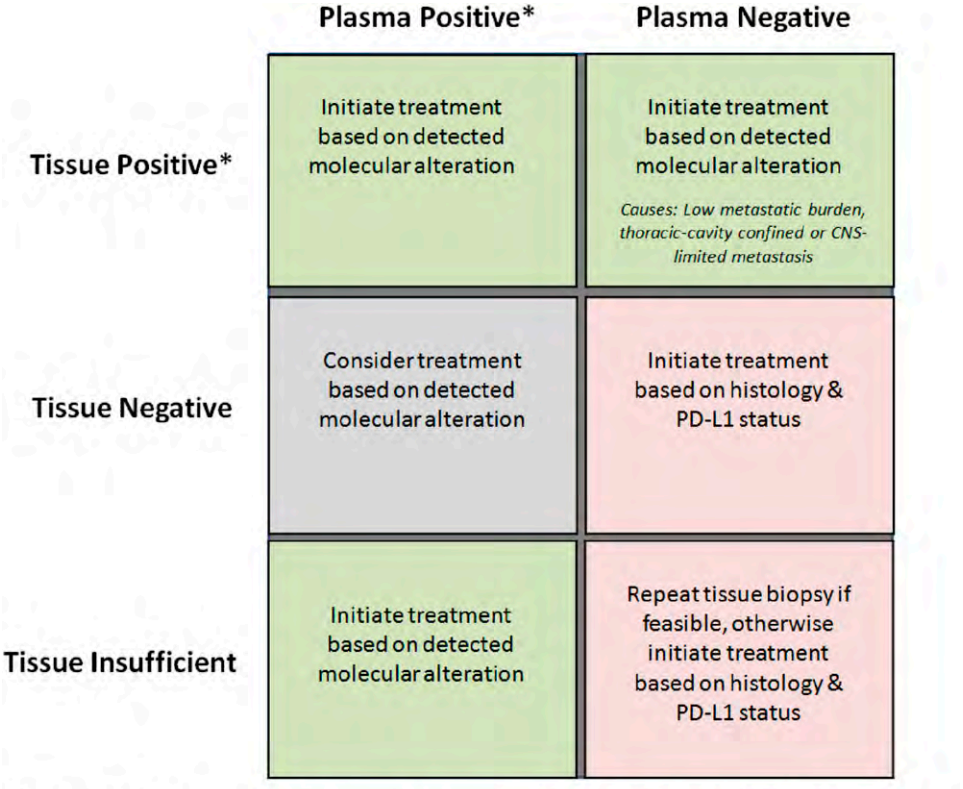
As molecularly targeted approaches are most successful when directed against ubiquitous alterations that confer

global susceptibility, it is plausible that responses may be less pronounced for patients with discordant positive plasma. Indeed, studies suggest that some patients with plasma-only alterations will not respond to treatment with molecularly targeted therapy.[74] For example, although small numbers limit definitive conclusions, the response rate to osimertinib was considerably lower for patients positive for T790M by plasma alone compared with those positive by tissue and plasma in one study.[74] Similarly, several studies have demonstrated that the ratio of a mutant allele to the wild-type allele or other ubiquitous driver events in plasma correlates with response to treatment.[65,74,85] Despite these intriguing findings, these studies have been limited in size and have not established a consistent threshold for predicting response to treatment. As such, additional studies are necessary to determine which patients within this heterogeneous group benefit most from treatment with targeted agents. Although this hypothesis is best explored using a large, prospective study to assess the impact of plasma allelic fractions on treatment outcomes, a study that selectively or exclusively enrolls patients that are tissue-negative and plasma-positive for target alterations may be difficult to execute. Given the compelling evidence suggesting that plasma-only alterations are viable targets, it is our practice to offer approved therapies to patients with plasma-only alterations. In contrast, if plasma detects alterations without approved therapies, we strongly favor repeating a tissue biopsy, if feasible (Fig. 1). If repeat tissue sampling is not feasible, we recommend pursuing standard chemotherapy or immunotherapy prior to exploring investigational agents.

CONCLUSION

Lung cancer is a heterogeneous disease with a variety of clinical and radiographic presentations and diverse underlying histologic and molecular features. Approaches to treatment of lung cancer are similarly versatile, with agent selection heavily influenced by pathologic evaluation. Comprehensive histologic and molecular assessment is a necessary component of successful treatment strategies. Although insight into underlying biology has improved prognosis for subgroups of patients with NSCLC, viable targets remain elusive for many patients. The strides made in treating common histology tumors should inspire efforts to characterize rarer and mixed histology tumors, entities for which generic therapies have been minimally effective. Even among cancers with typical features and defining molecular drivers, the inherently complex and dynamic nature of lung cancer limits the chances of cure. To ensure ongoing success, diagnostic approaches must be as flexible as therapeutic maneuvers. Indeed, therapeutic victory is reliant on an accurate understanding of a cancer's vulnerability. Given the limitations of serial sampling and the growing body of evidence establishing the reliability of liquid biopsies, this technology will likely be integrated into clinical practice, particularly for those patients with oncogene-addicted lung cancers. Despite its

FIGURE 1. Proposed Framework for Incorporating Plasma Genotyping Results Into Clinical Practice



*Positive = identification of a validated target alteration (e.g., *EGFR* sensitizing mutations, *ALK* rearrangement)

current strengths, additional modifications are necessary to improve sensitivity of liquid biopsy to level the playing field between tissue and plasma genotyping. Nonetheless, the potential for liquid biopsy to capture relevant alterations outside of the scope of single-site sampling and identify actionable alterations in patients with inadequate or inaccessible tissue specimens suggests that this technology will have a durable presence in clinical practice as an adjunct for the treatment of patients with advanced NSCLC at diagnosis and during the course of treatment.

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Role of Chemotherapy and Targeted Therapy in Early-Stage Non–Small Cell Lung Cancer

Shirish M. Gadgeel, MD

OVERVIEW

On the basis of several randomized trials and meta-analyses, adjuvant chemotherapy is the accepted standard of care for certain patients with early-stage non–small cell lung cancer (NSCLC). Patients with stage II, IIIA, or large (≥ 4 cm) IB tumors are candidates for adjuvant chemotherapy. The survival improvement with adjuvant chemotherapy is approximately 5% at 5 years, though certain trials have suggested that it can be 8% to 10%. Neoadjuvant chemotherapy also has shown a survival advantage, though the volume of data with this approach is far less than that of adjuvant chemotherapy. The combination of cisplatin and vinorelbine is the most well-studied regimen, but current consensus is to use four cycles of any of the platinum-based chemotherapy regimens commonly used as front-line therapy for patients with advanced-stage NSCLC. Trials to define biomarkers that can predict benefit from adjuvant chemotherapy have not been successful, but results of other such trials are still awaited. On the basis of the benefit observed with targeted agents in patients with advanced-stage disease and driver genetic alterations in their tumors, ongoing trials are evaluating the utility of these targeted agents as adjuvant therapy. Similarly, clinical benefit observed with checkpoint inhibitors has prompted assessment of these drugs in patients with early-stage NSCLC. It is very likely, in the future, that factors other than the anatomy of the tumor will be used to select patients with early-stage NSCLC for systemic therapy and that the choice of systemic therapy will extend beyond platinum-based chemotherapy.

The 5-year survival in patients with resected NSCLC ranges from 25% to 75%.[1] The primary reason for death in these patients is recurrence of the cancer, which suggests that a proportion of patients with early-stage NSCLC have micrometastatic disease that remains untreated with surgery alone. One of the major advances in the management of NSCLC during the last 15 years has been that adjuvant chemotherapy has become the standard of care on the basis of clinical trials data that showed survival improvement with the use of adjuvant chemotherapy. This review discusses adjuvant chemotherapy, the accepted criteria for the use of adjuvant chemotherapy, the available data about the use of neoadjuvant chemotherapy and adjuvant targeted therapy, and ongoing clinical trials.

ADJUVANT CHEMOTHERAPY

Clinical trials to assess the benefits of adjuvant chemotherapy in patients with resected lung cancer have been conducted since the late 1960s. None of these trials demonstrated a survival advantage. However, a meta-analysis published in 1995 suggested a benefit with use of platinum-based chemotherapy, with a 13% reduction in the risk of death that did not reach statistical significance.[2] This meta-analysis spurred an interest in conducting more trials to assess adjuvant chemotherapy, particular with newer agents approved for use in the late 1990s. A possible reason that adjuvant trials of the past did not demonstrate a survival advantage was the lack of chemotherapy drugs with sufficient efficacy. A Southwest Oncology Group (SWOG) study that evaluated the addition of vinorelbine to cisplatin was among the first studies to demonstrate that combination chemotherapy provided superior survival compared with single-agent cisplatin in patients with advanced NSCLC.[3] Subsequently, other chemotherapy agents introduced in the late 1990s, such as paclitaxel, gemcitabine, and docetaxel, also improved outcomes when combined with a platinum agent compared with single-agent cisplatin in patients with metastatic NSCLC.[4-6] These results prompted the evaluation of these newer combinations, such as cisplatin/vinorelbine, as adjuvant therapy.

Two trials, one conducted in North America and the other in Europe, assessed the chemotherapy regimen of cisplatin and vinorelbine as adjuvant therapy (Table 1). The North American trial, JBR-10, conducted by National Cancer Institute of Canada, enrolled 482 patients with completely resected stage IB and II NSCLC, and these patients were

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TABLE 1. Adjuvant Trials Using Newer Platinum-Based Combinations

Trial	No. of Patients	Stage	Chemotherapy	Median Follow-up (Years)	5-Year Survival Benefit (%)	Hazard Ratio, p
JBR-10[7]	482	IB to II	Cisplatin/vinorelbine	9.3	11	0.78, .04
ANITA[8]	840	I to IIIA	Cisplatin/vinorelbine	6.3	8.6	0.80, .017
CALGB 9633[9]	344	IB	Carboplatin/paclitaxel	6.1	3	0.83, .12
LACE[10*]	4,584	I to IIIA	Several	5.2	5.4	0.89, .005

*LACE was a meta-analysis that included trials to evaluate cisplatin-based adjuvant chemotherapy that were conducted after 1995 and had enrolled at least 300 patients.

randomly assigned either to four cycles of cisplatin and vinorelbine chemotherapy or to observation.[7] At a median follow-up time of 9.3 years, adjuvant chemotherapy resulted in a significant improvement in survival (adjusted hazard ratio [HR], 0.79; 95% CI, 0.62–1.00; p = .05) and a 5-year survival improvement of 11% (67% with chemotherapy vs. 56% with observation). Though the study design planned for four cycles of chemotherapy, the median number of cycles delivered was three. The major adverse events were fatigue, anorexia, nausea, and febrile neutropenia. Two patients died as a result of chemotherapy-related toxicity.

In the European ANITA trial, 840 patients with resected stage IB/IIIA disease were randomly assigned to observation or cisplatin/vinorelbine chemotherapy.[8] After a median follow-up time of 76 months, the median survival was 65.7 months in the patients who received chemotherapy and was 43.7 months in the patients who did not (adjusted HR, 0.80; 95% CI, 0.66–0.96; p = .017). Survival at 5 years was improved by 8.6%. Toxicities observed in this trial were similar to those in the JBR-10 trial, and seven patients died as a result of chemotherapy-related toxicities.

To gain a better perspective, several meta-analyses have been conducted. The LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis included all adjuvant trials that evaluated cisplatin-based chemotherapy, were conducted after 1995, and enrolled more than 300 patients (Table 1).[10] This analysis showed that the HR for death was 0.89 (95% CI, 0.82–0.96; p = .005) and that the absolute benefit in survival at 5 years with adjuvant chemotherapy was 5.4%. There was a trend toward greater benefit with cisplatin/vinorelbine chemotherapy compared with older regimens used in these trials. A cumulative dose of greater than 300 mg/m^2 of cisplatin also improved survival compared with lower doses. Fifty-nine percent of the patients received at least 240 mg/m^2 of cisplatin. Among the patients who received chemotherapy, the rate of grade 3 or 4 toxicities was 66%, and the rate of toxicity related death was 0.9%. Similar results were observed in the other meta-analyses.[11,12]

One trial has evaluated a carboplatin-based treatment regimen as adjuvant therapy. In CALGB 9633, patients with resected stage IB NSCLC were randomly assigned to carboplatin and paclitaxel or to observation.[9] At a median follow-up time of 74 months, there was a trend for survival advantage, but it was not statistically significant (HR, 0.83; 95% CI, 0.64–1.08; p = .12). Because most adjuvant trials were conducted with cisplatin-based regimens, there is a preference to use cisplatin for adjuvant therapy. However, in patients with NSCLC who cannot receive cisplatin because of comorbid illnesses or intolerance of cisplatin, carboplatin is an accepted substitute.

Long-term follow-up of the IALT (International Adjuvant Lung Trial), one of the first trials to demonstrate a survival advantage with adjuvant therapy, showed that the benefit was not sustained.[13] The HR for survival advantage at 5 years was 0.86, and it declined to an HR of 0.91 at a median follow-up time of 7.5 years. This decline in benefit during longer follow-up was caused by an increase in non–lung cancer-related deaths, which raised the concern of late toxicities from chemotherapy used in this trial. Patients in this study were treated with chemotherapy drugs that are not commonly used. A similar decline in efficacy was not observed with long-term follow-up of either the ANITA or the JBR-10 study, which suggests that choice of chemotherapy agents maybe relevant in terms of long-term toxicities.

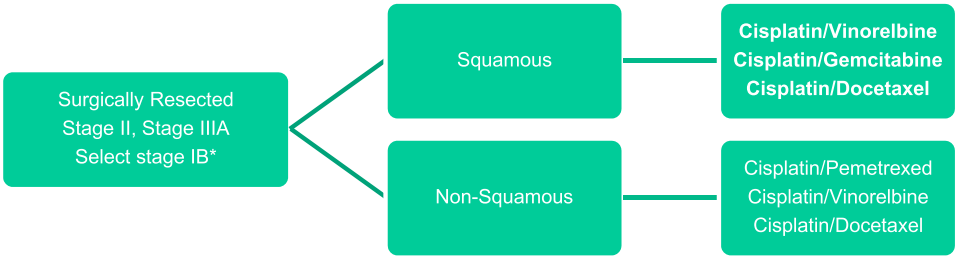
KEY POINTS

- **Adjuvant chemotherapy improves survival by at least 5% at 5 years in patients with early-stage NSCLC.**
- **The stage of the cancer determines if a patient is a candidate for adjuvant chemotherapy. Patients with stage II or IIIA disease are candidates for adjuvant chemotherapy. Certain patients with stage IB NSCLC (tumors ≥ 4 cm) may also be considered for adjuvant therapy.**
- **Four cycles of a platinum-based chemotherapy regimen is the accepted standard. Cisplatin can be substituted with carboplatin in appropriate patients.**
- **Neoadjuvant chemotherapy can result in survival improvement similar to adjuvant chemotherapy.**
- **Ongoing trials will determine the role of targeted therapy and immune therapy in patients with early-stage NSCLC.**

VARIABLES INFLUENCING THE USE OF CHEMOTHERAPY

The data from adjuvant trials show that the 5-year survival in patients with resected NSCLC without adjuvant chemotherapy is 25% to 75% and that this rate is improved by 5% to 10% with adjuvant therapy. These data suggest that not everybody needs chemotherapy and that the benefits of adjuvant chemotherapy are modest. Therefore, it is important

FIGURE 1. Treatment Schema for Adjuvant Therapy



Certain patients with stage IB (particularly patients with tumors ≥ 4 cm) can be considered for adjuvant therapy. Four cycles of adjuvant chemotherapy are usually administered. Chemotherapy is usually started 6 to 12 weeks after surgery. Delayed chemotherapy also may provide survival advantage. Neoadjuvant chemotherapy has shown benefit and can be considered if thought to be in the best interest of the patient. Carboplatin-based therapy can be used if there is a concern about cisplatin use.

to be familiar with factors that predict a greater potential for benefit from adjuvant therapy.

Clinical Variables Influencing Benefit From Adjuvant Therapy

Stage. The LACE meta-analysis showed that the benefit with adjuvant therapy varied according to stage. In patients with stage IA disease (104 patients), the HR was 1.40 (95% CI, 0.95–2.06), which suggests a detriment with adjuvant chemotherapy. These data must be viewed with a level of caution, because the numbers are relatively small. Nonetheless, adjuvant chemotherapy should not be considered in patients with stage IA disease. There was a trend for benefit in patients with stage IB disease (HR, 0.93; 95% CI, 0.78–1.10). The benefit was notable in patients with stage II and stage III disease (HR, 0.83; 95% CI, 0.72–0.95). The test for interaction between survival benefit from adjuvant chemotherapy and stage of NSCLC was significant (test for trend p = .04). Thus, the benefit from adjuvant chemotherapy may be proportionally greater in patients with higher-stage disease, particularly in patients with nodal metastases.

The benefits of adjuvant therapy in patients with stage IB disease were assessed in retrospective analyses of two trials. In CALB9633, patients with stage IB disease were randomly assigned to adjuvant carboplatin and paclitaxel. The overall results did not show a survival benefit in these patients. However, a post hoc analysis demonstrated that adjuvant chemotherapy improved survival in patients with tumors of 4 cm greater from a median of 77 months to a median of 99 months (HR, 0.69; 90% CI, 0.48–0.99; p = .043).[9] In patients with tumors less than 4 cm, there was a trend toward inferior survival among patients who received chemotherapy (HR, 1.01; 90% CI, 0.69–1.48; p = .49).

A similar retrospective analysis was conducted by the investigators of JBR-10. This study included patients with both stage IB and stage II disease. Although the overall results showed improved survival with adjuvant therapy, the benefit was restricted to patients with stage II disease (HR, 0.68; 95% CI, 0.55–0.97; p = .01), and there was no benefit in patients with stage IB disease (HR, 1.03; 95% CI, 0.7–1.52; p = .87). Furthermore, analysis restricted to patients with stage IB disease showed that patients with tumors of 4 cm or greater had improved survival with chemotherapy (HR, 0.66; 95% CI, 0.39–1.14; p = .13), whereas patients with smaller tumors did not (HR, 1.73; 95% CI, 0.98–3.04; p = .06).

It is important to remember that these data from CALGB 9633 and JBR-10 are based on retrospective analyses. However, on the basis of these data and the LACE meta-analysis, the consensus that has emerged is to use adjuvant chemotherapy in patients with tumors that have metastasized to regional lymph nodes (hilar or mediastinal) and in patients with large (≥ 4 cm) tumors (Fig. 1).

Age. The median age of U.S. patients with lung cancer is 71, and the median age of patients enrolled in adjuvant trials is approximately 61. Thus, the applicability of the data from these trials to the population of older adults may be limited. Population-based studies have shown that the use of adjuvant chemotherapy is lower in older adults.[14,15] In an analysis of the National Cancer Database the odds ratio of receipt of adjuvant chemotherapy in patients older than age 75 was only 0.11 and, among patients age 66 to 75, was 0.38 compared with patients age 55 or younger. Similar results were reported in a population-based study from Ontario, Canada. The JBR-10 investigators evaluated the benefits of adjuvant therapy in patients age 65 or older and found that these patients did derive survival benefit with adjuvant therapy (HR, 0.61; 95% CI, 0.38–0.98; p = .04).[7]

The LACE meta-analysis investigators also evaluated the benefits of adjuvant chemotherapy in patients age 70 or older and found a trend toward survival advantage in these patients (HR, 0.90; 95% CI, 0.70–1.16; p = .29).[10] On the basis of these retrospective analyses, adjuvant chemotherapy should be considered in older adults. However, a level of caution should be exercised in patients age 75 or older. Only 23 patients in this age group were enrolled in the JBR-10 trial, and this group experienced a trend toward inferior outcomes with adjuvant chemotherapy (HR, 2.35; 95% CI, 0.84–6.58; p = .09). A proper assessment of the risk-benefit ratio is important before adjuvant chemotherapy is initiated in very old adults. Cisplatin may have a greater propensity to cause toxicities in these patients, also; therefore, carboplatin should be considered in older patients.

Performance status. Stage and performance status are the most important prognostic factors in patients with NSCLC. All of the adjuvant trials excluded patients who had poor

performance statuses. Some patients do experience a decline in performance status after thoracic surgery. Utility of adjuvant therapy in these patients is unclear. However, a recent analysis of data in the National Cancer Database showed that delaying chemotherapy from the accepted standard of 6 to 9 weeks after surgery does not reduce the survival benefit from adjuvant therapy.[16] Similar data were also reported by Booth et al.[17] In their retrospective analysis of the Ontario Cancer Registry, the median time to start of adjuvant chemotherapy was 8 weeks. However, a third of the patients started adjuvant chemotherapy after 10 weeks, and their survival was not inferior to patients who received chemotherapy within 10 weeks of surgery. Thus, even if patients require a longer time to recover from lung cancer surgery, adjuvant therapy could be considered after the patient has recovered.

Pathologic Variables

Histology. Histology has emerged as an important determinant of choice of chemotherapy in patients with NSCLC, particularly with the use of pemetrexed. The combination of cisplatin and pemetrexed was evaluated in a randomized phase II trial; its primary objective was to assess the clinical feasibility of delivering this combination as adjuvant therapy compared with cisplatin/vinorelbine.[18] Clinical feasibility was defined as no grade 4 neutropenia/thrombocytopenia; grade 3 or 4 febrile neutropenia or thrombocytopenia with bleeding; and no grade 3 or 4 nonhematologic toxicity. The study showed that feasibility rates were 95.5% with the pemetrexed combination versus 75.4% with the vinorelbine combination. Dose delivery was 90% of planned dose with pemetrexed combination and was 66% with the vinorelbine combination. Overall toxicity also was less with the cisplatin/pemetrexed combination. ECOG1505 evaluated the benefits of added bevacizumab to a variety of cisplatin-based chemotherapy regimens.[19] The study failed to show any benefit with the addition of bevacizumab. In a retrospective analysis of the trial, no difference in outcomes was observed with any of the chemotherapy regimens used. However, among patients with nonsquamous disease (patients whose tumors had any non–small cell histology other than squamous), the cisplatin/pemetrexed combination had significantly less grades 3 to 5 toxicities compared with other regimens ($p < .001$). No notable differences in toxicities were observed in regimens used in patients with squamous cell disease. Thus, results of two separate studies, TREAT and E1505, suggest that the combination of cisplatin/pemetrexed is better tolerated as adjuvant therapy. The data from E1505 also suggest that platinum-based chemotherapy combinations used in patients with advanced-stage disease can be considered in the adjuvant setting.

Histology also may have relevance for the choice of the platinum analog. CISCA (cisplatin vs. carboplatin) was a meta-analysis of randomized trials to compare cisplatin- with carboplatin-based treatments in patients with advanced NSCLC.[20] This meta-analysis showed that patients who received carboplatin-based therapy had a nonsignificant increase in the hazard of mortality compared with patients who received cisplatin-based chemotherapy (HR, 1.07; 95% CI, 0.99–1.15; $p = .100$). However, in patients with nonsquamous disease, carboplatin-based regimens were associated with statistically significant inferior survival (HR, 1.12; 95% CI, 1.01–1.23; $p = .098$); there was no difference in outcome among patients with squamous histology. Though these data are in patients with advanced cancer, the CISCA meta-analysis suggests that cisplatin should be the preferred platinum for adjuvant therapy, particularly in patients with nonsquamous histology. It is important to note that this meta-analysis included trials conducted before the availability of pemetrexed, an effective chemotherapeutic agent in patients with nonsquamous NSCLC.

Other pathologic features. Certain tumor pathologic features are associated with worse prognosis. These include visceral pleural invasion and angiolymphatic invasion.[21-24] Though it is accepted that presence of these features is associated with worse outcomes, it is not known whether adjuvant therapy in patients with tumors that have these features, but do not meet any other criteria for adjuvant therapy, provides any survival benefit. If these features are present, the prognostic implications of these features with the patient should be discussed; adjuvant therapy occasionally may be considered in patients with tumors of 4 cm or smaller without lymph node metastases that have these pathologic features.

The National Comprehensive Cancer Network guidelines state that pathologic features of poorly differentiated tumor, vascular invasion, visceral pleural invasion, and lung neuroendocrine tumors should be considered high-risk features and that the presence of these high-risk features should be included in the decision-making process about adjuvant therapy.[25]

NEOADJUVANT CHEMOTHERAPY

Systemic chemotherapy in patients with NSCLC has the capacity to treat not only the micrometastatic disease but also clinically evident cancer in the chest. Thus, neoadjuvant chemotherapy has the potential to address all sites of disease simultaneously. In addition, preoperative chemotherapy may be better tolerated than postoperative chemotherapy. For these reasons, neoadjuvant chemotherapy in patients with early-stage NSCLC has generated interest.

In the early 1990s, two small randomized trials demonstrated that neoadjuvant chemotherapy can improve survival. Rosell et al[26] evaluated neoadjuvant cisplatin, mitomycin C, and ifosfamide in patients with stage IIIA disease. Similarly, Roth et al[27] evaluated neoadjuvant cisplatin, etoposide, and cyclophosphamide in the same group of patients. Both trials showed a survival advantage and sparked additional assessment in the neoadjuvant approach.

One of the largest studies conducted in the United States to evaluate neoadjuvant chemotherapy was S9900.[28] Patients with stage IB/IIIA disease were randomly assigned to surgery alone or to three cycles of carboplatin/paclitaxel followed by surgery. The plan was to enroll 300 patients per

arm, but the study closed after 354 patients were enrolled in the study because data about benefits of adjuvant therapy became available during the conduct of the study; it became challenging to continue to randomly assigned patients to surgery alone. Among the patients enrolled, there was an improvement in survival (median, 62 vs. 41 months; HR, 0.79; p = .11) and progression-free survival (median, 33 vs. 20 months; HR, 0.80; p = .10) with neoadjuvant chemotherapy, but this improvement was not statistically significant, possibly because of lower-than-planned enrollment. The surgical resection rate among randomly assigned patients was similar at 87% among patients who had surgery alone and 84% among patients who had neoadjuvant chemotherapy. Postoperative adverse events were similar among patients who did and did not undergo neoadjuvant chemotherapy. However, the postoperative mortality was higher among patients in the neoadjuvant chemotherapy arm who underwent pneumonectomy (4 of 24 vs. 0 of 26 in the surgery-alone arm). Another trial, CHEST (chemotherapy in early-stage NSCLC trial) evaluated neoadjuvant cisplatin and gemcitabine followed by surgery versus surgery alone.[29] This study enrolled only 270 of the planned 700 patients. Both progression-free survival (HR, 0.70; p = .003) and overall survival (HR, 0.63; p = .02) were significantly improved with neoadjuvant chemotherapy. The study found that the survival benefit with neoadjuvant chemotherapy was restricted to patients with stage IIB/IIIA disease (HR, 0.42; p < .001). In patients with stage IB/IIA disease, the majority of whom were stage IB, there was no improvement in survival with neoadjuvant chemotherapy (HR, 1.02; p = .94).

Several meta-analyses of studies to evaluate neoadjuvant chemotherapy have been performed.[30-32] These meta-analyses suggest that neoadjuvant chemotherapy does improve survival, with an absolute benefit of 5% to 6% at 5 years; this rate is similar to the benefit observed with adjuvant chemotherapy.

Few trials have compared neoadjuvant and adjuvant chemotherapy. A prominent study was the NATCH trial that randomly assigned patients with stage I or stage II, T3N1 NSCLC to surgery alone, to neoadjuvant chemotherapy with carboplatin and paclitaxel followed by surgery, or to surgery followed by adjuvant chemotherapy with the same regimen.[33] The study failed to demonstrate improvement in survival either with neoadjuvant or adjuvant chemotherapy. It is possible that the reason for lack of survival advantage with chemotherapy was that greater than 70% of the patients in each arm had stage I disease—a group that the LACE meta-analysis showed may not derive benefit from chemotherapy. However, outcomes with neoadjuvant chemotherapy were similar to adjuvant chemotherapy, which suggested that there is neither an advantage nor a disadvantage with neoadjuvant chemotherapy compared with adjuvant therapy. However, 97% of the patients in the neoadjuvant group started chemotherapy, compared with 66% in the adjuvant group (p < .0001), which suggests that neoadjuvant chemotherapy may be better tolerated than adjuvant chemotherapy.

An indirect meta-analysis to compare preoperative and postoperative chemotherapy was conducted by Lim et al.[34] It is important to note that the majority of the trials included in this analysis did not directly compare the two approaches. More than 10,000 patients were included in this analysis, though the number of adjuvant trials far exceeded trials that assessed neoadjuvant chemotherapy. This analysis showed that both overall survival and disease-free survival were similar with adjuvant or neoadjuvant chemotherapy.[34]

In summary, chemotherapy improves survival in patients with stage IB/IIIA NSCLC who have undergone surgical resection, irrespective of administration before or after surgery. The data for adjuvant chemotherapy are far more robust than the data for neoadjuvant chemotherapy; therefore, adjuvant chemotherapy should be the preferred approach. However, if there are concerns about surgical resection, then in the author's opinion neoadjuvant chemotherapy could be considered and the feasibility of surgical resection could be re-evaluated after chemotherapy.

PREDICTORS OF CHEMOTHERAPY SENSITIVITY

Only a proportion of patients with advanced-stage and early-stage NSCLC benefit from currently available chemotherapy drugs. Therefore, there has been an interest in identifying markers that can predict for benefit of, or lack thereof from, chemotherapy drugs. Several molecular markers, such as *ERCC1*, *RRM1*, *BRCA1*, and thymidylate synthase (TS), have been assessed independently and collectively to identify patients most likely to benefit from specific chemotherapy drugs. The expectation was that assessment of such molecules may spare patients who are unlikely to derive benefit from toxicities of chemotherapy drugs. However, despite promising results in pilot studies, randomized studies have failed to demonstrate the predictive utility of these markers.[35-37]

The ITACA (International Tailored Chemotherapy Adjuvant Therapy) phase III trial is evaluating the predictive utility of the mRNA expression levels of molecular markers *ERCC1* and TS.[38] Patients will undergo assessment of both markers by quantitative reverse transcriptase polymerase chain reaction. Patients were randomly assigned to investigator's choice of platinum-based chemotherapy or chemotherapy defined by the molecular markers. Patients with tumors that had high *ERCC1* and high TS received single-agent docetaxel; patients with high *ERCC1* and low TS received single-agent pemetrexed; patients with low *ERCC1* and high TS received cisplatin and gemcitabine; finally, patients with low *ERCC1* and low TS received cisplatin and pemetrexed. The study has completed enrollment, and the results are awaited.

Currently, no factor other than histology is predictive of benefit of, or lack thereof from, specific chemotherapy in patients with NSCLC. Despite this, several laboratories continue to perform assessments of these markers in tumors of patients with NSCLC. For now, therapy should not be based on the results of these markers.

Genomic Markers

Lung cancer, like most cancers, is a result of genetic alterations that initiate an oncogenic phenotype in the affected tissue. There is a notable interest in identification of specific gene signatures that can provide prognostic and predictive guidance. Genomic assessment is conducted routinely to determine adjuvant therapy for breast cancer.[39] Various investigators have proposed different genomic signatures as prognostic markers and/or predictive markers in resected NSCLC by using different testing platforms.

Chen et al[40] analyzed 125 patients with resected stage I to III NSCLC with different histologic subtypes by microarray gene expression analysis and identified a prognostic score that was based on the expression of five genes. All of the tissues analyzed were fresh-frozen. The patients with high gene scores had a lower median survival than patients with low gene scores (20 vs. 40 months; $p < .001$). In a multivariable analysis, the five-gene score was significantly ($p = .03$) associated with death, as were patient age and tumor stage.

Kratz et al[41] defined a 14-gene signature on paraffin-embedded tumor specimens of patients with nonsquamous NSCLC. The investigators were able to categorize patients into three distinct prognostic categories. The 5-year survival rates in the three different categories were 74% in low-risk group, 58% in the intermediate-risk group, and 45% in the high-risk group. Among 330 total patients with stage I NSCLC, the median survival times were 113 months in the 78 low-risk patients, 88 months in the 104 intermediate-risk patients, and 70 months in the 151 high-risk patients. The investigators confirmed the results in an independent cohort of resected NSCLC obtained from a database in China. The ability to use formalin-fixed and paraffin-embedded tissue to generate such a gene expression–based score has greater clinical utility than signatures derived from studies that used fresh-frozen tissues.

Apart from assessment of genetic signatures, investigators also have assessed prognosis on the basis of levels of certain microRNAs (miRNA), which are small noncoding RNAs that function in regulation of gene expression by targeting either the 3-prime or 5-prime region of specific mRNAs. Expression levels of various miRNAs are altered in cancers, including lung cancer.[42] Several investigators have identified that expression of certain miRNAs may have prognostic relevance. This is a new and exciting area of research and could complement the prognostic utility of gene expression signatures.

Although assessment of gene expression to predict prognosis and benefit from adjuvant chemotherapy is a rational approach, none of the studies to date have proven the clinical value of gene signatures in prospective trials. In addition, the technologies, the tissue sources, and gene sets have varied among reports, and this variance severely limits the clinical applicability of gene signatures in current practice.

ADJUVANT TARGETED THERAPY

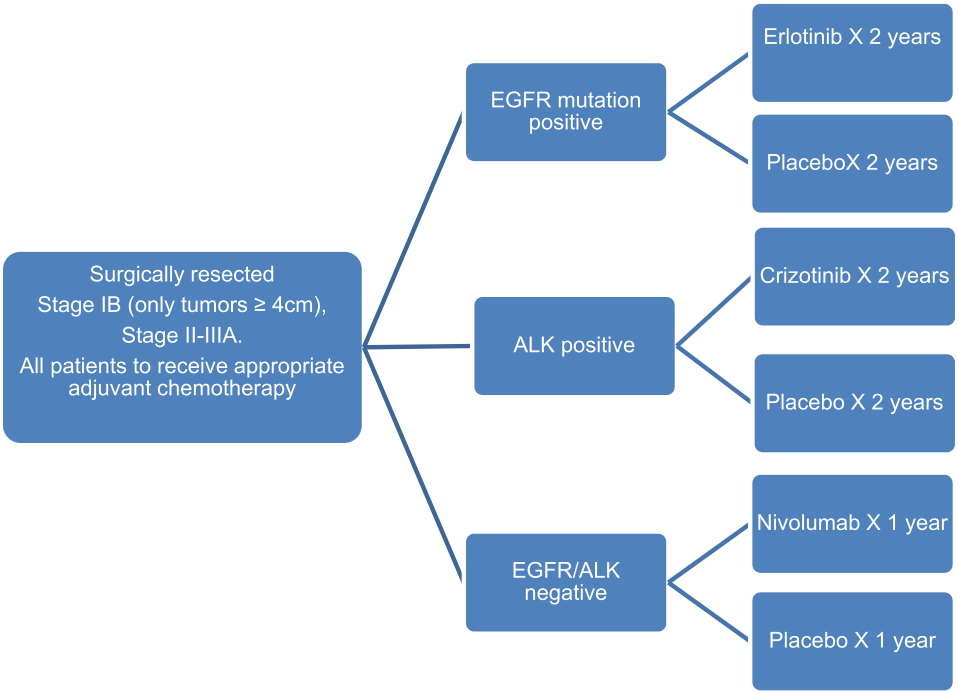
EGFR Inhibitors as Adjuvant Therapy

One of the major advances in the management of NSCLC is the identification of driver genetic alterations that can be targeted for therapeutic benefit. The first driver genetic alteration that was successfully targeted for therapeutic benefit was *EGFR* mutation. Approximately 10% to 15% of patients with NSCLC, particularly those with adenocarcinomas of the lung, have mutations in the tyrosine kinase domain of the *EGFR* gene. Exon 19 deletions and the point mutation L858R in exon 21 constitute 90% of all *EGFR* mutations identified in NSCLC. Randomized trials have shown that patients with advanced NSCLC who are positive for these *EGFR* mutations derive greater clinical benefit from EGFR tyrosine kinase inhibitors (TKIs) than standard front-line chemotherapy.[43] On the basis of these data, there is a clear interest in evaluation of these drugs as adjuvant therapy in patients with *EGFR* mutation–positive NSCLC. Retrospective analysis has suggested that adjuvant EGFR TKIs can provide clinical benefit in patients with *EGFR* mutation–positive NSCLC.[44] However, as yet, there are no conclusive prospective data to support the use of these drugs as adjuvant therapy.

The largest trial to evaluate EGFR TKIs as adjuvant therapy was the RADIANT trial.[45] In this trial, patients were eligible if their tumors were positive for *EGFR* expression as assessed by immunohistochemistry or fluorescent in situ hybridization. Patients were randomly assigned in a 2:1 fashion to receive 150 mg daily of erlotinib for 2 years or to placebo. Patients who were candidates for adjuvant chemotherapy received this treatment before start of the study therapy. The primary endpoint of the study was improvement in disease-free survival. The study failed to demonstrate a disease-free survival or survival advantage with the use of adjuvant erlotinib. Of the 973 patients enrolled in the study, 161 patients had exon 19 deletion or L858R *EGFR* mutations. In this population of patients, the disease-free survival was superior with erlotinib (HR, 0.61; 95% CI, 0.384–0.981; $p = .0391$). However, the difference could not be considered statistically significant because of hierarchical testing that allowed assessment of statistical significance of secondary endpoints only if the primary endpoint was statistically significant. At the time of data analysis, the follow-up was too limited to assess survival differences.

In another randomized trial, BR19, gefitinib was evaluated as adjuvant therapy in all patients and was not restricted to *EGFR* mutation–positive NSCLC. The study closed early after gefitinib failed to show survival advantage in patients with advanced NSCLC in the ISEL trial. The study enrolled 503 patients with resected stage IB/IIIA NSCLC, and patients were randomly assigned in a 1:1 manner to gefitinib or placebo. Patients received gefitinib for a median of 4.8 months. Gefitinib did not improve survival in these patients. Only 15 patients had *EGFR* mutations—seven of whom received gefitinib, and eight of whom received placebo. There was a suggestion of worse survival among the seven patients with *EGFR* mutation–positive tumors who received gefitinib (HR, 3.16; 95% CI, 0.61–16.45; $p = .15$). These results have to be viewed with some level of caution because of the small number of patients with *EGFR* mutations, early closure of the study, and the short duration of gefitinib administered to these patients.

FIGURE 2. ALCHEMIST (NCT02194738) Trial Design



The SELECT trial was a single-arm, multicenter, phase II study to assess erlotinib as adjuvant therapy in patients with stage IA to IIIA *EGFR* mutation–positive NSCLC.[46] Patients received erlotinib for 2 years. The study was designed to assess the ability of adjuvant erlotinib to improve 2-year disease-free survival from 76% (on the basis of historical data) to 86%. The 2-year disease-free survival in the 100 patients enrolled in the study was 89%. Of the 29 patients who experienced recurrence, 25 developed disease recurrence after erlotinib treatment was stopped. The median time to recurrence after treatment stopped was 8.5 months. In addition, the duration of treatment was significantly shorter in patients who had recurrence compared with those who were recurrence free at the time of data analysis ($p = .027$). These data suggest that duration of therapy with an EGFR TKI may have relevance in the adjuvant setting. Data from studies in gastrointestinal stromal tumors (GIST), which also have driver genetic alteration, have shown that 3 years of adjuvant therapy with imatinib provides greater benefit than 1 year of therapy.[47] In that trial, only 69% of the patients completed at least 22 months of therapy, whereas only half of the patients in the RADIANT trial completed all 24 months of therapy. Thus, it is possible that prolonged delivery of adjuvant EGFR TKIs is essential for improved outcomes in *EGFR* mutation–positive NSCLC.

Several ongoing or recently completed trials are addressing the use of adjuvant EGFR TKIs. The largest such effort is the ALCHEMIST trial (NCT02194738), conducted by all of the cooperative oncology groups in the United States under the leadership of the National Cancer Institute (Fig. 2). Patients with stage IB to IIIA disease will undergo molecular analysis. If their tumor has an *EGFR* mutation, then they could enter the *EGFR* mutation substudy that plans to enroll 410 patients and will randomly assign patients to erlotinib for 2 years or to placebo. The primary endpoint of the study is overall survival. The ALCHEMIST trial also has a substudy to evaluated the role of adjuvant crizotinib in patients with resected *ALK*-positive NSCLC. Other trials (C-TONG 1104, NCT01405079; WJOG6401L) are comparing adjuvant EGFR TKIs to adjuvant platinum-based chemotherapy by using disease-free survival as the primary endpoint. Finally, a trial in the United States (NCT01746251) is randomly assigning patients to receive adjuvant afatinib for either 3 months or 2 years to assess the relevance of duration of therapy.

The available data do not conclusively demonstrate that adjuvant EGFR TKIs provide a survival advantage in patients with early-stage lung cancer. Therefore, adjuvant EGFR TKIs currently are not considered the standard of care.

Bevacizumab

Bevacizumab is a monoclonal antibody that targets VEGF. Angiogenesis is an important component of carcinogenic phenotype; therefore, targeting oncogenic angiogenesis for therapeutic benefit has been of interest for a long time. E4599 demonstrated that the addition of bevacizumab to the chemotherapy of carboplatin and paclitaxel improved survival in patients with advanced nonsquamous NSCLC.[48] Other studies conducted did not document an overall survival benefit in patients who received bevacizumab with chemotherapy.

The survival advantage observed with the addition of bevacizumab to chemotherapy in E4599 was the basis of E1505, a study that evaluated the efficacy of bevacizumab added to adjuvant chemotherapy.[19] The study randomly

assigned 1,501 patients with stage IB to IIIA disease who had undergone surgical resection with appropriate lymph node sampling to receive four cycles of platinum-based adjuvant chemotherapy with or without 1 year of bevacizumab. Among the patients randomly assigned to receive bevacizumab, only 37% of the patients completed an entire year of treatment. Neutropenia, hypertension, and overall grade 3 to 5 toxicities were more frequent in patients who received bevacizumab. There was no difference in survival among patients who were randomly assigned to receive bevacizumab and patients who were not (HR, 0.99).

IMMUNOTHERAPY

The ability to evade immune surveillance is an important aspect of the oncogenic phenotype. Thus, activation or restoration of immune surveillance could treat and eradicate cancers.

Vaccines

Therapeutic vaccines have been evaluated as adjuvant therapy in patients with resected lung cancer. Both tumor-based vaccines and peptide-based vaccines have been evaluated in lung cancer. The largest study to test this strategy in the adjuvant setting was the MAGRIT trial, a study that evaluated the melanoma-associated antigen (MAGE)–A3 vaccine.[49] MAGE-A3 is expressed on the surface of several cancers, including NSCLC, and is not expressed on normal tissues other than the placenta and testis. A randomized phase II study suggested that an adjuvant MAGE-A3 vaccine could enhance both disease-free survival and overall survival.[50] MAGRIT was a randomized phase III study that evaluated more than 13,000 patients; 2,312 of these patients were randomly assigned in a 2:1 manner to receive the vaccine or placebo during 27 months. Of the patients randomly assigned, approximately 50% had received adjuvant chemotherapy. The schedule of the vaccine and placebo was similar to the phase II trial of 13 doses administered over 27 months. The study failed to show an improvement in disease-free survival in the overall population (HR, 1.02; p = .74) or in patients who had received adjuvant chemotherapy (HR, 1.10; p = .36).

Other vaccines have been evaluated for the management of patients with NSCLC, both in early and advanced stages.[51-54] Though some of the trials have shown very promising results, none have conclusively demonstrated survival improvement in a randomized phase III study. Whether this approach will prove to provide meaningful benefit as adjuvant therapy remains to be seen.

Checkpoint Inhibitors

Tumors can evade immune surveillance by activating inhibitory checkpoints on T cells. Two of the most well-studied checkpoints are PD-1 and its ligand, PD-L1. Inhibition of the PD-1 signaling pathway by antibodies directed against either PD-1 or PD-L1 has led to dramatic clinical benefits in a minority of patients with advanced NSCLC.

Three drugs that target the PD-1 signaling pathway have been approved for the treatment of advanced NSCLC. Pembrolizumab is a fully humanized IgG4 antibody against PD-1. On the basis of randomized phase III studies, the drug has been approved for front-line therapy in patients with advanced NSCLC whose tumors have high PD-L1 expression.[55] It is also approved for patients with NSCLC who have PD-L1–positive cancers and who were previously treated with a platinum-based chemotherapy.[56] Nivolumab is also a fully humanized IgG4 antibody against PD-1. Currently, it is approved for patients with advanced NSCLC who were previously treated with platinum-based chemotherapy irrespective of the tumor PD-L1 expression.[57,58] Recently, atezolizumab, a fully humanized antibody that targets PD-L1, was approved for use in patients with advanced NSCLC who were previously treated with platinum-based chemotherapy.[59]

There is a great deal of interest in the evaluation of these agents in early-stage NSCLC. Several randomized trials are evaluating these agents in the adjuvant setting. The ALCHEMIST trial was modified recently to randomly assign patients whose tumors are not *EGFR* mutation–positive or *ALK* mutation–positive to nivolumab or placebo. Results of these trials are eagerly awaited. Whether the benefit will be restricted to patients with tumors that express a high level of PD-L1 or those that have other biomarkers remains to be seen.

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MELANOMA/SKIN CANCERS

Advances in the Treatment of Advanced Extracutaneous Melanomas and Nonmelanoma Skin Cancers

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OVERVIEW

Cutaneous malignancies make up the greatest proportion of all human cancers and include melanomas as well as nonmelanoma skin cancers (NMSCs) such as basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), as well as less common Merkel cell carcinoma (MCC), cutaneous lymphomas, cutaneous adnexal tumors, Kaposi sarcomas, and other sarcomas. Each of these NMSCs differ significantly in biology, clinical behavior, and optimal treatment recommendations from each other and from cutaneous melanoma. Similarly, less common extracutaneous melanomas, such as mucosal (MMs) and uveal (UMs), are unique biologic and clinical entities that require distinct diagnostic and management considerations. In this review, we summarize recent advances in biology and treatment of extracutaneous melanomas and NMSCs, including MMs, UMs, cSCC, BCC, and MCC.

Cutaneous malignancies make up the greatest proportion of all human cancers and include melanomas as well as NMSCs such as BCC and cSCC, as well as less common malignancies such as MCC, cutaneous lymphomas, cutaneous adnexal tumors, Kaposi sarcomas, and other sarcomas. Each of these NMSCs differ significantly in biology, clinical behavior, and optimal treatment recommendations from each other and from cutaneous melanoma. Similarly, less common extracutaneous melanomas such as MM and UM are unique biological and clinical entities from cutaneous melanoma and require distinct management considerations.

In this review, we summarize recent advances in our understanding and management of a subset of advanced extracutaneous melanomas and NMSCs, including MMs, UMs, cSCC, BCC, and MCC.

EXTRACUTANEOUS MELANOMAS

Melanoma is a heterogeneous collection of diseases arising from melanocytes within the skin, uveal tract of the eye, and mucosal surfaces of the body. Although the majority of cases arise from cutaneous surfaces, approximately 3%–5% of cases arise from the uveal tract of the eye, and approximately 2% arise from the mucosal surfaces of the body.[1,2]

UM arises from melanocytes anywhere along the uveal tract, with the majority of cases arising from the choroid (approximately 85% of cases) and the remaining cases from the iris or ciliary body.[3] Despite definitive primary therapy with enucleation or radiotherapy, nearly 50% of patients will develop metastatic disease.[4] Survival from the time of diagnosis of metastatic disease is poor, with overall survival (OS) ranging from 6 to 13 months.[5,6] The biology of UM is distinct from that of cutaneous melanoma; thus, treatments that have been effective for advanced cutaneous melanoma, including chemotherapy, molecularly targeted therapies, and immunotherapies, have been less effective in UMs and have not impacted outcomes in this rare disease.

MM arises in any mucosal epithelium containing melanocytes, such as that of the respiratory, gastrointestinal, and urogenital tracts. The most commonly affected sites include the head and neck, anorectal region, and vulvovaginal region. In general, management of localized MM consists of wide local excision if negative margins can be achieved with or without adjuvant radiotherapy; however, because of anatomic constraints, this approach is not always possible. Sentinel lymph node biopsy is unproven in these cancers, although elective regional lymph node dissection may be considered in some subtypes. Data are lacking on the benefit of systemic adjuvant therapy with interferon or ipilimumab, the currently approved adjuvant treatment options available for cutaneous melanoma at high risk of recurrence. Adjuvant therapy with the combination of temozolomide and cisplatin as well as single-agent high-dose interferon showed survival benefit when compared with observation in a single-institution study that has not been validated in subsequent larger trials.[7] Overall, most patients

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develop and die of disseminated disease. Disease-specific survival for MM at 5 years is markedly decreased compared with that of cutaneous melanoma (25% vs. 80%).[2]

Uveal Melanoma

In contrast to cutaneous melanoma, which is subdivided into those that harbor activating mutations in *BRAF*, *RAS*, or loss of function of *NF1*, UM is characterized by mutations in the G-α-protein subunits *GNAQ* or *GNA11* in approximately 80%–95% of cases.[8-11] Mutations in *GNAQ* or *GNA11* result in disabling of their intrinsic GTPase activity and constitutive activation of downstream pathways, including the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathways. More recently, mutations in *PLCB4*, a downstream effector of *GNAQ* and *GNA11*,[12] and recurrent activating mutations in the G-protein–coupled receptor *CYSLTR2*, have been identified as oncogenic drivers that contribute in a mutually exclusive manner from *GNAQ* and *GNA11* mutations to UM.[13] BRCA1-associated protein 1 (*BAP1*) is a tumor suppressor that is mutated in approximately 47% of primary UMs and associated with metastasis and poor prognosis.[14] *SF3B1* mutations have been identified in 18% of primary UMs and *EIF1AX* mutations in 48% of primary UMs and are associated with an overall more favorable prognosis, although *SF3B1* mutant UM is a subset characterized by atypical presentations and late occurrences of distant disease.[15,16]

KEY POINTS

- **Extracutaneous melanomas and NMSCs represent a biologically and clinically heterogeneous group of diseases, each of which requires unique management considerations.**
- **Although single-agent immunologic checkpoint blockades have limited efficacy in advanced uveal melanoma, other immune-based treatment strategies including the use of novel T-cell redirection as well as adoptive T-cell transfer therapies are being pursued based upon promising preliminary data. Preclinical data demonstrate the efficacy of epigenetic targeting of uveal melanoma via histone deacetylase inhibition as well as bromodomain targeting, with clinical trials testing this strategy ongoing.**
- **Both targeted therapy and immunologic checkpoint blockade have activity in mucosal melanoma but with less favorable outcomes than for cutaneous disease, and continued investigation of novel therapies is needed.**
- **Immune checkpoint blockade with agents targeting the PD-1/PD-L1 pathway has shown antitumor activity in two clinical trials for advanced Merkel cell carcinoma. There is also promise for immune checkpoint blockade in combination with radiotherapy and other treatments for advanced Merkel cell carcinoma. In addition, testing in the neoadjuvant and/or adjuvant setting is also critical and should be prioritized.**
- **Further study of immunotherapy with PD-1 and PD-L1 inhibitors is ongoing for advanced SCC and BCC.**

Emerging therapies for primary uveal melanoma. Treatment of primary UM can be subdivided into either globe-preserving therapy or enucleation. In the United States, the majority of primary UMs are treated with plaque brachytherapy based on results of the Collaborative Ocular Melanoma Study that evaluated plaque brachytherapy versus enucleation for medium-sized choroidal melanomas.[17] Although current treatment modalities for primary UM achieve excellent local control, complications leading to vision loss in the affected eye are common, and new approaches for local therapy are still needed.

ICON-1 is one novel therapy for primary UM currently in development. This human immunoconjugate protein targets a modified version of human factor VII, the ligand of tissue factor, which is commonly overexpressed in primary UM.[18] ICON-1 binds to UM cells overexpressing tissue factor and signals an immune response to eliminate pathologic tissue while leaving normal tissue intact. A phase I clinical study of ICON-1 in patients with UM who are planned to undergo enucleation or brachytherapy is currently enrolling (NCT02771340).

AU-011, another investigational therapy for primary UM, is a viruslike particle that binds to cancer cells and is conjugated to infrared molecules that can be activated by an ophthalmic laser, allowing for selective targeting of UM cells. This therapy is based on preclinical data in ovarian and lung cancer models demonstrating that human papillomavirus-like particles selectively bind to heparan sulfate proteoglycans on the disrupted epithelium of cancer cells while leaving the surrounding healthy tissue unharmed.[19] AU-011 has been granted an orphan drug designation by the U.S. Food and Drug Administration, and a clinical study of AU-011 in UM is currently in development.

Emerging therapies for metastatic uveal melanoma. Treatment strategies adapted from cutaneous melanoma have generally been ineffective in UM, and thus, no standard of care therapy exists for advanced UM. Systemic chemotherapy with dacarbazine- or cisplatin-based regimens demonstrated response rates of 0%–10% in metastatic UM.[20-23] More recently, molecularly targeted therapies for the MAPK and/or the PI3K/Akt pathways have been conducted in metastatic UM. A randomized phase II study of the MAPK kinase inhibitor, selumetinib, versus chemotherapy in advanced UM demonstrated a modest improvement in progression-free survival (PFS) with selumetinib treatment, but no OS benefit. A subsequent phase III study of selumetinib and dacarbazine versus dacarbazine alone showed no improvement in either PFS or OS.[24-26] Liver-directed therapies such as embolization or hepatic arterial chemotherapy infusion have controlled UM in selected patient populations but without OS benefit.[27-29] Treatment approaches currently being investigated for advanced disease include combination targeted therapies, immune-based strategies, and epigenetic agents. Given the poor outcomes in this disease and current lack of effective therapies, rationally designed clinical trials investigating novel therapeutic approaches for advanced UM are urgently needed and should be prioritized in this disease.

Immune-based therapies in uveal melanoma. Immune checkpoint inhibitors have demonstrated limited efficacy in metastatic UM, with durable responses in less than 5% of patients. Two prospective clinical trials of CTLA-4 blockade with ipilimumab, as well as a prospective study of tremelimumab, demonstrated very low response rates and short PFS of less than 3 months: the phase II GEM-1 trial evaluated ipilimumab, at a dose of 10 mg/kg, in treatment-naive patients with metastatic UM and reported only one response in 13 evaluable patients.[30] A subsequent multicenter phase II trial by the Dermatologic Cooperative Oncology Group (DeCOG) evaluated ipilimumab at a dose of 3 mg/kg in 45 pretreated and eight treatment-naive patients with metastatic UM and reported no responses. The median PFS was 2.8 months, and median OS was 6.8 months.[31] A prospective multicenter phase II study of tremelimumab in advanced UM was stopped early for futility with no responses in the first 11 patients and a median PFS of only 2.9 months and median OS 12.8 months, likely reflecting the natural history of advanced UM.[32]

Similarly, results of PD-1/PD-L1 checkpoint blockade in metastatic UM have been disappointing. Studies evaluating PD-1/PD-L1 inhibition in UM thus far have been limited to small retrospective case series. A retrospective analysis of 25 patients with metastatic UM treated with pembrolizumab through an expanded access program reported two partial responses and stable disease in six patients.[33] The largest case series to date analyzed 58 patients with metastatic UM treated with anti–PD-1 or anti–PD-L1 therapy across nine different academic centers.[23] The response rate was 3.6% (two partial responses), and stable disease for 6 months or longer was observed in 8.9% (five of 56 evaluable patients). Median PFS and OS were 2.8 (95% CI, 2.4–2.8 months) and 7.6 months (95% CI, 0.7–14.6 months), respectively.[23] PD-L1 status was not reported in this retrospective analysis.

Overall, clinical benefit with immune checkpoint inhibition in metastatic UM is rare, and these therapies should not be standard in metastatic UM. Differences in tumor mutational landscape, with UM being characterized by fewer genetic mutations, may explain in part the inferior outcomes of immune checkpoint inhibition in UM versus cutaneous melanoma.[34,35] Further investigation of the biology of this distinct melanoma variant and its profound resistance to single-agent immunotherapy, possibly because of an unfavorable microenvironment in its commonest metastatic site, the liver, require further exploration. There is an ongoing study of pembrolizumab in metastatic UM (NCT02359851) and two ongoing studies of combined CTLA-4 and PD-1 blockade with ipilimumab and nivolumab in metastatic UM (NCT01585194 and NCT02626962).

Investigation of other immune-based therapeutic strategies are ongoing with promising early results. Glycoprotein 100 (gp100) is a tumor-associated antigen that is strongly expressed in both cutaneous and UM.[36] IMCgp100 is a recombinant T-cell receptor currently in development that recognizes the gp100 antigen presented by HLA-A2 on its targeting end and binds and activates $CD3^+$ T lymphocytes on its effector end, thus allowing cytotoxic T cells to be redirected toward the gp100-expressing UM cells. The first-in-human phase I study of IMCgp100 enrolled 84 HLA-A*02–positive patients with advanced melanoma, including 16 patients with advanced UM.[37] Subjects were treated with intravenous IMCgp100 at two separate dosing regimens: weekly or daily for 4 days, every 3 weeks. The most common adverse events included rash (100%), pruritus (64%), pyrexia (50%), and periorbital edema (46%). Grade 3 or 4 adverse events were observed predominantly in the first 3 weeks of study treatment and included rash (23%), lymphopenia (8%), and hypotension (6%), which was associated with trafficking of $CD3^+$ T cells to the tumor environment and chemokine release. An intrapatient dose-escalation design was subsequently implemented to mitigate the hypotension observed during the first few weeks of therapy.[37] Results of the 15 evaluable patients with UM enrolled in this first-in-human study were recently presented at the 2016 Society for Melanoma Research Congress. The majority of patients with UM enrolled in this study had liver metastases and elevated lactate dehydrogenase. A partial response was achieved in 20% (three patients) and stable disease in 47% (seven patients) of patients with UM at 8 weeks. The disease control rate was 53% at 16 weeks and 40% at 24 weeks.[38] Based on these promising results, there is an ongoing phase I/II study of IMCgp100 in patients with advanced UM using an intrapatient dose-escalation regimen (NCT02570308), with a pivotal randomized clinical trial in development.

Investigation of other immune-based therapies in UM is ongoing. A study of dendritic cell vaccination in 14 patients with metastatic UM demonstrated four responses and a median OS of 19.2 months.[39] A phase II study of autologous tumor-infiltrating lymphocytes in metastatic UM is currently enrolling (NCT01814046).

Epigenetic therapies in uveal melanoma. Given that UM is a genetically simple disease characterized by few somatic insults compared with cutaneous melanoma,[34,35] other factors such as epigenetic alterations may be important in the pathogenesis of UM. This is supported by evidence that genes associated with a high-risk, class 2 phenotype, such as *PHLDA1*, seem to be regulated through epigenetic modifications.[40] Additionally, preclinical data in UM cell lines support the role of histone deacetylase inhibitors (HDACi) in reversing the phenotypic and biochemical cell changes associated with *BAP1* loss and metastatic potential in UM cells.[41,42] In UM cell lines, epigenetic modification with four different HDACi (including valproic acid, trichostatin A, LBH-589 or panobinostat, and vorinostat), induced G1 cell-cycle arrest, melanocytic differentiation, and gene expression changes consistent with reversion to a class I phenotype.[42] Additionally, valproic acid was capable of inhibiting growth of UM tumors in vivo. There is an ongoing clinical study of vorinostat in metastatic UM (NCT01587352). Additionally, HDACi is also being explored as a strategy in the adjuvant setting in an ongoing clinical study of adjuvant sunitinib or valproic acid in high-risk patients with UM (NCT02068586).

Recent preclinical data suggest that epigenetic therapies targeting the bromodomain and extra-terminal domain (BET) family of proteins may be a promising new strategy in UM. The BET family of proteins, including BRD2, BRD3, BRD4, and BRDT, are epigenetic regulators that bind to acetylated lysine residues on histones and direct the assembly of nuclear complexes that regulate DNA replication, chromatin remodeling, and transcription.[43,44] BRD4 is a key regulator of transcriptional elongation by recruiting positive transcriptional elongation factor complex to chromatin and activating RNA polymerase II–dependent transcription. It is considered a nononcogenic regulator of cancer growth, in part through activation of the Myc transcriptome.[45] BET inhibition has shown antitumor activity in preclinical studies in hematologic malignancies[45,46] and selected solid tumors.[47-50] It is hypothesized that UM may be particularly susceptible to BET targeting given the relatively high incidence of Myc amplifications observed and preclinical data supporting epigenetic targeting in UM.[51]

In preclinical studies, JQ1, a first-generation BET inhibitor that competitively displaces BRD4 from acetylated histones, demonstrated potent cytotoxic activity in *GNAQ* and *GNA11* mutant cell lines, but not wild-type cells.[52] Microarray analysis of cell lines treated with JQ1 revealed changes in expression in genes involved in cell cycle regulation, apoptosis, and the DNA damage response. Interestingly, concomitant silencing of Bcl-xL and Rad51, regulators of apoptosis and the DNA damage response, respectively, was sufficient to induce apoptosis independent of Myc expression.[52] Small-molecule inhibitors of BET proteins are currently in clinical development. Based on intriguing preclinical data, clinical investigation of BET protein inhibition in UM may be warranted.

Mucosal Melanoma

The biology and clinical outcomes of MM differs significantly from that of cutaneous melanoma. A recent analysis of updated survival data for melanoma subtypes was based on information from 3,454 patients diagnosed with metastatic melanoma from 2000 to 2013, including 237 patients with MM.[6] The median OS for patients with advanced MM was 9.1 months (95% CI, 7.6–9.8), which was significantly shorter than that for patients with other subtypes of melanoma, including UM. This trend appears to have continued even in more recent years, as it persisted even in the cohort of patients diagnosed in 2011 to 2013. No notable differences in survival were found for the subsets of MM defined by the primary site (anorectal, head and neck, vulvovaginal, or other).

BRAF-activating mutations occur far less frequently in mucosal than in cutaneous melanoma, whereas KIT mutations are found more often in MM. Genomic sequencing of 10 MMs demonstrated that somatic mutation rates were significantly lower than those found in sun-exposed cutaneous melanoma and that more copy number and structural variations were present in the mucosal tumors.[53] Although data with direct comparisons are lacking, one summary review suggests that KIT mutations are observed more frequently in vulvovaginal and anal melanoma than in sinonasal melanoma.[54] A study of 467 anorectal melanomas identified driver mutations in 95% of tumors.[55] Affected genes included *KIT*, *NF1*, other elements of the MAPK pathway, and *SF3B1*. Conversely, a small study of melanomas from the female genital tract showed a low mutational burden for genes in the MAPK/ERK, PI3K/AKT, and GNAQ/11 pathways.[56] Another study of melanoma from the female urogenital tract showed that NRAS mutations were more prevalent than KIT mutations in this tumor type (21% vs. 4%).[57] Of the mutations identified in this study, three of the NRAS mutations were in exon 3 (codon 61), one was in exon 2 (codon 12), and the KIT mutation was in exon 17 (codon 820).

Molecularly targeted therapy directed at KIT as the oncogenic driver. Because of the frequency of KIT mutations and other genetic aberrations such as gene amplification in MMs, imatinib has been investigated as a potential therapeutic agent. In a multicenter, single-arm phase II trial, 28 patients with advanced or unresectable melanoma with KIT mutation or amplification were treated with imatinib 400 mg twice daily.[58] Among the 13 patients with MM in this study, four had stable disease (reported at 10–20 weeks), one had a transient partial response, one had a partial response lasting 53 weeks, and one had a complete response lasting 95 weeks. The relative number of responses was similar to those found in the patients in the study with KIT alterations in acral melanomas (one out of 10 with complete response and two out of 10 with partial response). In a subsequent phase II trial, 43 patients with KIT mutation or amplification, including 11 with MM, were treated with imatinib 400 mg daily.[59] Four patients with MM had imatinib escalated to 800 mg daily at the time of disease progression on the lower dose but did not respond to the higher dose. Toxicity of the regimen was dose-limiting grade 3 to 4 edema, nausea, fatigue, and anorexia. Subgroup analysis for the mucosal group was not reported, but for the overall cohort, 10 patients achieved partial response (23%), and 13 had stable disease at 8 weeks or later. The median PFS was 3.5 months. In a later phase II trial of imatinib 400 mg daily in 24 patients with KIT mutated or amplified melanoma, seven patients had partial responses, and five had stable disease ranging in duration from approximately 3 to 11 months.[60] The only objective responses were reported among the 17 patients with MM. Of note, all responders had KIT mutations, and none had amplification of KIT.

The response rates to imatinib have prompted investigation of the effects of other tyrosine kinase inhibitors in the MM population. An early report of the use of dasatinib in two patients with L576P KIT-mutated MMs showed a rapid radiologic response in both, as well as improvement in symptomatic control in one of the patients, but the responses were short-lived (3 to 4 months).[61] More recently, data from the second stage of the U.S. cooperative group study E2607 were presented at the 2016 ASCO Annual Meeting.[62] In this study, subjects received 70 mg of dasatinib orally twice a day. The first stage included 51 subjects with acral melanoma, MM, or melanoma of chronically sun-damaged

skin regardless of mutation status, of whom three turned out to have a KIT mutation, and the second phase had 22 patients with KIT-mutated melanoma. Of note, accrual to this study suffered due part to the rapid adoption of drugs such as imatinib and dasatinib for patients with advanced MM and KIT mutations based on the prior experience and general enthusiasm about molecularly targeted therapy, particularly for a disease that had historically been so difficult to treat. Twenty-nine of the subjects across the two stages had MM, and three had partial responses, but responses occurred both in individuals with KIT-mutated and KIT wild-type tumors, presumably because dasatinib is a "dirty" kinase inhibitor without specificity for KIT. Nilotinib was also tested in a small study of KIT-mutated advanced melanoma refractory to at least one prior KIT inhibitor or with brain metastases. Among 19 patients with MM in this study, only two partial responses and a high rate of dose-limiting toxicity were reported.[63]

The overall status of KIT-targeted therapies in MM remains a subject of investigation, including efforts to better understand the dependence of cells carrying this mutation on KIT and other pathways that may be targetable with small molecules or other classes of agent. So far, however, the responses to these agents are not durable, as they are in single pathway-driven malignancies like chronic myeloid leukemia and gastrointestinal stromal tumors; therefore, it is critical to study mechanisms of both intrinsic and acquired resistance to KIT inhibition. Melanoma cells with acquired resistance to KIT inhibition have been found to have activation of MAPK and PI3K signaling and remain sensitive to concurrent inhibition of these pathways.[64] Opportunities may be identified for vertical or horizontal inhibition of more than one pathway with molecularly targeted therapy. Although the tolerance of these single-agent kinase inhibitors at full doses may be limited, many toxicities are nonoverlapping and may permit investigation of full or near-full doses of each class of agent.

Immune checkpoint inhibitors in mucosal melanoma. Ipilimumab use in the population with MM has been described in several studies, all of which were only for patients previously treated with systemic therapy, generally consisting of single-agent or combination chemotherapy, which provides very low (less than 10%) objective response rates in this subset of melanoma. In one small report with six evaluable patients with MM, one subject had a partial response, which is the number expected from the data in cutaneous melanoma.[31,65] Disease control rate, defined as stable disease lasting at least 12 weeks plus all objective responses, was 50%; however, no patients survived at the 2-year endpoint. Another retrospective case series of 33 patients with metastatic MM treated with ipilimumab after failure of cytotoxic chemotherapy showed an overall response rate of 6.7%, with one complete responder, one partial responder, and six with stable disease. The disease control rate of 24% was very similar to that which has been reported in much larger series for unselected melanoma.[66] The largest study reported to date consisted of 71 patients with pretreated metastatic MM in the Italian ipilimumab expanded access program.[67] In this group, the disease control rate was 36% and the overall response rate 12%. The rate of immune-related toxicity was similar for MM to that reported for unselected patients with melanoma.

A small case series detailed the use of combination ipilimumab and external beam radiation therapy in four women with locally recurrent MMs of the vagina or cervix.[68] Patients received up to four doses of ipilimumab concurrently with radiation to 3,000 to 6,020 cGy. Two subjects had grade 3 adverse effects (colitis and dermatitis, both of which could have been radiotherapy-related, but the contribution of the checkpoint-blocking antibody could not be determined). One subject had a complete response to the combined-modality therapy and did not proceed to surgery. Three subjects underwent resection after combination therapy, and two were found to have residual melanoma at that time. After resection of viable tumor, two patients remained disease-free at 20 and 38 months.

Recent data have shown that PD-1 inhibitors have efficacy in patients with MM, although the rates of response may be somewhat lower than in cutaneous melanoma. Shoushtari et al[69] reported an objective response rate of 23% (95% CI, 10%–40%) to first- or subsequent-line use of nivolumab or pembrolizumab in 35 patients with MM. The majority of these patients had M1c disease and brain metastases; most were wild-type for BRAF, NRAS, or KIT mutations. Over 75% had prior therapy, most often with ipilimumab, and had progressed without an initial response.[69] Of the 24 patients with MM and no benefit from prior ipilimumab, five patients had an objective response to a PD-1 inhibitor. Evaluation of 84 patients with MM treated with pembrolizumab in the KEYNOTE-001, 002, and 006 studies has been presented in abstract form. This study showed an overall response rate of 19% (95% CI, 12%–29%) with durable responses of up to 27 months. Of note, activity was seen both in patients with prior treatment with ipilimumab and in those who were treatment-naive.[70] A recent pooled analysis of 86 patients with MM who received nivolumab, either alone or in combination with ipilimumab, reported a similar response rate to single-agent nivolumab (23%) but a better response to the combination of nivolumab and ipilimumab (37%).[71] Toxicity in the patients with MM was similar to that seen in patients with cutaneous melanoma on these regimens. Based on these data, combination therapy with nivolumab and ipilimumab may be the preferred regimen in patients with MM who can tolerate it. The role of tumor biomarkers such as immunohistochemical expression of PD-L1 to predict benefit remains no more clear in MM than it is currently for cutaneous melanoma and a variety of other malignancies.

Research Directions

Current research directions include investigation of novel tyrosine kinases as well as the combination of targeted therapies with immunotherapies in this population. As with targeted therapies in other oncologic settings, responses to tyrosine kinase inhibitors may be of limited duration

because of primary or acquired resistance to these agents. Use of a multikinase inhibitor may bypass or prevent the development of resistance to targeted agents. In contrast, the natural history of rapid progression of mucosal disease may not allow the time required for an initial response to immunotherapy as well. Therefore, a combination of agents from these categories may provide a synergistic effect to overcome these obstacles to disease response.

NONMELANOMA SKIN CANCERS

NMSC is the most common cancer in humans and the most frequently observed malignancy in whites. Approximately 57%–80% of NMSCs are BCC, and 20%–25% are cSCC. MCC is a rather rare, but increasingly observed type of NMSC even more associated with immunosuppression, older age, and ultraviolet (UV) damage than other NMSCs. NMSC represents a major global economic and health burden. More than 2.1 million individuals in the United States are diagnosed with NMSC each year, with the vast majority (80%–90%) localized in the sun-exposed areas of the head and neck.[72]

The overall mortality rates for NMSCs are low in general, although MCC is a highly aggressive malignancy with a disease-specific mortality rate in a range of 25%–50%, reflecting a high rate of dissemination at the time of diagnosis, especially for large primaries, which are often mistaken for benign lesions or BCCs. All three types of NMSC discussed in this study are characterized by the risk of local recurrence, which, in some cases, can be predicted by specific clinical and pathologic features such as the size and location of the primary tumor.[73] The risk of aggressive cSCCs and MCCs is extremely high in immunosuppressed patients, such as those with solid-organ transplants, particularly if these patients already have a history of sun-damaged skin.[74]

Based on current guidelines, the primary treatment of NMSC is surgical. The complete excision, ideally with Mohs surgery or micrographic surgery of the primary tumors, is mandatory to prevent local relapses. The safety margins for cSCC and BCC are typically in a range of 0.5 to 1 cm, whereas in MCC, a 1- to 2-cm minimum excision margin is recommended. Mohs and micrographic surgery allow an evaluation of the completeness of tumor resections on cryostat-fixed or paraffin-embedded tumors, respectively. Particularly in NMSC of the face and in relapsing tumors, this technique is the standard of care. Selective lymph node dissection (SLND) is not recommended for the surgical management of cSCC or BCC. In contrast, an SLND has been established as a routine in patients with MCC. The SLND offers the potential to assess regional nodes for occult disease and an appropriate selection for further treatment. Typically, patients with a positive SLND are referred to a complete lymphadenectomy.

Adjuvant radiotherapy is typically recommended for patients with a high-risk MCC, resulting in a better local control with a significantly decreased number of local relapses by the use of adjuvant radiotherapy with a typical dose of 50–60 Gy in conventionally fractionated 2-Gy doses. There is no proven effective adjuvant treatment of cSCC and BCC. Therefore, neither adjuvant irradiation nor systemic treatment is offered in most centers to those patients, even if they are estimated to have a high risk of relapse.

Cutaneous Squamous Cell Carcinoma

Despite the use of routine surgery and radiotherapy for advanced cSCC, not all patients are cured. In a recent paper,[75] clinical features such as tumor thickness of more than 6 mm, localization on or near the ear, and immunosuppression have been associated with increased risk of local relapse and death. A satisfactory systemic treatment of advanced SCC has not been established so far, because of the poor therapeutic index of cytotoxic agents and insufficient information about immunotherapy. In patients with medical contraindications to surgery or radiotherapy, platinum-based regimens, either as single agents or in combinations, have been typically used in the past. However, despite a high response rate of up to 80%, the median response duration are only 4 to 6 months. There is no evidence that chemotherapies have an impact on OS for NMSC, and prospective randomized clinical trials are lacking.

Because cSCCs frequently demonstrate EGFR overexpression, antibodies to EGFR have been studied for the treatment of advanced disease. A 36-patient phase II study of cetuximab showed a response rate of 45%, but with a relative short response duration of 4 months.[76] In some cases, cetuximab has been used in combination with radiotherapy as in head and neck cancer, with some evidence of disease control but an unknown contribution to OS. Lapatinib showed activity in a neoadjuvant trial (two of eight patients had disease regression) and may warrant further evaluation in this setting as well as in immunocompromised patients with more advanced cSCC.[77]

Because most cSCCs carry a high mutational burden,[78] a specific genetic UV signature, and overexpression of PD-L1 in keratinocytes, blockade of the PD-1/PD-L1 pathway is a promising new treatment approach. Very recently, some case reports suggest the usefulness of PD-1 antibodies in patients with advanced or metastatic cSCC, with some demonstrating dramatic and complete responses even in heavily pretreated patients.[79-81] In 2016, a phase II trial on a new PD-1 antibody, REGN 2810, in patients with locally advanced and metastatic cSCCs who are not candidates for surgery or radiotherapy has been initiated (NCT02760498).

Basal Cell Carcinoma

The vast majority of BCCs are easy to treat by conventional surgery but very difficult to treat when unresectable or, rarely, metastatic. The “sonic hedgehog” signal transduction pathway was identified as crucial for the progression of BCCs and is commonly associated with mutations in the tumor-suppressor gene *PATCHED* and the tumor oncogene *SMOOTHENED*. Competitive inhibitors of S*MOOTHENED*, namely vismodegib and sonidegib, have been developed with some success, and are now approved based on responses in unresectable and/or metastatic BCC.

The multicenter, international, nonrandomized "ERIVANCE" study enrolled 104 patients with locally advanced and metastatic BCC and treated them with vismodegib at a flat dose of 150 mg daily.[82] In patients with metastatic BCC, the response rate was 30%, whereas in the patients with locally advanced BCC, the response rate was 43%, including a complete response rate of 21%. Typical adverse events included muscle spasms, alopecia, dysgeusia, weight loss, and fatigue. The results of this study led to the approval of vismodegib for advanced BCCs by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). A subsequent large safety study of vismodegib enrolled 1,227 patients with locally advanced or metastatic BCC (STEVIE).[83] The interim analysis confirmed the previous results with an objective response seen in 302 of 453 (66.7%) patients with locally advanced disease, of which half were complete responses. Of the 29 patients with metastatic BCC the response rate was 37.9% (two complete and nine partial responses). No previously unreported treatment-related adverse events have been observed in this safety study.

More recently, another hedgehog inhibitor, sonidegib, was evaluated in a multicenter, randomized, double-blind phase II trial (BOLT).[84] This study compared two different dosages of sonidegib (200 mg or 800 mg orally daily) using a primary endpoint of objective response. Twenty of 55 patients (36%) receiving sonidegib at a dose of 200 mg and 39 of 116 patients (34%) receiving sonidegib at a dose of 800 mg achieved an objective response. The 200-mg dose was better tolerated compared to the 800-mg dose, with treatment discontinuations in 22% and 36% of the treated patients in each dosing group, respectively. Only typical adverse events specific for sonic-hedgehog inhibitors have been observed in this trial. These results led to the FDA and EMA approval of sonidegib at a dose of 200 mg daily for patiens with locally advanced and metastatic BCC. There are no clear differences between vismodegib and sonidegib in terms of response rates and tolerability.

Although hedgehog inhibitors provide responses in roughly 60% of patients with unresectable BCCs and multiple BCCs from the BCC syndrome, including approximately 30% with complete responses, many patients discontinue treatment despite ongoing response because of toxicities, mainly fatigue, dysgeusia, and muscle cramps. Because platinum-based chemotherapies and EGFR inhibitors are only occasionally used in BCC and do not achieve long-term benefit, there remains a critical need for better advanced BCC treatment.

The rationale to use PD-1 antibodies for BCCs is the known high mutational burden and a clear genetic UV signature.[85] Case reports on successful treatment with PD-1 antibodies in advanced BCCs have been published recently.[79,81] An expansion arm for patients with BCC with progression or intolerance of hedgehog inhibitor therapy has been recently initiated on the ongoing phase I study of REGN2810 in patients with advanced malignancies (NCT02383212).

Merkel Cell Carcinoma

Local, regional, and distant metastases are frequently observed in patients with MCC. For patients who are not good candidates for surgery or radiotherapy, systemic chemotherapy is typically administered based on the biologic similarity of MCC to small cell lung cancer in its aggressiveness and high (over 50% response rate) but short-term (average less than 6 months) responsiveness to platinum-based chemotherapies with or without radiotherapy. The advanced age and comorbidities of many patients with advanced MCC limit their tolerance of chemotherapy.

Two studies published in 2016 showed the effectiveness of immune checkpoint inhibitors for patients with advanced and metastatic MCC. Avelumab, an anti–PD-L1 monoclonal antibody, was investigated in a phase II trial for stage IV chemotherapy-refractory MCC and showed a response rate of 31.8% in 88 patients, with eight complete and 20 partial responses. Of interest, responses were ongoing in 82% of the patients at the time of analysis (median follow-up of 10.4 months).[86] Another phase II trial studied pembrolizumab, an anti–PD-1 antibody, in treatment-naive patients with MCC. Among 25 evaluable patients, 56% responded, including four complete responses. At a median follow-up of 33 weeks, only two of the 14 responders relapsed. Of interest, the responses were independent of the presence of the Merkel cell polyomavirus in tumor.[87]

These encouraging data led to a recent uptake of the available PD-1 antibodies pembrolizumab and nivolumab (not yet studied in MCC) as the new standard for advanced MCC.[88,89] It is very likely that these PD-1 (pembrolizumab)/PD-L1 (avelumab) antibodies will become the new backbone for development of even more powerful immunotherapy regimens, which may include radiotherapy and may be applied in the adjuvant setting, for this aggressive but highly immunogenic cancer.

CONCLUSION

The biologic and clinical heterogeneity of cutaneous malignancies and noncutaneous melanomas provide a number of unique opportunities and challenges for preclinical and clinical investigators. The differential response to molecularly targeted and immunomodulatory therapies provides the opportunity to assess variable biomarkers of sensitivity and mechanisms of primary and secondary resistance. The rarity of some of these malignancies, particularly in the advanced disease setting, is a challenge that investigators can overcome with growing awareness of these diseases and increasing collaboration between investigators. As described above, there are important advances being made in our understanding of the biology and treatment of patients with advanced extracutaneous melanomas and nonmelanoma skin cancers that will lead to improved outcomes for these patients.

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Operable Melanoma: Screening, Prognostication, and Adjuvant and Neoadjuvant Therapy

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OVERVIEW

The importance of reducing the numbers of patients with late-stage melanoma, identifying which patients are most likely to progress, and treating these patients at the earliest possible stage cannot be overemphasized. Improved screening of patients prior to diagnosis has the advantage of identifying early-stage disease that is for the most part treatable by surgical methods. The process of melanoma screening is rapidly evolving through population-based programs, mobile health technologies, and advanced imaging tools. For patients with newly diagnosed melanoma, accurately estimating disease prognosis has important implications for management and follow-up. Prognostic factors are individual host- or tumor-related factors or molecules that correlate with genetic predisposition and clinical course. These include clinical covariates and host and tumor proteomic/genomic markers that allow the prognostic subclassification of patients. Adjuvant therapy for high-risk surgically resected melanoma targets residual micrometastatic disease with the goal of reducing the risk of relapse and mortality. In the United States, three regimens have achieved regulatory approval for adjuvant therapy, including high-dose interferon alpha, pegylated interferon alpha, and ipilimumab at 10 mg/kg. Phase III trials have reported benefits in relapse-free survival (all regimens) and overall survival (high-dose interferon alpha and ipilimumab). The management of locally/regionally advanced melanoma may benefit from neoadjuvant therapy, which is the subject of several ongoing studies. Recent studies have shown promising clinical activity and yielded important biomarker findings and mechanistic insights.

Investigators in the field of melanoma research have recently developed effective targeted and immune therapies for advanced disease, creating an increased awareness for the role that melanoma can play as a model for the management of other cancers. As a model for cancer care, melanoma has several advantages. For the most part, the primaries are visible to the naked eye and can be easily removed, studied, followed for response to therapy, and used as an in vivo source of immune stimulation. Genetic and clinical risk factors for melanoma are well established, a clear causal environmental factor (ultraviolet radiation) is known for melanoma, and melanoma has a high mutational load. These characteristics allow melanoma to serve as a model cancer for the development and optimization of processes, technologies, and therapeutic regimens that will enhance screening, prognostication, and adjuvant/neoadjuvant therapy for melanoma. It is highly likely that these methods will prove useful for many other, less accessible tumors as well.

Screening is important because early detection of melanoma, like many cancers, is associated with substantial improvements in survival.[1,2] Because of the visibility of most melanomas on the skin, approximately 70% are detected prior to metastatic spread to lymph nodes or distant sites.[2] Screening programs have the potential to improve early detection and reduce mortality from melanoma. Successful screening requires transdisciplinary teams and approaches, including (1) population and public health teams to identify and reach the at-risk population; (2) mobile health technology teams to develop, test, and implement phone-based screening tools; and (3) imaging, computer vision, and photonics teams to enhance the sensitivity and specificity of melanoma identification. Through the use of these screening programs and methodologies, it may be possible to substantially reduce the number of individuals requiring further treatment, resulting in reduced morbidity and mortality and improved quality of life for the individual, and reduced costs to society as well.

Surgery remains the mainstay of curative treatment for patients with operable melanoma. Thereafter, patients are treated in a risk-adjusted way, largely based on the American Joint Committee on Cancer (AJCC) staging system and outcome of a sentinel lymph node biopsy. These practices have allowed the identification of different risk groups and have informed decisions on intensity of follow-up, adjuvant therapy, and involvement in clinical trials. Prognosis-driven clinical care has the major advantage of being robust and

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thoroughly validated, and these factors are generally able to be assessed at the time of diagnosis. Current prognostic discriminators tend to divide patients in broad groups and do not provide enough information to accurately predict the likely outcome on an individual patient basis. As an example, it is clear that sentinel node positivity confers a higher risk of recurrence than a negative sentinel node biopsy, yet the majority of patients who develop metastatic disease have had a negative sentinel node biopsy.[3]

Melanoma is a clear example of how understanding the molecular basis of the tumor and the interaction with the host (i.e., immune system and tumor microenvironment) has led to unprecedented advances in the treatment of advanced disease and the potential for similar benefits in the adjuvant setting. Large clinically annotated tumor banks of primary tumors are being interrogated to better understand the biology of melanoma, predict its behavior, and develop new preventative and adjuvant strategies.[4]

Systemic adjuvant therapy may benefit patients with resected melanoma who carry a high postoperative risk of relapse and death. Patients with melanoma AJCC stages IIB–IIC, III, or IV whose risk of mortality exceeds 35%–40% at 5 years have historically been categorized as high risk.[1] For these patients, residual micrometastatic disease believed to be the source of future disease recurrence may be eliminated with adjuvant therapy. Interferon alpha (IFN-α) has been extensively tested in randomized controlled trials (RCTs) of adjuvant evaluating multiple regimens varying by the formulation of interferon (IFN), dose level (high, intermediate, or low), treatment duration, and route of IFN administration. IFN was shown to have a consistent effect in reducing the risk of relapse across most adjuvant RCTs as well as in four major meta-analyses of IFN adjuvant trials. A reduction in mortality risk was only significantly shown in two of three Eastern Cooperative Oncology Group and U.S. Intergroup RCTs that investigated the 1-year high-dose interferon (HDI) regimen versus observation (E1684 trial) and the ganglioside GMK vaccine (E1694 trial). This overall survival (OS) advantage, although small, was also observed in the three largest meta-analyses of adjuvant IFN RCTs.

Ipilimumab at a dose of 10 mg/kg as adjuvant therapy has been shown to significantly reduce the risk of relapse and the risk of death in stage III melanoma, but with a relatively high risk of serious toxicities experienced at this dose. This is notable because the dose of ipilimumab approved for the treatment of inoperable metastatic melanoma is 3 mg/kg, which is almost half as toxic as the 10-mg/kg dose. The ongoing U.S. Intergroup Trial E1609 is currently testing ipilimumab at 3 mg/kg or 10 mg/kg compared with HDI among patients with stage III and IV melanoma and is expected to guide the field on the relative safety and efficacy of ipilimumab at 3 and 10 mg/kg versus HDI in the adjuvant setting. Adjuvant studies investigating PD-1 blockade or molecularly targeted therapy are either ongoing or have completed accrual. Ongoing neoadjuvant studies are also testing novel immunotherapeutic and molecularly targeted agents and combinations. Here, we review the latest updates in melanoma screening, prognostication, and adjuvant and neoadjuvant therapy. We also review the current evidence and identify what we feel to be the likely clinical developments in the next few years.

KEY POINTS

- **Various organizations generally agree that individuals who have an increased risk for melanoma should be screened regularly by a provider.**
- **There are a number of important clarifications of definitions and changes in some of the classifications in the forthcoming version 8 of the American Joint Committee on Cancer staging system of melanoma.**
- **Tumor gene expression profiling is becoming an important prognostic tool with promising emerging data but is not yet a standard of care.**
- **In the United States, three regimens have achieved regulatory approval for adjuvant therapy, including high-dose interferon alpha, pegylated interferon alpha, and ipilimumab at 10 mg/kg.**
- **The management of locally/regionally advanced melanoma may benefit from neoadjuvant therapy, which is the subject of several ongoing studies.**

SCREENING FOR PRIMARY MELANOMA

Screening Guidelines

The American Academy of Dermatology[5] (AAD) currently recommends that every individual perform a regular skin self-examination and that anyone who notices "any unusual spots on their skin, including those that are changing, itching, or bleeding, should make an appointment with a board-certified dermatologist" and that "…people with an increased risk of melanoma or a history of skin cancer should talk to a dermatologist to determine how often they should receive a skin exam from a doctor." The U.S. Preventive Services Task Force[6] concluded that "the current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults," but it also states that "This recommendation applies to asymptomatic adults who do not have a history of premalignant or malignant skin lesions. Patients who present with a suspicious skin lesion or who are already under surveillance because of a high risk of skin cancer, such as those with a familial syndrome (e.g., familial atypical mole and melanoma syndrome), are outside the scope of this recommendation statement." Furthermore, "For people aged 20 or older who get periodic health examinations, a cancer-related check-up should include health counseling and, depending on a person's age and gender, examinations for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, and ovaries…," according to an American Cancer Society[7] statement on screening that includes melanoma. International recommendations for melanoma screening exist for several countries, including the United Kingdom, Germany, the Netherlands, Australia, and New Zealand.[8-14] In general, these guidelines recommend a complete skin examination

by a medical provider every 3–12 months for individuals with an increased risk of skin cancer, including those with features such as a vulnerable phenotype (fair skin, freckles, red or blonde hair, numerous and/or atypical melanocytic nevi, etc.), a personal history of melanoma, a family history of melanoma or nonmelanoma skin cancer, actinic damage, or immunosuppression. The Royal Australian College of General Practitioners[15] suggests that regular screening be provided to individuals who have a sixfold or higher risk of melanoma and that those with average or moderate risk (two- to fivefold elevation) should be screened "opportunistically" when they are being seen for some other purpose by a medical provider. Taken together, these various organizations generally agree that individuals who have an increased risk for melanoma should be screened regularly by a provider.

Screening Methods

Despite general agreement that screening of high-risk patients is important, methods recommended for screening are not as uniform. The AAD[16] suggests screening individuals during a visit with a provider and also encourages its membership to participate in community-based free skin cancer screenings. Screenings may also be performed by primary care or nondermatologist specialty providers, but the rate of skin cancer screenings that occur in a nondermatologist clinic-based setting is low, at approximately 10%–15%.[17,18] As part of a basic dermatology curriculum, the AAD has an online learning module on performance of a total body skin examination, which includes examination of the entire skin surface (including the scalp, hair, nails, and mucous membranes of the eyes, mouth, anus, and genitalia; www.aad.org/education/basic-derm-curriculum/suggested-order-of-modules/the-skin-exam). Although this module is designed for medical providers, the AAD also has online resources and brochures to teach lay people how to perform a skin self-examination, which includes the same principles (www.aad.org/public/spot-skin-cancer/learn-about-skin-cancer/detect). Skin self-screening is important because approximately 53% of melanomas are detected by the patient. Interestingly, dermatologists detect melanoma at an earlier stage, but 80% of melanomas that are detected by dermatologists are seen incidentally rather than during a screening examination.[19] Overall, methods of comprehensive skin examination are accessible and can be readily applied to melanoma screening.

Detecting Suspicious Lesions

With respect to the identification of melanoma during a skin examination, the AAD has long promoted the ABCDs of melanoma, a mnemonic for visual signs that suggest a pigmented lesion is at risk for being melanoma, including asymmetry, border irregularity, color variation, and diameter greater than 6 mm.[20] The AAD has extended the ABCDs to include an E for evolution, to capture the fact that a changing lesion can be suspicious.[21] The ugly duckling sign has also gained acceptance as a clue to malignancy, capturing the concept that a pigmented lesion with a different clinical appearance relative to others on the same individual may be a more sensitive marker of melanoma than the ABCDEs.[22] In addition to these clinical tools for detecting suspicious lesions, dermoscopic evaluation, using polarized light and magnification, has been refined and has become an essential component of a good skin screening examination.[23] Multispectral and hyperspectral dermoscopy as well as in vivo confocal microscopy and optical coherence tomography are in development and may become next-generation gold standards for melanoma screening.[24,25] The final frontier may well be the application of machine learning and artificial intelligence to the problem, creating a more objective and reliable interpretation of digital images of nevi and melanoma that surpass that of the human eye.[26]

PROGNOSTIC FACTORS FOR PATIENTS WITH OPERABLE MELANOMA: WHAT IS NEW?

AJCC Staging

The AJCC staging for melanoma has been revised (cancerstaging.org/references-tools/deskreferences/pages/default.aspx) and version 8 will come into use on January 1, 2018. At the time of this writing, the survival outcomes data on which this revision is based have not yet been published. Notable changes for primary and locoregional disease include the following:

- All principal T-category tumor thickness ranges are maintained, but T1 is now subcategorized by tumor thickness strata at 0.8-mm thickness.
- The tumor mitotic rate was removed from staging criteria for T1 tumors.
- Sentinel lymph node tumor burden is not used to determine N-category group.
- Nodal disease is classified as clinically occult or clinically detected.
- Microsatellites, satellites, and in-transit metastases are clarified.
- The contribution of lactate dehydrogenase in designating the M subcategories is revised.

Clinical implications and likely developments. These revisions clarify several areas of uncertainty and make more accurate staging easier. The development of staging algorithms linked to outcomes data, readily accessible in the form of an app, will be a key resource for clinicians and patients. Further, investing in the discovery and validation of prognostic biomarkers will allow us to more accurately stage our patients and several exciting developments are emerging in this area as we summarize next.

Circulating Tumor Cells, Cell-Free DNA, and Circulating Tumor DNA

Techniques used to detect circulating tumor cells (CTCs) in the blood of patients with melanoma are based on the expression of melanocyte-specific markers, distinctive physical properties, or melanocyte-specific nucleic sequences.[27] Marker-based technologies have been shown to be prognostic in metastatic melanoma but are limited by the fact

that there is no single marker uniformly expressed in melanoma and that the number of CTCs is lower than in other tumors.[28] The isolation by size of epithelial tumor cells is a direct method for CTC identification and has been validated for melanoma but is labor intensive and operator dependent.[29] A major focus has been on the detection of CTCs by the analysis of mRNA melanocyte-specific transcripts; tyrosinase, Melan-A/Mart-1, gp-100, and the MAGE proteins are commonly used, with reverse transcription polymerase chain reaction. A number of studies examined this strategy in stage I–III melanoma.[30] In the Sunbelt trial, reverse transcription polymerase chain reaction was performed on peripheral blood mononuclear cells at baseline for 207 patients with stage III disease using four markers: tyrosinase, Melan-A/Mart-1, MAGE3, and gp-100. Baseline reverse transcription polymerase chain reaction status was not associated with substantial differences in outcomes.[31] Hoshimoto et al[32] evaluated patients with stage III disease entering a randomized adjuvant melanoma vaccine program. Samples were drawn only once after the radical surgery and CTCs were detected using a multimarker reverse transcription polymerase chain reaction. The presence of two or more positive biomarkers was significantly associated with shorter distant metastasis–free survival (hazard ratio [HR], 2.13; 95% CI, 1.20–3.76; p = . 009).

The analysis of cell-free DNA in plasma in the metastatic setting has been shown to be predictive of survival and can be used to monitor response to treatment and identify the emergence and mechanisms of resistance.[33] These techniques are being applied to high-risk patients with resected disease in the context of randomized adjuvant trials.

Clinical implications. The results of cell-free DNA analysis from large adjuvant trials are awaited.

Gene Expression Profiling

Gene expression profiling (GEP) to determine prognostic and predictive factors has enormous potential in both the metastatic and adjuvant settings. Several profiles have been identified but, apart from incorporation of the 15 gene–based DecisionDX-UM assay into the staging of uveal melanoma, none have yet received overwhelming support. DecisionDx-Melanoma is a GEP based on 28 genes and is available commercially. This assay was initially developed on a discovery panel of 107 cases with stage I–IV cutaneous melanoma and was expanded to a training set of 268 cases, including the discovery set.[34] A further 104 independent cases were then studied as validation. Patients were classified in a binary way as having either low risk (class 1) or high risk (class 2). GEP and AJCC stage were independent predictors of metastatic risk (HR, 9.55 vs. 5.40, respectively). A second study of the subgroup of 217 patients with a sentinel node (SLN) biopsy (58 SLN+ and 159 SLN−) showed that both SLN+ and GEP class 2 were important predictors of disease-free survival, distant metastasis-free survival, and OS.[35] In multivariate analysis, for each point, GEP had a higher HR and only GEP was notable for OS. The greatest discrimination was seen for the 42% of patients who had an SLN− biopsy but were identified as class 2 and had a 5-year OS of 55%. This was very similar to the 57% 5-year OS for the patients with a SLN+ biopsy who were identified as class 2. More recently, a study on a further 334 primary tumors in which 29% of patients went on to develop distant metastases reported that the sensitivity, specificity, and positive and negative predictive power of both SLN and GEP were very similar.[36] Of note, 13 of 83 patients with an SLN− biopsy (16%) went on to have a distant metastatic event, and 10 of these patients (77%) were class 2. The authors concluded that DecisionDX-Melanoma deserves prospective evaluation. This is a fair assessment.

The use of samples retrospectively identified to develop a molecular predictor is entirely justifiable, but there are many examples in which early results are not borne out in randomized trials. The recent failure of the MAGE3 ASCI vaccine for patients with stage III disease, and the failure of the molecular predictor to identify those likely to benefit, despite a very strong signal in a phase II study, is a salutatory lesson.[37] Furthermore, we must consider the consequences of adopting this technology. A validation study of the clinical impact on 156 patients reported that changes in management (e.g., changes in the use of imaging as follow-up, and changes in the frequency of clinical review) were observed for 82 patients (53%), with the majority of class 2 patients (77%) undergoing management changes compared with 37% of class 1 patients (p < .0001). The role of imaging in the follow-up of patients with melanoma remains unclear, and the variation in clinical guidelines reflects this. European Society for Medical Oncology guidelines indicate that there is currently no consensus on the frequency of follow-up examinations and the use of imaging techniques. The National Comprehensive Cancer Network guidelines advise considering imaging patients with stage IIB–IV NED. More important will be whether decisions on adjuvant therapy can be made on the basis of GEP, given that this has not been included as a stratification factor in the pivotal studies. Given the multitude of randomized controlled adjuvant trials that have been carried out in melanoma, there is an opportunity for independent validation of this technology in a randomized sample of patients.

Clinical implications. GEP is becoming an important tool for clinical decision making but is not yet a standard of care.

Vitamin D

Most human diets provide little vitamin D, so humans rely on synthesis from sunlight. Over the last 8 years, the role of vitamin D in melanoma has been increasingly recognized. Results from three large cohort studies indicate that vitamin D has an effect on both melanoma susceptibility and outcome.[38]

The initial report from the Leeds group described a prospective cohort study of 872 patients with a Breslow thickness greater than 0.75 mm.[39] Higher vitamin D levels at diagnosis were associated with a lower Breslow thickness (p = .002), were protective of risk of relapse (HR, 0.79; 95% CI, 0.6–0.96; p = .01) for a 20-nmol/L increase in serum level,

and were associated, to a lesser extent, with a reduced risk of death (HR, 0.83; 95% CI, 0.68–1.02). In multivariable analyses (adjusted for tumor thickness), death from melanoma was associated with a low vitamin D level at recruitment (< 20 nmol/L vs. 20–60 nmol/L; HR, 1.52; 95% CI, 0.97–2.40; p = .07) and smoking duration at diagnosis (HR, 1.11; 95% CI, 1.03–1.20; p = .009).

The Melan Cohort Study measured vitamin D levels for 1,171 patients.[40] The investigators found that vitamin D levels were inversely related to AJCC stage (p, .001), Breslow thickness (p < .001), and ulceration (p, .001). However, they found no association with risk of relapse. In a large study from MD Anderson Center, investigators prospectively collected samples from 1,042 patients with melanoma to assess C reactive protein (CRP) and vitamin D levels. After adjustment for age, sex, disease stage, blood-draw season, and log-transformed CRP, vitamin D levels remained significantly associated with outcome measures for OS (HR, 1.02; 95% CI, 1.01–1.04; p = .0051), melanoma-specific survival (HR, 1.02; 95% CI, 1.00–1.04: p = .048), and disease-free survival (HR, 1.02; 95% CI, 1.00–1.04; p = .0427). Similar results have been reported for smaller series of patients.[41,42]

Clinical implications. There is currently insufficient evidence to establish a cause-and-effect relationship between vitamin D and melanoma recurrence and death, or to define the potential mechanisms for such an effect. Nevertheless, recommendations to measure vitamin D levels at baseline and advise supplementation if they are low have been added to some national guidelines and do not seem unreasonable.

Other Prognostic Factors

Many other potential prognostic factors have been studied and some have made their way into clinical guidelines and clinical practice, despite a lack of randomized data. These include S-100β, melanoma inhibitory activity, CRP, lactate dehydrogenase, and serum cytokines.[43] In a retrospective study, investigators examined 127 patients with primary melanoma who were followed up with regular imaging and assessment of S-100β levels and subsequently had a recurrence of the disease.[44] Beyeler et al[44] reported that 37% of patients with recurrent disease had elevated S-100 at the time of recurrence, and it was the first indicator in 5.5%. Increased S-100β was more common for patients with regional nodal disease or metastatic disease than local recurrence or in-transit metastases. A further study of 296 patients with stage II or III disease in which metastasis occurred for 41% reported a sensitivity of detection of relapse of 29% for S-100β, 22% for melanoma inhibitory activity, and 2% for lactate dehydrogenase.[45] Serum S-100β protein was found to be an important prognostic marker among high-risk patients with melanoma participating in the E1694 adjuvant trial and may improve patient selection for adjuvant therapy.[43] Multiplex analysis of serum cytokines in high-risk patients treated with IFNα in the E1694 adjuvant trial showed that baseline proinflammatory cytokine levels may predict 5-year relapse-free survival (RFS) with IFNα.[46] A follow-up study reported a four-marker signature consisting of baseline serum tumor necrosis factor-RII, transforming growth factor-alpha, TIMP-1, and CRP that is prognostic of worse survival in high-risk surgically resected melanoma in the E1694 trial.[47] In addition, in the E1697 adjuvant trial, an early on-treatment (after 1 month of adjuvant IFNα) proinflammatory cytokine signature consisting of interleukin 2 receptor alpha, interleukin 12p40, and IFN predicted 1-year RFS with IFNα but not observation in intermediate-risk surgically resected melanoma.[48] Overall, some melanoma follow-up guidelines (e.g., National Comprehensive Cancer Network and National Institute for Health and Care Excellence) state that blood tests are not indicated in follow-up, whereas others (e.g., European Society for Medical Oncology) present the data but do not make a recommendation.

Clinical implications. Although lactate dehydrogenase has a defined role in the AJCC staging of melanoma, the roles of S-100β, MIA, CRP, and cytokine profiles remain unclear and unproven and efforts to validate them in the context of randomized studies (e.g., E1609 trial) are ongoing.

ADJUVANT AND NEOADJUVANT THERAPY OF MELANOMA

Randomized Clinical Trials of Adjuvant Therapy That Led to Regulatory Approval

The immunomodulatory effects of IFNα have been widely studied and include antiangiogenic activity, differentiation-inducing and proinflammatory effects, as well as direct antitumor proapoptotic and antiproliferative activity.[49] Studies testing IFNα at a high dose (> 10 MU/dose) as adjuvant therapy first included the North Central Cancer Treatment Group NCCTG 83-7052 study[50] and the Eastern Cooperative Oncology Group ECOG E1684 trial.[51] In the E1684 trial, the HDI regimen consisted of an intravenous induction phase administered at 20 MU/m^2 for 5 consecutive days a week for 4 weeks, followed by a subcutaneous maintenance phase at 10 MU/m^2 three times a week for 48 weeks. Eligibility criteria required regional elective lymph node dissection for patients without clinical evidence of nodal involvement. This study enrolled 287 patients and the majority had clinically detectable nodal disease or recurrent melanoma after prior surgery. The study was reported after a median follow-up of 6.9 years, showing that HDI improved both RFS and OS compared with observation. Five-year RFS was 37% (95% CI, 30%–46%) versus 26% (95% CI, 19%–34%) and 5-year OS was 46% (95% CI, 39%–55%) versus 37% (95% CI, 30%–46%) in favor of HDI.[52] The HRs and key findings are summarized in Table 1. In terms of toxicity, the incidence of grade 3 and 4 adverse events was 67% with HDI and two early hepatotoxicity grade 5 events were reported. The U.S. Food and Drug Administration approved HDI as an adjuvant therapy in 1995.[8] The E1690 trial investigated HDI and low-dose IFN for 2 years compared with postoperative observation was first reported after a median follow-up of 4.3 years. Five-year RFS was 44% with HDI, 40% with low-dose IFN, and 35% with observation.[53] Compared with observation, HDI significantly improved RFS (p = .03). On the other hand, no OS benefit was seen, with 5-year OS rates of 52%, 53%, and 55% with

TABLE 1. High-Risk Melanoma Adjuvant Trials Leading to Regulatory Approval in the United States

Study	Stage at Study Entry	Size	Adjuvant Regimen vs. Control	Median Follow-up at Reporting (Years)	Hazard Ratio				Key Findings
					RFS	p Value	OS	p Value	
E1684	T4, N+	287	HDI vs. Observation	6.9	0.61	.001	0.67	.01	Majority bulky nodal or recurrent disease
									Greatest benefit in high tumor burden (N1)
				12.6	0.72	.02	0.82	.18	At 12.6 years, competing causes of death may have affected OS analysis
E1690	T4, N+	642	HDI or LDI vs. observation	4.3	0.78	.05	1.0		Consistent RFS benefit
									Unlike E1684, E1690 did not require ELND
				6.6	0.81	.09	1.0		Cross-over of 38 Obs patients to HDI at nodal relapse
E1694	T4, N+	880	HDI vs. GMK vaccine for 96 weeks	1.3	0.67	.0004	0.72	.023	Minority bulky nodal disease
									Greatest benefit in lower tumor burden (T4, N−)
				2.1	0.75	.006	0.76	.04	RFS correlates with OS (as in E1684)
EORTC 18991	N1 (occult), N2 (bulky)	1,256	Pegylated IFN-α vs. observation	3.8	0.82	.011	0.98		RFS benefit seen in N1 (occult) but not in N2 (bulky) disease
				7.6	0.87	.055	0.96		Greatest benefit seen in N1 with ulcerated primary
EORTC 18071	N1,2,3 (except in transit)	951	Ipilimumab 10 mg/kg vs. placebo	5.3	0.76	.0008	0.72	.001	Consistent RFS and OS benefits
									Substantial toxicity at this dose requiring close follow-up and expertise in irAE management

Abbreviations: ELND, elective lymph node dissection; EORTC, European Organisation for Research and Treatment of Cancer; HDI, high-dose interferon; IFN-α, interferon alpha; irAE, immune-related adverse event; LDI, low-dose interferon; Obs, observation; OS, overall survival; RFS, relapse-free survival.

HDI, low-dose IFN, and observation, respectively (Table 1). It is noteworthy that unlike the E1684 trial, the E1690 trial did not require elective lymph node dissection, and a retrospective analysis showed cross-over of 38 patients at nodal recurrence from the observation arm to standard-of-care HDI adjuvant therapy. This cross-over may have affected the OS analysis, which is supported by the observation that OS in the observation arm of the E1690 trial was superior to that in the E1684 trial (median 6 vs. 2.8 years). U.S. Intergroup Trial E1694 followed and tested patients who received HDI versus the ganglioside vaccine GMK, which consisted of ganglioside GM2 coupled to keyhole limpet hemocyanin and was combined with the adjuvant QS-21. HDI was significantly better than GMK in regard to RFS (HR, 0.67) and OS (HR, 0.72) in the intent-to-treat analysis.[52,54] A pooled analysis of HDI trials with follow-up through April 2001 was later conducted and included the two observation controlled trials (E1684 and E1690). At a median follow-up of 12.6 years and 6.6 years for the E1684 and E1690 trials, respectively, HDI maintained substantial RFS benefits.[55] However, no substantial improvement in OS was seen. In the E1684 trial with the relatively very long follow-up in the intent-to-treat analysis of OS, competing causes of death were not accounted for and may have confounded OS data.[51,53-55]

In the European Organisation for Research and Treatment of Cancer EORTC 18991 trial, pegylated interferon alfa-2b was compared with observation as adjuvant therapy for patients with AJCC stage III melanoma.[22] The adjuvant 5-year subcutaneous regimen consisted of an induction phase (6 μg/kg a week for 8 weeks) followed by a maintenance phase (3 μg/kg a week). The study showed significant improvement in the primary endpoint of RFS (HR, 0.87; 95% CI, 0.76–1.00; p = .05; median follow-up 7.6 years) in favor of pegylated interferon alfa-2b, whereas no substantial differences in distant metastasis–free survival or OS were seen. In the subgroup analysis, patients with ulcerated primary melanoma and microscopic nodal metastasis appeared to derive the greatest RFS and OS benefits. The median duration of treatment was 14 months and the toxicity attrition rate was 37%. Four major meta-analyses of adjuvant IFN RCTs have been reported since 2002, and all have concluded that adjuvant IFN therapy has substantial RFS benefits.[56-58] The

largest and most recent was the Cochrane Analysis of Adjuvant Melanoma Trials, which included 17 RCTs and 10,499 participants.[58] This meta-analysis estimated HRs of 0.83 (95% CI, 0.78–0.87) and 0.91 (95% CI, 0.85–0.97) in terms of RFS and OS, respectively.

Ipilimumab is an anti-CTLA4 fully humanized immunoglobulin G1 kappa monoclonal antibody. In the treatment of patients with inoperable sage III/IV melanoma, ipilimumab significantly improved OS when tested at 3 mg/kg versus the Gp100 peptide vaccine,[59] and at 10 mg/kg combined with dacarbazine versus dacarbazine alone.[60] EORTC 18071 was an adjuvant trial of the 10-mg/kg dose of ipilimumab versus placebo for patients with resected stage III melanoma.[61] This trial demonstrated significant benefits in RFS and OS with adjuvant ipilimumab. At a median follow-up of 5.3 years, median RFS was 27.6 months (95% CI, 19.3, 37.2) versus 17.1 (95% CI, 13.6, 21.6), with an HR of 0.76 (95% CI, 0.64, 0.89; p = .0008). For OS, the HR was 0.72 (95% CI, 0.58, 0.88; p = .001). Five-year survival rates were 65% versus 54% for OS and 41% versus 30% for RFS. Safety results demonstrated a high rate of immune-related adverse events, including a 41% rate of grade 3/4 immune-related adverse events and five grade 5 events secondary to immune-related adverse events after treatment with ipilimumab.

The Leading Ongoing Adjuvant Studies in High-Risk Resected Melanoma

U.S. Intergroup Trial E1609, lead by the Eastern Cooperative Oncology Group/American College of Radiology Imaging Network, is testing ipilimumab at 3 mg/kg or 10 mg/kg as adjuvant therapy in high-risk resected stage III (IIIB, IIIC) and IV (M1a, M1b) melanoma versus HDI (NCT01274338). This study has two coprimary endpoints (RFS and OS) and is trying to answer important questions related to the relative safety of ipilimumab at 3 and 10 mg/kg as well as their efficacy relative to HDI. Early results from this trial are expected to be presented during the 2017 ASCO Annual Meeting. CheckMate 238 is an adjuvant trial testing PD-1 blockade with nivolumab versus 10 mg/kg of ipilimumab and accrual was completed in 2015 (NCT02388906). KEYNOTE-054 is testing adjuvant therapy with pembrolizumab compared with placebo (NCT02362594). U.S. Intergroup Trial S1404 is comparing adjuvant therapy with pembrolizumab to the control arm of standard adjuvant therapy with HDI or ipilimumab at the dose of 10 m/k. Adjuvant trials of molecularly targeted therapy in BRAF-mutant high-risk resected melanoma are also ongoing and have completed accrual. These include COMBI-AD, which is comparing the combination of dabrafenib and trametinib to placebo (NCT01682083), and BRIM8, which is comparing vemurafenib to placebo (NCT01667419).

Neoadjuvant Therapy of Locally and Regionally Advanced Melanoma

Neoadjuvant therapy has the potential to significantly improve the clinical outcome of patients with locally/regionally advanced melanoma, particularly in this era of newer and effective targeted and immunotherapeutic agents. Such studies also provide access to biospecimens before and during therapy, allowing for the conduct of biomarker and mechanistic studies that may have an important impact in drug development. On the other hand, neoadjuvant therapy carries the risk of toxicity from systemic therapy and the risk of delaying the indicated surgical procedure, although the chances of cure with surgery alone are low in patients who may be eligible for neoadjuvant therapy. Previous neoadjuvant studies tested chemotherapy with temozolomide in a phase II study, in which oral temozolomide was given at 75 mg/m^2 per day for 6 weeks of an 8-week cycle with two cycles administered preoperatively. The clinical activity was limited and similar to the response rates in metastatic disease.[62] Biochemotherapy was tested in two studies in the neoadjuvant setting. The biochemotherapy regimen consisted of cisplatin, vinblastine, dacarbazine, interleukin-2, and IFNα.[63,64] The response rates approached 40%–50%, including pathologic complete remission of 6%–11%. However, biochemotherapy therapy was subsequently abandoned after the results of RCTs of metastatic disease showed no survival advantage over chemotherapy.[65] Neoadjuvant immunotherapy studies in melanoma reported to date included HDI, 10 mg/kg of ipilimumab, and the combinations of HDI with ipilimumab (3 or 10 mg/kg), nivolumab with ipilimumab, and dabrafenib with trametinib.[66-68] In the neoadjuvant HDI study, among 20 patients, 3 had pathologic complete remission and the overall clinical response rate was 55%. Substantial nodal infiltration by CD3+/CD11+ monocyte-derived dendritic cells was found among responders.[69] In the neoadjuvant ipilimumab study, no pathologic complete remission was seen and the clinical response rate approached 10%. Mechanistically, substantial findings were reported, including the impact of ipilimumab on downregulating myeloid-derived suppressor cells and inducing tumor-specific T-cell responses and T-cell memory, found to be associated with clinical benefit.[70] Notably, the combination of HDI and ipilimumab yielded a 39% rate of pathologic complete remission or microscopic residual disease after 6 weeks of neoadjuvant therapy. Although 10 mg/kg of ipilimumab was associated with increased toxicity compared with 3 mg/kg, the clinical activity was similar.[66] These studies yielded evidence of promising clinical activity and important biomarker and biologic findings that further illuminate the underlying mechanisms of action.[70,71] These findings support later combination studies of IFNα and pembrolizumab and a modified regimen of ipilimumab and nivolumab (both ongoing). Studies of other molecularly targeted and immunotherapeutic agents and combinations are ongoing in the neoadjuvant setting, and updates from ongoing studies are expected to be presented during the annual meeting.

CONCLUSION

Screening for melanoma includes performing a clinical screening examination among appropriate high-risk individuals, applying a rigorous method of examination, and

using strategies and technologies to enhance detection of suspicious melanocytic lesions before metastasis. The field of biomarkers of prognosis is progressing at a rapid pace, with several important leads reported in recent years. Large validation studies are needed, given the important implications that such biomarkers may have in the care of patients with melanoma. As adjuvant therapy for high-risk resected melanoma, substantial benefits were shown with IFNα (HDI, pegylated IFN) and ipilimumab in RCTs. Phase III trials have reported benefits in RFS (all regimens) and OS (HDI and 10 mg/kg of ipilimumab). The toxicity of ipilimumab is dose dependent; after the recent regulatory approval of adjuvant ipilimumab at 10 mg/kg, it has become urgent to evaluate the relative safety and efficacy of ipilimumab at the two dose levels that were tested in the E1609 trial. Other ongoing adjuvant trials are testing BRAF/MEK inhibitors for patients with BRAF mutant melanoma and anti–PD-1 antibodies, with early results expected in the coming 2–3 years. Neoadjuvant therapy of locally/regionally advanced melanoma offers the potential to significantly improve the clinical outcome of these patients and several studies are ongoing in this area.

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Systemic Therapy Options for Patients With Unresectable Melanoma

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OVERVIEW

There has been a therapeutic revolution in the treatment of metastatic melanoma over the past decade. Patients presenting with inoperable disease have several therapeutic options, which can include both targeted and immune therapy. Immune checkpoint inhibitors have demonstrated an improvement in overall survival and led to some durable responses. However, toxicity, especially in combination regimens, can be severe. Adverse events should be anticipated, diagnosed as early as possible, monitored, and managed. Combination BRAF and MEK inhibition has also been shown to improve overall survival in patients with V600E-mutated melanoma. Responses to therapy are often rapid, and treatment is not associated with immune-related adverse events. Current trials are under way to determine which option is optimal as frontline therapy for patients with V600E melanoma. In patients with progressive disease despite standard therapies, clinical trials are recommended. There are several promising agents in development.

The MAPK or ERK pathway has been well described, and a detailed discussion of the pathway is beyond the scope of this review. However, as an overview, Fig. 1A outlines the ERK pathway in a normal cell. A receptor tyrosine kinase is activated by binding of its ligand, which ultimately leads to RAS activation and the generation of RAS-GTP. This promotes RAF hetero- and homodimerization among the three isoforms of RAF: A-RAF, B-RAF, and C-RAF. In Fig. 1A, a B-RAF/C-RAF heterodimer is shown, along with RAF monomers. The RAF dimer can activate MEK, which activates ERK, leading to cellular proliferation through several pathways. ERK activation also leads to negative feedback mediated through DUSP6, which suppresses RAS-GTP formation and serves to modulate the activity of the pathway under normal circumstances.

TARGETED THERAPY

General Pathway Overview

In a melanoma cell harboring a BRAF V600E mutation, the pathway is quite different. The V600E mutant BRAF is sufficient to hyperactive MEK even as a monomer. This leads to hyperactivated ERK and cellular proliferation. It also leads to strong negative feedback on to RAS, which helps prevent dimerization of RAF molecules.

Thus, in BRAF V600-mutated melanoma cells, ERK activation is driven by BRAF V600 monomers, whereas in the normal cell, ERK activation takes place through RAF dimers. This distinction is critical and explains the unique therapeutic index of RAF inhibitors. In a BRAF V600E–mutated melanoma cell, the RAF inhibitor binds to the monomers and inhibits their function. This suppresses MEK and ERK and leads to cell death. However, in a normal cell, when a RAF inhibitor binds to one of the RAF molecules of a dimer, it causes activation of the other RAF molecule, which leads to some increase in ERK activation. This paradoxical activation is thought to play a role in the cutaneous toxicities caused by RAF inhibitors. RAF inhibitors have also been found to increase proliferation of malignancies driven by RAS mutations,[1,2] underscoring the importance of verifying that the melanoma harbors a BRAF V600 mutation before treating with a RAF inhibitor.

Medical Efficacy of RAF Inhibitors and RAF/MEK Combinations

Two RAF inhibitors are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of BRAF V600-mutant melanoma: vemurafenib and dabrafenib. Both drugs have been shown in randomized trials to have superior progression-free survival (PFS) compared with dacarbazine. The improvements in median PFS were 5.5 months[3] and 5.1 months,[4] respectively. However, the estimated PFS at 1 year was less than 30% for vemurafenib (not reported for dabrafenib). This highlights the observation that BRAF V600E–mutated melanomas quickly develop resistance to single-agent RAF inhibitors. We now know that common mechanisms of resistance are amplification and/or overexpression of the mutated *BRAF* allele, a splicing variant of mutated BRAF that permits dimerization with

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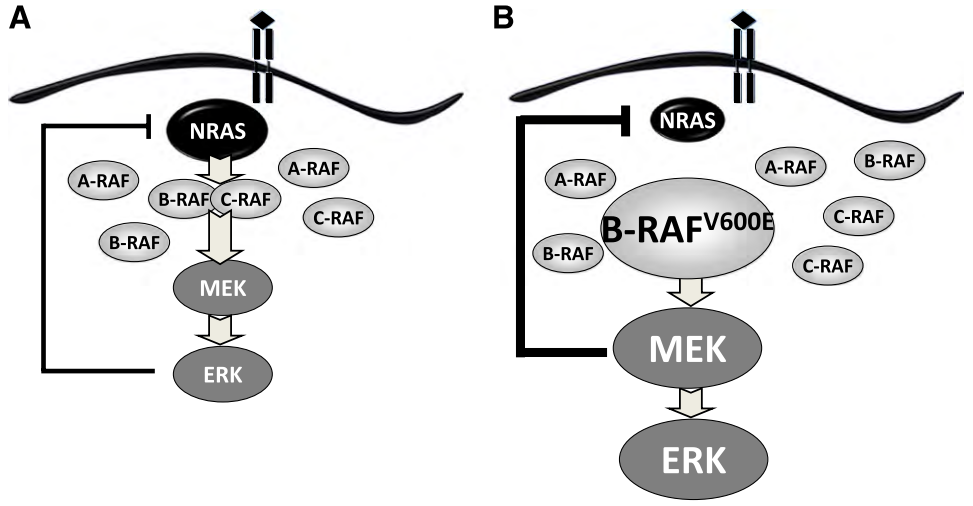
FIGURE 1. MAPK Kinase Pathway



In a BRAF wild-type cell (A), activation of a receptor tyrosine kinase at the cell surface results in NRAS activation. This promotes RAF activation by homo- and heterodimerization, leading to MEK and ERK activation. Negative feedback mechanisms serve to modulate NRAS activation and thus output through the pathway. In a BRAF V600E–mutated melanoma cell (B), MEK is activated directly by BRAF V600E monomers. This leads to hyperactivation of ERK and strong negative feedback, which inhibits RAF dimerization.

wild-type RAF protein even in the absence of activated RAS, and the appearance of an upstream activating *NRAS* mutation.[5,6]

In an attempt to foil the melanoma cell's ability to develop resistance, RAF inhibitors have been combined with MEK inhibitors. Two different RAF inhibitor/MEK inhibitor combinations are currently FDA approved for use in patients with melanoma harboring a BRAF V600 mutation: dabrafenib/trametinib and vemurafenib/cobimetinib. In randomized phase III trials comparing the combination with the RAF inhibitor alone, these combinations have shown median improvements in PFS of 1.2 months[7] and 5.1 months,[8] respectively (Table 1). Although these differences were statistically significant, the magnitude of benefit was perhaps disappointing. Despite this, both combinations were associated with improved overall survival (OS) compared with RAF inhibitor alone. The improvement in OS despite a relatively minor improvement in PFS, especially for the dabrafenib/trametinib combination, suggests the possibility that a minority of patients experience prolonged PFS. This is supported by the PFS curves from the dabrafenib/trametinib trial, which do indeed suggest a plateau at about the 18-month time point.[7] A plateau in the PFS curve from the vemurafenib/cobimetinib trial was less evident, but there was minimal follow up beyond 18 months. Therefore, the data are consistent with the notion that the combination of a RAF and MEK inhibitor can lead to prolonged PFS in a minority of patients harboring a BRAF V600E mutation and that this can improve OS. As result, standard of care is currently a RAF/MEK inhibitor combination rather than a single-agent RAF inhibitor. A randomized trial testing a third RAF/MEK inhibitor combination, encorafenib/binimetinib, has been completed. Array Biopharma announced in a press release in September 2016 that combination encorafenib plus binimetinib had a PFS of 14.9 months as compared to 7.3 months for vemurafenib.

KEY POINTS

- **Immune checkpoint inhibitors have demonstrated an improvement in overall survival and led to some durable responses.**
- **Combination BRAF/MEK inhibition leads to rapid responses and has shown an improvement in overall survival.**
- **Both combination BRAF/MEK inhibition and immunotherapy are first-line options for patients with BRAF-mutated V600E melanoma.**
- **Adverse events should be anticipated, diagnosed as early as possible, monitored, and managed.**
- **There are several promising agents in development targeting both BRAF resistance mechanisms and immune checkpoint agonists and antagonists.**

Toxicity of RAF/MEK Inhibitor Combinations and Management Guidelines

It is not surprising that, in general, RAF inhibitor plus MEK inhibitor combinations are associated with more toxicity than single-agent RAF inhibitors. Compared with dabrafenib alone, the dabrafenib/trametinib combination was associated

TABLE 1. Improvement in PFS and OS With RAF/MEK Inhibition Compared to RAF Inhibition Alone

	PFS (Months)	OS (Months)	Reference
Dabrafenib/ Trametinib	1.2	6.4	Long et al[7]
Vemurafenib/ Cobimetinib	5.1	4.9	Ascierto et al[8]

Abbreviations: OS, overall survival; PFS, progression-free survival.

with a higher incidence of fever, chills, and diarrhea.[7] However, there were some adverse events (AEs) that were less frequent with the combination, such as arthralgia, hand-foot syndrome, alopecia, keratoacanthoma, and cutaneous squamous cell carcinoma, which are thought to be mediated by paradoxical activation by RAF inhibitors and thus blocked by MEK inhibition. Overall, 7% of patients in the dabrafenib group had to discontinue therapy because of AEs, compared with 11% in the combination group. Fever and chills were the most common reasons for discontinuing the dabrafenib/trametinib combination. Experience has shown that this toxicity needs to be managed actively by discontinuing treatment until the fever has resolved. Usually treatment can be restarted, but over the first 1 to 2 months, several drug holidays may be needed. Also, nonsteroidal anti-inflammatory drugs or low-dose prednisone (5–10 mg/day) can be helpful.

Similarly, the combination of cobimetinib/vemurafenib was associated with more toxicity than vemurafenib alone. Patients receiving the combination were more likely to experience nausea, vomiting, photosensitivity, and elevations in transaminases. Patients receiving cobimetinib/trametinib also experienced more creatine phosphokinase elevations with decreased ejection fractions and serous retinopathy, both of which are considered MEK inhibitor–associated AEs. Distinct from dabrafenib/trametinib, the cobimetinib/vemurafenib combination is not associated with pyrexia. However, similar to the dabrafenib/trametinib experience, AEs led 14% of patients to discontinue combination therapy, compared with only 7% of patients receiving vemurafenib alone. Also, similar to dabrafenib/trametinib, the combination of cobimetinib/vemurafenib was associated with a lower incidence of arthralgia, alopecia, keratoacanthoma, and cutaneous squamous cell carcinoma.

Treatment With BRAF/MEK Inhibitors

First-line therapy for patients with BRAF V600E–mutated melanoma. Patients with melanoma who harbor a BRAF V600E mutation have two first-line treatment options: RAF/MEK inhibition therapy and checkpoint inhibition. Both are known to have high response rates and to be associated with improved OS. One of the remaining questions in the field is which treatment should be recommended first? Clinical trials combining checkpoint inhibitors with MAPK pathway inhibitors are under way, but until these trials provide data for guidance, first-line therapy for most patients in this situation will be either RAF/MEK or checkpoint inhibition.

Checkpoint inhibitors appear to lead to a higher percentage of durable responses, and for this reason, checkpoint inhibitor therapy is often selected as the first-line therapy, even if the melanoma is known to harbor a BRAF V600E mutation. On the other hand, there are clinical situations in which a RAF inhibitor may be preferred as first-line therapy, such as a patient with rapidly progressive disease or an active autoimmune disease or a patient who requires immunosuppressive therapy for some other reason. At present, patients with brain or bone metastases are often offered RAF inhibitors as first-line therapy because RAF inhibitors are known to have activity in these disease sites, while the response rate to checkpoint inhibitors at these sites is not well characterized. However, this could change as additional studies are performed. Ipilimumab was shown to have a 22% response rate in patients with brain metastases not on steroids,[9] and a recent small trial with pembrolizumab in patients with melanoma with brain metastases reported responses in four of 16 patients.[10] The response rate of brain metastases to the nivolumab/ipilimumab combination has not yet been reported, but an ongoing study is evaluating this concept (CheckMate 204).

Treatment of melanoma with non-V600 BRAF mutations. Clinical research in melanoma has naturally focused largely on the V600E and K mutations, as these are by far the most common BRAF mutations. In addition, these mutations result in the highest ERK activation and, through feedback mechanisms, presumably are the most suppressive of RAS-GTP. This ensures that RAF remains monomeric and, as a result, highly susceptible to inhibition by vemurafenib or dabrafenib. However, as more melanoma tumors are sequenced by next-generation sequencing techniques, we are learning that many melanomas harbor BRAF mutations at codons other than 600. Figure 2 shows data from 167 patients with melanoma in the MSKCC cBioPortal database[11,12] in whom a BRAF mutation was identified. In 33% of cases, the mutation was not at codon 600. Many of these mutations were within the kinase domain, and some are known to be oncogenic, although the level of ERK activation is thought to be lower than for a V600E mutation.[13] Most of the other BRAF mutations are of unknown oncogenic potential, and many may be simply passenger mutations.

It is common for these less activating non-V600 BRAF mutations to be found with concomitant RAS mutations or loss of NF1. This is consistent with in vitro data showing that cells harboring these mutations are not sensitive to RAF inhibitors.[13] Treatment of these tumors with pathway inhibitors remains a subject for clinical trials. These cells may be sensitive to MEK inhibitors but will probably require inhibition at more than one level of the pathway.

IMMUNOTHERAPY WITH CHECKPOINT INHIBITORS

General Pathway PD-1/CTLA-4 Overview

CTLA-4 and PD-1 (CD279) belong to the so-called immune checkpoint molecules, meaning that they physiologically participate in the negative control of the immune response. These molecules exert their action at different levels. CTLA-4 is expressed on T cells and regulates the early stages of T-cell activation in the lymphoid organs. Approximately 22 days after naive T cells have been activated by the binding of their antigen, expression of CTLA-4 counteracts the costimulation interaction replacing CD28 and binding to both CD80 and CD86 with a much higher affinity than that of CD28, thus ending the process of T-cell activation.[14,15] TREG cells also express CTLA-4 and are susceptible to antibody-dependent

cell-mediated cytotoxicity after the binding of anti-CTLA-4 antibody to Fcγ receptors expressed on tumor-associated monocytes or macrophages.

Thus, the anticancer effect of the blockade of CTLA-4 results from the enhancement of T-cell activation in lymphoid organs, as well as from TREG depletion in the tumor microenvironment. As a result of this nonspecific activation of the immune response, by broad effector T-cell activation and TREG depletion, especially given that TREG cells have a critical role in self-tolerance, a broad spectrum of immune-related AEs was expected. Indeed, in murine models, knocking out CTLA-4 induced lymphoproliferation and serious autoimmune diseases. Certain polymorphisms in the human CTLA-4 gene are associated with an increased risk of autoimmune diseases,[16,17] including rheumatoid arthritis, Addison disease, celiac disease, Crohn disease, type I diabetes, and thyroid disorders.

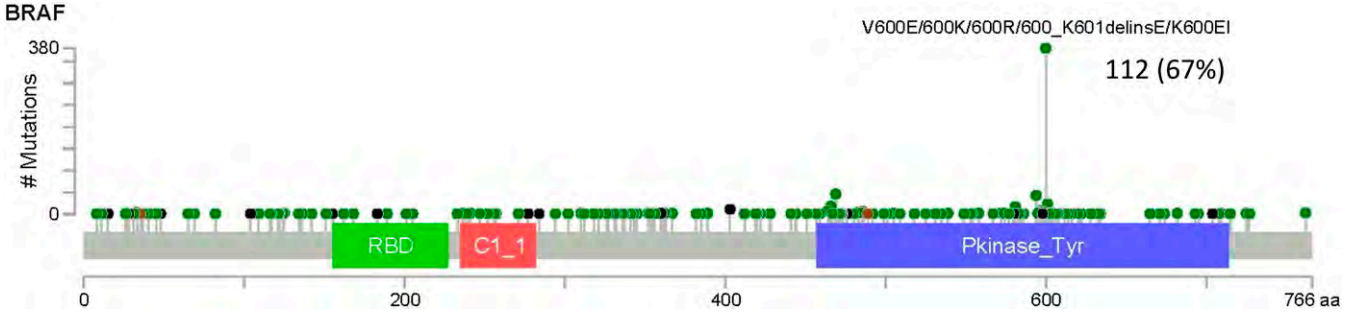
PD-1 is also negative regulator of T-cell activity but acts mainly within the peripheral tissues. In the context of cancer, PD-1 is expressed on activated tumor-infiltrating lymphocytes (mainly $CD4^+$ T cells) as well as on B cells, natural killer cells, monocytes, and dendritic cells.[18] When engaged with one of its two ligands, PD-1 phosphorylation activates intracellular phosphatases that lead to a dramatic downregulation of antigen receptor signaling with decreased proliferation as well as decreased cytokine production. The two PD-1 ligands are PD-L1 (B7-¹H and CD274) and PD-L2 (B7-DC and CD273).[19] PD-L1 can be expressed on tumor cells and is induced by interferon gamma but can also be expressed within the tumor microenvironment by immune-infiltrating cells, including infiltrating macrophages. PD-L2 is expressed by antigen-presenting cells. In preclinical models, inhibition of the interaction between PD-1 and PD-L1 generates antitumor activity and enhances autoimmunity with an autoimmune phenotype distinct from that observed in mice that are deficient in CTLA-4.[20]

Review of Clinical Efficacy Data

Single-agent CTLA-4 inhibition: ipilimumab. CTLA-4 was the first immune checkpoint receptor to be clinically targeted. Initially two fully humanized monoclonal antibodies directed against CTLA-4 were evaluated in patients with metastatic melanoma, an IgG1, ipilimumab, and an IgG2, tremelimumab. Only ipilimumab development was successful in this population of patients, with the demonstration of a significant survival benefit compared with a peptide-base vaccine in pretreated patients.[21,22] Although the response rate was low, about 10%, and median PFS was only 2 to 3 months, the reduction of the risk for death was significant. A second phase III trial, comparing ipilimumab in combination with dacarbazine versus dacarbazine monotherapy, demonstrated a similar survival benefit, with a significant advantage over chemotherapy.[23] However, the combination of dacarbazine did not seem to add any benefit, and the hepatotoxicity was higher, so this combination was not pursued. Ipilimumab is given in four infusions at 3-week intervals, and the two major phase III trials used two different doses of ipilimumab, 3 and 10 mg/kg. The drug was approved in 2011 at the lower dose of 3 mg/kg, but a recent trial demonstrated an OS benefit of the dose of 10 mg/kg compared with 3 mg/kg).[24] However, the toxicity is also higher with a higher dose. With the hindsight we have today, we know that the survival curve of ipilimumab reaches a plateau after 3 years, with a stable survival rate of 23% to 25%, and that patients who respond to ipilimumab and are alive at 3 years have a high probability of remaining alive. Thus we can reasonably hope that some patients who were treated several years ago are definitely cured. Both ipilimumab and tremelimumab are currently being actively investigated for the treatment of other cancer types.

Single-agent anti–PD-1 inhibition: nivolumab and pembrolizumab. The human and humanized PD-1–blocking monoclonal IgG4 antibodies nivolumab and pembrolizumab, respectively, were rapidly and successively developed for patients with metastatic melanoma in recent years. Pembrolizumab was evaluated in KEYNOTE-001, a multicohort phase I study that enrolled 655 ipilimumab-naive or ipilimumab-pretreated patients, and was approved by the FDA on the basis of the results of this study in September 2014.[25,26] KEYNOTE-002, a phase II trial in patients pretreated with ipilimumab, and KEYNOTE-006, a large phase III trial testing two doses of pembrolizumab compared with

FIGURE 2. BRAF Mutations Among 167 Patients With Melanoma With BRAF Mutations on the MSKCC cBioPortal[11,12]



Mutations at codon 600 accounted for 67% of BRAF mutations, but gene alterations were seen throughout the gene, as depicted by the green circles. Red arrows indicate alterations that are known to be oncogenic. All are within the kinase domain. Data are lacking regarding most of the other mutations shown.

ipilimumab, confirmed the spectacular results of the phase I study.[27,28] When analyzing these studies together, we observed an objective response rate of about 35% to 40%, median PFS of about 6 months, and median OS of about 2 years with pembrolizumab.

Nivolumab followed a parallel and similarly successful development in patients with metastatic melanoma, with a large phase I study enrolling 117 patients,[29,30] a phase II study, and the phase III Checkmate 037 trial comparing nivolumab with chemotherapy in patients pretreated with ipilimumab.[31] All these trials were largely positive and confirmed the benefit of nivolumab, with response rates, median PFS, and OS similar to those seen in pembrolizumab-treated patients. Nivolumab obtained FDA and European Medicines Agency approval in 2014 and 2015, respectively.

Combination PD-1/CTLA-4 inhibition: ipilimumab and nivolumab. Because CTLA-4 and PD-1 have distinct mechanisms of action, combined blockade of these two receptors was evaluated in patients with metastatic melanoma. In a phase I trial combining ipilimumab and nivolumab, promising results were observed in a cohort of 53 patients, with response rates of about 50% and dramatic and rapid tumor regression in most of the responders.[32] In a double-blind, randomized phase II study, Checkmate 069, evaluating ipilimumab and nivolumab compared with ipilimumab and in a phase III trial evaluating the same combination compared with each of the agents separately, a similarly high response rate and prolonged PFS of close to 1 year were demonstrated.[33,34] Results on OS will soon be available.

Toxicity of Immunotherapy and Management Guidelines

Checkpoint inhibitors represent a revolution in the treatment of metastatic melanoma and more generally in the field of cancer, with several FDA and European Medicines Agency approvals obtained and many others pending in various cancer types. However, their use is not devoid of AEs, and as expected from their mechanisms of action, most of these AEs result from an exacerbated immune activation, some of them mirroring genuine autoimmune diseases. The term immune-related AEs (irAEs) is now commonly used to describe these AEs.

Grade 3 to 5 AEs are more frequent with ipilimumab than with anti–PD-1 monotherapies, 23% to 25% versus 13% to 15%, respectively. When used in combination, toxicities are much more frequent and severe, with AEs of any grade observed in almost every patient and grade 3 to 5 AEs in 55% to 60%, and 40% of patients interrupting treatment of toxicity.[35] Because some of these irAEs can be severe and even fatal, their early diagnosis and management is of paramount importance.

Ipilimumab. The most frequent AEs associated with ipilimumab are pruritus (in 25%–35% of patients), diarrhea (in 23%–33% of patients), rash (in 15%–33% of patients), and fatigue (in 15%–28% of patients). Grade 3 and 4 AEs are reported in 20% to 27% of patients, the most frequent being diarrhea (in 3%–6% of patients).[35] At the dose of 10 mg/kg, AEs are more frequent, as recently published in a European Organisation for Research and Treatment of Cancer trial evaluating ipilimumab 10 mg/kg in the adjuvant setting in a population of patients at high risk for relapse, in which five patients died in relation to the treatment.[36]

Enterocolitis and/or diarrhea. Colitis is reported in 8% to 22% of patients treated with ipilimumab, but the diagnosis of colitis is not standardized and does not always rely on a colonoscopic examination. The incidence of diarrhea and colitis increases with the dose of ipilimumab.[35] Grade 3 diarrhea is the most frequent AE leading to discontinuation of treatment by patients receiving ipilimumab. Arthralgia is observed in up to one-fourth of patients presenting with ipilimumab-induced enterocolitis. Endoscopic investigations show erythema, mucosal friability, or ulceration, predominantly in the distal colon. Histologic features of ipilimumab-induced colitis include neutrophilic inflammation, lymphocytic infiltration, or both.[37] Inflammation of the oral mucosa, esophagus, stomach, duodenum, and ileum might also occur. Several lines of evidence suggest that ipilimumab-induced enterocolitis is a peculiar form of inflammatory bowel disease with features of ulcerative colitis (inflammation predominating in the colon) and Crohn disease (reflecting possible involvement of the distal ileum and granuloma).[38,39] Fatal bowel perforation can rarely occur, especially if the colitis is not readily recognized and treated.

Skin-related events. Skin-related irAEs occur in 43% to 45% of patients receiving ipilimumab, with nonspecific maculopapular rash, pruritus, and vitiligo being the most commonly observed skin AEs. They are usually of low grade and do not impair treatment continuation, although rare cases of patients presenting with life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.[35]

Endocrine-related events. Ipilimumab can affect the endocrine system, especially the pituitary gland, and 6% to 8% of patients present with panhypopituitarism or isolated anterior pituitary hormone deficiency. Symptoms can be quite pleomorphic and include fatigue, headache, vertigo, memory difficulties, and visual disturbances that can be confounded with brain metastases. When an endocrinopathy is suspected, a complete endocrine work-up is necessary to determine pituitary, thyroid, adrenal, and gonadal functions, and imaging of the brain and pituitary gland can also be performed to look for an enlarged pituitary gland and potential brain metastases.[35,40]

More rarely, irAEs such as pancreatitis, hepatitis, neurologic toxicities including Guillain-Barré syndrome, meningoradiculoneuritis, granulomatous inflammation of the central nervous system, and aseptic meningitis; ocular toxicities including episcleritis, uveitis, and autoimmune polymyositis; and immune cytopenia have been reported.[35,41]

Anti–PD-1 antibodies. Anti–PD-1 monotherapies with pembrolizumab or nivolumab are associated with fewer irAEs than ipilimumab. Drug-related AEs of any grade reportedly occurred in 70% to 80% of patients, but only 13% to 15% present with grade 3 or worse AEs.[35,41]

The most common AEs of any grade are fatigue (in 24% to 35% of patients), pruritus (in 10% to 23%), rash (in 12% to 21%), and diarrhea (in 11% to 20%) and are of low grade in the vast majority of patients (≥ 95%).

Unlike with ipilimumab, anti–PD-1-induced diarrhea and colitis are rare, and fewer than 2% of patients present with grade 3 or 4 diarrhea or colitis. Overall, pembrolizumab-related grade 3 and 4 AEs occurred in 12% to 14% of patients. The spectrum of autoimmune AEs reported with anti–PD-1 monoclonal antibodies is also distinct from that observed with ipilimumab. Thyroid dysfunction is more frequent with anti–PD-1 therapy; about 10% of patients have definitive hypothyroidism requiring hormone replacement therapy, often preceded by transient hyperthyroidism. In contrast, colitis and hypophysitis are more frequent with ipilimumab. Pneumonitis is also more frequent with anti–PD-1 treatment than with ipilimumab (2%–4% vs. 1%) but is rarely severe.

Treatment-related AEs rarely lead to discontinuation of anti–PD-1 treatment, in fewer than 10% of patients.

Toxicity of ipilimumab/nivolumab combined therapy. The combination of ipilimumab and nivolumab results in more frequent, rapid, and severe AEs. Any grade treatment-related AEs are observed in more than 90% of patients and reach grades 3 to 5 in 53% of patients. The most common AEs are rash (55%), pruritus (47%), fatigue (38%), diarrhea (34%), nausea (21%), and pyrexia (21%). Elevated levels of lipase (13%), aspartate aminotransferase (13%), and alanine aminotransferase (11%) are the most common grade 3 and 4 AEs. The onset of the majority of the AEs occurs during the 12-week induction phase, when the two drugs are administered concomitantly.[32,35,42,43] Treatment interruption for toxicity is required in 40% of patients, which does not seem to affect the benefit of treatment of those patients who are responding.

Management of AEs. The successful management of toxicities requires that AEs be anticipated, diagnosed as early as possible, monitored, and treated appropriately.[35,40,44] Obtaining clear information from patients and the physicians involved in their management is critical. Close collaboration with expert specialists, such as gastroenterologists, hepatologists, endocrinologists, neurologists, and dermatologists, can be useful. In general, grade 1 and 2 AEs are managed symptomatically and do not require treatment discontinuation. For persistent grade 2 AEs, dose skipping and symptomatic treatments are prescribed. Treatment discontinuation is recommended when grade 2 AEs persist despite the symptomatic measures after 1 to 2 weeks and for patients with grade 3 or 4 AEs. In the latter cases, referral to an organ specialist can be considered. If AEs are immune mediated, and after ruling out an active infection, corticosteroids are indicated in patients with persistent grade 2 or grade 3 or 4 irAEs. Typically 0.5 to 1 mg/kg of prednisone is prescribed and should be continued until symptoms resolve, then very progressively tapered over at least 4 weeks.

Rash and pruritus are usually mild to moderate and treated symptomatically with emollient antihistamines and/or topical steroids or systemic steroids when refractory or severe.

For grade 1 and 2 diarrhea, antidiarrheal agents (loperamide) and oral hydration are prescribed. In case of persistent grade 2 or grade 3 or 4 diarrhea, sigmoidoscopy or a colonoscopy is recommended. Other causes of enterocolitis, such as ischemia and/or infection, should be excluded by performing a stool test for viral (cytomegalovirus), bacterial pathogens, and *Clostridium difficile* toxins, and checkpoint inhibitor treatment should be discontinued and rehydration and systemic steroids initiated. Steroid treatment can be orally administered in grade 2 disease but may require intravenous administration of high doses of steroids (1–2 mg/kg) for more severe cases, also with intravenous rehydration. In severe cases, treatment with checkpoint inhibitors should be permanently discontinued. If symptoms do not improve significantly after 5 days of intravenous corticosteroids, treatment with 5 mg/kg doses of the anti-TNF antibody infliximab should be initiated, and patients should be closely monitored because of the risk of bowel perforation.

Endocrine disorders. Plasma levels of cortisol, adrenocorticotropic hormone, and thyroid hormones should be regularly monitored and checked immediately in the case of symptoms or biology suggestive of endocrinopathy. Hormone replacement can be a therapeutic emergency in cases of hypophysitis and should sometimes be initiated without waiting for a confirmed diagnosis, with immediate hospitalization and intravenous administration of corticosteroids with mineralocorticoid activity. Endocrinopathies are usually irreversible and require lifelong hormonal replacement.

Symptoms suggestive of rare AEs such as pneumonitis, uveitis, and/or neuropathies should be looked for by monitoring patients for any sign of dyspnea, eye pain or blurred vision, or neurologic abnormality.

In patients with preexisting autoimmune disorders, treatment should be discussed on a case-by-case basis, and a potential flare of the autoimmune disease should be put in balance with the potential benefit from the treatment in the context of a metastatic and fatal disease.

The potential relationship between irAEs and clinical response to checkpoint inhibitors is not completely elucidated. A positive correlation between vitiligo and patients' objective response rates was found in a prospective study of 67 patients treated with pembrolizumab.[45]

In Which Patients Is Immunotherapy Appropriate?

Many new questions are arising with this new treatment paradigm. The identification of biomarkers would allow us to address the critical questions of which patients to treat with immunotherapy and, more specifically, with monotherapy as opposed to a combination of immunotherapies or, in the case of BRAF mutation, the optimal way to sequence or combine targeted anti-BRAF agents with immunotherapy.

Role of PD-L1 testing in selecting patients for single-agent PD-1 versus combination. PD-L1 expression on tumor cells and/or immune cells has been well studied, and in almost every study, high expression of PD-L1 is associated with a better clinical outcome during treatment with anti–PD-1, nivolumab, or pembrolizumab.[46,47] This association is weaker

in the context of the ipilimumab/nivolumab combination, although the response rates are higher in the subgroup of patients with high PD-L1 expression.[48]

However, the positive or predictive value of PD-L1 expression is not sufficient as a single marker to guide treatment. Many reasons can be put forward to explain this. First, there are technical issues that are not standardized: several antibodies are used by different companies, these distinct antibodies do not recognize the same portion of the molecule, and their respective performance in recognizing PD-L1 expressed on tumor or immune cells is variable.[46] The threshold of positivity is different from one antibody to another, and standardization of techniques has not been performed. In addition, we know that the single expression of PD-L1 can result from an intrinsic intracellular molecular pathway and does not always result from the surrounding presence of activated T cells secreting interferon gamma. Indeed, the presence of T cells and, more precisely of $CD8^+$ T cells, in the active margin of the tumor seems a critical parameter for response to PD-1 immunotherapy.[49]

Furthermore, expression of PD-L1 is variable in distinct metastases, and even expresssion in various areas of the same metastasis render different results. Thus, selection based on PD-L1 expression is very difficult.

Although we have data suggesting that the expression of PD-L1 has a less important impact on response to the combination of ipilimumab and nivolumab than on the benefit of anti–PD-1 monotherapy, PD-L1 immunostaining alone currently does not appear to be a strong and reliable enough marker to guide treatment decisions, and more predictable biomarkers or marker combinations are actively being investigated.

Genetic instability and neoantigens. Mutations generated in the cancer cell genome that favor the genetic instability of cancer cells can give rise to neoantigens. In accordance with murine experimental data that demonstrated that these neoantigens could be involved in cancer immunosurveillance,[50,51] recent data in patients have shown that the mutational landscape influences response to immunotherapy with checkpoint inhibitors and that tumors with the highest rates of mutation and generating numerous neoantigens were more sensitive to immunotherapy with CTLA-4 and PD-1 inhibitors.[52,53] However, not all neoantigens can generate T-cell clones able to eliminate the tumor cells, and a process of tumor clone immunoediting induced by specific T cells results in complex mutational landscape dynamics.[50]

Treatment strategies in patients with BRAF-mutant melanoma. In patients with BRAF-mutant melanoma, whether to initiate treatment with a combination of targeted anti-$BRAF^+$ and anti-MEK agents compared with immunotherapy is a frequent question. The combination of these two strategies is promising on the basis of several preliminary studies recently presented at international meetings. Several randomized phase II and phase III trials are presently exploring these questions. Today, in countries where both targeted agents and checkpoint inhibitors are available, until controlled data from randomized trials are available, most physicians prescribe targeted agents for aggressive and rapidly progressive metastatic disease, when a fast response is critical to obtain, and favor immunotherapy for slowly progressive disease. In the intermediate situation, physician choices vary. One element that would favor immunotherapy over targeted agents is that we now have some evidence that patients in complete response following immunotherapy with checkpoint inhibitors can stop treatment, and, with close to 3 years of follow-up, many patients do not relapse, whereas most patients who stop targeted therapy after responding to the treatment seem to relapse.[54]

Patients with high lactate dehydrogenase remain a high medical need. Finally, although we have dramatically improved the prognosis of patients with metastatic melanoma, some populations of patients present a particularly challenging situation and have very low benefit from both targeted agents and immunotherapy. This is the case for patients with high lactate dehydrogenase, which is usually, but not always, associated with a high tumor load. For these patients, new treatment strategies are urgently needed.

OPTIONS WHEN APPROVED TARGETED AND IMMUNOTHERAPY AGENTS FAIL

Role of Alternative Approved Agents

Although immunotherapy and targeted therapy are the most efficacious therapies for patients with metastatic melanoma, many patients will develop disease progression while on these therapies. Additional therapeutic options are often needed. Given the many promising agents in clinical trial development, the ideal scenario is that patients progressing on first- and second-line therapies would be enrolled in a clinical trial. However, this is not always feasible for a variety of reasons, including access to clinical trials, patient eligibility, and other reasons. In this scenario, there are approved agents for the treatment of metastatic melanoma in certain clinical settings. These options include interleukin-2 (IL-2), talimogene laherparepvec (T-VEC), chemotherapy, and radiation.

High-dose IL-2 was one of the major therapies before the approval of targeted therapy and immune checkpoint blockade. However, this therapy was available only to patients with excellent performance status, good organ function, and access to specialized inpatient units administering this therapy. It was approved on the basis of durable remission in 1% to 5% of the treated population. Considerable toxicities include capillary leak syndrome, fever, infection, and cardiopulmonary and renal failure.[55] The role of IL-2 in the era of newer therapies is generally reserved for patients who have progressed on other lines of therapy and are not eligible for clinical trials. Current clinical trials are exploring combination therapies with IL-2 and other agents, but its future role in treatment combinations is still unclear.

T-VEC is an attenuated oncolytic herpes simplex virus containing a granulocyte macrophage colony-stimulating factor (GM-CSF) gene. Antitumor benefit occurs through the production of GM-CSF within the tumor, which enhances cellular immunity along with a direct effect from viral infection and

lytic replication. T-VEC was approved by the FDA in 2015 for the treatment of patients with unresectable and injectable cutaneous, subcutaneous, or nodal disease. It is only for patients with limited or no visceral disease and patients must have an easily accessible (nodal or skin) metastases. In a phase III trial of T-VEC versus GM-CSF, the overall response rate was 26.4% versus 5.7%, respectively. The durable response rate was higher in patients treated with T-VEC compared with GM-CSF (16.3% vs. 2.1%). Subset analysis demonstrated an improvement in OS among stage III and IVM1a patients. However, OS among all subsets was not significantly improved. Responses have been seen in both injected and noninjected lesions. Common toxicities included fatigue, chills, pyrexia, and injection-site pain.[56]

Before the approval of immune checkpoint inhibitors and targeted therapy, cytotoxic chemotherapy was the mainstay of therapy in patients with metastatic disease who were not candidates for or had progressed on IL-2. Despite the common use, no clinical trial has shown a survival benefit for cytotoxic therapy. Commonly used regimens include dacarbazine, temozolomide, and carboplatin and paclitaxel. Dacarbazine has a response rate of 8% to 20%. Toxicities include nausea and emesis and bone marrow suppression.[57,58] Temozolomide is an oral analog of dacarbazine and can cross the blood-brain barrier. Clinical trials comparing it with dacarbazine have not shown any statistically significant improvement in survival or progression.[59,60] Carboplatin and paclitaxel are both widely used agents but have never been compared with dacarbazine or temozolomide in a randomized trial. Response rates in a phase III trial comparing carboplatin and paclitaxel to carboplatin and paclitaxel with sorafenib demonstrated no benefit to adding sorafenib. However, the response rates in both arms were 18% to 20%, demonstrating the clinical activity of the combination regimen.[61]

Radiation therapy (RT) has long been used as a palliative measure for pain control and management of brain metastases. Various fractionation schemes have shown effectiveness in treating painful sites of extracranial metastatic disease.[62] The brain is a frequent site of melanoma metastases. Autopsy studies have demonstrated up to 75% of patients will develop evidence of brain metastases during their course of illness.[63] Whole-brain RT used to be the standard treatment of these patients. However, now that systemic therapies have shown dramatic improvements in OS, whole-brain RT should not be considered as standard of care for most patients given the concern about long-term toxicities.[64] Alternatives to whole-brain RT include stereotactic RT. Additionally, both immune therapy and targeted therapy have shown response in the brain.[65,66] The optimal management of patients with melanoma brain metastases is yet to be established. Several ongoing clinical trials are exploring this area.

Alternative Genomic Targets

As discussed above, the treatment of patients with metastatic melanoma who harbor a BRAF mutation with BRAF and MEK inhibitors has resulted in improvements in both PFS and OS. Unfortunately, most patients will develop resistance to targeted therapy and develop disease progression. Several mechanisms have been proposed. Three main areas of resistance have been targeted for potential therapeutic intervention to help overcome resistance. These include alteration of the immune system by targeted therapy, activation of the PI3K-mTOR pathway, and reactivation of the MAPK pathway leading to continued ERK activation. MAPK reactivation has been demonstrated in 79% of tumors developing resistance[67] through a variety of mechanisms, including BRAF splice variant, BRAF amplification, secondary activating mutations of NRAS or MEK1 and MEK2, and overexpression of RAF1 and MAP3K8-COT kinases.[6,68-71] ERK inhibitors are currently in clinical trials.[72] In addition, various compounds are in trials in combination with BRAF inhibitors targeting parallel signaling pathways, reviewed by Welsh et al.[72] Increasingly, BRAF and MEK inhibitors are being recognized for their role in the tumor microenvironment. Treated patients have shown increases in $CD4^+$, $CD8^+$, and $PD\text{-}1^+$ lymphocytes.[73] Because of these changes, several ongoing trials are combining targeted therapy with immune checkpoint inhibitors.

NRAS mutations occur in approximately 20% of patients with melanoma. With this mutation, activation of the MAPK pathway occurs upstream of BRAF. Although to date, directly inhibiting mutated NRAS has not been possible, an alternative strategy is to block the pathway downstream at the level of MEK. The MEK inhibitor binimetinib has shown an objective response rate of 20% and median PFS of 3.7 months in a phase I/II trial.[74] The NEMO trial randomized 402 patients with melanoma harboring an NRAS mutation in a 2:1 ratio to binimetinib, a MEK inhibitor, or dacarbazine. The primary endpoint was PFS by independent review. This trial was presented at the 2016 ASCO Annual Meeting and demonstrated an improvement in PFS of 2.8 versus 1.5 months ($p < 0.001$). However, OS was not significantly improved.[75] These data are consistent with the understanding that NRAS-mutated melanomas are MEK dependent, but there appears to be little long-term clinical benefit with MEK inhibition so far. We await longer follow-up on this trial and the formal publication.

Additional observations in the NRAS cohort of patients have shown dysregulation in the CDK4/6-RRB1 pathway. A phase I/II trial with ribociclib (a CDK4/6 inhibitor) and binimetinib demonstrated PFS of 6.7 months and an overall response rate of 41%.[76,77] When presenting the data at the 2014 ASCO Annual Meeting, Sosman et al[76] reported that among 22 patients treated with binimetinib and LEE011, there were seven partial responders but no complete responders. Toxicity was tolerable and consisted mostly of cutaneous toxicity and creatine phosphokinase elevations. Further investigation of this combination is ongoing.

Fewer than 10% of newly diagnosed melanomas are either acral or mucosal. These patients generally have a poorer prognosis compared with those with cutaneous melanomas. Approximately 20% of these patients will harbor

a mutation in the growth factor receptor c-KIT. A phase II trial of imatinib in patients with metastatic mucosal, acral, or chronically sun-damaged skin with mutation or amplification of KIT demonstrated a best overall response rate of 29%. The overall disease control rate was 50% but varied on the basis of KIT status (77% mutated vs. 18% amplified). Median OS was 12.5 months with median time to progression of 3.7 months.[78,79] A phase II study examined nilotinib in patients with a KIT mutation or activation who were either intolerant or refractory to a prior KIT inhibitor (cohort A) or with brain metastases (cohort B). Three of 11 patients in cohort A reached the primary endpoint of 4-month disease control. Median OS was 14.2 months in cohort A. Cohort B demonstrated limited efficacy in KIT-mutated patients with brain metastases.[79]

The National Cancer Institute's MATCH (Molecular Analysis for Therapy Choice) trial seeks to pair patients with molecular abnormalities in their tumor tissue with agents targeting their mutation. The trial is not unique to melanoma but includes mutations that can be present in melanoma. Patients enrolling in the match trial agree to undergo a biopsy for DNA sequencing of tumor tissue. If a molecular abnormality is found in the tumor tissue that is targeted by one of the drugs in the trial, patients are further screened for enrollment. If they meet eligibility requirements, they begin therapy on the specific arm targeting the mutation (NCT02465060).

Alternative Immune Targets

Although the anti–PD-1 drugs nivolumab and pembrolizumab are the most commonly used medications targeting the PD-1/PD-L1 interaction, several anti–PD-L1 drugs are being studied in combination and as single agents. A phase I study of atezolizumab showed an overall response rate of 26%.[80]

Most current immunotherapy options in melanoma attempt to expand or induce tumor antigen–specific immune responses in vivo. Adoptive cell therapy isolates tumor antigen–specific T cells from patients, either from peripheral blood or resected tumor, expands the cells, then reinfuses them to the patients. Initial studies of adoptive cell therapy demonstrated limited clinical benefit. However, when lymphoablation occurred before transfer of tumor-infiltrating lymphocyte and was followed by IL-2, response rates up to 50% were demonstrated. Of these responses, up to 20% were durable.[81-86] Similar to IL-2, adoptive cell therapy is available only to a limited number of patients with excellent performance status, ability to travel to a specialized center, and the ability to wait without treatment of several weeks while the cells expand. As technology improves for this technique and the expansion of cells is available at multiple centers, the use of this therapy is expected to increase.

The term abscopal effect is used to describe the impact of RT on areas outside of the radiation treatment field. The decrease in the sizes of tumors outside the radiation field was hypothesized to be related to a systemic inflammatory or immune response from the radiation. Early in the use of immunotherapy in melanoma, several case reports showed a response to immunotherapy following the addition of RT after the patient had progressed on immunotherapy alone or an increase in T-cell activation.[46,87] This has led to speculation that RT may have a role in patients who have failed to respond to immunotherapy or developed progression after an initial response. However, this has not yet been proved in a controlled clinical trial. Additionally, ongoing trials are administering RT in combination with immunotherapy to see if the initial response rates are higher.

There are several targets in current development both preclinically and in early-phase trials. This includes both immune checkpoint agonists and antagonists. Immunostimulatory targets include 4-1BB, CD27, and OX40. Of these, 4-1BB potentiates effector responses in lymphocytes necessary for tumor immunity. However, initial development was slowed because of the incidence of hepatitis and cytopenia. Additional clinical trials are now investigating this agent.[88] Immunosuppressive targets include IDO, LAG-3, and TIM-3. LAG-3 is an immune checkpoint inhibitor that maintains immune tolerance. It binds to effector T cells and acts as a ligand for MHC class II proteins. Drugs focusing on these targets are currently being studied as a single agents and in combination with anti–PD-1 therapy.

CONCLUSION

The treatment of advanced melanoma has drastically changed over the past decade. The previously standard therapies, dacarbazine and high-dose IL-2, are now reserved only for situations in which all immunotherapy and targeted agents have failed and no clinical trials are available. Targeted therapy for patients whose tumors harbor the BRAF mutation achieves high response rates and OS benefit with combination BRAF/MEK inhibition. Single-agent BRAF inhibitors should not be used, as randomized trials have established increased clinical benefit (OS and PFS). Treatments containing PD-1 antibodies are clearly superior to CTLA-4 antibodies in the frontline setting; however, the question of upfront BRAF/MEK inhibition versus immunotherapy has yet to be answered. Combination immunotherapy with ipilimumab/nivolumab shows higher response rates and higher toxicity rates compared with single-agent immunotherapy, and survival data will be available in the near future. Biomarkers such as PD-L1 status are still controversial and cannot yet be used for routine clinical decision making.

Novel targets in both immunotherapy and targeted therapy are currently being explored in a variety of clinical trials. Studies with new combinations such as immunotherapy with intralesional or targeted therapy are also being evaluated. The future of melanoma management is rapidly changing, although the backbone of treatment at this time is PD-1 antibodies and BRAF inhibitors (for tumors with BRAF mutations).

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PATIENT AND SURVIVOR CARE

Addressing the Survivorship Care Needs of Patients Receiving Extended Cancer Treatment

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OVERVIEW

Cancer survivorship care and research has typically focused on the health care needs of people with cancer following the acute phase of treatment. Work in this area, however, has faced challenges in identifying when treatment is complete for many forms of cancer. Acknowledging this challenge, the scope of survivorship research is often expanded to include patients also receiving maintenance or prophylactic therapy. Inherent in this expanded definition is the recognition that for many individuals, cancer is a chronic disease requiring extended treatment over many years. Three distinct patient populations can be identified for which extended treatment poses important survivorship care needs that, to date, have not been adequately addressed. The first group includes patients receiving extended endocrine therapy, such as women with breast cancer receiving tamoxifen and/or aromatase inhibitors as well as men with prostate cancer receiving androgen deprivation therapy. The second group includes patients receiving extended targeted therapy to control disease, as exemplified by patients with chronic myelogenous leukemia receiving treatment with tyrosine kinase inhibitors. A key issue in both of these patient groups is the need to identify and address factors that contribute to difficulties in maintaining high levels of adherence to the prescribed therapy over extended periods of time. The third group includes patients receiving novel therapies for advanced or metastatic cancer that can extend life for prolonged periods. A key issue for this group is the need to understand and address their unique supportive care needs.

The number of cancer survivors (i.e., people living with diagnoses of cancer) continues to grow and is expected to reach 18 million individuals in the United States by 2022.[1] The growth in the number of survivors has, in part, stimulated the development of a field known as cancer survivorship. Although definitions vary, cancer survivorship care and research is widely viewed as focusing on the health and life of a person with cancer beyond the acute diagnosis and treatment phase. According to the National Cancer Institute's Office of Cancer Survivorship, research in this area seeks to "prevent and control adverse cancer diagnosis and treatment-related outcomes…, to provide a knowledge base regarding optimal follow-up care and surveillance of cancers, and to optimize health after cancer treatment."[2]

Although the focus of cancer survivorship has been on the period following acute diagnosis and treatment, work in this area has acknowledged the challenges inherent in identifying the end of the acute or primary phase for many forms of cancer treatment.[3] Indeed, attempts to summarize cancer survivorship research often refer to studies of individuals who have completed curative treatment or have transitioned to maintenance or prophylactic therapy.[4] Inherent in this expanded definition is recognition that for many individuals, cancer will be a chronic disease requiring extended treatment over many years.[5]

With growing acceptance of the need to expand the scope of cancer survivorship care and research to include patients on extended treatment, we offer an in-depth examination of three distinct patient populations. In each instance, we identify major survivorship issues related to receiving extended treatment and the current status of efforts to understand and address these issues. First, we discuss the patient population receiving extended treatment to prevent disease recurrence or progression. Issues encountered by early-stage patients receiving hormonal therapy for breast and prostate cancer are used to illustrate the survivorship care needs of this patient population. Second, we focus on the population receiving extended treatment to control disease. Issues encountered by patients receiving targeted therapy for chronic myelogenous leukemia (CML) are used to illustrate the survivorship care needs of this patient population.

Third, we discuss the population with advanced or metastatic disease receiving extended treatment to slow disease

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progression, control symptoms, and maintain quality of life (QOL). Issues encountered by patients receiving novel therapies for advanced or metastatic cancers are used to illustrate the survivorship care needs of this patient population. A concluding section identifies cross-cutting themes and directions for future research.

EXTENDED ADJUVANT ENDOCRINE THERAPY

Adjuvant therapy for cancer is prescribed for patients in whom all known disease has been treated with either primary surgery or radiation therapy. With control of the local disease completed, the focus of adjuvant therapy is to eliminate occult metastatic cancer that may have disseminated in the months and years before the primary tumor was discovered. In this setting, the treatments are directed against preventing a recurrence (local or distant) of disease. Cytotoxic chemotherapy or radiation therapy are usually time limited in duration (6–12 months); however, endocrine therapies can extend over many years. Indications for the use of adjuvant therapy are related to the risk for recurrence, and this is usually dictated by the size of the tumor, its local extent, and other histologic and biologic features (e.g., grade, hormone receptors, gene expression profile). Breast and prostate cancers represent two very common adult cancers in which extended hormonal (endocrine) therapies are applied, and for which excellent data from large randomized trials support the value of targeting the hormonal milieu of the patient's body as a means of preventing recurrent disease from manifesting itself. Endocrine therapies may be given as the sole adjuvant therapy in both breast and prostate cancer or may follow chemotherapy and radiation. For both patients with breast cancer and those with prostate cancer, there may be untoward side effects from antagonizing the normal hormonal environment, and these may limit the ability to maintain adherence to these treatments over a long period of time.

Breast Cancer Adjuvant Endocrine Therapy

All women with nonmetastatic primary breast cancer, whose tumor expresses estrogen and/or progesterone receptor, are considered appropriate candidates for adjuvant endocrine therapy. This also includes women with stage 0, noninvasive, intraductal cancers for whom the primary indication is breast cancer prevention in the ipsilateral or contralateral breast.[6] This approach to management evolved over many years of randomized trials, in which initially only women with relatively high absolute risks for recurrence were exposed to adjuvant endocrine therapy. However, over the past 30 years, and as supported in a National Institutes of Health consensus conference in 2000, all women with hormone receptor positive tumors larger than 1 cm were deemed to benefit from 5 years of adjuvant tamoxifen.[7] Subsequently, additional studies supported the use of aromatase inhibitors as an alternative for 5 years in postmenopausal women, and further studies identified settings in which adjuvant endocrine therapy should be continued for up to 10 years.[8] Although the specific choice of endocrine therapy may differ according to the woman's menopausal status, all of the current approaches to endocrine therapy require daily oral therapy for a minimum of 5 years.

From the earliest clinical use of adjuvant tamoxifen, adherence to ongoing therapy was recognized as an issue.[9] In this report from Partridge et al,[9] up to 50% of women were nonadherent to tamoxifen therapy by 4 years, and this was most common among younger, older, and nonwhite women. Even in clinical trials of adjuvant tamoxifen therapy, diminished adherence rates at 5 years were noted in highly motivated patients; for both tamoxifen and placebo, only 23% of women were taking their study medications at 5 years in the NSABP B-14 trial.[10] In the recently reported NSABP B-35 trial comparing anastrozole with tamoxifen in patients with ductal carcinoma in situ,[6] only 64% of participants completed the study medications at 5 years, with no difference between the two endocrine therapies. Finally, in a large observational study within an integrated health system, adherence to clinically prescribed endocrine therapy[11] was reduced, with the finding of early discontinuation (in the first year of therapy) among younger and older women and poor persistence into the fifth year of treatment. An additional report from this same cohort showed increased mortality among women who were nonadherent.[12]

What are the barriers to initiation and adherence among women who are prescribed adjuvant endocrine therapy? In Sidebar 1, we list the most common issues identified in the literature[13-17] and in clinical experience. Interventions to enhance adherence should focus on these common issues, with an important focus on effective communication about the clinical value and magnitude of treatment benefit, with the assurance that potential side effects will be addressed. These are issues that should be addressed as part of initial treatment discussions and decisions. Furthermore, ongoing follow-up should be conducted by a member of the clinical team to assess any challenges to continued adherence, especially addressing ongoing complaints and any financial concerns that may make continued persistence with treatment an issue.

KEY POINTS

- **There are challenges to identifying when treatment is complete for many forms of cancer.**
- **Cancer is a chronic disease requiring extended treatment over many years.**
- **Extended treatment poses important survivorship care needs for patients receiving extended endocrine therapy, extended targeted therapy to control disease, and novel therapies for advanced or metastatic cancer.**

Prostate Cancer Endocrine Therapy

Unlike the setting of breast cancer, endocrine therapy of prostate cancer is often limited to neoadjuvant use before radiation therapy or short-term adjuvant therapy after radiation. This is usually provided only to patients with high-risk

SIDEBAR 1. Common Barriers to Adherence to Endocrine Therapy in Patients With Breast Cancer

- Lack of knowledge about the role and benefits of endocrine therapy
- Uncontrolled treatment-associated symptoms (vasomotor symptoms, arthralgia, vaginal symptoms)
- Concerns about rare but serious toxicities (e.g., blood clots, stroke, endometrial cancer, fracture)
- Cost of the medications
- Distrust of health system and poor communication with medical staff
- Lack of perceived risk for recurrence

local disease. However, there is another larger group of patients, who have undergone prostatectomy or radiation therapy for local disease, in whom endocrine therapy is initiated for a rising prostate-specific antigen level without evidence of definitive metastatic disease. These patients are likely to be on long-term endocrine therapy, without evidence of clinically symptomatic disease, for which long-term adherence is an issue. Of course, men with metastatic prostate cancer are also on long-term endocrine therapy, and this situation is more comparable to patients with CML described in the next section.

Similar to breast cancer, endocrine therapy for prostate cancer manipulates a man's hormonal environment and focuses on androgen deprivation as a first maneuver. This can be accomplished either with orchiectomy or regular injection of a gonadotropin-releasing hormone analog. Sometimes this is combined with an oral anti-androgen agent (e.g., bicalutamide), but more often antiandrogen therapies are added at the time of prostate-specific antigen level progression or for locally recurrent disease. The patient is said to have "castrate-resistant prostate cancer," and a variety of other androgen-targeted oral therapies are added. All of these therapies are associated with a variety of symptoms associated with low testosterone, including hot flashes, breast enlargement or tenderness, weight gain, decreased libido, and impotence. In addition, there may be body image and mood changes.

Although the symptoms of androgen therapies have been described in clinical trials and observational studies, relatively little is known about how these symptoms affect adherence to endocrine therapy. In a recent study, Jung et al[18] found that many men did not have adequate information about their treatments and that their reports of symptoms to their physicians were not addressed. Many of the findings in this survey study were similar to what has been reported about women with breast cancer. However, we could find no other reports in the literature on this topic, and thus this is an important gap. In addition, the newer antiandrogen therapies are very expensive, with monthly costs for enzalutamide and abiraterone estimated to be in excess of $8,000.[19] This is certainly another major barrier to long-term adherence.

EXTENDED TARGETED TREATMENT TO CONTROL DISEASE

Targeted cancer therapies represent a new generation of drugs designed to treat cancer by interfering with molecular targets that play a critical role in growth, progression, and spread of the disease. One of the first and most successful examples of how targeted therapies can improve outcomes occurred in the treatment of CML. With approximately 8,000 new diagnoses annually in the United States,[20] CML accounts for 20% of new adult leukemias. On the basis of research showing the cause to be formation of the *BCR-ABL* oncogene that produces a constitutively active tyrosine kinase,[21] the oral medication imatinib was evaluated because it is a potent inhibitor of this enzyme.[22] Clinical trials confirmed its efficacy[23,24] and demonstrated clinically important differences in QOL favoring imatinib[25] over the existing regimen of interferon and cytarabine. Eight-year survival rates for patients with CML have since improved from less than 20% historically to 87% in the imatinib era.[26] The success of imatinib is widely considered a model for the development of other targeted cancer therapies.[27] Several second-generation tyrosine kinase inhibitors (TKIs) have since been approved for use against CML,[27] and other oral medications targeting tyrosine kinase pathways have been or are being developed for many other forms of cancer.[28] Treatment of CML typically requires daily oral administration of a TKI over an extended period of time. Discontinuation of medication is generally not recommended unless patients achieve a deep molecular response.[29] Among those patients who do achieve a deep molecular response, studies suggest that only 40% will stay in remission after stopping first-line treatment.[29]

Adherence Issues

The necessity of taking an oral medication for an extended period, combined with the potential for missed doses that can result in impaired cytogenetic and molecular responses,[30,31] points to the importance of understanding and promoting medication adherence in patients with CML prescribed TKIs. A recent meta-analysis of 40 studies concluded that, depending on the assessment method, 25% to 33% of patients with CML are not adhering to their prescribed regimens.[32] Research on predictors of adherence in this patient population is more limited. A systematic review of this literature identified drug-related adverse events and forgetfulness as common reasons for intentional and unintentional nonadherence, respectively.[33] These findings suggest that efforts to maintain adherence should include reminders to take medication as well as effective management of medication side effects.

Side Effects and Symptoms

Although imatinib and similar TKIs are better tolerated than many of the regimens they replaced,[25] evidence suggests they are not without side effects. Common side effects of imatinib, dasatinib, and nilotinib observed in clinical trials include pain, diarrhea, nausea, and fatigue.[34] On the basis of the National Cancer Institute's Common Toxicity Criteria,

adverse event rates for any grade for these symptoms among patients taking imatinib were found to be 43.7% (nausea), 36.5% (pain), 34.5% (fatigue), and 32.8% (diarrhea).[24] Similar adverse rates for these symptoms have been observed for nilotinib and dasatinib.[27] These toxicities were generally low grade, but even low-grade toxicities that persist for months or years in patients on chronic therapy have the potential to greatly impair function and overall QOL and contribute to nonadherence.

It should be noted that Common Toxicity Criteria adverse event reports are based on clinician ratings and may represent underestimates of symptoms for which assessment through patient self-report represents the "gold standard" (e.g., fatigue).[35] More recent studies using patient self-report measures suggest that fatigue is among the most common and problematic symptoms experienced by patients with CML.[36-40] One study in particular speaks to the clinical importance of fatigue in patients with CML. Efficace et al[37] evaluated the relationship of symptoms, clinical features, and demographics to QOL. Fatigue (as measured by the Functional Assessment of Chronic Illness Therapy Fatigue Scale[41]) was independently associated with worse QOL on all scales of the SF-36[42] and had the highest inclusion frequency of all variables examined. The presence of fatigue was also associated with greater symptom burden, a factor related to poorer TKI adherence in patients with CML.[31] These findings led the investigators to conclude that fatigue is the main factor limiting QOL in patients with CML who receive long-term TKI therapy.[37]

Interventions to Promote Adherence and Manage Symptoms in Patients With CML Prescribed TKIs

Despite its importance, we are aware of only one published randomized controlled trial evaluating an intervention designed to promote oral medication adherence in patients with CML.[43] In this study, 86 patients with CML who had been on TKIs for at least 6 months were randomized to an intervention group or a usual-care control group. The intervention combined a nurse-conducted medication counseling session with supporting educational materials and access to daily text message reminders to take medication. At 9-month follow-up, self-reported medication adherence had increased significantly more often in the intervention group than in the control group (60% vs. 33%, respectively). Seventy percent or more of patients rated the counseling and educational materials as useful. In contrast, only one-third of patients chose to receive text message reminders, and only 27% of them perceived them as useful.

Despite the high prevalence of treatment-related symptoms, we could identify no published randomized controlled trials evaluating symptom management interventions for patients with CML on TKI therapy. Given research suggesting its clinical importance, the development of interventions to address fatigue should be viewed as a high priority. In the absence of an understanding of the pathophysiology of TKI-related fatigue,[37] clinical practice guidelines for addressing fatigue in cancer survivors[44] may suggest promising strategies. Although evidence was viewed as insufficient to recommend pharmacologic therapies, evidence was sufficient to recommend physical activity interventions and cognitive behavioral therapy.[44] An example of the latter is an intervention demonstrated to be effective against severe fatigue in disease-free survivors following completion of cancer treatment.[45] This intervention addresses six possible contributory factors (insufficient coping with cancer, fear of disease recurrence, dysfunctional fatigue-related cognitions, sleep dysregulation, activity dysregulation, and low social support or negative social interactions) and is delivered in a series of face-to-face sessions by a trained therapist. A recent publication describes the successful adaptation of this intervention for use in patients with TKI-related fatigue and for internet delivery to improve patient access.[46] A small-scale randomized controlled trial of this adapted intervention is currently under way.[47]

Summary of Survivorship Care Needs of Patients With CML on Extended Therapy

Patients with CML are in the vanguard in that they are one of the first cancer populations for whom disease control is typically achieved exclusively with the use a targeted therapy agent prescribed over an extended period of time. Although much less toxic than earlier regimens, TKIs for CML have been found to commonly produce side effects that adversely affect QOL and contribute to intentional nonadherence to daily oral dosing. Accordingly, survivorship care needs of this patient population include effective management of common treatment-related symptoms (e.g., fatigue) and assistance in maintaining high levels of medication adherence. Development of interventions to effectively meet the needs of this population is still at a very early stage.

EXTENDED TREATMENT OF PATIENTS WITH ADVANCED OR METASTATIC DISEASE

Patients with advanced or metastatic cancer often receive treatments with the goal of slowing disease progression, controlling symptoms, and maintaining QOL. Historically, treatment of many patients with advanced cancers rarely extended life beyond 1 year.[48-54] However, the expected survival of numerous patients with advanced cancer has improved significantly in recent years, following the advent of novel genotype-directed therapies[55-60] and immune checkpoint–targeting agents.[61-66] Thus, as the paradigm has shifted toward more effective treatment of patients with advanced cancer, so too have the supportive care needs of this unique group of cancer survivors.

Supportive Care Needs of Survivors With Advanced Cancer

Patients with advanced cancer often experience multiple symptoms, both physical and psychological, as well as issues related to prognostic uncertainty, financial distress, and the need for caregiving support from family and friends. Notably, patients with advanced cancer who receive extended treatments and survive for prolonged periods likely experience

SIDEBAR 2. Unique Supportive Care Needs of Survivors With Advanced Cancer

- Physical and psychological symptoms
- Maintaining quality of life
- Prognostic uncertainty
- Making informed treatment decisions
- Financial burden
- Family caregiving demands

issues similar to all patients with advanced cancer, but limited research has focused on the unique survivorship needs of this population (Sidebar 2).

Symptoms Experienced by Patients With Advanced Cancer

Patients with advanced cancer frequently experience numerous physical and psychological symptoms that are often under-recognized by their clinicians.[67-70] Symptoms such as pain, dyspnea, fatigue, nausea, and lack of appetite can lead to poor QOL and psychological distress for patients and their family members.[71-73] However, research demonstrates that clinicians often fail to reliably detect their patients' symptoms and frequently underestimate their severity.[74-77] In addition, studies suggest that patients may underreport their symptoms to their clinicians, often resulting in worse symptom management.[70,78-80] Thus, there is a critical need to recognize and address symptoms in patients with advanced cancer. Moreover, research is needed to better understand the symptom support needs of patients with advanced cancer who receive extended treatments and survive for prolonged periods.

Patients' symptoms represent a modifiable target for interventions aimed at improving patient outcomes.[81-83] A randomized trial of an intervention in which patients in the outpatient setting completed electronic self-reports of their symptoms and had their symptom reports delivered to their clinicians demonstrated better symptom control for those receiving the intervention compared with usual care.[82] More recently, a web-based patient-reported symptom monitoring intervention with automated reporting to clinicians for severe or worsening symptoms was compared with usual care in 766 patients with cancer in the outpatient setting.[81] Patients who received the intervention reported better QOL and experienced fewer hospitalizations. These studies highlight the importance of symptom monitoring interventions, and future work should further investigate the efficacy of these interventions among long-term survivors living with advanced cancer.

Prognostic Uncertainty

Patients with advanced cancer often misunderstand their prognosis and the goals of their treatment.[84,85] Recent advancements in cancer therapies have further complicated oncologists' ability to effectively communicate an accurate assessment of their patient's prognosis.[86] However, little research exists regarding the increasing challenge of how clinicians should communicate with patients about their prognosis in the modern era of targeted anticancer therapies. This is important, because patients with accurate perceptions of their prognosis are more empowered to make informed treatment decisions and plan for their future.[87-90] Moreover, research has shown that patients with advanced cancer prefer their oncologists to provide honest and accurate prognostic disclosure early in the disease course.[91] Consistent with these preferences, expert groups have recommended that clinicians initiate communication about prognosis at the time of diagnosis and that these discussions continue longitudinally, throughout the cancer trajectory.[92,93] By initiating these discussions early, and incorporating new information as it becomes available, clinicians can help patients better understand their prognosis and make more effective decisions about their care.

The Financial Burden Experienced by Cancer Survivors

Increasingly, studies have shown that patients with cancer experience substantial financial burden related to the disease and its treatment, yet financial burden among cancer survivors remains understudied.[94-98] Prior work demonstrates that patients with histories of cancer experience financial issues such as job loss, missed work, and trouble obtaining affordable health insurance.[99-102] Notably, cancer survivors often need long-term health care for years after their initial diagnosis, and the high out-of-pocket medical costs coupled with the loss of income can further compound their economic hardship.[103-105] This financial burden can negatively affect their health outcomes, including poorer QOL, increased symptom burden, and potentially higher mortality.[98,106,107] Importantly, in the modern era of cancer therapeutics, with patients living longer and drug prices increasing exponentially increasing, patients with advanced cancers are particularly vulnerable to the adverse financial consequences of their cancer.[103,108] Survivors' financial burden may influence their decision to forgo needed care or to not properly adhere to prescribed therapies in an effort to defray costs[109-111] and thereby jeopardize their health.[12,112,113] Thus, the financial burden experienced by cancer survivors is an important issue with the potential to impact the quality of their survivorship care.

Family Caregivers of Patients With Cancer

Patients with advanced cancer often require assistance from friends and family as they navigate their cancer course.[114,115] Unfortunately, family caregivers are often neglected when considering the unique supportive care needs of patients with advanced cancer. Family caregivers often experience a substantial symptom burden, including fatigue, sleep disturbance, depression, and anxiety.[116-118] Caregiving demands can negatively affect family caregivers' QOL and affect their ability to effectively care for their loved ones.[119,120] As novel cancer therapies continue to change the survival trajectory for patients with advanced cancer, efforts are needed to understand how best to support family caregivers throughout the patient's course.

Summary of Survivorship Care Needs of Patients With Advanced Cancer Receiving Extended Therapies

Patients with advanced cancer often experience issues related to symptoms, prognostic uncertainty, financial distress, and caregiving. Importantly, numerous studies have demonstrated the efficacy of palliative care interventions to address the unique supportive care needs of these patients.[121-126] On the basis of ample evidence, ASCO guidelines recommend dedicated palliative care services for patients with advanced cancer early in the disease course, concurrent with active treatment.[127] However, minimal data exist to determine the role of palliative care interventions for patients with advanced cancer who receive extended treatments and survive for prolonged periods. Future studies are needed that focus on the unique survivorship needs of this population to develop effective ways to support these patients throughout their cancer trajectory.

CONCLUSION AND FUTURE DIRECTIONS

For many people with cancer, their care will involve extended treatment over considerable periods of time. This reality challenges the paradigm that has defined survivorship care and research as focusing on the period after patients complete a relatively brief period of active treatment. Organizations such as ASCO have already acknowledged that survivorship care and research should also include patients receiving maintenance or prophylactic therapy for cancer.

As described above, patient populations receiving extended treatment include individuals receiving hormonal therapy for breast and prostate cancer, as well as individuals receiving targeted therapy such as TKIs for CML. A major survivorship issue for these patients is the need to identify and address factors that contribute to difficulties in maintaining high levels of adherence to prescribed therapies over extended periods of time. This situation is especially challenging, because patients control when they take their medicine. A key driver of nonadherence with these agents is adverse side effects that impair QOL (e.g., arthralgia and fatigue). This situation underscores the importance of achieving adequate symptom control among patients receiving extended treatment. Unfortunately, there has been relatively little research addressing issues of adherence and symptom management with oral anticancer agents. Recognizing this gap, the National Cancer Institute recently released a funding opportunity announcement designed to encourage research on oral anticancer medication utilization, delivery, and adherence.[128]

The other population described above includes patients with advanced or metastatic cancer who are receiving novel therapies that can extend life for prolonged periods of time. This population has a number of survivorship needs, including effective symptom management, help in dealing with prognostic uncertainty and financial distress, and family caregiver support. None of these issues has been systematically studied, despite the growing numbers of patients with advanced or metastatic disease experiencing longer survival with novel therapies. An immediate and important research goal is to evaluate the potential benefits of palliative care services for these individuals, given ample evidence regarding the efficacy of these services for patients who are newly diagnosed with advanced disease.

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Bench-to-Bedside Approaches for Personalized Exercise Therapy in Cancer

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OVERVIEW

The past 2 decades have witnessed a growing body of work investigating the feasibility and efficacy of exercise therapy on a broad array of outcomes in many different oncology scenarios. Despite this heterogeneity, the exercise therapy prescription approach and the dose tested has been largely similar. Thus, current exercise therapy prescriptions in the oncology setting adopt a one-size-fits-all approach. In this article, we provide an overview of personalization of exercise therapy in cancer using the principles of training as an overarching framework. Specifically, we first review the fundamentals of exercise prescription in chronic disease before focusing attention on application of these principles to optimize the safety and efficacy of exercise therapy on (1) cancer treatment–induced cardiovascular toxicity and (2) tumor progression and metastasis.

The field of exercise oncology is now recognized as an emergent subdiscipline of oncology research and practice.[1-5] Evidence supporting the efficacy of structured exercise therapy in the other major chronic diseases (e.g., coronary artery disease, heart failure) became standard of care in the 1960s and 1970s.[6-8] In sharp contrast, the first investigation of exercise therapy for patients with cancer did not occur until the late 1980s, although consistent publications in this field did not occur until the late 1990s.[1] Since these first investigations, the past 20 years have witnessed a relative explosion in the area of exercise oncology, with well over 200 studies examining the role of exercise (or physical activity) for patients with solid and hematologic malignancies.

Of importance, despite considerable heterogeneity in study endpoints and study populations/settings, the exercise therapy prescriptions tested across these studies are relatively similar.[1] Specifically, almost all studies closely adhered to the national exercise guidelines for patients with cancer (guidelines that are identical to exercise recommendations for all adults): endurance (aerobic) exercise either alone or in combination with resistance training, prescribed at a moderate intensity (50%–75% of a predetermined physiologic parameter, typically age-predicted heart rate maximum or reserve), achieved in two to five sessions per week for 10–60 minutes per session, with the ultimate objective of achieving at least 150 minutes of moderate-intensity or at least 75 minutes of vigorous-intensity exercise per week.[3,9] Thus, current exercise therapy prescriptions in the oncology setting adopt a one-size-fits-all approach, which is essentially analogous to all patients with cancer, regardless of age, histology, or oncogenic somatic genotype, receiving a similar type, dose, and schedule of anticancer therapy.[10]

Systematic reviews and meta-analyses do, however, indicate that exercise therapy following a generic prescription is safe, tolerable, and efficacious (at improving symptom control outcomes) for patients with cancer both during and following primary therapy.[3,11] Nevertheless, several important caveats must be considered when interpreting these data: (1) the effects of exercise therapy are compared against a nonintervention (usual care) control group and the marked deleterious consequences of a sedentary lifestyle (i.e., deconditioning) are well established; (2) meta-analyses and systematic reviews do not include more recent data, including data from three large randomized controlled trials, which contrast current conclusions; and, most importantly, (3) there are insufficient data to comprehensively evaluate whether the safety or efficacy of exercise therapy differs as a function of cancer-related medical (e.g., type, treatment, stage) or even exercise prescription characteristics (e.g., dose, schedule). Thus, it is not known whether alternative dosing and scheduling prescriptions that adopt a more personalized approach confer superior efficacy. A strong rationale to test alternative approaches in cancer is provided by more than 50 years of research and practice in the athletic arena.[10] Exercise scientists have continued to elucidate the determinants of human performance to continually refine and personalize exercise training dosing and scheduling to

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minimize injury and maximize performance. The fundamental basis of all athletic training prescriptions adheres to the tenets of human exercise physiology known as the principles of training.[10]

This article aims to provide an overview of the evidence supporting personalization of exercise therapy in cancer using the principles of training as an overarching framework. Specifically, we first review the fundamentals of exercise prescription in chronic disease before focusing attention on the application of these principles to optimize the safety and efficacy of exercise therapy on (1) cancer treatment-induced cardiovascular toxicity and (2) tumor progression and metastasis.

FUNDAMENTALS OF EFFECTIVE EXERCISE PRESCRIPTION IN CHRONIC DISEASE

Adoption of a personalized approach to exercise therapy prescription in clinical populations requires fundamental understanding of the underlying disease pathophysiology in question, providing insight into the unique limitations to exercise.[12,13] Such insights can be obtained from objective evaluation of a patient's baseline physiologic status to identify appropriate exercise intensities to personalize the prescription.[10,14,15] For aerobic training prescriptions, an incremental cardiopulmonary exercise test (CPET) is the assessment of choice for the accurate quantification of cardiorespiratory fitness and integrative evaluation of cardiovascular, respiratory, skeletal muscle, and neuromuscular responses to exercise.[16-18] Furthermore, exercise contraindications, adverse cardiovascular responses (e.g., hypertension, ischemia), and exertional symptoms can also be evaluated; such parameters are critical to prescribe safe as well as efficacious prescriptions.[16,19] Assessments of muscular strength, muscular endurance, and balance can also offer important insight regarding a variety of additional functional limitations[20-22] and how the patient is adapting to the exercise prescription.[23] Thus, a single or small battery of tests performed at baseline during short-duration training programs (4 to 12 weeks) or at regularly chosen intervals throughout longer interventions can help optimize the training prescription.

The utilization of specific metabolic or ventilatory responses to CPET is shown to be superior to more generic prescriptions, such as those that use a percentage of maximal heart rate or maximal oxygen consumption (%VO2max),[24-26] because considerable individual variability exists for the metabolic stress imposed by any given exercise load (i.e., percent of VO2max).[27] More specifically, the utilization of blood lactate or ventilatory responses to incremental exercise can identify unique training zones that anchor different intensities of training to the two lactate or ventilatory thresholds (LTs or VTs, respectively) and VO2max for each individual independent of disease severity or baseline fitness.[28] This approach allows for the generation of three (Fig. 1A) or sometimes five (Fig. 1B) unique training zones related to specific metabolic events that are associated with different types of endurance performance.[28,29]

Following objective evaluation of a patient's baseline physiologic status, the next step for effective exercise prescription is to systematically design the training regimen using specific principles of training. The most important aspects of these principles have been described previously[10] and will be briefly discussed here.

Individualization

All exercise training programs should be tailored to the physiologic status of each individual.[10,26] Even among international elite-caliber athletes, considerable differences exist in the initial fitness level (including VO2max), the adaptive response to training, nutritional/sleep status, and thus the exercise stimulus dose required to achieve the desired physiologic adaptation.[30,31] In chronic disease states, the level of heterogeneity is substantially amplified with comorbidities, chronic low-grade inflammation, altered sympathovagal balance, and pharmaceutical interactions that collectively alter training dose tolerability and adaptive response.

Specificity

Different types, intensities, durations, and frequencies of exercise therapy can confer markedly distinct physiologic adaptations. However, few studies specifically tailor the training prescription to optimally target the desired physiologic or performance outcome. Unlike molecularly targeted therapies, exercise therapy can cause markedly different adaptations depending on the exercise load and/or stimulus.[32] For example, high-intensity, short-duration exercise sessions (i.e., Zone 3; Fig. 1A) above LT2/VT2 interval exercise for approximately 30 minutes activate mitochondrial biogenesis and capillarization within skeletal muscle, which do not commonly occur in response to low-to-moderate

KEY POINTS

- **There is a growing body of work investigating the feasibility and efficacy of exercise therapy in cancer.**
- **Exercise therapy prescriptions can be personalized to the physiologic status of each individual using the principles of training as a framework.**
- **A nonlinearized approach that utilizes undulating training stress (achieved through varying the intensity and duration of training load) is safe and efficacious for improving cardiorespiratory fitness as well as other important clinical outcomes for several different clinical populations, including patients with cancer.**
- **The importance of performing the appropriate amount of exercise at intensities that permit recovery and adaptation is underscored by clinical and preclinical studies indicating that systems already under stress may have increased susceptibility to exercise-induced pathology.**
- **The CHALLENGE and INTERVAL trials will provide important and novel insights addressing the fundamental question of whether increasing exercise exposure following a cancer diagnosis alters disease outcomes.**

intensity, longer-duration training (i.e., Zone 1; Fig. 1A) at LT1/VT1 and below for approximately 60 minutes or longer.[33-35] Although the specific prescription for every desired physiologic adaptation is not known, a considerable body of research has identified the necessary dose, intensity, and/or duration of exercise to achieve a large number of physiologic adaptations to guide this fundamental approach to exercise therapy dosing.[32]

Progressive Overload

Physiologic adaptation requires an exercise load to challenge system homeostasis beyond that habitually performed.[10,36] Repetitive exposure to a training load above habitual levels promotes adaptation (allostasis),[37,38] with subsequent increases in training load required for continued adaptation. It is important to stress that progressive overload only confers physiologic adaptation with adequate rest and recovery (another key principle of training) to maximize the adaptive response.[10,36,39] Rest and recovery are essential elements of any exercise therapy prescription (similar to drug-free breaks) because biologic resynthesis only occurs during rest, allowing the affected system(s) to adapt (supercompensation).[39] Chronically overloading a system without adequate rest and recovery can lead to fatigue, maladaptation, and illness (allostatic overload or overtraining).[37,40] This could stimulate worsening symptoms or inferior clinical outcomes in certain clinical populations. Several other principles, including the variety of the training type and stimulus, regularity, reversibility of the training adaptation, and maintenance and accommodation of exercise load, are also important considerations but are beyond the scope of this review.

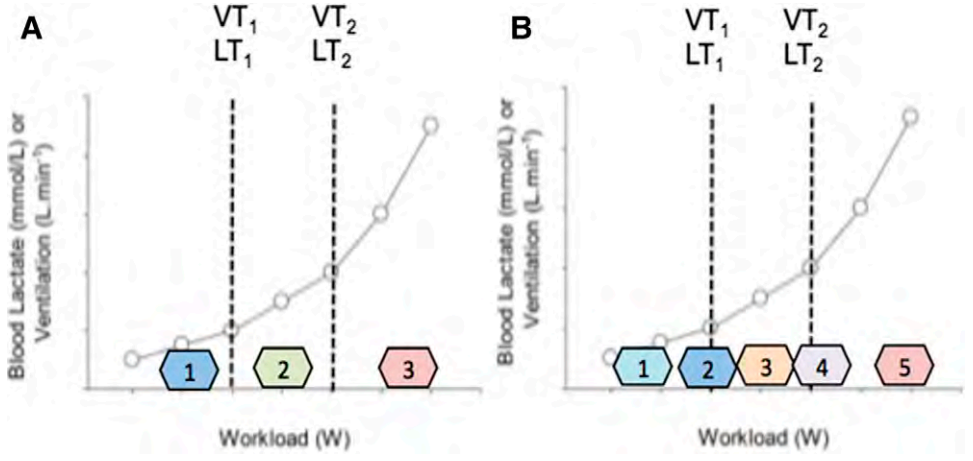
Exercise Sequencing/Scheduling

A key component of exercise training in line with the principles of training is the systematic sequencing or scheduling of training to optimize physiologic adaptation and enhance performance (known as periodization).[41] In athletes, training stress is structured in a cyclic pattern with planned changes in training volume and intensity,[42,43] with the goal of optimizing performance for a specific competition. Clearly, in most circumstances, clinical patients are not preparing for a specific competition, although analogous events in oncology could be preparing for surgery or cytotoxic therapy. Irrespective of the scenario, periodization is a key aspect for appropriately managing training stress to optimize treatment while helping to avoid excessive fatigue[44] even with similar training volumes or loads being performed.[45-50] Few studies have used periodization in the clinical setting, and there are many periodization models that could be used.[41,46,51,52] However, in the limited available data, a nonlinearized approach that utilizes undulating training stress (achieved through varying the intensity and duration of training load) is safe and efficacious for improving cardiorespiratory fitness as well as other important clinical outcomes for several different clinical populations, including patients with cancer.[53-56] A recent randomized controlled trial in chronic obstructive pulmonary disease (110 patients) demonstrated that patients treated with a nonlinear periodized prescription led to superior improvements in exercise tolerance (measured as constant load exercise time) and disease-specific, health-related quality of life compared with a generic exercise prescription.[56] Further work testing and adopting different periodized approaches to optimize exercise training appears warranted.

Training-Intensity Distribution

Although it is somewhat counterintuitive, superior performance in endurance events has consistently been associated with higher volumes of lower-intensity training (i.e., exercise in Zone 1; below LT1/VT1 in Fig. 1A).[28,57,58] Furthermore, performance of the majority of training (approximately 75%) in Zone 1 (Fig. 1A) offset with 15%–20% of training load at high intensities (i.e., Zone 3; Fig. 1A) confers superior

FIGURE 1. Exercise Intensity Zones



(A) Three-zone model: Zone 1 below ventilatory (VT)/lactate (LT) threshold 1; Zone 2 above VT1/LT1 and below VT2/LT2; Zone 3 above VT2 and below peak oxygen consumption. (B) Five-zone model: Zone 1 below VT1/LT1; Zone 2 equal to VT1/LT1; Zone 3 below VT2/LT2; Zone 4 equal to VT2/LT2; Zone 5 above VT2 and below peak oxygen consumption.
Abbreviations: LT, lactate threshold; VT, ventilatory threshold.

improvements in endurance performance outcomes (including VO2max) compared with utilizing one intensity of training, such as high-intensity interval training, training near the LT/VT, or high-volume training at low intensities.[29] This polarized approach to training[28,29] demonstrates the importance of utilizing individualized exercise intensities with higher relative training loads to improve cardiorespiratory fitness, but it also highlights the importance of performing an appropriate amount of exercise at intensities that permit recovery and adaptation.

In summary, personalized training based on a framework of key principles of training that use evidence-based approaches is postulated to result in superior physiologic adaptations leading to improved clinical outcomes. The remainder of this review will provide an overview of the application of these principles to effective exercise prescription and scheduling in the oncology setting.

PERSONALIZATION OF EXERCISE THERAPY TO MITIGATE TREATMENT-INDUCED CARDIOVASCULAR TOXICITY

Five-year relative cancer-specific survival rates for the 10 most common malignancies improved from 58% in 1977 to 73% in 2012.[59] As a result, patients diagnosed with these malignancies now have sufficient longevity (with the exception of lung cancer) to be at risk for normal age-related pathologies, predominantly cardiovascular diseases (CVDs) including heart failure, coronary artery disease, and stroke.[60,61] Moreover, CVD is more common (twofold to fourfold higher risk) and occurs at an earlier age than that observed in the general population.[62,63] The underlying pathogenesis of this heightened and accelerated CVD-risk phenotype relates to the direct (e.g., cytotoxic/radiation-induced injury) and indirect (e.g., effects secondary to therapy, such as deconditioning) effects of adjuvant therapy.[60] Importantly, the risk of cardiovascular-related toxicity is likely to increase with continual improvements in cancer-specific mortality,[59] trends toward extended adjuvant therapy in which patients are exposed to drug therapy for longer periods of time,[64] and testing and approval of novel targeted therapies with unique cardiovascular safety profiles.[65]

Despite the importance and changing landscape of the cardiovascular safety profile in cancer, an established standard-of-care approach to either prevent and/or treat such disorders does not yet exist.[66] Exercise therapy is an established cornerstone of CVD prevention and treatment in multiple nononcologic settings.[67] Exercise therapy improves a patient's CVD risk profile via favorable alterations in insulin sensitivity, lipid profile, and blood pressure with concomitant improvements in the reserve capacity of the skeletal muscle/vasculature/cardiovascular axis.[68-72] In contrast, the efficacy of exercise therapy to prevent/offset CVD in the oncology setting has received minimal attention. Recent epidemiologic data from our group indicate that postdiagnosis exercise exposure is independently associated with graded reductions in CVD events for patients with primary breast cancer[73] and adult survivors of childhood Hodgkin lymphoma.[74] These data provide the initial rationale to develop a program of work to comprehensively elucidate the efficacy and mechanisms of exercise therapy on cardiovascular toxicity for patients with cancer. Building on the concepts introduced in the first section, here we draw on work from cardiovascular medicine as well as exercise oncology to provide an overview of novel approaches to the optimization of exercise therapy on cardiovascular toxicity via adoption of the principles of training.

Individualization

Use of generic prescriptions that fail to consider the baseline physiologic status of any individual increases the propensity for underdosing and/or overdosing of exercise therapy; such considerations may be particularly important in cancer. For example, use of an estimated or age-predicted maximum heart rate may provoke overtraining among patients with primary breast cancer receiving or previously treated with polychemotherapy. Such agents increase the risk of autonomic dysfunction,[23,24] wherein an elevated resting heart rate decreases heart rate reserve.[75,76] To circumvent use of heart rates to individualize training for patients with cancer, researchers have a number of alternative options, such as workloads (e.g., treadmill speed and power output) corresponding to a specific percentage of VO2peak (e.g., 55%, 65%) elicited during CPET.[77,78] Moreover, utilization of the aforementioned blood lactate or ventilatory responses to incremental exercise to identify unique training zones has been used to further refine individualized exercise prescriptions.[54,79] This approach abrogates therapy-induced declines, or improvements in VO2peak.[54,79] Nevertheless, even with the adoption of this approach, notable heterogeneity in VO2peak is evident. For example, in a study of 50 men with localized prostate cancer who were randomly assigned to 24 weeks of aerobic training (5 days per week; 30–60 minutes at 55%–100% VO2peak) or to the usual-care control following radical prostatectomy,[80] we found that the mean change in VO2peak in the exercise group was +2.4 mL/kg per minute, but the individual change in VO2peak ranged from approximately −18% to +32%. Similarly, Leon et al[81] reported a significant group mean increase in high-density lipoprotein cholesterol ($p < .001$) and a decrease in triglycerides ($p < .01$) among 675 sedentary individuals who completed 20 weeks of aerobic training (3 days per week; 30–50 minutes at 55%–75% VO2peak). However, marked individual variability in high-density lipoprotein cholesterol (−24% to +66%) and triglyceride (−3% to +8%) delta change was observed. Thus, the heterogeneity in response supports, by definition, the adoption of personalized medicine approaches in exercise oncology. Similar to oncology-targeted agents, exercise prescriptions must be specific to the pathophysiology of the primary subclinical (e.g., exercise intolerance, left ventricular dysfunction, hypertension) or clinical (e.g., heart failure, coronary artery disease) CVD phenotype to improve patient morbidity and mortality.

SIDEBAR 1. Clinical Vignettes

Patient 1 is a 65-year-old woman with pre-existing hypertension with stage II, node-positive primary breast cancer undergoing anthracycline and paclitaxel chemotherapy. On a CPET with echocardiography, her VO2peak was 15.2 mL/kg per minute (16% below sex- and age-matched sedentary values), and she had a peak heart rate of 150 beats per minute, a peak CO of 9 L/min, and a calculated peak cardiac output and arterial venous difference of 11 mL/dL. It was determined that impaired VO2peak was reduced primarily because of inotropic incompetence resulting in reduced peak stroke volume. Accordingly, the exercise therapy prescription is designed with a focus on high-intensity aerobic training (as part of a larger prescription that also includes adequate rest and recovery as well as lower-intensity training sessions), given the evidence that high-intensity exercise has been shown to be superior to low-intensity exercise at improving left ventricular contraction[78] and in lowering blood pressure.[79]

Patient 2 is a 55-year-old man with hyperlipidemia undergoing androgen-deprivation therapy for prostate cancer. On a CPET with echocardiography, his VO2peak was 20.8 ml/kg per minute (35% below age-matched sedentary values), and he had a peak heart rate of 162 beats per minute, a peak CO of 15 L/min, and a calculated peak cardiac output and arterial venous difference of 11 mL/dL. It was determined that VO2peak was reduced primarily because of impaired peak cardiac output and arterial venous difference. As a result, the targeted exercise prescription is designed to focus on combined moderate-intensity aerobic and resistance training, based on the findings that moderate-intensity exercise is superior to vigorous exercise in lowering triglycerides[80] and, in the setting of reduced peripheral oxygen uptake, targeted muscle training is critical to improving VO2peak.[81]

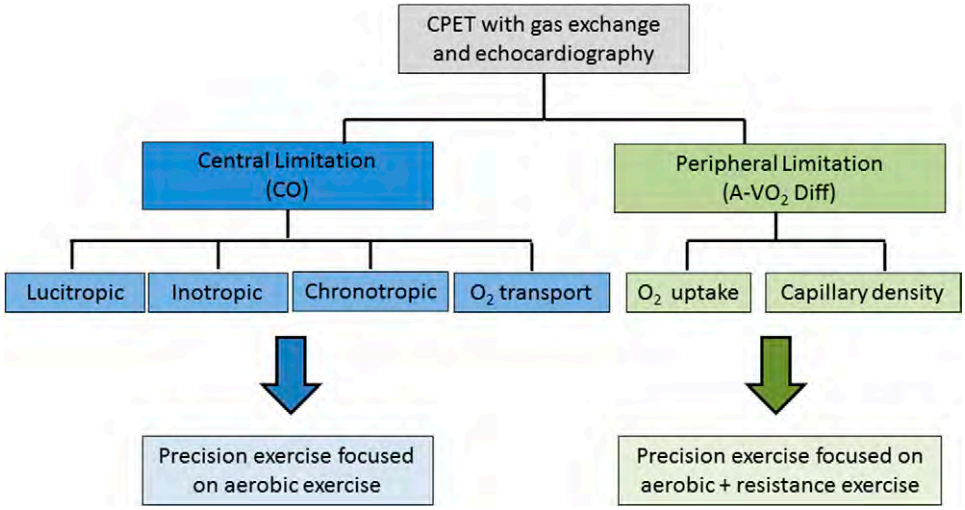
Specificity

Clearly, application of generic exercise prescriptions to offset different CVD-cancer phenotypes will be associated with heterogeneous responses. To facilitate practical understanding of precision exercise therapy for patients with an exercise-intolerance phenotype, Fig. 2 presents a three-step framework. The first step is to perform a CPET with gas exchange to determine VO2peak and to obtain an echocardiogram to determine peak cardiac output. The second step is to determine the underlying limitation to VO2peak. In accordance with the Fick equation,[16] where VO2 is equal to the product of cardiac output and arterial venous difference, the primary limitation can be identified as a central limitation (e.g., decreased cardiac output owing to lusitropic, inotropic, or chronotropic incompetence) or as a peripheral limitation (e.g., decreased cardiac output and arterial venous difference owing to decreased capillary density or impaired oxygen utilization by the exercising skeletal muscles). The third step is to use exercise prescriptions targeted to the primary limitation to unveil the full therapeutic potential of exercise therapy to augment VO2peak (Fig. 2). To illustrate the potential applicability of personalized exercise therapy, data from two representative patients are presented (Sidebar 1).

Progressive Overload

Nonlinear prescriptions vary between low, moderate, and high intensity to target various physiologic systems involved in the cardiovascular response to exercise therapy.[10] To date, approximately six trials, in various oncology settings, have

FIGURE 2. Three-Step Framework to Facilitate Practical Application of a Personalized Approach for Patients With Cancer With Exercise Intolerance



Abbreviations: A-VO2 Diff, cardiac output and arterial venous difference; CO, cardiac output; CPET, cardiopulmonary exercise test; O2, oxygen.

explored the safety, tolerability, and initial efficacy of nonlinear prescriptions.[10] For example, our group conducted a phase II randomized trial to determine the efficacy of 12 weeks of nonlinear aerobic training (3 days per week, 15–45 minutes per session ranging in intensity from 60%–100% peak workload) in attenuating anthracycline-induced changes in VO2peak.[79] Intention-to-treat analysis indicated that VO2peak decreased by 1.5 ± 2.2 mL/kg per minute (−9%) in the usual-care group and increased by 2.6 ± 3.5 mL/kg per minute (+13%) in the exercise group (between-group difference, p = .001). Importantly, this was the first study to show significant improvements in VO2peak among patients with breast cancer receiving adjuvant chemotherapy; other studies using linear prescriptions reported nonsignificant improvements in VO2peak in exercise groups.[77,82]

The importance of performing the appropriate amount of exercise at intensities that permit recovery and adaptation is underscored by clinical and preclinical studies indicating that systems already under stress may have increased susceptibility to exercise-induced pathology. For example, an ancillary analysis of 90 patients with cancer from the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial who were randomly assigned to aerobic training (three times per week, 20–45 minutes at 60%–70% heart rate reserve) or the usual-care control revealed that the incidence of cardiovascular mortality or cardiovascular hospitalization was significantly higher in the exercise group versus the usual-care group (41% vs. 67%; adjusted hazard ratio, 1.94; 95% CI, 1.12–3.16; p = .017).[83] In preclinical work, Huang et al[84] demonstrated that strenuous exercise (90 minutes twice a day for 14 days) resulted in left ventricular hypertrophy, myofibril disarray, and increased fibrosis in juvenile mice exposed to anthracycline-containing therapy. It is important to note that neither study adhered to a nonlinear or progressive overload approach. Whether a nonlinear approach is superior to a linear exercise prescription in improving CVD phenotypes and conferring reductions in clinical events in cancer remains unknown. As an initial step, our group is comparing the effects of nonlinear versus linear aerobic training on changes in VO2peak among 174 patients with primary breast cancer with exercise intolerance.[85]

PERSONALIZATION OF EXERCISE THERAPY TO MODULATE TUMOR PROGRESSION AND METASTASIS

The majority of research efforts in exercise oncology to date have, and continue to, focus on the efficacy of exercise therapy to mitigate acute and chronic patient-reported and/or physiologic toxicities associated with cytotoxic therapy.[1] However, in recent years, a parallel line of investigation is focusing on the antitumor effects of exercise among patients with or who at risk for cancer.[4] Studies in this arena were launched by work showing for the first time that (self-reported) exercise was inversely associated with the risk of recurrence and cancer-specific mortality in primary breast cancer. Specifically, Holmes et al[86] found that compared with less than 3 MET-hrs·wk^{-1} of physical activity (i.e., all types of physical activity including structured exercise were evaluated), the adjusted relative risk of death from breast cancer was 0.50 (95% CI, 0.31–0.82) for 9–14.9 MET-hrs·wk^{-1} (i.e., equivalent to approximately 150–250 minutes of moderate-intensity exercise per week) among 2,987 patients with primary breast cancer. Since the publication of this seminal work, approximately 26 studies have evaluated whether exposure to exercise and general physical activity following a cancer diagnosis alters disease pathogenesis. In a recent systematic review, postdiagnosis exercise was associated with, on average, a 37% reduction (95% CI, 0.54–0.73) in the risk of cancer-specific mortality, comparing the most- versus the least-active patients.[87]

The available observational data, together with ancillary data from small randomized trials showing that exercise therapy alters circulating levels of various factors postulated to underpin the exercise/cancer progression relationship (e.g., sex and metabolic-steroid hormones and growth factors, immune/inflammation axis effectors),[5] have led to the popular assertion that sufficient data exists to initiate large-scale, phase III trials to definitively test the efficacy of exercise on disease outcomes among patients with cancer.[87-90] Indeed, two such trials are currently underway: the Colon Health and Life-Long Exercise Change (CHALLENGE) trial includes 962 patients with resected stage III colorectal cancer,[91] and the Intense Exercise for Survival Among Men With Metastatic Castrate-Resistant Prostate Cancer (INTERVAL) trial includes 866 patients with metastatic prostate cancer.[92] There is little argument that adequately powered randomized controlled trials remain the gold standard and provide the best evidence of causality. In this respect, the CHALLENGE and INTERVAL trials will provide important and novel insights addressing the fundamental question of whether increasing exercise exposure following a cancer diagnosis alters disease outcomes. Nevertheless, several important knowledge gaps exist that preclude the optimal design of definitive exercise trials. These include, but are not limited to, the following: (1) identification of the optimal treatment dose and schedule, (2) mechanistic understanding of how exercise might delay and/or prevent cancer progression, and (3) predictors of response to guide patient selection. Parallel translational studies that address these research gaps will permit continual refinement of exercise dosing to optimize the safety and efficacy of exercise therapy as a candidate antitumor strategy.[4] To facilitate such efforts, we provide an overview of these knowledge gaps in the following section, using the concepts of individualization, specificity, and progressive overload from the principles of training.

Individualization

Classically, individualization of exercise is considered only from the perspective of improvements in exercise performance (using parameters such as CPET, age, and concomitant comorbidities). Clearly, consideration of these factors is essential when designing any exercise prescription irrespective of the therapeutic target; however, we postulate that

additional factors must be considered when designing exercise trials with therapeutic intent (i.e., the primary endpoint of interest is tumor specific). These factors can be broadly categorized into tumor-related and host-related factors.

Tumor-related factors. Human cancer is a biologically heterogeneous disease with well-defined clinical and molecular subgroups. Stratification by clinical and molecular subgroups in all solid tumors reveals stark differences in prognosis as well as response to conventional and novel anticancer treatments. Given this, the notion that tumor response to exercise may also differ by such characteristics appears plausible. To this end, investigators have started to explore whether the relationship differs as a function of tumor features. In terms of clinicopathologic features (e.g., tumor stage, estrogen receptor status), Holmes et al[86] found that exercise exposure (≥ 9 metabolic equivalents of task hours of physical activity per week) was associated with a substantial 50% reduction in breast cancer death in estrogen receptor (ER)–positive tumors compared with a nonsignificant 9% reduction in ER-negative tumors. At least three other independent observational studies also found that ER-positive tumors were more responsive to exercise.[93-95] In corroboration and extension of this work, we found that increasing exercise exposure was not associated with a reduction in the risk of recurrence or breast cancer death for 6,211 patients (i.e., unselected cohort).[94] However, stratification by clinical subtype indicated that the hormone receptor–positive, HER2-negative clinical subtype was preferentially responsive to exercise; exercise did not reduce the risk of breast cancer death in the other two clinical subtypes (i.e., HER2-positive or triple-negative clinical). In terms of molecular features, a series of studies from the same group reported that tumor *PTGS2* positivity, *CTNNB1* negativity, and expression of *CDKN1B* (p27) predict sensitivity to exercise in colorectal cancer.[96-98] Clearly, such findings are hypothesis generating, requiring validation in independent cohorts and biologic confirmation in preclinical studies. Nevertheless, as in oncology drug trials, tumor-related factors likely contribute to exercise efficacy and therefore may, in turn, inform patient selection (into exercise trials) as well as provide further information on how to individualize the exercise therapy prescription.

Host-related factors. To date, personalized oncology medicine has focused predominantly on elucidation of tumor-centric factors to predict therapeutic response. More recent work, however, has highlighted the importance of how host-related factors (e.g., genetic predisposition, circulating concentrations and function of immune surveillance phenotypes, inflammatory or metabolic effectors, gut microbiota) contribute to and/or modify the antitumor activity of conventional and novel agents. To our knowledge, whether host-related factors modify or predict tumor response to exercise therapy has not been investigated, although initial insights can be gleaned from related work. For instance, Bonanni et al[99] investigated the effects of 4 weeks of metformin compared with placebo on markers of tumor proliferation (Ki-67) for 200 patients with primary breast cancer prior to surgical resection. Intention-to-treat analyses indicated no differences in Ki-67 between study arms; however, a differential effect of metformin was observed in secondary, unplanned analyses as a function of baseline insulin resistance. Specifically, pretreatment insulin resistance (i.e., homeostasis model assessment index > 2.8, fasting glucose [mmol/L] × insulin [mU/L]/22.5) was associated with a nonsignificant mean proportional decrease in Ki-67 of 10.5%, whereas noninsulin resistance was associated with a nonsignificant increase of 11.1% in Ki-67. These data were corroborated in a subsequent trial, indicating that the efficacy of metformin differed as a function of homeostasis model assessment index as well as other circulating metabolic factors and tumor clinical subtype.[100] Together, these data suggest that the efficacy of metformin differs as a function of host and tumor-related characteristics in primary breast cancer.

There is a long history of work in general exercise physiology focused on exercise genomics, which is essentially, the application of genome-wide association studies as well as targeted approaches to further understanding of the interaction between genetic predisposition and related pathways to predict human response to physical activity and exercise training interventions. Not surprisingly, this work has focused on genetic predictors of exercise or sports performance, with a paucity of work examining whether the germline DNA profile predicts the primary incidence of cancer or outcomes after a cancer diagnosis. Indeed, to our knowledge, only two studies to date have investigated this question. Nkondjock et al[101] found no association between physical activity levels and risk of breast cancer among women with a *BRCA* mutation, whereas King et al[102] reported that exercise delayed/reduced the lifetime risks of ovarian cancer by 54% in *BRCA1* mutation carriers and 23% for *BRCA2* mutation carriers. To our knowledge, whether the association between exercise and disease outcomes for patients with cancer differs on the basis of genetic predisposition (sequencing of germline DNA) has not been evaluated.

Specificity

Adoption of a generic prescription for oncology therapeutic-intent studies is problematic because it assumes that the exercise load required to optimally modulate the cardiovascular system and tumor outcomes is the same, or that exercise-induced modulation of tumor outcomes is dependent on improvements in cardiorespiratory fitness. This assumption has not been directly tested in the oncology setting and has surprisingly received little attention in other clinical settings; nevertheless, at least one trial provides some initial insight. Kraus et al[103] investigated the effects of three aerobic training prescriptions that differed in total weekly duration and intensity on cardiorespiratory fitness and lipoproteins for 84 overweight men and women with mild-to-moderate dyslipidemia for 6–8 months. Of interest, improvements in fitness were similar in the high-intensity prescriptions (i.e., high-duration/high-intensity [65%–80% of VO2peak]; low-duration/high-intensity), yet improvements in lipoprotein

profiles were consistently superior with high-duration/high-intensity training, indicating that the effects of exercise on different end points differ as a function of the exercise stimulus. Thus, the exercise prescription must be specific and targeted to the primary endpoint or system(s) or pathway(s) known or postulated to underpin the effects of exercise on the primary therapeutic target. For example, in the context of breast cancer, current observational data suggest that ER-positive tumors are particularly responsive to exercise,[94] creating the rational hypothesis that exercise prescriptions should be designed to optimally inhibit ER activity, its ligands, or coactivating pathways. Similarly, in tumors with *PIK3CA* mutations, prescriptions could be designed to optimally modulate circulating metabolic growth factor ligands that regulate the phosphoinositide 3-kinase/AKT/mTOR signaling cascade.[104] Rational dosing loads and schedules could be conceived, tested, and validated in clinically relevant animal models prior to testing and validation in human investigations. Such translational studies will be an exciting area of future research in exercise oncology.

Progressive Overload

There is minimal understanding of the complex interplay between the underlying concept of progressive overload and alterations in whole-organism, tissue, and cellular biology to regulate disease phenotypes,[105] including cancer pathogenesis. Observational studies indicate an inverse linear dose-response relationship between exercise and cardiovascular events, supporting the hypothesis that higher exercise doses cause linear improvements in cardiovascular risk profiles.[73,74] However, parallel observational data with cancer outcomes as the endpoints of interest indicate, in general, a nonlinear relationship.[87] In other words, increasing exercise is associated with linear reductions in the risk of recurrence and cancer mortality but only up to a specific threshold; exercise exposure beyond this threshold is associated with an attenuated effect on cancer outcomes, suggesting that an upper threshold or optimal dose of exercise exists to impact cancer outcomes. The importance of elucidating the dose-response effect in exercise and cancer outcomes is underscored by preclinical data studies showing that moderate-intensity exercise (forced swimming, 8 minutes per day, 9 weeks) reduced metastatic burden in the lung, whereas strenuous exercise (forced swimming, 16 or 32 minutes per day, 9 weeks) accelerated metastasis.[106] Similarly, the conventional treatment approach is delivery of the maximum tolerated dose, because the maximum tolerated dose is considered to provide optimal cancer cell killing. However, elegant preclinical work demonstrated that the conventional maximum tolerated dose accelerates the emergence of resistant clones, whereas evolution-based approaches (e.g., initial tumor control with intense doses then maintenance with smaller, variable doses) may prolong progression-free survival.[107] Such a dosing schedule is somewhat analogous to a nonlinear exercise prescription that adheres to the concept of progressive overload; no study to date has compared the antitumor activity of standard versus nonlinear exercise dosing on tumor outcomes.

CONCLUSION

On the basis of progress over the past decade, it is anticipated that exercise therapy will become an increasingly important strategy in cancer prevention and control efforts over the next 2 decades. Continued progress in this arena will require close attention to the adoption of the concepts presented here to optimize the safety and efficacy of exercise in cancer. We focused attention on cardiovascular toxicity and oncology endpoints in cancer, but the concepts and approach described can be applied to essentially any endpoint, including patient-reported outcomes. It is hoped that attention to these issues will provide the platform for constructive dialogue with the view toward the development of standardized exercise guidelines for patients with cancer.

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Improving Cancer Care Through the Patient Experience: How to Use Patient-Reported Outcomes in Clinical Practice

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OVERVIEW

Poorly controlled symptoms are common and debilitating during cancer treatment and can affect functional status and quality of life, health care resource utilization, treatment adherence, and cancer survivorship. Historically, the patient experience, including symptoms during treatment, has not been tracked or documented in the patient health record. Measurement of patient-reported outcomes (PROs), including symptoms, is an essential component to cancer care focused on the illness impact to the patient and family. PROs can be useful at the individual level for monitoring and promoting symptom care both in the clinic and remotely and at the population level for aggregating population data for use in research and quality improvement initiatives. Implementation of PROs in cancer clinical care requires a carefully thought out process to overcome challenges related to integrating PROs into existing electronic health records and clinical work flow. Issues with implementing PRO collection may include making decisions about measurement tools, modes of delivery, frequency of measurement, and interpretation that are guided by a clarification of the purpose for collecting PROs. We focus on three aspects of PRO use: (1) improving care for individual patients, (2) analyzing aggregated data to improve care and outcomes overall, and (3) considerations in implementing PRO collection.

Continuing advances in cancer treatment and targeted therapies have improved cancer survival and outcomes. However, cancer and its treatment are accompanied by distressing symptoms and serious toxicities that affect functioning and quality of life.[1] Patients arrive in the therapeutic setting with varying levels of symptoms. Once cancer treatment begins, another profile of symptoms commences as toxicities and treatment-related complications develop. Symptom burden is negatively correlated with a patient's quality of life, and distressing symptoms can persist long after treatment.[2,3] Dealing with the demands of treatment and the accompanying symptoms, toxicities, and worries dominates the patient and family experience. Standard symptom care includes providing patients with a variety of prescriptions for symptom treatment and written educational materials on symptom management at the beginning of treatment and instructions to call the oncology clinic if symptoms are not well controlled. Despite this, there is evidence that patients rarely call and that symptom burden remains considerable.[4] When symptoms are poorly controlled, they can result in emergency department visits, unplanned hospitalizations, delays in treatment, and lack of adherence and persistence with an effective treatment course.[5-8] Symptoms commonly linger after initial treatment is complete. Survivors requiring prolonged maintenance therapy after initial treatment, such as hormonal therapy, often discontinue their medication due to symptoms, even though it has clearly been shown to prolong disease free survival.[9,10]

Improving cancer outcomes requires a focus not only on the tumor but also the illness experience and its impact on patients and their families. With an increasing emphasis on value-based care rather than fee-for-service, the patient's perspective on what brings value is central to improving outcomes.[11] Measurement of outcomes, including the patient experience, is also an essential component to systematically monitor and improve care. Historically the patient experience, including symptom presence and severity, has not been systematically tracked or consistently documented in the electronic health record (EHR) in contrast to other data elements, such as laboratory values or tumor markers. Adding patient-reported outcomes (PROs) and data to routine clinical care requires substantial planning, logistics, and adjustment in care delivery practices. Technology now permits electronic capture of patient-reported symptoms, functioning, and quality of life, but adoption into routine care is slow. In a recent perspective, Basch[12] identified three challenges limiting adoption: lack of integration of PRO data

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into EHR systems, lack of reimbursement for implementation and monitoring PROs, and lack of effective processes for integration into the clinical care work flow.

Despite current barriers that dampen adoption, a growing number of cancer care organizations are implementing electronic PRO measurement, sharing their experiences, and improving care and outcomes on the basis of the data.[12] As the benefits of systematic PRO collection and integration in clinical care become more widely known, the tipping point for adoption will rapidly occur. PROs have several important uses. They can be used during the clinical encounter to intensify symptom care and improve quality of life, and they can be used to remotely monitor patients and intervene in between clinic visits. In addition, they can be aggregated into population-level data and used to guide quality improvement initiatives. Through analysis of large PRO data sets, they can also be used to provide patients with information and decision aids in choosing among treatment options or understanding the likely patient experience and recovery course of a particular treatment approach. In this article we summarize our session at the 2017 ASCO Annual Meeting on the use of PROs in clinical practice. We focus on three aspects of PRO use: (1) improving care for individual patients, (2) analyzing aggregated data to improve care and outcomes overall, and (3) considerations in implementing PRO collection.

USING PROS AT THE POINT OF CARE FOR INDIVIDUAL PATIENTS

Many cancer clinicians and researchers are aware of the importance of measuring both the tumor response as well as the individual's experienced response. Analytic reports have emphasized the relationships between quality of life and survival outcomes. Today's rapid expansion of genomic profiling adds another dimension to what has been termed personalized or precision medicine. Cancer care that attends to genetic risk, tumor profiles, and biologic responses, yet omits systematic assessment and treatment of the patient's personal experience, is incomplete. Too often, the care system priorities of logistics and cost take precedence, and patient-centered care remains a frequently espoused ideal without meaningful implementation and evaluation. The first step in addressing the priority concerns of a patient treated for cancer is to assess those priorities. Since the 1960s, cancer clinicians and researchers have used various approaches to patient-reported information and data as the subjective component of a comprehensive assessment. Although there is a universal understanding that the patient's self-appraisal does not always match the clinician's appraisal, we still grapple with how to reconcile differing perspectives. The path to a reliable and valid patient-reported symptom or quality-of-life instrument is neither simple nor rapid. Contemporary understanding of usability, literacy, and cultural sensitivity issues demands instrument and program testing in diverse settings and populations.

Patient-provider communication is required for adequate symptom management. Clinicians obtain information about patients using several methods, including physical examination, imaging, clinical chemistry, and direct questioning of the patient to obtain history and symptoms. There is considerable evidence that patients and physicians do not communicate well with respect to this last category of patient-reported data. In a study from the Memorial Sloan Kettering Cancer Center, 467 patients with breast, lung, genitourinary, or gynecologic cancer completed symptom questionnaires at a total of 4,034 clinic visits. Their reports were compared with those recorded by doctors and nurses treating those patients at the same visits as a part of standard institutional documentation. Clinicians dramatically underestimated symptom incidence. For instance, at 1 year, appetite loss was reported by about a third of patients but was documented in the case notes of fewer than one in 20.[13]

This study is complemented by an extensive literature. Xiao et al[14] conducted a systematic review that included no fewer than 36 papers comparing physician- and patient-reported symptoms in cancer and documented consistent evidence that clinicians "underestimate the incidence, severity, or distress of symptoms experienced by cancer patients." Thus to be accurate, the patient experience, including symptoms, needs to be reported by the patient and clearly documented and tracked in the patient's health record.

Thoroughly discussing symptoms and quality-of-life issues in the face-to-face clinic visit can promote partnership between clinicians and patients,[15] validate the patient's experiences, enhance communication and satisfaction[16] and reduce symptom distress.[17] However, our current health system is characterized by limited face-to-face patient-clinician contacts. Time constraints within the context of an exam visit and patients' hesitancy to verbally report certain symptoms[18] can result in missed or undercommunicated symptoms and quality-of-life issues of important clinical significance.[19] PRO assessment prior to the actual face-to-face encounter and summarized data and graphs displaying trends over time greatly improve the likelihood that symptoms can be addressed efficiently during the visit.

KEY POINTS

- **Measurement of PROs is an essential component of cancer care.**
- **PROs are useful at the individual level for monitoring and promoting symptom care both in the clinic and remotely.**
- **PROs are useful at the population level for aggregating population data for use in research and quality improvement initiatives.**
- **Issues with implementing PRO collection may include making decisions about measurement tools, modes of delivery, frequency of measurement, and interpretation that are guided by a clarification of the purpose for collecting PROs.**
- **Clinician champions are essential to accelerate the adoption of PROs in clinical practice.**

Various strategies to enhance patient-clinician communication have been studied. Trials in the United States, Canada, Australia, and northern Europe have shown symptom and quality-of-life clinical screening with or without supportive intervention to be feasible and clinically beneficial with regard to communication and, most important, patient outcomes. Table 1 provides a summary of some of these trials. The methods of delivery vary widely, and only a minority conducted usability and feasibility testing. Several large trial[20-23] interventions included a substantial component of personal contact by study nurses or coordinators, minimizing the practicality of such interventions outside of the research setting. Yet we see evidence that clinicians can readily use PRO summaries in practice,[24,25] and such use results in significantly enhanced communication and improved patient experience.[23,26] Questions remain, however, on the cost-effectiveness of programs in which patients monitor symptoms and quality of life, and feedback is given to clinicians who may or may not intervene appropriately.[27]

There is copious evidence from high-quality randomized trials that beyond being valid and feasible, integrating electronic patient-reported data in clinical care improves both care processes and care outcomes. Berry et al[17,26] conducted two randomized trials in a total of 1,512 ambulatory patients starting active cancer therapy at two comprehensive cancer centers in Seattle and Boston. All patients completed online symptom questionnaires but, in the first trial, were randomly assigned to have a graphical summary of symptoms and quality-of-life concerns reported or not reported to the clinical team. The probability that a symptom was discussed during a consultation differed between groups only if the patient reported the symptom as problematic on the electronic questionnaire ($p = .03$), providing clear evidence that reporting of electronically gathered patient-reported data to doctors did influence the subsequent consultation. Of particular interest, there was no difference in consultation time. In other words, patient-reported data appear to improve the quality of the consultation without increasing the duration of the consultation.[26] The intervention in the second randomized trial added a patient-facing intervention to the graphical clinician summary: self-monitoring between visits and communication coaching and self-management instructions tailored to each problematic symptom. Again, the intervention enhanced patient provider communication,[34] and the intervention patients reported significantly less symptom distress and depression than the control group patients.[17]

Cleeland et al[38] examined the effects of electronic patient-reported outcomes on postoperative outcomes. One hundred patients undergoing thoracotomy for lung cancer or lung metastasis, 60% of whom were aged over 60, received automatic telephone calls and completed interactive voice response system symptom reports twice weekly for 4 weeks. Using a similar approach to that of Berry et al,[26] patients were then randomized to have their reports forwarded to clinical staff members or not. Patients in the experimental arm had a far greater reduction in severe symptoms over time than controls. This was particularly apparent for the pain endpoint, with 60 severe pain events in controls compared with only 20 in patients on the intervention arm. There were also statistically significant differences between groups in symptom interference and patient satisfaction.[38]

The largest trial, which was recently reported by Basch et al,[23] involved 766 participants undergoing chemotherapy for advanced solid tumors. Participants were randomized to electronic symptom reporting on tablets in clinic and via email from home or to routine symptom monitoring from clinicians. Health-related quality of life was measured for all patients at 6 months. In the usual care control group, 53% of patients experienced worsening of quality of life during the trial, 18% improved, and 29% were unchanged. In contrast, only 38% of patients in the intervention group had poorer quality of life at 6 months, with 34% improving and 28% unchanged ($p < .001$ for difference between groups). Given the high morbidity in this population, these quality-of-life differences translated to a statistically significant difference is emergency department visits. Survival was also higher in the electronic symptom reporting group, with 75.1% 1-year survival compared with 68.6% in controls. If a drug were found that could reduce mortality while improving quality of life and decreasing urgent care visits, we would consider such a drug to be standard of care.

Patient-reported data can identify patients at risk for missed chemotherapy, adverse events, and even shortened survival. For example, nonadherence to oral chemotherapy or hormonal agents has been related to severity of cancer symptoms and side effects[36,39] as well as demographic variables such as gender,[34,40] marital status,[36,40,41] and working status.[31] PRO tracking systems can monitor side effects and facilitate adherence and resolution of unpleasant side effects. PRO use can also decrease inappropriate health care utilization. Symptom and quality-of-life monitoring and interventions have been shown to reduce unplanned hospital admissions and emergency department visits.[23,42,43] Finally, PRO monitoring that results in improved symptom and quality-of-life outcomes may contribute to extending survival, as there is emerging evidence that depression and anxiety[44,45] and fatigue[46] are significant independent predictors of survival.

USING PROS FOR CLINICAL DECISION MAKING THROUGH USE OF PRO DATABASES

The adoption of systematic PRO use in clinical practice allows PRO data to be aggregated and used for clinical decision support and quality improvement initiatives, or what has been termed data integration. The theory behind data integration is that if a patient is asked a question once electronically, the response can be reused for multiple different purposes: clinical care, research, and quality assurance. The Division of Urology at the Memorial Sloan Kettering Cancer Center has played a leading role in piloting the concept of data integration. Urology patients complete electronic questionnaires about recovery of erectile and urinary function after radical prostatectomy at home via an email link

TABLE 1. Selected Cancer Symptom and Quality-of-Life Assessment and Intervention Studies With Multisymptom PRO Outcome Evaluation in Patients With Cancer at the Point of Service During Active Curative or Palliative Treatment, 2004 to 2016

First Author, Year; Country	Sample	Design; Intervention	PROs	Usability Testing	Feasibility testing	Satisfaction or Acceptability Measure	Significantly Enhanced Communication Outcomes	Significantly Improved Outcomes on Specific PROs
Velikova, 2004,[28] 2010[29]; U.K.	N = 286; mixed dx, 73% women, 83% metastatic in cancer specialty clinic	RCT; in clinic PR using touchscreen PCs with graphed results to MD	EORTC QLQ-C30); HADS; FACT-G; MCQ	Yes	Yes	Yes	Communication subscale of MCQ at 3 months	General, emotional, physical and functional well-being of FACT-G; over time 3+ months
Boyes, 2006[30]; Australia	N = 80; mixed dx, 60% women, stage NR, in cancer specialty clinic	RCT; in clinic PR using touchscreen PCs with graphed results to MD	Physical symptoms; HADS; SCNS	No	No	Yes	Not tested	Better physical symptoms at second clinic/study visit
Rosenbloom, 2007[21]; U.S.	N = 213; breast, colorectal, lung; 67% women; 56% stage IV	RCT; in clinic PR on paper, research RN interview plus info passed to clinic RN	FACT-G; FLIC; brief POMS-17;MOS-PSQ III	No	No	No	Not tested	None
Carlson, 2010[31]; Canada	N = 1,134; lung and breast cancer, 73% women; 19% stage IV in cancer specialty clinic	RCT; in clinic PR using touchscreen PCs, screening with triage; graphed results to MD	DT; PSSCAN	No	Yes	No	Not tested	In breast cancer, lower DT scores at 3 months
Hilarius, 2008[32]; Netherlands	N = 219; mixed dx, 70% women, 32% receiving palliative therapy in community hospital clinic	Pre-post; PR in clinic on touchscreen PC with graphed results to RN	PRO survey regarding whether particular issue discussed; SF-36; FACT-BCS; FACT-C; FACT-L	No	No	Yes	More topics discussed at fourth clinic/study visit	None
Ruland, 2010[33]; Norway	N = 145; lymphoma and leukemia, 38% women in cancer specialty units and clinics	RCT; PR on tablet PC in clinic or hospital unit with printed summary to MDs and RNs	19 cancer symptom categories	Yes	Yes	Yes	No	Less discomfort, better eating/drinking, sleep/rest and sexuality up to 1 year
Klinkhammer-Schalke, 2012[20]; Germany	N = 200; breast cancer; 100% women; mixed stages in community hospitals	RCT; PR in hospital just before discharge; referral to experts for issues related to physical, psychosocial, pain and nutrition/fitness issues	EORTC QlQ C-30 & Breast-25	No	Yes	No	Not tested	Better Global QOL and emotional function at 6 months; physical and emotional function at 9 months; arm symptoms at 12 months

Continued

TABLE 1. Selected Cancer Symptom and Quality-of-Life Assessment and Intervention Studies With Multisymptom PRO Outcome Evaluation in Patients With Cancer at the Point of Service During Active Curative or Palliative Treatment, 2004 to 2016 (Cont'd)

First Author, Year; Country	Sample	Design; Intervention	PROs	Usability Testing	Feasibility testing	Satisfaction or Acceptability Measure	Significantly Enhanced Communication Outcomes	Significantly Improved Outcomes on Specific PROs
Berry, 2014,[17,34] 2015,[35] 2015[36]; U.S.	N = 752; mixed dx, 48% women, 28% stage IV in cancer specialty clinic	RCT; in clinic PR using home access or touchscreen PCs with graphed results to clinicians, plus electronic communication coaching and tailored self-care instruction	SDS; EORTC QLQ C-30; EORTC-CIPN-20; PHQ-9; PINS; PROMIS pain interfere; skin changes	Yes	Yes	Yes	Number of patient to provider statements for problematic symptoms and QOL	Lower symptom distress on SDS and lower depression on PHQ-9 at end of treatment
Basch, 2016[23]; U.S.	N = 766; mixed dx, 58% women, advanced solid tumors in cancer specialty clinic	RCT; in clinic PR touchscreen PCs + home access with graphed results to RN+MD and auto-alerts to nurses who provided telephone support	EuroQol EQ-5D	No	Yes	Yes	Not tested	Better QOL on EuroQol EQ-5D
Steel, 2016[22]; U.S.	N = 261; liver, gallbladder cancers, primary and metastatic; 27% women, 100% advanced in cancer specialty clinic	RCT; in clinic PR via interview + home access or with face—face care coordination in clinic + telephone support	CES-D; BPI; FACT-G; FACT-Fatigue; FACT-Anemia; FACT-Hep	No	No	No	Not tested	Depression on CES-D and QOL on FACT-G at 6 months
Watson, 2016[37]; Canada	N = 1,274; mixed dx; gender % NR; stage NR; population based, provincial specialty clinics	Pre-post; paper PRO results given to RN or radiation therapist for discussion with patient; referrals made as needed	ESAS; CPC; FACT-G	No	Yes	No	Not tested	Fewer severe symptoms on ESAS and fewer problems on CPC reported in 10 month post period

Abbreviations: PRO, patient-reported outcomes; dx, diagnosis; RCT, randomized controlled trial; PR, patient report; PC, personal computer; MD, medical doctor; NR, not reported; RN, nurse.

or in the clinic on tablets. The data are presented to surgeons at follow-up visits in the form of a report. This allows surgeons to focus the consultation on relevant aspects of patients' recovery. Take, for instance, a patient who has recovered urinary but not erectile function. Instead of starting the consultation with a list of general questions (e.g., "Are you using pads?", "Do you have to rush to the bathroom?", "Are you able to get an erection?"), the surgeon is able to say, "Your urinary function seems reasonable but you seem to be having erectile dysfunction. Do you want to talk about that?"

The use of electronically reported patient data in prediction modeling aids in clinical decision making. In a report provided to urologists at Memorial Sloan Kettering Cancer Center following patients after radical prostatectomy, there are several prediction models that inform clinical decision making. First, in Fig. 1A, actual patient recovery is plotted against expected recovery for the individual patient. For instance, the patient is an older man with only moderate erectile function at baseline. The graph shows that his expected erectile function was estimated using linear regression, predicting postoperative function using patients' age and erectile function before surgery. Second, we can make predictions about future progress based on a patient's progress to date. The patient, for instance could be told even at 6 months that he was unlikely to recover erectile function and that a referral to sexual medicine might be appropriate.

As another example, Fig. 1B shows the life expectancy calculation based on data electronically reported by a patient with prostate cancer about his comorbidity and general health status. Patients and providers are given the probability that a man will die of other causes within 10 and 15 years and then the probability that he will die of prostate cancer, taking into account the risk for other-cause mortality.[47] This life expectancy information aids in deciding whether active treatment of the patient is warranted or whether the patient's disease is better followed through an active surveillance program.

Additionally, there is increasing use of PROs for developing quality improvement initiatives focused on clinical care of symptoms and improvement of patient quality of life. PROs provide unique information about the patient's perspective on what brings value.[11] Measurement of outcomes, from the perspective of the patient, is an essential component to systematically monitoring the care provided in any institution or care setting. PROs may be useful for studying patients' experiences with care, for assessing hospital care quality, and for developing standing methods for monitoring symptomatic adverse effects to medications.[48-50] Troeschel et al[51] described the use of PROs to develop symptom management quality improvement reports, demonstrating feasibility and acceptability. At a clinical care level, PROs provide valuable information about clinician symptom management effectiveness and value from the patient perspective.[51,52] Importantly, PRO databases provide an efficient method for collecting and tracking patient-based data related to care effectiveness, care outcomes, and care satisfaction.

CONSIDERATIONS IN IMPLEMENTING SYSTEMATIC PRO MEASUREMENT

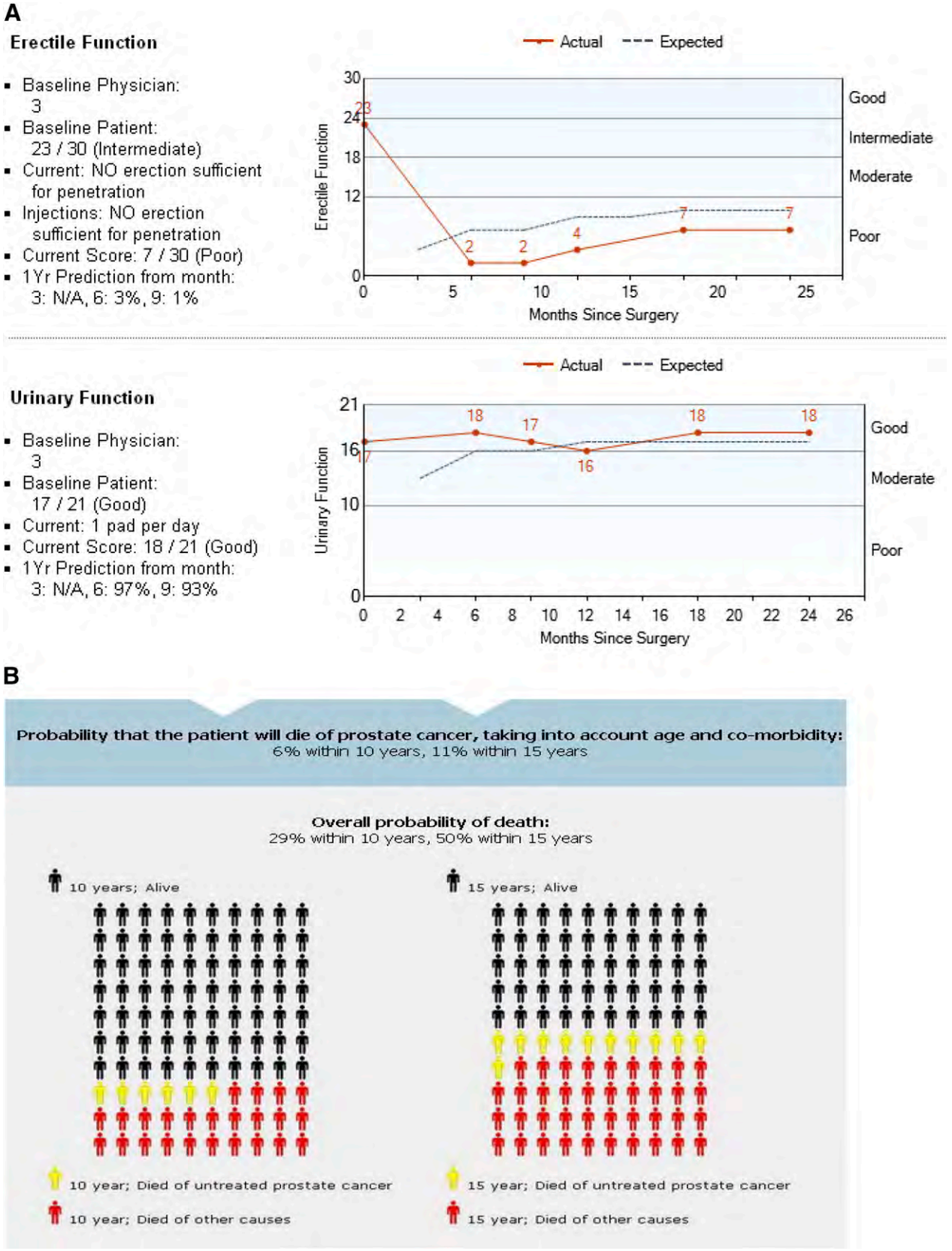
Successful implementation of PRO measurement and routine use in clinical practices or to track outcomes requires a number of choices and a carefully thought through process. The International Society for Quality of Life Research offers a very helpful guide for planning PRO implementation.[53] To begin the process, practices should clarify the purpose for collecting PROs. For example, is it to improve individual patient care or to track outcomes using pooled data for quality improvement? Design decisions will vary on the basis of the primary purpose. Subsequent choices, such as questionnaire selection, frequency of delivery, and immediacy of scoring, depend on a clear understanding of purposes. If both patient-level and population-level data are desired, some compromise in selection will be needed. Assessment of resources that will be needed for PRO implementation and availability of technology and technical support for patient and for staff and clinician users is also an important early consideration.[54]

Choosing the questionnaire(s) to use should be based on the domains to be measured, which may include symptoms, functional performance, and/or quality of life. Patient burden must be balanced with the completeness of measurement. Another consideration is whether to use generic measures that can be compared with population norms and used across cancers throughout the continuum of care. Generic measures are often used if the primary purpose is to track outcomes. If, however, the primary purpose is to improve care at the individual patient level, using disease- or treatment-specific measures is recommended because they better capture the pertinent symptoms the patient is experiencing. Knowing the expected symptoms in a particular patient population and treatment scenario also influences questionnaire choice. Patients become annoyed when they complete lengthy symptom questionnaires and yet key symptoms they find bothersome are not assessed.

Symptom assessment questionnaires can be a series of single-item measures of individual symptoms or multiple items for each symptom. Single items are concise, address patient burden, and allow the greatest number of symptoms to be addressed, whereas multiple items for each symptom may be more precise and valid but reduces the number of symptoms that can be assessed because of burden. Some multi-item scales, such as the PROMIS measures, come in computerized adaptive testing formats that allow rapid assessment with fewer questions per assessment than the static version. Choosing particular questionnaires should match the focus of the desired assessment such as symptom presence, severity, frequency, or burden.

Although studies have found that patient acceptability of PRO measurement is generally high, especially if they see the data being used to address their needs, questionnaire selection needs to address health literacy, readability, availability in various languages, and the quality of visual display or format.[55] Patients need an explanation of the purpose of collecting PROs, especially if frequent assessments are

FIGURE 1. Electronic Patient-Reported Data Can Be Used Immediately by Clinicians to Aid in Medical Decision Making



(A) Expected versus observed erectile and urinary function after radical prostatectomy for an individual patient. Expected recovery is estimated using data collected from other patients with similar characteristics (e.g., similar age and baseline function). (B) Probability of death of prostate cancer and other causes using data reported by the patient regarding general health status.

planned. PRO measurement can increase patients' satisfaction and engagement in their care if the patients understand the purpose.[56]

An important consideration in implementation design is the mode of delivery. Technology advances make electronic delivery feasible, but there is cost associated with deploying tablets or installing computer kiosks or other devices to collect PROs in clinic settings. To be useful at the point of care, PRO data should be immediately available and integrated into the EHR, because it is the single source of all other patient data. EHR vendors have been slow to facilitate PRO integration, although patient portals have evolved to include some PRO questionnaires that can be pushed to patients for completion prior to clinic visits.[53]

Frequency of measurement is another decision point. When tracking outcomes and change over time is the primary purpose, periodic measurement is appropriate. Consideration should be given whether assessments should be based on calendar dates, such as quarterly, or timed to phases in care transition or some combination. However, when the primary purpose is improving the individual patient experience, more frequent assessment is needed. Commonly, measurement is paired with a clinic visit and can be completed at home prior to the appointment or at check-in for the visit. Collection in the clinic involves consideration of work flow and participation of front-end staff members in facilitating collection. Adoption of PRO measurement can be hampered by clinicians' concern that it will be disruptive to work flow. Attention to integration is critical.

If improving individual patient care is the objective, monitoring between clinic visits may also be considered. This overcomes several key issues in symptom management, namely, that patients may not initiate calls to clinicians about poorly controlled symptoms, and symptoms normally peak at various times during the interim period between visits and are therefore missed if measurement is only timed with a scheduled visit. Although feasible, remote monitoring does add burden to clinicians in monitoring and responding to intensify care. Severity thresholds can be set to automatically alert clinicians of poorly controlled symptoms, thereby decreasing the burden of reviewing all PRO data reported. This, combined with automated self-care coaching based on the symptom severity reported, can significantly improve symptom outcomes.[4] Mooney et al[4] recently reported on a clinical trial of automated home monitoring of PROs in which patients receiving chemotherapy reported daily symptom presence and severity for 11 symptoms. The intervention group immediately received automated self-care coaching based on the specific symptom pattern reported, and automated alerts were sent to a nurse practitioner who used a guideline-based decision support system to call patients and adjust care for poorly controlled symptoms. The intervention group had significantly less symptom severity across all symptoms ($p < .001$), with a symptom reduction burden of nearly 43% compared with usual care. Examining days when participants reported one or more severe or one or more moderate symptoms, intervention participants had 67% fewer severe days and 39% fewer moderate days compared with the usual care group ($p < .001$ for both). As telehealth approaches become more widespread, remote PRO monitoring may extend care beyond the walls of the health systems to patients and families at home.

Scoring and interpretation of PROs also requires substantial planning when used for individual patient care.[57] Immediacy of the data and scoring is imperative. Integration in the EHR is ideal. Protocols must be designed to clarify who will receive the reports, what are clinically actionable thresholds, who will be responsible for follow-up, and whether any automatic referrals are generated. The design of reports is also important. Use will improve if interpretation is easy and concisely addresses and displays the data. For example, will only numeric scores be presented, or can they be accompanied by simple visual graphs to clearly spot out-of-norm values and trends over time? Other considerations include whether a copy of the data will be provided to the patient as a part of the care planning and to engage the patient in self-care. A final consideration is whether guideline-based decision support recommendations should be provided to clinicians so that they can efficiently take the next steps to improve care for poorly controlled symptoms and quality-of-life concerns.[58] Measurement of PROs alone with not improve patient outcomes unless clinicians act on the data.[59]

Clinical champions are essential to create enthusiasm and accelerate the adoption process. Involvement of clinicians and staff members in thinking through the many decisions and designing and adapting processes to fit with work flow and clinic characteristics is exceedingly important. Greater value will be gained beyond the individual patient level, by involving clinicians in examining aggregated data and generating quality improvement initiatives as needed. Ongoing clinical analysis of the real-world patient experience of cancer and its treatment through PROs is an important component for a rapid learning system to improve cancer care.[60]

CONCLUSION

There is considerable evidence that patient-reported data are poorly documented by clinicians. Collection of patient-reported data using electronic tools has been shown to be accurate and feasible in both the clinical and research settings and has been demonstrated, in randomized trials, to improve both quality of life and mortality endpoints. An added benefit of collecting patient-reported data is the documentation of the patient perspective on care endpoints, which then can be used to direct quality improvement initiatives. Collection of PROs is now feasible and generally well accepted by patients. It is consistent with a patient-centered philosophy and a value-based care framework. Systematic PRO collection, integration in the EHR, and use of the data to improve care now provide both a broader and richer approach to evaluating cancer outcomes. Implementation requires the commitment of resources, thoughtful planning and monitoring, and clinical champions who see the value and are willing to work through the process of adoption.

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Pain and Opioids in Cancer Care: Benefits, Risks, and Alternatives

Mike Bennett, MD, FRCP, FFPMRCA, Judith A. Paice, PhD, RN, and Mark Wallace, MD

OVERVIEW

Pain remains common in the setting of malignancy, occurring as a consequence of cancer and its treatment. Several high-quality studies confirm that more than 50% of all patients with cancer experience moderate to severe pain. The prevalence of pain in cancer survivors is estimated to be 40%, while close to two-thirds of those with advanced disease live with pain. Progress has occurred in the management of cancer pain, yet undertreatment persists. Additionally, new challenges are threatening these advances. These challenges are numerous and include educational deficits, time restraints, and limited access to all types of care. New challenges to access are occurring as a result of interventions designed to combat the prescription drug abuse epidemic, with fewer clinicians willing to prescribe opioids, pharmacies reluctant to stock the medications, and payers placing strict limits on reimbursement. A related challenge is our evolving understanding of the risks of long-term adverse effects associated with opioids. And reflective of the opioid abuse epidemic affecting the general population, the potential for misuse or abuse exists in those with cancer. Guidelines have been developed to support oncologists when prescribing the long-term use of opioids for cancer survivors. The challenges surrounding the use of opioids, and the need for safe and effective alternative analgesics, are leading to intense interest in the potential benefits of cannabis for cancer-related pain. Oncologists are faced with questions regarding the types of cannabis available, differences between routes of administration, data concerning safety and efficacy, and legal and regulatory dynamics.

Pain remains a disturbingly common consequence of cancer and its treatment. In a large study of more than 5,000 adults with cancer, 56% suffered moderate to severe pain at least monthly.[1] A large systematic review of 52 studies confirmed this high prevalence, with 53% of people at all stages of cancer experiencing pain.[2] Although there is evidence that the management of cancer pain has improved, undertreatment remains common and new challenges are threatening the fragile progress that has previously been made.[3] These challenges are numerous and include educational deficits, time restraints, and limited access to all types of care.[4] Comprehensive cancer pain management includes a thorough assessment along with the use of pharmacologic, nonpharmacologic, integrative, and interventional therapies.[5] Reimbursement for many of these therapies is limited, particularly for nonpharmacologic techniques such as mental health counseling, physical or occupational therapy, massage, and integrative medicine. As a result, access to cancer pain management is often restricted to pharmacologic therapies.

Opioids are the mainstay of this pharmacologic management and are essential for those with pain from advanced disease. However, our evolving understanding of the risks of long-term adverse effects, including the potential for misuse or abuse, raises concerns about the long-term use of opioids for cancer survivors.[6] These challenges surrounding the use of opioids, and the need for safe and effective alternative analgesics, are leading to intense interest in the potential benefits of cannabis for cancer-related pain.

OPIOIDS IN ADVANCED CANCER: ACCESS, EFFICACY, AND OUTCOMES

Access

Cancer that is locally progressive or has metastasized is frequently painful. A systematic review by van den Beuken-van Everdingen showed that pain prevalence rises with disease progression and affects about 64% of patients with advanced cancer.[2] About 45% of all patients with advanced cancer experience pain of moderate to severe intensity (at least 5 on a 0–10 pain rating scale).[1,2]

Morphine and other strong opioids are key to managing pain in advanced cancer. Since 1986, the focus of cancer pain treatment has been the use of strong opioids based on the World Health Organization's (WHO's) "analgesic ladder."[7] Globally, 8.2 million people die of advanced cancer each year, and the WHO estimates that around 6 million of

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these patients have inadequate or no access to strong opioids largely because there has been no increase in availability of opioids for decades in the world's poorest but most populated countries.[8,9] This is largely because of government regulations that restrict supply and access.[10] Even in developed countries in which there is good access to opioids, at least 32% of patients with cancer are undertreated for their pain.[3] There is understandable concern about abuse of prescription opioids in contexts other than advanced disease, and there is increased tightening of prescribing regulations for opioids in the United States in particular.[11] This restrictive attitude toward opioids should not be allowed to exacerbate the existing undertreatment of pain in advanced cancer.[12]

Retrospective cohort analyses estimate that only 43%–48% of U.K. patients with cancer receive a strong opioid before their death,[13,14] though this might be as high as 60% in Norway.[15] Ziegler et al[14] demonstrated that median time between initiation of strong opioids and death for 6,080 patients was 9 weeks, with increasing age associated with significantly later initiation of treatment, consistent with other studies.[13,15] Patients who died in the hospital were less likely to be prescribed a strong opioid while at home, compared with those who died in hospice, and were more likely to commence strong opioids late. These variations were not explained by cancer type, duration of disease, or socioeconomic deprivation. This suggests that poor pain control at home may result in admission to and subsequent death in the hospital. Therefore, earlier pain assessment might lead to improved access to opioids and improved outcomes for patients.

Even in developed countries, patients with cancer appear to access strong opioids relatively late in their disease. One methodological issue with these epidemiologic data are that they cannot be matched with individual patient-reported pain data. This means that it remains uncertain whether this pattern of opioid access closely matches the patients' onset of pain before death or highlights undertreatment. The latter seems more likely based on known epidemiology of duration of cancer pain in large cohorts.[1]

KEY POINTS

- **Cancer pain is prevalent throughout the disease trajectory, yet undertreatment continues to be a significant problem.**
- **Clinical experience, research, and systematic reviews all demonstrate the efficacy of opioids in relieving cancer pain, particularly in the setting of advanced disease.**
- **Despite efficacy in relieving cancer pain, the long-term use of opioids is associated with previously unrecognized adverse effects, including endocrinopathy, neurotoxicity, sleep-disordered breathing, and, in some circumstances, misuse or abuse.**
- **In an aim to provide comfort, improve function, and limit adverse effects, multimodal interventions that include pharmacologic and nonpharmacologic therapies are needed to treat cancer pain.**
- **Although not recommended as first-line therapy, cannabis may be considered as an adjuvant analgesic in the management of refractory cancer pain.**

Efficacy

How effective are strong opioids for patients with cancer pain? Initial observational studies that evaluated the WHO ladder suggested that this approach could control pain in around 73% of patients with cancer.[16,17] In absolute terms, one randomized trial that compared morphine with oxycodone in patients with cancer pain showed that both strong opioids provided good pain control in 75% of patients.[18] Both strong opioids produced approximately a 3-point mean reduction on a 0–10 pain rating scale at a group level, although these data were not compared with response to placebo. There were no differences in adverse effects.

A meta-analysis of clinical trials of strong opioids has provided more detailed and comparative data. The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom published a detailed meta-analysis confirming that there were no significant differences in efficacy between morphine, oxycodone, transdermal fentanyl, and transdermal buprenorphine.[19] Specifically, there were no differences in efficacy or adverse effects between morphine and oxycodone—probably the most frequently prescribed strong opioids for cancer pain globally.[20] Overall, there were no differences in burden of adverse effects across all strong opioids, though transdermal opioids were significantly less likely to cause constipation than oral opioids (odds ratio 0.43; $p < .002$).

Another recently published randomized trial directly compared these same four strong opioids (morphine, oxycodone, transdermal fentanyl, and transdermal buprenorphine). Corli et al[21] showed no differences in efficacy between all opioids (all of which produced approximately a 3-point mean reduction on a 0-10 pain rating scale at a group level) and, interestingly, showed no differences in prevalence of constipation. The only significant differences occurred between morphine and fentanyl in the incidence of hallucinations (13.2% vs. 2.4%; $p = .001$) and severe confusion (15.5% vs. 6.3%; $p = .018$) that favored transdermal fentanyl.

In summary, strong opioids are very effective interventions for cancer pain resulting in a 75% response rate and reducing average pain intensity from 6 to 3 on a 0–10 pain scale.[20,21] When compared with the early evaluations of the WHO analgesic ladder, these more recent data imply that the effectiveness of the WHO approach is based entirely on strong opioids, with no substantial contribution from other approaches. These studies underpin international guidance on strong opioids for cancer pain that advises first-line treatment with either morphine, oxycodone, transdermal fentanyl, or transdermal buprenorphine based on efficacy.[5,22] In the United Kingdom, NICE guidance recommends morphine as a first-line opioid because of its substantially cheaper cost.[19]

Outcomes

What is a meaningful outcome for a patient with cancer pain? Understandably, patients express that they want to be pain free, although, in general, they do not actually expect their pain to be relieved completely.[23] Bender et al[24] identified that patients are keen to understand the cause of their cancer pain, what to expect, options for pain control (including addressing concerns about strong opioids), and how to cope with cancer pain including talking with others and finding help. A number of qualitative studies have revealed that patients seem to determine whether their pain is controlled by whether they can perform activities or tasks and maintain relationships with family or friends.[24,25]

To perform these activities, patients frequently try to reduce interference from both pain and the cognitive effects of analgesia to maintain as much function as possible.[26] This commonly leads to trade-offs between pain and analgesia, impacting medication adherence. The concept of trading off has not been well described in medical literature, but it is clearly seen as important by patients in reaching outcomes that are meaningful for them. For this reason, clinicians should seek to understand patient preferences for cancer pain management when initiating and managing strong opioids.

Key priorities for clinicians regarding pain management strategies for patients with advanced cancer should be to help them achieve a balance between pain and adverse effects of analgesia to optimize physical function and to provide support for self-management.[27,28] Overly simplifying these important outcomes to a numerical rating of pain intensity is likely to be poorly sensitive (patients may be content with the balance of their pain management yet report higher pain scores) or poorly specific (patients may judge their pain control unsatisfactory despite lower pain scores because they struggle with opioid adverse effects, which severely limits their function). A focus on determining interference from pain or analgesia in daily activities and understanding the degree of self-efficacy (ability to cope) are more important measures of successful pain management.

OPIOIDS IN CANCER SURVIVORS: BENEFITS, RISKS, AND CHALLENGES

Currently, there are approximately 15.5 million cancer survivors in the United States, and this number is expected to grow to 26.1 million by 2040.[29] Of these individuals, more than two-thirds have lived 5 years or more after diagnosis, and 44% have survived 10 years or more.[29] Much of these impressive figures in survivorship are because of extraordinary advances in the development of more effective cancer therapies. Unfortunately, many of these highly effective treatments also lead to persistent pain syndromes. As a result, studies suggest the prevalence of pain in cancer survivors may be 40% or higher.[2,30,31]

Benefits and Risks

Although opioids have a clear and primary role in the care of pain associated with advanced disease, their role in relieving pain in cancer survivors is less apparent. The recent ASCO Clinical Practice Guideline Management of Chronic Pain in Survivors of Adult Cancer outlines the results of a systematic review of studies investigating chronic pain management in cancer survivors.[6] One systematic review of randomized controlled trials of opioids for relief of cancer pain found few high-quality, long-term trials.[32] In a large study of more than 500 subjects randomly assigned to receive one of four opioids for 28 days, the worst and average pain intensity decreased over 4 weeks with no significant differences between drugs.[21] Changes in therapy, including dose escalation, switches to other opioids, and the addition of adjuvant analgesics, were common, and close to 15% of patients were nonresponders.[21] Although clinical experience suggests that select patients may obtain safe and effective pain control with opioids, there are no studies that guide clinicians as they consider a trial of opioids in cancer survivors.

Aligned with unclear long-term efficacy is an increasing awareness of the adverse effects associated with prolonged use of opioids (Sidebar). Mental clouding, effects on libido and fertility, hyperalgesia, and sleep disorders can all affect employment, relationships, and overall quality of life.[33-35] Provocative and troubling early data from laboratory models suggest that opioids may affect immune function[36,37] and tumor progression,[38,39] yet it is too early to determine if these findings are clinically meaningful. Of particular concern in the face of the current opioid abuse epidemic is that cancer survivors treated with opioids may also develop opioid or other substance abuse disorders as has been documented in people with chronic noncancer pain.[11,40,41]

Risk Mitigation

Methods to mitigate the risk of harm include careful assessment and awareness of adherence monitoring. Screening tools are available to determine risk of misuse, although none have been validated in an oncology population to date. Key factors that have been found to be associated with opioid misuse/abuse in those with a noncancer diagnosis include male sex, age younger than 65, opioid misuse history, depression, family history of substance use disorders, current smoking, past or current incarceration, and posttraumatic stress disorder.[42-45]

Adherence monitoring may include use of a controlled substance agreement, review of data from prescription drug monitoring programs, periodic drug testing, pill counts, and education.[46-51] After review of assessment data and information obtained from urine drug screening and a prescription drug monitoring program, a decision is made to prescribe based on risk stratification. If risk is low and the pain warrants use of an opioid, the oncologist may decide to prescribe. If the risk of abuse is moderate or high, the oncologist must decide if the severity of the pain is seriously affecting the patient's physical or mental well-being and if there are reasonable alternatives. If the effect of pain is severe and there are no other reasonable alternatives, and the risk of abuse and/or diversion is manageable, a trial of opioids may be considered. Regardless of level of

SIDEBAR. Adverse Effects Associated With Long-Term Opioid Use[6,33-35]

- Constipation
- Mental clouding
- Upper gastrointestinal symptoms (pyrosis, nausea, bloating)
- Endocrinopathy (hypogonadism/hyperprolactinemia)
- Fatigue
- Infertility
- Osteoporosis/osteopenia
- Reduced libido
- Reduced frequency/duration or absence of menses
- Neurotoxicity
- Myoclonus
- Other changes in mental status (including mood effects, memory problems, increased risk of falls in elderly patients)
- Risk of opioid-induced hyperalgesia (incidence and phenomenology uncertain, but escalating pain in tandem with dose-escalation raises concern)
- Sleep-disordered breathing
- Increased risk of concurrent benzodiazepine in patients predisposed to sleep apnea
- New-onset sleep apnea
- Worsening of sleep apnea syndromes

risk, nonopioid and nonpharmacologic therapies should always be optimized.

If opioids are prescribed, adherence monitoring should continue, with the frequency dictated by the level of risk (Table 1).[6] If opioids are ineffective or serious adverse effects occur, careful reconsideration of therapy must occur.

Given the severity of the opioid misuse/abuse epidemic, oncology clinicians must be attentive to the potential for diversion, and those with cancer may be targeted as potential sources of prescription drugs. Education about safe storage and disposal has been shown to increase awareness and improve safe practice by patients.[52]

CANNABINOIDS IN CANCER PAIN MANAGEMENT

Over the past 20 years, the public and medical community's attitude toward cannabinoids has been shifting. Although it remains illegal federally, over half of the U.S. states have legalized the medicinal use, with a handful legalizing recreational use. With this changing landscape comes many challenging questions from oncology providers and patients:

- What role do cannabinoids play in alleviating pain?
- Should physicians recommend cannabinoids for the treatment of pain, particularly pain related to cancer?
- What are the risks and side effects?
- How do patients obtain and use a cannabinoid drug?
- How should physicians who choose to recommend cannabinoids select appropriate patients and monitor them?
- What are the legal and regulatory issues that providers and researchers face in dealing with cannabinoids?

Cannabis Content

The cannabis plant contains over 400 chemical compounds, of which at least 80 are cannabinoids.[53] Delta-9-tetrahydrocannabinol (Δ9-THC) is the most well-known and the primary psychoactive compound in cannabis.[54-56] It mimics the action of anandamide, an endogenous cannabinoid in humans, having approximately equal affinity for the CB1 and CB2 receptors.

Cannabidiol (CBD) is the second most abundant compound in cannabis after THC.[55] It is thought to have wider medical applications than THC, which has fueled the demand for medical marijuana and pharmaceuticals with higher CBD concentrations compared with recreational marijuana.[57] CBD is generally considered to have no psychoactive effects, but clinically it has been reported to reduce seizures, improve muscle spasm, and reduce inflammation.[54,56] It has a very low affinity for the CB1 and CB2 receptors and may act as an inverse agonist/antagonist.[54,55] These interactions with the CB receptors may attenuate some of the psychotropic effects of THC.[54]

In addition to whole-leaf cannabis plants, there is another class of phytocannabinoids collectively referred to as cannabis-based medicine extracts. These are derived by extracting compounds directly from cannabis plants. There are two subtypes of cannabis-based medicine extracts: (1) those produced by pharmaceutical companies under well-regulated, controlled conditions and undergoing rigorous clinical trials and (2) those produced and sold in medical marijuana dispensaries without any regulatory oversight or clinical trials.

Pharmacology of Cannabinoids

The precise pharmacology of most cannabinoids remains unknown. However, researchers have elicited major mechanisms underlying the active compounds in cannabis including THC, CBD, and cannabinol. Complicating this is the highly variable absorption because of the plethora of delivery forms and routes. These include inhalation and ingestion as well as absorption via oral, sublingual, topical, or rectal application.[58] For centuries, the primary means of delivering cannabinoids has been via the inhaled smoke of cannabis or hashish. The variable concentration of THC and other cannabinoids in cannabis, lack of controlled production and testing in most medical marijuana products, and the diversity of delivery routes makes prediction of pharmacologic effects difficult.[56]

In general, the inhalation of cannabis results in a fast predictable plasma concentration of cannabinoids that is short lived allowing for fine titration to affect. Ingestion results in a delayed, variable peak plasma concentration that is more prolonged. Transmucosal delivery results in peak plasma levels similar to ingestion but more rapid and of shorter duration. These different delivery methods can be clinically

used depending on the situation. For example, most patients prefer ingestion at night for the prolonged effect, while inhalation is the preferred method during the daytime (Wallace M, personal experience).

Cannabinoid/Opioid System Interactions

With the prescription opioid overdose crisis in the United States, there is concern over the increasing use of medicinal cannabis and its effects on this crisis. Studies have demonstrated that states with medicinal cannabis legalization have actually seen a reduction in opioid analgesic overdose.[59] A recent retrospective cross-sectional survey of patients with chronic pain using medicinal cannabis showed a 64% decreased opioid use, decreased side effects of medications, and an improved quality of life.[60] In another study of cannabinoid-opioid interaction, 21 subjects with chronic pain taking twice-daily sustained-release morphine or oxycodone inhaled vaporized cannabis three times daily for 5 days. This resulted in a 27% reduction in pain with no altered plasma opioid levels. Pulse oximetry did not show any lowered oxygen saturation suggesting that cannabinoids do not worsen opioid-induced respiratory depression.[61]

TABLE 1. Risk Stratification and Adherence Monitoring[6]

Action	Low Risk	Moderate Risk	High Risk
Risk stratification*	No history of alcohol abuse or drug abuse, no family history of alcohol or drug abuse	Remote history of alcohol or drug abuse	Recent history, or multiple episodes, of alcohol or drug abuse
	No history of a major psychiatric disorder	History of addiction with a sustained period of recovery and a strong system to help sustain recovery	History of addiction with limited or no system to sustain recovery
	Older age	Questionable family history of alcohol or drug abuse	Strong family history of alcohol or drug abuse
	No smoking	History of major psychiatric disorder that has been managed effectively	History of major psychiatric disorder
	Stable social support	Younger age	
		Smoking	
		History of physical or sexual abuse	
		Lack of social support	
		Involvement with others engaging in drug abuse	
Adherence monitoring and mitigation	At least annual adherence monitoring	At least semiannual adherence monitoring (more frequent at higher levels of assessed risk)	Adherence monitoring at least every 2–3 months and more frequent visits
	Monitoring should usually include:	Monitoring should usually include:	Monitoring should usually include:
	• Detailed interviewing about drug-related behavior	• Detailed interviewing about drug-related behavior	• Detailed interviewing about drug-related behavior
	• Questioning of family members and record review from other treating physicians	• Questioning of family members and record review from other treating physicians	• Questioning of family members and record review from other treating physicians
	• Check of prescription monitoring program	• Check of prescription monitoring program	• Check of prescription monitoring program
			• Urine drug screen
	• Urine drug screen	• Urine drug screen	• Pill counts
Respond to aberrant behaviors	Reconsideration of treatment to determine whether nonopioid therapies can be better used	Reconsideration of treatment to determine whether nonopioid therapies can be better	Reconsideration of treatment to determine whether nonopioid therapies can be better used
			Refills limited or not permitted
			Small frequent prescriptions
			No concurrent use of more than one opioid (e.g., no prescription of a second short-acting drug for breakthrough pain in those prescribed a long-acting drug for daily use)
			Mandated consultation with addiction specialists/psychiatrist

*The level of risk conferred is indicated by the presence of one or more factors itemized in the corresponding risk categories.

Cannabinoids as Analgesics

There are a limited number of randomized controlled trials involving cannabinoids for the treatment of pain. Stimulated by the burden of chronic pain globally and the need to find safer, nonopioid therapeutic targets, the number of studies has been rising. Complicating this area of research, however, are complex federal regulatory issues because of the Schedule I status of cannabinoids and the lack of standards for cannabinoid form and administration across various studies. The studies differ in the type of cannabinoid (i.e., plant, extract, synthetic), route of administration (i.e., inhalation, ingestion, mucosal absorption), and dosing that create unique challenges in interpretation. All of the current studies have focused on THC. There are no studies focusing on CBD, although there is increasing interest given its lack of psychoactivity. To date, all of the cannabis supplied by the National Institutes of Health that has been used in current studies had CBD levels of less than 1%. A summary of select randomized controlled trials across several pain conditions is highlighted in Table 2.[61-75]

Risks and Side Effects of Cannabinoids

As with any potential therapy, cannabinoids carry risks and adverse effects. The most common cannabinoid side effects include sedation, dizziness, dry mouth, and dysphoria. Other significant side effects include cognitive impairment, anxiety, and psychosis. It is important to note that most of the published side effects of cannabis and cannabinoids come from the study of their recreational use. A recent study of cannabis for the treatment of chronic pain had no more adverse effects than matched controls.[77]

The abuse potential of cannabis is controversial. Although cannabis abuse is prevalent, animal studies show that cannabinoids do not seem to be as robust as other agents (e.g., heroin, cocaine, nicotine).[78] There appears to be opposing effects of high- and low-dose THC, with high-dose producing aversion and low-dose producing pleasure.[79] This therapeutic window has been demonstrated in human studies.[80] Plasma levels of THC between 5 and 15 ng/mL appear to be therapeutic for pain relief; however, this relief is lost at levels above 15 ng/mL (Wallace M et al, unpublished data).

With chronic cannabis use, tolerance develops to the physiologic (i.e., cardiovascular) and subjective (i.e., high) effects, and abrupt termination in habitual users will result in withdrawal symptoms similar to opioids. However, withdrawal is less likely to occur or is associated with fewer symptoms when the dose of THC consumed is low.[81,82]

Regulatory, Professional, and Legal Considerations

Possession and use of cannabis remains illegal under U.S. federal law. Since 1970, cannabis has been listed by the U.S. Drug Enforcement Administration as a Schedule I drug with "high potential for abuse," "no currently accepted medical use," and "lack of acceptable safety for use under medical supervision."[83] This is in direct contrast to its legal status within many U.S. states for medicinal and recreational use. This has created confusion for many providers and patients.

Neither the U.S. Food and Drug Administration nor any other federal regulatory agency currently oversees or regulates the production and distribution of cannabis or the myriad cannabis-based products sold in medical marijuana dispensaries. Moreover, there is no national oversight, and

TABLE 2. Summary of Published Cannabis-Based Studies on Pain[61-76]

Pain Type	Cannabinoid Tested	Outcome	Adverse Effects	Reference
Chronic pain	THC/Cannabidiol (SL spray)	Decreased pain	Mild	Blake, 2005
		Decreased pain	Mild	Notcutt, 2004
	THC (SL spray)	Decreased pain	Mild	Notcutt, 2004
	Cannabidiol (SL spray)	No effect	Mild	Notcutt, 2004
Neuropathic pain	Cannabis (smoked)	Decreased pain (dose dependent)	Mild	Wallace, 2015
		Decreased pain (high dose)	Mild	Ware, 2010
		Decreased pain (high dose)	2 cases of toxic psychosis	Ellis, 2008
		Decreased pain (high dose)	Mild	Wilsey, 2008
		Decreased pain	Mild	Abrams, 2007
	Nabiximols (SL spray)	Decreased pain	Mild	Serpell, 2014
		Decreased pain	Mild	Nurmikko, 2007
		Decreased pain	Mild	Rog, 2005
		Decreased pain	Mild	Berman, 2004
	Cannador (oral)	Decreased pain	Mild	Zajicek, 2003, 2005
Cancer pain	Nabiximols (SL spray)	Decreased pain with low and middle dose; no effect with high dose	Mild	Portenoy, 2012
		Decreased pain, nabiximols; increased pain, THC	Mild	Johnson, 2010

limited state regulation of the labeling, concentration, dosing, or purity of cannabis and cannabis-based products. Thus, it is often left up to the growers, processors, and distributors of medical cannabis in states where it has been legalized to self-regulate. Lastly, neither cannabis nor any of these products have undergone the large-scale clinical trials necessary for showing clear efficacy for a particular indication. Efforts are emerging to provide better oversight of herbal marijuana processing and distribution.

Marijuana laws vary widely among those states that have passed some form of legalization, and each clinician must be familiar with the state in which they practice. Because marijuana is not approved by the U.S. Food and Drug Administration, no state requires a physician to write a prescription. There has been a push by the American Medication Association to enact federal legislation protecting physicians who prescribe cannabis.

Some states provide guidelines for recommending medicinal cannabis. In the absence of guidelines, clinicians who choose to recommend cannabis should manage their patients in accordance with good medical practice. This involves becoming familiar with the safety and efficacy of medical cannabis and counseling patients on their responsibilities and on the side effects. Patients should then be monitored to assess the clinical effects, adverse effects, and impact on function and quality of life. Appropriate documentation in the patient's medical record should be made.

CONCLUSION

Cancer pain remains prevalent, yet undertreatment continues, in part due to concerns regarding the use of opioids. The efficacy of opioids in advanced disease has been clearly established, however, questions remain about the safety and effectiveness of opioids in long-term survivors of cancer. As a result of challenges surrounding opioids, alternative analgesics, including cannabis, are being studied. Risks and benefits, as well as regulatory and legal issues, must be carefully considered when recommending these treatment options.

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Using the New ASCO Clinical Practice Guideline for Palliative Care Concurrent With Oncology Care Using the TEAM Approach

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OVERVIEW

Palliative care alongside usual oncology care is now recommended by ASCO as the standard of care for any patient with advanced cancer on the basis of multiple randomized trials that show better results with concurrent care than with usual oncology care. Some benefits include better quality of life, better symptom management, reduced anxiety and depression, less caregiver distress, more accordance of care with the wishes of the patient, and less aggressive end-of-life care. Several studies show a survival advantage of several months, and many show considerable cost savings: better care at an affordable cost. However, there are not enough palliative care specialists available, so oncologists must practice exemplary primary palliative care. Protocols used in the clinical trials, similar to those designed for new chemotherapy agents, help oncologists use the TEAM approach of extra time, typically an hour a month spent with the palliative care team; education, especially about prognostic awareness and realistic options, which include formal setting of goals of care and discussion of advance directives; formal assessments for symptoms and for spiritual and psychosocial health; and management by an interdisciplinary team. These are all potentially accomplished by an oncology practice to replicate the services provided by concurrent palliative care.

Every patient with advanced cancer should be treated by a multidisciplinary palliative care team—in addition to her or his oncologist—within 8 weeks of diagnosis.[1] The guidelines are summarized in Sidebar 1 at the end of this document.

The main conclusions that led to the ASCO Guideline are straightforward:

1. Do not wait to refer all patients with advanced cancer to an interdisciplinary palliative care team until the end of life. Waiting is still the norm for most oncologists, who refer either not at all (68% in one recent series) or late in the last month of life (32%). Patients referred earlier received better care and saved the health system $6,687 per person.[2]
2. Caregivers may be referred, too.
3. An interdisciplinary team is best. However, many oncology practices do not have available hospice and palliative medicine–trained specialists and teams available, given a shortage of 6,000 to 10,000 palliative care practitioners. Others only have hospice available, and these programs may not participate in the Medicare Choices Program that allows concurrent care.[3]

ON WHAT EVIDENCE ARE THE GUIDELINES BASED? HOW COMPELLING IS THE EVIDENCE?

To oncologists, this guidelines update may be similar to the incorporation of trastuzumab as treatment in the adjuvant breast cancer setting—a major advance that was based on several landmark trials, but without clarity about how to use the treatment or which regimen was best (a full year, as used in the CALGB-NCCTG study, or just 12 weeks, as used in the Finn-HER study, or even 2 years?). Regardless, it was an advance that should be incorporated into practice.

The evidence is striking: multiple randomized trials in patients with advanced pancreatic, lung, and gastrointestinal cancers, and in even patients who underwent hematopoietic stem cell transplantations, show the benefits of concurrent care. Not a single trial shows harm (Table 1).[4-19]

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ACADEMIC MODELS

To improve the quality cancer care, standardized criteria, or triggers for palliative care consultation, were developed on an inpatient solid tumor service. Professionals on the service performed a 3-month pilot intervention in which patients who met eligibility criteria automatically received a palliative care consultation. For 6 weeks before the intervention, the inpatient solid tumor census was examined daily to identify patients who met eligibility criteria. This was the usual-care group, so palliative care consultations were not mandated but could be obtained if requested by the primary team. Patients were eligible if they met one or more of the following criteria (Fig. 1): (1) advanced cancer (stage IV solid tumor or stage III lung or pancreatic cancer); (2) prior hospitalization within 30 days; hospitalization lasting longer than 7 days; and (3) any active symptom, including pain, nausea/vomiting, dyspnea, delirium, and psychological distress. Patients who were admitted for routine chemotherapy or a planned procedure, or who were unable to speak English, were excluded.

The palliative care consultation followed a standardized approach that used the National Comprehensive Cancer Network guidelines and core elements of palliative care as detailed in the National Quality Forum. Specifically, this approach included the following: (1) symptom assessment and treatment using the Edmonton Symptom Assessment Scale; (2) establishment of goals of care and advance care plans using standardized communication protocols; and (3) transition planning. The palliative care team was composed of (at a minimum) one board-certified palliative care physician, one nurse practitioner, one social worker, a chaplain, and one or two trainees. Recommendations to consulting physicians were made using standardized palliative care team chart notes and in person or by telephone. Patients were seen daily to monitor implementation and results of treatment recommendations and to assess new and ongoing symptoms. The palliative care teams conducted or assisted with discussions about new or changing goals of care, communicated bad news, and conducted or assisted with associated treatment adjustments. The teams also worked with the social workers and families of the patients to facilitate transition management consistent with goals of care according to available resources.

Overall, 39% of patients in the pre-intervention group and 80% in the intervention group ($p < .0001$) received a palliative care consultation (Table 2). Univariable analysis to compare the pre-intervention group with the intervention group demonstrated a decrease in 30-day readmission rates decreased from 35% to 18%, respectively ($p = .04$). Hospice referral rates increased from 14% to 26% in the pre-intervention and intervention groups, respectively ($p = .03$), and receipt of chemotherapy after discharge decreased from 44% to 18%, respectively ($p = .03$). In addition, there was no significant change in length of stay ($p = .15$) or use of the intensive care unit ($p = .11$) between the two groups. Overall, place of discharge was different between the groups ($p = .004$). Patients in the intervention group were more likely to be discharged to home with home-based services (32% vs. 19%), home hospice (15% vs. 8%), or inpatient hospice (11% vs. 6%) and were less likely to be discharged to subacute rehabilitation facilities (3% vs. 13%).[21]

KEY POINTS

- **Concurrent palliative care alongside usual oncology care is now recommended by ASCO for all patients with advanced cancer.**
- **Concurrent specialty care should start within 8 weeks of diagnosis and be delivered by an interdisciplinary team.**
- **There are not enough palliative care specialists, therefore oncologists can adapt the methods used by the palliative care teams in the randomized trials.**
- **Dedicate an extra hour a month for this. Start with symptom, psychosocial, and spiritual assessments. Inquire about their understanding of their situation. Then bring up goals of care and create advance directives. Whenever the prognosis changes or when reviewing scan results, ask the patient, "Would you like to talk about what this means?"**
- **Set up a hospice information visit when it is possible the patient could die within the next 6 months to ensure that the transition is planned and smooth.**

COMMUNITY PRACTICE MODELS

Where you live when you are diagnosed with cancer matters.[20] In 2013, the Centers for Disease Control and Prevention reported that the top five states with the highest cancer mortality rates were geographically outlined in southern United States, and Louisiana was among them. Patients with cancer in Louisiana, unfortunately, are diagnosed with high rates of advanced cancer, have high symptom burdens, and have high palliative care needs. Central Louisiana services a large rural area, and small community hospitals have limited resources to provide formal palliative care programs. Limited resources include time to deliver palliative care services in busy ambulatory oncology practices and staffing with expertise in palliative care to deliver inpatient and outpatient palliative care services. CHRISTUS St. Frances Cabrini Hospital in Alexandria, Louisiana, is a 240-bed facility with a comprehensive cancer center to deliver cancer services in one location. The oncology outpatient team includes four medical oncologists, a radiation oncologist, a nurse practitioner, a nurse navigator, and a social worker. Within the cancer center, palliative care tools used by the social worker include the Distress Thermometer and the Patient Health Questionnaireafter patient referral at a pivotal moment during diagnosis. Patients are referred at the time of diagnosis and/or at the initiation of cancer-directed therapy, which often is within 8 weeks of diagnosis, but patients may be referred at any point along the trajectory of care.

Unlike academic programs, small community hospitals often have limited resources to provide formal palliative care programs. Limited resources here also include time and staffing. CHRISTUS St. Frances Cabrini Hospital in Alexandria

TABLE 1. Summary of Recent Studies Comparing Usual Care to Usual Care With Palliative Care

	Patient Experience					
Study First Author and Year (Population)	**QOL**	**Symptoms**	**Anxiety Depression**	**Caregiver Distress**	**Survival**	**Cost**
Brumley et al, 2007 (one of three cancers)[4]	NM; satisfaction increased	NM	NM	NM	Equal	−$7,550 per person (p = .03); more likely to die at home, less likely to visit ED, admit to hospice
Gade et al, 2008 (one of three cancers)[5]	Increased (p = .04)	NM	NM	NM	Equal	−$4,885 per person (p = .001); fewer ICU admissions (p = .04), longer hospice stays (p = .04)
Bakitas et al, 2009 (cancer)[6]	Increased (p = .02)	p = .06	Less depressed mood (p = .02)		Longer by 5.5 months (p = .14 [NS])	Equal
Temel et al, 2010 (lung cancer)[7]	Increased (p = .03)	NR	Less depression (p = .01)		Longer by 2.7 months (p = .02)	No change in costs despite the longer survival; cost per day was $117 lower.[8]
Farquhar et al (cancer as cause of breathlessness)[9]	Increased	Improved: reduced patient distress from breathlessness (p = .049)	Equal	Equal	Equal	Total costs, £354 ($444) less; better QOL; dominates cost-effectiveness
Zimmermann, 2014 (cancer)[10]	Increased (p = .05)	Equal (3 months; p = .33) improved (4 months; p = .05)	Equal	Improved (p = .003)	Equal	Equal
Higginson et al, 2014 (dyspnea, most cancer)[11]	Equal	Improved: mastery of breathlessness (p = .048); equal dyspnea	Equal	NR	Equal	Equal
Bakitas et al, 2015 (cancer)[12,13]	Equal (p = .30)	Equal (p = .09)	Equal mood	Lower depression and stress, (p = .02 and .01, respectively) but not better QOL	Longer by 6.5 months; 1-year OS, 63% vs. 48% (p = .038)	NR; equal resource use
Ferrell et al, 2015 (lung cancer)[14,15]	Increased (p < .001)	Improved (p < .001)	Improved (p < .001)	Improved: better well-being and less distress (p = .001); less burden (p = .008)	Longer by 6 months (NS)	NR; more advance directives: 44% vs. 9% (p < .001)
Grudzen et al, 2016 (patients with cancer in emergency departments)[16]	Increased (p = .03)	ND	Equal	ND	Longer by 5.2 months (p = .20 [NS])	Equal: only 25%–28% use of hospice in both groups
Temel et al, 2016 (lung or gastrointestinal cancer)[17]	Increased at week 12 (p = .34) and at week 24 (p = .01)	NR	Improved (p = .048)	NR	Too early to tell	NR; more likely to discuss end of life wishes: 30% vs. 14.5% (p = .004)
El-Jawahri et al, 2016 (bone marrow transplantation)[18]	Smaller decrease (p = .045)	Less increase (p = .03 at 2 weeks); equal at 3 months	Improved depression and anxiety (p < .001)	No change in QOL or anxiety; less increase in depression (p = .03)	Too early to tell	NR

Continued

TABLE 1. Summary of Recent Studies Comparing Usual Care to Usual Care With Palliative Care (Cont'd)

	Patient Experience						
Study First Author and Year (Population)	**QOL**	**Symptoms**	**Anxiety Depression**	**Caregiver Distress**	**Survival**	**Cost**
Maltoni et al, 2016 (pancreatic cancer)[19,20]	Increased (p = .04)	NR; FACT-Hep, HCS, and TOI all better with palliative care	Equal	Equal	Equal: OS 32%–37% at 1 year	NR; NS improvements in chemotherapy use in the last 30 days, hospice LOS, place of death

Abbreviations: FACT-Hep, Functional Assessment of Cancer Therapy—Hepatobiliary; HCS, Hepatobiliary Cancer Subscale; ICU, intensive care unit; LOS, length of stay; ND, not determined; NM, not measured; NR, not reported; NS, not significant; OS, overall survival; QOL quality of life; TOI, trial outcome index.

FIGURE 1. Eligibility Criteria for Automatic Palliative Care Consultation Among Hospitalized Patients With Solid Tumors

Eligibility Criteria
1. Advanced Cancer (stage IV solid tumor or stage III lung or pancreatic cancer)
2. Prior hospitalization within 30 days (excluding routine chemotherapy)
3. Hospitalization lasting longer than 7 days
4. Active symptoms including pain, nausea/vomiting, dyspnea, delirium, and psychological distress

cancer-intensive pharmacotherapy such as intravenous chemotherapy or immunotherapy to symptom burden–designed therapeutic plans or hospice), this has not yet been implemented. At this time, palliative care specialists provide urgent ambulatory services during high disease–burden symptom crises, existential crises, or family and caregiver management crises. Access to experts in palliative care provides tremendous stewardship for the delivery of complex

TABLE 2. Outcomes of Patients: Comparison of Pre-Intervention Control to Intervention Group

	No. (%) of Patients		
Characteristic	**Pre-Intervention (n = 48)**	**Intervention (n = 65)**	**p Value**
Palliative care consultation	19 (39)	52 (80)	< .0001
30-day readmission	17 (35)	13 (18)	.04
Hospice referral	7 (14)	17 (26)	.03
Mean (SD) length of stay, days	11 ± 12	14 ± 14	.15
ICU use	5 (10)	2 (3)	.11
Median (IQR) number of days in the ICU	1 (3)	0.3 (2)	.08
Disposition			.004
Home without services	25 (52)	16 (25)	
Home with services	9 (19)	21 (32)	
Home with hospice	4 (8)	10 (15)	
Subacute rehabilitation	6 (13)	2 (3)	
Inpatient hospice	3 (6)	7 (11)	
Chemotherapy after discharge			.03
Yes	21 (44)	12 (18)	
No	27 (56)	53 (82)	

Abbreviations: IQR, interquartile range; SD, standard deviation.

Louisiana offers a formal palliative care inpatient consultation service and an inpatient hospice unit run by a board-certified palliative care physician and nurse practitioner. Although a formal combined palliative oncology ambulatory program has been proposed, in which the patient would visit with both an oncology provider and a palliative care specialist for symptom control visits or transitional management visits (e.g., when a patient is transitioning from aggressive care among patients, especially those with comorbidities, such as cardiovascular disease, diabetes, kidney disease, and liver disease.

The greatest challenge for guideline implementation in a small community hospital is time (scheduling a combined or same-day visit or a different-day separate palliative care visit). The current inpatient palliative care program and hospice unit remain busy, which thus inhibits burgeoning

TABLE 3. Components of TEAM-Based Palliative Care

Component	Use in Trials	What Is Known
Time	A structured palliative care visit at least an extra hour a month, every month; not just once.	Provider does not have to be the doctor. Advanced practice nurses may be better for this.
Education	Structured and recurrent discussions about prognosis, symptom management, and communication with the health care team.	Usual topics include, on a recurring basis, the following: (1) Medically appropriate options for treatment. This is best done by listing the treatments used and their outcomes, especially with recurrent disease. If appropriate, reinforce patient and family work as advocates. (2) After a scan that shows progressive disease is the perfect time to revisit prognosis and advance care planning. "Would you like to talk about what this means?" (3) Advance care planning. Recent data suggest DPMA does not make any difference, there has to be a living will or advance directive.[24] (4) Use of hospice for best possible care, and arranging a hospice information visit when the disease is predictably going to take the person's life within 3–6 months, or even longer.
Assessment	Formal assessments for symptoms (ESAS, MSAS-C, CAPC rounding tool), spirituality (FICA, or "Are you a religious or spiritual person?"), and psychosocial status (Distress Thermometer, others)	After these formal symptom assessments, move onto goal setting. Use questions such as: (1) How do you like to get medical information? (2) What is your understanding of your disease? (3) What is important to you? (4) What are you hoping for? (5) Have you thought about a time when you might become sicker, such that you would need and advance directive or living will? (Some motivational interviewing)
	It is not sufficient to just ask "How are you?" Patients and families are sometimes reluctant to share their problems for fear that nothing can be done, the oncologist will stop treating their cancer, or they will be labeled as a complainer.	The questioning was incorporated into a temporary tattoo that gives oncologists a script to start the most difficult discussions (Fig. 1).
Management	Use set protocols and an interdisciplinary team (advance practice nurses, social work, chaplain, doctors).	Giving people knowledge of their realistic options and a plan of action was shared across all the studies.
		An oncology office that does not have established social work or chaplain ties should develop them, much as ties are developed with surgeons or radiation oncologists.

Abbreviations: APN, advance practice nurse; CAPC, Center to Advance Palliative Care; DPMA, durable power of medical attorney; ESAS, Edmonton Symptom Assessment Scale; FICA, faith, importance, community, actions; MSAS-C, Memorial Symptom Assessment Scale-Condensed; TEAM, time, education, assessment, and management.

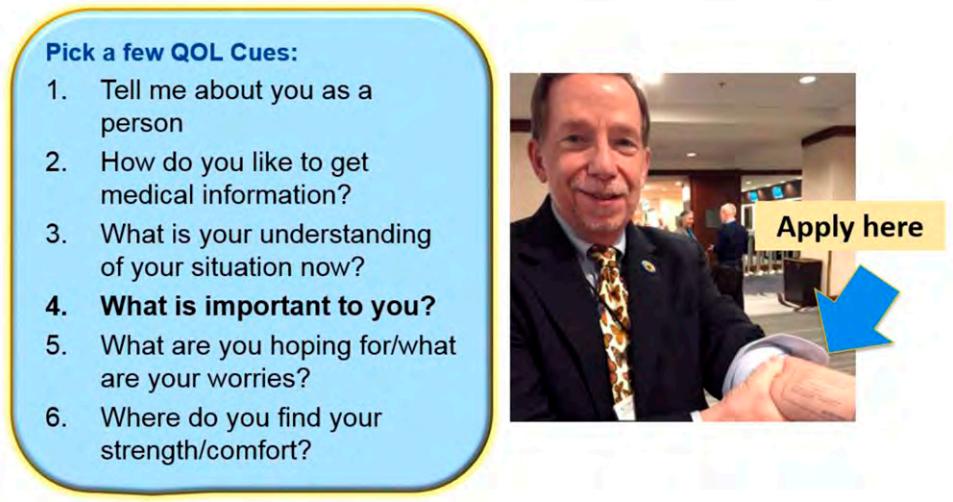
growth and development of combination programs for these resources in an ambulatory clinic. Oncology provider visits often occur at 15- to 20-minute intervals. The volume of patients that must move through the practice and treatment areas of intravenous infusion and radiation requires management of space and time efficiently. A 1-hour palliative care visit is a challenging component to include within the existing oncology operational model for a same-day visit. Conversely, more than one third of patients at CHRISTUS St. Frances Cabrini Hospital travel 30 minutes or more to the facility; some travel 1 hour and 30 minutes for care, and this makes separate-day palliative care visits less desirable and increases the risk for noncompliance.

There has been a surge in the number of agencies delivering hospice care in Louisiana; more than 200 agencies statewide offer the opportunity for concurrent care. Although this offers choice for providers and patient/families, it also offers competing interests for smaller communities/hospitals that seek to provide a systematic approach to palliative care with valid and reliable tools for assessment and delivery of care.

WHERE CAN I GET THE TOOLS AND TECHNIQUES FOR OUR PRACTICE TO OFFER PALLIATIVE CARE METHODS USED IN RANDOMIZED CLINICAL TRIALS?

The CHRISTUS St. Frances Cabrini Hospital service has tried to take the salient points from all the recent trials and incorporate them into the TEAM (time, education, assessments, and management) approach. A recent meta-analysis about palliative care included 43 randomized controlled trials with data from 12,731 patients and found improvements in patient quality of life and symptom burden, but the range and intensity of the interventions studied varied so much that this study is not comparable to this series of more cancer-focused team interventions.[22] The methods of a multi- or

FIGURE 2. A Communication Tattoo Used at Johns Hopkins



Provided by Rebecca Kirch, JD. Tattoos available from Dr. Smith for $0.50 each.

interdisciplinary team approach to concurrent palliative care used in these trials are in Table 3.[23]

Time is one factor to the success of palliative care; an extra hour a month, after initial consultation, was recorded in all of the studies. Oncologists cannot complete a palliative care visit within a 20-minute visit that concentrates on response to chemotherapy. These palliative care visits can be in person or by phone/telemedicine. Underlying principles, though, are that the visit must be structured and that it should last at least an hour a month, regardless of which practitioner is involved. Most trials have included palliative care advance practice nurses and doctors on the team, as we do in practice.

Education was a component of all of the clinical trials. In the monthly visits with the palliative care team, the patient and family can explore realistic options. Prognostic awareness (or the ability to admit a potential life-ending illness) appears to be key and requires coaching as well as direct communication by the health care provider. More than two-thirds of patients with stage IV incurable lung and colorectal cancer thought their palliative chemotherapy,[24] radiation,[25] and/or surgery[26] could cure them. An excellent communication guide is available.[27]

Knowledge works: patients with prognostic awareness, especially those who completed advanced medical directives more than 30 days before death, die less often in the hospital (19% vs. 50% in Australia[28]) and use hospice care more and for longer durations.[29] In the non–small cell lung cancer trial by Temel et al,[7] those in the palliative care group who had prognostic awareness received (ineffective fourth- or fifth-line) intravenous chemotherapy near the end of life 9% of the time versus 50% in the usual care group.

Those who have end-of-life discussions (about goals of care, understanding of illness) are more likely to be satisfied, die at the place of their choosing, and have less distressed relatives.[30] However, physicians must start the conversations. Those patients who had prognostic discussions with their physicians revised their self-reported estimates by a 17.2-month decrease, which more accurately reflected reality (months not years). These patients expressed no more depression, sadness, or anxiety; completed advance directives more often; and received better end-of-life care.[31]

The palliative care team must work with the oncologist, especially about prognosis, although the two teams may have starkly different views on prognosis and medically appropriate treatment. Most palliative care practitioners use a script to approach what the patient and family knows, and wants to know, before they talk about prognosis. Our service found that a temporary tattoo on the inner forearm, visible to the oncologist or advance practice nurse, was helpful to remember how to start difficult conversations[32] (Fig. 1). After physicians review questions and understand the comprehension and goals of the patient and family, motivational interviewing is easier (Fig. 2). An example of motivational interviewing is, “You are doing okay now, but have you thought about a time in the future when you might be sicker and need and advance directive or living will?”

It is simple for oncologists to address understanding and prognosis with a patient after any scan that shows progressive disease. A study found that only four of 64 oncologist discussions about scan results had frank prognosis discussions; the authors suggested addition of the question “Would you like to talk about what this means?” to allow the patient some control about providing permission to disclose crucial information.[33]

Formal assessment tools, as used in nearly all of the trials, also are key to the process of identifying physical symptoms, psychosocial distress, and spiritual distress and are key to identifying how the patient and family are coping. Although oncologists may believe that spiritual assessment is not part of their job description, 87% of patients with cancer want physicians to know their spiritual needs; yet, only 6% were ever asked. Receiving spiritual care from the medical team was associated with a doubling of the use of hospice, and

TABLE 4. Goals of Care Discussion Template for Epic, Cerner, or Other Electronic Medical Records

Care Discussion Point	Template Question
General questions	How do you like to get medical information?
	Full and completely honest, or something else?
	How about prognosis?
	What is your understanding of your situation?
	What is important to you?
	What are you hoping for?
	Are you getting the best care possible? We don't want to leave medical stones unturned.
	Recognize that not all things have a medical fix.
Questions studied in clinical trials	Do you have a will?
	Do you have a living will or advanced directive?
	What does it say about CPR? (For patients imminently dying in the hospital as a result of their cancer, the success rate of CPR is zero.)
	Who do you want to make medical decisions, if you can't?
	Have you discussed this with her/him?
	Are there spiritual issues to be settled?
	Are there family issues to be settled?
	Are there financial issues to be settled?
	Have you met with hospice yet? (Plan for at least 3–6 months before death, which, for most diseases, is predictable. This really helps the transition if and when hospice is needed, and it helps people with congestive heart failure who use hospice live longer.)
	Have you thought about where you would like to be for your death, if and when?
	Legacy work: (1) Let's start doing a life review: what do you want people to remember about you? (2) What's important to you? (3) What are you hoping for? (4) What do you want to accomplish in the time you have?
Living day to day	Exercise
	Diet
Other instructions	How to call or reach me:
	Office
	Days
	Nights
	Cell
	Email

the number of patients who died in the intensive care unit (a marker of poor quality of care) decreased from 22% to 0%.[34] Yet, as oncologists, we fail at this task: in an audit of care given to patients with glioblastoma on our service, no patient had a formal outpatient symptom, spiritual, or coping assessment or a formal statement of prognosis. Perhaps as a consequence, 37% were hospitalized in the last month of life for an average of 9 days, only 17% had any advance directives in the charts, and nearly 40% received chemotherapy in the last month of life.[35] We hope to do better by using the formal tools used in the randomized trials.

Management by a consultant interdisciplinary team also was a key component of the randomized trials. In one Australian trial for patients who received palliative care, a structured regular meeting of the interdisciplinary team with recommendations to the primary care physician, was the only way that care actually improved.[36] Most practices will have some components of the interdisciplinary team in place: social workers, chaplains, advance practice and oncology nurses, and physicians. A key step is to identify patients at risk for complications and discuss their care at a weekly interdisciplinary team meeting to troubleshoot. Such forward thinking of anticipatory care, like calling patients the day after a new chemotherapy regimen, has been a successful technique used by oncology medical home models that led to reduced hospitalizations and lower costs.

SIDEBAR 1. The Integration of Palliative Care Into Standard Oncology Care: ASCO Clinical Practice Guideline

Guideline Question

Should palliative care concurrent with oncology care be standard practice?

Answer: Yes, unequivocally. And EARLY, within 8 weeks, not at the end of life.

Key Recommendation

- Patients with advanced cancer, inpatient and outpatient, should receive dedicated palliative care services early in the disease course, concurrent with active treatment. Referring patients to interdisciplinary palliative care teams is optimal, and services may complement existing programs. Providers may refer caregivers of patients with early or advanced cancer to palliative care services.

Specific Recommendations

- Patients with advanced cancer should be referred to interdisciplinary palliative care teams (consultation) that provide inpatient and outpatient care early in the course of disease, alongside active treatment of their cancer. *(Type: evidence based, benefit outweighs harms; Evidence quality: intermediate; Strength of recommendation: strong).*
- Palliative care for patients with advanced cancer should be delivered through interdisciplinary palliative care teams with consultation available in both outpatient and inpatient settings *(Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).*
- Patients with advanced cancer should receive palliative care services, which may include a referral to a palliative care provider. Essential components of palliative care include may include:
  - rapport and relationship building with patient and family caregiver(s)
  - symptom, distress, and functional status management (i.e., pain, dyspnea, fatigue, sleep disturbance, mood, nausea, or constipation)
  - exploration of understanding and education about illness and prognosis
  - clarification of treatment goals
  - assessment and support of coping needs (i.e., provision of dignity therapy)
  - assistance with medical decision making
  - coordination with other care providers
  - provision of referrals to other care providers as indicated.
- For newly diagnosed patients early palliative care involvement, within 8 weeks of diagnosis, is suggested. *(Type: informal consensus, Evidence quality: intermediate; Strength of recommendation: moderate)*.
- Among patients with cancer with high symptom burden, high expectant needs, or great anticipation of experiencing overlapping phases of care, (diagnosis, staging, treatment, and end of life), outpatient programs of cancer care should provide and use dedicated resources (palliative care clinicians) to deliver palliative care services to complement existing program tools *(Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).*
- For patients with early or advanced cancer for whom family caregivers will provide care in the outpatient setting, nurses, social workers, or other providers may initiate caregiver-tailored palliative care support, which could include telephone coaching, education, referrals, and face-to-face meetings. For family caregivers who may live in rural areas or be unable to travel to clinic, offering telephone support over face-to-face support may be offered *(Type: evidence-based; Evidence quality: low; Strength of recommendation: Weak).*

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/palliative-care-guideline and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

The essential components of the multidisciplinary team are still unknown. When Muir et al[37] offered palliative care in oncology offices with just a physician and advance practice nurse, patients experienced better symptom management—a 21% decrease in symptom burden, an increase in oncologist satisfaction (necessary for the palliative care team to continue to work with oncologists), and an 87% increase of consultations in 2 years. Their efforts saved each oncologist more than 4 weeks of time so that the practice could offer more regular oncology services, or so that oncologists could take some time off to avoid burnout.[35] We believe that these services are essential and that providers, patients, and families

greatly appreciate them, so these services are incorporated within the budget. Most offices in the Louisiana service had substantial financial counseling available but did not have social workers or chaplains, so some of the nonreimbursable services, such as chaplaincy or social worker, may be omitted; however, the omission would need formal testing before it could be endorsed. US Oncology has adopted the best practice model of appointing someone in the office, usually a social worker or nurse, to review advance care planning within the first visits of diagnosis of a life-ending illness, and the result was advance care planning increases to 80%.

The Johns Hopkins service adopted a formal goals of care discussion format in EPIC to capture some of the practical parts of these difficult conversations. Just as laboratory values or radiographs appear on the screen, so does this format, as an EPIC SmartPhrase, appear on the screen; practitioners type in the answers and print the patient information, which contributes to meaningful use and is easy to send to referring health care practitioners so that all can be on the same page (Table 4). Although this tool was not used in the randomized controlled trials, it is being used in them now for patients who receive concurrent care in phase I trials, and it appears to be a useful work-simplifying tool.

CONCLUSION

The TEAM approach works in practice like it did in the clinical trials, if the protocol is followed. Appoint someone, if not the oncologist, to perform the assessments. Use every worse scan or change in Eastern Cooperative Oncology Group performance status to ask "Would you like to talk about what this means?" and give real numbers about prognosis and options. Make a point of having a goal of care discussion at several points as the prognosis changes, using the template in Table 4. Ensure that most of your patients have advance medical directives completed months before they die. Last, if you involve specialists in palliative care, as suggested by the ASCO guideline for every patient with advanced cancer, ensure that it happens within 8 weeks of diagnosis.

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PEDIATRIC ONCOLOGY

Advances in the Treatment of Pediatric Bone Sarcomas

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OVERVIEW

Bone tumors make up a significant portion of noncentral nervous system solid tumor diagnoses in pediatric oncology patients. Ewing sarcoma and osteosarcoma, both with distinct clinical and pathologic features, are the two most commonly encountered bone cancers in pediatrics. Although mutations in the germline have classically been more associated with osteosarcoma, there is recent evidence germline alterations in patients with Ewing sarcoma also play a significant role in pathogenesis. Treatment advances in this patient population have lagged behind that of other pediatric malignancies, particularly targeted interventions directed at the biologic underpinnings of disease. Recent advances in biologic and genomic understanding of these two cancers has expanded the potential for therapeutic advancement and prevention. In Ewing sarcoma, directed focus on inhibition of EWSR1-FLI1 and its effectors has produced promising results. In osteosarcoma, instead of a concentrated focus on one particular change, largely due to tumor heterogeneity, a more diversified approach has been adopted including investigations of growth factors inhibitors, signaling pathway inhibitors, and immune modulation. Continuing recently made treatment advances relies on clinical trial design and enrollment. Clinical trials should include incorporation of biological findings; specifically, for Ewing sarcoma, assessment of alternative fusions and, for osteosarcoma, stratification utilizing biomarkers. Expanded cancer genomics knowledge, particularly with solid tumors, as it relates to heritability and incorporation of family history has led to early identification of patients with cancer predisposition. In these patients through application of cost-effective evidence-based screening techniques the ultimate goal of cancer prevention is becoming a realization.

Ewing sarcoma (ES) is a small, round blue cell tumor characterized by oncogenic fusions between *EWSR1* or, less often, *FUS* and genes of the *ETS* family (*FLI1* being the most common; Table 1).[1,2] In pediatric patients, ES arises in bone in 80% of patients with occurrence in axial bones slightly more common than occurrence in appendicular bones; conversely, in adults as many as 75% of primary ES arise in soft tissue. The remaining cases of ES arise in soft tissue locations. ES occurs in patients age 0 to 50 with the median age somewhere between age 13 and 17. Poor prognostic factors include presence of metastatic disease at diagnosis, age 18 or older at diagnosis, primary site in the pelvis, large tumor, and poor histologic necrosis after induction chemotherapy.[3]

Diagnosis of ES is usually straightforward when biopsy of a typical-appearing mass in a patient of the appropriate age demonstrates a small, round blue cell tumor with intense membranous CD99 staining, and cytogenetics, and fluorescent in situ hybridization, or reverse-transcription polymerase chain reaction demonstrate an associated fusion. It is important to note that fusions involving *EWSR1* and *FUS* are seen in a variety of other sarcomas, as well (Table 1). Thus, a fluorescent in situ hybridization result indicating a fusion involving *EWSR1* is not pathognomonic for ES. In addition, there is increasing recognition of the so-called Ewing-like sarcomas. This ill-defined group of malignancies is characterized by the presence of alternative fusions such as CIC-DUX4 and CCNB3-BCOR and histopathology not entirely classic for ES, including less uniform CD99 immunohistochemistry. The Ewing-like sarcomas appear to represent as many as 5% of the Ewing family of sarcomas, and are thought to occur more often in soft tissue locations and in older patients, and they may have a worse outcome.[2,4]

Successive trials of chemotherapy intensification in ES have resulted in improved outcomes with 5-year overall survival in 1975 to 1977 versus 2002 to 2008 increasing from 58% to 83%. Chemotherapy treatment of ES includes vincristine, doxorubicin, etoposide, and ifosfamide and/or cyclophosphamide. In the United States, all patients receive intensively timed (cycles of every 2 weeks) vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide with growth factor support. In much of Europe, patients receive induction with vincristine, ifosfamide, doxorubicin, and etoposide with consolidation therapy depending on risk factors. Patients with localized disease and

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TABLE 1. Translocations in Ewing and Ewing-like Sarcomas and EWSR1- and FUS-Containing Translocations in Other Sarcomas

Diagnosis	Translocation	Frequency of Ewing (%)
Ewing sarcoma	EWSR1-FLI1	90
	EWSR1-ERG	4
	EWSR1-FEV	< 1
	EWSR1-ETV1	< 1
	EWSR1-ETV4	< 1
	FUS-ERG	< 1
	FUS-FEV	< 1
Ewing-like sarcoma	CIC-DUX4	
	CCNB3-BCOR	
	BCOR-MAML3	
	ZC3H7B-BCOR	
Other sarcomas with EWSR1, TAF15, or FUS fusions		
Desmoplastic small round cell tumor	EWSR1-WT1	
Myoepithelial tumor	EWSR1-PBX1	
	EWSR1-POU5F1	
	EWSR1-ZNF444	
	FUS-KLF17	
	EWSR1-KLF17	
Extraskeletal myxoid chondrosarcoma	EWSR1-NR4A3	
	TAF15-NR4A3	
Myxoid round cell liposarcoma	FUS-DDIT3	
	EWSR1-DDIT3	
Various histologies	EWSR1-ATF1	
Various histologies	EWSR1-CREB1	

KEY POINTS

- **Germline cancer risk mutations are commonly detected in patients with bone sarcomas, particularly osteosarcoma.**
- **The implications of identifying germline cancer risk mutations are significant enough to warrant a consideration of referral of all patients with bone sarcoma, particularly those with osteosarcoma, to a cancer risk clinic.**
- **By focusing on the transcriptional activity of the most common fusion found in Ewing sarcoma (ES), EWSR1-FLI1, investigators have identified promising new therapeutic avenues in this disease.**
- **As trials of new therapeutic approaches derive from research on EWSR1-FLI1, accurate molecular characterization of all patients with ES enrolled in clinical trials is essential.**
- **Clinical investigation in osteosarcoma is currently focused on conducting phase II trials of novel agents for which preclinical studies and the osteosarcoma genomic landscape suggest potential activity (including immunotherapy, receptor tyrosine kinase inhibitors, and modulators of bone development).**

poor histologic necrosis after six cycles of vincristine, ifosfamide, doxorubicin, and etoposide induction therapy benefit from consolidation therapy with autologous stem cell transplant with busulfan and melphalan conditioning.[5,6]

THE GERMLINE IN EWING SARCOMA

ES has not classically been thought to be associated with cancer predisposition syndromes, although it has always been of interest that ES rarely occurs in African populations. More recently, links to heritable germline variants and mutations have been proposed.[7] Oncogenic fusions have been found to preferentially bind to GGAA microsatellite repeats,[8] and a large genome-wide association study analysis recently demonstrated three candidate loci associated with ES.[9] Further analysis of one of these candidate loci, *EGR2*, demonstrated cooperation between the susceptibility variant and microsatellite length that regulates a major driver of ES.[10] Whole-genome or whole-exome sequencing has identified pathogenic or likely pathogenic germline mutations in 13.1% of 175 patients with ES. Several of these mutations occurred in genes with a known susceptibility to sarcoma, such as *TP53*; however, several heterozygous carriers of mutations associated with recessive conditions, particularly Bloom syndrome and Fanconi anemia, were identified, suggesting that heterozygous

mutation carriers of recessive DNA repair conditions may have increased ES susceptibility.[11] Genetic epidemiology studies such as Project GENESIS (Genetics of Ewing Sarcoma International Study; Children's Oncology Group trial AEPI10N5) are enrolling patients to further study genetic risk for ES.[12]

USING EWING SARCOMA BIOLOGY TO ADVANCE CARE

The genomic landscape of ES presents a challenge for the development of targeted therapies. The somatic mutation frequency of ES tumors is among the lowest in human cancer.[13,14] There are few, if any, recurrent "actionable" mutations, with the most commonly identified mutations being loss of *STAG2* and *CDKN2A*.[15-17] The one recurrent mutation, the EWSR1-FLI1 transcription factor, found in 85% of tumors is widely appreciated as the oncogenic driver.[1] Unfortunately, EWSR1-FLI1 is a transcription factor and therefore poses challenges as a drug target. Nevertheless, because of the known dependence of the tumor on this target, investigators have approached EWSR1-FLI1–directed therapeutic targeting with two complementary strategies. For example, several groups have sought to develop innovative methods to directly target EWSR1-FLI1, and this has led to the identification of a number of interesting lead molecules. This approach is balanced by efforts that capitalize on the changes in gene expressed induced by EWSR1-FLI1 to target nonmutated but important oncogenes such as *IGF1* and *PARP*.

ES cells depend on the continued activity of EWSR1-FLI1 to maintain the malignant phenotype. An elegant pathway analysis has shown that as a single mutation, EWSR1-FLI1 both blocks differentiation and drives proliferation.[18] Consistent with this finding, silencing of EWSR1-FLI1 expression in ES cells blocks proliferation and places the cell in a dedifferentiated state that no longer clusters with Ewing tumors by gene expression profiling and principal component analysis and instead clusters with mesenchymal stem cells.[19,20] Recent evidence suggests that even the level of EWSR1-FLI1 expression confers adverse properties to subsets of cells within the tumor such as the ability to establish tumors or migrate.[21,22] Nevertheless, the global effect of EWSR1-FLI1 supression on the overall tumor phenotype is clearly supression of growth. Studies that have blocked EWSR1-FLI1 using either small interfering RNA or small molecules clearly demonstrate impressive suppression of ES xenograft growth that is proportional to the degree of EWSR1-FLI1 suppression.[23-25]

To identify EWSR1-FLI1 inhibitors, investigators have used a variety of techniques ranging from mechanism-based approaches, candidate compound methods, and high-throughput screening. This has led to the identification of a number of compounds that fit the following criteria of being EWSR1-FLI1 inhibitors to varying degrees: (1) impact expression of specific downstream targets of EWSR1-FLI1 such as NR0B1; (2) reverse established EWSR1-FLI1 genome-wide signatures using approaches such as gene set enrichment analysis[8,26]; and (3) defined mechanism of action. Given the complexity of transcription, the finer details of the mechanism of EWSR1-FLI1 blockade are not known for even some of the most well-established inhibitors. The first example used a gene signature screening approach to identify cytarabine as an EWSR1-FLI1 inhibitor.[27] This compound translated to the clinic but due to unusual accrual patterns, it is not clear how many patients in the phase II study were patients positive for EWSR1-FLI1.[28] Subsequent to this study, a protein interaction approach led to the identification of YK-4-279 that disrupted an interaction between EWSR1-FLI1 and DHX9.[29] Shortly thereafter, a cell-based screen led to both the identification of Englerin A and mithramycin,[23,30] the latter an antibiotic that was repurposed for a clinical trial in ES. Unfortunately, liver toxicity prevented the drug from accumulating to serum levels high enough to block EWSR1-FLI1 activity, and the study was prematurely terminated (P.J. Grohar, unpublished data, 2017). This clinical study opened the door to the identification of two second-generation mithramycin analogs EC8042 and EC8105 as less toxic and more potent alternatives, and these continue to be further developed for the clinic.[31] A number of other compounds have been identified as EWSR1-FLI1 inhibitors by a variety of approaches including a screening approach (midostaurin/PKC412),[32] direct interrogation of DNA binding (low-dose actinomycin and shikonin),[33,34] or a candidate compound approach (JQ1).[35-38]

Two of the more established inhibitors are trabectedin and LSD1 inhibitors.[39] In a study that identified EWSR1-FLI1 repressed genes, a direct interaction was found between EWSR1-FLI1 and the nucleosome remodeling and histone deacetylase corepressor complex, of which LSD1 is a member.[40] Subsequent to this study, it was shown that inhibition of LSD1 of the nucleosome remodeling and histone deacetylase complex with a small-molecule inhibitor HCI2509 both induced EWSR1-FLI1–repressed genes and repressed EWSR1-FLI1–induced genes and effectively reversed EWSR1-FLI1 activity on a genome-wide scale.[24] This reversal of EWSR1-FLI1 activity markedly impaired ES xenograft growth.[24] Second-generation inhibitors are now under development, and the clinical translation of these compounds is expected in the near future.

Trabectedin has also been characterized as an EWSR1-FLI1 inhibitor.[39] Early preclinical studies suggested a hypersensitivity of Ewing cells to trabectedin. In the phase I trial of trabectedin, a patient with ES was an extraordinary responder. The patient had widely metastatic disease and achieved a complete response to single-agent therapy.[41,42] Subsequently, trabectedin was shown to block EWSR1-FLI1 activity at the promoter, mRNA, protein, and gene signature levels of expression.[39] More recently, it was shown that the drug redistributes EWSR1-FLI1 within the nucleus to the nucleolus, leading to a marked change in the nuclear distribution of the fusion protein.[43] Interestingly, this effect requires high concentrations of drug perhaps offering a clue why a patient with ES responded in the phase I trial, but the phase II trial in with trabectedin was given over 24 hours did not demonstrate activity in ES.[44] The effect of trabectedin is potentiated by combination with other agents, including insulin-like growth factor 1 receptor (IGF1R)–directed therapies, which mitigates drug resistance or irinotecan via suppression of the WRN helicase.[45,46] Anecdotal responses to trabectedin

and irinotecan in combination in the clinic have recently been reported.[47,48] Finally, the second-generation compound lurbinectedin, which has been found to have an improved toxicity profile compared to trabectedin, also suppresses EWSR1-FLI1, causes the same nuclear redistribution of the protein, maintains synergy with irinotecan, and induces the transdifferentiation of ES cells in xenografts.[43] There is clinical interest in further developing lurbinectedin in combination with irinotecan as an EWSR1-FLI1–directed therapy.

Targeting nonmutated oncogenes of high biologic importance in ES is an approach for identifying therapeutic avenues complementary to direct targeting of EWSR1-FLI1. In many cases, these targets are directly linked to EWSR1-FLI1. For example, a considerable amount of literature supports the therapeutic targeting of *IGF1* in ES, and ES cells have been found to be very sensitive to IGF1 blockade both in vitro and in vivo.[49,50] This sensitivity may be related directly to EWSR1-FLI1 as it is known that EWSR1-FLI1 drives expression of the IGF1R and suppresses expression of the negative regulator of IGF1, IGFBP3.[51-53] Furthermore, EWSR1-FLI1 regulates the expression of a number of micro-RNAs that regulate the IGF1 pathway.[54] It is possible that dysregulation of IGF signaling by EWSR1-FLI1 aids in the process of malignant transformation of ES cells, and this has been suggested by an NIH3T3 model of anchorage-independent growth.[55] Therefore, the Sarcoma Alliance for Research Through Collaboration phase II trial of IGF1R antibody R1507 was met with considerable enthusiasm, and 115 patients with ES accrued in just over 2 years.[56] Impressive clinical responses were seen in a subset of patients, and the overall response rate was 10%. Similar response rates have been seen across a number of different phase II studies of IGF1R inhibition in ES, and one meta-analysis summarizes the response rate for 311 patients with ES treated with all different IGF1R inhibitors as complete response in 0.9%, partial response in 9.9%, and stable disease in 21%.[57] The Children's Oncology Group AEWS1221 trial builds on these phase II results. It is a randomized phase III trial evaluating the combination of the IGF1R antibody with interval compressed therapy in newly diagnosed patients with metastatic ES (NCT02306161).

An alternative approach has focused on targeting the DNA damage response in ES. It is known that there is a baseline level of DNA damage in ES cells that may stem from direct protein interactions with EWSR1-FLI1 or transcriptional changes in expression of targets of EWSR1-FLI1.[58] A screen of 639 cell lines that looked for relationships between cellular sensitivity to 130 agents relative to 64 fully sequenced cancer genes led to interest in PARP inhibitors (PARPi) in ES.[59] Among the most noteworthy findings was a highly important relationship that linked the EWSR1-FLI1 mutation with sensitivity to the PARPi olapirib. A concurrent independent study also identified the sensitivity of ES cells to PARP blockade and suggested a direct protein-protein interaction with EWSR1-FLI1 and PARP as well as DNA-dependent protein kinase.[58] The first clinical evaluation of PARPi in ES had no patients with objective responses and four patients with stable disease.[60] However, combination of PARPi with other therapies, particularly irinotecan and temozolomide, has demonstrated noteworthy activity in preclinical models, and studies translating these combinations to patients are accruing (NCT01858168, NCT02392793, and NCT01286987).[61-64]

In summary, because of the low mutational burden in ES, a number of investigators have focused on directly targeting the recurrent fusion, the EWSR-FLI1 transcription factor. Progress has been made and a number of promising compounds have been identified including the LSD1 inhibitor, trabectedin, and lurbinectedin, which block expression of key downstream targets of EWSR1-FLI1 and reverse expression of the gene EWSR-FLI1 gene signature. As the mechanisms of action are elucidated, these compounds, or second-generation versions, and others will emerge as bona fide EWSR1-FLI1 inhibitors and translate to the clinic in the very near future. In addition, targeting inherent sensitivities in ES established by EWSR1-FLI1 is a promising approach with clinical trials of IGF1R antibody and PARPi underway.

CONSIDERATIONS FOR CLINICAL TRIAL DESIGN IN EWING SARCOMA

Close readers of the section above discussing ES biology for advancing care will note the extent to which the emphasis is on targeting either the EWSR1-FLI1 fusion directly or the downstream consequences of transcriptional activity of the EWSR1-FLI1 fusion. The extent to which the biology of alternative ES fusions such as EWS-ERG and FUS-ERG mirrors that of EWSR1-FLI1 fusion driven ES is not known. Early studies suggest that at least the gene expression pattern of the Ewing-like sarcomas driven by alternative fusions such as CCNB3-BCOR and CIC-DUX4 is distinct from that seen in EWSR1-FLI1–positive ES.[65] Because clinical trials in ES have not required translocation testing for enrollment, it is unclear what proportion of the sarcomas of enrolled patients have alternative fusions. As alternative fusions and Ewing-like sarcomas appear to be more common in older patients, the proportion of patients enrolled on ES clinical trials for which cancer lacks a traditional ES-associated fusion is anticipated to be lower in trials focused on children and adolescents. Notably, in the phase II trial of R1507 led by the Sarcoma Alliance for Research in Cancer, 65% of patients were older than 15 years, and 43% of patients had extraskeletal disease. It has become clear that in the current era of molecular diagnostic tools that it will be essential to define the fusion present in patients enrolled on ES clinical trials.

CLINICAL AND DEMOGRAPHIC FEATURES AND TREATMENT OF OSTEOSARCOMA

Although ES and osteosarcoma are often discussed together due to their similarities, the most obvious being origin in bone, in fact, the two malignancies are markedly different. Similar to ES, osteosarcoma is a malignancy that occurs primarily in children, adolescents, and young adults with a median age of diagnosis of 15 to 19 years. Osteosarcoma has several histologic subtypes, but in all subtypes, the histopathologic hallmark is the presence of malignant osteoid. Difficulties with diagnosis are unusual but do arise when

osteoid is sparse in nonosteoblastic subtypes, and as a result, the only matrix seen on the biopsy specimen is fibroblastic or chondroblastic. In addition, determining grade can sometimes be challenging particularly with surface osteosarcomas including the periosteal and parosteal subtypes. Approximately three-quarters of osteosarcoma occurs in appendicular locations. Factors portending a poor prognosis include presence of metastatic disease, axial tumor location, larger tumor size, and older age.[66]

In the 1970s and 1980s, the chemotherapy agents high-dose methotrexate, doxorubicin, and cisplatin (termed MAP) and ifosfamide with or without etoposide (IE) were identified to be active in osteosarcoma. Unlike in ES, intensifying cytotoxic chemotherapy has not, in multiple randomized trials, improved outcome.[67] Also unlike in ES, phase II trials of new cytotoxic chemotherapy agents such as topotecan have not been encouraging. Consequently, therapy and prognosis, 10-year overall survival of 70% for patients with localized disease, has not changed significantly in over three decades,[68] and treatment options for recurrent disease are very limited.

THE GERMLINE IN OSTEOSARCOMA

Osteosarcoma has been associated with cancer predisposition syndromes caused by highly penetrant germline mutations including Li-Fraumeni syndrome (LFS; *TP53* mutations) and retinoblastoma (*RB1* mutations) and has also been reported to occur in rare predisposition syndromes related to the DNA helicase (*REQ4*, *WRN*, and *BLM* mutations) and ribosomal protein pathways (*RPS19*, *RPL5*, *RPL11*, *RPL35A*, *RPS24*, *RPS17*, *RPS7*, *RPS10*, and *RPS26* mutations).[69,70] In osteosarcoma, estimates indicate that as many as 10% of cases diagnosed before age 30 may be due to underlying *TP53* germline mutations or rare variants[71]; some have speculated that this rate may be even higher when osteosarcoma occurs in very young children younger than 5 years. Although these underlying syndromes can be considered relatively rare in general in osteosarcoma, chromosomal aneuploidy remains a frequent finding in this pediatric tumor, suggesting that DNA repair defects leading to chromosomal instability may predispose individuals to development of osteosarcoma.[72,73] Single nucleotide polymorphisms can also be associated with many diseases including cancer. Genome-wide association studies have examined the role of single nucleotide polymorphisms in osteosarcoma with varying results, including the association of germline single nucleotide polymorphisms and risk for metastasis in osteosarcoma significance[74-78]; all of this indicates the genetic causation of osteosarcoma is much greater than previously known.

USING OSTEOSARCOMA BIOLOGY TO ADVANCE CARE

Clear themes about the osteosarcoma genome emerged from investigations using early genomics techniques such as karyotype, array comparative hybridization, and PCR, and these themes have since been confirmed with next-generation sequencing. Whole-exome sequencing from about 100 osteosarcoma tumor normal pairs and whole-genome and RNA sequencing from about 50 osteosarcoma tumor normal pairs has been published in two major sequencing studies.[79,80] The most frequent somatic genomic alterations in osteosarcoma are *TP53* and *RB1* inactivation. When comprehensive approaches to detecting genomic alterations are used, *TP53* loss is present in virtually every tumor. *TP53* alterations are most often structural variants (usually in intron 1), but mutations are also common. On rare occasions, *MDM2* amplification has been observed and reported to be more common in tumors from older patients with osteosarcoma. *RB1* is most often disrupted by deletion, and somatic mutations or structural variations occur only rarely. Osteosarcomas display evidence of chromoplexy and chromothripsis patterns of frequent structural variants resulting from a series of catastrophic genomic events. Copy number alterations and structural variants are the predominant mechanisms by which cancer gene protein function is altered, whereas point mutations and small insertions and deletions appear to be less common. These genomic studies also allude to the fact that osteosarcoma is a cancer with a high degree of intratumoral, intrapatient, and interpatient heterogeneity.[79,80]

Several lines of evidence, reviewed in more detail elsewhere,[81] support a critical role for the phosphoinositide 3-kinase/mTOR pathway in osteosarcoma survival and proliferation, pointing to the possibility of phosphoinositide 3-kinase/mTOR inhibitor activity in osteosarcoma.[82,83] The oncogene *MYC* has been known to be amplified in about 40% of osteosarcomas for some time. Recent next-generation sequencing studies have confirmed the presence of *MYC* amplification as a common event. *MYC* amplification has been correlated with poor outcome, a finding that needs to be confirmed in a large uniformly treated patient population and in a prospective trial.[84] Until recently, *MYC* has not been a tractable therapeutic target. However, emerging drug classes demonstrating activity in preclinical models of MYC-driven cancers include the bromodomain, aurora kinase, CDK9, and dual P phosphoinositide 3-kinase–histone deacetylase inhibitors.[85-89] The most statistically significant deleted gene region after 13q14-containing *RB1* (q-value 9.14 x 10-18) and 17p13-containing *TP53* (q-value 4.94 x 10-11) is 9p21-containing *CDKN2A/B* (q-value 2/43 x 10-6). A total of 10% to 20% of osteosarcomas have been reported to have CDKN2A/B deletion.[90] Other cell cycle gene alterations in osteosarcoma include *CDK4*[91] amplification, which is interesting in that CDKN2A/B inhibits the CDK4-cyclin D (CCND1/2/3) complex. Amplification of both *CCNE1*[92] and *CCND3* have been reported in osteosarcomas.[79]

A number of receptor tyrosine kinase growth factors have been demonstrated to be expressed on osteosarcomas, including MET, PDGFRA, PDGFRB, KIT, IGF1R, ERBB2, the vascular endothelial growth factor receptors, and others.[93] However, activating mutations in these genes are rarely found in osteosarcoma,[79] and at least in the case of IGF1R and ERBB2, responses to targeting antibodies do not seem to be associated with expression.[94,95] That said, it is clear that the broad tyrosine kinase inhibitors have clinical activity in recurrent osteosarcoma, with the phase I trial of cediranib

having one out of four patients with osteosarcoma with a response[96] and an osteosarcoma-specific phase II trial of sorafenib[97] demonstrating efficacy. There are case reports of response to pazopanib monotherapy or in combination with immune checkpoint inhibitor nivolumab.[98,99] Phase II clinical trials of pazopanib, regorafenib, and cabozantinib in patient populations, including osteosarcoma, are ongoing.

Other noteworthy biologic processes for which evidence suggests both an important role in osteosarcomagenesis and a potential for therapeutic approaches not discussed in detail in this review are immune evasion and perturbed development. There has been a great interest in exploring enhanced immune surveillance as a therapeutic approach in osteosarcoma, resulting in completed phase III trials of interferon alpha and mifamurtide and ongoing phase II trials of immune checkpoint inhibitors. These trials have produced continued interest in immune modulation but have not yet definitively proven the efficacy of any particular immunotherapy approach. The mifamurtide trial has been variably interpreted, resulting in diverging regulatory decisions and variable use of mifamurtide, whereas the interferon alpha failed to demonstrate improved outcome for those who received this therapy.[100,101] There are ongoing efforts to explore chimeric antigen receptor T-cell therapy (for example, NCT02107963). Osteosarcoma arises from osteoblasts, and the interrelated WNT and NOTCH pathways involved in development have both been implicated.[102,103] Interaction between receptor activator of nuclear factor κB and receptor activator of nuclear factor κB ligand is involved in both bone homeostasis and osteosarcoma and a phase II trial of the receptor activator of nuclear factor κB ligand antibody, denosumab is underway in relapsed osteosarcoma (NCT02470091).

CONSIDERATIONS FOR CLINICAL TRIAL DESIGN IN OSTEOSARCOMA

For a number of reasons, listed below and discussed in further detail elsewhere,[104-106] the osteosarcoma research community is currently focused on conducting phase II trials with the aim of identifying novel agents or combinations of novel agents and chemotherapy active in osteosarcoma.

1. Definitive phase III trials in osteosarcoma require 5 years of patient accrual when conducted internationally and more if conducted nationally.
2. The resources required for a definitive phase III trial in osteosarcoma are considerable, and therefore, previous evidence of activity in the clinic, preferably from an informative II trial, is desirable.
3. There are no standard second-line therapies for relapsed osteosarcoma, and the clinical behavior of recurrent osteosarcoma is predictable, facilitating clinical trial design in the relapsed setting.
4. Phase II trials in patients with recurrent osteosarcoma are needed to provide novel treatment options, and such osteosarcoma-specific phase II trials have been shown to accrue rapidly.

Given the heterogeneity of osteosarcoma, ideally trial enrollment would be based on presence or absence of predictive biomarkers. However, there are challenges to be overcome before it is possible to design such precision trials in osteosarcoma. Although studies published to date suggest which genes or pathways may be most often altered in osteosarcoma, the currently available data are inadequate to clearly delineate the frequencies of cancer gene alterations or the extent to which the identified genomic events are mutually exclusive. Further, preclinical studies in fully characterized (sequenced) osteosarcoma models linking genomic alterations to specific therapeutic vulnerabilities have not yet been published. Basing trial selection on gene alterations (so-called basket trial) in osteosarcoma faces an additional challenge. Given the genomic mechanisms most common in osteosarcoma, copy number, and structural alterations, assays optimized to detect these types of variants are needed. Although currently existing clinical sequencing tests do detect copy number alterations in many of the genes commonly affected in osteosarcoma, standards for calling thresholds predictive of therapy response are lacking. None of the currently existing assays is yet optimized for detecting structural events across a wide variety of cancer genes.

IMPLICATIONS OF GENOMICS FOR PATIENT MANAGEMENT: CLINICAL CANCER GENETIC TESTING FOR PATIENTS WITH PEDIATRIC SARCOMA

Diagnosing ES and osteosarcoma at an earlier stage will facilitate improved cure rates, and prevention is an ultimate goal. The incidence of germline hereditary cancer predisposition mutations is estimated to be approximately 20% for the overall cancer patient population[107] and at least 10% in pediatrics.[14,108-111] When family history is included, the number of children in a survivorship clinic meeting eligibility for genetics referral and testing approaches 30%.[112,113] Moreover, the combination of rare and specific childhood tumors with family history increases the risk for underlying germline mutations substantially (e.g., *TP53* mutations associated with choroid plexus carcinoma[114,115] or adrenocortical carcinoma[116]). In pediatrics, sarcomas appear to be the disease most closely associated with inherited cancer predisposition. A recent study found that nearly half of (adult) patients with sarcoma have pathogenic monogenic and polygenic variation in known and novel cancer genes, and 5% had pathogenic mutations in genes associated with actionable management guidelines.[117]

Genetic screening for cancer predisposition is based on several characteristics, most importantly, diagnosis, age, and family history.[110,118-122] Assessment of family history must be incorporated into any heritable risk assessment in pediatric patients.[112] However, family history recording and assessment has been a weakness in the oncology community.[123,124] Challenges for family history collection include lack of time, lack of training, lack of accuracy, and lack of family history tools for clinicians and their patients.[125,126] In many clinical trials and genomic research studies, family history has been omitted or incompletely recorded and/or reported. This, along with de novo mutations and incomplete pene-

trance, presents barriers when interpreting family history as a risk factor for cancer predisposition. In fact, a recent germline study for cancer predisposition genes in select pediatric cancer subtypes found that recorded family history in the medical record could not be used to predict risk for carrying a cancer predisposition gene mutation.[14,127,128] Given the current limitations of its collection, family history cannot be the only factor in deciding to test pediatric patients with cancer, particularly those with bone sarcomas, for inherited cancer predisposition mutations; a striking family history should support genetic testing, but its absence does not rule against testing. Regardless, the pediatric oncology community should continue to record family history for each patient, and providing regular updates to the history could improve our identification of those patients at high risk for hereditary cancer.

Early identification of hereditary cancer predisposition is important for several reasons. First, it allows clinicians to answer perhaps the most important question from parents: "Why did my son or daughter get cancer?" Although such knowledge does not have a direct effect on patient outcomes, providing an answer to this question goes a long way in setting families' minds at ease. Secondly, establishing a genetic causation through a newly identified cancer predisposition mutation then alerts other family members to a possible increased risk of malignancy. These family members who would otherwise not have known about a potential health risk can then be referred for genetic counseling regarding the option of being tested for the familial mutation. Finally, and most clinically relevant, through identification of hereditary cancer predisposition syndromes providers can use preventive techniques for early surveillance to identify cancers early, decreasing morbidity and mortality of malignancy. Although many different cancer predisposition syndromes exist that include children,[110,118-122] standardized surveillance protocols have not yet been developed for all of these syndromes. Nevertheless, two recent examples to demonstrate the ability of surveillance to identify early tumors in syndromes affecting children include LFS and hereditary paraganglioma and pheochromocytoma syndrome.[129,130] LFS is caused by germline mutations in *TP53* and associated with breast cancer, brain tumors, adrenal tumors, leukemia, and sarcoma. Surveillance strategy, including rapid sequence whole-body MRI for LFS-associated tumors, has been reported to be advantageous in this patient population and to improve clinical outcome through early tumor detection.[131-133] An analysis model of LFS surveillance demonstrated its cost-effectiveness (C. R. Tak, BS; E. Biltaji, PhD; W. Kohlmann, MS, CGC; L. Maese, DO; C. M. T. Sherwin, PhD; D. I. Brixner, PhD; J. D. Schiffman, MD; unpublished data, University of Utah, March 2017). A recent workshop sponsored by the Pediatric Cancer Working Group of the American Association of Cancer Research was convened in Boston, Massachusetts in October 2016 (American Association of Cancer Research Special Workshop on Childhood Cancer Predisposition) to provide consensus-driven recommendations for early tumor screening for pediatric patients with cancer predisposition syndromes andmanuscripts presenting these recommendations are in development).

A potential for expanded unbiased germline testing of a large number of individuals is the newborn screening program. Currently, the newborn screening program is the largest application of genetic testing in medicine and identifies genetic mutations and protein levels indicative of disease that can be influenced by early intervention. Diseases screened range from the most frequently encountered disease, primary congenital hypothyroidism occurring in 1:1,800 newborns, to the extremely rare inborn errors of metabolism like beta-ketothiolase deficiency and hydroxymethylglutaric aciduria occurring in 1:1 million newborns.[134,135] Pediatric cancer occurs in 1:408 children before age 15 and 1:285 children before the age of 20, with an estimated genetic cause in 10% to 20%; this implies that a mutation in a known cancer predisposition gene potentially could be found in 1:1,500 to 1:3,000 of newborns screened for inherited genetic cancer predisposition, which is within the epidemiologic criteria already established for the newborn screening program.[136] However, the newborn screening program for cancer predisposition cannot be undertaken until issues of genetic counseling, consent, variant interpretation, and follow-up surveillance are incorporated. Until genetic testing for mutations in cancer predisposition genes becomes universal for all healthy children, we recommend the consideration of genetic testing for cancer risk genes in all children diagnosed with sarcoma. Such testing needs to be coordinated through referral to cancer genetics clinics with genetic counselors and oncologists who can discuss the benefits, risks, and subsequent management of genetic risk for the patient being tested and also, importantly, for the patient's family.

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Breast Cancer After Childhood, Adolescent, and Young Adult Cancer: It's Not Just About Chest Radiation

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OVERVIEW

Women who have been treated for a childhood, adolescent, or young adult cancer are at an increased risk for developing breast cancer at a young age, and breast cancer accounts for the most common subsequent malignant neoplasm among female childhood and adolescent cancer survivors. Risk of breast cancer in these survivors appears to be a multifaceted relationship between constitutional factors, exposures to radiation therapy (RT) and chemotherapy, and genetic predisposition. Given the significant morbidities and mortality associated with a breast cancer diagnosis, it is imperative that health care providers understand the risks, biology and genetics, recommended surveillance guidelines for early detection, and potential prevention strategies for women who have survived pediatric and young adult cancer.

Women who have been treated for a childhood, adolescent, or young adult cancer are at an increased risk for developing breast cancer at a young age.[1,2] In fact, breast cancer is the most common subsequent malignant neoplasm among female childhood and adolescent cancer survivors. Breast cancer risk in childhood, adolescent, and young adult survivors seems to be a composite of host-related factors, treatment-related exposures including RT and chemotherapy, and genetic predisposition. Given the significant morbidities and mortality associated with a breast cancer diagnosis, it is vital that health care providers understand the risks, biology and genetics, recommended surveillance guidelines for early detection, and potential prevention strategies in women who are pediatric and young adult cancer survivors.

BREAST CANCER RISK IN CHILDHOOD, ADOLESCENT, AND YOUNG ADULT SURVIVORS

Evidence to date suggests that female survivors of childhood, adolescent, and young adult cancers exposed to chest RT are at the highest risk for developing breast cancer. In a recent report of women exposed to chest RT in the Childhood Cancer Survivor Study (CCSS), the cumulative incidence of breast cancer by age 50 is 30%.[1] Meanwhile, in a subsequent report by the CCSS, for women who have never been exposed to chest RT, the cumulative incidence of breast cancer by age 45 was 4.5%—lower, but still a fourfold increased risk compared with the age-matched general population.[2]

The highest rates of breast cancer in childhood, adolescent, and young adult female survivors are observed in those who were treated for Hodgkin lymphoma (HL).[3] Among HL survivors, breast cancer accounts for approximately 40% of excess malignancies, and the increased risk of breast cancer described among HL survivors is primarily attributable to the RT techniques that treated the full length of the mediastinum and bilateral axillae, and consequently also irradiated a significant volume of normal breast tissue.[3-7] This increase in risk is minimal in the first 5 years after treatment, but it becomes significantly elevated thereafter and may only plateau or decline when survivors are in their 60s.[8]

It is noteworthy that treatment-related breast cancer, which of course produces significant morbidity among those affected, accounts for a small proportion of deaths among female survivors. For example, the CCSS found that among 15,050 female 5-year survivors of childhood cancer, 3% of deaths (49 of 1,603 deaths) were because of breast cancer.[9] Similarly, among childhood HL survivors, with a median follow-up of 23.8 years, 35% of deaths were attributed to HL, while 4.2% were attributable to breast cancer. Further, female HL survivors with subsequent breast cancer diagnoses had a comparable mortality risk to those with no second cancer.[10]

Age Effects

Several studies have shown that the standardized incidence ratio of developing breast cancer increases substantially with younger age at RT. Among patients treated before

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age 20 with 35 to 45 Gy mantle RT, the standardized incidence ratios of breast cancer vary widely and are typically reported to be 50 to 100 compared with age-matched populations.[7,11,12] The long-term cumulative incidence of breast cancer among these survivors is also substantially elevated. For example, the CCSS reported that among 5-year HL survivors, the cumulative incidence of breast cancer 30 years after treatment was 18.3%,[10] and a U.K. study estimated that for women who were younger than age 20 and received less than 40 Gy with no alkylating chemotherapy, the cumulative incidence of breast cancer at age 40 year was 40.5%.[13] Although some have postulated that adolescent breast tissue is particularly susceptible to radiation-related carcinogenesis, most clinical evidence does not support the conclusion that risk is higher among adolescents than younger children.

Most studies reveal relative risks (RR) of breast cancer decrease with increasing age at the time of HL treatment. For example, in a Dutch study, survivors who had received RT before age 20 had up to an 18-fold higher standardized incidence ratio (SIR), whereas there was no significant increase in risk among women who were older than age 40 during RT. Similar findings have been reported by others.[6,13,14] Absolute risk and cumulative incidence are also elevated among women treated with mantle RT during young adulthood (Fig. 1). In one study, the 30-year cumulative incidence of breast cancer was 19% for women who were treated between the ages of 20 to 30,[4] and Travis et al estimated that for HL survivors treated at age 25 with a chest radiation dose of 40 Gy or greater without alkylating agents, the cumulative incidence of breast cancer by age 55 was 29.0%.[15]

Radiation Dose-Volume Risk Relationship

Studies evaluating the relationship between radiation exposure and breast cancer risk have found increasing risk associated with irradiation of a large volume of breast tissue (e.g., among patients receiving whole-lung RT) and have generally reported a linearly increasing risk of breast cancer over the 20 to 40 Gy range (commonly used in the treatment of HL).[1,16-18]

For example, in a large case-control study of women treated for HL when they were age 30 or younger, Travis et al found that the cancer risk was increased eightfold for areas of the breast receiving greater than 40 Gy compared with less than 4 Gy (p value for trend < .001).[16] In a similar case-control study of breast cancer in a cohort of 6,647 female survivors of childhood cancer, radiation dose was estimated to the site of breast cancer for 120 cases and 464 controls (not all patients were treated for HL).[17] A linear increase in breast cancer risk with increasing dose was found, with an odds ratio of breast cancer that was 11-fold higher among breast sites with exposures of 40 Gy compared with those with no radiation exposure (Fig. 2).[18]

These studies provide important information about the biologic dose-risk relationship that had previously been a matter of controversy. However, it is important to understand that these studies do not provide patient-level risk estimates. The unit of analysis in these studies was not the patient, but rather the breast sites where tumors arose (and the same anatomic site among matched controls). It would not be correct, for example, to infer from the CCSS study that a patient prescribed 40 Gy mantle RT had an 11-fold higher odds ratio of breast cancer than a patient not receiving RT. This is because the dose to the breast can differ significantly from the prescribed dose depending on the volume of breast tissue in the RT field, and indeed the doses to each breast can differ significantly for the same patient (Fig. 3).[16-18] A more appropriate inference from these studies would be that increasing breast doses from 5 to 40 Gy are increasingly carcinogenic, and efforts to reduce the radiation dose to the breast tissue below 40 Gy should reduce the risk of treatment-related breast cancer. This is relevant to understanding contemporary RT for patients with HL, for example, which uses lower prescribed doses (20–30 Gy) than the 36 to 45 Gy commonly used in many studies of second cancer risk.

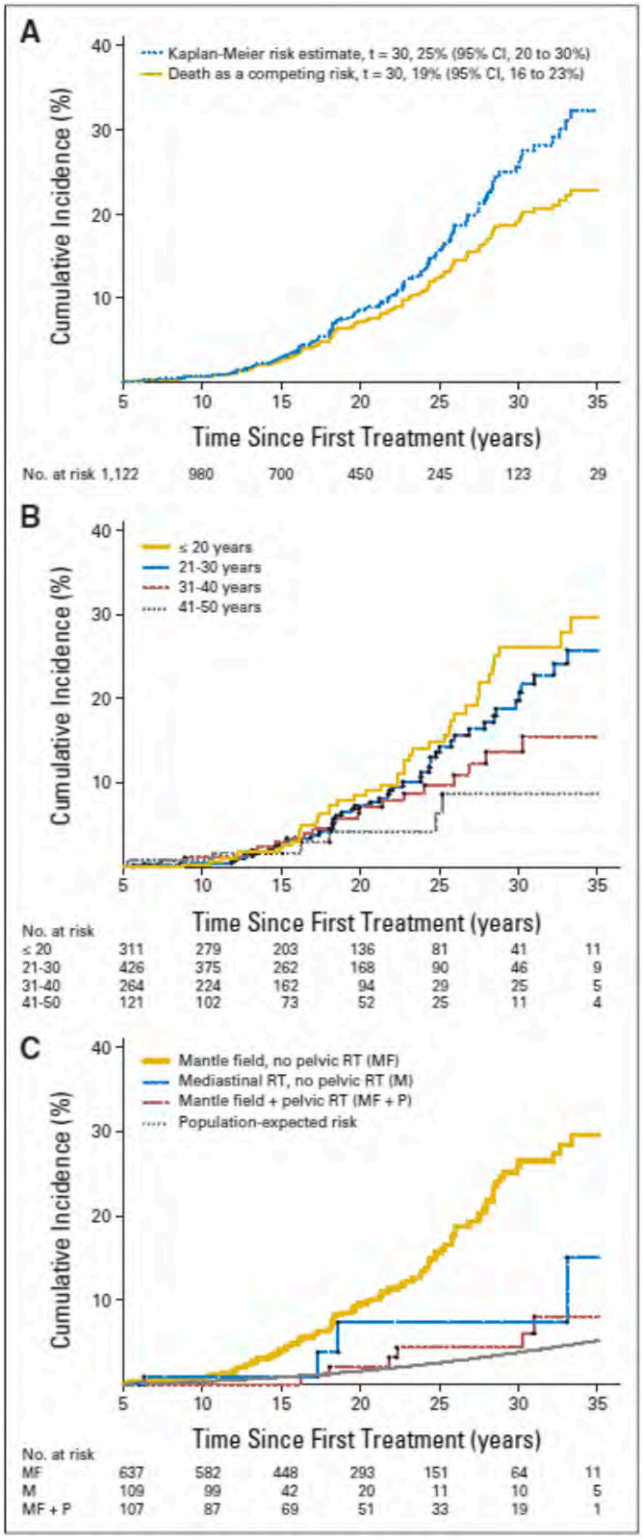
In addition to dose, the volume of breast tissue exposed is also a critical contributor to risk. Moskowitz et al evaluated the risk of breast cancer among 1,230 female survivors of childhood cancer treated with chest RT within 5 years of diagnosis.[1] As expected, they found that women who had been treated with high doses of RT for HL had significantly elevated risks, but notably, those who had received whole-lung RT (and thereby whole-breast exposure) in lower doses (median, 14 Gy) also had a comparably high risk of breast cancer, with a cumulative incidence by age 45 exceeding 25% and a standardized incidence ratio of 43.6.[1] Women treated with mediastinal-only RT had half the risk of breast cancer compared with women treated with similar doses of mantle field radiation. Similar findings were observed in survivors of Wilms tumor who received whole-lung radiation.[19]

These findings illustrate the importance of considering both volume of breast tissue exposed and dose when assessing breast cancer risk.

KEY POINTS

- **Women treated for childhood, adolescent, and young adult cancer are at an increased risk of breast cancer at a young age.**
- **The highest risk of breast cancer is observed in women treated with chest radiation for HL, though other treatment- and host-related factors are associated with elevated risk.**
- **Genetic factors appear to be associated with risk; survivors, particularly sarcoma and leukemia survivors, and those with familial risk should be referred for genetic counseling.**
- **In women exposed to chest radiation, surveillance with mammography and breast MRI are recommended starting at age 25 or 8 years after exposure, whichever occurs last.**
- **Prevention measures are being explored to mitigate survivors' risk.**

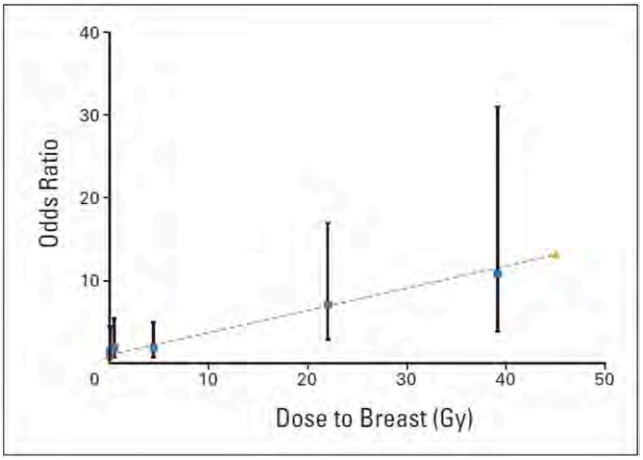
FIGURE 1. The Cumulative Incidence of Breast Cancer After Hodgkin Lymphoma, Median Age at Treatment 26.3 Years



(A) Cumulative risk and incidence of BC (both invasive and ductal carcinoma in situ). (B) Cumulative incidence of BC according to age at first treatment. (C) Cumulative incidence of IBC according to radiation fields and population-expected risk.[4]

Abbreviations: BC, breast cancer; IBC, inflammatory breast cancer; RT, radiotherapy.

FIGURE 2. Risk of Breast Cancer According to Dose to Breast Site Among Survivors of Childhood Hodgkin Lymphoma[18]



Implications for Contemporary Radiation Exposures

The long follow-up required to fully characterize the risk of breast cancer following RT means that most estimates of radiation-related breast cancer risk apply to outdated treatment. For example, prescribed RT doses are typically 15% to 50% lower for contemporary patients receiving adjuvant RT than among survivors evaluated in the breast cancer risk studies cited above, who were typically prescribed 35 to 45 Gy. German Hodgkin Study Group (GHSG) trials, for example, have demonstrated the effectiveness of 30 Gy following ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine) for intermediate-risk disease, and the GHSG HD10 trial demonstrated that a 20 Gy prescribed dose is adequate for patients with selected early-stage favorable risk disease.[20] Similarly, prescribed RT doses on contemporary pediatric protocols are less than half what they were for survivors followed in the CCSS study.[21] Moreover, the large mantle fields that are the basis for the risk estimates cited above were replaced by involved-field RT, which typically treated lymph node areas with radiologic evidence of involvement plus the immediately adjacent uninvolved echelons of lymph nodes. Further, most contemporary protocols use involved-site RT (also referred to as involved-node RT), which encompasses only involved lymph node areas without any elective treatment of uninvolved sites.

For female patients receiving mediastinal RT, the transition from mantle fields to mediastinal involved-field RT decreased the mean breast dose by approximately 65%, largely because of the exclusion of the axilla, and the further reduction in treatment volume to involved-site RT and the lower prescribed dose used in contemporary treatment reduces the breast dose on average to approximately 10% to 15% of what it was for most patients treated on the observational studies described above.[22] A critical feature of the transition to involved-site RT is that the dose to normal tissues is much more variable among individuals, depending on the anatomic distribution of disease and the resulting RT target volume (Fig. 3). Patients with anterior mediastinal disease located primarily above the carina will typically have mean breast doses of 1.5 to 3.5 Gy, whereas involvement of axillary and subcarinal lymph nodes, and the resulting increase in RT target volume, will increase the breast dose, despite that patients are nominally receiving the same RT (i.e., involved-site RT). A practical consequence is that moving forward, judgments about risk-benefit trade-offs of RT should likewise be more individualized than has historically been the case.

An important issue is whether these breast dose reductions will actually translate into true reductions in breast cancer risk. Emerging clinical evidence suggests that this will be the case. A meta-analysis of over 9,000 patients treated on 37 randomized trials found a significantly greater risk of breast cancer with extended-field RT (which routinely included the axillae) than involved-field RT (which generally excluded the axillae; odds ratio, 3.25, p = .04).[23] A cohort study of 1,122 female 5-year survivors of HL found that mantle field RT was associated with a 2.7-fold increased risk of breast cancer compared with RT to the mediastinum alone (Fig. 1),[4] and a recent update from the same investigators again found a significantly lower risk of breast cancer among patients who received supradiaphragmatic RT not including the axilla than among those who received complete mantle field RT (hazard ratio, 0.37; 95% CI, 0.19–0.72).[3] These results provide important evidence that the reductions in breast dose associated with more restrained RT doses and volumes can translate into clinically evident reductions in breast cancer risk. It is important to note, however, that other changes in patient treatment (e.g., reduction in alkylator exposure and increasing utilization of breast cancer screening among survivors) may also influence breast cancer risk compared with historic cohorts.

FIGURE 3. Fitted Breast Cancer Risk by Radiation Dose to the Breast and Ovary, Results From the Childhood Cancer Survivor Study, Based on 120 Breast Cancer Cases and 464 Controls[18]

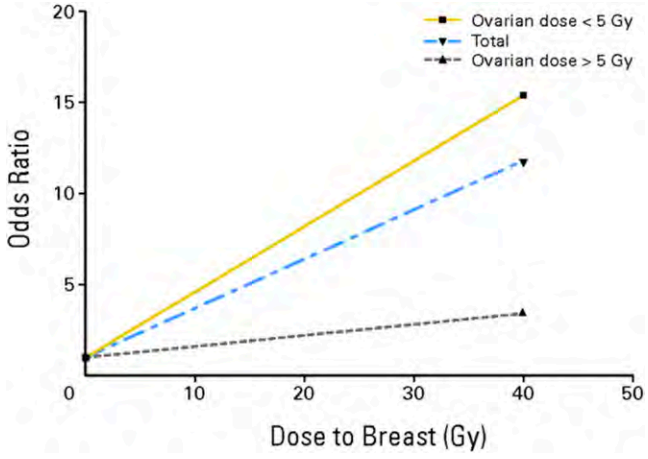


TABLE 1. Effects of Fertile Lifespan After Irradiation to the Breast on Breast Cancer Risk (Invasive and DCIS) According to Age at First Treatment [4]

	All Ages < 41	Age < 21	Age 21–30	Age 31–40
No. of patients	715	201	323	191
No. of events	98	36	40	22
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 3*				
Premature menopause**				
Menopause at age 41 or later	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Menopause before age 41	0.4 (0.2–0.8)	0.2 (0.0–0.8)	0.1 (0.0–0.5)	1.3 (0.4–3.6)
Model 4*				
Years intact ovarian function**				
< 10 yr	0.3 (0.2–0.6)	0.1 (0.0–0.6)	0.1 (0.0–0.3)	1.2 (0.4–3.5)
10–20 yr	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
> 20 yr	5.3 (2.9-9.9)	11.9 (3.7–37.9)	6.0 (2.3–15.4)	3.2 (0.3–30.7)

*Adjusted for each other, radiation field size, age at first RT to the breast and time since first RT to the breast, smoking, obesity, nulliparity, oral contraceptive use; calendar time was used as the time scale.
**Unknown age at menopause was modeled as a separate category.
Abbreviations: DCIS, ductal carcinoma in situ; HR, hazard ratio; Ref, referent.

CHEMOTHERAPEUTIC AND HORMONE-RELATED RISK FACTORS FOR BREAST CANCER

Several studies among adolescent/adult survivors of HL have shown that alkylating chemotherapy in combination with chest RT substantially decreases the RT-related risk of breast cancer, by about 50%.[3,4,16,17,24] In a large British HL cohort study, breast cancer risk increased by 4.6-fold compared with the female general population among those treated with combined modalities and 14.4-fold after RT alone, while no breast cancers occurred among women treated solely with chemotherapy.[13]

In a large international case-control study, risk of breast cancer decreased with increasing number of alkylating agent cycles (p = .003 for trend); the RR associated with nine or more cycles of alkylating chemotherapy compared with no alkylating chemotherapy was 0.2 (95% CI, 0.1–0.7).[16] In a large Dutch cohort study,[3,4] chemotherapy regimens with higher cumulative procarbazine doses were associated with a greater reduction of breast cancer risk, with 30% and 67% risk reductions for regimens with less than 8.4 g/m^2 procarbazine and more than 8.4 g/m^2 procarbazine, respectively. Interestingly, however, a large study in childhood cancer survivors did not show a reduced breast cancer risk after alkylating chemotherapy in combination with chest RT, compared with chest RT alone.[11]

The substantial risk reduction associated with chemotherapy in HL survivors appears to be due to the high frequency of premature menopause in chemotherapy-treated patients,[4,17,25] and the resulting reduction in the exposure to ovarian hormones. De Bruin et al[4] reported that 30% of all women reached menopause before age 41; such an early menopause was associated with a 60% (95% CI, 20%–80%) reduced risk of breast cancer (Table 1). A strong decrease in breast cancer risk (about 60%) has also been observed among women who received a castrating dose of 5 Gy or more to the ovaries, compared with those who received lower doses (Fig. 3).[4,16-18] These results indicate that ovarian hormones are a crucial factor to promote tumorigenesis once RT has produced an initiating event.

In the Dutch study, a long versus short duration of intact ovarian function after radiation was a strong predictor of subsequent breast cancer risk.[4] Women with less than 10 years of intact ovarian function after RT had a 70% (95% CI, 40%–80%) decreased risk of breast cancer compared with women with 10 to 20 years of ovarian function after irradiation, while those with more than 20 years of intact ovarian function after RT had a 5.3-fold (95% CI, 2.9–9.9) increased risk of breast cancer (Table 1). These risk reductions were observed both among women treated before age 21 and among those treated between ages 21 and 30. Among women treated between ages 31 and 40, cumulative exposure to endogenous estrogens was not associated with risk for breast cancer, possibly because these women were closer to natural menopause at time of treatment.[4] A recent British study confirmed these findings and reported a 3.6-fold risk increase for women who had 25 or more premenopausal years after the start of RT.[25]

It is not yet known whether current less-gonadotoxic chemotherapy, such as ABVD, is also associated with reduced risk of RT-associated breast cancer. Furthermore, we do not yet know whether hormone replacement therapy (HRT) for chemotherapy-induced premature menopause affects RT-associated breast cancer risk. HRT is an established risk factor for breast cancer[26,27] and might counteract the protective effect of chemotherapy. Remarkably, in the international case-control study by Travis et al,[16] the relation between

alkylating agent treatment and breast cancer risk differed between North America and European centers. Within Europe, significant reductions in risk were observed (for 6 cycles: RR, 0.33; 95% CI, 0.15–0.65; $p < 0.001$ for trend), while in North America, the RR associated with six cycles of alkylating agent therapy was close to unity. These discrepant results may be due to the much higher prevalence of HRT in North America compared with Europe. Published studies had only limited information on HRT.[4,11,25,28] Therefore, large internationally pooled studies are required to investigate the safety of HRT use in cancer survivors at increased risk of RT-associated breast cancer.

Several studies have examined the effect of other reproductive factors on the risk of RT-associated breast cancer. A recent British study observed stronger RT-associated risk of breast cancer among women who were irradiated close to menarche, suggesting greater carcinogenicity of radiation when the breast is developing.[25] No modifying effects have been observed for other risk factors such as age at first birth, parity, and weight, but none of the published studies included enough women to detect smaller interaction effects or risk modification by infrequent exposures.

A recent analysis from the CCSS investigated breast cancer risk in childhood cancer survivors without a history of chest RT.[2,29] The study showed an overall fourfold elevated risk compared with the general population; risks were especially increased after treatment for sarcoma and leukemia. A novel finding was that alkylating agent and anthracycline-containing chemotherapy increased breast cancer risk in a dose-dependent manner. This is an important finding that could have clinical implications extending beyond the population of childhood cancer survivors treated without chest RT. Unfortunately, however, as most survivors received chemotherapeutic agents from both classes, and numbers were rather small, the agent-specific contributions could not be distinguished, nor could potential interaction be assessed. As most of the breast cancers (85%) followed sarcoma or leukemia, which are known to be associated with Li-Fraumeni(-like) syndromes, the authors speculated that the increased risk of breast cancer might be due to interaction between chemotherapy and genetic predisposition.[2] International collaborative cohort and case-control studies among childhood cancer survivors are warranted to achieve statistical power to disentangle the independent and joint effects of different chemotherapeutic agents, primary childhood cancer diagnosis, and genetic factors.

GENETICS OF BREAST CANCER AFTER CHILDHOOD, ADOLESCENT, AND YOUNG ADULT CANCER

In the past decade, substantial progress has been made in understanding inherited susceptibility to breast cancer in the general population as well as in high-risk families.[30-32] Despite these advances, relatively little is known about inherited predisposition to breast cancer occurring in survivors of childhood, adolescent, and young adult cancer. Similar to our understanding of cancer predisposition more broadly, research to date has evaluated separately rare, highly penetrant mutations in known cancer predisposition genes that confer high risk of breast cancer as well as more common, lower penetrant mutations and polymorphisms that increase risk to a lesser extent. A key challenge for studying genetics of breast cancer in survivors is the need to evaluate potential joint effects of inherited susceptibility and prior cancer treatments.

The most well-understood genetic predisposition syndrome associated with breast cancer in childhood cancer survivors is the Li-Fraumeni syndrome, associated with a germline mutation in the *TP53* gene. Patients with Li-Fraumeni syndrome are at particularly high risk for developing bone and soft tissue sarcomas, central nervous system tumors, leukemias, adrenocortical carcinomas, and melanomas.[33,34] Often, multiple sequential tumors are seen in a single patient.[35] Li-Fraumeni syndrome should be suspected in childhood sarcoma, leukemia, or brain tumor survivors who develop breast cancer as a young adult, even in the absence of the typical treatment exposures (e.g., chest radiation) that confer high breast cancer risk. Recent findings by Henderson and colleagues in their CCSS study examining breast cancer in women never exposed to chest radiation support this notion.[2] In contrast to survivors who received chest RT, in which HL survivors are most common, 85% of breast cancers diagnosed in the women never exposed to chest radiation occurred in sarcoma and leukemia survivors. Two additional women with breast cancer were survivors of central nervous system tumors, also associated with Li-Fraumeni syndrome. The data from that study further suggested potential gene-chemotherapy interactions associated with breast cancer risk, given the observation of dose-response association with alkylator and anthracycline chemotherapy exposure in the cohort. However, further research will be needed to understand potential joint effects of inherited susceptibility with chemotherapy exposures. Additionally, because individuals with Li-Fraumeni syndrome are thought to be radiosensitive, future investigations should evaluate the magnitude of breast cancer risk after chest RT in known germline *TP53* mutation carriers. Based on available data to date, survivors of childhood, adolescent, and young adult cancers associated with Li-Fraumeni syndrome tumors should be referred to genetic counseling to obtain a detailed family pedigree, education, and potential genetic testing for *TP53* testing, regardless of prior therapeutic exposures.

Data are conflicting on the role of major cancer predisposition genes other than *TP53* in the development of breast cancer after childhood, adolescent, and young adult cancer. In a large cohort study of families with mutations in *BRCA1* or *BRCA2*, no excess risk of childhood cancer was observed.[36] However, in a separate study by Magnusson and colleagues, there was a substantial risk of childhood cancers associated with families with a *BRCA2* mutation that was not observed among families carrying a germline *BRCA1* mutation.[37] Supporting Magnusson's findings are the results of a whole-genome and whole-exome sequencing project in 1,120 patients with childhood cancer by Zhang and colleagues

to examine for germline mutations. The most common germline mutation after *TP53* (50 patients, 4.5%) was *BRCA2* (six patients, 0.5%), whereas *BRCA1* was only identified in one (0.01%) of the 1,120 patients sequenced.[38] However, breast cancer risk was not evaluated in these studies.

Moving beyond relatively rare mutations that confer moderate to high risk for breast cancer, several studies also have examined the role of polymorphisms in breast cancer after childhood, adolescent, and young adult cancer. A Dutch and U.K. case-control study of breast cancer after HL by Ma and colleagues reported an association with *FGFR2* but not other established breast cancer susceptibility loci in their population.[39] Using the genome-wide association study approach, Best and colleagues found variants at 6q21 implicating *PRDM1* in the etiology of RT-related second cancers after HL,[40] but that study was not specific to the outcome of breast cancer. Most recently, Morton and colleagues conducted a genome-wide association study of subsequent breast cancer in female survivors of childhood cancer, pooling data from CCSS and the St. Jude Lifetime Cohort for a study population of 207 female survivors who developed breast cancer and 2,774 without any second cancer.[41] They found nearly twofold increased risk per allele for a variant at 1q41 (nearest gene *PROX1*) only among survivors who received 10 Gy or greater breast radiation exposure. Two rare variants also showed promising associations that differed by treatment exposures, including a variant at 11q23 (nearest gene *TAGLN*) for survivors with 10 Gy or greater breast radiation exposure and a variant at 1q32.3 (nearest gene *RPS6KC1*) for survivors with greater than 10 Gy breast radiation exposure. Overall, the results from these studies support the idea that inherited susceptibility beyond high-risk cancer predisposition syndromes may modify the effect of radiation exposure on breast cancer risk after childhood and adolescent cancer. Importantly, whole-exome sequencing is currently being undertaken in both the CCSS and the St. Jude Lifetime Cohort study populations to identify genetic factors that may confer risks for breast and other subsequent neoplasms in childhood cancer survivors. Combining these genomics studies with the detailed treatment data and long-term follow-up in both cohorts holds great promise for further elucidating the genetics of breast cancer after childhood cancer.

BREAST CANCER SURVEILLANCE AND PREVENTION

The rationale for breast cancer surveillance in cancer survivors at increased breast cancer risk is for breast cancer detection at earlier, more treatable stages. This is particularly relevant in cancer survivors as most would have previously received RT and cytotoxic therapy, thus limiting breast cancer treatment options.

Earlier studies have shown that mammogram screening in high-risk cancer survivors is indeed associated with earlier breast cancer detection.[42-44] In a prospective cohort study of 90 women who had received mantle field RT for HL,[42] 8 of 10 mammographically-detected cancers were node-negative. A study from Stanford University on breast cancer after HL found that 46% of the breast cancers diagnosed before 1990 compared with 76% of the cases diagnosed after 1990,[44] when mammogram screening was more routinely performed, were of stage 0 to 1 (p = .05). In the National Notification Risk Assessment and Screening Program from the United Kingdom for women who had received supradiaphragmatic RT for HL,[43] all five invasive breast cancers detected through the mammography screening program were node-negative, while 7 of 13 (54%) women diagnosed outside of the screening program had node-positive breast cancers.

In more recent years, the role of breast MRI screening has been explored in cancer survivors with history of chest RT.[45-47] In a prospective screening study, 148 women treated with mediastinal RT for HL at age 35 or younger underwent annual breast MRI and mammogram screening over a 3-year period.[45] The sensitivity of mammogram compared with MRI for breast cancer detection were 68% and 67%, respectively, and increased to 94% when both modalities were used. The improved sensitivity was at the expense of slightly reduced specificity with an overall false-positive rate of 8.9%. However, the false-positive rates diminished from 13.4% by 9% to 2%, respectively in years 1, 2, and 3, likely because of the availability of prior MRI scans for comparison. Of the 18 screen-detected breast cancers, 17 were preinvasive, or subcentimeter and node-negative cancers. The role of breast MRI and mammogram screening was also evaluated in 104 childhood cancer survivors treated with chest RT.[46] In this study, the sensitivity of mammogram versus MRI were 70% and 80%, respectively, and increased to 100% when both were used. Among the 10 cases of screen-detected breast cancers, half were preinvasive, and all were node-negative. The addition of breast MRI to mammogram, therefore, appears to improve the sensitivity of breast cancer detection and allows detection at very early stages. Hodgson et al quantified the reduction in breast cancer mortality with early breast cancer screening in survivors of childhood HL using mathematical modeling.[48] For a patient irradiated at age 15, the estimated absolute risks of breast cancer mortality by age 75 were 16.65%, 16.28%, and 15.38%, respectively, in women without early screening, with early mammogram screening starting at age 25, and with early screening with both mammogram and MRI.

Several guidelines are available on breast cancer screening in cancer survivors.[49-55] Most recommend both mammogram and breast MRI screening in women who have received chest RT between ages 10 and 30 or prior to age 30. For those treated for childhood cancers, screening is recommended to start at age 25, or 8 years after treatment, whichever occurs last. For women treated as young adults, it is recommended that breast cancer screening starts 8 years after treatment or by age 40, whichever occurs first.

Despite the well-documented breast cancer risk in women who have received chest RT at a young age, multiple studies have shown a lack of awareness of the increased risk among survivors, low adherence to breast cancer screening, and

knowledge gap regarding breast cancer risk and screening recommendations among providers.[55-61] Interventional programs have been developed to improve awareness and adherence to screening guidelines.[43,62,63] In the National Cancer Institute–funded EMPOWER study conducted among women participants of the CCSS who were exposed to chest radiation,[63] a tailored intervention using mailed information and telephone interviews promoting breast cancer screening was compared with a control of general health information by mail followed by heart health telephone interview. Women randomly assigned to receive tailored intervention were significantly ($p < .01$) more likely to report a surveillance mammogram by 12 months. However, there was no significant difference ($p = .48$) in reporting a surveillance breast MRI, which may be related to costs and ordering physician preference.

Limited data are available on the role of chemoprevention for breast cancer in survivors of childhood and young adult cancers. A phase II multicenter randomized placebo-controlled trial is currently ongoing evaluating the use of low-dose tamoxifen (a synthetic selective estrogen receptor modifier) 5 mg daily for 2 years in female survivors who have received a dose of 12 Gy or higher to the chest at younger than age 40.[64] Surrogate endpoints for breast cancer risk are being used, including mammographic breast density, tissue biomarkers, sex steroid hormones and insulin growth factors, and circulating biomarkers of breast cancer.

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Data Commons to Support Pediatric Cancer Research

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OVERVIEW

The falling costs and increasing fidelity of high-throughput biomedical research data have led to a renaissance in cancer surveillance and treatment. Yet, the amount, velocity, and complexity of these data have overcome the capacity of the increasing number of researchers collecting and analyzing this information. By centralizing the data, processing power, and tools, there is a valuable opportunity to share resources and thus increase the efficiency, power, and impact of research. Herein, we describe current data commons and how they operate in the oncology landscape, including an overview of the International Neuroblastoma Risk Group data commons as a paradigm case. We outline the practical steps and considerations in building data commons. Finally, we discuss the unique opportunities and benefits of creating a data commons within the context of pediatric cancer research, highlighting the particular advantages for clinical oncology and suggested next steps.

Simply, a data commons consists of cloud-based infrastructure that includes storage for data and the computational resources and tools for analysis.[1] The research community interacts with a data commons in several ways: (1) through the submission of data, (2) by requesting and downloading data, or (3) by collecting and analyzing data on the data commons infrastructure. By facilitating these tasks, the presence of a data commons relieves the need for the researcher to purchase and manage local storage, compute, or processing tools.

There are many sources of international genomic data, both public and private, and notably some specific to pediatric cancer.[2] The examples here focus on the data available through formal mechanisms at U.S. federal agencies such as the National Cancer Institute (NCI) and the National Center for Biotechnology Information (NCBI). The NCBI hosts the Database of Genotypes and Phenotypes (dbGaP), which contains a collection of studies focused on the interaction of genotype and phenotype in humans.[3] The NCI has funded the Therapeutically Applicable Research To Generate Effective Treatments (TARGET) consortium, which is a collaboration of investigators comprised mainly of members of the Children's Oncology Group (COG), a clinical trials group devoted exclusively to childhood and adolescent cancer research.[4] TARGET researchers collaborate with the COG to access clinical expertise and biospecimens across the network, with the goal of producing genomics data that will facilitate molecular discoveries and aid translation of those findings into effective therapies. The NCI also funds the Genomic Data Commons (GDC) that centralizes, standardizes, and makes accessible data from large-scale NCI programs such as TARGET and its adult equivalent, The Cancer Genome Atlas (TCGA).[5]

Data commons share four requirements. First, storage and compute resources must be available for cloud-based analysis of data. Until recently, the most efficient and cost-effective storage was local, on premises, managed arrays of hard drives. The availability of cheap, reliable cloud-based storage obviates the need for researchers to purchase and manage their own storage or compute clusters. Second, a data commons must access publicly available data sets. This includes data from NCI-controlled resources, such as dbGaP and TARGET, but also could include data from any source. Note that "publicly available" does not mean "freely available." In many cases, access to the data will be controlled and only available through an application process. For genomic data, whole-exome or whole-genome data deposited in dbGaP or TARGET is only available after the investigator completes an application and once their sponsoring institution completes the necessary materials transfer agreement. Third, a data commons must contain software services and tools to enable cloud-based analysis of the data. Increasingly, researchers do not have the means or expertise to provision their own servers and tools or keep up with updates and new versions. Centralized access to tools facilitates a common platform for analysis across data sets. Fourth, data must conform to the FAIR digital compliance model (Findable, Accessible, Interoperable, Reusable).[6,7]

To be findable, data must contain sufficient metadata to be persistently identifiable and distinguishable from other objects. For example, a genomic sequence should contain machine-readable metadata that ties it back to the origi-

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nal source in a unique and persistent way. Accessible data are defined as requiring appropriate authorization via a well-defined protocol. Individual-level genomic data stored in the genomic data commons is accessed once the user receives authorization via the dbGaP system. The GDC authenticates users to access these data based on information passed through from dbGaP. Interoperability is key to building a successful data commons, and key components are shared vocabularies and ontologies. Furthermore, the data must be machine actionable. By being both syntactically parseable and semantically machine accessible, data can be shared between systems, facilitating a degree of sharing and interoperability that is currently a rare commodity. If these three criteria are met—findability, accessibility, and interoperability—the data can be reusable, if the metadata and other descriptors are sufficiently rich that the data can be linked to other sources. Furthermore, these descriptors should allow linkage back to the original source. Increasingly, documentation of data lineage is being required for publication, and observation of these FAIR principles will help to ensure sufficient data provenance.[8]

CURRENT OVERVIEW OF U.S. DATA COMMONS

Across biomedical disciplines, communities have acknowledged the need to "eliminate data silos and promote data sharing."[9,10] The concept of collective research that led to the success of the human genome project exemplifies how open, rapid sharing of data can accelerate discovery. In both oncology and pediatric medicine, data commons projects have been created and are already being used in research.

In pediatrics, the development of a collaborative chronic care network for children with Crohn's disease and ulcerative colitis called ImproveCareNow has allowed researchers and clinicians to collaborate to improve care and outcomes.[11,12] As of March 2015, the ImproveCareNow network had data from 73 centers, including 8,205 patients.[12] Additionally, patients play a key role in the ImproveCareNow collaborative chronic care network through input from a patient advisory council and also by providing patients the opportunity to share their stories, test new ideas, or contribute their data.[13]

In October 2016, a new collaboration, Cavatica, was announced between the Children's Brain Tumor Tissue Consortium Consortium and the Pacific Pediatric Neuro-Oncology Consortium. Cavatica also works in partnership with Seven Bridges, which provides a cloud-based environment for analyzing genomic data.[14] The goal of the collaboration is to create a data analysis platform that will help researchers collaboratively access and share data about pediatric cancers, congenital disorders, and rare diseases, such as epilepsy and autism. In building the Cavatica platform, one of the goals is to ensure that adult and pediatric data can intersect in meaningful ways. Therefore, Cavatica will interoperate with the GDC, existing NIH data repositories, and other emerging data commons.[14] Cavatica provides data access and shared use via a combination of models depending on the data source. Access to all NIH-managed data requires dbGAP approval, whereas other datasets and projects are managed by project-specific administration or a data depositor's Data Use Committee. One aspect of interoperability is accomplished by harmonizing key data concepts with those provided by the GDC and providing an application program interface (API) layer that allows querying of these concepts across multiple commons. At the same time, Cavatica allows for defining additional fields for projects, as important disease and pediatric-specific concepts may not be defined as part of the GDC. As described in the general data commons model above, by leveraging cloud technology, researchers can set up collaborative projects in Cavatica that link together data sets for coanalysis and sharable results. Additionally, all of the data, as well as the workflows run on the data, have unique identifiers that allow for reuse and reproducibility of analyses.

In addition to funding the GDC, the NCI also funds the Cancer Genomics Cloud Pilots. These projects are all designed to make cancer genomics data broadly accessible, computable, and usable by researchers worldwide, with the goal of fostering the molecular diagnosis and treatment of cancer. The GDC launched in June 2016 and serves as an integral part of the National Cancer Moonshot and the President's Precision Medicine Initiative.[5] Within the GDC, genomics data and associated clinical data can be stored and analyzed, allowing researchers to compare finding across studies. One of the key GDC initiatives was to harmonize the NCI's cancer genomics data. This included both processing the genomic data with uniform pipelines as well as developing a data model with uniform terms and definitions for biospecimen and clinical data. The GDC currently contains approximately 5 petabytes (a petabyte is 1,000,000 gigabytes) of data, which includes legacy data that were transferred from previous NCI projects as well as the newly stored harmonized data. There are approximately 42 types of cancer represented across 14,200 patients with a total of over 578,000 files. The data include 10 major types, ranging from raw sequencing

KEY POINTS

- **A data commons consists of cloud-based infrastructure that includes storage for data and the computational resources and tools for analysis.**
- **The research community interacts with a data commons in several ways: (1) through the submission of data, (2) by requesting and downloading data, or (3) by collecting and analyzing data on the data commons infrastructure.**
- **Pediatric cancer is rare, and the paucity of childhood cancer cases makes it particularly challenging to study.**
- **The next important step in systematically addressing pediatric cancer is the creation of shared and well-curated pediatric cancer data commons that would accelerate discovery through existing cohorts.**
- **A consortium-led approach would help to develop robust processes for data contribution, data attribution, data sharing, collaborative discovery, shared analysis, and further provides for interoperability and access of data.**

data and raw microarray data to copy number variation, simple nucleotide variation, and gene expression. The data are derived from 17 different experimental strategies, with the major ones being RNA expression (RNA-Seq), whole-exome sequencing (WXS), whole-genome sequencing (WGS), micro-RNA sequencing (miRNA-Seq), and genotyping array.

The current GDC system is a hybrid cloud that is based upon OpenStack running at an on-premise University of Chicago data center and on Amazon Web Services. In its current operations, the GDC uses these cloud-based services for internal operations, for processing data submitted via GDC's bioinformatics pipelines, and for responding to user requests through the GDC API, but the cloud-based services are not directly exposed to GDC users. The GDC provides APIs and a set of core tools built over the API, including the data portal and a data download tool. Key to the concept of the commons is the ability to seed an ecosystem in which people can create custom tools over the data and APIs to meet their needs. This is beginning to emerge around the GDC with projects such as TCGABiolinks and the related TCGABiolinksGUI.[15,16] These projects use the GDC API and provide a model for how data commons can foster applications that further improve the accessibility of data.

The NCI Cloud Pilots provide GDC users with the ability to use public clouds to execute their own bioinformatics pipelines on GDC data that have already been imported to the Cloud Pilot or are accessed directly through GDC API. For other custom analyses over NCI data, researchers currently have access to the following NCI cloud pilots: (1) FireCloud, developed by the Broad Institute, (2) the Cancer Genomics Cloud developed by Seven Bridges Genomics, and (3) the Institute for Systems Biology Cancer Genomics Cloud. Via these pilots, different ways of leveraging cloud capabilities on platforms such as Amazon Web Services and Google Cloud Platform are being investigated to inform future cloud and commons architectures. Each of the pilots has suites of tools, including APIs and user interfaces, to facilitate access and use of large-scale data sets relevant to the cancer research community.[7]

These examples of current developments in both pediatrics and oncology offer insight into the possible ways in which data commons can be organized and used across research communities. The potential to foster significant collaborative efforts and results holds great promise for the pediatric oncology community as well.

NEED FOR PEDIATRIC ONCOLOGY DATA COMMONS

Pediatric cancer is rare, and advances in diagnosis and treatment have been made through large consortium-driven trials. The total number of new pediatric cancer diagnoses per year in the United States is around 16,000.[17] There are about 3,000 new cases per year of the most common pediatric cancer, acute lymphoblastic leukemia, whereas the most common solid tumor, neuroblastoma, affects 800 new children each year. In contrast, there were 1.7 million new cases of adult cancer in the United States predicted for 2016.[18] For perspective, the total number of new pediatric cancer cases per year in the entire United States is about equivalent to the number of new breast cancer cases in Florida alone.[19] The paucity of childhood cancer cases makes it particularly challenging to study, and the emergence of data commons for pediatric cancer could be a transformative innovation.

PARADIGM CASE: THE INRG DATA COMMONS

In 2004, an International Neuroblastoma Risk Group (INRG) Task Force formed with representation from cooperative children's cancer groups in North America, Europe, Australia, and Japan. The initial charge of this multiconsortium group was to statistically analyze prognostic markers on a combined patient data set to establish an international risk group classification system. Working with statisticians from each geographic area, a standard data dictionary was created to map all of the data elements into this framework. This initiative led to development of a database that contained information on 32 clinical elements from 8,800 patients with neuroblastoma diagnosed around the world between 1990 and 2002. During the following decade, data were added to the database under supervision of cooperative group statisticians, and over a dozen high-impact, peer-reviewed papers were published.[20-23]

In 2012, the University of Chicago Center for Research Informatics (CRI) set out to remedy three severe limitations inherent in the INRG database. First, at the time, the data remain sequestered in a single flat spreadsheet, not readily available except through an onerous and lengthy data request process. Furthermore, until the request was processed, the researcher would have little insight into the feasibility of the study. The second limitation was that biospecimen availability presented a particularly difficult challenge. In the United States, most biologic samples for pediatric subjects with cancer are collected through COG clinical trials or tumor registries. These specimens are stored in a common repository at Children's National Medical Center in Columbus, Ohio. To request samples, the researchers must first query sample availability for their cohort of interest and await a response. So, even before an application for specimens can be submitted, the researchers can waste precious time waiting to document specimen availability. A third challenge facing neuroblastoma researchers was that associated genomic data were not linked to the clinical phenotype information in the INRG database, and furthermore, there were no associated resources such as storage and compute available for analysis.

Realizing these challenges, University of Chicago faculty Dr. Susan Cohn, co-chair of the INRG, and Dr. Samuel Volchenboum, director of the CRI, leveraged philanthropic funding to finance a partnership between the CRI and the University of Chicago Center for Data Intensive Science, directed by Dr. Robert Grossman. Given their experience in building and managing the NCI GDC, the Center for Data Intensive Science was the ideal partner for CRI in setting up a neuroblastoma data commons to address the above

challenges.

Key to this development was the establishment of an international governance process. Led by Dr. Volchenboum, the INRG Data Governance Committee met via phone conference several times and presented twice to the international neuroblastoma community at meetings in Cologne, Germany (2014), and Cairns, Australia (2016). This group consisted of an international team of attorneys, ethicists, and neuroblastoma subject matter experts. The work product was (1) a set of operating principles for the INRG, (2) a data-use agreement for researchers wanting data from the INRG, and (3) a data-contributor agreement, for those wanting to deposit data into the INRG.

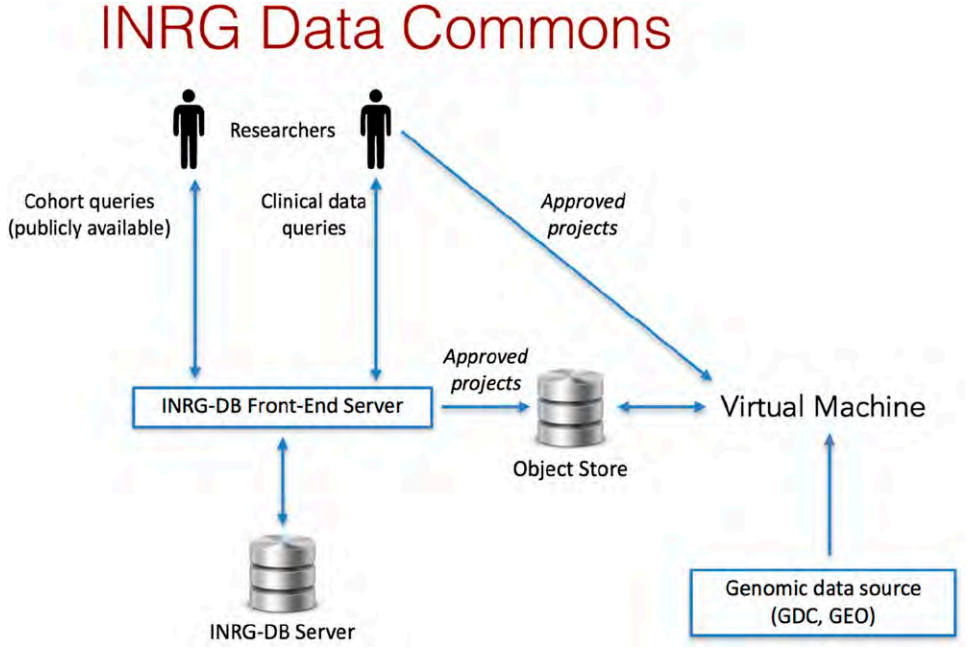
Because the University of Chicago was acting as a service provider for the INRG, a memorandum of understanding was established between the INRG and the University of Chicago that covered the responsibilities of both groups. The CRI designed and built a database to house the INRG phenotype data, and a front-end interface was created to allow anyone to query the entire cohort of neuroblastoma patients (Fig. 1). Currently, over 18,000 neuroblastoma patients are represented in the database, spanning a period from 1980 to present.[24] Data are updated at regular intervals. In addition to phenotype information, the database can filter on biospecimen availability via an API at the COG Biospecimen Repository. As a result, a search process that took weeks or months previously can now be accomplished in a few minutes.

The process of linking phenotype and genotype information is often made difficult by the lack of a common associated identifier. Fortunately, COG assigns a Universal Specimen Identifier (USI) to each sample collected. The USI is associated with any subsequently generated samples, data, or other information. In the case of the genomic data, all samples in the TARGET data set have USIs that link back to the phenotype data in the INRG database, permitting easy association of data sets.

As illustrated in Fig. 1, central to the data commons is an application and approval workflow that requires users to formally request clinical data through a project approval portal. Access to the genomic data are governed separately through the NCBI's own mechanisms, and this approval is passed through to the GDC. Once the necessary permissions have been secured, including from the INRG Executive Committee for clinical data, from the NCBI for genomic data, and from the University of Chicago for establishment of the virtual infrastructure, the system deposits the clinical data into an object store, and a virtual machine is launched in which the user can use command line tools for data analysis. Genomic data can be pulled from the GDC through the GDC API and lined up against the clinical data for subsequent analysis.

In summary, the Neuroblastoma Data Commons enables research over clinical data in the INRG database and associated genomic information pulled from the GDC or the NCBI's Gene Expression Omnibus in a cloud-based infrastructure. The process is governed by an international data governance committee, and the University of Chicago acts as a service provider with a formal agreement with the INRG on behalf of the COG, the German Gesellschaft für Pädiatrische Onkologie und Hämatologie, the Japanese Advanced Neuroblastoma Study Group, the Japanese Infantile Neuroblastoma Cooperative Study Group, and the Society of Pediatric Oncology Europe Neuroblastoma Group.

FIGURE 1. INRG Data Commons Design and Workflow



This figure illustrates the relationship between the INRG database and the permissions and technology that allow researchers to access the data.

PRACTICAL ISSUES IN BUILDING DATA COMMONS

With the establishment of the INRG Data Commons, other pediatric solid tumor groups have expressed interest in building similar pediatric cancer data commons. Efforts are underway with groups representing pediatric sarcoma, germ cell tumors, and brain tumors to collect and standardize data and build data commons. In considering development, it is useful to use a paradigm, which is emerging for building cancer data commons. Key elements have been drawn from data science, data governance, and engineering.

Figure 2 outlines this paradigm and some of the important issues and steps in building a pediatric cancer data commons. Because data commons are ultimately a shared community resource, engaging stakeholders from the outset of the design is critical to defining the data model and achieving standardization. Furthermore, cooperation from consortium members is critical in defining scope and being able to collect data from multiple sources. Finally, cooperative group members will serve as a resource throughout the process for advice and governance, maximizing the chance for an accepted, usable, and successful data commons. Other key considerations that must be considered are: identifying a funding source and infrastructure; engaging a project team; and identifying relevant data sources.

Once the basic purpose and structure is defined, then establishing governance policies and procedures such as contributor and user agreements is integral to the functioning of the system. Standards for data definition, format, and ontologies must be agreed upon across the group, and engaging external experts in this area such as the Clinical Data Interchange Standards Consortium can help guide the process. The Clinical Data Interchange Standards Consortium mission is "to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of health care."[25] Once standards are established, the project team can create a data dictionary and map various elements that can be used to create database. A front-end query engine allows users to easily access information about the data commons and increases impact by lowering the threshold for determining key questions about sample size and statistical power.

The final steps to ensure continued success of a data commons includes the creation and execution of a robust communication and education plan that will inform potential contributors and users about the data commons on a regular basis. In conjunction with ongoing stakeholder engagement, this will help to build a sustainable data commons for the future. An essential component of the consortium is real patient and family engagement. Only in building such a model can we authentically empower patients and foundations to take an active role as data producers in their participation and contribution to research.

FIGURE 2. Paradigm for Building Pediatric Cancer Data Commons

Paradigm for pediatric cancer data commons

1. Engage cooperative groups
2. Define scope
3. Identify funding
4. Choose infrastructure
5. Engage team
6. Identify data sources
7. Establish governance
8. Create agreements
9. Establish standards
10. Create database
11. Build front-end tools
12. Establish back-end connections to data sources and infrastructure
13. Create and execute communication and education plans
14. Create sustainability model

This figure offers a model, drawn from the fields of data science, data governance, and engineering, of the critical steps in building a successful and sustainable pediatric cancer data commons.

NEXT STEPS: FUTURE OF PEDIATRIC CANCER RESEARCH

Like data-driven progress in adult cancers, "big data" genomics in pediatric cancers requires a shared computation/harmonization infrastructure and, more importantly, the necessary associated availability of well-curated genomic and phenotypic data from large cohorts of pediatric patients. But because of the paucity of pediatric cancer cases, children with cancer are failing to benefit from the technological revolution driving the precision-medicine age. Although 5-year survival rates for children diagnosed with cancer have improved in recent decades, survival rates remain very low for some types of cancer, especially for metastatic tumors and those with high-risk genetic features. Despite steady advances in diagnosis, treatment, and follow-up, cancer remains the leading cause of death from disease in children in the United States.[26,27]

We propose that the next important step in addressing pediatric cancer is the creation of a shared and well-curated pediatric cancer data commons or an ecosystem of connected data commons. This fully empowered data commons would accelerate discovery through existing cohorts and would include a consortium-led approach to developing robust processes for data contribution, data attribution, data sharing, collaborative discovery, and shared analysis and further provide for interoperability and access of data. This can be accomplished by utilizing the paradigm offered here (Fig. 2) to ensure comprehensive and collaborative development of the data commons infrastructure, policies, and processes.

One of the most promising benefits of developing a shared and well-curated pediatric cancer data commons or ecosystem is the ability to develop novel personalized medicine approaches to treating pediatric cancer. In personalized medicine, interventions are tailored to individual variation in risk and treatment response.[28] Genomics elevates personalized medicine by allowing for precise classification of an individual's disease and potentially expected responsiveness to treatment. A combination of the characterization of cancers and known responsiveness to treatment allows for

targeted interventions. These targeted therapies could be especially beneficial for children who may live many years after treatment and are at risk for treatment-related late effects. Currently, one in 1,000 individuals in the United States is a childhood cancer survivor, which means there are numerous survivors who are at increased risk for long-term health consequences resulting from their treatments.[29] Personalized medicine offers the opportunity to identify cohorts of children most in need of aggressive treatment while reducing exposure to ineffective therapies.[27]

The future of pediatric cancer research depends on our ability to develop collaborative data commons and to bring together data, research expertise, and clinical practice to translate the benefits of these collaborations into real change for children. Advances in genomic profiling, along with the democratization of data storage and compute resources, have resulted in a computational landscape ideally positioned for studying pediatric cancer. What remains is a focused and systematic effort to collect, standardize, and combine multiple disparate phenotypic, genomic, and other data sets from children with cancer into one or more connected data commons. If built with robust data governance and a well-conceived sustainability model, these resources could have a transformative effect on pediatric cancer research, resulting in novel and better ways to diagnose and treat children with oncologic diseases.

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New Classification for Central Nervous System Tumors: Implications for Diagnosis and Therapy

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OVERVIEW

The 2016 World Health Organization Classification of Tumors of the Central Nervous System (WHO 2016) represents a noteworthy divergence from prior classification schemas. This new classification introduced the concept of "integrated diagnoses" based on a marriage of both phenotypic (microscopic) and genotypic parameters, with the intended goals of improving diagnostic accuracy and patient management. The result is a major restructuring in many of the brain tumor categories, with the codification of multiple new tumor entities and subgroups. It is therefore imperative that pathologists, clinicians, and neuro-oncology researchers alike rapidly become familiar with this new classification schema. Many of the diagnostic updates set forth in the WHO 2016 have impacted brain tumor types that commonly arise in the pediatric age group, particularly within the diffuse glioma, ependymoma, and embryonal tumor categories. This review gives a brief overview of (1) the WHO 2016 as it relates to pediatric central nervous system (CNS) tumors, with an emphasis on molecular diagnostic tools used in the clinical arena, (2) ongoing and developing approaches to the molecular and genomic classification of pediatric CNS tumors, and (3) the impact of this new classification schema on clinical trials in pediatric neuro-oncology.

Historically, the classification of CNS tumors has relied exclusively on findings from microscopy and immunohistochemical (IHC) analysis. The explosive exploration into the (epi)genetic and transcriptomic factors influencing tumorigenesis in brain tumors has led to the discovery of numerous important prognostic and predictive determinants. It is clear that many pediatric brain tumors, though histologically resembling their adult counterparts, bear strikingly different genetic profiles. With the recognition that various "molecular signatures" may also provide diagnostic utility,[1] a major revision to the prior 2007 World Health Organization Classification of Tumors of the CNS[2] was undertaken. The resulting WHO 2016 incorporates both microscopic and molecular parameters into CNS tumor classification.[3] The WHO 2016 provides a major restructuring to a number of brain tumor groups, particularly diffuse gliomas and CNS embryonal tumors. What follows is a summation of the major tumor groups within the WHO 2016 most relevant to pediatric neuropathology/neuro-oncology, including an overview of molecular diagnostic tools that are becoming the standard of practice in diagnostic work-up.

OVERVIEW OF NEW CLASSIFICATION AND MOLECULAR DIAGNOSTIC TOOLS IN PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS

Pediatric Diffuse Gliomas

Diffuse midline glioma (DMG), H3 K27M-mutant is a newly recognized entity in the WHO 2016, defined as an "infiltrative midline high-grade glioma with predominantly astrocytic differentiation and a K27M mutation in either *H3F3A* or *HIST1H3B*/*C*."[3,p. 57] The majority of diffuse intrinsic pontine gliomas (DIPGs) qualify for this designation, as do many pediatric diffuse gliomas arising in other midline locations (i.e., thalamus and spinal cord). Mutations involving *ACVR1* are present in a considerable proportion of DIPGs, the majority with concomitant K27M mutation of H3.1.[4,5]

The K27M mutation defining this entity results in a lysine to methionine substitution at position K27 in *H3F3A* (encoding histone H3.3) or *HIST1H3B*/*HIST1H3C* (encoding histone H3.1). Histones play an integral role in transcriptional regulation, predominantly via post-translational modification of histone tail regions. Trimethylation at the K27 position is associated with repression of gene expression. The EZH2 catalytic site of the polycomb repressive complex 2 (PRC2) is responsible for this methylation; K27M mutation interferes with EZH2/PRC2 methyltransferase activity, resulting in globally diminished H3K27me3 levels (hypomethylated state) and derepression of PRC2 target genes.[6] H3 K27M mutations are found in approximately 80% of DIPGs (H3.3 > H3.1) and nearly half of DMGs arising in the thalamus and spinal cord.[3]

Most K27M-mutant DMGs are hypointense on T1 and hyperintense on T2/fluid-attenuated inversion recovery MRI studies. Intratumoral contrast enhancement, necrosis, or hemorrhage may be present. DIPG presents as an expansile lesion centered within the pons (Fig. 1A) and often shows

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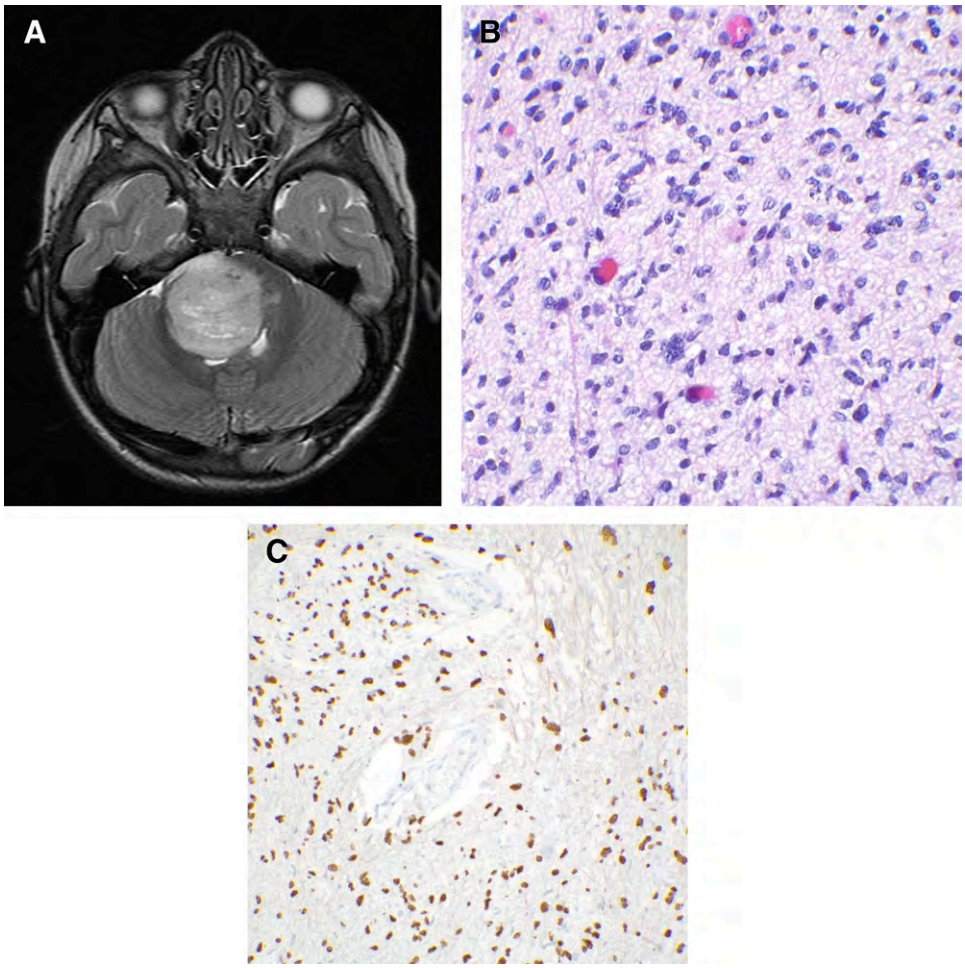
FIGURE 1. Example of a DMG



H3 K27M-mutant presenting as a diffuse intrinsic pontine glioma, hyperintense on this T2-weighted axial MRI (A). Histology was that of a high-grade astrocytoma with moderate pleomorphism (B). Mutant-specific immunohistochemistry for H3 K27M showed strong staining of the tumor cell nuclei (C).

KEY POINTS

- **The WHO 2016 represents a major restructuring of brain tumor classification, incorporating both microscopic and molecular parameters.**
- **H3 K27M diffuse midline glioma, *RELA* fusion ependymoma, and molecular-based medulloblastoma subgrouping are new WHO 2016 additions important in pediatric neuro-oncology.**
- **The WHO 2016 also introduces a molecular definition for atypical teratoid/rhabdoid tumors, and the new entity embryonal tumor with multilayered rosettes, C19MC-altered.**
- **Gene expression and DNA methylation profiling have been and continue to be powerful tools in identifying molecular subgroups and therapeutic targets in pediatric brain tumors.**
- **Current and upcoming clinical trials are incorporating a variety of genetic determinants (mutation status and molecular-based tumor subgrouping) into treatment stratification schema.**

locoregional infiltration. A gliomatosis-cerebri–type pattern of diffuse parenchymal involvement, leptomeningeal, and/or intraventricular spread may also be present.

K27M-mutant DMGs present histologically as infiltrative gliomas, typically with an astrocytic cytomorphology. Though some contain deceptively bland tumor cells, others harbor cells with striking pleomorphism. The WHO 2016 specifies that "mitotic activity is present in most cases, but is not necessary for the diagnosis; microvascular proliferation and necrosis may be seen."[3] That said, DMG, H3 K27M-mutant may histologically resemble diffuse glioma ranging from low-grade diffuse astrocytoma to glioblastoma (Fig. 1B). For DIPGs, there is evidence to support that these variable histologic appearances are not predictive of clinical outcome independent of H3 K27M-mutant status, although this same association has not been established for DMGs arising elsewhere.[7,8] Detectable H3 K27M mutation in a pediatric DMG correlates with a much worse prognosis in comparison with DMGs lacking this signature.[7,9] In DIPGs, some groups have identified distinct molecular subgroups, and there is evidence to suggest that the type of H3 K27M mutation (H3.3 vs. H3.1) may convey variable tumor phenotype and prognosis.[4,10]

A variety of additional alterations of genes involved in chromatin and transcription regulation (*ATRX*, *BCOR*, and *MYC*) and the RAS–phosphoinositide 3-kinase, Rb, and TP53 pathways has been demonstrated in pediatric DMG, either in addition to or independent of H3 K27M mutation.[11,12] This emphasizes the fact that not all pediatric DMGs qualify for the pathologic diagnosis of DMG, H3 K27M-mutant. To be designated as such requires demonstration of H3 K27M mutation. This may be accomplished by direct sequencing, but it is also readily demonstrated via immunohistochemistry; mutant-specific antibody targeting H3 K27M (which detects both H3.3 and H3.1 K27M mutation) will show diffuse nuclear positivity (Fig. 1C), whereas H3 K27me3 antibody will show loss of nuclear staining.[13,14] Pediatric DMGs lacking the signature H3 K27M mutation should be histomorphologically classified (astrocytoma vs. oligodendroglioma) and graded (WHO grade II to IV), followed by assessment of 1p/19q codeletion and/or isocitrate dehydrogenase status as appropriate based on histologic findings. This is therefore similar to the histologic-molecular workup of adult diffuse gliomas in accordance with the WHO 2016 classification schema.[3]

Pediatric Ependymomas

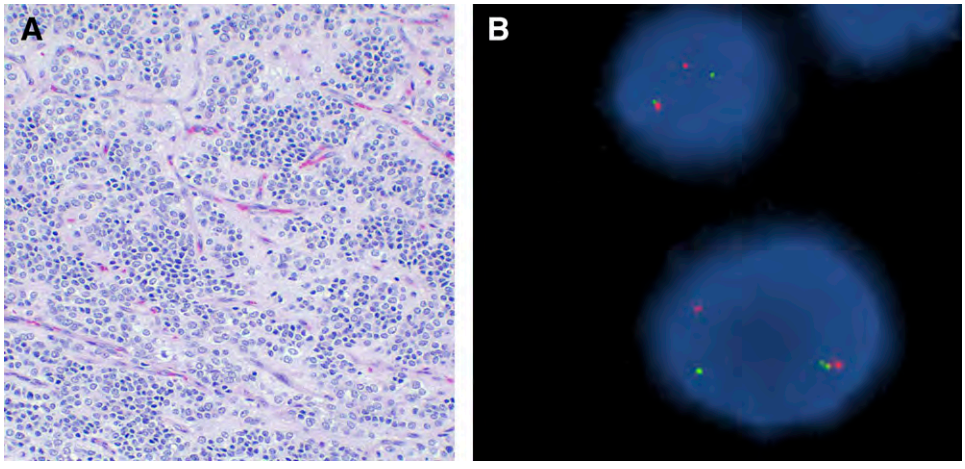
Ependymomas represent the third most common pediatric brain tumor, accounting for 30% of intracranial tumors in children younger than 3 years. The focus to refine the accurate classification of ependymomas has shifted from one centered primarily upon developing objective histologic grading criteria to one that takes advantage of genetic and/or epigenetic classifiers. Ependymomas do not share a unifying molecular signature. On the contrary, ependymomas have been shown to represent multiple genetically distinct subsets, relative to age of occurrence, location, and biologic potential.[15-17]

To that end, the WHO 2016 introduced a new molecularly defined entity: ependymoma, *RELA* fusion-positive.[3] This genetically defined ependymoma accounts for 70% of pediatric supratentorial ependymomas, although it has occasionally been encountered in adults.[18,19] The oncogenic fusion *C11orf95-RELA* fusion is the most commonly demonstrated alteration, resulting in aberrant activation of the nuclear factor-κB signaling pathway.[18-20] These fusions often arise through chromothripsis, and occasionally *C11orf95* or *RELA* may fuse with other partners.[19]

RELA fusion-positive ependymomas may histologically resemble other conventional ependymomas, though clear cell morphology and branching capillaries are often present[20] (Fig. 2A). L1CAM expression detectable by immunohistochemistry (Fig. 2B) correlates well with the presence of *RELA* fusion[19]; however, definitive diagnosis requires demonstration of signature fusions. Given the varied array of breakpoints and rare alternate fusion partners, fluorescence in situ hybridization (FISH) represents the current method of choice for assessment. Typically, break-apart FISH assays using locus-specific probe pairs targeting opposing ends of the *RELA* and *C11orf95* regions are used, with fusions demonstrated as split signals as seen in Fig. 2C.

The importance in identification of *RELA* fusion-positive ependymomas stems from a large multi-institutional study in which this group of genetically defined supratentorial ependymomas represented the most biologically aggressive of the supratentorial ependymal tumors. In that study, supratentorial subependymomas and ependymomas with Yes-associated protein 1 fusions both had comparably better prognoses.[15] The WHO 2016 does not prescribe specific molecular testing to either diagnose or otherwise subgroup other ependymal tumors; however, it emphasizes that multiple groups have independently identified biologically and molecularly distinct subgroups of pediatric infratentorial ependymomas; posterior fossa (PF)–group A tumors arise in infants/young children and are biologically aggressive akin to *RELA* fusion-positive ependymomas, whereas PF-group B tumors arise in older children and have a better prognosis.[21-23] Recent studies indicate that PF-group A ependymomas exhibit a distinct epigenetic phenotype, and

FIGURE 2. Example of a Pediatric Supratentorial Ependymoma, *RELA*-Fusion Positive



On histologic examination (A), these lesions often exhibit delicate branched capillaries and clear cell appearance. (B) Dual-color FISH using probes flanking the *RELA* locus show single red and green signals (break-apart), confirming the presence of *RELA* fusion.

assessment of H3 K27me3 status by IHC shows promise in differentiating between group A and B tumors.[24,25] It is likely that subsequent WHO updates will incorporate additional ependymoma genetic subgrouping in line with the aforementioned findings.

Pediatric Embryonal Tumors

Medulloblastoma. Medulloblastoma (MB) is a primitive CNS embryonal tumor arising in the cerebellum. Historically, the management of patients with MB has centered upon traditional prognostic factors for patient risk stratification: age, extent of resection, presence of metastatic disease, and histology.[26,27] On the basis of these parameters, current multimodality treatments afford standard-risk patients with MB 5-year event-free survival rates of 79% to 85%, whereas high-risk patients have a 5-year event-free survival rate of 55% to 70%.[28-31]

A limitation of traditional MB risk stratification is that it did not account for the molecular heterogeneity of this disease. Multiple groups (Pomeroy et al,[32] Cho et al,[33] Kool et al,[34] and Northcott et al[35]) have elucidated the MB (epi)genomic landscape. This led to a consensus recognition of four genetically defined subgroups, each with a distinct gene expression, mutation/copy-number alteration, and methylome profile, as well as typical patient demographic, histologic, and prognostic features.[36] In response, the WHO 2016 included two distinct diagnostic classifications for MBs: one genetically defined and the other histologically defined.[3]

The WHO 2016 histologically defined MB classification is essentially a recapitulation of well-defined microscopic definitions present in prior classifications[2]; these include classic, desmoplastic/nodular (DN), large-cell/anaplastic (LCA) MB, and MB with extensive nodularity.[3] Histologic classification provides relevant clinical information in cases in which molecular classification cannot be performed. For instance, extensively nodular and DN MBs correlate exclusively with a sonic hedgehog (SHH)–activated signature, whereas the majority of LCA MB are either group 3 or SHH activated.[37] LCA MB has repeatedly been shown to correspond to aggressive biologic behavior.[38,39]

The four WHO 2016 genetically defined MB subgroups are as follows:

Medulloblastoma, WNT-activated

Accounting for 10% of MB, WNT-activated tumors arise in older children and adults.[40,41] Most are classic histology; survival rates range from 90% to 95% with standard therapy, with rare LCA WNT-activated MB retaining a good prognosis.[37,42,43] IHC demonstration of nuclear β-catenin in tumor cells is a useful method to identify WNT-activated MB in the clinical laboratory, although the WHO 2016 states optimal evaluation combines IHC β-catenin analysis with detection of monosomy 6 or *CTNNB1* mutation.[34,39] Other recurrent alterations include *APC*, *DDX3X*, *SMARCA4*, and *TP53* mutations.[44] *TP53* mutations do not appear to confer a worse prognosis in the WNT-activated group.[45]

Medulloblastoma, SHH-activated

SHH-activated tumors account for 30% of MBs and exhibit a heterogeneous biologic potential based on several additional factors, especially *TP53* mutation status.[36,45] Although gene expression or methylation profiling remain the gold standard for MB subgroup identification, GAB1 and Yes-associated protein 1 detection by IHC provides a surrogate assay for identification of SHH-activated status for purposes of pathologic workup[37] (Fig. 3).

Medulloblastoma, SHH-activated and TP53 wild-type

SHH-activated, *TP53* wild-type MBs are typified by mutations involving *PTCH1*, *SMO*, or *SUFU*; frequent copy-number alterations include *PTCH1* or chromosome 10q loss.[46] These MBs exhibit a bimodal age distribution, targeting infants and adults.[44] Histologically, extensively nodular and DN MBs predominate and are associated with a good prognosis[45,47]; the biologic potential of those with LCA or classic histomorphology is less defined.

Medulloblastoma, SHH-activated and TP53-mutant

In addition to a defining somatic or germline mutation of *TP53*, SHH-activated, *TP53*-mutant MBs often harbor amplifications of *GLI2*, *MYCN*, or *SHH*.[46] LCA morphology, 17p loss, and metastatic disease at presentation are more common in this subgroup, most tumors arising in children 4 to 17 years.[45,46] Diffuse nuclear p53 accumulation by IHC correlates well with the presence of *TP53* mutation.[48] These tumors are associated with poor clinical outcomes and are typically quite refractory to conventional and even SMO-targeted therapies.[45,46]

Medulloblastoma, non-WNT/non-SHH

The WHO 2016 includes MB group 3 and group 4 as provisional variants in the non-WNT/non-SHH subgroup, as these two groups are not as genetically well separated as WNT- and SHH-activated subgroups.[33,49] Although they have been shown to cluster into two groups based upon their gene expression or methylomic signatures, neither group 3 nor group 4 MB have specific driving signaling pathways. IHC assessment of GAB1, Yes-associated protein 1, and β-catenin are useful in excluding these MBs from SHH and WNT subgroups; however, gene expression or methylation profiling is required for definitive subgroup identification.

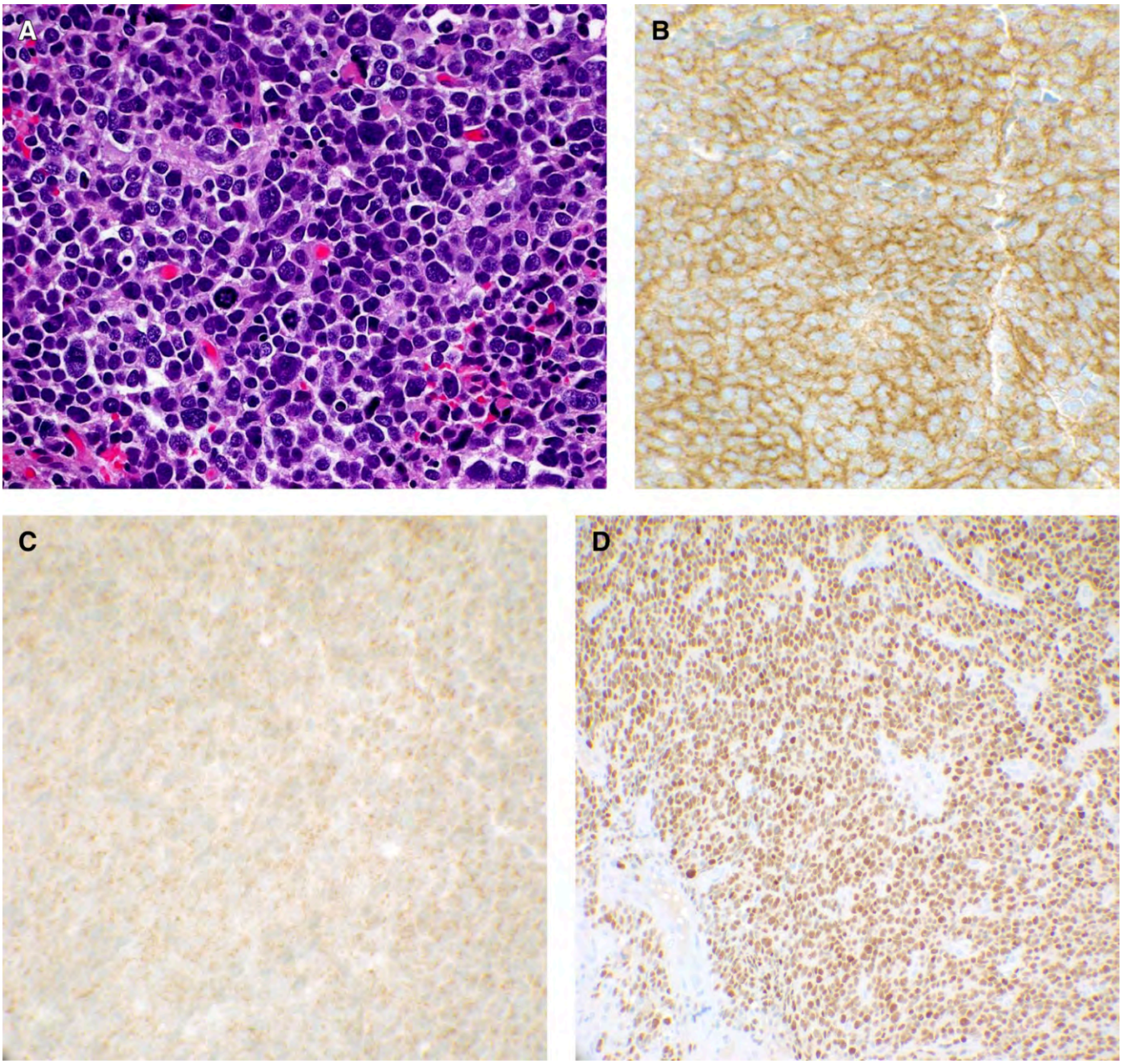
Group 3

Group 3 tumors account for approximately 20% of MBs, arising nearly exclusively in children, particularly infants.[34] This MB group carries the worst prognosis, with almost 50% of patients presenting with metastatic disease.[34,36] Most are classic or LCA histology. *MYC* amplification and isochromosome 17q are frequent cytogenetic findings.[34]

Group 4

Group 4 accounts for the majority of MB cases (approximately 40%), occurs more commonly in children at a

FIGURE 3. Example of an MB, *SHH*-Activated, and *TP53*-Mutant



This MB exhibited large-cell/anaplastic histology (A). Immunohistochemistry for β-catenin (B) showed only cytoplasmic staining; however, the lesion was diffusely positive for GAB1 (C). Pathologic diffuse nuclear staining for p53 was also seen by IHC (D), and *TP53* mutation was subsequently demonstrated by targeted sequencing.

peak age of 10s, and affects males three times as often as females.[36] Most tumors are classic histology. Up to 80% harbor copy-number alterations on chromosome 17 including 17p deletion, 17q gain, or isochromosome 17q.[36] *MYCN* amplifications may also be encountered. Prognosis is variable and overall intermediate; almost one-third of patients present with metastatic disease at diagnosis.[34,36]

Other embryonal tumors. Embryonal tumor with multilayered rosettes, C19MC-altered is another new entity introduced in WHO 2016. These aggressive embryonal tumors arise in infants throughout the CNS, sharing a genetic signature unique to this group, namely, amplification involving a cluster of microRNAs termed C19MC.[50,51] High-resolution molecular techniques established that most tumors previously classified as ependymoblastoma, medulloepithelioma, and embryonal tumor with abundant neuropil and true rosettes, exhibit these C19MC alterations and comprise a single clinicopathologic entity.[52,53] In fact, any CNS embryonal tumor with demonstrable C19MC alteration qualifies for this diagnosis under the WHO 2016.[53] C19MC amplification is readily identified by FISH analysis and tends to correlate with increased expression of LIN28A by IHC; only

demonstration of the former is diagnostic, however, as LIN28A expression may rarely be encountered with alternate pathologies.[53,54] The diagnostic categories of Embryonal Tumor with Multilayered Rosettes, Not Otherwise Specified (NOS), and Medulloepithelioma are reserved for those tumors lacking C19MC abnormalities but with pathology otherwise typical of these diagnoses.

The WHO 2016 made additional updates relative to CNS embryonal tumors. The diagnosis of atypical teratoid/rhabdoid tumor (AT/RT) now requires demonstration of inactivation of either *SMARCB1* (*INI1*) or *SMARCA4* (*BRG1*). This is readily accomplished through IHC assessment of the respective nuclear proteins. The phrase "CNS embryonal tumor with rhabdoid features" is applied for pathologically similar tumors when INI1 and BRG1 are found intact. Lastly, embryonal tumors that do not qualify for any of the aforementioned diagnoses are classified as CNS embryonal tumor, NOS; the phrase "primitive neuroectodermal tumor" has been completely abandoned.

APPROACHES TO MOLECULAR AND GENOMIC CLASSIFICATION IN PEDIATRIC BRAIN TUMORS

As noted above, the WHO 2016 took steps forward in acknowledging the importance of molecular subgrouping in selected entities, with several classes now linked with defined alterations. Although this is an important first step, the relationship between genetic alterations and defined molecular classes is not always a clear-cut one-to-one match. For example, *BRAF V600E* mutation occurs in a variety of distinct histologic and molecular groups. Thus, more comprehensive methods of subgrouping, looking at (epi) genome- or transcriptome-wide profiles, are becoming an increasingly important part of the diagnostic toolbox. In this review, we provide a short overview of some of the molecular classification approaches that have been or are currently being applied to pediatric brain tumors and an outlook as to where these methods may lead us in the future.

Gene Expression Profiling

One of the earliest technologies to bear fruit in terms of molecular subgrouping of pediatric brain tumors was the gene expression microarray, allowing for a global profiling of the bulk tumor transcriptome. A seminal study by Pomeroy et al[32] demonstrated the power of such profiling to distinguish clear biologic subtypes of embryonal tumors (MB, AT/RT, and primitive neuroectodermal tumors [PNETs]) that also had strong prognostic power. This study was the first to define a uniform SHH-activated MB subgroup that would later become one of the core subgroups of this disease. Subsequent transcriptome-profiling studies defined slightly different numbers (between four and six) of MB molecular groups, with WNT- and SHH-activated groups proving more consistent than non-WNT/non-SHH tumors.[49,55,56] The current international consensus defines four groups, with generically named group 3 and group 4 as well as WNT- and SHH-driven tumors,[36] although new studies on larger cohorts are starting to identify substructure within these core groups. An attempt to make this expression-based subgrouping more applicable to routine practice involved the development of a NanoString-based, targeted expression assay, which demonstrated robust performance on suboptimal samples.[57] This has been somewhat superseded by other methodologies, however, and is not currently widely used.

Global transcriptome analysis has identified molecular subgroups in a variety of other pediatric brain tumors. In glioblastoma, gene expression analysis revealed prognostically distinct subgroups and also demonstrated the dramatic differences compared with adult counterparts that would later be corroborated by other profiling techniques.[58,59] In ependymoma, a global overview of tumors across various anatomic sites indicated distinct molecular subgroups linked with defined cellular compartments and patterns of oncogenic drivers.[60] A large study of PF ependymoma further defined two principle subsets of ependymoma occurring in this location, termed PF-A and PF-B, differing in terms of copy-number alterations, age distribution, and prognosis.[21]

Overall, gene expression profiling benefited from an early-mover advantage in terms of the maturity of the technology becoming the first method of choice for molecular subgrouping; it remains a powerful tool for exploring tumor heterogeneity. Several groups originally identified using this method have stood the test of time and remain the backbone of current schema. Limitations, however, include (1) a need for good-quality RNA to conduct the profiling (restricting the use of archival samples), and (2) the risk that extremes of expression in stromal or inflammatory cells can dilute some of the signal in samples with lower tumor cell purity. Thus, gene expression analysis has not truly entered routine diagnostic use. It remains to be seen whether newer technologies such as RNA sequencing as a method of transcriptome-based classification (independent of its clear usefulness in terms of, for example, fusion gene identification) may enter the future diagnostic arena.

DNA Methylation Analysis

The technology that has now somewhat overtaken expression profiling in the molecular subgrouping arena is DNA methylation analysis. The range of pediatric brain tumors that have been subjected to such profiling is steadily increasing, with most of the main entities covered to a greater or lesser extent. In MB, it was shown that DNA methylation analysis can recapitulate the expression-based subgroups in a highly robust manner.[61,62] Subsequent studies in other tumors either confirmed this close association with gene expression or revealed further structure that had not previously been identified through transcriptomic analyses. For example, location-specific differences in the genomic profiles of pilocytic astrocytoma, as previously alluded to through gene expression,[63,64] were confirmed at an epigenetic level.[65] DNA methylation groups of pediatric glioblastoma were found to precisely match to the distinct histone 3 mutation types seen in this disease.[66] Furthermore, a subset of histone wild-type glioblastomas were found to show

methylation patterns more closely resembling pleomorphic xanthoastrocytoma, with *BRAF V600E* mutations, 9p21 deletions, and a better outcome.[9] In ependymoma, a large study looking at tumors across ages and locations led to an integrated scheme of nine molecular subgroups: three each in the spinal, PF, and supratentorial compartments.[15] Many of the subgroups revealed in these different tumor types have been shown to be linked with defined genetic alterations that may represent drug targets, convey prognostic significance, or both.

The power of methylation-based analysis to identify novel tumor entities in an unbiased way was demonstrated on a recent study of samples histologically diagnosed as PNETs.[67] As well as highlighting a high degree of misdiagnoses of other known entities, four novel groups were defined that each had a striking association with a clear pathogenetic mechanism, thereby expanding the catalog of CNS tumor types. This was part of the reason why the term PNET has now been abandoned in WHO 2016.

Based on these positive examples, work is ongoing to produce a broadly applicable, pan-brain cancer classification scheme based on DNA methylation array data. It is thought that the principle of epigenetic subgrouping works so well because the chromatin structure and DNA marks retain a fingerprint or memory of the developmental decisions made in the life history of the tumor cell of origin, making it principally suitable across all tumor types. To improve access to such a system for any center generating such data, the Heidelberg groups have made this tool freely available online in the form of a web-based analysis and reporting system (www.molecularneuropathology.org). The site, and the algorithm behind it, will be continuously updated as new insights into novel subgroups are obtained.

The benefits of array-based DNA methylation analysis include minimal tissue requirements and robust performance from archival, paraffin-embedded material. Although it suffers from the same problems of normal cell contamination as gene expression profiling, DNA methylation data are partly buffered from this effect by the largely binary nature of most CpG sites in the genome, being either fully methylated or completely unmethylated. Although there may be exceptions in which somatic alterations impose an extreme shift in DNA methylation, such as in the CpG island methylator phenotype seen in the presence of isocitrate dehydrogenase mutations, the fingerprint of cellular origins appears to be clear enough in most cases that it remains constant both spatially throughout a tumor tissue and temporally from primary to relapse samples. It is currently therefore the method of choice for many molecular stratification applications.

Further Classification Approaches

Although gene expression and DNA methylation have been the most widely adopted characterization tools because of their relative ease of use, low cost, and scalability, multiple alternative tools are being used that promise to give an ever more detailed picture of molecular heterogeneity. For example, one recent study investigated the impact of distinct DNA copy-number alterations on prognosis within the consensus MB subgroups and identified marker combinations that may provide an added level of predictive power.[68] Such alterations have the added benefit of being detectable by FISH, a more widely available assay technique. Though some changes are almost pathognomonic, such as isodicentric 17q in MB or 7q34 duplication in pilocytic astrocytoma, other alterations are found across a spectrum of entities (e.g., gain of 1q in multiple histologies). Thus, it is likely that copy-number changes will predominantly be of use only in concert with other subgrouping approaches.

Next-generation sequencing–based approaches also show tremendous promise in terms of both classification and the ability to detect potential therapeutic targets. Although deep whole-genome sequencing is currently restricted in its clinical applications for both technical and cost reasons, sequencing targeted panels of cancer-specific genes are becoming widely available (for example, Kline et al,[69] Sahm et al,[70] and Ramkissoon et al[71]). Global mutational profiling can also provide information about signatures of mutagenic processes acting in a given cell,[72] which may prove to be of diagnostic or therapeutic use in the near future. For example, signatures of BRCAness have been suggested as predictive markers for poly-ADP ribose polymerase inhibitors (reviewed in Lord and Ashworth[73]), whereas hypermutated tumors may respond better to immune checkpoint inhibitors.[74]

Sequencing of histone modifications in their chromatin context via chromatin immunoprecipitation sequencing has recently displayed its use in classifying tumors based on an epigenetic fingerprint of cellular wiring. Mapping of enhancer elements using the H3K27Ac mark, for example, confirmed the previously described structure of MB subgroups[75] and delineated among three different subsets of AT/RT.[76] Looking in closer detail at so-called superenhancer elements,[77] with substantial accumulation of K27Ac in a defined region, can also provide extremely valuable information as to the core regulatory transcription factor networks active in a cell and give additional hints as to precise cells of origin for the different molecular subgroups.[75]

Finally, the application of single-cell sequencing techniques, such as those described by Patel et al[78] and elsewhere, has the potential to inform on intertumoral as well as intratumoral heterogeneity at an exquisitely detailed resolution. This step-change in the power to interrogate functionally distinct cellular subclones and aspects such as tumor-microenvironmental interplay will likely further modify the landscape of molecular classification moving forward.

IMPACT OF WHO 2016 ON CLINICAL TRIALS IN PEDIATRIC NEURO-ONCOLOGY

The ability to translate the notable advancements in the classification of pediatric CNS tumors into improved patient treatment, defined by improved survival and/or decreased morbidity, unfortunately continues to lag significantly behind. The next decade will likely see a major change in

how clinical trials are performed as we recognize the importance of specific pathways in tumorigenesis and the increasing availability of therapies that target those pathways. We are moving away from the nonspecific and toxic approaches of radiation and chemotherapy and toward precision medicine; only a few examples of this are currently available.

Many of the drugs beginning to impact clinical trials are pathway inhibitors, not true targeted drugs. Perhaps the best example of a true targeted inhibitor exemplifying the goals of precision medicine is the BRAF V600E inhibitors vemurafenib or dabrafenib. These agents recognize the BRAF V600E point mutation with exquisite specificity, resulting in inhibition of its signaling. By contrast, many downstream mitogen-activated protein kinase kinase or nonspecific epigenetic agents such as histone deacetylase inhibitors affect broad pathways but are not specific for the mutations they are targeting (i.e., BRAF-KIAA1549, H3K27M, or INI1).

High-Grade Gliomas

The improved understanding of the mutational profiles of pediatric high-grade gliomas (HGGs) and their distinction from adult HGGs has become an important guidepost in the development of pediatric clinical trials. The differences between the tumors in these two age groups highlight the need for separate trials in many circumstances, especially in relation to isocitrate dehydrogenase 1 and epidermal growth factor receptor VIII mutations that are common in adult tumors but rare in their pediatric counterparts.[79] Similarly, although the role of methylguanine-DNA methyltransferase expression is an important prognostic and treatment component of adult HGG,[80] it has not been as clearly impactful in pediatric patients, perhaps secondary to the lower incidence of methylguanine-DNA methyltransferase promoter methylation that supports a more resistant phenotype to agents such as temozolomide. Other than *BRAF V600E* mutation in a small percentage of pediatric HGGs, targetable mutations in these tumors are limited and thus, so are meaningful clinical trials. The WHO 2016 recognition of H3K27M-mutated midline glioma adds a molecular component to the pathologic classification of these tumors,[3] but not a clear treatment option. Pathway targets such as histone deacetylase inhibitors are being tested in several upfront and relapsed clinical trials, but to date have not changed the outcome of these aggressive pediatric gliomas. The remainder of the molecular analyses routinely being performed (such as p53, ATRX, platelet-derived growth factor receptor, etc.) does not have currently available effective inhibitors that penetrate the CNS. One important change in the WHO 2016[3] is the recognition of anaplastic pleomorphic xanthoastrocytoma, a WHO grade III tumor that can now be treated as an HGG. Previously, pleomorphic xanthoastrocytoma, regardless of anaplasia, was considered grade II and thus not eligible for HGG trials. Many of these patients also possess the *BRAF V600E* mutation,[81] most diverted from typical HGG trials to those focused on targeting this specific mutation.

Low-Grade Gliomas

The WHO 2016 made very few changes in the low-grade glioma (LGG) classification schema. Pilomyxoid astrocytoma, previously grade II, was reassigned as a variant of grade I pilocytic astrocytoma[3] but this change is unlikely to affect most clinical trials because grade I and II LGGs are treated similarly. The major advances in the molecular classification of pediatric LGGs (presence of the *BRAF V600E* point mutation in 10% and the *BRAF-KIAA1549* truncated fusion duplication in 75%) as well as rarer mutations are mentioned in the WHO 2016, though were not included as entity or subgroup-defining classifiers.[82] Nonetheless, many pediatric LGG clinical trials are now incorporating mutation status into treatment stratification. For example, *BRAF V600*E-mutated LGGs are going on to targeted trials through several different consortia, predominantly at the time of relapse. For the truncated fusion *BRAF-KIAA1549* forms, which are paradoxically stimulated by *BRAF V600E* drugs and thus contraindicated for this group of patients, downstream inhibitors of this pathway are undergoing clinical testing. This includes mitogen-activated protein kinase kinase and mTOR inhibitors, both of which are being used in recurrent/progressive disease. The one exception is the use of mTOR inhibitors in tuberous sclerosis-associated subependymal giant cell astrocytomas. A smaller percentage of pediatric LGGs have non-*BRAF*–mutated targets such as *FGFR1*, *NTRK*, or others. Though not diagnostic of specific tumors, status for these mutations will likely be included in basket trials of multiple agents.

Ependymoma

The WHO 2016 recognized the new molecularly defined *RELA* fusion-positive ependymoma. Although this molecular subgroup has some prognostic implication, there are no specific treatment options that currently affect clinical trials. Other recently recognized molecular subtypes of ependymoma,[83] including Yes-associated protein 1 supratentorial and group A and B infratentorial tumors, were mentioned in the WHO 2016, though were not codified as diagnostic entities/subgroups. Ependymomas are therefore still staged and treated on standard existing criteria (degree of resection, location, and presence of anaplasia).

Medulloblastoma

The WHO 2016 introduced considerable changes to MB classification, some of which may affect clinical trials. Four new MB molecular subgroups were introduced as noted above; this WHO 2016 schema differs somewhat from the four genomic consensus categories widely used around the world.[36] MB WNT-activated, the best prognostic group, is now being evaluated in a series of radiation, chemotherapy, or combined radiation/chemotherapy reduction strategies. The treatment of these patients requires not only demonstration of nuclear β-catenin staining by IHC, but also sequencing confirmation of *CTNNB1* mutation along with monosomy 6. Similarly, although SHH tumors can be classified by a number of validated approaches,[84] not all tumors will be

appropriate for SHH-targeted therapy, as the current array of approved drugs targeting this pathway does not inhibit signaling for three (*SuFu*, *Gli*, and *Mycn*) of the five (*Ptch* and *Smo*) common genes involved.[46] The WHO 2016 identifies a new category of MB SHH-activated, *p53*-mutated based on a number of papers suggesting a very poor outcome in this group,[45] and an international amendment of the consensus grouping will likely soon follow. The final WHO 2016 category includes all non-WNT, non-SHH MBs (combined group 3 and 4) in one class. Targeted approaches for groups 3 and 4 have not yet been part of major clinical trials. The recognized poor prognosis of *MYC*-amplified group 3 MBs[68] is not included in the WHO 2016; however, as new therapeutic interventions targeting MYC become available, differentiating this subgroup from other non-*MYC*–amplified patients in groups 3 and 4, in whom the prognosis is intermediate, will become important.

A major change in the WHO 2016 is the reclassification of what were previously referred to as CNS PNETs and are now grouped under multiple headings. One recognized subgroup of these, those with the C19MC amplification, has become a new entity. For the other tumors of this class, the general category of embryonal tumor NOS must suffice for clinical trial entry. Historically, clinical trials have treated these tumors (under the heading of PNET) like high-risk MB and pineoblastoma. What will continue to complicate the clinical trial development of this class of heterogeneous tumors is the growing recognition that many of them are probably not true ETs, but rather undifferentiated glioblastoma multiforme, ependymomas, and others.[67]

CONCLUSION

The many examples in the literature, and touched upon above, highlight the power of molecular subgrouping as an additional tool in the diagnostician's armamentarium. In most cases, this additional biologic information clearly enhances patient stratification in terms of outcome prediction and identification of therapeutic vulnerabilities. It is almost inevitable that more complex genome-wide profiling of methylomes/transcriptomes and molecular alterations will increasingly enter the diagnostic routine and likewise upcoming versions of the WHO classification. This naturally raises issues of access to necessary technology and expertise and the broad applicability of classification schema in different socioeconomic regions. These issues will hopefully be resolved, as costs come down and more laboratories offer such testing. In the meantime, the added value of molecular stratification means that it is incumbent on us to ensure that diagnostic standards follow and adapt to the latest research findings as much as is practicable, without resorting to a lower common denominator. Although this may make it challenging to compare with historical epidemiologic data and previous clinical trial outcomes, these hurdles are outweighed by the long-term benefit to patients that can be expected from precision diagnostics and better matching to targeted therapies.

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PROFESSIONAL DEVELOPMENT

Collaborating With Advanced Practice Providers: Impact and Opportunity

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OVERVIEW

Although significant progress has been made in cancer care, access to coordinated, high-quality care across the cancer care continuum remains a challenge for many patients. With significant workforce shortages in oncology anticipated, physician assistants (PAs) and nurse practitioners (NPs)—known collectively as advanced practice providers (APPs)—are considered to be a part of the solution to bridging the gap between the supply of and demand for oncology services. APPs are integral to the provision of team-based care in oncology, and optimizing the roles of all members of the patient's care team is vital to ensuring the teams are cost-effective and that each team member is performing at the functional level intended. Studies have shown significant patient, physician, and APP satisfaction with collaborative care models, and APPs are well positioned to enhance value for patients in the oncology setting. Understanding the full scope of APP impact can be challenging as it extends well beyond direct patient care. As rapid progress in cancer care continues, innovative approaches to care delivery will be necessary to ensure patients' access. Effective oncologist–APP partnerships will be key to providing optimal, value-centered care to patients.

In 2017, an estimated 1,688,780 new cases of cancer will be diagnosed in the United States.[1] As of January 2016, there were more than 15 million cancer survivors in the United States, and this number is expected to exceed 20 million by 2026.[2] Although significant progress has been made in cancer care, leading to marked improvement in survival, access to coordinated, high-quality care across the cancer care continuum remains a challenge for many patients. Additional challenges to the system, as eloquently described in the Institute of Medicine's 2013 report, *Delivering High-Quality Cancer Care Charting a New Course for a System in Crisis*, include[3]:

- An aging population,
- The escalating cost of cancer care,
- Complexity related to the marked advances in the understanding of cancer biology,
- Limitations on tools to improve quality of care, and
- Workforce shortages.

These challenges are interwoven with the uncertainty of the current health care (and health care reform) landscape, changing reimbursement models, productivity and access pressures, and provider burnout risk and have the potential to stress a health care system that is already overwhelmed. This, in turn, may lead to additional barriers to patients' access to care.

Significant workforce shortages are anticipated in the near future with the Association of American Medical Colleges projecting a shortage of 61,700 to 94,700 physicians by 2025.[4] In 2007, Erikson et al projected a shortfall of approximately 2,550 to 4,080 oncologists by 2020 based on their analysis of the supply of and demand for oncology services.[5] A follow-up study, conducted by Yang and colleagues, projected the supply of and demand for oncology services extending out to 2025. This study was largely confirmatory of the work by Erikson and colleagues, with the anticipated workforce shortages being somewhat delayed than initially anticipated.[6]

PAs and NPs, known collectively as APPs, are highly trained and skilled health care providers and, as such, are an integral part of the health care team. APPs are able to provide a broad range of services in the oncology space and have been consistently identified as a part of the solution for bridging the anticipated gap between the supply of and demand for oncology services.[5-7] Services APPs provide include, but are not limited to, those related to prevention, screening, surveillance, and diagnosis; supportive care during the course of active treatment; long-term follow-up and survivorship care, and counseling on disease specifics, treatment, and prevention. APPs are instrumental in conducting goals of care and prognosis discussions and providing care at the end of life. APPs also often participate in clinical research activities. APP educational preparation is of a more generalist nature (i.e., PAs) or population-focused nature (i.e., NPs). As such, specialty knowledge for APPs is largely acquired through a blend of self-directed learning, practice-based training, and mentoring. Effective and

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appropriate training of APPs in the oncology practice setting is key to APPs developing the necessary competencies for taking on expanded roles in the practice, such as ordering chemotherapy and performing a range of procedures.[8]

Successful integration of APPs has occurred within community and academic oncology settings, and patient satisfaction with a collaborative care model has been noted to be high.[7,9] A recent retrospective study looking at adherence to ASCO's Quality Oncology Practice Initiative (QOPI) measures at a single center showed oncology attending physicians, fellows, and APPs performed similarly across the quality measures tracked.[10] Although this was a small single institution study, it suggests consistency of performance across oncology providers with opportunity to both reinforce positive practice behaviors and improve as a team together. Additionally, APPs have been shown to increase oncologists' productivity.[5,7,11] Interestingly, 73.1% of American Society of Clinical Oncology census practices reported employing APPs in 2015, a marked increase from 52% reported by the 2014 census practices.[12] Although an increase in the utilization of APPs in oncology practices to help expand access to care is encouraging, the total oncology APP workforce capacity is unknown. The American Academy of Physician Assistants indicated that as of December 2016, there are more than 115,000 certified PAs in clinical practice, and the American Association of Nurse Practitioners indicated that as of October 2016, at least 220,000 NPs are licensed in the United States.[13,14] Although an exact head count of APPs practicing in oncology is unclear, previous analysis suggests it is less than 5% of the total number of APPs in clinical practice.[15] Research is currently underway to mitigate the gap in knowledge about the oncology APP workforce capacity and to better understand this workforce.

TEAM-BASED CARE IN ONCOLOGY

Health care delivery has historically occurred in more of a siloed fashion whereby each person does his or her part for the care of the patient but does not work interdependently with others in the process of providing that care. What distinguishes a team of providers from a group of providers caring for a patient is that within a true team construct, all providers work interdependently to achieve a common goal.[16] In a group of providers caring for a patient, each person contributes independently to reach a common goal or product.[16] When groups of providers care for a patient, the risk of that care being fragmented is high, which can lead to suboptimal outcomes for patients. Cancer care is becoming increasingly complex for a multitude of reasons, underscoring the need for highly effective teams to deliver this care.

Pillars of team-based health care, as described in the Institute of Medicine's discussion paper *Core Principles & Values of Effective Team-Based Health Care,* include[17]:

- Shared and valued goals, which are clearly understood by all team members,
- Clear roles,
- Mutual trust,
- Effective communication, and
- Measurable processes and outcomes.

Team-based care must be patient-centric and coordinated, with all the tasks needing team completion to be well defined. Roles and responsibilities of each team member, including patients and their caregivers, should be clear. Cultivating support among all members of the team is a key part of team formation and ongoing development. The patient's needs should drive the composition his or her care team, and defining the tasks that must be completed for the patient ensures completeness of care. Once these tasks are defined, identifying the member or members of the team who have the appropriate training and experience to carry out each function is key. As part of the groundwork for constructing the team, developing a responsibility assignment matrix may be helpful in delineating roles and responsibilities of team members, and appropriate workflows can then be established accordingly. For optimal team functioning, each member of the team performs those duties consistent with the fullest extent of his or her license (as applicable), education, training, experience, and competency. This leads to the formation of teams that are cost-effective, provides assurance that the patient's and caregiver's needs are being met by the most appropriate members of the team, establishes accountability, eliminates duplicative work effort, and ensures each member of the team is performing at the functional level intended. A thoughtfully planned introduction of the team to the patient and caregiver should occur at the start of engagement to appropriately frame expectations. This allows the patient and caregiver, at the initiation of care, to develop a clear understanding of each team member's role and to recognize how their needs will be met. Furthermore, this step helps foster the development of trust between the patient, caregiver, and care team, which enhances the effectiveness of the therapeutic relationship.

When determining roles and responsibilities for APPs, it is important to think of this in the context of whatever duties the APP is taking care of or services the APP is providing would otherwise be done or provided by the physician in the absence of the APP. To better understand APP time and effort allocation, Moote and colleagues performed a self-reported time study of 2 weeks' duration in an academic

KEY POINTS

- **APPs are highly trained and skilled health care providers who are integral to providing team-based care in oncology.**
- **Cancer care is complex, which underscores the need for highly effective teams to deliver this care.**
- **Role optimization for all members of the team is important to ensure each team member is performing at the functional level intended.**
- **APP contributions to practices and patient care extend well beyond direct patient care activity.**
- **APPs are well positioned to enhance value for patients in the oncology setting by positively impacting outcomes that matter to patients.**

medical center. This showed APPs were spending only approximately 36% of their time in direct patient care, defined as billable and bundled services.[18] Care facilitation services, defined as services that would otherwise require a physician to perform, made up about 49% of APP time and effort and included such activities as assisting with rounds, providing patient education, writing progress notes and other patient documentation, and preparing discharge summaries.[18] Although the amount of APP time and effort devoted to providing direct billable services was limited in this group, this study illuminates the extended amount of time spent by APPs in activities that do not necessarily generate work relative value units (wRVUs) but that are needed as part of patient care and which would otherwise be done by the physician if the APP were not carrying out these functions. As such, the authors felt there was room to further optimize APP practice in this setting through closer alignment of the roles and responsibilities of the APPs with that of physicians.[18]

Optimizing roles may not necessarily require adding additional resources. Elnahal and colleagues recently developed a strategy to improve workflows in a multidisciplinary clinic without increasing their human resources.[19] This was accomplished by incorporating the military acuity model, ultimately realigning workload to be commensurate with the skill set and competency of each team member.[19] This strategy enabled them to increase their clinic volume by more than 30%, decrease the number of postclinic emergency department visits from 9.9% to 7.9%, and decrease the number of postclinic patient phone calls with unresolved issues from 34% to 22%.[19]

Although some teams are relatively high functioning almost organically, investing time and effort in team training has important implications as it has been demonstrated to improve patient safety.[20] In an outpatient oncology setting, Bunnell and colleagues instituted team training with their breast cancer staff including physicians, APPs, nurses, pharmacists, and support staff.[21] The team training intervention was notable for improving communication, perceptions of improved efficiency, quality, and patient care safety; relationships/interactions among team members; and patients' perception of how well their care was coordinated.[21]

Deliberately working as a team takes time, effort, and patience. The team must go through natural developmental stages that include forming, "storming," "norming," and performing as psychologist Bruce Tuckman has described.[22] Establishing and maintaining a high level of performance as a team requires ongoing development and nurturing of the team to sustain both the team itself and the individuals that it comprises.

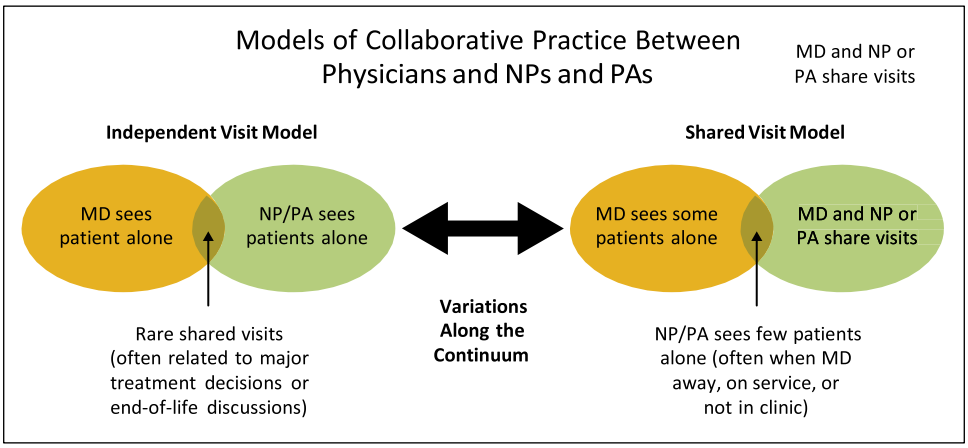
CARE DELIVERY MODELS

APPs practice in two categories of clinical practice models: comanagement and autonomous. In the comanagement model, physicians and APPs are jointly involved in each patient encounter, providing direct patient care. In the autonomous model, APPs provide medical services to patients without the physical presence of the physician (in accordance with state laws and regulations and facility or practice policy). In a single institutional analysis, Buswell and colleagues evaluated collaborative practice models deployed in their center.[9] Three general models were identified and described as the independent visit model (IVM), the shared visit model (SVM), and the mixed visit model (MVM).[9] In the IVM, as defined by Buswell et al, APPs and physicians each saw their patients as independent visits for at least two-thirds of the time.[9] In the SVM, as defined by Buswell et al, at least two-thirds of patient visits were seen as shared visits between the physicians and APPs.[9] The MVM thus represented a blend of visits seen as either independent visits or shared visits, with neither type of visit predominant (Fig. 1).[9] In this analysis, physicians were very satisfied with both the IVM and SVM; APPs were very satisfied with the IVM and moderately satisfied with the SVM. Patient satisfaction scores, although variable across models, were generally high for both the IVM and SVM.[9] Productivity across all three models was similar.

Many factors can influence the care delivery model(s) a practice utilizes, including the patient population itself, facility or practice policy, overarching goals of integrating an APP into the practice, and the nature of the physician–APP partnership. Patients' access to oncology services can be problematic as the demand for oncology services increases. By jointly identifying appropriate cohorts of patients for the APP to see as independent visits and creating same-day access for patients who must be seen urgently but who do not need to be seen in an emergent care setting, physicians and APPs can together expand access to oncology services. Symptom management is often a cornerstone of APP practice in oncology, and having APPs focus on this aspect of patient care can help make patients more comfortable and improve quality of life for patients and their caregivers.[23]

Within the respective patient population, it is important to balance the patient panels for both the physician and the APP as a means of preserving the workforce. Specifically, although shifting a significant proportion of patient follow-up visits to the APP may improve access to the oncologist for new patient visits or more complicated patient follow-up visits, it is easy to imagine a diminished level of professional satisfaction for an oncologist whose panel is exclusively the highest acuity patients. Anecdotally, oncologists have described the importance of a balanced template and appreciate the opportunity to see patients who are doing well or who have less complicated courses in addition to seeing more complex patient visits. As a context for this concern, it is essential to note Shanafelt and colleagues' observation that although oncologists largely indicated satisfaction with their choice of both career and specialty, those who spent the greatest amount of time in direct patient care were identified as being at the highest risk for professional burnout.[24] Professional burnout is an entity that bears close surveillance and, even more importantly, prevention, in the face of impending workforce shortages. Recent studies have shown the incidence of burnout in oncologists and oncology PAs to

FIGURE 1. Models of Collaborative Practice Between Physicians and NPs and PAs



Abbreviations: NPs, nurse practitioners; PAs, physician assistants.

be 45% and 35%, respectively, and prevention strategies will be vital for ensuring patients' access to oncology care.[24,25]

It is also crucial that care teams and care delivery models nimbly adjust to the shifting nature of how and where oncology care is provided. With more care that was traditionally delivered in the inpatient setting now being conducted in the outpatient setting and more oral therapies now available for patients, novel means of delivering care and monitoring patients is key and can include such entities as telemedicine and home visits, as appropriate. APPs, as collaborating partners with oncologists, can leverage their knowledge, skills, and expertise to lead innovative care delivery efforts to provide high-quality, patient-centric care.

VALUE AS THE PLATFORM FOR CARE DELIVERY

Although operational effectiveness remains paramount to optimizing the delivery of health care services, quality—not quantity—of the services provided and the value of those services to patients are rightly the focus. Any strategic plan deployed in the current era must, at its very foundation, be centered on value. Value in health care is defined as the outcomes achieved as proportionate to the dollars spent to achieve those outcomes.[26,27] Care for a medical condition such as cancer typically involves a number of multidisciplinary providers rendering a variety of services. Value, in this context, is derived from the combined efforts of the providers across the full cycle of patient care, and all providers are accountable for that value.[27] With this in mind, never has team-based care in oncology been as important as it is now. As we shift from a fragmented system focused on all we can deliver to patients to a patient-centric system with care teams constructed based on patient and caregiver needs, we have the opportunity to optimize the value of the care we provide to our patients.[28]

APPs are well positioned to enhance value for patients by improving outcomes while keeping costs relatively flat, decreasing costs without diminishing outcomes, or both. In a retrospective study looking at patients with acute myelogenous leukemia admitted for reinduction chemotherapy, outcomes of a PA/attending physician team were compared with a house staff/attending physician service. Although intensive care unit transfers and in-hospital mortality were similar across both groups, length of stay, readmission rates, and consulting service utilization were decreased in the PA/attending physician team compared with the house staff/attending physician team.[29] This study suggests the PA/attending service model could deliver care with increased operational efficiency while decreasing health service use but without negatively impacting outcomes.[29] In another retrospective study, outcomes for patients with locally advanced oropharyngeal cancer receiving 7 weeks of concurrent chemotherapy and radiation therapy were evaluated prior to and following the initiation of an NP-led clinic. With the implementation of the NP-led clinic, patients were seen weekly to evaluate the profound toxicities they experienced in association with combination therapy. Previously, patients were seen at the beginning of treatment, in the middle of therapy, and at the end of treatment. The data demonstrated that with the implementation of the NP-led clinic, rates of hospitalization for toxicities lowered (12% vs. 28%), chemotherapy dose reductions decreased (6% vs. 48%), and 90% of patients seen in the weekly clinic went on to complete all seven cycles of chemoradiation, compared with 46% prior to the implementation of this intervention.[30] Although long-term outcomes could not be determined by a retrospective review, one could hypothesize that maintaining dose density and intensity would translate into improved long-term outcomes.

A key component of improving value is measuring outcomes and, more specifically, outcomes that matter to patients. Porter describes an outcomes measure hierarchy composed of three tiers.[27] The first tier refers to the patient's health status attained or retained; the dimensions encompassed in this tier include survival and the degree of recovery or health attained or retained by the patient.[27]

The second tier, which focuses on the recovery process, encompasses the dimensions of the amount of time it takes to recover and for the patient to return to his or her normal level of functioning or the best level of functioning that can be achieved.[27] Tier two also includes a focus on mitigation of issues the patient may experience from treatment or care, ranging from adverse effects and discomfort from treatment to errors in diagnosis and other complications.[27] In the third tier, the sustainability of health is the focal point with the dimensions of this including recurrence of disease and/or long-term complications of the original disease and/or treatment of the disease.[27]

Although APPs may have a limited ability to influence survival, they can have a significant impact on other outcomes important to patients, including functional status, return to usual activities, symptom control and reduction of suffering, management of late effects, and minimizing wait times.

UNDERSTANDING APP IMPACT

Understanding APP impact in its entirety remains challenging as APP clinical activity can be hidden in shared visits, and APPs are often partaking in activities that do not generate billing activity or wRVUs but that would otherwise be done by the physician in the absence of the APP, thus reducing the physician's availability to see and evaluate patients.

When evaluating the impact of APPs, it is helpful to think beyond the productivity aspect to fully understand the value proposition of APPs. The concept of productivity is relatively concrete and relates to the volume and work intensity of services provided.[31] It can be assessed using such standardized measurements such as wRVUs, volume of patients seen, and billing and collections data. Although this can be helpful in understanding productivity, it has its limitations as severity of illness and patient acuity are not factored into the measurements.[31]

Establishing and tracking direct billable services provided by an APP is one important metric to consider but can be challenging given the variety of collaborative practice models used and varying APP roles. In particular, within the SVM, services are billed and revenue is generated under the physician's name and national provider index (NPI) number, and thus the services provided by the APP may be less transparent and not easily captured or tracked. This likewise makes looking exclusively at wRVUs of APPs a problematic approach for understanding the scope of their contributions. This can, however, be a very useful metric if an APP's practice is primarily composed of independent visits and/or procedures. Additionally, services rendered during the global period, such as postoperative visits, do not generate incremental revenue or wRVUs. These visits, however, would need to be conducted by the physician if the APP was not seeing the visits, thus preventing the physician from partaking in other revenue/wRVU-generating clinical activity such as surgery. Tracking productivity in an inpatient setting is equally complex as care and costs may be entangled among many different health system providers and departments. Although national productivity benchmarking metrics from organizations such as the American Medical Group Association and the Medical Group Management Association provide robust productivity metrics associated with APPs working in the primary care setting, there is a relative lack of national benchmarking productivity metrics available for specialty care such as oncology.

Capturing the number of visits or encounters by the APP may be a way of increasing understanding of the APP's workload, providing there is attribution for shared visits. Although billing and collections data may have some relevance in understanding productivity, it is essential to recognize that practices set charges and payers set fee schedules. This can also become an issue in the SVM with the relative invisibility of the APP in this construct. As another challenge, not all payers enroll APPs. This does not necessarily mean, however, that the payer will not reimburse for services provided by APPs. The payer contracts may stipulate the services provided by the APP be billed under the physician's name, even when provided as independent visits. It is imperative to review payer contracts to ensure compliance and optimization of reimbursement. An understanding of the APP's distribution of time and effort, and hence the "big picture," is essential to comprehending the spectrum of ways in which the APP is contributing to the practice. Care facilitation, teaching and training students and new employees, administrative responsibilities, and research are all activities that bring value to the practice but may not result in billing activity or wRVUs.

In response to this issue, Gilbert and Sherry convened a group of APPs within a single comprehensive cancer center to create and pilot metrics related to APP practice and performance.[32] The overarching goal of this initiative was to demonstrate APP contributions through a standardized framework that addressed the salient areas of quality of care and productivity. One of the challenges in creating this metrics card was to ensure the metrics appropriately encompassed the many facets of the APPs' role across multiple oncology subspecialties.[32] Likewise, data pertaining to the specific metrics identified needed to be easily trackable, which, in any setting, is often a difficult endeavor. The metrics were organized into four performance categories: financial impact, professional development, patient satisfaction, and quality indicators (Fig. 2).[32] Future work in this area beyond the pilot entails establishing a benchmark for each metric with an expectation that all APPs achieve 80% or higher on each metric.[32]

Establishing effective tracking of all APP clinical activity and sharing this data with the APP is critical to ensure accuracy, bearing in mind the data are only as reliable as the systems set up to collect and analyze the data. It is also important to consider that the APP will likely need some time to get up and running in the clinical practice once integrated, and productivity measurement should be interpreted accordingly. As part of the onboarding process, APPs would benefit from training on billing practices and requisite documentation to ensure both compliance with payer policies and the appropriate level of billing. In some cases, it may be

FIGURE 2. Metrics Categories, Definitions, and Measurement Devices

Table. Metrics Categories, Definitions, and Measurement Devices

Metrics category	Definition	How metrics are measured
Financial impact	Practice volume, RVU, and billing for AP independent-visit volume and AP shared-visit volume	Electronically
Professional development	Publications, presentations, participation in research or cancer center/hospital-based quality improvement committees, precepting/mentoring students, continuing education credits, conference attendance, scholarships/grants/awards, or pursuing an advanced degree	Self-reported
Patient satisfaction	Press Ganey reports	Online Press Ganey reports
Quality indicators (on patient encounters)	Medication and allergy reconciliation; pain assessment, plan, and documentation; smoking status assessment and implementation of smoking-cessation plan; closure of the patient encounter in the EMR within 7 days of the visit date	Electronically

Note. RVU = relative value unit; AP = advanced practice provider; EMR = electronic medical record.

more helpful to evaluate the productivity of the APP–physician unit or the practice as a whole and compare this to the corresponding productivity data prior to the APP starting in the practice, looking for an incremental increase. If team productivity falls short of established goals, it is necessary to engage in thoughtful exploration of this to establish the root cause(s) so that fitting interventions can be designed accordingly.

CONCLUSION

With the growing complexity of cancer care and impending workforce shortages, team-based care in oncology provides the opportunity to deliver coordinated, high-quality, high-value, patient-centered oncology care. Thoughtfully constructed teams of individuals who work interdependently to accomplish shared and valued goals can positively impact outcomes that matter to patients. As an integral part of the patient's care team, APPs contribute to practices and patient care in many ways. Although their contributions may not always be easily measured, they are central to the care of the patient. Studies have demonstrated significant patient, physician, and APP satisfaction with collaborative care models, and collaboration with APPs has been shown to increase oncologists' productivity. As rapid progress in cancer care continues, innovative approaches to care delivery will be necessary to ensure patients' access. Effective oncologist–APP partnerships will be key to providing optimal, high-value care to patients.

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For Our Patients, for Ourselves: The Value of Personal Reflection in Oncology

Lidia Schapira, MD, Jane Lowe Meisel, MD, and Ranjana Srivastava, FRACP, OAM

OVERVIEW

Caring for patients with cancer is a great privilege as well as an emotionally and intellectually challenging task. Stress and burnout are prevalent among oncology clinicians, with serious repercussions for the care of patients. Professional societies must provide guidance for trainees and practicing physicians to mitigate the negative consequences of stress on their personal lives and medical practice. Reflection, reading, and writing about personal experiences provide outlets for fortifying personal reserves and promoting resilience to allow us to recognize the joy and meaning of our work and to forge connections with our peers. Herein, we present some of our own reflections on how and why one might take time to write, and about the power of the written word in oncology and medicine.

In the field of oncology, we are all connected by our desire to improve the lives of patients afflicted with cancer. However, whether one is primarily clinical or spends most of his or her time conducting research, the work can be inspiring and humbling, while proving tremendously difficult. In a professional landscape that values clinical and research productivity by numbers of patients seen and manuscripts published, reflection can serve to provide perspective and maintain some balance in our personal and professional lives.

I attended a progressive junior high school, governed by the philosophy that 12- and 13-year-olds are often so focused on their emotional lives that this reality needed to be incorporated into the curriculum rather than ignored. Therefore, in class, we were assigned to write about our personal experiences. Delving into our emotions in our writing and then sharing our pieces with the class allowed us not only to understand the power of the written word and to aspire to harness it but also to connect with one another at a time that can be inherently insecure and lonely.

Oncologists are very different from seventh graders, but the process of putting our experiences into words and sharing them with others is, in many ways, even more important. This process can help us make sense of difficult conversations with patients, the impact of our work on our home lives, or challenges encountered in the laboratory. In a recent survey conducted by ASCO evaluating burnout and career satisfaction, almost 45% of the nearly 1,500 oncologists surveyed were burned out on the emotional exhaustion and/or depersonalization domain of the Maslach Burnout Inventory.[1] More hours spent on patient care were positively correlated with the risk for burnout, a concerning finding given the projected shortage of oncologists over the coming years and the need for many of us to start seeing higher volumes of patients.

Burnout happens not just because we are too busy but also because many of us do not have a way to process, either by ourselves or with our colleagues, the gravity of our experiences and what they mean to us. Consider this: many of us, as our stacks of medical journals arrive in the mail, turn first to the *New England Journal of Medicine*'s "Perspective" section, *JAMA*'s "A Piece of My Mind," or the *Journal of Clinical Oncology*'s "Art of Oncology" (AOO). We devour these pieces, hungry for stories and looking for connections. It was through this lens that our session on the use of narrative in oncology was conceptualized.

We believe that reading and writing about our experiences may allow us to achieve greater self-awareness and more of a sense of community among colleagues and, through this, allow us to be better at what we do and to derive greater enjoyment from it. What follows here is a personal account of the journey of one inspiring and prolific oncologist-writer, Dr. Ranjana Srivastava (Part I), and a piece on the power of stories from Dr. Lidia Schapira, the current editor of AOO (Part II). Our hope is that these reflections will inspire our readers to think more deeply about the power of narrative in our field and the different ways they might use it to further their own personal goals.

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PART I: THE WRITER'S JOURNEY

It was nearing the 10th anniversary of the loss of my twin pregnancy when I felt an urge to write about it.[2] I can't say that I had been dwelling substantially on the loss or that the 10th year felt any more significant than, say, the 1-year or the 5-year mark. If truth be told, life had been very good to me after that tragedy, with the healthy arrival of three children, a fulfilling profession, and much more. The valuable perspective gained from a career as an oncologist meant that my grief wasn't as paralyzing as I had feared. But clearly, as the anniversary approached, the event must have been somewhere in my subconscious because I felt the need to expunge it.

That column ended up becoming one of the world's most widely read and shared columns in the *Guardian* that year. What touched me most was the tenderness and humanity of exchanges the column elicited in what truly felt like a global village. Complete strangers sent me their wishes and forwarded the essay to others going through the same experience. Voltaire was right: writing is the painting of the voice.

I am a medical oncologist and writer. I have written books and essays, and for the past few years, I have been a regular columnist on medicine and society for the *Guardian*, which was founded in 1821 as the *Manchester Guardian* and now has a global reach. I am also an essayist for the *New England Journal of Medicine*. In this personal reflection, I will track my own journey while answering some of the commonly asked questions of why, what, and when to write.

Why Write?

This is the easiest one. As oncologists, we are witness to life's deepest and most intimate moments. These moments move, inspire, frighten, teach, and challenge us. Who do we tell about the pregnant mother with advanced breast cancer or the successful businessman with metastatic melanoma who goes from diagnosis to death in 4 weeks? Who will share our heartache at looking after a grandfather whose greatest lament is not that he is dying but that his children can't find the time to visit? Who will admire with the same intensity the patient whose face glows with dignity and courage even as cancer invades her skin? Our patients stir a range of emotions with us, not all of which we necessarily feel like speaking aloud. We fear that our family and friends may not understand us or that they may find our stories gloomy or upsetting. But we know that acknowledging our raw emotions, our learnings and feelings, is critical if we are to be better doctors. Human beings find meaning through stories, we connect through stories—and our stories demand to be written, though not everything we write needs to be published.

I started writing when I was 11, but it is only in the past decade that I have started publishing widely.[3] Most of what I write is for private consumption, catharsis, and making sense of the world. My writing centers me; knowing this means that if the market for my writing were to fall away, I'd still gain personal satisfaction from the habit.

KEY POINTS

- **Writing about our experiences as oncologists can help us understand them with greater clarity.**
- **Learning to set aside small blocks of time for writing, reading, and reflection is a useful strategy.**
- **Reading about the experiences of others in our field can help us feel more connected to colleagues, providing a form of social support.**
- **Reflecting upon one's reactions to the written word facilitates self-awareness.**
- **Reading and writing narratives in oncology may strengthen us emotionally, allowing us to be more fully present for our patients and our loved ones.**

What to Write

The history of medicine is replete with fine writers, and it's really no wonder when you think of the fertile grounds for writing that being a doctor provides. We just have to turn up to work to stumble upon stories. The lives of our patients and our own lives intertwine to provide us with rich experiences and powerful learnings, and as long as we tune into human stories, there will never be a shortage of ideas.

However, one thing that concerns doctor-writers is the matter of consent. Is it ethical to write about our patients, who trust us with their secrets? Should one always seek consent when writing? What happens if we unintentionally end up offending a patient, or for that matter a colleague, through our writing? The impetus, and the temptation, to be published can exert such a pull that it's easy to cross the line between telling a story and breaching patient confidentiality.

Something every modern writer must be aware of nowadays is that writing has an unprecedented digital footprint. Once you hit send, you can't control the ways your work is read, interpreted, and used. It is also always and readily available, even if you'd like it to go away. This is something I have become increasingly aware of in writing for high-profile platforms such as the *Guardian* and the *New England Journal of Medicine*. Editorial assistance is important, but it's just that, assistance; as the author, one must own and defend one's writing.

It is impractical and unnecessary to always get consent to write. Furthermore, I think that the very act of seeking consent changes the nature of writing—it's difficult to render a totally honest interpretation of an event and write without fear or favor. At the same time, no doctor wants to hurt a patient or jeopardize a valuable and therapeutic relationship. Because I write almost exclusively about patients, here are some rules of thumb I follow.

I ask myself why it's important to write about what happened. Is there a meaningful and universal message to share? Could what I write inform, educate, or empower someone? Or is it because I am annoyed and need to vent? I work mostly in a highly socioeconomically disadvantaged community with a high proportion of non-English-speaking

refugees and asylum seekers. It's safe to say that the vast majority of my patients would never come across my writing, but I always ask myself how they would feel if they were to stumble upon it. Would they be hurt, or would they feel heard? Would they feel exploited or understood? Would they say I had misrepresented them, or would they consider me their advocate?

There are things I never write about without prior consent. These have included attending the funeral of a patient I was fond of, acknowledging a gift from a dying patient, reporting an intimate but unique consultation, and encounters for which it would be immediately obvious to a reader that the story was about him or her or a loved one. No one has ever withheld consent when I have explained the reason for my writing; patients and their relatives are very generous and thoughtful in offering their experiences as teaching moments. Across many years of writing, I have attracted the ire of only one patient, who believed that I had been loose with the facts of her case. She chastised me for abusing my position and refused to accept my apology. In fact, her story was an all too common one, but in telling it, I had obviously skirted unacceptably close to her personal experience. This was one of the lowest points of my writing career, as I felt guilty about causing a dying patient distress and sad that I had not had an opportunity to make amends. But her rebuke has stayed with me and made me more cautious and more considerate.

Ultimately, writing about medicine relies on personal integrity and having a moral compass that detects right from wrong before an editor or one's audience has the opportunity to do it. It means thinking deeply about one's intent, endeavoring to set aside personal bias, and then having the courage of one's conviction.

Finally, this is a one-line mental checklist I tick each time I write: "Will I be able to hold my head high in clinic tomorrow if I publish this?"

When to Write

"How do you find the time?" I once asked a famous writer. "And what do you do about writer's block?"

"Nonsense," she said briskly. "When you show up to work, do you suffer from oncologist's block? Writing is a job. It takes commitment."

Several of my colleagues lament that they used to write well until careers in medicine put waste to their dreams of becoming authors. Now, between juggling patients, configuring career progression, and raising their families, they just don't have the time to write.

A barrier I identified early on in my writing career is that the idea of having unlimited time, no distractions, a spotless desk, a cabin in the woods, or a house overlooking the ocean was never going to be my reality! With a busy clinical load and young children, there was never a good time to write. I spent the day doing my regular job, and by nighttime, I was too exhausted to write.

But I never gave up writing a journal, filling it with mostly mundane observations and reflections, not realizing that the mere habit of writing was important. I stuck to nice pens and sought out beautiful leather-bound journals to enhance the meditative quality of longhand writing.

But it didn't feel like enough. Finally, the urge to write more and communicate with an audience became so great that I had to confront the reality: I could either write amid the chaos of work and home or not write at all. So, slowly, I trained myself to write among the chatter of children, keeping an eye on the trampoline and another on the screen. I became adept at stealing moments to write: between school pickups and sports drop-offs, while waiting in the car for swim school to finish, or perched on the edge of a bath. I learned to write a few lines if a patient unexpectedly canceled or if a meeting was delayed. I also learned to write in my head when I went jogging. Going for a run in the early morning before the hustle and bustle of the day begins is a fine way of sifting through my thoughts. Now, with a deadline every fortnight, I must and can write almost anywhere.

I have no set time to write, but I do know that when an encounter lingers in my mind, it's a signal to write. I turn the encounter in my mind, let myself feel uncomfortable or challenged or gratified, until gradually the essence of the experience becomes clearer and I am ready to write. Then, the words seem to tumble out. The hardest part of writing is getting started. Now, I worry less about perfection and more about getting the words down on paper. It's much easier to edit than get started.

I have had to make some compromises. I love the slowness of writing by hand, which allows you to turn your thoughts in your mind, but I can write like this only in my journal now. The rest of my work is done on a laptop, but because I don't like carrying it everywhere, I save my work in the cloud so I can access it from anywhere in the world. In the same way as many people work on talks and presentations in the airport lounge or on a flight, I write wherever I can.

But perhaps the most deliberate, and the hardest, decision I have had to make is to not undertake full-time clinical work to make some room for writing and its necessary companion, reflection. This has inevitably meant somewhat restricted career opportunities, with academic and financial ramifications, but for me it seems like a fair price to pay for the tremendous job satisfaction of being a doctor and a writer, able to serve not only my patients but a world of people. To have a few hours in the week to read widely, experiment with different forms of writing, and reflect upon the meaning of being a doctor seems like a luxury that many of our time-starved, emotionally fatigued colleagues are eager to embrace. They need to know that if good medicine is about advocacy, we can serve society through various means. Research and clinical work are two time-honored ways, but writing and public speaking are legitimate means of democratizing medicine.

The celebrated physician and writer Anton Chekov observed, "Medicine is my lawfully wedded wife and writing my mistress. When I tire of one, I spend the night with the other. Though it's disorderly, it's not so dull, and besides neither of them loses anything from my infidelity."[4]

Nurturing the art of medicine through reflection and writing is important. It allows the development of a therapeutic, creative, and educational outlet. We must not consider it an unaffordable luxury but an essential tool for improving our own lives and those of our patients.

PART II: THE POWER OF STORIES

A Case for Reading

Reading essays published in medical journals gives us the opportunity to reflect, alone and collectively, on important aspects of practice that are essential but often overlooked. Ethical dilemmas come into sharper focus, and the emotional toll of practice is assuaged by feeling connected to peers or to the writer. Even if we read when we are alone, the act of reading establishes a virtual connection to the writer, editor, and fellow readers. It provides a form of social support that is so often lacking in the workplace and offers validation of the experiential and intellectual aspects of our complex professional lives. Doctors have traditionally kept their worries to themselves and paid a price for their stoicism and emotional isolation. By stimulating reflection and conversation, reading can foster self-awareness and self-expression.

Furthermore, reflecting on one's reaction to text nurtures our sense of purpose and vocation, helping us maintain perspective and balance in our lives. Reading a story or personal reflection forces us to slow down and inspires us to daydream. In those moments when time seems suspended, we allow our minds to roam, occasionally stumbling or straying, always searching for what is normally tucked behind conscious thoughts and hardly ever allowed to surface. We connect with our sense of vocation, with ideas we once cherished and then discarded or forgot, and with desires we may not have known existed. In the act of reading, we are lifted and transported by the creativity of our peers, whose artistry gives us new insights into old problems and language to describe what seemed beyond the reach of words. Stories, poems, photo essays, and commentaries provide a platform for reflection that allow us to explore other perspectives and other ways of being in the world. In other words, reading stimulates our empathic abilities, bringing ideas and dreams into sharper focus.

Stories and opinion pieces serve another useful professional function, in that they shape our professional discourse.[5] I can easily quote essays that shaped my views on important topics; their messages remain fresh and powerful years after publication. We also learn, from our colleagues' experience, how to frame and discuss challenging topics so that our communication is clear and supportive. Stories and reflections expand our vocabulary and our mind-set, at times providing guidance and focus that can improve our clinical performance. Reading can, by all of these mechanisms, help reduce perceived levels of work-related stress and even contribute to our well-being. Perhaps reading even helps reduce the risk of professional burnout, although this is impossible to prove. What is clear, however, is that the ability to remain curious and to imagine something that does not yet exist is indispensable for success in research and innovation.

Composing a persuasive and coherent narrative is also essential for achieving one's goals on personal and professional fronts and may contribute to professional satisfaction. Successful grant writers persuade readers to invest in their dreams. Trusted mentors help junior colleagues bring their ambitions and projects into focus. Clinicians function as coeditors for their patients' narratives through attentive listening and deliberate communication. Thus reading serves to prepare us for the work of empathic listening.

Reading also brings us into contact with talented storytellers. Listening to stories provides another powerful venue for enjoyment and has become easily accessible in the era of podcasts and audio books. Stories can keep us company on our commute to work or while sitting in the car waiting for a child to finish practice or during workouts. We can read privately, quietly or out loud, and reread at our own pace. Stories are extraordinary tools for teaching ethics and interpersonal and relational skills. They give us access to complex emotions and deepen our appreciation for another's suffering or heroism. Stories surprise and entertain us, expand our intellectual reach, and challenge our creativity. Persuasive commentaries can influence opinion and have a transformative effect on education and practice. Because we inevitably spend so much of our time reading medical notes, scientific papers, and manuscripts, reading stories provides a welcome escape into a world of colorful characters, poignant storylines, and insightful messages.

Essays published in medical journals are often personal narratives written by one individual, although increasingly these narratives have multiple authors, suggesting a collaboration and a team effort.

They are selected for publication on the basis of their messages, originality, and artistry, as well as their perceived relevance for the community of readers, and this varies depending on the orientation of the journal. Editors envision that readers turn to text as a springboard for reflection and that they appreciate writes' willingness to share personal doubts, to expose their vulnerabilities, and to let us peek at their inner landscapes.

"Art of Oncology" in the *Journal of Clinical Oncology*: The Stories We Tell

The *Journal of Clinical Oncology* has invited the submission of personal essays, poems, and art forms for publication within the "Art of Oncology" section since 2000. Since its inception, AOO has published essays on a broad range of topics that represent the human side of cancer from the perspectives of patients, advocates, and clinicians. Under the skillful leadership of Charles Loprinzi and then David Steensma, AOO struck a chord with the global readership of the journal. I had the privilege of succeeding Dr. Steensma as consultant editor at the end of 2014, and I enjoy working with a brilliant and wise editorial board to select submissions we feel contribute to shaping our professional culture. We look for essays that have timely and relevant messages, written with humility and candor.

Great essays capture our attention from the start. Some are funny or whimsical, others sorrowful or nostalgic. Through an assortment of storylines and scenarios, we travel imaginary roads and grapple with common dilemmas. Essays help us witness others' suffering and celebrate their heroism and provide a safe release for the emotional toll of working in oncology. Despite enormous scientific progress, those of us involved in the care of patients know the grief and sorrow that accompany a career in oncology. Reading can help us get through a tough day.

Writers write about what they know. Doctors and nurses spend a lot of time listening to stories and are familiar with plot, protagonist, setting, dialogue, and theme. Oncologists struggle to find meaning in tragedy and humor in daily minutiae and to maintain a healthy balance between their work and home lives. Several essays addressed these issues in the past year. In "What Mommy Does," Melissa Mark[6] describes her struggle to shield her young daughter from learning that her mother's work involves the care of children who are dying and how this changed after the child overheard a telephone conversation with a hospice nurse while taking her evening bath at home. Megan Caram[7] coins a new term, "oncologist's guilt," to describe the conflicting emotions she experienced during her 3-month maternity leave. She describes feeling as if she were "abandoning" patients and contrasts the healthy period of attachment between a newborn and his mother with the feelings of dependence that are inherent to close therapeutic relationships.

William Meyer[8] shares his heartbreak over the death of his own grandchild from cancer. His inner pain is almost palpable as he writes about feeling a sense of "abject failure to help the ones most dear [to you] despite years of training and supposed 'expertise.'" He concludes the essay on an unsettled note: "these are not easy feelings to come to grips with, and perhaps the sharing of further insight on these experiences will require the passage of time." Indeed, with time we can find meaning and integrate painful experiences into the larger tapestry of our lives, as told by Jonathan Finlay[9] in "A Ruby Anniversary." On the 40th anniversary of his last "encounter with seminoma," he embraces his fortune and believes he is a better physician because of his own experience as a patient with cancer.

Coming to terms with grief and loss is a recurrent theme for AOO. In her remarkable essay "Pieces of Grief," Erica Kaye describes the visceral reaction she experienced after the death of a patient in the intensive care unit, a death that forced her to face her emotional exhaustion.[10] Katherine Reeder-Hayes[11] describes being overcome by emotion and crying, as she is standing alone in her new, empty home at midnight, listening to bluegrass playing on the radio, a paintbrush in her hand. Reeder-Hayes writes about beloved patients, whose passing affects us very deeply. Daniel Rayson[12] explores both sides of the clinical relationship in his wonderful essay "White Knuckling." He delves into the lived experience of a young, dedicated oncology nurse who is experiencing symptoms of burnout and trying her best to encourage and comfort her patient, a tough, retired neonatal intensive care unit nurse who voices her ambivalence about continuing to fight her metastatic cancer, fully aware that she will die of this disease. Rayson captures the imaginary dialogue that occurs in the infusion unit, while the patient receives her infusion of bisphosphonate, giving voice to the trauma experienced by oncology nurses who are on the front lines of cancer teams, delivering solace and cheer together with powerful anticancer therapies.

Authors write to share their stories and to give advice. Laura Melton[13] draws a parallel between a patient who successfully compartmentalized his illness until the very end and clinicians who cope with loss by compartmentalizing their feelings. She acknowledges that this emotional distancing provides a buffer that allows "us to be fully present without feeling overwhelmed" and also warns us that artificial boundaries are porous and may crumble during transitions between work and home life. David Korones[14] writes about caring for an adolescent with a pontine glioma who insisted that she did not want to know her prognosis, describing the tension he experienced in trying to reconcile his patient's request not to know with the evidence supporting full disclosure of prognostic information.

Reading through these essays, we find common ground with colleagues we have never met. Essays also serve to express regret and remorse, as in Nikhil Barot's[15] tale of a patient who died of complications of an unwanted diagnostic bronchoscopy. The author wishes he had listened more carefully when she refused the procedure and asked to be allowed to go home to die, ending his story with a very simple and effective "and you sit and think and think." Reena George[16] expresses remorse at having judged and dismissed the unreasonable requests from the daughter of a patient with advanced cancer, until she understood that they stemmed from a desperate and loving desire to help her dying mother. These sincere reflections can be therapeutic for both writer and reader.

CONCLUSION

Cancer clinicians need stories to recalibrate their emotional lives, to make sense of their experiences, and to learn from one another. Writing can serve as an outlet for self-expression or a mechanism for making sense of complex experiences. Writers write for fun, for therapy, to share stories and opinions, to honor a patient or colleague, for atonement, and sometimes for the glory of being published. Essays bring joy and insight to readers, allowing them to slow down and reflect and to refuel their emotional reservoirs.

It is our hope that reading also stimulates dialogue and helps foster a culture of collegiality among oncologists. Talking about our reactions to the written word can help us get to know one another and contribute to the professional development of junior colleagues and trainees. Reading, reflecting, and sharing stories serve an important role in the professional development of oncologists. Stories can guide us to find our own sources of inspiration and support and strengthen our therapeutic skills. In turn, this will affect the lives of patients and family caregivers struggling to cope with the unwanted burden of illness.

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Mastering Resilience in Oncology: Learn to Thrive in the Face of Burnout

Fay J. Hlubocky, PhD, MA, Miko Rose, MD, and Ronald M. Epstein, MD

OVERVIEW

Oncology clinician burnout has become a noteworthy issue in medical oncology directly affecting the quality of patient care, patient satisfaction, and overall organizational success. Due to the increasing demands on clinical time, productivity, and the evolving medical landscape, the oncology clinician is at significant risk for burnout. Long hours in direct care with seriously ill patients/families, limited control over daily responsibilities, and endless electronic documentation, place considerable professional and personal demands on the oncologist. As a result, the oncology clinician's wellness is adversely impacted. Physical/emotional exhaustion, cynicism, and feelings of ineffectiveness evolve as core signs of burnout. Unaddressed burnout may affect cancer clinician relationships with their patients, the quality of care delivered, and the overall physical and emotional health of the clinician. Oncology clinicians should be encouraged to build upon their strengths, thrive in the face of adversity and stress, and learn to positively adapt to the changing cancer care system. Fostering individual resilience is a key protective factor against the development of and managing burnout. Empowering clinicians at both the individual and organizational level with tailored resilience strategies is crucial to ensuring clinician wellness. Resilience interventions may include: burnout education, work-life balance, adjustment of one's relationship to work, mindful practice, and acceptance of the clinical work environment. Health care organizations must act to provide institutional solutions through the implementation of: team-based oncology care, communication skills training, and effective resiliency training programs in order to mitigate the effects of stress and prevent burnout in oncology.

Dr. A is 11 years past his medical oncology fellowship training and remains motivated to provide the optimal oncologic care for every patient and family member he sees. He works in a vast urban health care system with a patient panel of 110 to 120 patients per week. Dr. A is affable, has a hardy personality, and is admired by patients, nurses, staff, and his partners. Recently, Dr. A became partner, working long hours to achieve this lifelong dream. However, Dr. A is feeling physically exhausted of late, irritable, sad, and ineffective, as it seems as though his clinical duties never cease. At home, he calls his patients and spends most evenings in front of a computer completing patient notes or orders. Dr. A is unable to sleep most nights and spends little time engaging in leisure activities, such as running or attending his son's piano recitals. Currently, Dr. A is on in-patient service and gives weekly hour-long lectures to oncology fellow trainees at an affiliated academic hospital. He reports feeling cynical regarding the future to his colleague Dr. Z and questions, "Is any of this worth it?"

Although the oncology clinician, like Dr. A, is adequately equipped and expert at providing benevolent care to patients with cancer and their families, sadly, the greater majority of clinicians like Dr. A fail to provide self-compassion and care when it is most needed as symptoms associated with burnout arise. Dedicated empathic clinicians like Dr. A respond with self-blame when he is unable to perform at optimal levels. Little if any sympathy has been given to the physician especially the oncologist, who, despite best efforts at "toughing it out," fails to meet all work duties, with his role as physician directly conflicting with his role as parent. As a result, Dr. A feels physically and emotionally depleted, cynical, and ineffective. However, Dr. A may readily face these challenges and address burnout by developing and mastering resilience skills.

A BRIEF OVERVIEW OF BURNOUT IN ONCOLOGY: FOCUS ON RESILIENCE

A comprehensive review and analysis of burnout, including prevalence, symptoms, risk factors, related concepts, as well as individual and organizational interventions for consideration for both the practicing oncology clinician and healthcare institution was presented at the ASCO Annual Meeting in 2016 and documented.[1] A brief succinct overview of the seminal concepts and issues associated with burnout will be presented in this review with a focus on resilience.

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Burnout: What It Is and Why It Matters

For over a decade now, it is estimated that approximately 45% to 80% of practicing oncologists worldwide in countries such as the United States, Europe, and Australia experience symptoms associated with burnout.[2-4] Specifically, burnout has been identified as a work-related syndrome that manifests as a result of the interaction between the oncology clinician and the organization.[5-11] Burnout is characterized by three core symptom domains: physical and emotional exhaustion, cynicism and depersonalization (sense of disengagement), and low sense of professional accomplishment (ineffectiveness; Sidebar 1).[5-14] These three-dimensional signs of burnout exist along a continuum characterized by distinctly unique symptoms and an overlap of symptoms.[5-14] For example, cynicism and depersonalization is traditionally characterized by pessimism or depression (which are also key symptoms of emotional exhaustion), isolation, detachment, and demoralization. Burnout is not a disease. Burnout is a stable, chronic,and insidious process with the initial core physical exhaustion and negative emotional symptoms slowly developing over the course of 1 year as interpersonal and occupational stressors arise and persist.[5-14]

SIDEBAR 1. Three Domains of Burnout

1. Physical and emotional exhaustion
2. Cynicism and depersonalization
3. Ineffectiveness

Risk Factors

Multiple individual and organizational factors have been identified as contributing factors responsible for clinician burnout in health care.[6,9-27] Individual contributors are internal dispositional risk factors consisting of sociodemographic (e.g., younger age; female gender presents with emotional exhaustion, whereas male physicians present with cynicism, single/unmarried marital status, and medical trainee status) as well as personality (e.g., extraversion and conscientiousness) characteristics. Recent evidence revealed that physicians who experience unaddressed burnout are less likely to identify with medicine as a calling, a duty to serve the greater good, adversely affecting both the clinician and patient.[27]

However, given the changing landscape of the present-day health care system, recent research equally centers on specific external, occupational, and organizational risk factors that are important contributors driving oncologist burnout.[6,9-27] These stressors are work-related factors that do not meet the clinician's interpretation of the job or work expectations. For example, today, the oncology clinician is exposed to extended work hours, increased time in direct patient care, high occupational demands, lack of control over daily tasks, increased administrative responsibilities, increased time and use of electronic health record systems, limited decision making regarding patient care services, unclear job expectations, lack of social support, educational debt, and the evolving medical landscape.[19-21] The identification of these internal and external factors is of extreme importance to help promote and tailor individual, and primarily organizational, interventions designed to prevent and target unaddressed burnout and build resilience.

KEY POINTS

- **Burnout has three domains: physical and emotional exhaustion, cynicism and depersonalization, and feelings of ineffectiveness.**
- **Resilience has three components: strength of the individual, rise above adversity, and positive adaptation.**
- **Resilience is the key protective factor against burnout, as it shapes the individual's efficacy, engagement, and personal accomplishment.**
- **Resilience interventions include: education, integrate work/personal life, adjust relationship to work, mindfulness training, and work environment.**
- **Organizations must address oncology clinician burnout through the direct implementation of successful, feasible, effective resilience model interventions.**

When Does It Start?

Although less understood, it is entirely possible that the risk for burnout for some oncology clinicians begins early in their career during medical training.[12-27] Several studies demonstrate that residents and medical students have high rates of burnout and disproportionate rates of depression and suicide. Every year, the United States loses approximately 400 physicians to suicide, the equivalent of at least one entire medical school.[28] Though all medical schools provide a course in psychiatry to provide student insight into behavioral issues as related to patients, traditional curricula ignore these issues as related to medical students own development. Residency curricula are even less attuned to these issues. In fact, medical students are at higher risk for some psychiatric disorders than the general population, and suicidal ideation among them is estimated to be a very high 11.2% to 20%,[29,30] with higher rates among African-American respondents.[31] As a result of stigma, self-reported data likely underestimate these numbers. The prevalence and severity of depressive symptoms increases throughout school and rates of depression are higher in females than their male counterparts.[30,32] Additional risk factors may include that 31% of medical students have a low sense of personal accomplishment, and 22% demonstrate at risk behaviors for alcohol use.[32] Regarding mental health disorders, an estimated 12% of all medical trainees had probable major depression and 9.2% had probable mild to moderate depression with higher rates among medical students (versus residents) and women.[31] Although medical students demonstrate higher physical quality of life scores than the general population, they also report overall lower mental quality of life scores.[5] Even after completion of formal medical training, physicians continue to have elevated rates of psychiatric

disorders in comparison with the general population. Of note, male physicians complete suicide at a rate 70% higher than the population at large and female physicians at a startlingly high rate of 400%. To date, suicide is the only cause of death with risks greater for physicians than the general population.[15,25,26,29]

Burnout itself is not formally diagnosed as a disorder, given it is primarily recognized as an occupational-related condition; however, it shares similar symptomology with psychiatric disorders such as depression and post-traumatic stress disorders that are identified as precursors to the development of burnout development as well as consequences of burnout.[6,10,11,19-21,33-38] The long-term personal and professional consequences associated with unaddressed burnout are of primary concern. Long-term unaddressed burnout may lead to personal consequences such as chronic health conditions (heart disease and obesity) or mental health conditions (depression, anxiety, substance use, and suicide).[6,10,11,19-21,33-38] Professionally, long-term burnout leads to diminished quality care, reduced professional satisfaction, and overall accomplishment.[19,20]

For Dr. A, symptoms of physical exhaustion and negative emotions arise coupled with cynicism as work responsibilities increase and quality family time decreases. His feelings of ineffectiveness in the role of an oncologist adversely affect and directly conflict with his role as father and husband. Such symptoms indicate that Dr. A is in need of developing resilience skills to enhance his quality of life as well as optimize professional satisfaction. This evidence reveals the complex yet salient aspects and issues associated with burnout warranting intervention.

WHAT IS RESILIENCE: THEORY AND SCIENCE

Resilience, specifically psychological resilience, is a multifaceted theory that places emphasis on the human capacity to cope with, overcome, and become strengthened by adversity.[39-52] Current clinical and research efforts center on the strengths of the individual, rather than the individual's vulnerability, as a means of empowerment to rise above adversity, and persevere, resulting in positive adaptation (Sidebar 2). To date, the theory and study of resilience has shifted from a focus on the long-term adverse consequences of trauma to a focus on strength, triumph, and competence to build interventions tailored to foster resilience.[42,47,49-51] The concept of resilience grew from within the developmental psychology by the study of children who were able to thrive, survive, and overcome negative abusive childhood environments with poor parenting.[43,45] Resilience has also been applied to survivors' populations of war, trauma, and the military.[42,45,48,49]

SIDEBAR 2. Three Components of Resilience

1. Strength of the individual
2. Rise above adversity
3. Positive adaptation

Resilience: Supports Health and Enhances Coping Through a Psychobiologic Mechanism

Current research approaches enhance our understanding of the concept of resilience by placing an emphasis on specific factors that support human health and enhance coping rather than highlighting stress-related factors associated with disease.[39,41,42,47,49] Although evidence indicates environmental, neurologic, social and cultural factors are associated with the development of resilience, from a psychobiological perspective, resilience is believed to be a physiological positive adaptation to stress as it is associated with maintenance of the following: somatic, autonomic (sympathetic and parasympathetic), and central nervous systems.[39,53-55] The specific brain regions associated with resilience involve the prefrontal cortical region and amygdala. Additionally, decreases in the stress hormone cortisol, neuropeptide Y (an anxiety neurotransmitter), and 5-dehydroepiandrosterone prevent initiation of the stress response by decreasing sympathetic nervous system activation.[39,53-55] Also, elevated levels of the neurotransmitters serotonin and dopamine ("the reward center") and neuropeptide oxytocin have also been linked to resilience.[53-55] Positive emotions (e.g., happiness; optimism) play a crucial role in the development of resilience. Although it may appear that certain individuals are genetically predisposed to effectively cope with stressful situations, resilience is not necessarily an inherited trait, but rather a skill that can be learned and mastered. Yet, despite this strong scientific evidence, questions surround how to adequately describe and define resilience due to its complexity.

How Is Resilience Defined?

No universally accepted definition of resilience exists given its complex nature encompassing social, psychological, biologic, and cultural factors that act together to determine how the individual responds to stress.[6,39,42,50,51] The definitions of resilience continue to advance and grow. However, most definitions and researchers agree that for resilience to be demonstrated, both adversity and positive adaptation must be present.[42,44-52] Resilience is a positive response to adversities in the form of everyday minor stressors to key life-altering events. Resilience has been described as both a trait and a process, either present or absent, inherited or learned; however, according to Southwick, a well-known resilience expert, and colleagues,[42,47,49] it likely exists on a continuum ever present to differing dimensions across several life domains influenced by psychological characteristics within the stress process. Ideally, resilient individuals persevere in the face of adversity and life stress leading to transformative positive growth, acceptance, and a sense of greater meaning in life. For example, a clinician who is unable to positively adapt to work stress may successfully adapt to his personal life, or theoncology clinician may be more resilient during the late phase of career, yet not another phase such as in early residency.[42,47,49] As a result of interaction with the environment, resilience may change depending on the individual's response to stress and interactions with others in the environment.[42,47,49]

The Interplay Between Burnout and Resilience

Although several protective factors shield the individual against the development of burnout, such as peer support, communication skills training, and self-care, resilience is the key protective factor against burnout, as it shapes and enhances the individual's efficacy, engagement, and personal accomplishment.[6-8] Christine Maslach, a psychologist who has studied burnout extensively believes that burnout involves not simply the interaction between the individual and organization, but also the individual's attitudes, self-appraisal, and appraisal of others.[6-8] As such, burnout can be viewed as a barometer that measures a potentially toxic environment which did not support the clinician to manage his needs and emotions.[6-8] Moreover, Maslach and colleagues found that consideration of the individual's emotions promotes the individual's sense of control, commitment, and self-efficacy that further protects the individual from burnout.[6-8] In addition, several key emotional personality variables associated with resilience significantly minimizes the potential vulnerability to developing burnout, including a sense of coherence, thriving, hardiness (commitment, control), optimism, emotional competence, learned resourcefulness, self-efficacy, locus of control, potency, stamina, and personal causation.[6-8,45] The individual's ability to sustain and activate these resources in response to stress leads to a transformative active coping style required to directly address stressors and adversity.[6-8] Research on physician resilience supports Maslach's hypothesis. Zwack and Schweitzer[56] conducted an interview study of 200 physicians in Germany to identify health-promotion strategies used by senior physicians to maintain resilience. Three core domains were identified to illustrate strategies and attitudes used to activate resources that lead to active coping and the promotion of resilience, including: job-related fulfillment; behavioral practice (e.g., leisure activities, limit work hours, and professional development activities); and shift in attitudes (e.g., acceptance and attention to positive work endeavors).[56] In summary, despite stressful work conditions, physicians were able to activate resources to engage in positive coping strategies needed to foster resilience. As the cancer clinician like Dr. A learns to gain self-awareness and self-regulation of his emotions, which include thoughts and feelings, this enables him to build resources to find solutions to the issues at hand in a complex, ever-changing medical environment. Resilience, in the face of adversity, enables the cancer clinician to be armed with a broad spectrum of skills to develop more solutions to problems and positively adapt to the situation.

Resilience Interventions

Evidence-based, resilience-focused approaches have been promoted as burnout-prevention programs for clinicians tailored to enhance clinicians' individual skills building and workplace engagement factors.[57-59] These approaches, as well as mindfulness-based stress reduction programs, are believed to help foster clinician wellness by preventing and targeting unaddressed burnout directly. Therefore, from an institutional perspective, it is in the best interests of any health care organization to implement and support oncology clinician wellness efforts aimed at promoting clinician resilience as a means to maximize value and improve overall quality of care.

HEALTH PROFESSIONAL RESILIENCE: TACKLING BURNOUT IN ONCOLOGY

Dr. A had promised his son he would attend tonight's piano recital; however, one of his patients coded in clinic. The use of mindfulness training to build resilience skills would be of benefit for Dr. A. Rather than becoming angry and engaging in self-criticism with statements such as, "How does this always happen to me? I'm the worst father," reframing critical thoughts and providing self-compassion with gratitude and acceptance would be beneficial to Dr. A in this situation. In response, phrases such as "I will try to end clinic earlier on recital days. I'll ask Z if he will cover for me. I am a good father and love my son. I'm glad I was here for my patient" are reflective of resilience training.

Although the toll of burnout has been clearly described, it is not as clear what to do to help clinicians become more resilient, engaged with work, and truly thriving in their professional roles. Resilience is not merely restoration to a prior (balanced) state of being. Resilient organisms not only bounce back, they also grow in ways to prevent future trauma and promote growth.[59] Resilience does not necessarily lead to greater engagement; it is possible to be both resilient and burned out, surviving but not thriving—the walking wounded. Interventions should not merely try to prevent and mitigate burnout, they should also promote positive mood, physical and psychological health, joy, and flourishing in their clinical roles.

Recently, West and colleagues[57] reviewed 15 randomized trials and 37 cohort studies to address burnout. On average, interventions reduced overall burnout from 54% to 44%, as measured on the Maslach Burnout Inventory. Although individual (e.g., mindfulness, discussion, and stress management) and organizational (e.g., work environment changes and reduction in work hours) interventions produced similar improvements in burnout in the review by West et al,[57] Panagioti et al[60] suggested that institutional interventions might be more effective. Both expressed a need for testing of a wider range (and combinations) of interventions with larger sample sizes.

Studies of resilience in the general population have mostly focused on people who experienced extreme trauma that had a beginning, middle, and end, unlike the ongoing vicarious trauma experienced by oncologists and other clinicians dealing with serious illness and death. Yet, there are lessons to be learned. Psychiatrists Southwick and Charney[49] interviewed former prisoners of war, Special Forces instructors, and civilians who had experienced severe psychological traumas such as rape, sexual abuse, the loss of a limb, or cancer. They found that in spite of these extreme events, remarkably only a small percentage developed depression or post-traumatic stress disorder. They identified 10 resilience

factors: realistic optimism, facing fear, moral compass, religion and spirituality, social support, role models, physical fitness, brain fitness, cognitive and emotional flexibility, and a sense of meaning and purpose. Personality was found to be important also. The ability to form warm and caring relationships with others, so-called secure attachment, is associated with greater resilience, as is a perception of personal autonomy and perceiving oneself as competent.[61] Conversely, cognitive rigidity, excessive need for certainty, and low emotional intelligence are associated with lower resilience. These traits, to some extent, are determined by early life experience and genetics, but are mutable.

Education and Training Are Important

For example, stress inoculation is a principle of applying graded and increasing levels of stress during training to ensure that the individual progressively adapts to stressors. Clearly, stress inoculation is not the modus operandi in clinical training in which the introduction to human suffering is more intense and uncontrolled.

Better integration of work life and personal life confers greater resilience through helping individuals use the strengths developed in one domain to inform the other. This integration is not merely a balance between work (presumed to be aversive and stressful) and life, that which happens only when outside of work. Integration refers to finding meaning in work, setting appropriate but not rigid boundaries, and finding ways to engage more fully with work when the going gets rough.

Adjusting one's relationship to work is key. Many wellness programs emphasize healthy activities outside of work—time with family, vacations, exercise, yoga, etc. However, these approaches outside of work may have limited effect on resilience at work unless they are accompanied by a fundamental change in the workplace or one's relationship to it, especially one's attitudes and orientation toward the challenges in the workplace.

Mindfulness training is one of the most widely studied approaches. Mindfulness refers to intentional awareness of one's own thoughts and feelings, nonjudgmentally, with the goal of promoting clarity and compassion (Sidebar 3). By focusing on awareness and not relaxation, mindfulness training can help individuals be more aware of burnout in its early phases—noting changes in the body (e.g., headaches and muscle tension), emotions (irritability and sarcasm), or thoughts (blaming self or others)—before it becomes unmanageable, name it, and accept that it is present.[62] Being more mindful of one's own inner experience can build skills to mitigate burnout and enhance resilience, such as perspective-taking and cognitive reappraisal.[49,59] Mindfulness also addresses some of the biologic underpinnings of resilience. For example, mindfulness programs for military recruits promoted self-awareness and enhanced "healthy" gene expression, providing one plausible pathway toward enhanced resilience.[63]

SIDEBAR 3. Three Components of Mindfulness

1. Intention: intentional awareness of thoughts
2. Attention: ability to pay attention in the present, nonjudgmentally
3. Attitude: goal to promote acceptance and self-compassion

Mindfulness approaches emphasize "turning toward" difficult and potentially aversive challenges, identifying the earliest signs of stress, adopting an attitude of curiosity and beginner's mind, the capacity to see a familiar situation with new eyes. Turning toward distressing situations is possible only if one can lower one's level of reactivity and wait momentarily before reacting, mitigating stress before it becomes overwhelming. Various contemplative practices, including formal meditation and "mindful moments" during the workday, can help individuals recognize stressors more readily, respond to them sooner, and develop positive attitudes rather than fearful avoidance (Sidebar 4). Our study of 70 primary care physicians included mindfulness meditation, structured narrative exercises and appreciative inquiry (a strength-based interview approach), and discussion of key topics such as errors, grief and loss, meaningful moments, self-care, witnessing suffering, and communication with patients. After the program, physicians were not only less burned out and experienced less psychological distress, but they also reported greater empathy and better relationships with their patients.[62,64] Their personalities changed to be more attentive and resilient, and the effects endured. Key elements of the program, according to participants, were a greater sense of community, having acquired self-awareness skills, and giving themselves permission to care for themselves in the interest of being more available to their patients. Subsequent studies suggest that patient ratings of their physicians also improved.[65]

The Work Environment

Healthy clinical teams promote resilience; supportive social environments lead to greater resilience. A supportive

SIDEBAR 4. Take a Mindful Moment During Your Workday

Oncology clinicians routinely wash their hands between patients multiple times a day. Now is the time for a mindful moment: simply focus, pay attention to the sound of the water: its temperature, weight, and the way it feels on your hands. Look at the water, how it falls. Your thoughts may wander—do not worry, acknowledge them, and return your attention back to the water. Notice the smell of the hand soap, its texture, and weight on your skin. Your thoughts may wander—do not worry, return your focus to the water.

SIDEBAR 5. Principles of Well-Functioning Primary Care Practices That Might Be Adopted in Oncology (adapted from Sinsky et al[68])

- Proactive planned care, with previsit planning and previsit laboratory tests
- Sharing clinical care among a team, with expanded rooming protocols, standing orders, and panel management
- Sharing clerical tasks with collaborative documentation (scribing), nonphysician order entry, and streamlined prescription management
- Improving communication by verbal messaging and in-box management
- Improving team functioning through colocation, team meetings, and work flow mapping

social environment is associated with increases in neurotransmitters and hormones associated with well-being (and their corresponding receptors), presumably because of social epigenetic processes. For example, supportive environments lead to increased production of dopaminergic receptors in key areas of the brain, receptors that are involved in the brain's reward circuits. Conversely, the toxic combination of high responsibility, low sense of control, and isolation sets the stage for a sense of exhaustion, powerlessness, and helplessness.[66] Putting clinicians in morally compromising situations, excessive cognitive load because of interruptions and dysfunctional electronic health record systems, the increase in meaningless documentation and regulatory requirements, and placing increasing pressure on clinicians to see more patients without regard to quality are environmental influences that must be addressed by health care teams and health care institutions.[67,68] Merely reducing work hours will likely not be effective in promoting resilience without enhancing the work environment.

Sinsky et al[68] suggest a set of changes to enhance the work environment that may hold promise in reducing burnout and enhancing clinician resilience and well-being. Their suggestions revolve around shared care and teamwork and are based on observations of primary care physicians who report greater joy in practice. However, many of these changes could be adopted in oncology outpatient settings. These are listed in Sidebar 5. Although not directed at resilience per se, these enhance the quality of clinicians' workday and merit further investigation.

Just as individuals can be mindful of their level of burnout and well-being, health care organizations can monitor these as quality indicators and disseminate findings to raise collective awareness and resolve.[69] In this case, leadership is key; individual practitioners are more likely to thrive in those organizations in which the leadership has a demonstrated commitment to clinician well-being. Case reports of health care organizations that have implemented organizational approaches to clinician resilience emphasize principles that are summarized in Sidebar 6.[70] Although there are few controlled trials and institutions tend to report their own positive outcomes (improvements in burnout, distress, and the clinical environment), these suggestions are sensible and pragmatic; we cannot afford to delay until results of larger randomized trials are available.

THE JOY INITIATIVE: A STUDY OF POSITIVE PSYCHIATRY AND MINDFULNESS TRAINING ON LEVELS OF LIFE SATISFACTION AND WELLNESS

Among medical students, mindfulness meditation has been demonstrated to decrease symptoms of anxiety.[71] Mindfulness-based stress reduction interventions also decrease tension/anxiety, depression, severity of stress, and mood disturbance scores on the Profile of Mood States and confusion/bewilderment in this population. Similarly, these studies have also revealed increases in vigor/activity, trainees feeling more effective in managing stressful situations, and increased empathy.[72,73] Cognitive behavioral therapy and positive psychology exercises have also proven effective

SIDEBAR 6. Nine Principles of Organizational Leadership That Can Promote Clinician Resilience and Well-Being (adapted from Shanafelt and Noseworthy[70])

1. Acknowledging and assessing the problem
2. Recognizing the behaviors of leaders that can increase or decrease burnout
3. Using a systems approach to develop targeted interventions to improve efficiency and reduce clerical work
4. Cultivating community at work
5. Using rewards and incentives strategically
6. Assessing whether the organizations actions are aligned with the stated values and mission
7. Implementing organizational practices and policies that promote flexibility and work-life balance
8. Providing resources to help individuals promote self-care
9. Supporting organizational science (study the factors in your own institution that contribute to the problem, and invest in solutions)

in decreasing depressive symptoms and improving positive attitude and happiness/outlook on life for clinically ill individuals and the general population,[71-75] but there have been no studies to date demonstrating efficacy in the medical student population. A systematic review of stress management programs designed for medical students did identify three mindfulness-based interventions for medical trainees that demonstrated positive outcomes; however, to date, no interventions focusing on emotional resilience training skills using cognitive behavioral therapy combined with mindfulness training have been identified.[76] The investigators at Michigan State University developed an easily pilot-deployable programmatic intervention to help students and residents discuss and address their own burnout issues to enhance trainee well-being and emotional health with a focus on developing strengths to face the emotional challenges of medical training.

Programmatic Intervention Design

Michigan State University Department of Psychiatry resident physicians created and taught 60-minute weekly classes for 10 weeks for students at the Michigan State University College of Osteopathic Medicine. Half of each session was devoted to mindfulness therapy and the other half to cognitive behavioral therapy exercises. The cognitive behavioral therapy exercises were created and written by our lead resident physician (M. Rose), primarily based on the philosophy and writings of Victor Frankl. Individual weekly topics included selecting and practicing joyful activities, identifying one's core strengths and virtues, creating a vision, naming goals, daily compassion, and practice of gratitude. Each session had weekly mindfulness exercises and homework. The mindfulness topics included breathing, body awareness, eating, walking, and sound. Each class session concluded with brief homework assignments that reinforced the week's theme.

Seven female and seven male students elected to participate in the intervention. A control group was approved near the end of the intervention consisting of 79 medical students who did not participate in the intervention. The Beck Anxiety Inventory, Fordyce Happiness Scale, and the Authentic Happiness Inventory were administered to both groups to assess the impact of the intervention. The Beck Anxiety Inventory is a 21-item self-report measure of anxiety. Higher scores reveal greater levels of anxiety. The Fordyce scale is a self-report happiness scale consisting of two parts. Section one measures the overall perception of mood (rating of 0–10), and the second part measures the percentage of time a subject estimates feeling happy, unhappy, or neutral. The Authentic Happiness Inventory is a 25-question survey assessing aspects of well-being including self-esteem, life purpose, and emotional supports. For the intervention group, these surveys were administered at the outset, midpoint, and termination of the 10-week intervention. For the control group, the surveys were administered at the termination (10-week intervention point) of the study. All data were analyzed using SPSS (IBM) and MYSTAT (SYSTAT; San Jose, CA).

RESULTS

Fourteen students participated in the Joy Initiative project (Fig. 1). None of the intervention participants withdrew from this study. Figure 1 depicts study participants results. The analyses revealed the mean Beck Anxiety Inventory scores of participating (intervention) students declined from 13.8 at the first session (standard deviation [SD] 8.1) to 6.8 (SD 6.8) after the last session. This decrease in scores was statistically significant ($p = .007$; 95% CI, −8.089, −1.711; degrees of freedom [df] 9; SD 4.4). There were no statistically significant differences between the means of male or female (intervention group) participants. The mean Beck Anxiety Inventory score for the 79 students in the control group was higher of 9.6 (SD 7.5), compared with the intervention group mean of 6.8 (SD 6.8). However, this difference between groups was not statistically significant ($p = .326$; 95% CI, −4.423, 11.756; df 8; SD 10.5). The mean Authentic Happiness Inventory Scores of participating (intervention) students improved, increasing from 79.2 (SD 9.6) to 87.3 (SD 13.9). The increase in Authentic Happiness Inventory scores between the beginning and endpoint of this intervention was a statistically significant change ($p = .046$; 95% CI, 0.186, 16.214; df 9; SD 11.2). There was a statistically significant difference between the female and male changes in scores, with female mean score difference 13.3 points higher than that of male mean scores ($p = .007$; 95% CI, 5.061, 21.605; df 7; SD [female] 4.676; SD [male] 5.586). At the conclusion of the 10-week intervention, the mean Authentic Happiness Scale Score of the Intervention Group was 87 (SD 13.9) compared with the Control Group 75 (SD 12.3; analysis of variance 8.8; df 1; $p = .004$). For the Fordyce Happiness Scale, Part One: for the intervention participants, the mean Fordyce Part One scores increased from 7.6 (SD 1.0) to 7.8 (SD 0.4). This difference was not statistically significant ($p = .182$; 95% CI, −0.419, 1.419; df 3; SD 0.6). There were no statistically significant differences between the means of male or female (intervention group) participants. The control group had a lower Fordyce Part One happiness score of 6.6 (SD 2.0) compared with that of the intervention group of 7.8 (SD 0.4). However, this difference between groups was not statistically significant ($p = .178$; 95% CI, −0.280, 1.080; df 4; SD 0.5). For Fordyce Part Two, the mean Fordyce Part Two scores improved for the intervention participants, increasing from 56.2 (SD 18.0) to 69.8 (SD 18.7). The difference between the two data sets was not statistically significant ($p = .090$; 95% CI, −2.058, 23.658; df 9; SD 18.0). There were no statistically significant differences between the means of male or female (intervention group) participants. The intervention group had a higher Fordyce Part Two happiness score of 69.8 (SD 18.7) compared with the control group of 54.5 (SD 23.9). However, this difference between groups was not statistically significant ($p = .102$; 95% CI, −37.699, 4.099; df 9; SD 29.2).

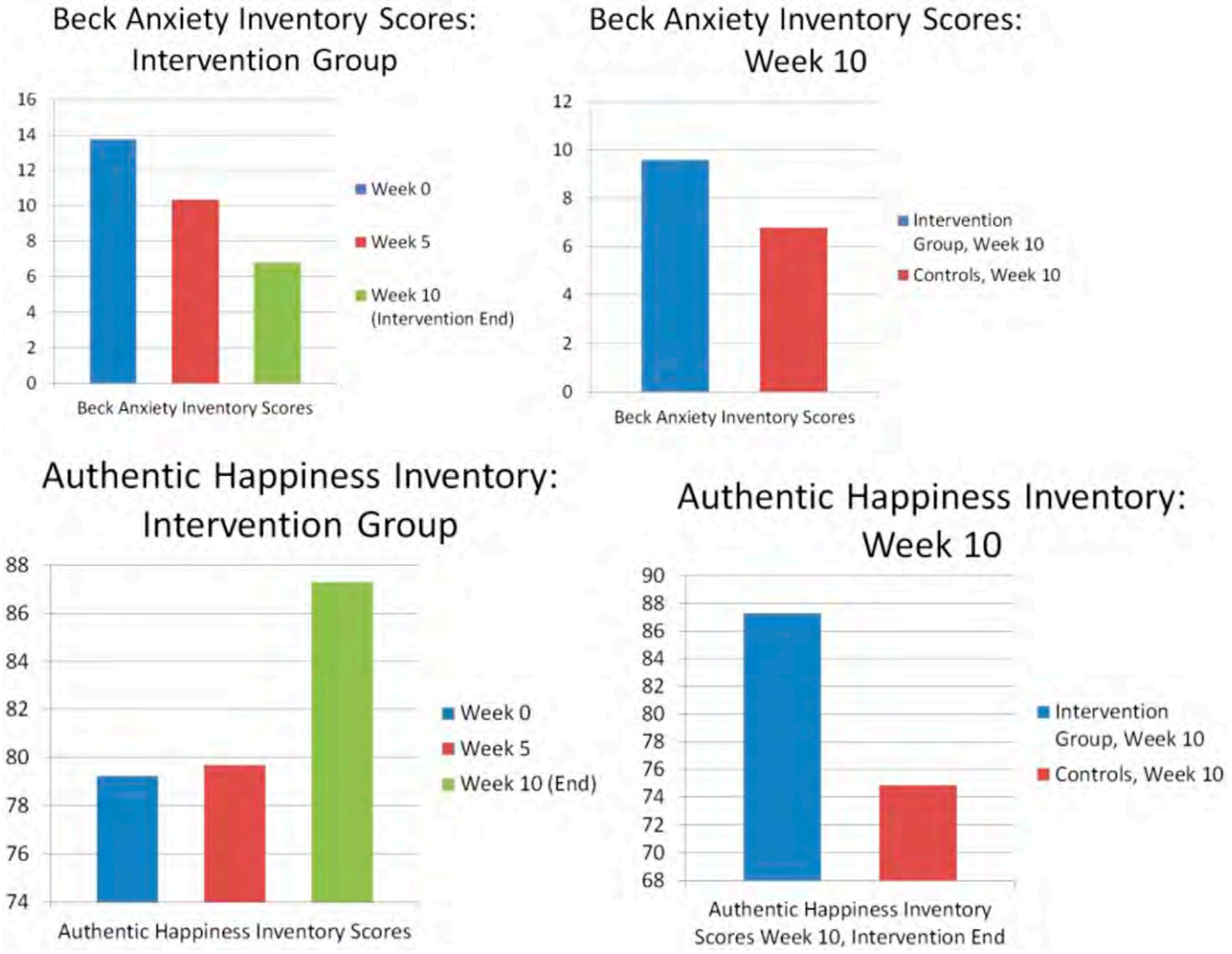
The availability of classroom space limited our intervention timing with respect to the academic schedule. The first measures were taken from the intervention group as soon as students returned from a 2-week winter break, at a time they might be expected to naturally feel most relaxed and

happy. In addition, the students provided reports via qualitative feedback that they very much enjoyed the class and looked forward to each week's session. None of the students provided negative feedback regarding the intervention. Students reported improved life satisfaction and increased ability to cope with stressors. One student recommended additional videos and interactive sessions, but reported overall satisfaction from participation. None of the participants withdrew from the study. The homework and techniques provided to students were intentionally brief, high-yield exercises, allowing them to practice these techniques while going to class and studying. Indeed, students also reported using the techniques demonstrated each week.

Institutional Response With a Long-term Impact

After the Joy Initiative pilot intervention study, the medical school administration provided support and funding for continuation of the project. Since these monthly "Joy Initiative Focus Group" meetings began, changes have been made on an administrative level. As a direct result of communication during these meetings, a new medical college staff position was created, a Program Officer for Outreach and Inclusion, with duties including coordination and provision of administrative support to continue the Joy Initiative monthly meetings. Student representatives from the medical school diversity committee spearheaded a lead role in the organization of the Joy Initiative events, and a minority student event related to the Joy Initiative was incorporated into student orientation activities for incoming medical students. The Joy Initiative Focus Group meetings continue on a monthly basis, with average attendance ranging from 50 to 70 students across 3 campus sites. In addition, the interventions used in this pilot study are now incorporated into formal elective classes offered at both the osteopathic and allopathic medical schools at Michigan State University, ("Happiness and Emotional Resilience Training for Health Care Providers Elective," Course PSC 591 301, Michigan State University College of Osteopathic Medicine; and "Resilience and Happiness Promotion for Health Care Providers," HM 590 Section 304, Michigan State University

FIGURE 1. Joy Initiative Participant Outcomes for Anxiety and Happiness



Outset, midpoint, and termination of the 10-week intervention compared with control group.

College of Human Medicine). Future programs should include a larger sample size with long-term follow-up to investigate whether students continue to use these tools years after the intervention to determine if they maintain high levels of satisfaction and low levels of depression, stress, and burnout. In addition, core components from the intervention could be used not only for all forms of trainees, but also for other health care professionals, including cancer clinicians, hematologist/oncologists, radiation oncologists, surgical oncologists, oncology nurses, and physician assistants.

CONCLUSION

Oncology clinicians are at increased risk for burnout; however, building resilience in the face of adversity to positively adapt to the changing health care system is key.

Although the optimal program to address burnout requires additional research, organizations must not delay to act. Organizations must set a precedent and address oncology clinician burnout through the direct implementation of successful, feasible, effective resilience interventions such as the Joy Initiative.

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Social Media for Networking, Professional Development, and Patient Engagement

Merry Jennifer Markham, MD, Danielle Gentile, PhD, and David L. Graham, MD

OVERVIEW

Social media has become an established method of communication, and many physicians are finding these interactive tools and platforms to be useful for both personal and professional use. Risks of social media, or barriers to its use, include perceived lack of time, privacy concerns, and the risk of damage to one's reputation by unprofessional behavior. Of the social media platforms, Twitter has become favored by physicians and other health care professionals. Although one of the most obvious uses of social media is for rapid dissemination and receipt of information, oncologists are finding that social media is important for networking through blogs, Facebook, and Twitter. These platforms also have potential for providing opportunities for professional development, such as finding collaborators through networking, participation in Twitter journal clubs, and participating in online case-based tumor boards. Social media can also be used for patient engagement, such as through participation in tweet chats. There is emerging data that patient engagement through these platforms may lead to improvement in some health-related outcomes; however, data are sparse for oncology-specific outcomes. Efforts are underway to determine how to assess how social media engagement impacts health outcomes in oncology patients.

Social media has evolved over the years to become an established method of communication in our current society. Eighty-six percent of Americans are internet users, and of those, almost 80% use Facebook, 32% use Instagram, and 24% use Twitter.[1] Sixty-two percent of Americans get their news on social media, primarily through Facebook, but increasingly through Twitter.[2] The awareness of social media and its relevance in society continue to grow, certainly bolstered by the fact that the newest U.S. president communicates regularly with the public through Twitter.

Social media refers to tools or platforms for the interactive, or social, sharing of user-generated content. Social media includes a wide variety of platforms for the sharing of words (e.g., Twitter, blogs), images (e.g., Pinterest, Instagram), and video (e.g., YouTube, Snapchat, Periscope). Sites such as LinkedIn tend to be used more for professional networking, and others, such as Doximity, are geared specifically toward social networking between physicians and other health care professionals. As social media technology evolves, so does the potential for personal and professional use of these platforms.

Twitter has become a favored forum for health care communication for physicians, patient advocates, and health care organizations. Through Twitter, a user can post messages ("tweets") of up to 140 characters, and assuming the user's account is public rather than private, these messages can be shared ("retweeted") by other Twitter users to their followers. The use of a hashtag (a word or phrase preceded by the # sign, such as #breastcancer or #myeloma) in a tweet serves to link the message to a conversation or a virtual community. Hashtags also are useful for searching for information about a topic on Twitter. Thompson et al describe in more detail the anatomy of a tweet and some basics of using Twitter, including valuable resources for those physicians just getting started, or wanting to get started, using the platform.[3]

It is difficult to estimate how many oncologists are active users of social media. A survey conducted of Canadian oncology physicians and oncology trainees found that 72% of respondents used social media.[4] The authors found that social media use varied by age, a typical finding in social media use surveys, such that 93% of oncology fellows and 72% of early-career oncologists reported social media use, compared with 39% of midcareer oncologists. When these oncologists and oncology trainees used social media for professional development, they reported that their goals were for networking (55% of respondents), sharing research (17%), and leadership development (13%).

One of the most obvious uses of social media is for rapid dissemination and receipt of information. Breaking news commonly appears on Twitter prior to appearing in newspapers or television news broadcasts. Medical research shared

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through social media also has potential to reach much broader audiences in a more rapid, real-time fashion. Because of this potential, many journals now have a presence on Twitter. For example, the journals of the American Society of Clinical Oncology (ASCO)—the *Journal of Clinical Oncology* (@JCO_ASCO), *Journal of Oncology Practice* (@JOP_ASCO), and *Journal of Global Oncology* (@JGO_ASCO)—are all represented on Twitter.

There are numerous blog posts and articles written by physicians, including oncologists, that describe why the use of social media has value for both personal and professional uses.[5-9] Here, we will discuss some of those potential uses for social media, including using social media for professional development, networking, and patient engagement. First, however, it is important to address the potential risks of social media use.

BARRIERS AND RISKS OF SOCIAL MEDIA USE

Adilman et al found that the most frequently cited barrier to using social media was not having enough time, as reported by 59% of participants.[4] Campbell and colleagues also identified a lack of time as a potential barrier; however, their research indicated that this is an area of disparate views among the physicians they studied. Although some physicians felt the time needed to use social media was an impediment to patient care, others felt time was not problematic.[10] Other potential barriers along this theme that are anecdotally cited by physicians include decreased productivity that may result from time spent on social media, lack of time to learn how to use social media effectively, and being overwhelmed by social media and technology overload.

Privacy concerns are frequently reported as barriers to social media use.[4,10,11] Although most physicians who use social media, and especially Twitter, enjoy the engagement with the general public, patients, and patient advocates, some physicians are concerned about engaging with patients on social media and avoid social media use for this reason. Another concern is the permanence of anything shared on social media. For example, a deleted tweet on Twitter is not truly gone. A common expression is that posts shared on social media are written in pen, not pencil.

Health care organizations who employ or work with physicians are concerned about the potential harms from unprofessional or unethical behavior on social media. Physicians themselves are worried about inadvertently sharing misinformation or sharing something unprofessional.[10] Unethical or unprofessional information shared on social media could pose a risk to a physician's or a health care organization's reputation. An early study by Chretien and colleagues examined the tweets of self-identified physicians on Twitter to determine whether physicians were behaving unprofessionally.[12] Of the 260 users they collected data on, a total of 5,156 tweets were analyzed. One hundred forty tweets (3% of total tweets) were categorized as unprofessional. Thirty-eight of the tweets (0.7%) contained potential patient privacy violations, 33 (0.6%) contained profanity, 14 (0.3%) contained sexually explicit material, and four (0.1%) included discriminatory statements. Twelve tweets contained possible conflicts of interest, such as promoting health products sold on their website, and 10 tweets were statements about medical therapies that were counter to existing medical knowledge or guidelines.

Many health care organizations have established policies for social media use to be proactive in establishing rules and guidelines for online professionalism. Dizon and colleagues catalog some of the common concepts in social media policies and give practical guidance for using social media in the oncology practice.[13] ASCO published online its "Ten Tips for Use of Social Media" that serves as a quick resource for responsible physician use of Twitter and other social media platforms (www.asco.org/sites/www.asco.org/files/asco_socialmedia_card.pdf). Additional ASCO-related resources for social media use can be found in Table 1.

KEY POINTS

- **Social media participation allows for rapid and real-time information sharing and receiving, and physicians are finding platforms such as Twitter to be valuable for health care communication.**
- **Networking through social media allows physicians to make connections with others with similar interests, foster collaboration, and gain support for personal and professional growth.**
- **Professional development opportunities exist through social media, such as through networking (including through Twitter at medical meetings) and participation in Twitter journal clubs and online case-based discussions and tumor boards.**
- **Patients and patient advocates are engaging with each other, physicians, and health care organizations through social media using platforms such as Facebook and Twitter, including participation in tweet chats.**
- **Patient engagement in social media may lead to improvement in some health-related outcomes.**

SOCIAL MEDIA FOR NETWORKING AND PROFESSIONAL DEVELOPMENT

Professional development and networking go hand in hand on social media. Networking and connecting with other physicians on social media is one of the main benefits of participation. Traditionally, physicians have interacted and engaged with physicians in their own communities and medical centers, with networking limited by physical location. With Twitter, however, a physician can meet and interact with physicians around the world who may have similar professional or research interests, thus creating opportunities for the sharing of ideas, collaboration, and connection. By using cancer-specific hashtags on Twitter, oncologists can participate in discussions and network with colleagues in these virtual communities centered around common cancer interests.[14] Some examples of common cancer-specific hashtags are listed in Table 2.

Interacting through blogs or online forums provides additional opportunities for networking with colleagues. ASCO

TABLE 1. ASCO-Related Resources for Social Media

Resource	Twitter Handle or Website
ASCO	@ASCO
ASCO publications	
Journal of Clinical Oncology	@JCO_ASCO
Journal of Oncology Practice	@JOP_ASCO
Journal of Global Oncology	@JGO_ASCO
The ASCO Post	@ASCOPost
Cancer.Net	@CancerDotNet
Conquer Cancer Foundation	@ConquerCancerFd
ASCO University Course: Use of Social Media	https://goo.gl/cYqH6J
Ten Tips for Use of Social Media	https://goo.gl/m11SDL
Social Media for Cancer Care Providers 101	https://goo.gl/JsE8C6
Practical Guidance: The Use of Social Media in Oncology Practice[13]	https://goo.gl/sKG2KG
Roundtable: The Use of Social Media in Oncology Practice (Podcast)	

Connection (http://connection.asco.org) is a relevant hub of information and networking opportunities for ASCO members, from commenting on ASCO Connection blogs (thus engaging with the authors and other commenters) to participating in the ASCO Connection Discussion forums. Doximity and LinkedIn are other sites often used for professional networking.

Twitter has become the next frontier for the traditional journal club, moving the discussion about a journal article out of the classroom and into the public, international space.[15] Thangasamy and colleagues describe their experience with the international urology journal club (#urojc) on Twitter.[16] Each month, the moderators of #urojc host a 48-hour discussion focusing on recently published journal articles. The extended time allows for Twitter users in different time zones to participate. Over a 12-month period, 189 unique users representing 19 different countries participated in their monthly #urojc Twitter discussion. Two oncology-specific Twitter journal clubs include the radiation oncology (#radonc) journal club moderated by @Rad_Nation and the bone marrow transplant journal club (#bmtojc) hosted by the American Society for Blood and Marrow Transplantation (@ASBMT).

TABLE 2. Examples of Common Cancer-Specific Hashtags

Hashtag	Topic
#AYACSM	Adolescent and young adult cancer
#BCSM	Breast cancer
#CRCSM	Colorectal cancer
#GynCSM	Gynecologic cancer
#HNCSM	Head and neck cancer
#KCSM	Kidney cancer
#LCSM	Lung cancer
#LeuSM	Leukemia
#LymSM	Lymphoma
#MMSM	Multiple myeloma
#PallOnc	Palliative oncology
#PancSM	Pancreatic cancer
#PCSM	Prostate cancer
#PedCSM	Pediatric cancer
#SCSM	Sarcoma
#SurvOnc	Cancer survivorship

Tweet chats are regularly held on Twitter by several groups, always organized around a hashtag and led by a moderator or several moderators. For example, the Breast Cancer Social Media (#BCSM) chat began in 2011 as a conversation on Twitter and has grown into a robust virtual community (@BCSMChat; http://bcsm.org/). The #GYNCSM monthly tweet chat (@gyncsm; http://gyncsm.blogspot.com/) centers around discussions about gynecologic cancers and was established in 2013. Participants in these chats, and in other cancer-related tweet chats, include medical oncologists, surgeons, radiation oncologists, nononcology physicians, nurses, psychologists and other health care professionals, patients, patient advocates, and health care organizations. Physician participation in tweet chats provides the opportunity to network with colleagues doing similar work, meet potential research collaborators, advocate for patients, and engage with patients and patient advocates.

Participation in online case-based discussion is another opportunity for professional development. Located on the ASCO Connection Discussion (https://connection.asco.org/discussion), the Molecular Oncology Tumor Board has been an active online tumor board since January 2015. These educational modules are presented in blog post form and consist of a case presentation followed by several discussion questions, with the discussion moderated by specialist physicians. Users of the ASCO Connection can provide answers and further discussion in the comments

of the blog post. A similar case-based educational opportunity is provided by the moderators of the TeamHaem blog (https://teamhaem.com/), with a focus on hematology cases. The moderators (@TeamHaem) present a case on their blog and then request discussion on Twitter using the hashtag #TeamHaem to organize the discussion. Follow-up blog posts include updates about the case based on discussions held on Twitter.

Networking with colleagues and other health professionals at meetings through Twitter is now mainstream. Over the last several years, Twitter use at the annual meeting of ASCO has grown significantly.[17,18] Attendees of the meetings routinely share information about abstracts being presented, scientific breakthroughs, or observations about the meeting. This allows for a much broader audience for the scientific research being shared, extending the reach of the information presented. Those who are not in attendance—or even those attendees who are attending different sessions in different rooms—can stay up to date on the news coming out of the meeting halls. Those attendees who are sharing tweets may find that composing tweets during a meeting—which requires editing the content to be shared to a maximum of 140 characters—can allow for reflection and better understanding of the information.[19] Connecting virtually with colleagues at the meeting has the potential to foster broader discourse on research studies, provide opportunities to collaborate, and create new friendships. And, importantly, opportunities exist through "tweet-ups" to meet Twitter friends in person at social gatherings geared specifically for that purpose.

The opportunity for support and online mentorship is not to be overlooked. Reaching out on Twitter, for example, with a simple message of frustration or joy can generate responses that provide support and acknowledgment that we are not alone. For example, when one of our authors (Markham) sent a tweet after an emotionally challenging week caring for patients with cancer, it was met with supportive responses and, ultimately, a collaboration and friendship.[20]

In addition to connecting through Twitter, there is potential for networking in private or closed Facebook groups. The European Society for Medical Oncology (ESMO) sponsors a closed Facebook group, the ESMO Young Oncologists group, for early-career oncologists. Examples of two robust, interactive groups that exist for women physicians are the Physicians Mom Group (PMG) and the Hematology and Oncology Women Physician Group. As of February 2017, the PMG Facebook group had over 66,000 members, and the Hematology and Oncology Women Physician Group had 646 members. Because they are out of the public eye, the conversation among physicians and oncologists in these groups can be more in depth and personal, and these groups have become a place for support, both personal and professional, and friendship. Radiation oncologist Miriam Knoll (@MKnoll_MD) described her experience with the PMG Facebook group as follows: "As physicians and individuals, we need to give and accept support from our fellow colleagues. Think about it: Where else could a physician share a moment of frustration or achievement with 50,000 colleagues and receive immediate feedback including 2,000 likes and hundreds of supportive comments? This is the unique platform of PMG."[21]

SOCIAL MEDIA FOR PATIENT ENGAGEMENT

"Patient engagement" is a term that is gaining great use in health care discussions. Reading the term on the surface, it is hard to argue against encouraging patients to take a more active role in their care. A difficulty in the discussions is that there is not a clearly accepted definition of patient engagement. This is further complicated by the near-synonymous use of the phrases "patient activation" along with "patient- and family-centered care." An often-used definition of patient engagement has been advanced by Angela Coulter and focuses on the activities by patients and health care professionals to "promote and support active patient and public involvement in health and health care and to strengthen their influence on health care decisions."[22] The expanded use of social media platforms by various health care institutions has raised the question of their impact on patient engagement and whether that impact could be shown to translate to improved outcomes.

There are certainly some social media platforms that may lend themselves to improving patient engagement more than others. The simple presence of a website is likely not adequate. A study of patient's perception of specialty society websites in Australia, Europe, and the United States gave an average rating of 3.2 out of 10, with the majority of patients rating the websites as failing to meet an "adequate" standard of information delivery.[23] More health care institutions are moving toward mechanisms with a greater level of interactivity. Facebook, having a monthly active user base of more than 1.5 billion and a high level of potential interactivity, is an attractive platform. Twitter, with more than 300 million accounts, has the capacity for interaction with the use of retweets, but only 2% of original tweets are retweeted. Pinterest, in contrast, may have fewer users, with less than 70 million visits per day, but the rate of "re-pins" can be as high as 80%, suggesting a greater level of engagement.[24] YouTube, with more than a billion active users but less interactivity, has a potential for education and information dissemination. As an example, one review of YouTube videos in 2014 found more than 280 videos on preparation prior to colonoscopy, each with more than 5,000 views.[25] Blogs and webcasts/podcasts provide the lowest level of interactivity but can still be useful as educational platforms.

The practice of patients using the internet to find health information has been long recognized. Thackery et al in 2013 reported that nearly 75% of patients will begin looking for health care information via a search engine, but nearly 33% will ultimately use social media sites as well by the time their search is completed.[26] Although patients turn to social media for gathering health information, they may be less likely to actively interact with other social media users

to share information. A survey of more than 3,300 patients found that less than 4% were willing to communicate with their physician regarding health goals or test results via social media. Only 11.7% were willing to engage in peer coaching with other patients through Facebook.[27] These results have led to the recognition that patients who are "information altruists" are required for these communities to truly succeed. These patients must be willing to engage with other patients, caregivers, researchers, and other stakeholders within social media platforms.[28]

Objective data of the impact of social media in improving patient engagement and outcome results specifically in the area of oncology are lacking, so a more generalized review is needed. One measure of patient engagement is the "Patient Activation Measure," a tool that uses responses to 13 statements to assess a patient's level of engagement. Patients defined as "less activated" by this tool are more likely to have unmet medical needs and delay medical care.[29] Chronically ill patients who are "more activated" are more likely to adhere to treatment and obtain regular chronic care.[30] What was not assessed by these studies, however, was the impact of different interventions on the activation scores. Grosberg et al has reported a positive impact of social media use and patient activation.[31] Camoni is a Hebrew-language social media site established in 2008. Participants in the four largest communities on the site, namely diabetes, pain, depression, and hypertension, were surveyed from 2012 through 2013. Their survey found that increased frequency and duration of visits to the site were associated with increased Patient Activation Measure scores. Interestingly, no difference was seen between active participants and "lurkers" (i.e., those who visited the site but did not interact with other participants).

Research regarding the impact of social media interventions on nononcology health outcomes, however, are more abundant. Lelutiu-Weinberger et al reported in 2015 the results of an online intervention program to reduce HIV risk in young men who have sex with men.[32] Their program modified an in-office program recognized as effective in reducing risky behaviors such as failure to use condoms. Although the studied population of 41 men was small, significant reductions in risk behaviors were seen between baseline and follow-up. Improvements were also observed in knowledge of the connection between substance use and sexual risk. Saberi and Johnson reported a correlation between internet use for health care engagement purposes and improved clinical outcomes in HIV-positive individuals.[33] They recruited nearly 1,500 respondents via a multitude of social media platforms. Use of the internet for health care engagement was associated with a significantly higher chance of antiretroviral therapy adherence and chance of an undetectable HIV viral load. The significance impact was confirmed on multivariate analysis.

Attai et al reported outcomes related to participation in "tweet chats" for patients with breast cancer in 2015.[34] The Breast Cancer Social Media tweet chat was established in 2011. The number of Twitter users using the #BCSM hashtag increased to more than 14,000 in 2014. A survey of those users obtained 206 responses. Participation was associated with a significantly lower rate of extreme/high anxiety levels. An interesting impact was that 28.4% of participants reported subsequent volunteer efforts, representing a surrogate marker for increased engagement.

The potential use of social media to assist with clinical trial improvement is also of interest. Descriptions of mechanisms in place to assist with accrual through social media exist, but little research exists regarding their effectiveness. Khatri et al reported the impact of free social media efforts on a U.K. trial determining the impact of nonsteroidal anti-inflammatory drugs following gastrointestinal surgery.[35] They reported 18.2% of the needed accrual occurring in a short time period. Their click-through rate was 33.7% compared with previously reported rates of 3.2% for paid Facebook advertising of a breast cancer trial.[36]

Online communities have also been associated with cost improvements. A U.K. mental health community, the Big White Wall, was established in 2007. This community allows patients to perform self-assessments, join guided support programs, and even receive live therapy via Skype. An economic evaluation of the program reported in 2011 showed that members of the community had, on average, one less visit to a general care practitioner, hospital, or emergency department. Factoring in the per patient cost of the program, this led to a net savings of $615 per patient per year.[37]

Sawesi et al reported a systematic review of the literature regarding the impact of health information technology on patient engagement and health behavior change.[38] In their summary of 160 papers, 82.9% of papers reported improvement in patient engagement after using IT platforms. The only statistically significant impact, however, was seen in those platforms that were internet based. Seventy-five percent of internet-based IT interventions defined as "usable" showed positive health outcomes. Eleven percent of studies showed no impact on health behavior. Undesirable effects, including increased anxiety, were noted in 18%.

The data that exist are intriguing and suggest a substantial impact on patient engagement and subsequent improvement in health care outcomes. More research is needed, however, to define the impact of social media interventions in the oncology population. We are at a nascent enough point that the questions to be addressed and the mechanism to address them are as of yet undefined, and what is needed is a mechanism to identify the most appropriate mechanism to study the issue. To that end, a group of oncology health professionals interested in social media for improving cancer care has been established to start to explore these questions.[39] COSMO, the Collaboration for Outcomes of Social Media on Oncology, aims to define a mechanism whereby we can better assess the ongoing impact of efforts involving social media to benefit oncology patients. Through these mechanisms and subsequent trials, we can aim to better define whether these are worthwhile efforts in which to continue.

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The Road of Mentorship

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OVERVIEW

Mentorship can be the cornerstone of professional development and career satisfaction. There is literature to support that mentorship not only improves job satisfaction, but also improves productivity, facilitates personal growth, and can rekindle our passion while lessening the risk of compassion fatigue. Mentorship is a developmental relationship that changes as the relationship evolves. There are two broad categories of mentorship: traditional and transformational. There are four subtypes within each of those areas: formal, informal, spot, or peer. Mentorship is critical to the professional development of junior colleagues. Good mentorship is guiding and steering younger partners and other colleagues toward paths of success. As a mentor, one should be looking for opportunities for formal professional development and engagement of mentees. Self-motivation is the hallmark of the successful mentee. The mentee should be able to set his or her own goals, strive to actively seek feedback, ask questions, and keep an accurate record of progress. Although the onus is on the mentee to reach out, mentorship has bidirectional value directly related to the efforts of both parties. There are many benefits to mentorship, such as the promotion of learning, personal development, improved job satisfaction, and improved job performance. Barriers exist, including the rapidly changing landscape of oncology, time constraints, lack of self-awareness, and generational differences. Through a career, mentoring needs will change, as will mentors.

Mentorship can be the cornerstone of professional development and career satisfaction. Although there is not a lot of mentorship research specific to oncology, there is literature to support that mentorship not only improves job satisfaction, but also improves productivity, facilitates personal growth, and can rekindle our passion while lessening the risk of compassion fatigue.[1]

Mentorship is a developmental relationship that changes as the relationship evolves. Like any relationship, there is risk of dysfunction. Mentorship is intended to be a learning relationship to guide individuals in their own way to sort through their career challenges whether directly related to oncology practice or psychosocial functions as an oncologist. Both mentees and mentors must have self-awareness. There needs to be a balance of support and challenge. A mentorship contract can be used to clarify expectations, set boundaries, and define objectives.[2]

It is important to understand what mentorship is not. Mentorship should not be confused with preceptorship. A preceptor is a teacher as in the fellowship model of training. Nor is a mentor a faculty advisor. Mentorship is different from sponsorship. A sponsor is more of a coach or advocate in the work place who has some leadership power who can lean in with you, whereas a mentor listens and guides while providing practical insight and constructive criticism. Ideally, a good mentor helps the mentee achieve his or her full potential. Successful mentorship is a two-way street that requires clear expectations on both the mentee and mentor's parts, open communication, dedication, and feedback along the journey.

There are two broad categories of mentorship: traditional and transformational. Traditional mentorship is the model of the older and wiser physician sharing knowledge and guiding the young and inexperienced physician, as we more often see in academics and research. Conversely, transformational mentorship lacks the hierarchy. The mentor and mentee are considered equals and learn from one another as we often see in the community setting.[1] Within each of those areas, one may engage in formal, informal, spot, or peer mentorship opportunities.

Given different needs, most people will be exposed to all four subtypes of mentorship. Formal mentorship is more structured and may be initiated through a professional organization or institution. For those in research, there is often a formal mentoring relationship in which the mentor is appointed. Informal mentorship often occurs on an ad hoc basis and may exist over a long period. Informal mentoring may be done by colleagues, individuals more senior to you, or even those outside your department or institution. Spot mentoring is typically a single conversation with someone with whom you seek expert advice. For example, you have a complicated patient with a rare malignancy, and you seek

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out your department chair for advice. Lastly is peer mentorship. Peer mentoring is typically a small group of individuals at a similar career stage who meet regularly to support one another.

Although this article focuses on the roles of the mentor and mentee, it is important to recognize that the institution in which they practice also plays a key role. Today, oncologists practice in a variety of settings that impacts options and support for mentorship. Ideally, the institution or practice helps to foster mentorship opportunities. In some settings that means dedicated time or funding, and in other settings, it is formally connecting mentees and mentors. Regardless of the size of the practice or type of setting (academic, government, community, etc.), it is about creating a culture the promotes mentorship and champions the recognition of the mentorship process and the value to the mentee, mentor, and institution. Fostering a culture for mentorship can start in the trenches.

GETTING STARTED

During one's career, mentorship needs change. It is important to assess your needs. For example, during early career, the focus often is in the transition from trainee to attending, technical skills needed for your institution, having difficult conversations, and work-life balance. During midcareer, needs may include professional development, leadership skills, keeping up with the literature, and volunteering (such as on ASCO committees). During late career, needs may focus on becoming a mentor, leadership in the community, and transitioning to retirement.

Once you understand your needs, you seek mentors. It is not about one person meeting all needs. Often you ask mentors for specific areas based on their expertise or your view of them as a role model for that need. For example, as an early career oncologist with less technical skill in end-of-life communication, you may seek guidance from an oncologist who the nurses view as good at those discussions or even the local palliative care provider. It can provide an opportunity for you to exchange expertise. You teach the palliative care provider something about prognostication from an oncology viewpoint, and the palliative care provider helps you improve your skill with having difficult conversations. That type of mentorship could be formal, in which you ask the provider to enter a partnership with that expectation, or the experience could be informal, in which you ask to observe during a family meeting.

As you begin on the journey of mentorship, it is important to be open to formal, informal, spot, and peer mentoring opportunities. Additionally, not all mentors will be oncologists. For example, as a midcareer oncologist wanting to be more active at your local hospital, you may find that your hospital's chief of staff could be a good mentor for leadership skills. Likewise, you may find peers from other institutions at a similar stage in their career that provide an opportunity for peer mentorship in which you learn from one another, sharing knowledge as you grow together. Working as an ASCO volunteer creates many opportunities to network and find mentors or mentees. Attending the ASCO annual meeting provides the chance for spot mentoring as well.

Finally, do not give up. Mentorship to an extent is about chemistry and trust. Often you may find a mentorship opportunity once a friendship has developed. Although similar personalities may create an opportunity to build rapport and foster comfort for open communication, the down side is that it is easier to stay within your comfort zone. Often you may learn more from someone who looks at things from a different perspective.[2]

KEY POINTS

- **Mentorship is a developmental relationship that changes as the relationship evolves and can serve as the cornerstone of professional development and career satisfaction.**
- **There are two broad categories of mentorship: traditional and transformational. Within each of those areas, there are four subtypes of mentorship: formal, informal, spot, or peer.**
- **Mentorship is critical to the professional development of our young colleagues.**
- **Good mentorship is guiding and steering junior partners and other colleagues toward paths of success.**
- **Self-motivation is the hallmark of the successful mentee.**

TENETS OF A GOOD MENTOR

Mentorship is critical to the professional development of our young colleagues. Mentorship relationships may differ from highly structured with very specific goals, assignments, and timelines to less clearly articulated relationships with variable meeting schedules and less deliverables. It must be a relationship that is based on mutual trust and value. It is important to be aligned regarding the goals of the relationship, as the goals in professional development can be variable. Professional success for our colleagues may be based on satisfying certain criteria for advancement—key positions, publications, or managing collaboration. In private practice, success is initially measured by your ability to build a practice, be a good partner, and contribute to your community and later your ability to lead. Mentorship in an academic setting may be a more formalized relationship, whereas mentorship in private practice is often an informal process benchmarked by communication, education, dissemination of social capital, support, and presentation of opportunities for professional growth and development. Leaders in oncology have new skills to learn in managing the organization's business and development needs, leadership, and strategy and managing change.

Good mentorship is guiding and steering junior partners and other colleagues toward paths of success. This may mean introducing them to critical relationships within the institution or community. It also means introducing them to referring physicians, endorsing their addition to the practice, and giving them opportunities to contribute to community or organizational efforts and lead. Sometimes it also means

helping them navigate obstacles and derailing behaviors that could affect professional success. Not all mentorship relationships are formalized. They do not have a particular cadence or duration, though sometimes in more structured relationships, they will. Although formal mentorship relationships may have structured communication timelines, informal mentorship relationships may have varied communication, sometimes communicating several times a week, a few times a month, or only a few months out of the year. Most mentorship relationships span over many years, even decades. Most mentorship relationships have value to both mentor and mentee. In community practice, these relationships are more collaborative, as there is an egalitarian nature to the organizational structure, and in academic settings, these relationships are more hierarchical.

Some of the best advice a mentor can give to a mentee in early practice is the importance of "the four A's" of practice success: ability, availability, affability, and alacrity.[3] There is tremendous value in being ready and happily willing to give good counsel to your referring providers. When you easily help people solve problems, you become their partner in problem solving. With changes in oncology, an individual's success is less about the individual and more about the teams they lead. Expertise in leading teams of clinical and research collaborators and optimizing communication within the team is critical to professional development. With the advent of the oncology care model and other alternative payment models in our practice, we are dependent on well-integrated team-based care. As a practitioner, we are more dependent than ever on the many hands that help the patients we serve.

MEETING NEW LEADERSHIP CHALLENGES: WHAT GOT THEM HERE WILL NOT GET THEM THERE

Mentors help identify sources of professional growth. As a new clinician enters practice, there are a new set of challenges, new competencies that medical training does not prepare you well to navigate, and new obstacles that even mastery of "the four A's" and great team dynamics will not adequately prepare you to tackle. In clinical practice, you have to work with many collaborators: hospital systems, community support organizations, and referring providers. There are also new challenges in understanding the business of medical practice. For most young doctors, the business challenges are new and require some supplemental knowledge. Monthly review of financial statements and understanding the structures of collaboration with these partnering organizations frequently requires additional knowledge of finance, operations, strategic planning, and negotiation. Certainly, leading a practice and managing conflict and challenges internal and external to your practice requires new skill sets. Some doctors pick these new competencies up very naturally, but most of us require additional training. Becoming competent in these areas for a physician leader can help dramatically with leadership success. Advising junior oncologists to consider supplemental education in finance and operations via remote courses (such as www.coursera.org/) and to read books on leadership, conflict resolution, managing change, and influence (such as the *Crucial Conversations* series by Patterson and colleagues). Some physicians may elect to pursue additional degrees, such as a master's degree in business administration or health care administration. In the academic world, the challenges in leadership are also new and require new skill sets. They may include more business knowledge, but certainly require knowledge of leading teams, strategy, and organizational development. As a mentor, one should be looking for opportunities for formal professional development and engagement of mentees.

SIDEBAR. Vital Aspects for Successful Mentorship Partnerships per Allen and Poteet[9]

- Establish an open communication system with reciprocal feedback
- Set standards, goals, and expectations
- Establish trust
- Care for and enjoy each other
- Allow mistakes
- Participate willingly
- Demonstrate flexibility
- Consider constraints to mentoring
- Learn from others
- Work on common tasks
- Be open and comfortable

FORMAL PROFESSIONAL DEVELOPMENT

Identify and recommend formal leadership development for mentees. Many large academic institutions, hospital systems, and large practices have formal leadership development programs. Sometimes these programs can be accessed through professional organizations, like ASCO's leadership development program (www.asco.org/training-education/professional-development/leadership-development-program) or possibly internally within your own group or health system. Some community oncology practices offer formal professional development. For example, Texas Oncology has developed a formal leadership development course that is statewide and resembles a mini-MBA that is managed in collaboration with a local business school. In the US Oncology Network, there are tier I, II, and III leadership-development courses designed for incremental leadership-development training for incrementally invested physicians. Participation in these programs is costly to the mentee in time and money, but formal leadership development is an investment in the future. Physicians are not the only ones who can benefit from this kind of leadership development. When thinking about mentees, we should include advanced practice practitioners, nurse practitioners, and physician assistants. In addition to leadership-development courses, mentees with high development potential may benefit from working with an executive coach.

OPPORTUNITIES FOR ENGAGEMENT

There is not one clear path for engagement, but meeting with your mentee and knowing their professional goals will help you identify opportunities for them to engage and lead. This requires a mentor to engage with their mentees about their goals of professional development, look at the landscape ahead, and know what opportunities they cannot see. Frequently, a mentor will have to leverage his or her social capital on behalf of the mentee to offer opportunities to lead in new arenas. This may come in the form of your recommendation to work with a local hospital or philanthropic group; it may come in the form of fostering engagement with professional organizations like ASCO, American Society for Radiation Oncology, Community Oncology Alliance, and American Association for Cancer Research, making the connections they need so they can lead research within a collaborative group and giving talks at national meetings to make a name for themselves in cancer care.

TENETS OF BEING A GOOD MENTEE

The traditional concept of mentorship in the medical field is primarily derived from academic practice. Academic medicine has long-standing formalized career paths (i.e., clinical track, medical education track, tenure/research track, etc.) with specific timelines, expectations, checklists, and requirements for career advancement that are generally consistent between institutions. These career-advancement guidelines can be readily found through the Office of Faculty Affairs or its equivalent at academic medical schools (e.g., Emory University: http://med.emory.edu/administration/faculty_affairs_dev/promotions.html). The requirements for promotion are some mix of scholarship, teaching, and service based on your specific track. There are even readily available guidelines and recommendations for mentor/mentee conversations according to timeline and academic track (e.g., University of Pennsylvania: www.med.upenn.edu/mentee/documents/mentor_guide.pdf). However, this type of formalism does not exist in the community medical setting, and there is significantly more variability in the concept of what career development means and the role of the mentee and mentor in nonacademic practice.

In community oncology practice, career development has no standard and can represent a variety of different scenarios depending on many factors including: practice type (hospital employed vs. physician owned), practice size, location (urban vs. not), role of research in the growing trend of hybrid-type community-academic practices, practice structure (existence of a cancer center or formal cancer program with physician administration), and involvement with accreditation organizations such as ASCO Quality Oncology Practice Initiative, American Society for Radiation Oncology, and Commission on Cancer, to name a few. An important initial step for the mentee in community practice is to know your specific interests and strengths and have a vision for what you would consider to be a successful career while considering the needs of your practice, group, or organization. In most community practices, the expectation is for a busy clinical practice with additional responsibilities performed either with relatively small amounts of protected time or "on your own time." Because of this structure, it is important not to overextend yourself by making too many commitments or getting involved in too many endeavors that will lead to failure, physician burnout, or both. It is imperative for the mentee to set personal goals and have an idea of individual strengths and what "you can bring to the table" to begin identifying a career path and, consequently, who the ideal mentor would be.

It is typical to have multiple mentors because of the various aspects of community oncology practice. It is common to have a different mentor for patient care/referral relationships, for hospital leadership/committee access and networking, and for research efforts. Another key distinction between academic and community mentorship is motivation. Academic mentors, especially midcareer faculty, are incentivized to provide quality mentorship as part of their advancement criteria, and their track record of successful mentorship is a metric that is scrutinized during the promotion process. That is generally not the case in the community setting, where these formalized systems are not in place. This underscores that the mentee should be aware that their mentors are providing their time, energy, and expertise for little to no external benefit, and as such, the mentee should be self-motivated, take initiative, and have an active role in the relationship, recognize and acknowledge the time and effort their mentor is providing, be flexible and understanding of the mentor's schedule, and be prompt for all interactions.

There is published literature on the characteristics of successful or failed mentoring relationships. A recent study surveyed medical mentors and mentees and found that successful mentoring relationships were characterized by reciprocity, mutual respect, clear expectations, personal connection, and shared values. Failed mentoring relationships were characterized by poor communication, lack of commitment, personality differences, perceived (or real) competition, conflicts of interest, and the mentor's lack of experience.[4] There are many areas of community oncology practice in which strong mentorship can be beneficial. A recent study published survey results of physicians in a community-based mentoring program and demonstrated that participants reported a variety of benefits, including setting goals (62%), planning next steps in their career (60%), gaining new insights (52%), completing a long-deferred goal (30%), reducing stress (19%), and improving self-confidence (19%).[5]

Self-motivation is the hallmark of the successful community-based mentee. The mentee should be able to set his or her own goals, strive to actively seek feedback, ask questions, and keep an accurate record of progress. The mentee cannot expect or rely on the mentor to do the heavy lifting. One of the most important aspects of the mentor is to be a guide on the road of mentorship, directing the mentee toward opportunities, but not doing the work for the mentee. A downside of nonacademic practice is the relatively reduced access to networks that form the governing bodies of

national organizations and journal editorial boards. A mentor can facilitate crossing the initial barrier to entering these organizations, which is usually the most difficult obstacle for successful engagement.

There are pitfalls to avoid as a mentee. Many pitfalls stem from being conflict adverse or lacking confidence. For example, a mentee who eludes conflict may over commit and agree to tasks that are irrelevant to his or her career or even allows himself or herself to be walked over. Someone who lacks confidence may not be comfortable asking for help or questioning the mentor. Vaughn and colleagues describe several mentee missteps to avoid.[6,7] Clear communication is key. Avoid assumptions. Instead, ask for clarification when needed. Feedback and constructive criticism are invaluable. Although the mentee should actively seek and be open to feedback, receiving constructive feedback can be a learned skill to help avoid being defensive or sensitive to criticism. In the community setting, there is generally less hierarchy between the mentor and mentee. It is helpful to know something about your mentor's life outside of work to develop a relationship and improve communication. However, do not try to force a friendship or become artificially close, as that can potentially detract from the intended tone of mutual respect.

The mentor-mentee relationship is meant to be mutually beneficial and has been shown to help with work-life balance and reduce rates of physician stress and burnout.[8] A successful relationship requires investment of time and effort from both the mentee and mentor, and emphasizing certain positive characteristics and avoiding known pitfalls can help maximize the success of both parties. Allen and Poteet[9] assembled details about vital aspects for successful mentorship relationships, which are outlined in the Sidebar.

CONCLUSION

Although the onus is on the mentee to reach out, mentorship has bidirectional value directly related to the efforts of both parties. There are many benefits to mentorship, such as the promotion of learning, personal development, improved job satisfaction, and improved job performance. Barriers exist, including the rapidly changing landscape of oncology, time constraints, lack of self-awareness, and generational differences. Through a career, mentoring needs will change, as will mentors. Nonetheless, mentorship over the long haul will likely result in your transition from mentee to mentor and hopefully maintain your passion for oncology while inspiring other young physicians.

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SARCOMA

Bone Sarcoma Pathology: Diagnostic Approach for Optimal Therapy

Andrew E. Rosenberg, MD

OVERVIEW

The pathologic interpretation of malignant bone tumors is one of the more challenging areas in surgical pathology. This is based on the reality that primary bone sarcomas are uncommon, demonstrate significant morphologic heterogeneity, and have a broad spectrum of biology. Accordingly, it is difficult for pathologists to acquire the necessary experience to confidently and accurately diagnose bone sarcomas. The task is further complicated by the fact that it requires the integration of clinical and radiologic information into the diagnostic process. Lastly, molecular aberrations in sarcomas are being newly discovered and their identification is often critical to make specific diagnoses. The pathologist's role in guiding optimal treatment in biopsy specimens is to make an accurate diagnosis and provide the grade and molecular aberrations when appropriate. The pathology report of resected tumors must confirm this information and assess the surgical resection margins and the percentage of necrosis if the sarcoma has been treated with neoadjuvant systemic therapy.

Sarcomas of the bone often pose diagnostic challenges to pathologists and clinicians. This reality is not surprising, as the tumors are uncommon and morphologically heterogeneous, possess a broad spectrum of biologic behavior, and require specific and complex therapeutic strategies to effect cure. Accurate diagnosis requires an integrated approach that assesses and correlates the clinical, radiologic, histologic, molecular, and prognostic characteristics of the malignancy. In most instances, this is best accomplished when members of a sarcoma multidisciplinary team collaborate to diagnose and stage the tumor and design and implement an optimal treatment plan.[1] Also important in guiding effective treatment is the assessment of tumor necrosis in neoplasms treated with neoadjuvant chemotherapy. This discussion provides fundamental knowledge about bone sarcomas and information that should be included in a pathology report that forms the foundation of patient management.

EPIDEMIOLOGY

The overall frequency of bone tumors is unknown, as most benign tumors are asymptomatic and are only detected as incidental findings. Some benign tumors are quite common, for example, fibrous cortical defects develop in 50% of boys and 20% of girls older than age 2, and hemangiomas of the spine can be identified in at least 10% of the population, indicating that benign tumors of the bone affect many millions of individuals.[2] On the basis of this information, it is estimated that benign bone tumors outnumber their malignant counterparts by at least 10,000 to 1. Accordingly, bone sarcomas are uncommon: they account for 0.2% of all malignancies with approximately 3,020 bone sarcomas newly diagnosed annually in the United States, and they are aggressive, resulting in 1,460 deaths each year.[3] The adjusted incidence rate for all bone and joint malignancies is 0.9 per 100,000 persons per year.

Sarcomas of the bone develop in all age groups. In many instances, however, there is a relationship between the patient's age and the specific location and type of tumor. As a group, bone sarcomas have a bimodal age distribution; the first peak occurs in patients age 10 to 20, and the second develops during the seventh decade of life. The risk of developing a bone sarcoma is equal in both of these age groups, but in absolute numbers, more bone sarcomas are diagnosed during the second decade of life. Statistically, the younger the patient, the more likely a bone tumor is to be benign, because benign tumors outnumber sarcomas, commonly occur in childhood, and diminish in frequency with age. Bone sarcomas affect males and females at a ratio of 1:0.7, and they develop in all parts of the skeleton. Most demonstrate a predilection for the pelvis, axial skeleton, and proximal long bones and rarely affect the small bones of the hands and feet.[4]

CLINICAL PRESENTATION

The clinical presentation of malignant bone tumors is highly variable and generally nonspecific. Symptoms are usually

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localized to the affected site and include pain, swelling, and mechanical disorders. The pain may be intermittent, constant, progressive, and radiating. Long-duration swelling is usually associated with benign lesions, whereas rapid swelling in conjunction with skin changes, such as red violaceous discoloration and the development of prominent blood vessels, is commonly a manifestation of malignancies. Mechanical dysfunction is usually in the form of restricted movement and may result from tumor bulk or synovitis caused by a periarticular mass. Systemic symptoms of fever, fatigue, and weight loss are usually associated with malignant bone neoplasms and are frequently indicative of advanced disease.

A minority (approximately 10%) of malignant primary bone tumors are complicated by a pathologic fracture. The fracture may be the heralding event, and it results from an enlarging tumor that destroys the underlying bone. Minimal trauma eventually causes the bone to fail and break, producing sudden excruciating pain, swelling, and hemorrhage.

CLASSIFICATION

The classification of bone sarcomas is based on the normal cell or tissue type that they recapitulate (Sidebar). The vast majority differentiates along the cell lines or tissue types that compose the skeletal system; only a small number have consistent and distinctive clinicopathologic features but lack a normal tissue counterpart. Further subclassification of bone sarcomas is based on their specific histologic characteristics, their relationship to the underlying bone, the presence of pre-existing conditions, and their biologic potential (i.e., grade). The classification system most commonly used is that presented in the World Health Organization's Classification of Tumours of Soft Tissue and Bone.[5]

GRADING AND PATHOLOGIC STAGING BONE SARCOMAS

The pathologist's attempt to predict the biologic behavior of bone sarcomas is reflected in the histologic grade. Grading systems similar to the National Cancer Institute and Frente Nacional de Combate ao Câncer schemes devised for soft tissue sarcomas have not been developed and universally applied to bone sarcomas. There are, however, grading schemes that some investigators have proposed for specific types of sarcomas, especially chondrosarcoma.[6] Regardless, all bone sarcomas—exclusive of Ewing sarcoma and other poorly differentiated round cell/spindle cell sarcomas, adamantinoma, and chordoma—are typically graded. The three-tiered grading system currently used is based on the assessment of standard morphologic criteria, including the degree of differentiation, cytologic atypia, mitotic activity, and necrosis. The goal of grading sarcoma is to distinguish sarcomas with a low probability of dissemination

KEY POINTS

- **Bone sarcomas are uncommon forms of neoplasms.**
- **An experienced musculoskeletal sarcoma multidisciplinary team should perform the diagnosis and treatment of bone sarcomas.**
- **Bone sarcomas are classified according to their normal tissue counterpart.**
- **Diagnosing bone sarcomas includes the integration of clinical, radiologic, and pathologic information.**
- **Pathology report should include the name and grade of the sarcoma, and for resected tumors, the margin status and assessment of neoadjuvant treatment effect, if used, must be identified.**

SIDEBAR. Classification of Primary Bone Sarcomas

Chondrosarcoma
- Conventional
- Dedifferentiated
- Clear cell
- Mesenchymal
- Secondary

Osteosarcoma
- Conventional
- Chondroblastic, fibroblastic, osteoblastic, mixed
- Parosteal
- Periosteal
- Intramedullary well differentiated
- Surface high grade
- Small cell
- Telangiectatic
- Secondary

Fibrosarcoma

Ewing sarcoma and other round cell sarcomas

Chordoma

Malignant vascular tumors
- Epithelioid hemangioendothelioma
- Pseudomyogenic hemangioendothelioma
- Angiosarcoma
- Kaposi sarcoma

Other uncommon entities
- Adamantinoma
- Liposarcoma
- Leiomyosarcoma
- Malignant peripheral nerve sheath tumor
- Primary non-Hodgkin lymphoma
- Synovial sarcoma

Undifferentiated high-grade pleomorphic sarcoma

(low grade; < 10% chance of metastasis) from those that are aggressive and have a significant risk of systemic spread (high grade; > 10% chance of metastasis). Accordingly, in the three-tiered system, grade 1 sarcomas are low grade and are usually hypocellular to moderately cellular. The tumor cells demonstrate mild cytologic atypia, closely resemble their normal tissue counterparts, and have few if any mitoses and minimal necrosis. For treatment purposes, grade 2 and 3 sarcomas are considered high grade and are moderately to densely cellular. The cells are moderately to severely pleomorphic and hyperchromatic and mitotically active with atypical forms, and a grade 2 or 3 tumor contains areas of necrosis. Generally, the focus of treatment of low-grade sarcomas is local control, whereas systemic therapy combined with local control is used to attempt to cure patients with high-grade sarcomas.

Staging bone sarcomas provides important prognostic information and offers guidelines for effective treatment. The two major staging systems used are those endorsed by the American Joint Commission on Cancer and the Musculoskeletal Tumor Society. The American Joint Commission on Cancer system incorporates tumor grade, size, location in the body, and status and location of metastases.[7] In contrast, the Musculoskeletal Tumor Society staging scheme is more focused on surgical staging and integrates tumor grade, anatomic extent, and presence of metastases.

BONE TUMOR SPECIMENS

The ability to make a primary diagnosis, document recurrence or metastasis, and assess treatment effect is based on the assessment of bone tumor specimens. The different types of tissue specimens include fine-needle aspiration cytology, needle core biopsy, open curettage (which yields multiple, irregular fragments of tissue), and en bloc resection. In specific instances, frozen section analysis can be performed to facilitate diagnosis and assess margin status.

Fine-Needle Aspiration

Cytologic evaluation has been reliably and successfully used for many years in the investigation and diagnosis of metastases to the skeleton. Fine-needle aspiration diagnosis of primary bone tumors is challenging because of the morphologic heterogeneity of the tumors and their relative rarity. Studies have shown that the fine-needle aspiration diagnosis of primary bone tumors has an accuracy rate of 70% to 90% when the goal is distinguishing benign from malignant lesions. Accordingly, it is not a technique that is typically used to render the primary diagnosis and grade the tumor, except in the hands of the most experienced cytologists. Knowledge of the cytologic appearance of primary bone tumors is important, however, because they may be inadvertently aspirated during the work-up of suspected metastatic disease, from which they must be distinguished.

Needle Core Biopsy

Needle core biopsy is often performed with CT or ultrasound guidance; we recommend that a minimum of three cores of tumor-bearing tissue be obtained for diagnosis. A frozen section can be performed on one core to confirm that diagnostic tissue is present, provide a provisional diagnosis, and facilitate triage of the remaining tissue, including generating touch preparation slides for fluorescent in situ hybridization analysis, if appropriate. A portion of the second core can be submitted for cytogenetic karyotype analysis when needed, and the remaining cores can be fixed in formalin and processed routinely for standard hematoxylin and eosin–stained slides. If the tissue requires decalcification, it should be done with solutions that preserve RNA and DNA such as EDTA.

Open Biopsy

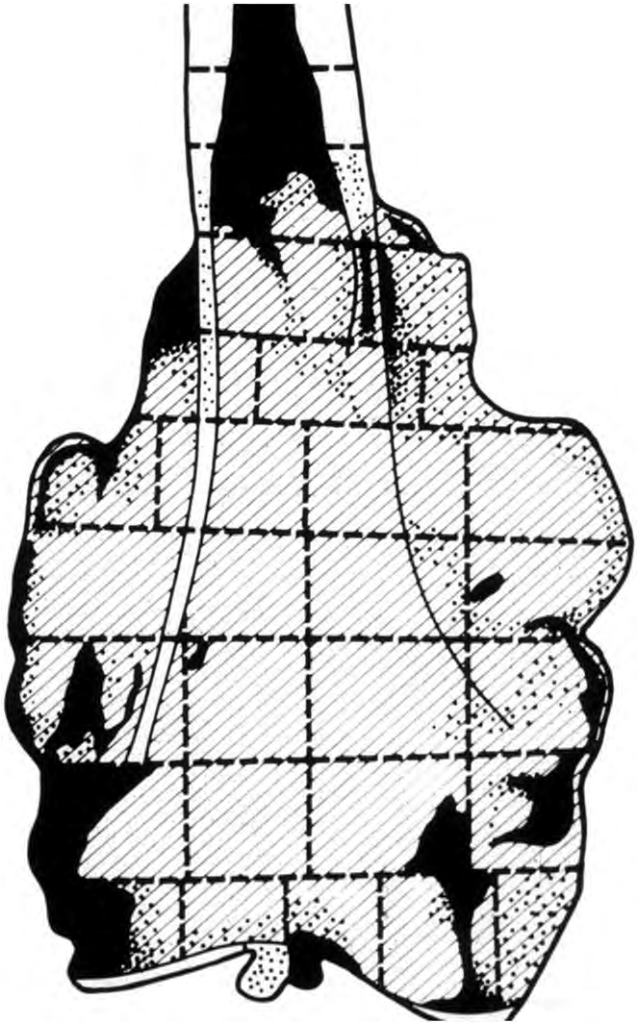
Open biopsy specimens often provide abundant tissue for analysis. These specimens may undergo frozen section analysis (see below) to help provide the surgeon with information that guides therapy at the time of surgery. Definitive curettage specimens should be fixed, decalcified, and thoroughly sampled (minimum of 10 cassettes if enough tissue is present).

Resections

Most malignancies are widely resected en bloc with a rim of normal tissue. The specimen should be oriented, and the soft tissue and bone margins should be carefully assessed grossly. The margins should be inked and the specimen transected with a bone saw along the plane of the greatest dimension of the tumor and its relationship to the closest soft tissue and bone margins. If needed, fresh tumor can be frozen for both diagnostic purposes and tissue triage. Subsequently, in most instances, a longitudinal slab 0.5- to 1-cm thick can be cut from the center of the specimen through the greatest dimension of the tumor. The remaining two hemispheres of tissue can then be "bread-loafed" at 0.5- to 1-cm intervals in the plane perpendicular to the cut surface of the slab. Sections demonstrating the proximity of the tumor to the closest soft tissue and bone margins should be submitted, and the tumor should be carefully dissected and sampled. This usually requires processing a minimum of one cassette per centimeter of tumor. The relationship between the tumor and the surrounding cancellous bone, cortex, articular surfaces, and neighboring soft tissues should be illustrated in some of these sections.

Resected tumors that have been treated with preoperative chemotherapy (osteosarcoma, fibrosarcoma, Ewing sarcoma, and other poorly differentiated round cell/spindle cell sarcomas, dedifferentiated chondrosarcoma, and mesenchymal chondrosarcoma) require determination of the percentage of tumor necrosis. To accomplish this, the central slab of tissue can be imaged and the tumor mapped and blocked out in its entirety (Fig. 1). A section of tumor per centimeter (as determined by its greatest dimension) should be processed from each of the remaining two hemispheres of the specimen. During histologic review, the amount of tumor necrosis on each slide can

FIGURE 1. Diagram for Mapping the Slab for Pathologic Assessment of Tumor Necrosis



be estimated, and these scores can then be averaged to calculate the overall percentage of tumor necrosis (Fig. 2). The location of the areas of viable and necrotic tumor can then be located on the map of the slab section, if necessary.

Frozen Section

Bone tumor specimens often undergo frozen section analysis. The tissue, including bone (except for pieces of cortex), can be frozen to construct a working diagnosis and allow for the appropriate triage of tissue. If the surgeon is going to perform a definitive procedure based on the frozen section diagnosis during the same operation, then all the tissue submitted for initial diagnosis should undergo frozen section analysis to avoid errors based on sampling. The pathologist should also understand the algorithm used by the surgeon to prevent patient mismanagement, and if there is uncertainty with the diagnosis, then it should be deferred until formalin-fixed tissue is available for histologic interpretation.

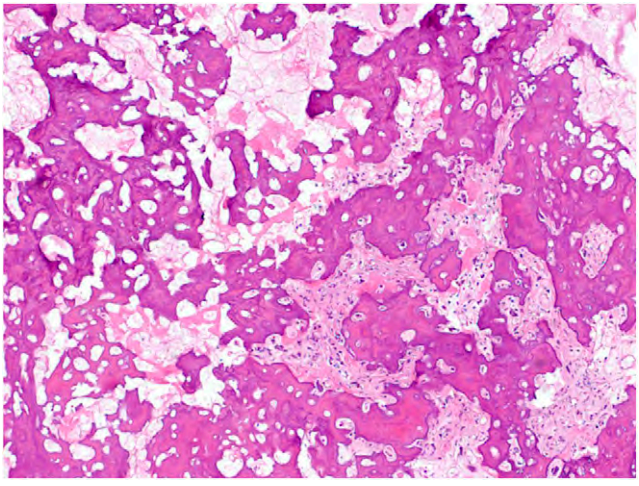
Histologic Distinction of Benign and Malignant Tumors

Distinguishing benign from malignant bone tumors is not always easily accomplished through the assessment of conventional histologic features such as the degree of cellularity, mitotic activity, and necrosis. This is because benign tumors such as chondroblastoma, osteoblastoma, giant cell tumor, and solid aneurysmal bone cyst can be densely cellular, demonstrate many mitoses, and have large areas of necrosis, whereas variants of osteosarcoma, chondrosarcoma, and fibrosarcoma may be relatively hypocellular and have few mitoses and little or no necrosis. Significant pleomorphism and atypia is a telltale sign of malignancy when accompanied by concurrent cellularity and mitotic activity. The absence of these features, however, should be interpreted with caution, as degenerative nuclear atypia, similar to that seen in ancient schwannoma, may be present infrequently in a variety of benign neoplasms.

A very important morphologic feature indicative of malignancy is an infiltrative growth pattern in which the tumor replaces the marrow elements, encases pre-existing bony trabeculae and percolates within haversian systems. This finding is strongly suspicious of malignancy, especially for bone- and cartilage-forming neoplasms. Hemangioma is the only benign tumor that routinely infiltrates the marrow cavity, although infiltration may also be present infrequently in desmoplastic fibroma. Other processes that can cause confusion with infiltration are fracture callus and a tangential plane of section through a well-delineated, but undulating, interface between tumor and surrounding bone. The converse is also important, in that most benign tumors have well-circumscribed margins, and it is uncommon for bone sarcomas to be well delineated along their entire margin.

The pathologic interpretation of bone tumor specimens is best accomplished by surgical pathologists experienced in this subspecialty. Even in the hands of experienced muscu-

FIGURE 2. Osteosarcoma Treated With Preoperative Chemotherapy Show Areas of Necrotic and Viable Tumor



loskeletal multidisciplinary teams, the accuracy of needle biopsy in diagnosing has been reported to be 80.8%, with a diagnostic error rate of 7.1% and nondiagnostic rates of 12.1%.[8]

CLINICAL REPORTING OF BONE TUMOR SPECIMENS

The surgical pathology report of biopsied and resected sarcomas should follow the guidelines proposed by the College of American Pathologists and include tumor type and grade, and if pretreated with cytotoxic therapy, the percentage of tumor necrosis should be indicated. The presence of precursor lesions or other conditions should be identified. The relationship of the tumor to important anatomic structures, such as large neurovascular bundles, articular surfaces, synovium, cruciate ligaments, etc., should be commented on. The status of the closest soft tissue and bone margins and the distances of the tumor to these surfaces must be carefully identified, measured, assessed, and recorded. If special histochemical stains, immunohistochemistry, electron microscopy, karyotype, or molecular analyses have been performed, then the results should be integrated into the report.

CONCLUSION

The accurate diagnosis of bone sarcoma is critical to optimal patient care. This process requires the integration of clinical, radiologic, pathologic, and molecular information so that the clinical treatment team is using optimal therapy based on the precise diagnosis, grade, percentage of necrosis, and surgical margin status of the sarcoma.

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Fertility, Cardiac, and Orthopedic Challenges in Survivors of Adult and Childhood Sarcoma

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OVERVIEW

The combination of cisplatin, doxorubicin, and methotrexate was established as the standard backbone of contemporary osteosarcoma therapy in 1986. Since then, however, further improving the survival of patients with osteosarcoma has been challenging—30% to 40% of patients with osteosarcoma still die of this disease. In addition, these patients often experience loss of fertility at a young age, short- and long-term treatment-related cardiotoxicity, and adverse orthopedic effects from surgical resection of the tumor or endoprosthetic reconstructions. Cancer treatment often markedly increases the risk of infertility later in life, causing many patients substantial distress and regret. Sperm banking and oocyte cryopreservation are standard of care and should be available to all at-risk patients. Newer techniques, such as autologous gonadal tissue transplant for prepubertal children, are being developed, and newer systemic agents have infertility risk profiles that remain undefined and warrant further study. Cost and access remain barriers to these options. The late effects of anthracycline-induced cardiotoxicity are also increasingly a problem for these patients. These effects are often progressive and can be disabling. Adding dexrazoxane to doxorubicin therapy significantly reduces the risk for most adverse cardiac outcomes without compromising the efficacy of induction chemotherapy. Limb salvage surgery remains the standard of care for treatment in the majority of patients with extremity sarcomas. Modular metal prostheses and allograft reconstructions comprised the majority of surgical procedures for limb salvage surgery. The most common mechanism of failure of these implants is infection and mechanical failure of the implant.

Currently, more than 640,000 adolescent and young adult (age 15 to 39) cancer survivors live in the United States. This number is expected to rise sharply during the next decade.[1] Survival depends greatly on the type and stage of cancer, but with a combination of local and systemic treatment, cure rates range from 85% among patients with stage I disease to 10% to 20% for patients with stage IV disease.[2] However, the cure has a cost: the same life-saving surgery, radiation, and anthracycline chemotherapy used to treat cancer often comes with the loss of fertility, early and late cardiotoxicity, and orthopedic problems. These outcomes include loss of spermatogenesis and premature ovarian failure; acute cardiomyopathy during chemotherapy and late cardiomyopathy in subsequent decades; infections and complications of limb-salvage surgery; and death.[3,4]

PRESERVING FERTILITY IN PATIENTS WITH SARCOMA

Oncofertility is a term coined in 2006 to describe the specific care patients with cancer require to preserve their present or future reproductive capacity.[5] The field is at the intersection of reproductive specialists and oncologists, and is designed to bring more and better reproductive options to cancer survivors.

Infertility can be distressing for adolescents and young adults, particularly those who have not started their own families. The effects of cancer-related infertility are long-standing, with increased grief and decreased quality of life reported even 10 years after diagnosis.[6,7] Up to 75% of nulliparous patients report wanting to have children.[8] Soft tissue sarcoma comprises 7% of the total number of cancer cases, and disproportionately affects children: it is the third most common childhood cancer,[9] accounting for 20% of cancers in children and 10% in adolescents and young adults.[10] It can present in a wide variety of locations and histologic types, with rhabdomyosarcoma accounting for almost one-half of cases.[9] As a result of the wide prevalence of soft tissue sarcomas among adolescents, and because treatment can typically result in infertility, efforts to preserve fertility before therapy can be beneficial in young patients with sarcoma.

As tumors of muscle and bone, sarcomas can arise anywhere in the body, especially in the thigh, pelvis, and

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retroperitoneum. Therefore, reproductive organs can potentially be in the radiation field or within the scatter region for radiation therapy. Increasingly complex treatment techniques, such as intensity-modulated radiation therapy, may improve clinical outcomes, although a larger area can be exposed to radiation, albeit at lower doses.[11] For males, even cumulative doses as low as 2 Gy to the gonads can affect fertility. For females, the damaging dose is age dependent; lower radiation doses can affect fertility more as age increases,[12] probably because of the natural decrease in the number of follicles with aging. Thus, the radiation dose most likely to cause ovarian failure decreases from 15 Gy in girls to 6 Gy in women.[13,14]

Systemic multiagent therapy, which includes alkylating agents, for patients with high-grade sarcoma is individualized, yet a concern for later fertility issues. Systemic therapy is considered a principle backbone of therapy for certain sarcomas, including Ewing sarcoma and rhabdomyosarcoma. It is well known that alkylating agents as part of systematic therapy can decrease fertility in both male and female cancer survivors.[15] In males, it inhibits spermatogenesis and can cause prolonged azoospermia. Although this effect is dose-dependent,[16,17] and though efforts are always made to avoid a toxic dose, the effects in combination regimens are additive and not fully understood.[18] Dacarbazine and taxanes usually cause only temporary sterility, but they can also have an additive effect when combined with alkylating agents.[19]

In females with sarcoma, abdominal or pelvic irradiation decreases ovarian reserves. Any radiation exposure to the uterus or ovaries increases the risk of infertility, and higher doses of radiation further increase this risk.[15] Additionally, alkylating agents commonly used for sarcoma, such as ifosfamide, carry a high risk of amenorrhea and subsequent infertility.[20]

All patients with sarcoma should be informed of the increased risk of infertility from treatment. If they are interested, or even undecided, they should be offered a fertility consult and a referral to a specialist as soon as possible, ideally before treatment is initiated.[21]

Options for preserving fertility continue to evolve. For males, sperm banking before treatment is the best way to preserve fertility. Before chemotherapy, viable sperm may be collected by masturbation, penile vibrostimulation, electroejaculation, or, in rare cases, testicular sperm extraction. Semen samples must be analyzed to ensure the presence of sperm. If sperm are absent or in sexually immature patients, sperm can be extracted by testicular biopsy.[22]

Both testicular sperm and cryopreserved ejaculated sperm require assisted reproduction with intracytoplasmic sperm injection for conception. After chemotherapy, nonobstructive azoospermia can also be treated with testicular sperm extraction, but success rates are limited, reaching 20% after exposure to alkylating agents.[23] Unfortunately, spermatogenesis is not always recovered, and a pregnancy can only be achieved through a sperm donor.

In females, age is critically important because follicular reserve decreases with time and decreases further with cancer treatment.[24] Given the potential impact of cancer treatment on female fertility, the risk of infertility and fertility preservation options should be discussed before cancer therapy is initiated. After cancer therapy is complete, fertility treatments may be less successful and many patients will often require donor eggs or surrogates.[21]

Oncofertility options for women most commonly include embryo and oocyte cryopreservation. Despite a high success rate and being a validated method for preserving fertility, embryo cryopreservation presents a unique problem: it requires sperm from the patient's partner or a donor, which is an unrealistic option for minors.[21] Oocyte cryopreservation is a practical alternative and should be recommended to all female patients at risk for infertility, with appropriate counseling. The process requires injecting follicle-stimulating hormone for egg retrieval, and it is only possible in post-pubertal females.[25] Delay in starting cancer therapy is a strong concern because a complete ovulation-and-egg retrieval cycle can take up to 4 weeks. However, with options such as natural cycle stimulation, egg retrieval can be done in less than 2 weeks.[26]

Other options for preserving fertility in prepubertal patients remain experimental. These options include in vitro maturation of immature eggs, autologous transplantation of cryopreserved ovarian tissue, and cryopreservation of testicular tissue.[21]

Oncofertility is a developing field for which the future still holds several challenges, from educating providers to determining the effects of new therapeutic agents on fertility. Newer agents that have improved survival in patients with sarcoma include trabectedin, a new DNA-binding molecule,[27] and several molecular-targeted agents including pazopanib and sunitinib, which are multikinase angiogenesis inhibitors,[28,29] and crizotinib and imatinib, which inhibit tyrosine kinases.[30,31] Animal studies show that targeted molecules are generally safer for fertility than conventional chemotherapy,[32] but long-term studies in humans are still required.

The biggest challenge of oncofertility is providing access to care to all patients. Costs can be prohibitive and are currently not covered by most insurance companies.[33]

KEY POINTS

- **Preserving fertility, treating cardiotoxicity, and minimizing orthopedic interventions and complications are integral aspects of caring for patients with sarcoma.**
- **Sperm banking and oocyte cryopreservation should be considered for all patients at risk of losing fertility.**
- **Adding the cardioprotectant dexrazoxane to cancer treatment can reduce anthracycline-related cardiotoxicity without compromising efficacy.**
- **Tumor resection and failed limb-preserving surgeries can result in serious infections and complications.**
- **The increasing number of survivors of sarcoma makes studying the late effects of treatment more important.**

TABLE 1. Cardiotoxic Effects of Selected Cytotoxic Agents

Treatment	Cardiotoxic Effect
Anthracyclines Daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone	Arrhythmias, pericarditis, myocarditis, HF, LV dysfunction
Liposomal anthracyclines Pegylated liposomal doxorubicin hydrochloride (DOXIL, CAELYX)	HF, LV dysfunction, arrhythmias
Antimetabolites Capecitabine, carmustine, clofarabine, cytarabine, 5-fluorouracil, methotrexate	Ischemia, chest pain, MI, HF, arrhythmias, pericardial effusions, pericarditis, hemodynamic abnormalities
Antimicrotubule agents Paclitaxel, vinca alkaloids	Hypotension or hypertension, ischemia, angina, MI, bradycardia, arrhythmias, conduction abnormalities, HF
Alkylating agents Busulfan, chlormethine, cisplatin, cyclophosphamide, ifosfamide, mitomycin	Endomyocardial fibrosis, pericarditis, tamponade, ischemia, MI, hypertension, myocarditis, HF, arrhythmias
Small-molecule tyrosine kinase inhibitors Dasatinib, gefitinib, imatinib mesylate, lapatinib, erlotinib, sorafenib, sunitinib	HF, edema, pericardial effusion, pericarditis, hypertension, arrhythmias, prolonged QT interval, ischemia, chest pain
Monoclonal antibodies Alemtuzumab, bevacizumab, cetuximab, rituximab, trastuzumab	Hemodynamic abnormalities, LV dysfunction, HF, thromboembolism, angioedema, arrhythmias
Interleukins Denileukin, IL-2	Hypotension, capillary leak syndrome, arrhythmias, coronary artery thrombosis, ischemia, LV dysfunction
Miscellaneous agents All-retinoic acid, arsenic trioxide, asparaginase, etoposide, IFN-α, lenalidomide, 6-mercaptopurine, pentostatin, teniposide, thalidomide	Electrocardiographic changes, QT prolongation, torsades de pointes, other arrhythmias, ischemia, angina, MI, HF, edema, hypotension, bradycardia, thromboembolism, and retinoid acid syndrome that includes fever, hypotension, respiratory distress, weight gain, peripheral edema, pleural-pericardial effusions

Abbreviations: HF, heart failure; LV, left ventricular; MI, myocardial infarction.

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CARDIO-ONCOLOGY IN SARCOMA SURVIVORSHIP

Table 1 summarizes cardiotoxic effects of select cytotoxic therapies. Doxorubicin is a major agent for treating osteosarcoma. Event-free survival is lower in regimens with lower cumulative doses or dose-intensity, but higher doses increase the risk of cardiotoxicity.[34,35] The cumulative doxorubicin dose (up to 450 mg/m^2) currently used in the United States to treat osteosarcoma is associated with acute cardiomyopathy during chemotherapy, late cardiomyopathy in subsequent decades, and death (Table 2). The hazard ratio of adverse cardiac outcomes in survivors who receive more than 250 mg/m^2 of anthracycline is two to five times as high as it is in those receiving doses less than 250 mg/m^2.[36] After 300 to 450 mg/m^2 of doxorubicin, the incidence of cardiomyopathy is readily apparent, with more than 25% of patients experiencing left ventricular systolic dysfunction beyond 15 years of follow-up.[37] Many long-term survivors are now between age 40 and 50, and they remain at risk for cardiac deterioration for the rest of their lives.

Trials using doxorubicin for osteosarcoma have reported a substantial incidence of acute cardiotoxicity. In one trial of 31 children and adults, cardiotoxicity required stopping doxorubicin administration in four patients.[39] In another, six of 164 patients experienced severe cardiotoxicity; five patients experienced events within 12 weeks of completing therapy.[40]

In 120 children and adults treated with bolus doses of doxorubicin in childhood (87 for acute lymphoblastic leukemia and 33 for nonmetastatic osteogenic sarcoma), 12 had transient early heart failure during or within 1 year after completing doxorubicin treatment.[41] Heart failure occurred later in 12 patients, seven of whom had also had early heart failure 3 to 16 years before. In three of the 12 patients with late heart failure, medical treatment failed; one underwent heart transplantation, one underwent heart-lung transplantation, and one died of documented ventricular fibrillation. Another five had initial episodes of heart failure at a mean of 10 years after completing doxorubicin treatment, including two women during the peripartum period and one during nonanthracycline chemotherapy for a relapse of cancer. When patients with clinical evidence of cardiotoxicity were excluded, the results were similar.[41]

Risk factors for cardiotoxicity with anthracycline therapy are described in Table 3. Multivariate analysis in this trial revealed that female sex and higher cumulative doxorubicin doses were associated with depressed left ventricular contractility ($p < .001$) and that these two variables interacted.[41] Independent and significant associations were found between a higher rate of administration of doxorubicin and increased left ventricular afterload ($p < .001$), left ventricular dilation, and depressed left ventricular function; between a higher cumulative doxorubicin dose and depressed left ventricular function ($p < .001$); between younger age at diagnosis and reduced left ventricular wall

TABLE 2. Characteristics of Different Types of Anthracycline Cardiotoxicity

Characteristic	Acute Cardiotoxicity	Early-Onset Progressive Cardiotoxicity	Late-Onset Progressive Cardiotoxicity
Onset	Within the first week of anthracycline treatment	< 1 year after completion of anthracycline treatment	≥ 1 year after completion of anthracycline treatment
Risk factor dependence	Unknown	Yes[a]	Yes[a]
Clinical features in adults	Transient depression of myocardial contractility	Dilated cardiomyopathy	Dilated cardiomyopathy
Clinical features in children	Transient depression of myocardial contractility	Restrictive cardiomyopathy and/or dilated cardiomyopathy	Restrictive cardiomyopathy and/or dilated cardiomyopathy
Course	Usually reversible after discontinuation of anthracycline	Can be progressive	Can be progressive

[a]See Table 3 for risk factors.

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thickness and mass and increased afterload; and between a longer time since completing doxorubicin therapy and reduced left ventricular wall thickness and increased afterload ($p < .001$).[41]

Late cardiotoxic effects of doxorubicin are increasingly a problem for survivors of childhood cancer. This cardiotoxicity is often progressive and can be disabling. However, given the efficacy of doxorubicin in treating childhood cancers, including osteosarcoma, many treatment initiatives have focused on preventing doxorubicin-related cardiotoxicity.

Dexrazoxane is a topoisomerase II inhibitor that protects against anthracycline-related cardiotoxicity, probably by scavenging free radicals and chelating heavy metals or by preventing the topoisomerase IIB–mediated DNA and mitochondrial damage induced by doxorubicin.[43,44] Used initially for cardioprotection in clinical trials of women with breast cancer receiving doxorubicin, dexrazoxane decreased the expected cardiotoxicity.[43] A recent meta-analysis of dexrazoxane use in children found that it substantially reduced the risk for most adverse cardiac outcomes.[45,46] In a study of 101 children with newly diagnosed metastatic osteosarcoma treated with trastuzumab, a humanized monoclonal antibody targeting HER2, in combination with cytotoxic chemotherapy and dexrazoxane, no patient developed clinical evidence of congestive heart failure after an average of 41.6 months of follow-up time.[47]

Dexrazoxane protects against cardiotoxicity without adverse outcomes in a wide range of cancers.[48] Its use has been endorsed by the American Heart Association and the American Academy of Pediatrics as a cardioprotectant in children and adolescents undergoing anthracycline-containing treatment protocols.[48] Doxorubicin has been used as the standard of good clinical care for all Dana-Farber Cancer Institute high-risk childhood acute lymphoblastic leukemia protocols involving anthracycline therapy since 2000 and on all Children's Oncology Group protocols involving treatment with at least 150 mg/m^2 doxorubicin or anthracycline administration at any dose with planned radiation treatment portals that may impact the heart since 2015.[49]

In a trial of children with osteosarcoma randomly assigned to receive doxorubicin with or without dexrazoxane, the dexrazoxane-treated children maintained higher mean left ventricular fractional shortening and were able to receive more doxorubicin.[50] In another trial, dexrazoxane reduced acute cardiotoxicity in young patients with sarcoma, but sample size limited the assessment of oncologic efficacy.[51] In a preliminary analysis of Children's Oncology Group protocols with random dexrazoxane assignments, long-term survivors of childhood cancer treated with doxorubicin and dexrazoxane appeared to have more preserved systolic function and reduced myocardial wall stress compared with

TABLE 3. Risk Factors for Anthracycline-Induced Cardiotoxicity

Risk Factors	Features
Total cumulative dose	Most important predictor of abnormal cardiac function
Age	For similar cumulative doses, younger age predisposes to greater cardiotoxicity (especially < 5 years)
Length of follow-up	Longer follow-up reveals higher prevalence of myocardial impairment
Sex	Females more vulnerable than males for similar doses
Concomitant mantle irradiation	Evidence of enhanced cardiotoxicity; not clear whether additive or synergistic
Others	Concomitant exposure to cyclophosphamide, bleomycin, vincristine, amsacrine, or mitoxantrone may predispose to cardiotoxicity; trisomy 21 and black race have been associated with a higher risk of early clinical cardiotoxicity
Rate of anthracycline administration	Higher rate was thought to predispose to greater toxicity, but current trials in children do not support this finding

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survivors treated with doxorubicin alone.[52] Schwartz et al showed that dexrazoxane did not interfere with the tumor cytotoxicity of preoperative induction chemotherapy in 242 children with leukemia enrolled in Children's Oncology Group protocol P9754.[53] Dexrazoxane was also not associated with acute cardiotoxicity in patients receiving either standard (450 mg/m^2) or intensified (600 mg/m^2) doses of doxorubicin.[53] Thus, dexrazoxane does not compromise response to induction chemotherapy.

In the study by Schwartz et al,[53] dexrazoxane was safely administered. It did not impair tumor response or interfere with cancer treatment efficacy. It also did not significantly increase the risk of secondary malignancy, and it allowed the cumulative doxorubicin dose to be increased in standard responders to induction chemotherapy. As well, in a randomized study of dexrazoxane administration with more than 12 years of follow-up, overall mortality did not differ by dexrazoxane status in three childhood cancer trials (1,008 patients).[54] These findings support the use of dexrazoxane in children and adolescents with osteosarcoma as it permits anthracycline dose-density increases without compromising overall long-term survival.

Cardiotoxicity secondary to anthracycline chemotherapy can be a devastating late effect of osteosarcoma treatment. Not only may it cause death and increase health care costs, but cardiac death was the second most common cause of late mortality in childhood cancer survivors reported by the Children's Cancer Survivor Study.[55] Heart failure, myocardial infarction, pericardial disease, and valvar abnormalities were substantially more prevalent in these patients than they were in siblings of cancer survivors.[36,56]

LONG-TERM OUTCOMES OF PATIENTS WITH SARCOMA AFTER ORTHOPEDIC SURGERY

Limb-salvage surgery remains the standard of care for treating patients with sarcomas of the long bones and is successful in about 90% of cases.[57] Innovations in implant design have increased the longevity of modular metal prostheses. Progress in allograft donation and processing has increased availability and survivability of allograft reconstructions. Despite advances in infection management and antibiotic development, the most common mechanism of failure in orthopedic interventions after treatment of sarcoma is infection. The second most common mechanism is failure of the construct from mechanical failure of the implant, whether from loosening of the implant away from the host or the fracture of the implant itself.[57-63] Amputation remains an option for these patients, and advances in prosthetic limbs allow a more active lifestyle, making this option more acceptable to patients.[64]

Bone Sarcomas

In bone sarcomas, after the primary lesion is removed, bones can be treated with what are termed the Five As: allograft, arthrodesis, arthroplasty (implanting metal modular oncologic endoprostheses), autograft, and amputation. The most common methods are arthroplasty and allograft. The method of reconstruction depends on the type of surgical resection (intercalary or intra-articular), the degree of residual bone loss, and the age of the patient. Adults more commonly receive modular endoprostheses, which allow immediate stability, immediate weight bearing, and do not rely on osseous integration as heavily as do allografts. The small bones and joints of younger and skeletally immature patients, as well as their potential growth, pose additional challenges.[59,61] Allografts often allow unique surgical approaches that can spare growth plates and thus are more commonly used in children.

Overall implant survival at 15 years for all endoprosthetic reconstructions is 80%.[57-63] Success is generally better in the upper arm than in the lower arm or the leg. Most limb-salvage procedures involve the proximal femur, the knee, and the distal femur or proximal tibia. Survival for proximal femur replacement is 93% at 5 years and 85% at 15 years.[62] Modular oncologic prostheses about the knee have about a 22% failure rate at 10 years. Infection is the most common mechanism of failure and has been up to 10% in large series.[62] The mechanism is aseptic loosening in about 5% of cases and implant fracture or failure in about 2%.[62] Functional outcome scores average 91%. Causes of prosthetic failure include soft-tissue failure, aseptic loosening, structural failure of the implant, infection, and local tumor recurrence.[57-63]

Overall allograft survival at 15 years is 70%.[65] As with modular prostheses, most reconstructions occur about the knee. Allograft reconstructions about the knee have about a 32% risk of failure at 10 years.[58,65] The primary mechanism of failure is infection. The 10-year risk of amputation is 11%. Functional outcome scores average 88%.[58] The most common mechanisms of failure are infection and failure of the reconstruction secondary to septic loosening and failure of the implant from infection, wear, or mechanical stresses at the host-bone interface that precludes long-term healing and osseous integration.

Infection is the most common method of failure for any long-bone reconstruction after sarcoma surgery.[57-65] Patients with a bone sarcoma typically undergo resection and reconstruction in combination after chemotherapy and are accordingly at risk for infection while immunosuppressed. Large surgical wounds are at particular risk for wound-healing complications. Breaching the skin can increase the risk of wound breakdown and infection, both of which endanger the reconstruction. The large bone defect left after resecting implants or allografts often precludes limb-salvage surgery and thus results in amputation.[58,59,64]

All methods of reconstruction are subject to failure-of-construct. In the setting of allograft, autograft and arthrodesis, failure of the allograft to heal to the host bone will allow the hardware to fail over time. The resulting hardware failure, pain, and subsequent revision surgeries may lead to amputation. Arthroplasty, especially to place a modular oncologic prosthesis or mega prosthesis, is uniquely susceptible to aseptic loosening. The large volume of bone loss places substantial stress on the bond between the implant

and the host site. This bond is often fixed with cement, and rotation forces incurred at this site are particularly likely to loosen it. Implant fixation techniques that foster osseous integration may improve long-term outcomes, but the weight bearing surfaces of these implants are still subject to wear at the bearing surfaces, especially in the young population who have more cycles on an implant.

Unique surgical procedures for children include vascularized bone grafting, rotationplasty, and growing prostheses.[59,61] The unique nature and small number of these procedures limits the amount of data about them. However, outcomes, such as retaining the limb with the use of an allograft, arthroplasty, or vascularized autograft, are better for both physical functioning and emotional acceptance than they are for amputation, which includes ablative surgery and rotationplasty.[59]

Pelvic reconstruction after sarcoma surgery also has unique circumstances and complications.[66] These reconstructions can include allografts, metal prostheses, or, alternatively, no reconstruction at all. Patient satisfaction varies, depending on volume of the pelvis removed and the age of patient at the time of resection. Patients who do not undergo reconstruction after pelvic resection (flail limb) have fewer complications and higher satisfaction scores.[66]

Soft Tissue Sarcomas

Most soft tissue sarcomas occur in adults, although the complications are quite similar in some soft tissue sarcomas in children, except for those related to growth. Soft tissue sarcomas are commonly treated with surgical resection and radiation therapy, which are responsible for complications. Radiation therapy involving the growth plate of a bone may halt growth in that bone. In addition, short- and long-term complications from treating soft tissue sarcomas can be related to surgery when combined with radiation therapy. Wound healing complications and fibrosis are the most common complications.

Preoperative radiation therapy is delivered in a lower dose to a smaller field, but the short-term insult to the skin interferes with early wound healing, which can lead to further stiffness, given the need for surgical debridement and wound care. Stiffness reduces the range of motion, limiting mobility and increasing pain. Radiation therapy after surgery provides a larger field and a higher dose, which can contribute to larger areas of stiffness and lymphedema. Radiation to large, deep, high-grade sarcomas can also contribute to radiation necrosis, with short-or long-term effects, including bone fractures requiring intramedullary fixation and the need to remove necrotic bone.[64] Once the bone has become necrotic, attempts to support bone healing without resection are fraught with complications, including multiple surgical procedures, pain, and unsatisfactory results.[67]

CONCLUSION

Worldwide, more than 28 million people live with cancer. This number could triple by 2030. With the increasing number of patients and improvements in cancer management that continue to reduce cancer death rates, the number of survivors is projected to increase rapidly, especially among those afflicted during childhood. In children and adolescents, the survival rate has jumped from fewer than 50% in the mid-1970s to 80% today. The growing population of childhood survivors is notable for its vulnerability to adverse health outcomes, many of which may not become clinically apparent until years after therapy has been completed.[38] Loss of fertility, cardiotoxicity, and orthopedic complications are three such adverse outcomes.

For prepubertal patients, preserving and perhaps transplanting testicular and ovarian immature tissue should be discussed as experimental options. The data support the use of the cardioprotectant dexrazoxane for all children who require anthracycline therapy for treatment of osteosarcoma to mitigate or prevent the development of cardiotoxicity, and developments in limb-salvage surgery should improve the orthopedic outcomes in these patients.

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The Current Landscape of Early Drug Development for Patients With Sarcoma

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OVERVIEW

Until recently, advancements in the treatment of patients with adult soft tissue sarcomas have been relatively slow. This is, in part, due to their heterogeneity and rarity. A better understanding of the biology and differences among the various histologies has led to substantial growth in novel strategies. In addition to novel cytotoxic chemotherapies, agents targeting platelet-derived growth factor receptor-α (PDGFRα), mTOR, and angiogenesis are areas of active investigation. Additionally, with the success of checkpoint inhibitors in other malignancies and early encouraging results of checkpoint inhibitors in some sarcoma subtypes, this approach is being widely investigated in various sarcomas. As we increasingly recognize and treat each sarcoma histology as a separate disease, it is important to spread awareness of the exciting clinical trials available to our patients with these rare malignancies.

Adult sarcomas are a complex and heterogeneous group of neoplasms. This complexity and their rarity hinder drug development, making advancements for patients with sarcoma frustratingly slow. Not only do these malignancies arise from distinct mesenchymal tissues such as adipocytic and smooth muscle, but within each subset exist histologies that behave very differently. Historically, sarcoma clinical trials have included all adult soft histologies, making it nearly impossible to see the efficacy of a particular treatment by diluting any potential effect. Fortunately, there has been major progress in the last few years. By recognizing sarcomas as the separate entities that they are and narrowing the types of sarcomas studied, two drugs have been approved by the U.S. Food and Drug Administration in the last year.

Despite the fact that sarcomas account for about 1% of all adult cancers, patients with sarcomas have accounted for a higher proportion of patients entered into phase I clinical trials. Classically, phase I trials have been dose-finding and toxicity-defining studies open to patients with all cancer types. However, recently, there has been greater emphasis on the initiation of phase I trials with an underlying biologic rationale that are limited to specific tumor types.

The sarcoma community has made major advancements in the understanding of the biology and drivers of several sarcomas. Notable examples are the approval of the tyrosine kinase inhibitor, imatinib, in gastrointestinal stromal tumors (GISTs) and dermatofibrosarcoma protuberans, and denosumab in giant-cell tumor of bone. These success stories have led to an increased interest in drug development in individual sarcomas, with many trials now enrolling specific sarcoma subtypes (Table 1).

EARLY-PHASE CHEMOTHERAPY AND TARGETED THERAPY TRIALS FOR PATIENTS WITH ADVANCED SARCOMA

Gastrointestinal Stromal Tumors

There are now three approved agents for patients with metastatic GISTs: imatinib, sunitinib, and regorafenib. However, there remains an unmet medical need for patients with GISTs whose disease is resistant to these three drugs and for patients with tumors harboring mutations resistant to the approved drugs. One of the mutations known to be resistant is the platelet-derived growth factor receptor-α (PDGFRα) D842V mutation. Although this is a rare molecular subtype of a rare disease, the treatment of patients is challenging. There are currently two drugs in development specifically for patients with tumors harboring this mutation.

Crenolanib is a type I, small-molecule inhibitor of FLT3 and PDGFGRα (including the D842V mutation). In a phase I/II trial, crenolanib demonstrated activity in PDGFRα D842V mutant GISTs, with three out of 16 partial responses and three out of 16 patients achieving stable disease. Furthermore, seven patients continued receiving crenolanib for over 6 months, and one patient each for 1 and 2 years, respectively. In addition, this agent was well tolerated. Consequently, a randomized, placebo-controlled trial of crenolanib in patients with GIST with tumors harboring the D842V mutation is in development (NCT02847429).

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TABLE 1. Select Targeted and Immunotherapy Trials in Soft Tissue Sarcomas

Trial Number	Histology	Drug	Target
NCT00942877	ASPS	Cediranib	VEGFR1-3
NCT01755195	STS	Cabozantinib	VEGFR2/MET
NCT01879085	STS	Vorinostat/gemcitabine/doectaxel	HDAC/cyctoxic
NCT02584647	MPSNT/STS	Pexidartinib/sirolimus	CSF-1R and KIT and Flt3/mTOR
NCT02846987	DD-LPS	Abemaciclib	CDK4/6
NCT03009201	STS	Ribociclib/doxorubicin	CDK4/6 and cytotoxic
NCT02601950	Synovial/INI1– tumors	Tazemetostat	EZH2
NCT02048371	LPS/bone	Regorafenib	VEGFR/PDGFR
NCT01391962	ASPS	Sunitinib vs. cediranib	VEGFR1-3
NCT02609984	Synovial/RC-LPS	CMB305/atezolizumab	NY-ESO-1 and PD-L1
NCT02979899	Angiosarcoma	TRC105/pazopanib	Endoglin/TRC105
NCT00902044	HER2+ sarcoma	HER2 CAR T cells	HER2
NCT02636725	ASPS/STS	Axitinib/pembrolizumab	VEGFR1-3 and PD-1
NCT01803152	STS	Dendritic cell vaccine with or without gemcitabine	T-cell proliferation
NCT02180698	STS	GLA-SE/radiation	TLR4
NCT02888665	STS	Doxorubicin/pembrolizumab	Cytotoxic and PD-1
NCT02815995	Multiple cohorts	Durvalumab/tremelimumab	PD-L1 and CTLA-4

Abbreviations: ASPS, alveolar soft part sarcoma; CAR, chimeric antigen receptor; DD-LPS, dedifferentiated liposarcoma; EZH2, enhancer of zeste homolog 2; GLA-SE, glucopyranosyl lipid adjuvant-stable emulsion; HDAC, histone deacetylases; LPS, liposarcoma; MPNST; malignant peripheral nerve sheath tumor; PDGFR, platelet-derived growth factor receptor; RC-LPS, round cell liposarcoma; STS, soft tissue sarcoma; TLR4, toll-like receptor 4.

Blu-285 is an oral mutation-specific inhibitor of PDGFRα D842V and KIT D816V and is currently in phase I development (NCT02508532). Although still in dose escalation, this drug has shown antitumor activity, with reduction in tumor size in 11 out of 12 patients with D842V tumors. The drug is well tolerated. Furthermore, updated results will be presented at the 2017 ASCO Annual Meeting.

DCC-2618 is a pan-KIT and PDFRα inhibitor in phase I development that has also reported encouraging clinical efficacy in pretreated metastatic GISTs (NCT02571036). An initial presentation of 24 enrolled patients reported seven metabolic responses by PET in seven KIT mutant GISTs. The most common treatment-emergent adverse events have included fatigue, lipase elevation, dyspnea, anemia, and decreased appetite.

KEY POINTS

- **Histology-based preclinical and clinical research has led to recent advancements in the treatment of patients with sarcoma.**
- **Early-phase clinical trials provide important treatment options for patients with certain sarcoma subtypes.**
- **Important molecularly defined subsets of gastrointestinal stromal tumors (GISTs) are primarily resistant or develop rapid secondary resistance to imatinib, which has led to several novel tyrosine kinase inhibitor trials for patients with GISTs.**
- **Novel approaches of targeting the immune system in sarcomas include targeting NY-ESO–expressing tumors and adoptive chimeric antigen receptor T-cell strategies.**
- **Single-agent checkpoint inhibitors have shown modest efficacy in only select sarcoma subtypes; thus, much of the focus is now on combined strategies such as radiation or tyrosine kinase inhibitors in combination with immunotherapies.**

Angiosarcoma

Angiosarcomas are aggressive tumors of endothelial origin associated with a very poor outcome. Endoglin is a protein that is overexpressed on endothelial cells and is essential for angiogenesis. Endoglin is upregulated, following VEGF inhibition, and enables continued angiogenesis despite this inhibition. Therefore, by targeting endoglin (which is upregulated following VEGF inhibition) and because endoglin is highly expressed in angiosarcoma, there is a clear rationale for combing anti-endoglin therapy with pazopanib. TRC105 is an anti-endoglin antibody that has shown promise in a phase IB/II trial. Of five originally enrolled patients with angiosarcoma, the progression-free survival was equal to or greater than 16.6 months.[1] An additional nine patients with angiosarcoma were treated with a combination of tRC105 and pazopanib with a median progression-free survival of 5.59 months, and notably, three of these patients had progressed on prior pazopanib. Based on these data, a randomized phase III trial of pazopanib with or without TRC105 will be performed in patients with metastatic angiosarcoma. The Italian Sarcoma Group is conducting a trial of trabectedin in combination with the PARP-inhibitor olaparib (NCT02398058).

Anthracyclines

GPX-150 is a doxorubicin analog that has shown promise in early-stage clinical trials in patients with metastatic sarcoma.[2] This compound has been modified in two locations, with the aim of reducing the cardiotoxicity of doxorubicin. Subsequently, an open-label phase II trial has been opened specifically for patients with metastatic soft tissue sarcoma (STS). The maximum tolerated dose in the phase I trial was 265 mg/m^2; in the phase II trial, patients with sarcoma were treated at this dose every 21 days to a maximum of 16 cycles.

PDGFRα

There has been substantial evidence of the role of PDGFRα in several sarcomas. Recently, the PDGFRα antibody olaratumab showed significant activity when given in combination with doxorubicin in a randomized phase II trial, leading to U.S. Food and Drug Administration approval and ongoing interest in this compound.[3] There are a number of ongoing early-phase trials of olaratumab, including a phase I/II trial of gemcitabine and docetaxel with or without olaratumab (NCT02659020), with overall survival as the primary endpoint of the phase II component, and a phase I trial in combination with a PD-1 inhibitor.

mTOR

mTOR inhibitors have been studied in several sarcoma studies with relatively limited success, with the exception of perivascular epithelioid cell tumors, which are rare malignancies characterized by activation of the mTOR pathway. A number of previous studies have reported the activity of mTOR inhibitors in this disease. ABI-009 is a nanoparticle, albumin-bound version of the mTOR inhibitor rapamycin. A phase II registration trial of ABI-009 has been commenced in patients with advanced perivascular epithelioid cell tumors (NCT02494570).

TAK-228 is a TORC1/2 inhibitor. There is an ongoing phase II trial of this agent in patients with complex genomic sarcomas exhibiting PI3 kinase pathway dysregulation (NCT02987959). This agent is administered orally at a dose of 3 mg.

EARLY-PHASE IMMUNOTHERAPY TRIALS FOR PATIENTS WITH ADVANCED SARCOMA

With promising results of immunotherapy in other cancer types, there are a number of ongoing trials in sarcomas investigating immunotherapy, including checkpoint inhibitors as well as adoptive T-cell therapy. With modest results reported for single-agent pembrolizumab in selective bone and STS subtypes in the phase II SARC028 study, novel trials are focusing more on combination approaches to target potential resistance mechanisms to checkpoint blockade.[4]

Combination Therapies

Evidence in other tumors has supported that combining checkpoint inhibitors with chemotherapy and radiation may improve responses which is believed to be related to the increased release of tumor neoantigens after necrosis from chemotherapy or radiation. Combination studies with chemotherapy include a phase II study of doxorubicin plus pembrolizumab for advanced STS (NCT0288665) and a phase II study of gemcitabine-based regimens or pegylated liposomal doxorubicin combined with pembrolizumab for solid tumors (NCT02331251). An additional study combining pembrolizumab with radiation for upfront treatment of patients with extremity sarcomas is planned through the Sarcoma Alliance for Research through Collaboration consortium.

Additionally, dual-checkpoint inhibition with drugs targeting both the PD-1/PD-L1 axis as well as CTLA-4 have shown superior activity in melanoma and non–small cell lung cancer compared with monotherapy. A phase II clinical trial of 80 patients with metastatic bone and soft tissue sarcomas randomly assigned to nivolumab versus nivolumab plus ipilimumab has completed accrual, with preliminary results expected at the 2017 ASCO Annual Meeting. This combination is also being investigated for pediatric solid tumors, including sarcoma, through the Children's Oncology Group (NCT02304458). A large, multiarm phase II study combining the CTLA-4 inhibitor tremelimumab plus the PD-L1 inhibitor durvalumab is also ongoing for patients with bone and soft tissue sarcomas (NCT02815995).

Tyrosine kinase inhibitors, including imatinib, pexidartinib, pazopanib, and axitinib, not only serve to disrupt cellular pathways critical for sarcomas, but have also been shown to impact the immune microenvironment within tumors. Preclinical studies of imatinib in GIST mouse models demonstrated an increased ratio of CD8$^+$ cytotoxic T cells to suppressive T-regulatory cells through inhibition of IDO1, as well as decreased PD-L1 expression on GIST tumor cells.[5,6] Pexidartinib blocks CSF1 signaling, leading to depletion of immunosuppressive macrophages and suppression of tumor growth in malignant peripheral nerve sheath tumor mouse models.[7] Pazopanib and axitinib suppress VEGF signaling, which is well known to promote accumulation of suppressive myeloid subtypes as well as inhibit T-cell migration and activation within tumors.[8]

In light of these findings, several other clinical trials are evaluating tyrosine kinase inhibitors in combination with checkpoint inhibitors in sarcomas. A phase I/II clinical trial is now ongoing for patients with malignant peripheral nerve sheath tumor and advanced STS with pexidartinib and sirolimus (NCT02584647), as well as a study of pexidartinib with pembrolizumab in solid tumors, including sarcoma and GISTs (NCT02452424). A phase I study of imatinib plus ipilimumab with an expansion cohort for patients with GIST is accruing (NCT01738139). Finally, a phase II study of axitinib plus pembrolizumab is ongoing for patients with advanced bone and soft tissue sarcomas, with a focus on patients with alveolar soft part sarcoma (NCT02636725).

Immunotherapy for NY-ESO-1–Positive Sarcomas

NY-ESO-1 is one of the best-characterized and most immunogenic cancer testis antigens. It is well documented that the

majority of synovial sarcomas express NY-ESO-1, and this opens up the potential for targeted immunotherapy for patients with this particular subtype. Although this disease is relatively sensitive to chemotherapy, particularly ifosfamide, the outcome for patients with pretreated metastatic disease is poor. A number of studies have reported the feasibility of targeting NY-ESO-1, with promising results. In addition, there are a number of ongoing trials. These include a pilot trial of genetically engineered NY-ESO-1–specific (c259) T cells in patients with HLA-A2–positive synovial sarcoma. A separate study is also ongoing for NY-ESO-1–positive myxoid/round cell liposarcomas, which also have a high rate of NY-ESO-1 expression. Another approach is to extract native NY-ESO-1–specific T cells using tetramer-based cell sorting after peptide-pulsed, dendritic cell–based stimulation.[9] Cells are then expanded in the presence of interleukin-21 and returned to the patients for adoptive therapy. This protocol is ongoing in a phase I trial for patients with NY-ESO-1–expressing synovial sarcomas and myxoid/round cell liposarcomas (NCT01477021), as well as in combination with radiation therapy (NCT02319824). Finally, a randomized, open-label phase II trial of CMB305 (sequentially administered LV305 and G305) that targets NY-ESO-1 with the PD-L1 inhibitor atezolizumab is accruing patients with locally advanced, relapsed, or metastatic synovial or myxoid liposarcomas expressing NY-ESO-1.

Adoptive Chimeric Antigen Receptor T-Cell Therapy for HER2-Positive Sarcomas

Subsets of sarcomas overexpress HER2, which has been targeted using a chimeric antigen receptor (CAR) T cell. Transduction of a self-activating CAR into the patient's harvested T cells avoids the requirement for HLA matching needed for engineered T-cell receptor approaches like the NY-ESO-1 strategy mentioned earlier. This approach demonstrated safety and tolerability with modest clinical responses in a phase I trial for 19 patients with osteosarcoma, Ewing sarcoma, and desmoplastic small round blue cell tumors.[10] Expansion with lymphodepleting chemotherapy is ongoing (NCT00902044).

CONCLUSION

In summary, recent years have seen remarkable growth in novel treatment strategies for sarcomas, with an increased emphasis on understanding genetic and molecular biology of various sarcoma subtypes to guide design of clinical trials and optimal patient enrollment for new targeted therapies. Although biomarkers of response to immunotherapy are just beginning to be explored, the observations of remarkable benefit in some patients provide hope for immunotherapy as a future established treatment paradigm. It is critical that patients and providers are aware of the rich opportunities for clinical trials for patients with sarcoma refractory to standard therapies.

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TUMOR BIOLOGY

Higher-Level Pathway Objectives of Epigenetic Therapy: A Solution to the p53 Problem in Cancer

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OVERVIEW

Searches for effective yet nontoxic oncotherapies are searches for exploitable differences between cancer and normal cells. In its core of cell division, cancer resembles normal life, coordinated by the master transcription factor MYC. Outside of this core, apoptosis and differentiation programs, which dominantly antagonize MYC to terminate cell division, necessarily differ between cancer and normal cells, as apoptosis is suppressed by biallelic inactivation of the master regulator of apoptosis, p53, or its cofactor p16/CDKN2A in approximately 80% of cancers. These genetic alterations impact therapy: conventional oncotherapy applies stress upstream of p53 to upregulate it and causes apoptosis (cytotoxicity)—a toxic, futile intent when it is absent or nonfunctional. Differentiation, on the other hand, cannot be completely suppressed because it is a continuum along which all cells exist. Neoplastic evolution stalls advances along this continuum at its most proliferative points—in lineage-committed progenitors that have division times measured in hours compared with weeks for tissue stem cells. This differentiation arrest is by mutations/deletions in differentiation-driving transcription factors or their coactivators that shift balances of gene-regulating protein complexes toward corepressors that repress instead of activate hundreds of terminal differentiation genes. That is, malignant proliferation without differentiation, also referred to as cancer "stem" cell self-renewal, hinges on druggable corepressors. Inhibiting these corepressors (e.g., DNMT1) releases p53-independent terminal differentiation in cancer stem cells but preserves self-renewal of normal stem cells that express stem cell transcription factors. Thus, epigenetic-differentiation therapies exploit a fundamental distinction between cancer and normal stem cell self-renewal and have a pathway of action downstream of genetic defects in cancer, affording favorable therapeutic indices needed for clinical progress.

The search for solutions to the fundamental problems of toxicity and resistance in oncotherapy reduces to a search for druggable differences between cancer and normal self-replication. Self-replication is the engine that drives all biologic evolution, including neoplastic evolution. Huge public and private efforts have focused on investigations of the mechanisms of cancer self-renewal and the development of candidate drugs that target this as the heart of the malignancy.[1] Fundamental differences between malignant and normal self-renewal have been identified. These distinctions have opened the door to novel treatments that target one, but not the other, and that are rational in the overall genetic and epigenetic context of cancer, including near universal p53-system inactivation.

LOSS OF DIFFERENTIATION AND CANCER

"Anaplasia" (loss of differentiation) and "dedifferentiation" were coined in 1890 during the earliest histologic examinations of cancer by Hansemann.[2] Today, we routinely use differentiation failure to distinguish malignant from benign tumors (e.g., adenocarcinoma from adenoma), while the degree of differentiation failure identifies more from less aggressive transformation (e.g., Richter syndrome from chronic lymphocytic leukemia, and acute myeloid leukemia [AML] from myelodysplastic syndromes [MDS]). Even when loss of differentiation is not readily apparent by light microscopy, it is evident by gene expression analyses. For example, grade 1 hepatocellular carcinomas, although "well-differentiated" by light microscopy, demonstrate suppression of hundreds of hepatocyte specialization genes relative to normal liver cells (Fig. 1).

Why?

Multicellularity, defined by cell specialization/differentiation, arose approximately 600 million years ago, after about 3 billion years of unicellular cell growth and division. More ancient cell growth and division, coordinated by MYC or its paralogs, thus had to be conquered by differentiation genes for ordered multicellularity to succeed.[5,6] The nature of this dominant regulation varies with differentiation stage.

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In developed tissues, cells are organized into functionally distinct differentiation stages (Fig. 2):

1. **Tissue stem cells** can self-replicate, but slowly. MYC activation is not vigorous; intervals between cell divisions extend to weeks or months, and proliferation kinetics are quiescent or linear[9-11] (reviewed in Li[12]). Stem cells also produce daughter cells committed to various lineages (multipotency).
2. **Lineage-committed progenitors** are lineage-committed daughter cells of stem cells that activate and stabilize MYC to high levels that result in intervals between cell divisions measured in hours[9-11] (reviewed in Li[12]) and exponential growth kinetics.[13-17] These cell divisions are coupled to advances along differentiation axes that activate, as governors of growth, terminal-differentiation programs that antagonize MYC and force cell cycle exits.[18-25] The coupling that exists between master transcription factor drivers of differentiation and those of cell growth and division can be observed biochemically.
3. **Terminally differentiated cells** do not actively divide. They focus instead on the execution of specialized functions to serve the interests and needs of the overall multicellular organism.

Thus, cancers suppress differentiation because progressive differentiation dominantly antagonizes MYC and terminates replication. The cause-effect relationship is, however, an area of scientific debate. One view is that increases in proliferation (e.g., by stabilization/amplification of MYC by *RAS* mutations, *MYC* copy number gains) cause decreases in differentiation. This mechanism is expected to occur in stem cells that can proliferate without differentiating (i.e., self-renew).[26,27] Another possibility is that loss of differentiation in lineage-committed progenitors (e.g., by disruption of transcription factor circuits that activate terminal-differentiation programs) converts exponential proliferation limited by terminal differentiation into exponential proliferation without differentiation (i.e., self-replication).[28] These divergent views should be reconciled by phenotypes of self-replicating, accumulating cancer cells, being either more stem cell–like or lineage-committed progenitor–like.

KEY POINTS

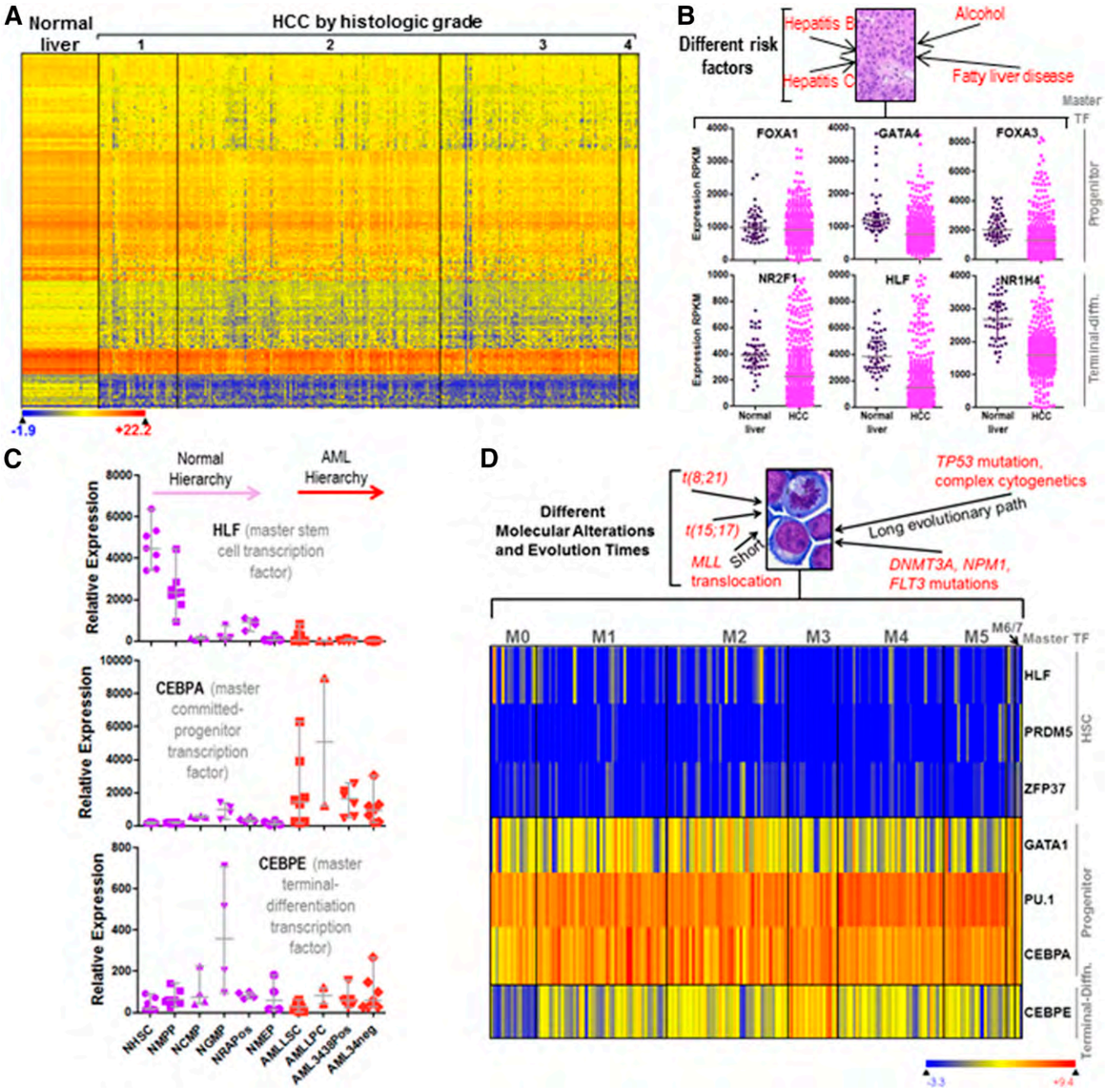
- **Neoplastic evolution stalls advances along differentiation continuums at its most proliferative points—in lineage-committed progenitors.**
- **This converts exponential proliferation usually coupled with differentiation into exponential self-renewal (proliferation without differentiation).**
- **The arrest hinges on corepressors, which are needed to epigenetically repress hundreds of terminal-differentiation genes.**
- **Corepressor inhibition releases p53-independent terminal-differentiation in cancer stem cells poised for these fates, but preserves self-renewal of normal stem cells.**

WHERE IN THE DIFFERENTIATION CONTINUUM ARE DIFFERENTIATION ADVANCES STALLED IN CANCER?

Because self-renewal is an inherent property of tissue stem cells, an intuitive expectation was that differentiation arrest is at the level of self-replicating tissue stem cells. The earliest investigation into this found that leukemia cells that initiated leukemia in immune-compromised mice were rare, with surface phenotype features resembling hematopoietic stem cells (HSCs; CD34+CD38–) of the normal hematopoietic hierarchy.[26] Leukemia thus seemed to recapitulate the hierarchical structure of normal hematopoiesis from which it is derived. The rare self-replicating stem cell–like cells were coined "leukemia stem cells" or LSCs (also called "leukemia-initiating cells"). A gain-of-function hit in this compartment presumably caused a decrease in differentiation.[26,27] Contradicting this initial report, however, several groups found that LSCs were much more common, having surface-phenotype features of lineage-committed progenitors (e.g., CD34+38+, CLL-1+, CD71+, CD90–, c-Kit–).[29-40] In fact, with the incorporation of additional parameters into the sorting strategy (e.g., CD90) to better discriminate HSCs from downstream committed progenitors, leukemia-initiating capacity was found to be absent from HSC-like cells but present in committed progenitors.[40-42] That is, LSCs were abundant and phenocopied lineage-committed progenitors, not rare HSC-like cells.[40-42] Reinforcing this conclusion, highly recurrent transforming genetic alterations exclusively linked with AML and not normal hematopoiesis (e.g., *NPM1*, *FLT3*, and *RAS* mutations) were detected only in cells with committed progenitor phenotype and not in HSCs.[41-44] Moreover, 85% to 97% of bone marrow cells in patients with de novo AML have granulocyte-monocyte progenitor surface phenotypes, not HSC phenotypes, accumulated at the expense of downstream mature cells.[40,45] Thus, self-replicating, accumulating, leukemia-initiating AML cells are stalled at a lineage-committed, intrinsically proliferative level of the hematopoietic hierarchy, whether at diagnosis or at relapse.[40-43]

To mitigate controversies arising from reliance on surface phenotypes, it is useful to examine functionally deterministic biology. Although there are hundreds of transcription factors in a cell, only a handful are masters that command cell fates. This was demonstrated by studies of murine knock-outs, enhancers, and, most strikingly, lineage-conversion, in which introduction of a few transcription factors converts any cell into a stem cell or a completely different lineage.[46-50] The master transcription factors that govern hematopoiesis are well documented. This facilitates analyses and interpretations for AML.[47] Counter to intuitive expectations, LSCs express miniscule levels of stem cell master transcription factors (e.g., HLF).[28,51,52] Instead, LSCs and AML cells from across the genetic spectrum of disease express very high, supra-normal levels of lineage differentiation–driving master transcription factors (e.g., CEBPA, PU.1) that usually drive granulomonocytic fate,[51,52] with lineage destinations, nonetheless, not being achieved (Fig. 1).

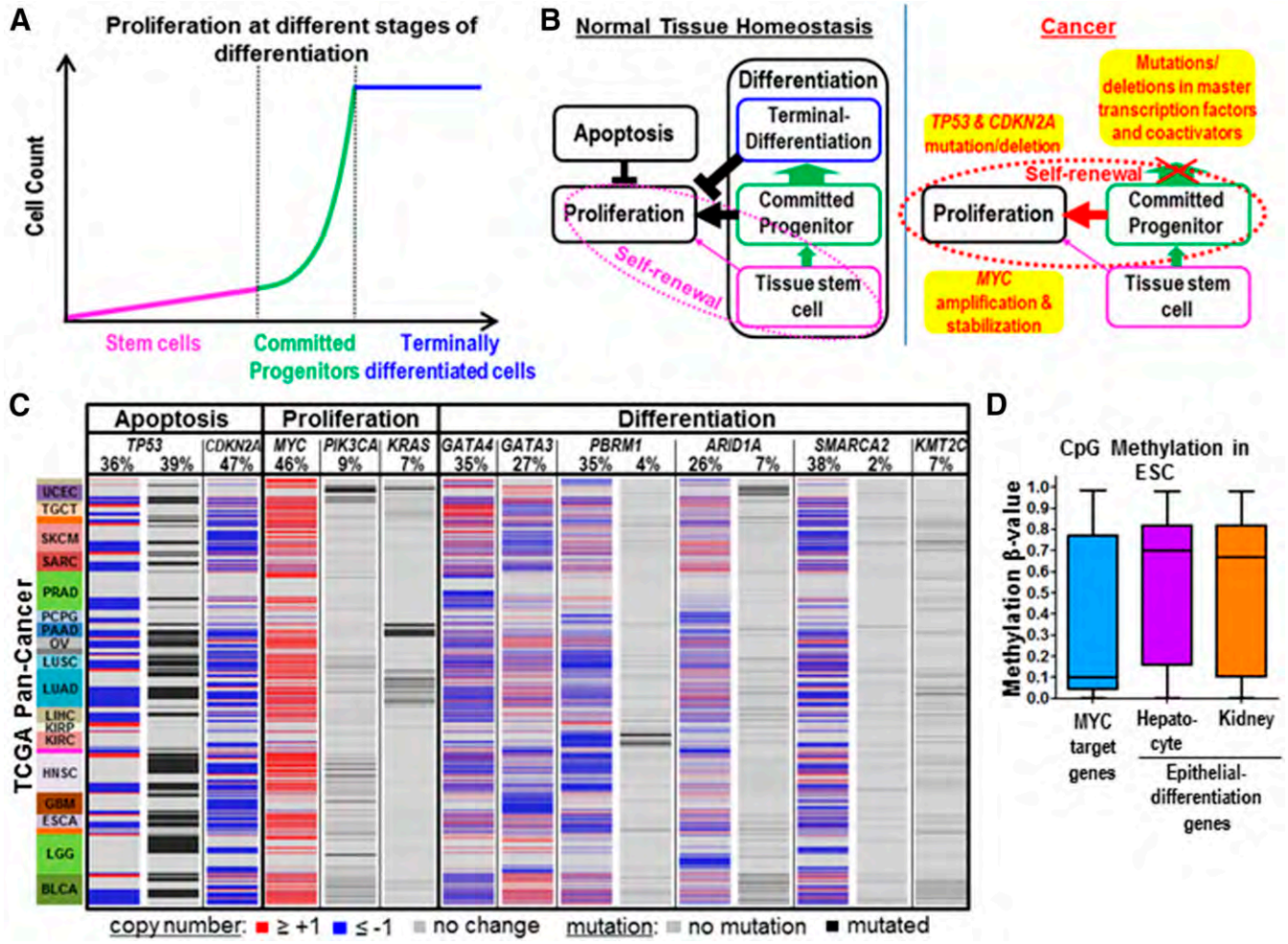
FIGURE 1. Differentiation Failure Features in Cancer, Whether It Is Obvious by Histologic Examination (AML) or Not (HCC)



(A) Hundreds of specialized hepatocyte differentiation genes with functions in lipid metabolism, coagulation factor synthesis, etc., are suppressed in HCC compared with normal liver (rows: 353 genes, columns: samples; TCGA RNA-Seq). (B) Different HCC-initiating insults produce similar relative preservation of master progenitor TF, but multifold repression of key terminal differentiation TF. (C) Leukemia "stem" cells express low levels of master stem cell TF, but supra-normal levels of master lineage differentiation-driving TF. Even so, key terminal differentiation genes (e.g., *CEBPE*) are repressed. The normal hematopoietic hierarchy expresses expected levels of these factors. Gene expression by microarray GSE24006.[3] Error bars = median ± range. (D) Different AML genetics but similar differentiation arrest of committed progenitors. AML morphologic subtypes (M0-M7) correspond to relative amounts of CEBPA, PU.1, and GATA1 that drive granulocytic, monocytic, and erythroid lineage-fates, respectively. Master stem cell TF: HLF, PRDM5, ZFP37; master commitment/early-differentiation TF: CEBPA, PU.1, GATA1; master late/terminal differentiation TF: CEBPE (rows: genes, columns: samples; TCGA RNA-Seq, n = 174).[4] Abbreviations: AML, acute myeloid leukemia; HCC, hepatocellular carcinoma; TCGA, The Cancer Genome Atlas; TF, transcription factors; RNA-Seq, RNA sequencing; NHSC, normal hematopoietic stem cells; NMPP, normal multipotent progenitors; NCMP, normal common myeloid progenitor; NRAPos, normal mature myeloid cells; NMEP, normal megakaryocyte erythroid progenitor; LSC, leukemia stem cells; LPC, leukemia progenitor cells.

Master transcription factors that produce stem cells compared with lineage-committed progenitors in solid tissues are not as comprehensively characterized as for hematopoiesis. Nonetheless, where the identity of these transcription factors is known, the cancers that arise from these tissues also express very high levels of master lineage-differentiation drivers. For example, malignant melanoma cells express high levels of the melanocyte differentiation drivers MITF and SOX10,[53,54] rhabdomyosarcomas express high levels of the muscle-specifying transcription factor MYOD,[55] clear

FIGURE 2. Terminal Differentiation Is the Apex Control on Proliferation



Loss of terminal differentiation causes malignant self-renewal, even as other genetic alterations suppress apoptosis and promote MYC protein levels. (A) Exponential proliferation in committed progenitors is self-limited by coupling to progressive maturation, culminating in activation of terminal differentiation programs. (B) Malignant self-renewal (red-dotted oval) is caused by loss of terminal differentiation, converting proliferation with differentiation into proliferation without differentiation (self-renewal). This contrasts fundamentally with normal tissue homeostasis, in which self-renewal is restricted to mostly quiescent stem cells (pink-dotted oval). (C) Apoptosis and proliferation have the same master transcription factors across histologies and species (p53 and MYC, respectively); differentiation has various master transcription factors/preferred coactivators, depending on lineage and maturation stage. Thus, genetic alterations that repress terminal differentiation are varied, but with a common theme of inactivating master transcription factors and/or their coactivators (TCGA pan-cancer, data from Xena browser). (D) Proliferation genes have chromatin that is poised for gene activation (low CpG methylation) even in the earliest tissue precursors (ESC), while renal and hepatocyte epithelial differentiation genes have repressed chromatin (high CpG methylation). This epigenetic gradient to activation of terminal differentiation likely interacts with coactivator loss for selective repression of terminal differentiation programs. MYC target genes = 5,716 CpG linked with 356 genes.[7] Hepatocyte genes = 4,729 CpG linked with 353 genes suppressed in HCC compared with normal liver. Renal genes = 9,496 CpG linked with 394 genes suppressed in RCC compared with normal liver. Plotted are medians of methylation values (β-values) by Illumina 450k CpG array for the three categories of CpG. β-values in ESC from GSE31848 (n = 19).[8]

Abbreviations: TCGA, The Cancer Genome Atlas; ESC, embryonic stem cells.

cell renal cell cancers (RCC) express very high levels of the renal epithelial-fate driving transcription factors PAX2 and PAX8, and hepatocellular carcinomas express very high levels of hepatocyte fate transcription factors FOXA1, FOXA3, and, to some extent, GATA4. Yet, morphologically and/or by gene expression analyses, hundreds of target differentiation genes are suppressed, not activated. Again, cancer cells are at intermediate, intrinsically proliferative points in differentiation continuums. For example, the medulloblastoma gene expression profile corresponds to a normal maturation stage that has a high proliferation rate and low levels of late cerebellar differentiation genes,[56] and squamous lung carcinoma cells also have gene expression profiles of intermediate stages of normal lung development and differentiation.[56,57]

Differentiation suspension is thus not at the level of stem cells but at the most proliferative point in the differentiation continuum, in committed lineage progenitors. Beneath superficial differences in histology and genetics, this is a common core to cancers.

Why?

Replication drives evolution and repopulation. Thus the logarithmically higher replication rate of lineage-committed progenitors compared with stem cells, together with less rigorous policing of the genome during this replication,[58] likely determine the committed-progenitor context of transformation and cellular accumulation. With intrinsic proliferation rates so skewed, even the slightest advantage is

amplified tremondously. Moreover, differentiation programs limiting exponential replication are evolutionarily recent overlays on substantially more ancient cell growth and division programs and, as described below, have many ways to fail.[5,6]

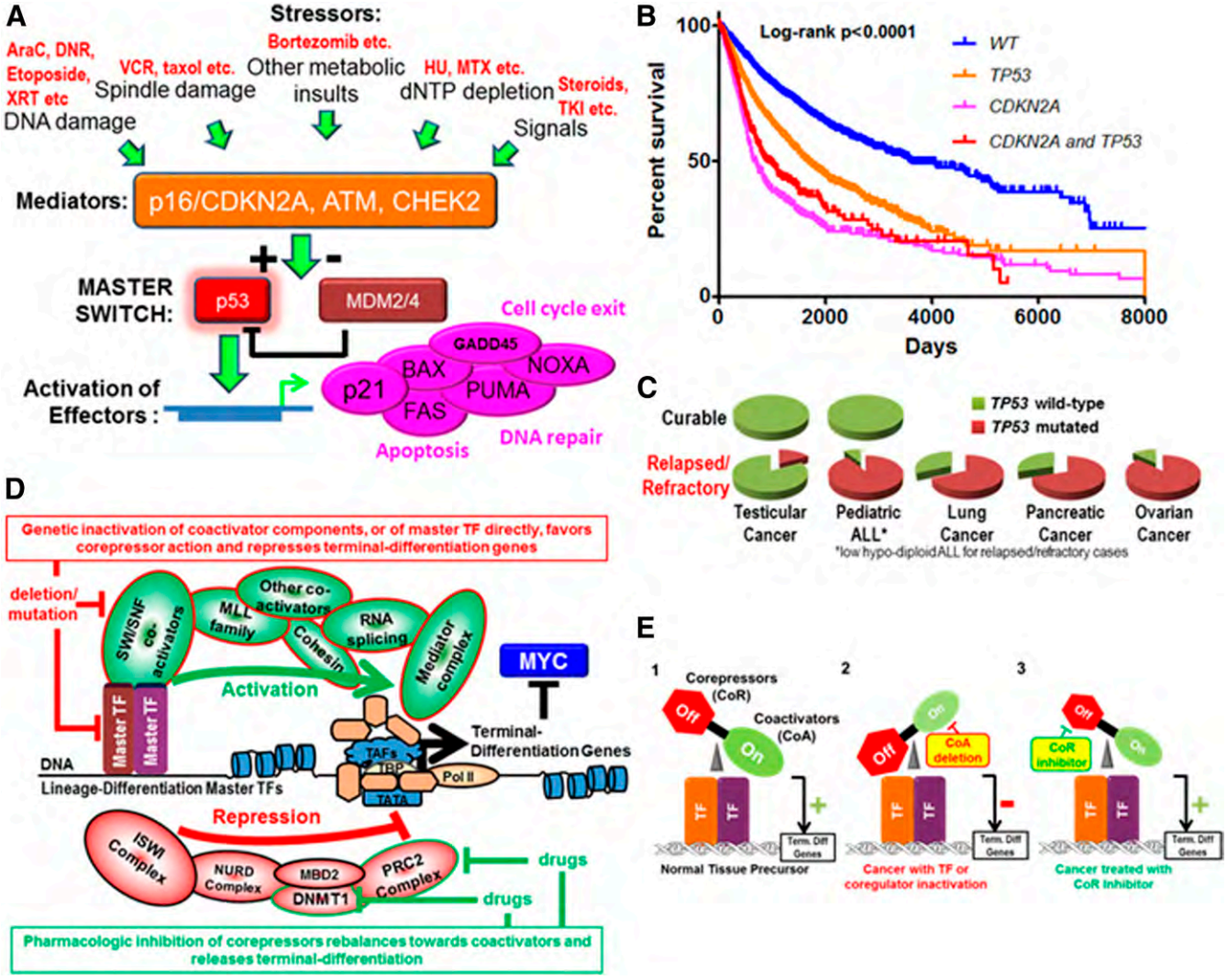
HOW IS DIFFERENTIATION STALLED DESPITE LINEAGE COMMITMENT?

A fundamental, observable property of cancers, common across histologies and genetics, is high expression of master transcription factor drivers of lineage differentiation, yet anomalously, suppression of terminal differentiation genes usually invariably induced by these commanders. The detailed molecular mechanisms underlying this incongruity have been characterized in several instances. There is a shared motif. Transcription factors integrate gene-regulating signaling inputs via dynamic interchange of opposing coactivators and corepressors[59-61]: coactivators create the chromatin modifications that facilitate gene activation, while corepressors execute the opposite function. The shared motif in cancer is that master transcription factor hub stoichiometry shifts toward corepressors and away from coactivators (Fig. 3) via genetic alterations described below.

Genetic Inactivation of Coactivators

A major revelation of the genomics revolution is the high rate at which various SWI/SNF family coactivators are inactivated in cancer genomes (Fig. 2). SWI/SNF are ATP-dependent chromatin remodelers that execute the most energetically expensive work in epigenetics, that of repositioning

FIGURE 3. Therapeutic Implications of Frequent Inactivating Mutations of p53 (*TP53*) and p16 (*CDKN2A*) and of Master Differentiation-Driving TF and Their Coactivators



(A) Most current treatments apply stress to cells upstream of p53/p16 circuitry with the goal of increasing p53 protein. This is a problem when p53 or p16 are missing or nonfunctional. (B) Overall survival TCGA Pan-Cancer (n = 5,364) stratified by TP53 mutation or bi-allelic deletion, CDKN2A biallelic deletion, or both alterations. (C) *TP53* mutation rates in curable compared with incurable disseminated malignancies. (D) Terminal differentiation suppression is by altered master differentiation-driving transcription factor hub composition, which favors CoR over CoA (E). Inhibiting druggable CoR (e.g., DNMT1) can rebalance toward CoA function and release terminal-differentiation programs, because cancer cells (including cancer "stem" cells) are poised for these fates with high master differentiation-driving transcription factor expression. These cell cycle exits do not require missing p53/p16.

Abbreviations: TF, transcription factors; CoR, corepressors; CoA, coactivator.

nucleosomes. Different SWI/SNF coactivators are inactivated in different cancers,[59-61] a phenomenom likely explained by preferences of lineage-driving transcription factors for specific coactivator subunits.[60,62] One example is the SWI/SNF coactivator *PBRM1*, which is universally inactivated in one or both alleles in clear cell RCC. PBRM1 coactivates for the highly expressed PAX2/PAX8 master transcription factor circuit that drives renal epithelial differentiation . Another example is *ARID1A,* which is frequently biallelically inactivated in hepatocellular carcinoma and a coactivator for GATA4/FOXA1 circuitry that drives hepatocyte epithelial differentiation. Master transcription factors also recruit and use splicing factors, cohesins and other coactivators to activate genes, and recurrent inactivating mutations/translocations in these and related factors (e.g., *TET2*) likely also contribute to the incongruity in cancer of high master differentiation-driving transcription factor expression yet also the repression of hundreds of differentiation target genes.[62]

Metabolic Inactivation of Coactivators

Abnormal gain-of-function mutations in isocitrate dehydrogenases (IDHs) that are highly recurrent in glioma and AML produce an oncometabolite—the *R*-enantiomer of 2-hydroxyglutarate—that inhibits alpha-ketoglutarate–dependent enzymes such as the TET family of DNA demethylation enzymes and the chromatin-remodeling lysine demethylases KDM4A and KDM4C, mutations of which have been linked to differentiation arrest.[63]

Translocations, Mutations, and Dislocations of Transcription Factors That Disrupt Corepressor/Coactivator Exchange

Usually, the retinoic acid receptor (RARA) exchanges corepressors for coactivators upon binding of its ligand retinoic acid to activate terminal-differentiation programs including the granulocyte differentiation program. For the leukemia fusion protein PML-RARA, corepressor/coactivator exchange is no longer achieved by physiologic concentrations of retinoic acid, and hundreds of granulocyte differentiation genes are repressed instead of activated.[64-66] RUNX1 is a key hematopoietic transcription factor that cooperates with master myeloid lineage differentiation–driving transcription factors such as PU.1 to exchange corepressors for coactivators.[62,67] In the leukemia fusion protein RUNX1-ETO, the domain of RUNX1 that effects this cooperation is replaced with corepressor-recruiting domains of the ETO protein.[68-70] Similarly, the EWS-FLI1 fusion protein, found in more than 85% of Ewing sarcomas, recruits corepressor complexes to arrest osteogenic differentiation.[71,72] *MLL* (KMT2A) translocations in leukemia and cancer invariably remove the histone methyltransferase domain of MLL that usually creates the epigenetic activation mark H3K4me2 or me3.

Inactivating mutations of *RUNX1* that are highly recurrent in myeloid malignancies also disrupt usual cooperation with PU.1 to exchange corepressors for coactivators.[62,67,68,73] GATA4 cooperates with FOXA1 in a similar way. Thus, *GATA4* haploinsufficiency in hepatocellular carcinoma, as with *RUNX1* haploinsufficiency in AML, shifts coregulator stoichiometry of the lineage differentiation–driving circuitry toward corepressors to repress instead of activate hundreds of terminal-differentiation genes. Because GATA4 is a master transcription factor driver of differentiation in all three germ layers, highly recurrent *GATA4* haploinsufficiency via frequent chromosome 8p deletions in several solid tumor malignancies could similarly underlie differentiation arrest.

The gene most recurrently altered in de novo AMLs is *NPM1*. Mutant NPM1 dislocates the master transcription factor PU.1 but not CEBPA from the nucleus to the cytoplasm, again disrupting differentiation-driving transcription factor hub balances toward corepressors.[74] The second most altered gene in de novo AMLs is *FLT3*; FLT3-activating mutations compromise transactivations by the differentiation driver CEBPA.[75]

Epigenetic Gradient to Activation of the Terminal-Differentiation Program

Proliferation genes (MYC target genes) are already poised or on, that is, DNA CpG hypomethylated, in the earliest tissue precursors, embryonic stem cells (Fig. 2D). By contrast, terminal-differentiation genes require substantial chromatin remodeling from hypermethylated (off) to hypomethylated (on) states during tissue ontogeny. This epigenetic gradient to activation of terminal-differentiation genes interacts with corepressor/coactivator balances in differentiation-driving transcription factor hubs to selectively suppress terminal-differentiation programs characteristic of cancers.

Founder Mutations ("First-Hits") Can Originate Many Commitment Decisions Antecedent to the Progenitor Cell of Transformation

Familial AML pedigrees demonstrate how founder mutations can originate in one compartment yet manifest their transforming properties far downstream, in daughter cells many commitment decisions removed from the cell of origin. For example, the most common cause of familial AML is loss-of-function mutations in *RUNX1*. RUNX1-deficient HSCs lineage-commit normally, but RUNX1 deficiency then compromises PU.1/CEBPA master transcription factor function, thus retarding maturation after commitment.[51,73,76] Similarly, point mutations in *CEBPA* that cause familial AML permit commitment but impede subsequent maturation.[30] In short, mutations may originate in germline or tissue stem cells but produce ectopic cell divisions/expansion in already highly proliferative lineage-committed daughter cells, where even a small advantage might be amplified tremondously, facilitating further evolution and transformation.

HOW THE APOPTOSIS PROGRAM IS SUPPRESSED IN CANCER

Apoptosis coemerged with differentiation/multicellularity to mediate orderly cell cycle arrests and suicide of stressed or damaged cells, in the interests of the larger cellular aggregate.[5,6] Thus, in common with differentiation, apoptosis

dominantly regulates MYC-coordinated cell growth and division. The master transcription factor p53 (*TP53*) and its key cofactor p16 (*CDKN2A*) are pan-histology, pan-species, master regulators of apoptosis. Dominance over MYC explains why *TP53* and/or *CDKN2A* are biallelically inactivated by mutation and deletion in approximately 80% of cancers, even as cancers simultaneously stabilize or amplify MYC by *RAS* mutations, PI3K/AKT pathway alterations, etc. p53/p16 inactivation in cancer has major treatment implications, discussed below.

THERAPEUTIC IMPLICATIONS

The way in which the three major metazoan programs of proliferation, differentiation, and apoptosis disconnect in cancer compared with normal cells is fundamental to treatment and its outcomes.

Treatment Implications of p53/p16 Deletion/Inactivation

Conventional medical and radiation therapy intends to use apoptosis (cytotoxicity), via stress applied upstream of p53, to antagonize MYC and terminate malignant replication (Fig. 3). The drugs may have different proximal molecular actions (e.g., topoisomerase inhibition [daunorubicin] or termination of DNA chain synthesis [cytarabine]), but the downstream objective is shared: to upregulate p53/p16 (reviewed in Kinzler et al[77]). This is a futile intent when p53 and/or p16 are absent/nonfunctional, but normal cells with intact p53/p16 are meanwhile destroyed.[78-83] Questions of drug sensitivity/resistance are usually investigated by looking for differences between sensitive and resistant cancer cells. Thus, the fact that more than 80% of cancer cell lines are p53- and/or p16-deficient to begin with can cause in vitro studies to underappreciate the role of p53/p16 in clinical resistance. Similarly, inactivation of p53/p16 is so commonplace in some cancer histologies that its impact on outcomes is hard to discern by studies of the individual cancer histology in isolation (reviewed in Kinzler et al[77]). It is highly illustrative, however, to note that the p53/p16 inactivation rate is close to zero in those few disseminated cancer types that are routinely cured by cytotoxic therapy (testicular cancer, pediatric acute lymphoblastic leukemia [ALL]), whereas rates approximate 80% in notoriously incurable disseminated cancers (e.g., pancreatic), and also to note relatively high rates ofp53/p16 inactivation in the few testicular cancer or pediatric ALL cases that are relapsed/refractory (e.g., > 90% in incurable low-hypodiploid ALL; Fig. 3C).[84-87]

In sum, p53/p16 inactivation is a difference between cancer and normal cells that hurts rather than helps when treatment goals are to activate apoptosis. Alternative pathways for antagonizing MYC and inducing irreversible cell cycle exits are thus needed for the majority of cancers, which lack functional p53 and/or p16.

Treatment Implications of Corepressor/Coactivator Imbalances in Master Transcription Factor Hubs

Malignant self-replication, also referred to as LSC/CSC self-renewal, needs corepressors to decouple differentiation from proliferation. Thus, pharmacologic reduction of corepressor activity compensates for genetic reduction of coactivators, releases terminal-differentiation fates intended by the master transcription factors resident in LSCs/CSCs, and thus terminates malignant cell self-renewal.[19,51,52,64,81,88,89] The same treatments increase self-renewal of normal tissue stem cells because these express high levels of master stem cell transcription factors, not differentiation drivers.[51,88,90-98] Normal committed progenitors, such as CSCs and LSCs, also differentiate.[51,88,90] Because MYC is subservient to terminal differentiation, replication is terminated even if MYC is stabilized and/or amplified by other genetic alterations typical of cancer.[19,51,52,81,88,89] Also, this pathway of terminating malignant self-replication does not require p53/p16, which is often missing, but is not needed for differentiation[19,51,52,81,89] (p53-null and p16/Cdkn2a-null mice develop/differentiate normally[99,100]). Finally, corepressor reduction operates downstream of the genetic defects in cancer cells that stalled differentiation in the first place. Cancers shrink and resolve because expansion derives from relentless self-replication that exceeds a high spontaneous death rate. The best illustration of these properties is, of course, clinical results.

First example of clinical differentiation-restoring therapy. Acute promyelocytic leukemia (APL) was converted from the AML subtype with the worst overall survival to the best by using retinoic acid and arsenic to reverse differentiation failure mediated by corepressors recruited by the leukemia fusion protein PML-RARA.[64-66,101] Overall survival of APL treated with differentiation therapy is better than for any other disseminated malignancy, including pediatric ALL, using only two drugs compared with the five or more used to treat ALL.[64,101] Differentiation restoration using different agents could yield similar benefits against other cancers.

DNMT1-targeting therapy. The corepressor DNMT1 is aberrantly enriched in master transcription factor hubs of multiple cancer types and has been scientifically validated as a pan-cancer target for differentiation-restoring therapy (reviewed in Saunthararajah et al[28]; Fig. 3).[19,51,52,81,89,102-126] DNMT1 can be depleted by decitabine, a deoxycytidine analog with a modified base that binds to and depletes DNMT1 after incorporation into DNA, without terminating DNA chain elongation and, thus, at low useful doses, without cytotoxicity. A favorable therapeutic index that spares normal stem cells is especially critical when treating MDS/AML in the elderly, as these cells are needed to reverse low blood counts that cause morbidity and death. Decitabine regimens approved to treat MDS, however, administer high doses that cause off-target cytotoxicity that requires pulse-cycled administration for recoveries. To generate clinical proof of concept of p53/p16-independent, noncytotoxic epigenetic-differentiation therapy, we treated patients with MDS with reduced decitabine doses (0.1–0.2 mg/kg/day compared with the U.S. Food and Drug Administration–approved 20–45 mg/m^2/day—a 75%–90% reduction) that avoid cytotoxicity. These well-tolerated doses were administered 1 to 3 days/week nonstop, instead of pulse-cycled 3 to 5 days straight once every 4 to 6 weeks. This increases

probabilities that cancer S-phase entries coincide with drug presence in cells, which is required because DNMT1 depletion by decitabine is S-phase dependent. The patients were elderly with a median age of 73. Many had disease that was relapsed/refractory to standard first-line treatments. Adverse events were related to neutropenia present at baseline, and antiemetics were not needed. Responses meeting MDS working group criteria occurred in 44% of subjects and were highly durable, with treatment-induced freedom from transfusion lasting a median of 1,025 days with several still ongoing at the time of the data analysis; 20% of the subjects were treated for more than 3 years, including several patients older than age 80.[52] Complete cytogenetic remissions were produced even in cases with biallelic inactivation of *TP53* and complex chromosome abnormalities. Noncytotoxic DNMT1 depletion was confirmed by serial bone marrow γ-H2AX and DNMT1 analyses. MYC master oncoprotein levels were markedly decreased by treatment.[52] In a subsequent report, a 100% response rate was observed in 21 patients with *TP53*-mutated/deleted MDS and AML.[127] Interestingly, p53 loss biases pyrimidine metabolism toward decitabine uptake, further facilitating the use of this agent to treat p53-null malignancies.[128]

Selective effects on LSC compared with HSC self-replication and the p53-independent mechanism of action of DNMT1-depleting therapy explains why 5-azacytidine and decitabine are the only two drugs approved for treatment of all MDS and are also routinely used to treat AMLs.[52,81,129,130] Unfortunately, these observations in myeloid malignancies are not readily extended to p53/p16-null solid tumor malignancies, not because of diminished validity of DNMT1 as a therapeutic target, but because decitabine and 5-azacytidine are inactivated within minutes by the pyrimidine metabolism enzyme cytidine deaminase (CDA) that is highly expressed in solid tissues.[102] CDA upregulation within malignant cells is also a mechanism of resistance in myeloid malignancies.[131,132] We thus combine decitabine with a CDA-inhibitor (tetrahydrouridine) for orally administered, noncytotoxic DNMT1-depleting treatment of *TP53*-mutated solid and liquid cancers (NCT02664181, NCT02847000, and NCT02846935).

Other examples of clinical epigenetic-differentiation therapy. IDH2 inhibitors in clinical trials are able to salvage chemorefractory (apoptosis-resistant) AML by terminal differentiation.[133] Inhibitors of FLT3 and of mutant-NPM1 nuclear export also restore terminal-differentiation observations in active clinical translation for chemorefractory AML.[74] KDM1A (LSD1) inhibitors are in clinical trials to treat refractory/relapsed myeloid malignancies and small cell lung cancer.[134-137]

Liquid or solid tumor malignancies? Although clinical differentiation-restoring treatments are most advanced in myeloid malignancies, decades worth of preclinical research has documented terminal differentiation of solid cancer cells in response to corepressor inhibition. Examples include aggressive, differentiation-impaired melanoma and breast cancer cells that resumed differentiation completely through cell cycle exits when exposed to an embryonic cell microenvironment that opens chromatin[138,139]; oocyte extracts, another microenvironment that induces DNA hypomethylation and removes repressive histone marks, terminating breast cancer cell tumorigenicity[140]; histone deacetylase inhibitors (HDACi) inducing terminal differentiation in a spectrum of solid cancer primary cells and cell lines, as well as leukemia cells[68,141-151]; genetic or pharmacologic suppression of KDM1A (LSD1), a component of the NURD corepressor complex, inducing terminal maturation in several solid cancer as well as leukemia models[72,134-137]; and DNMT1, validated by several groups as a molecular target for differentiation restoration of solid and liquid malignancies (reviewed in Saunthararajah et al[28]).[51,52,64,81,88,103-126] In short, new drugs and pharmacologies are needed for clinical translation, but molecular targets for normal stem cell sparing, p53-independent, epigenetic-differentiation treatment of solid malignancies have been identified and validated.

RESISTANCE

Corepressor inhibition exploits a distinction between malignant and normal stem cell self-renewal and hence offers a solution for toxicity. Nonetheless, all drugs are metabolized, must distribute into target cells, and have to successfully engage their molecular targets, providing multiple opportunities for escape from treatment effects. That is, treatment resistance still must be addressed. For example, decitabine and 5-azacytidine must traverse pyrimidine metabolism pathways to reach their target. These pathways have regulators in place that are designed to minimize nucleotide imbalances. Thus, the nucleotide load of administered decitabine or 5-azacytidine is countered by reflexive metabolic shifts that decrease drug uptake (reviewed in Saunthararajah et al[152]).[132] Nontoxic treatments targeting malignant self-replication can, however, be rationally combined. This point is illustrated by the more than 95% cure rate of APL when treated with only two such drugs, retinoic acid and arsenic. Other than in APL, there have been no clinical trials of combination therapy for explicit noncytotoxic epigenetic-differentiation goals, an omission that will be corrected moving forward (HDACi combined with 5-azacytidine or decitabine in clinical trials have been cytotoxic/cytostatic, antagonizing S-phase–dependent DNMT1-depletion by 5-azacytidine or decitabine [reviewed in Saunthararajah et al[152]]).[153]

CONCLUSION

Hippocrates said, "Natural forces within us are the true healers of disease." LSCs/CSCs contain very high levels of master transcription factor drivers of lineage fate and are poised for terminal differentiation. Corepressors are the druggable barriers that suspend execution of these naturally intended fates. Although differentiation therapy is a decades-old idea,[154-156] that corepressor/coactivator imbalance causes differentiation failure and thus malignant self-replication is a relatively recent concept. Drug development and clinical applications, which have dwelled on self-renewal driving failed differentiation, have thus been lagging. Even so,

clinical proof of principle that epigenetic, differentiation-restoring treatment can be a broad solution to toxicity, and to resistance from p53/p16-inactivation, already exists. Rational combinations of such treatments can solve other resistance problems to keep patients well and alive for even longer.

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Metabolic Alterations in Cancer and Their Potential as Therapeutic Targets

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OVERVIEW

Otto Warburg's discovery in the 1920s that tumor cells took up more glucose and produced more lactate than normal cells provided the first clues that cancer cells reprogrammed their metabolism. For many years, however, it was unclear as to whether these metabolic alterations were a consequence of tumor growth or an adaptation that provided a survival advantage to these cells. In more recent years, interest in the metabolic differences in cancer cells has surged, as tumor proliferation and survival have been shown to be dependent upon these metabolic changes. In this educational review, we discuss some of the mechanisms that tumor cells use for reprogramming their metabolism to provide the energy and nutrients that they need for quick or sustained proliferation and discuss the potential for therapeutic targeting of these pathways to improve patient outcomes.

Metabolic pathways are the means by which cells break down nutrients to acquire the energy and building blocks that they need for growth, proliferation, and the maintenance of critical cellular processes. Energy within cells is stored by adenosine triphosphate (ATP) molecules, which are both required and produced by metabolic pathways and thus are referred to as cellular energy currency. Cells generate ATP through respiration, of which there are two distinct mechanisms: aerobic and anaerobic. Both of these pathways require the initial uptake of glucose, which is converted through a series of steps known as glycolysis to pyruvate. However, at this point, what happens to pyruvate is typically dependent upon the environmental conditions surrounding the cell. Aerobic respiration, most often used by normal cells under normal, nonproliferating conditions, requires oxygen and results in the conversion of the glycolytic product pyruvate to acetyl coenzyme A (acetyl-CoA). The primary function of acetyl-CoA is to donate an acetyl group to the citric acid (also known as tricarboxylic acid, TCA, or Krebs) cycle. By continuing through the TCA cycle and electron transport chain (ETC) reactions, all of which take place in the mitochondria, the downstream metabolism of a single molecule of glucose by aerobic respiration yields a net gain of about 36 molecules of ATP and releases carbon dioxide as a byproduct. This process is often collectively referred to as oxidative phosphorylation (Fig. 1A). Anaerobic respiration, on the other hand, is far less efficient, producing a net gain of only two molecules of ATP per molecule of glucose metabolized and thus is typically only used during hypoxic or stressful conditions, as it does not require the presence of oxygen. During anaerobic respiration—also referred to as fermentation—pyruvate is converted to lactate and ethyl alcohol entirely within the cytosol. Although inefficient, this pathway can keep the cell alive during stressful conditions in which the supply of oxygen is low by generating enough ATP to continue sustained cycling through glycolysis (Fig. 1A).

Although normal or quiescent cells rely primarily on aerobic respiration/oxidative phosphorylation to meet their energy requirements, cancer cells appear to meet their increased demands for energy quite differently. Because tumor cells grow rapidly, they must increase the import of nutrients from their environment in an effort to maintain the pools of ATP and, even more importantly, carbon intermediates that serve as building blocks for the assembly of DNA, proteins, and lipids needed during cell growth and division. In the 1920s, Otto Warburg first made the observation that tumors took up markedly higher levels of glucose in comparison with normal tissues.[1] Furthermore, Warburg showed that even in the presence of ample oxygen, cancer cells produced much more lactate than normal tissues, suggesting that these cells were shuttling glucose through the glycolytic fermentation pathway.[2] The sustained use of this pathway to meet energy requirements under normoxic conditions is now termed "aerobic glycolysis," and the increased dependence on this pathway by cancer cells has

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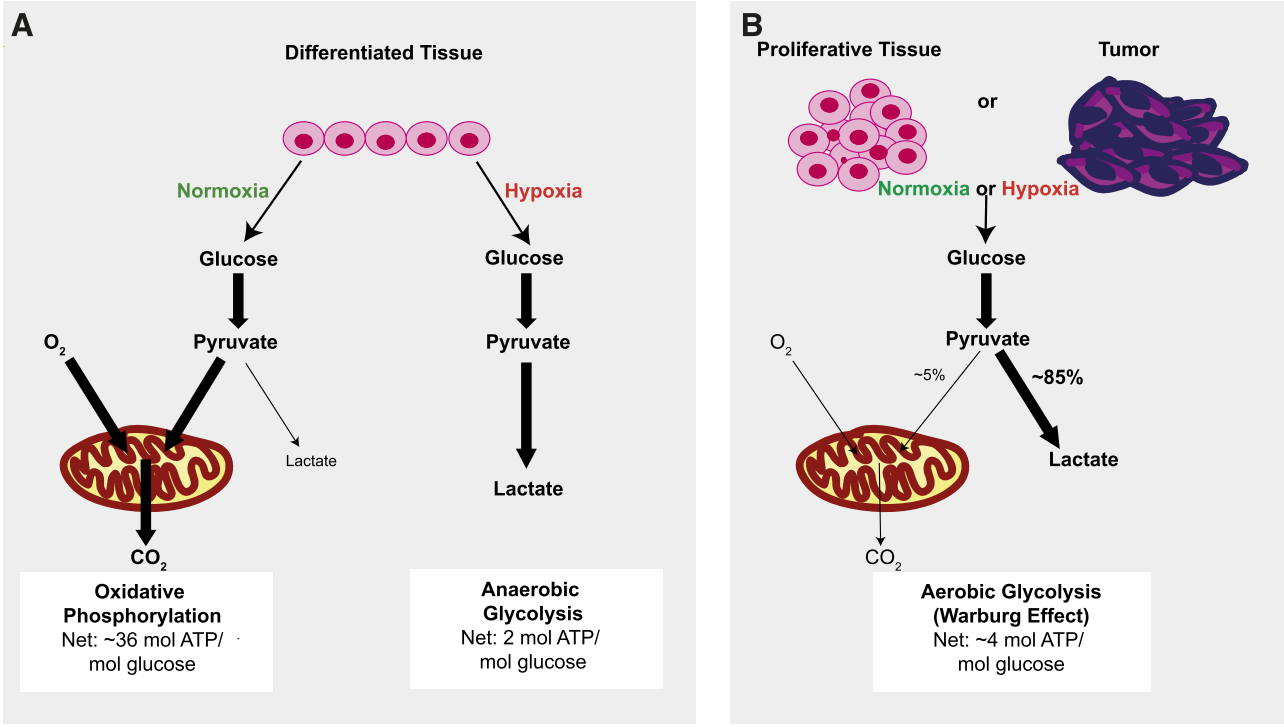
FIGURE 1. Metabolic Reprogramming in Tumor Cells: The Warburg Effect



(A) Under normoxic conditions, normal tissues convert the glycolytic product of pyruvate to cetyl coenzyme A, which is used in the mitochondria for the tricarboxylic acid cycle to begin the process of oxidative phosphorylation. In the absence of oxygen, pyruvate is converted to lactate, and sustained anaerobic glycolysis is used to meet requirements for energy and nutrients. (B) Tumor cells convert the majority of the glycolytic product pyruvate to lactate and replenish their nutrients and energy through sustained aerobic glycolysis, but maintain mitochondrial function and some oxidative respiration.
Abbreviation: ATP, adenosine triphosphate.

come to be known as the Warburg effect (Fig. 1A). In more recent years, this phenomenon has been confirmed in a number of different tumor types in different tissues and has proven useful for diagnostic imaging using ^{18}F-deoxyglucose positron emission tomography to detect the higher levels of glucose uptake observed in tumors in comparison with surrounding normal stroma.[3] It seems counterintuitive that rapidly dividing cancer cells would prefer the less efficient glycolytic pathway for meeting their energy demands. For this reason, Warburg originally hypothesized that the increased rates of aerobic glycolysis in cancer cells were attributable to impaired function of the mitochondria in these cells, requiring them to rely solely upon glycolysis to make ATP needed for survival.[2,4] This theory has been disproven in more recent years, however, as the majority of cancer cells have been found to maintain functioning mitochondria.[5] It has also become increasingly clear that tumor cells continue to carry out oxidative respiration in addition to sustained aerobic glycolysis (Fig. 1B) and that a likely advantage of this altered metabolic profile is the sustained production of glycolytic carbon intermediates required for the production of macromolecules needed by the rapidly dividing cells.[6]

Although the Warburg effect is perhaps the most recognized metabolic characteristic of many cancer cells, a broad range of metabolic alterations has been observed in tumors. In addition to increased glucose uptake, tumor cells have also been commonly shown to have higher levels of dependence on glutamine, which is a source of nitrogen for the synthesis of nucleotides and amino acids.[7] Interactions involving various intermediates of glycolysis, the TCA cycle, the ETC, and the pentose phosphate pathway, as well as lipid metabolism pathways, have all been shown to be altered in tumor cells and to play a role in tumorigenesis.[8] These metabolic changes can result from genetic aberrations in metabolic enzymes themselves, but can also be a downstream consequence of activating mutations in numerous growth factors and oncogenes, loss of tumor suppressor signaling, or epigenetic alterations,[7] all of which we will discuss in more detail in later sections of this review. Recent findings demonstrating the influence of metabolic pathways on tumor cell proliferation, growth, and differentiation have renewed interest in identifying susceptibilities of these pathways to therapeutic intervention, and thus the investigation of metabolic

KEY POINTS

- **Warburg metabolism is a common feature of tumor biology, but it only represents one way that tumors adapt metabolic processes to survival advantage.**
- **Mutations and modifications of Krebs cycle and electron transport function also underlie tumor cell physiology.**
- **Biometabolites find functional use in energy generation and as essential components of epigenetic features.**
- **Numerous directions are being investigated to harness energetic processes as therapeutic strategies for cancer.**

reprogramming as a hallmark of cancer has become an extremely active area of research in the last decade.[3]

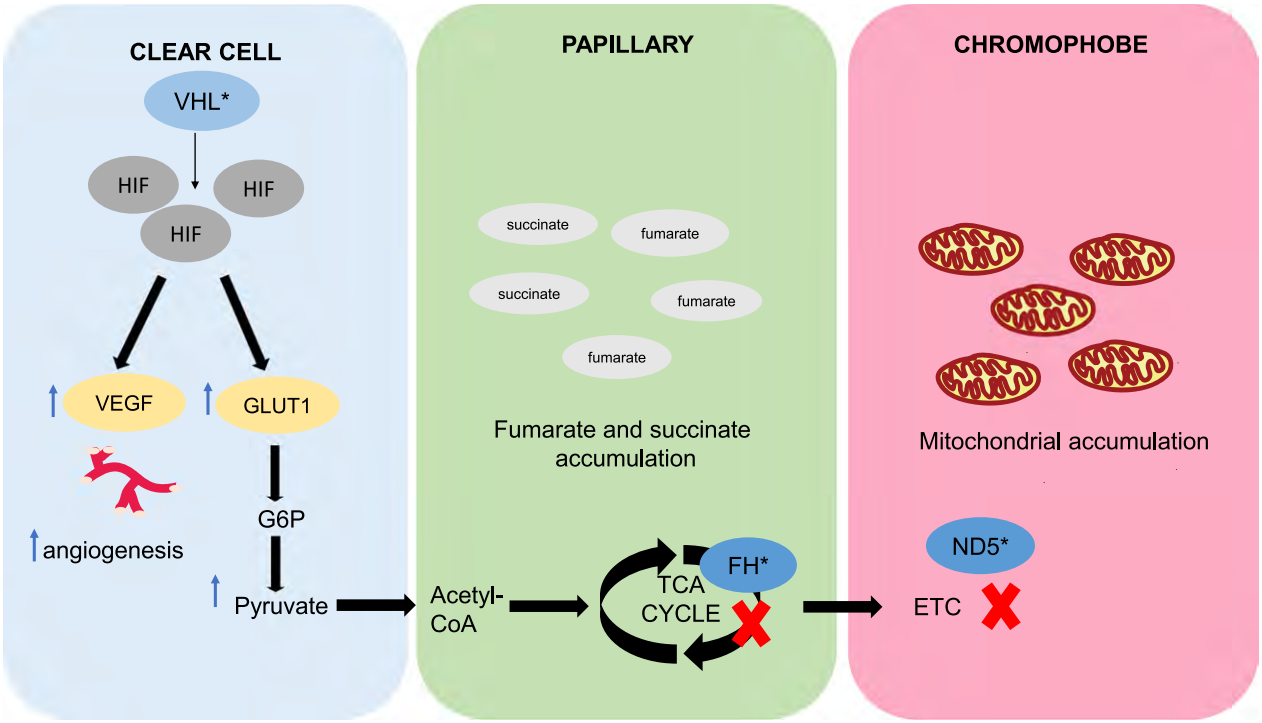
METABOLIC ALTERATIONS IN RENAL CELL CARCINOMAS

The renal cell carcinomas (RCCs) are prime examples of tumor types that are highly linked to alterations in metabolic pathways. There are three main subtypes of RCC: clear cell (ccRCC), papillary (pRCC), and chromophone (chRCC), each distinguished by unique histology and driver mutations.[9] Interestingly, although the overall mutational burden is relatively low in RCC in comparison with many other tumor types,[9] the vast majority of mutations identified in these tumors are in some way involved in the cell's ability to sense or respond to nutrients, oxygen, iron, or energy, suggesting that metabolic pathway alterations are key drivers of proliferation in all subsets of RCC.[10] Mutations resulting in dysregulation of specific steps of glycolysis, the TCA cycle, and the ETC pathways have all been found in subtypes of RCC, illustrating the diversity of metabolic alterations that may contribute to tumorigenesis (Fig. 2). Here, we discuss three examples of mutations that alter different metabolic pathways in RCC.

VHL Mutations in Clear Cell Renal Cell Carcinmoa

Mutations in the von Hippel-Lindau gene (*VHL*) are associated with a hereditary form of RCC found in patients with germline VHL disease but are also observed in nearly 90% of patients with sporadic clear cell kidney cancer (ccRCC).[11] The VHL protein is considered a tumor suppressor, and under normal circumstances, when there is enough oxygen and iron in the cell, it is part of a complex that binds to the hypoxia-inducible factors (HIFs) and targets them for degradation by ubiquitination.[12] In the majority of cases of ccRCC, inactivating mutations in *VHL* inhibit its ability to interact with the HIF proteins, and consequently the HIF proteins are stabilized, even during normoxic conditions. The HIF proteins are transcription factors that regulate the activity of a number of downstream genes, including glucose transporters *GLUT1* and *GLUT3*, endothelial growth factor, vascular endothelial growth factor (*or VEGF*), and platelet-derived growth factor.[10] The aberrant activation of these proteins and growth factors is believed to contribute to tumor growth and proliferation downstream of inactivating mutations in *VHL*. The up-regulation of *GLUT1* and *GLUT3* likely contributes to the faster rates and increased levels of glycolysis in these tumors. A number of glycolytic enzymes are also transcriptionally regulated by HIFs, including *HK1*, *HK2*, *GPI*, *PFKL*, *ALDA*, *ALDC*, *TPI*, *GAPDH*, *PGK*, *ENO1*, and *PKM*. Increased expression of these enzymes may also contribute to the increased glycolytic activity in the *VHL* mutant ccRCC tumors.[13] Finally, lactate dehydrogenase A (*LDHA*) expression is also transcriptionally regulated by HIFs. This enzyme converts the glycolytic product pyruvate to lactate,

FIGURE 2. Metabolic Alterations in RCC Subsets



Clear cell renal cell carcinoma (left panel) frequently exhibits mutations in *VHL*, resulting in stabilization of HIFs and their transcriptional targets, including VEGF and GLUT1, and thus is characterized by increased angiogenesis and up-regulated glycolysis. Mutations in *FH* and *SDH* in papillary renal cell carcinoma (middle panel) inhibit completion of the TCA cycle and result in accumulation of fumarate and/or succinate. Chromophobe renal cell carcinoma (right panel) is rare but associated with mutations in mitochondrial complex I enzymes, such as *MT-ND5*, leading to an inhibition of electron transport chain reactions and an accumulation of defective mitochondria.

Abbreviations: VHL, von Hippel-Lindau, HIF, hypoxia-inducible factor; TCA, tricarboxylic acid; ETC, electron transport chain.

and thus up-regulation of this enzyme contributes to the increased levels of lactic acid observed in tumors, a result of sustained aerobic glycolysis at the expense of the conversion of pyruvate to acetyl-CoA for use in mitochondrial oxidative phosphorylation.[13] Thus, *VHL* mutant tumors exhibit classic features of pseudo-hypoxic Warburg metabolism: up-regulated glycolysis, high levels of lactate production, and lower levels of oxidative phosphorylation.

An understanding of how the VHL and HIF pathways contribute to ccRCC tumorigenesis has provided the basis for most current treatments of patients with advanced ccRCC. Most current therapies target the *VEGF* signaling pathway, inhibiting angiogenesis.[10,14] Increased knowledge of the metabolic dependencies of RCC cells has also led to increased interest in targeting the HIF pathways and their metabolism-regulating targets. Recently, a HIF-2 agonist showed promise in reducing growth in a subset of cell lines in patients with ccRCC.[15] Agonists of GLUT1 and glycolytic pathway enzymes have also been investigated as potential therapeutic inhibitors of glycolysis in RCC.[16,17] Further characterization of the metabolic reprogramming that occurs in ccRCC has the potential to identify additional vulnerabilities of therapeutic value.

SDH and *FH* Mutations in Papillary Renal Cell Carcinoma

Mutations in several TCA cycle enzymes have been observed in pRCC. Succinate dehydrogenase (SDH) catalyzes the oxidation of succinate to fumarate in the TCA cycle. Germline mutations in the succinate dehydrogenase family subunits *SDHB*, *SDHC*, and *SDHD* have been identified in patients with familial paraganglioma/pheochromocytoma who are predisposed to developing pRCC tumors and in other patients with a family history of pRCC.[18] Likewise, germline mutations in fumarate hydratase (FH), the enzyme that catalyzes the conversion of fumarate to malate in the TCA cycle, have been found in patients with hereditary leiomyomatosis RCC and, very rarely, in sporadic cases of pRCC.[19] Because both *SDH* and *FH* mutations block normal TCA cycle and ETC activity, cells from these tumors take up almost no oxygen and rely primarily on glycolysis to supply energy and macromolecules needed for replication and growth. These tumors thus also exhibit Warburg metabolism and produce high levels of lactate.[10]

In the case of *SDH*-deficient tumors, succinate accumulates in the mitochondrial matrix as a result of loss of SDH function. Succinate, however, can also leak out into the cytosol, where it can inhibit the prolyl hydroxylation of HIF complexes, preventing them from being targeted for proteasomal degradation. In this way, succinate accumulation stabilizes the HIF transcription factors, thus promoting the activation of their downstream targets, creating a pseudo-hypoxic expression signature.[20] Therefore, in addition to defective mitochondrial respiration, *SDH* mutant cells also have increased expression of GLUT1, VEGF, and other growth factors and glycolytic enzymes, promoting cell growth and proliferation, angiogenesis, and means for up-regulating glycolysis. These tumors have also been shown to have increased vasculature.[18] Although it has not yet been well investigated because of the rarity of this tumor type, targeting the HIFs or the glycolytic pathway in these cells may have potential therapeutic value in these tumors.[10]

FH mutations similarly result in the accumulation of both succinate and fumarate as a result of the malfunction of the FH enzyme in the TCA cycle. Like succinate, fumarate can also move from the mitochondria into the cytoplasm, where it can interact with prolyl hydroxylases and prevent the degradation of HIF proteins.[21] Similarly to *SDH* mutant tumors, pRCC tumors with *FH* mutations have up-regulated expression of the HIF target genes involved in proliferation, glycolysis, and angiogenesis. Highly vascularized, these tumors grow very aggressively and have a pseudo-hypoxic gene expression profile.[22] Patients with these tumors typically have a poor prognosis, and more research is needed to identify improved therapies. The malfunctions of mitochondrial respiration and up-regulation of glycolysis in these cells appear to be key factors in their proliferation, and thus investigation of these pathways may be important for improving outcome for patients with *FH* mutations.

Electron Transport Chain-Complex I Mutations in Chromophobe Renal Cell Carcinoma

A third subset of RCC, known as chromophobe RCC (or chRCC), is the least common type of RCC. Like many of the RCCs, this type of tumor is associated with a hereditary disorder, Birt-Hogg-Dubé syndrome. Until more recent years, however, it was not known what genetic alterations contributed to sporadic cases of chRCC. Interestingly, PET/CT scans have demonstrated that, in contrast to other types of RCC, chRCC tumors are nonglycolytic, taking up very limited amounts of glucose.[23] In addition, gene expression profiling of these tumors indicated that genes involved in the TCA cycle and ETC pathways were up-regulated in these tumors.[24] Mitochondrial DNA sequencing has revealed that many chRCC tumors have mutations in genes involved in the ETC complex I, particularly in *MT-ND5*, and that these mitochondrial gene mutations also correlate with samples exhibiting an eosinophilic histologic phenotype.[24] This phenotype also correlates with an increase in mitochondrial mass resulting from an accumulation of mitochondria, possibly in compensation for hindered mitochondrial functioning.[9] Thus, the metabolic profile of chRCC appears to be very different from that of other types of kidney cancer. Although the mechanisms behind the accumulation of mitochondria in this tumor type remain to be investigated, it is clear that metabolic alterations may play an important role in growth of this rare tumor type, and hence further study of these pathways for potential use as biomarkers and therapeutic targeting is warranted.

In summary, the RCCs provide an illustration of the varied strategies used by cancer cells to augment growth through manipulations of their metabolic activities. These activities reveal possible critical dependencies, which, as has been referenced above, have been examined in terms of using

altered glycolysis for diagnostic as well as potentially therapeutic intervention. Below, we will highlight the emerging strategies to intervene in cellular metabolism for therapeutic benefit, including strategies currently approved in renal cancers and other malignancies, and new concepts that may apply in the future alone, or as adjuncts to treatments.

OTHER METABOLIC ALTERATIONS IN CANCER: CURRENT THERAPEUTIC TARGETS

A number of different kinds of genetic mutations have been associated with the dysregulation of metabolic pathways in various tumor types. The reprogramming of metabolism and alterations in metabolic flux of tumor cells compared with normal cells confers unique properties to these cells, which may prove to be useful for therapeutic targeting in patients wtih cancer. Here, we describe some of the pathways currently identified as regulators of metabolism in tumors and the current therapies targeting these alterations.

mTOR Inhibition

The mechanistic (previously mammalian) target of rapamycin (mTOR) is a serine-threonine protein kinase that forms complexes with other proteins and is involved in a number of cellular processes related to growth, proliferation, survival, motility, and protein translation.[25] mTOR signaling is commonly dysregulated in cancer through several different mechanisms. Although mutations in the *MTOR* gene itself can occur, it is more commonly activated downstream of gain-of-function mutations in the PI3K-AKT pathway or growth factors, or through inactivation of tumor suppressors such as PTEN. mTOR is also activated downstream of activation of 5'-adenosine monophosphate–activated protein kinase (AMPK), a protein that serves as an intracellular sensor of nutrients.[26] mTOR activation plays a key role in controlling intracellular metabolism through its involvement in protein translation and autophagy. The mTOR pathway has been shown to stimulate glutaminolysis by up-regulating the expression of MYC, which in turn up-regulates glutaminase, which converts glutamine to glutamate that can be used to make alpha-ketoglutarate for use in the TCA cycle.[27] mTOR activation is also known to play a role in the stabilization of HIF proteins, resulting in increased activation of their transcriptional targets, including GLUT1, VEGF, and other glycolysis enzymes.[28] Thus, activation of the mTOR pathway plays a role in the up-regulation of glycolysis, glutamine uptake, and angiogenesis in cancer cells.

Two mTOR inhibitors, temsirolimus and everolimus, have been approved in the United States and Europe for the treatment of solid tumors. These drugs bind to the mTOR complex 1 (mTORC1) by associating with FK506-binding protein12 (FKBP12), blocking the correct alignment of substrates to the catalytic cleft of this complex.[29] These drugs have shown benefits in delaying the progression and extending survival in advanced RCC, breast, and pancreatic cancers. However, resistance to these inhibitors appears to develop over time, possibly as a result of the accumulation of additional mutations in the mTOR pathway[30] or through negative feedback of the pathway itself, as inhibiting mTOR signaling can also up-regulate AKT signaling through insulin-like growth factor receptor 1 (IGF-1R).[31] Thus, continued research to find less resistant mechanisms for inhibiting mTOR is needed.

Metformin/Phenformin Inhibition of Oxidative Phosphorylation

As cancer cells are frequently known to be metabolically active and have very high levels of glucose uptake, it has been postulated that hypoglycemic drugs that have been used for treating diabetes could help to restore normal metabolism in these cells and prevent tumor growth. Two such drugs, metformin and phenformin, have shown some promise in targeting cancer cell metabolism. These organic compounds are known as biguanides, and it has been shown that diabetic patients taking them have a reduced risk of developing cancer.[32,33] The exact mechanisms by which biguanides regulate cellular metabolism is not yet well understood, but they are believed to interfere with mitochondrial complex I, inhibiting oxidative phosphorylation, while activating the AMPK signaling pathway.[34] Metformin and phenformin have been shown to delay progression of tumor cell growth in breast cancer[35] and melanoma[32] and have also exhibited antiangiogenic properties.[35] One disadvantage of treatment with these compounds is that they can induce severe acidosis in patients. More research is needed to determine the most effective dosage levels and which tumor types may be most susceptible to biguanide treatment.

Glutaminase Inhibition

Although cancer cells have been shown to have highly up-regulated glycolysis, demonstrated by the Warburg effect, they also maintain oxidative phosphorylation. In addition to glycolysis, many cancer cells appear to be dependent upon glutamine metabolism to supply the nutrients and biosynthetic precursors that they need for macromolecule synthesis.[36] The glutaminase enzyme converts glutamine to glutamate, which can be used to make alpha-ketoglutarate (α-KG), important in the TCA cycle. The TCA cycle intermediates are used in the synthesis of nucleic and fatty acids, and thus interfering with glutamine metabolism can have a profoundly detrimental effect on replicating cells.

Several mechanisms have been proposed for inhibiting glutaminase, including targeting ASCT2, the transporter that mediates glutamine uptake into cells, and the use of glutamine mimetics to competitively inhibit glutamine uptake and activity. Unfortunately, early clinical trials testing glutamine mimetics resulted in high levels of toxicity in patients.[37] More recently, however, several small molecule allosteric inhibitors of glutaminase activity have been identified, including CB-839, currently in clinical trials, and bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl) ethyl sulfide (BPTES). Targeting glutaminase activity has been shown to reduce oncogenic transformation in cancer cells,[38] and allosteric inhibitors of glutaminase have been used in combination with other chemotherapeutics to reduce tumor cell growth

in lymphoma,[39] lung,[40] and breast[41] cancer cell lines. Further research will likely focus on determining which tumors are most glutamine dependent and thus most susceptible to glutaminase inhibition. It will also be important to investigate the most efficient methods for targeting glutaminase activity in cancer cells while minimizing toxicity to others.

Inhibition of Isocitrate Dehydorgenase Enzymes 1 and 2

The isocitrate dehydrogenase enzymes (IDH1 and IDH2) are important metabolic enzymes that convert isocitrate to alpha-ketoglutarate by oxidative decarboxylation. α-KG is a key player in the TCA cycle, and thus these enzymes play an important role in oxidative phosphorylation. IDH1 and IDH2 also play a role in the generation of NADPH, a reducing factor that helps to protect the cell against oxidative damage.[42] Therefore, mutations in IDH1 and IDH2 are believed to both alter cellular metabolism and potentially increase rates of DNA damage attributable to altered NADPH protection. Mutations in IDH1 and IDH2 have been observed in several types of tumors, including leukemias, lymphomas, and gliomas. The mutations identified in IDH1 and IDH2 in cancers appear to be gain-of-function point mutations that occur at specific arginine residues that presumably alter the structure of these proteins. These mutations lead to increased conversion of α-KG to D-2-hydroxyglutarate.[43] High levels of D-2-hydroxyglutarate have been associated with increases in histone and DNA methylation, contributing to tumor progression.[42] It has also been shown that mutant IDH1 heterodimerizes with wild-type IDH1, inhibiting the activity of the wild-type enzyme and reducing levels of α-KG, which may play a role in the degradation of HIF proteins. Thus, mutant IDH1 may also play a role in the stabilization of HIFs and increased activation of their transcription factors involved in tumorigenesis and angiogenesis.[43]

Several targeted chemical inhibitors of the activity of specific IDH1 and IDH2 point mutants have been designed and have been shown to reduce D-2-hydroxyglutarate and growth in cells and mouse models.[43] Clinical trials using these inhibitors are ongoing in early stages. Another possible mechanism for inhibiting IDH1/IDH2 signaling is to deprive them of α-KG using glutaminase inhibitors as described above.[44] The study of IDH inhibition is ongoing in an effort to identify patients that may benefit from these therapies and which compounds and dosages are most effective.

Targeting Lipid Metabolism

Although altered glucose and glutamine metabolism have been the primary focus of work studying the changes in metabolism of cancer cells, another aspect of cellular metabolism that is unique in proliferating and cancer cells is the oxidation and synthesis of lipids. Lipids such as fatty acids serve as an additional energy source for cells and are required for membrane synthesis during cellular growth and division. Lipids can also play roles in cellular signaling by functioning as second messengers and as hormones.[45] Fatty acids, the primary building block of cellular membranes, can be obtained from environmental sources or the cells can synthesize these molecules de novo. Most normal adult cells prefer to get fatty acids from exogenous sources, but observations in cancer cells indicate that the de novo synthesis of fatty acids is highly up-regulated in many types of tumors.[46] The shift in fatty acid synthesis in tumors has been suggested as a potential target to limit cancer cell growth.

One potential target for limiting lipid synthesis in tumor cells is the fatty acid synthase enzyme complex, FASN, which has also been found to be up-regulated in some breast tumors.[47] Currently, several chemical inhibitors, as well as genetic ablation of FASN by RNA interference, are being tested for effectiveness in reducing tumor cell growth and proliferation.[47] These studies have been extended to other enzymes involved in fatty acid synthesis as well. Other potential targets for inhibiting fatty acid synthesis are the sterol regulatory element-binding proteins (SREBPs), which are upstream regulators of lipid synthesis.[47] So far, inhibitors of these molecules are in preclinical trial stages, as the investigation of potential side effects is necessary before they are given to patients.

INTERACTIONS BETWEEN METABOLISM AND EPIGENETICS

The metabolic reprogramming that occurs in cancer has far-reaching effects. In addition to altering metabolic pathways in response to nutrient uptake, metabolic changes also influence the epigenetic regulation of gene expression. Epigenetics are heritable changes in DNA that are not the result of an alteration in sequence and include histone modifications such as methylation, acetylation, and phosphorylation. These epigenetic changes can influence gene expression by enhancing or repressing the transcription of genes. Thus, epigenetic changes downstream of metabolic alterations can influence the expression levels of many genes in cancer cells, possibly giving them a survival and growth advantage. In addition, the reverse could also be true: Epigenetic alterations can influence cellular metabolism by altering the transcription of genes involved in metabolic pathways.[48] These processes are tightly linked, and we will discuss several possible mechanisms for these interactions here.

The methylation of DNA at CpG sites in promoters is a mechanism by which epigenetic modifications repress the expression of genes. In cancer, DNA methylation is often observed in the promoter sites of tumor suppressor genes. DNA methylation is mediated by DNA methyltransferases, and histone methylation is mediated by histone methyltransferases, both of which use an activated methyl donor from *S*-adenosylmethionine (SAM), a product of one-carbon metabolism. Dysregulation of carbon metabolism pathways in cancer can alter the levels of SAM and methyl donors available, thus influencing the epigenetic modifications and expression of genes in these cells.[49]

Another mechanism by which metabolic pathways can effect epigenetics is through the TCA cycle metabolites. Several histone demethylases require the TCA cycle protein α-KG as a cofactor for activation, and thus the levels of TCA cycle

intermediates may influence demethylase protein activity by competitive inhibition. Likewise, D-2-hydroxyglutarate, the protein made from α-KG by cancer cells with IDH1/IDH2 mutations (discussed above), inhibits the activity of α-KG–dependent demethylases. SDH and FH mutations that result in accumulation of succinate and fumarate in cancer cells can also act as competitive antagonists for inhibiting these α-KG–dependent demethylases. Thus, inhibition of demethylases in cancer cells by TCA cycle intermediates can result in hypermethylation of a variety of genes,[49] contributing to the repression of tumor suppressor genes and others.

Another metabolic molecule that contributes to epigenetic programming is acetyl-CoA. Acetyl-CoA fuels the TCA cycle and is involved in nearly all aspects of cellular metabolism, but is also used as a cofactor by enzymes that transfer acetyl groups, including histone acetyltransferases, which catalyze the addition of an acetyl group to histones. Histone acetylation is associated with transcriptional activation of genes. Thus, the availability of acetyl-CoA, highly influenced by cellular metabolism pathways, also plays a role in the epigenetic regulation of gene expression.[48,49]

These are just a few examples of ways in which metabolic alterations can influence the epigenetic regulation of gene expression. Thus, it must be considered that targeting metabolic pathways can also alter the epigenetic control of gene expression. Likewise, targeting epigenetic modification pathways also holds potential to alter gene expression, including that of metabolism pathway enzymes. Future research investigating the links between epigenetics and metabolism will hopefully provide greater understanding of the complexity of the interactions between metabolism and chromatin dynamics in both normal and cancer cells.

CONCLUSION

Proliferating cancer cells must maintain both sufficient energy and pools of metabolic intermediates for building macromolecules needed for proliferation, including DNA, proteins, and lipids. These tasks are accomplished in most cancer cells by adapting their metabolism to be more dependent upon aerobic glycolysis and glutaminolysis. The mechanisms behind the metabolic reprogramming that takes place in most tumor cells are diverse and include oncogenic activation, the repression of tumor suppressor signaling, epigenetic modifications, and mutations in metabolic enzymes themselves. As the metabolic profiles of tumor cells distinguish them from normal cells and are critical for their growth and survival, the metabolic signaling pathways have become desirable targets for therapeutic intervention in patients with cancer. Recent work has focused on identifying inhibitors of critical metabolism pathways and shows promise in targeting metabolism to improve patient outcomes, either alone or in combination with other targeted therapies.

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Value-Based Medicine and Integration of Tumor Biology

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OVERVIEW

Clinical oncology is in the midst of a genomic revolution, as molecular insights redefine our understanding of cancer biology. Greater awareness of the distinct aberrations that drive carcinogenesis is also contributing to a growing armamentarium of genomically targeted therapies. Although much work remains to better understand how to combine and sequence these therapies, improved outcomes for patients are becoming manifest. As we welcome this genomic revolution in cancer care, oncologists also must grapple with a number of practical problems. Costs of cancer care continue to grow, with targeted therapies responsible for an increasing proportion of spending. Rising costs are bringing the concept of value into sharper focus and challenging the oncology community with implementation of value-based cancer care. This article explores the ways that the genomic revolution is transforming cancer care, describes various frameworks for considering the value of genomically targeted therapies, and outlines key challenges for delivering on the promise of personalized cancer care. It highlights practical solutions for the implementation of value-based care, including investment in biomarker development and clinical trials to improve the efficacy of targeted therapy, the use of evidence-based clinical pathways, team-based care, computerized clinical decision support, and value-based payment approaches.

Cancer is a heterogeneous disease with variations that extend molecularly, clinically, and therapeutically, and the complex diagram of cancer treatment is evolving exponentially as more and more treatments are developed. This presents a challenge for physicians as they attempt to decipher the proper treatment profile and timeline for each patient with the lowest burden on the patient. Value-based care is a critical component of cancer treatment and should include an emphasis on quality of care as well as patient experience. This requires coordination and communication among all physicians and facilities involved in a patient's care to ensure that the patient is fully informed and engaged in the treatment approach across the trajectory of care. Ultimately, value-based cancer care requires the complicated tasks of balancing standardization and individualization of care, with transparency about the expected clinical and financial implications of care.

TUMOR BIOLOGY, CLINICAL IMPLICATIONS, AND REASONS FOR VALUE-BASED MEDICINE

The costs of cancer care continue to increase,[1] but, on average, the costs of cancer drugs amount to only 5% to 20% of the total costs of cancer care.[2] However, the average cost of some of the newer treatment options, such as combinations of checkpoint inhibitors, can cost as much as $100,000 per month.[2] This cost led the Institute of Medicine to define six elements of value in cancer care: safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity. ASCO developed a value framework that focuses on three elements that are easily measured and frequently reported in clinical trials: clinical benefit (effectiveness), toxicity (safety), and cost (efficiency).[3,4] These factors are vital to incorporate into care processes as oncology faces a growing and aging cancer population and increasing costs of oncology drugs—up 30% over 4 years.[5]

This creates an opportunity to leverage the value of genomics to arrive at personalized medicine and precision medicine that aims to cure cancers and improve quality of life without creating a financial burden for patients. The key for the success of precision medicine will be to balance the current system of organ-focused cancer classification and therapy with the new transforming model in which cancers are defined by their genetic makeup. As an example, lung cancer is not only histologically split between small cell and non–small cell lung cancer (15% and 85%, respectively) but also additionally delineated within non–small cell lung cancer into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (40%, 25% to 30%, and 5% to 10% of all lung cancer incidences, respectively).[6] This heterogeneity extends further with the introduction of complex molecular profiling within each subtype of disease. For example, in adenocarcinoma, the oncogene makeup consists of *KRAS* (32.2%), *EGFR* (11.3%), *BRAF* (7.0%), *NF1* (8.3%), *MET* ex14 (4.3%), *ALK* fusion (1.3%), *ROS1* fusion (1.7%), and numerous other oncogene mutations.[7] Meanwhile, in squamous cell lung carcinoma, the key candidate genes are *FGFR1* (20%), *SOX* (20%), *PIK3CA* (20%), *MDM2* (10%), *PDGFRA* (8% to 10%), *MET* (6%), and several other mutations.[8]

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This complex array in the frequency and variety of mutations within cancer subtypes is the driver behind the new era of targeted therapies that originally began with *EGFR* tyrosine kinase inhibitors, such as erlotinib and gefitinib. As an example of clinical benefit and efficiency, erlotinib has been shown to have a progression-free survival benefit in patients with advanced *EGFR* mutation–positive non–small cell lung cancer and was associated with more tolerability than standard chemotherapy for first-line treatment.[9] The identification of *EGFR* and other driver mutations within lung cancer and other cancer types has revolutionized cancer treatment to true personalized medicine in which the genetic makeup of a tumor is analyzed by next-generation sequencing or liquid biopsy to truly individualize cancer treatment.[10]

In our clinics, we consistently face the need for genomics and other omics analysis as well as their pairing with clinically effective and cost-effective therapies. As an example, a 67-year-old man with a history of localized squamous cell esophageal cancer was first diagnosed and treated with chemoradiation. Six months later, during his surveillance workup, an isolated left lower lung nodule was noted on imaging. The biopsy reportedly showed squamous cell carcinoma, and he underwent a left lower lobectomy with lymph node dissection in 2003. The pathology confirmed T1N0Mx well-differentiated squamous cell carcinoma, and he was treated with adjuvant fluorouracil and carboplatin followed by radiotherapy. He did well for 7 years after treatment and had no evidence of disease on serial imaging and endoscopies until a follow-up scan showed a new left upper lung nodule suspicious for primary adenocarcinoma along with multiple, nonspecific micronodules. Surveillance continued for 3 months, when a repeat chest CT showed steady progression of size and density of the left upper lobe nodule associated with increased uptake on PET imaging. Pathology showed squamous cell carcinoma in situ in the right lower lung, but the left lung nodule displayed well-differentiated adenocarcinoma (pT2aNX). Molecular marker testing on this tissue showed *EGFR* and *KRAS* wild-type genes, but there was not enough tissue for *EML4-ALK* testing.

The patient began treatment with five cycles of carboplatin and gemcitabine, which he tolerated well, and his disease was clinically stable. Twelve months later, however, a CT scan found an increase in the size of pulmonary nodules in the right lung as well as new nodules at the left base that confirmed progression of disease. A bronchoscopy was performed and showed squamous cell carcinoma. Treatment was switched to systemic chemotherapy with carboplatin and docetaxel, but the patient developed neutropenic fever that required hospitalization after cycle 1. This prompted a 20% dose reduction for cycle 2. Tissue from the bronchoscopy was sent for molecular testing, which identified seven genomic alterations and 17 variants of unknown significance. The patient subsequently stopped chemotherapy and was monitored with follow-up CT scans for 12 months.

At the next disease progression, a VeriStrat test was done; the result was VeriStrat Good, which indicated a potential benefit from *EGFR* inhibitor therapy. Thus, the patient received 150 mg of erlotinib daily. During erlotinib treatment, the patient developed an acneiform rash and diarrhea, which were managed supportively. A follow-up CT scan showed disease progression with increased lymphadenopathy as well as new lung and liver lesions. Erlotinib treatment was replaced with nab-paclitaxel for two cycles, which had to be stopped for recurrent bacterial infections and disease progression. Then, photodynamic therapy was started; although the patient responded well, with better breathing and fewer symptoms, there was little disease response. The patient subsequently died within 4 months. Figure 1 summarizes the oncologic history of the patient as a timeline.

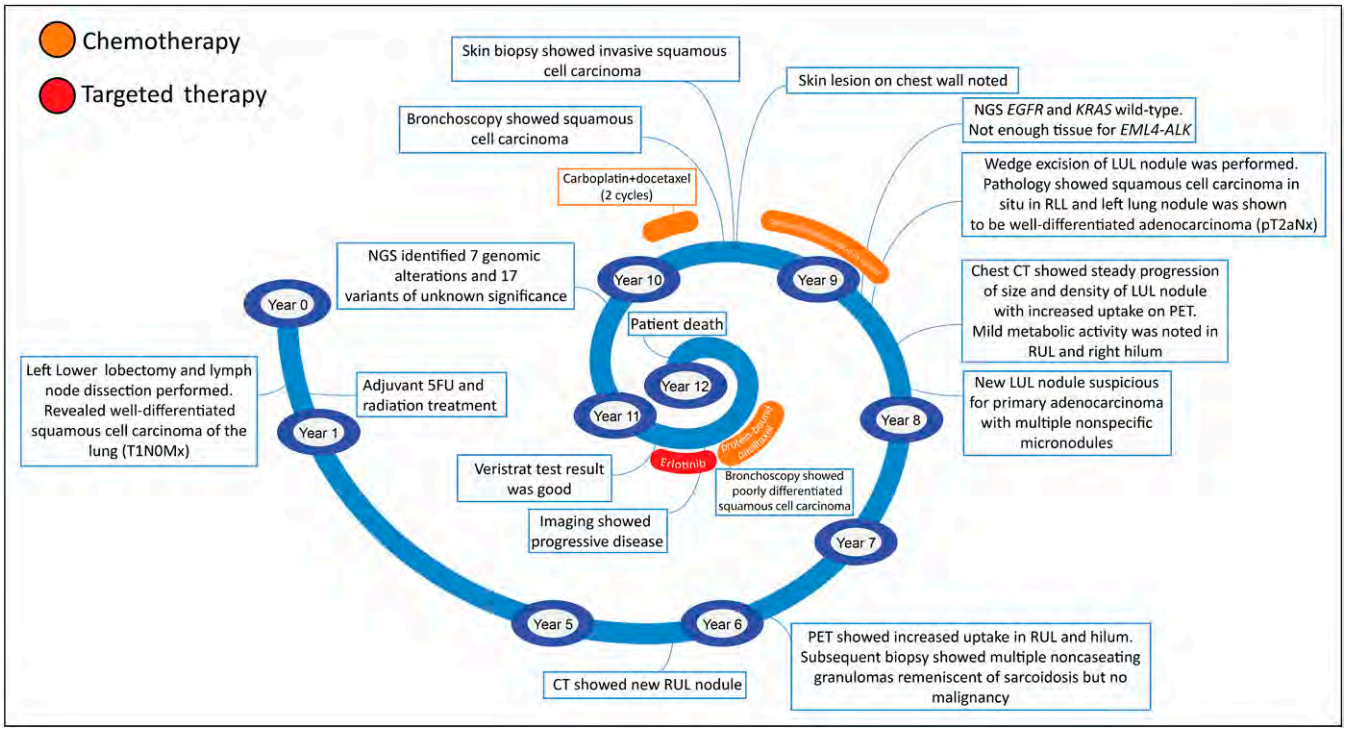
This patient case is not only a good example of the clinical benefit of targeted therapies but also allows us to understand the challenges of their use without reliable biomarker testing. Although it was determined by proteomic analysis that our patient would be a reasonable candidate for *EGFR* inhibitor therapy, the clinical results of erlotinib treatment showed no evidence of response. This extends to other patient cases, in which the presence of an *EGFR* mutation and treatment with an *EGFR* tyrosine kinase inhibitor or other targeted therapy does not guarantee response or absence of toxicity. However, it also highlights the value in understanding the entire omic structure of lung cancer, for which it is not only the tissue molecular testing by next-generation sequencing that plays a vital role but also the liquid biopsy, which may offer options for patients with advanced non–small cell lung cancer to detect mechanisms of acquired resistance, such as T790M.[11,12] As shown in this case, the next-generation sequencing was performed—with a test that costs anywhere between $5,500 and $5,800—but did not offer the patient any clinical options in terms of targeted therapy.[13] However, this approach to clinically understand the efficacy and the benefit of these omic tests highlights the importance of verifying and validating all omics testing in the new paradigm of precision medicine so that testing is affordable, in the best interest of the patient, appropriate, and also widely understood and accepted across national institutions (Fig. 2).

As oncology trends grow and evolve, it will be essential to reconsider the traditional clinical pathways to incorporate

KEY POINTS

- **Genomic, and other omic platforms, are currently utilized in oncology for certain diseases.**
- **The value of the omic platforms is not consistent throughout practices.**
- **As we think about value in oncology, pathways should also be considered.**
- **The financial implications of the various platforms and decision analysis must also be taken into account. This has to reflect patient benefit.**
- **As we move into value based medicine, we have to consider the heterogeneity of cancer and ultimately optimize therapy based on as much information available.**

FIGURE 1. Timeline of Oncologic History of a Patient



Abbreviations: 5-FU, 5-fluorouracil; LUL, left upper lobe; NGS, next-generation sequencing; RLL, right lower lobe; RUL, right upper lobe.

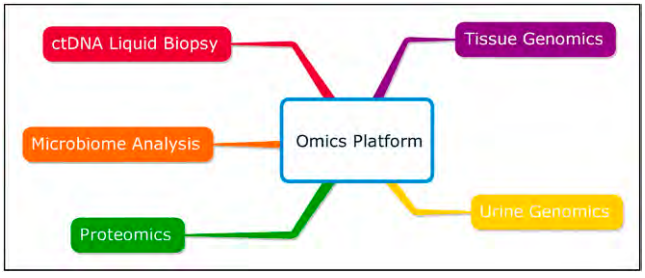
the transformation of cancer from an overarching disease into a larger number of molecularly defined diseases that have individualized therapeutic options.[5] Ongoing national clinical trials, including TAPUR, Basket, QUILT, and MATCH, are excellent examples of pooling national patient access to genomically determined targeted agents and capturing response and toxicity data to understand clinical benefit. It is hoped that, by including patients with many different pathologic cancers into targeted therapy trials that are based on similar genomic mutations, we can better understand efficacy and the tumor types that may or may not respond similarly on the basis of similar driver mutations.

ACTUALIZING INDIVIDUALIZED THERAPIES WITH PATHWAYS, TOOLS, AND PROCESSES TO ACHIEVE VALUE-BASED CARE

The foundations of any treatment plan are personal health information, performance status, diagnosis, and staging information, which are then paired with molecular data. Mutation status may include one or more targetable mutations, depending on the primary cancer site, and can be heterogeneous at diagnosis (across primary and metastatic sites). In addition, both mutation status and extent of disease can change with disease progression. The comprehensive treatment plan also is based on the setting (e.g., prevention, neoadjuvant, adjuvant, metastatic, induction, consolidation, and maintenance phases) as well as the line of each therapy, type and time of any past response, and sites of metastases. In addition, treatment plans may be modified for specific populations, such as adolescent/young adults, geriatric populations, and those with particular comorbidities or inherited gene mutations.

If oncologists expect to fully integrate these numerous data points to help guide the best care for each patient, clinical systems are needed to prompt for order and collection of discrete data to offer real-time decision support and

FIGURE 2. Omics Architecture Detailing Available Methods for Patient Oncogenic Testing



extractable data for outcome reporting. These systems will need rapid updatability, given the frequency of new discoveries that have clinical relevance for patients. Value-based care must be delivered by innovative clinical teams that work collaboratively with payer systems to avoid the growing regulatory burden that is increasing the administrative oncology work load[14] and straining a challenged oncology work force that faces increasing burnout.[15]

Given the explosion of molecular data to guide optimal treatment options, given the approval of some therapies only in a set sequence, and given more and more targetable mutations identified and linked to effective treatments for common and rare cancers, even doctors who specialize in one type of cancer can benefit from the collective wisdom of national experts at the point of care. Most oncologists, in fact, see patients whose diseases span the entire range of cancer diagnoses, stages, and molecular features. Having high-quality, expert decision support at the point of care can ensure appropriate molecular and other testing is done at the best time to optimize the chance of giving a patient the right therapy, including targeted therapies with supportive and palliative care, to achieve the best and most cost-effective health outcome.[16,17]

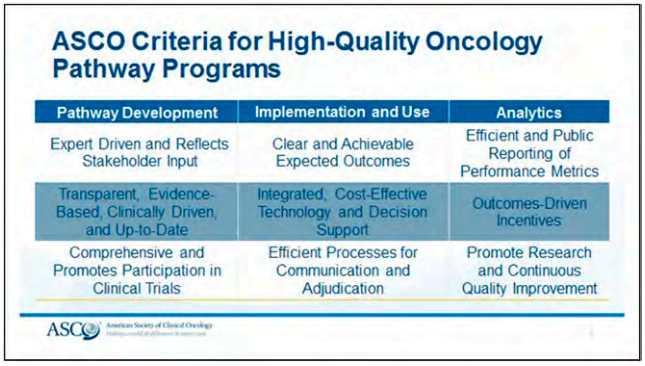
Pathways, thus, have become the tools to empower evidence-based cancer care plans. In addition, they have been shown to lower costs and still ensure the delivery of evidence-based care. Work published by the US Oncology group showed equivalent outcomes and significantly lower costs with their pathway program in both metastatic colon and lung cancers.[18,19] A pilot study of the UnitedHealthcare episode-based payment model, with practice-chosen pathways for breast, colon, and lung cancers, showed a 34% reduction in costs compared with their fee-for-service database.[20] The 3-year results (2009–2012) from an expanded pilot study in five practices reported the same 34% overall reduction in medical costs from before and after the pilot study, even with higher chemotherapy costs, because hospitalizations were markedly reduced.[21]

Adopting practice or group practice pathways, addressing and standardizing care processes, and using team-based care have been the pillars of groups who work with payers to achieve value-based care, which is generally accepted as a measure of outcomes achieved per monetary expenditure. Several groups have reported various aspects of improved outcomes with these approaches.[22-25] Team-based care, led by physicians, is another process to ensure caregiver teams work to the top of their license so that data are collected to empower and improve care while clinicians are allowed time to compassionately care for vulnerable patients.[26,27]

As pathways have proliferated, however, payers, patients, and clinicians have struggled to manage practical implementation into daily clinical practice, especially when different payers require different pathways to authorize payments. As pathways have helped payers understand complexities of care and guide their authorization processes, different payers have adopted different pathway systems and rules for coverage. A majority of cancer practices have or are adopting pathway programs, but they may have to use several in one practice to get authorizations and coverage for different patients who have the same disease types. This proliferation of payer pathways and the increase in the administrative burden led the ASCO board to empanel a Pathway Task Force in 2014. With extensive stakeholder input, the task force developed a policy statement of clinical pathways in oncology,[14] followed more recently by criteria for high-quality clinical pathways in oncology, depicted in Fig. 3. The goal is for all stakeholders to have criteria to ensure the pathway program a practice chooses is developed transparently and implemented efficiently, with analytic capabilities to evaluate short- and long-term impacts.

New clinical processes also are critical to ensure appropriate tumor testing at diagnosis and relapse to customize the treatment plan for a patient. Oncologists are networking with primary care physicians, interventional radiologists, and pathologists to ensure that tumors are tested accurately. Although technology has helped lower the cost of complex molecular and genetic assessments over time, batch testing, for now, is not standard, and high-cost molecular tests are often required in sequence, which requires tracking by busy clinicians. As costs continue to decline, larger molecular and genetic panels may be done at the time of either a liquid biopsy or tumor biopsy to ensure identification of any effective targetable mutations.

FIGURE 3. ASCO Criteria for High-Quality Oncology Pathway Programs



Reproduced with permission.[28]

With the major impact of improved cancer outcomes for patients from targeted therapy comes a rapid change phase in oncology to develop, study, and deploy new care processes, tools, and teams to incorporate best-practice options so that patients have access to timely and effective care. We can look forward to electronic medical record enhancements that facilitate collaboration and collection of discrete data about patients, diagnoses, and molecular mutations, as well as tracking of tests and therapies and their changes over time. Real-time decision support could provide pathway prompting for the best therapies and sequences of targeted and other treatments that consider specific patient populations, patient preferences, comorbidities, toxicities, and costs. Groups that use similar electronic medical record systems and larger big data collaborations with analytic systems, like ASCO CancerLinQ, Flatiron Health, and NantHealth, are all working to collect validated data to analyze clinical and financial outcomes partnered with patient and clinician satisfaction. These systems will guide oncologists as we continue to discover new targetable pathways, diagnostics, and therapies to achieve the triple aim outlined by the Institute of Medicine and the fourth aim, now recognized as essential for success: better health, better patient experience, lower costs, and improved clinician satisfaction.[29]

CANCER CARE DELIVERY AND COST-EFFECTIVENESS ANALYSIS IN THE ERA OF OMICS

One of the hoped-for benefits of precision medicine is that genomically targeted therapies will improve the value of cancer care. Cost-effectiveness analysis is an economic approach to assess the value of medical therapies, and it generally takes a societal perspective. The societal perspective is particularly relevant for policy makers, because the costs of medical care are diffused across society (e.g., in the form of higher taxes or more expensive health insurance premiums). Implicitly, opportunity costs also are experienced at the societal level: the decision to adopt higher-cost cancer therapies should translate to improved health outcomes for patients with cancer, but the opportunity cost of this decision may preclude government spending for other societal programs.

The value formula used in cost-effectiveness analysis is intuitively simple; costs associated with a new therapy or technology are placed in the numerator of the value equation, and an outcome measure of effectiveness (usually quality-adjusted life-years [QALYs]) is placed in the denominator. In most cases, the key assessment is an incremental analysis to compare a new therapy against a standard-of-care comparator. The quotient of incremental cost versus incremental benefit is then expressed as the incremental cost-effectiveness ratio (e.g., cost per QALY). Cost-effectiveness is only one of multiple approaches to define value; however, the simple principles of cost-effectiveness analysis provide an important starting point for any discussion of value.

At least three properties that are theoretically shared by targeted therapies should nominally enhance the cost-effectiveness of targeted agents relative to untargeted therapies. First, only a subset of the population will receive a targeted agent, (e.g., only patients with breast cancer that overexpresses *HER2* should receive trastuzumab).[30] In this way, patients who are unlikely to benefit from a targeted therapy are spared treatment and any accompanying toxicities. A second property of targeted agents is that they are designer drugs, which have a hypothesis-based mechanism of action to target an important oncologic process. Last, and related to the second property, targeted agents should have fewer off-target toxicities, which make them theoretically easier to tolerate.

Although the promise of enhanced efficacy from targeted therapies is increasingly being realized for many cancer types, improvements in efficacy only address the numerator of the value equation. The denominator of this equation, cost, usually is not included in journal articles that report drug efficacy. Nevertheless, cost is a critical real-world determinant of access to drug therapy. In some cases, access is rationed at the systemic or societal level, as in the United Kingdom, Canada, and many other nations that directly incorporate cost-effectiveness into drug coverage decisions[3,31,32]; in other cases, access is rationed at the individual level, as in the United States, where high medication copays are associated with nonadherence to life-sustaining therapy.[33]

The case of pertuzumab in metastatic breast cancer provides context for the relative contributions of both efficacy and cost toward the overall cost-effectiveness of therapy. The CLEOPATRA study demonstrated a 15.7-month improvement in overall survival for patients with *HER2*-positive, metastatic breast cancer who received pertuzumab as part of first-line chemotherapy.[34] This impressive efficacy result underscores the power of molecularly targeted therapy to improve patient outcomes, and very few oncologists or patients would discount the benefit of this survival improvement. However, drug cost is a key driver of cost-effectiveness, and the average sales price of pertuzumab in the third quarter of 2016 was $4,000 to $5,000 per 3-week treatment cycle.[35] A peer-reviewed cost-effectiveness analysis by Durkee and colleagues[36] estimated incremental costs associated with first-line pertuzumab use of $294,747 per patient and an incremental cost-effectiveness ratio of $472,668 per QALY ($206,335 per life-year).[36] Although no absolute thresholds exist in U.S. health care policy, these estimates generally are accepted as poor cost-effectiveness—even in the context of highly impressive treatment efficacy.

Pertuzumab is hardly an outlier in terms of pricing for targeted therapies. Another instructive case is that of necitumumab, a monoclonal antibody inhibitor of EGFR that was approved by the U.S. Food and Drug Administration (FDA) for the treatment of squamous cell lung cancer in November 2015. Because necitumumab is approved only for advanced squamous cell lung cancer, it stands to reason that a value-based price for necitumumab is best defined in that clinical setting. Unlike the case of pertuzumab, the survival benefit reported for necitumumab in advanced squamous cell lung cancer was small (overall survival, 11.5 months

in the necitumumab group, which was 1.6 months longer than in the control group).[37] Grade 3 or greater toxicities were more common with necitumumab than with control (72% vs. 62% of patients). After the study results were reported, but before necitumumab was approved by the FDA, Goldstein and colleagues[38] sought to define a value-based price for necitumumab. They calculated that necitumumab would be cost-effective at a willingness-to-pay threshold of $100,000 per QALY if priced at $563 per 3-week cycle, and that it would be cost-effective at a higher threshold of $200,000 per QALY if priced at $1,309 per cycle. Now that necitumumab has been approved and marketed, the actual cost per cycle is approximately $4,200.[35] As a result of this glaring desynchrony between value and price, necitumumab was recently removed from the National Comprehensive Cancer Network list of guideline-recommended therapies for metastatic squamous cell lung cancer.[39]

These examples demonstrate that targeted therapies are not any more inherently cost-effective than traditional cytotoxic therapies. Cost is an essential component of the value calculation under any framework. Even highly effective, minimally toxic therapies are of low value to patients and to society at large if exorbitant costs limit or prevent access. How, then, can the value of targeted therapies be improved? We submit that strategies to improve the value of targeted therapies should be directed at both the numerator and the denominator of the value equation.

To focus on the denominator of the value equation, strategies are needed to enhance efficacy and reduce toxicity of targeted therapies. Fortunately, this is an area in which cancer researchers are moving ahead full steam. A targeted therapy is only as good as the biomarker target, and strengthening the link between biomarker and efficacy is one example of a strategy to improve the value of targeted therapies. Cetuximab and panitumumab were initially approved in 2004 and 2006, respectively, for the treatment of chemotherapy-refractory colorectal cancer. After a growing body of data demonstrated that EGFR inhibitors were ineffective in roughly 50% of patients with colorectal cancer who had *KRAS* mutations,[40,41] the FDA restricted its approval of these agents in 2009 to patients who did not have *KRAS* mutations. Further research has continued to narrow the population of patients with colorectal cancer who are candidates for EGFR inhibitor therapy, after the finding that *NRAS* mutations[42] and right-sided tumors[43,44] also are predictors of poor efficacy from EGFR inhibitor therapy. With every step to narrow the population of patients with colorectal cancer who are eligible to receive EGFR inhibitor therapy, the average efficacy among treated patients should improve alongside the value of the drug. Much more work is needed to improve biomarkers for other molecularly targeted therapies; however, we are optimistic that the medical and scientific communities are up to this task.

Changing the numerator of the value equation for targeted therapies is a more complicated task. There is increasing anecdotal evidence that patients,[45] physicians,[46] and society at large will not tolerate a continuation of current trends in drug pricing, particularly in the United States, where drug costs are highest. Whether these sentiments will translate to legislative action to regulate drug prices is uncertain, although the current U.S. president and prominent members of Congress recently have discussed or proposed legislation to regulate drug prices. Alternative approaches for bringing drug prices into alignment with societal resources include value-based payment schemes, such as indication-specific pricing or performance-based pricing.

Indication-specific pricing is an approach that is particularly relevant for targeted therapies, which often hold many distinct indications, both approved and off label.[47] For example, trastuzumab has accepted indications that include the treatment of early-stage breast cancer, metastatic breast cancer, salivary duct cancer, gastroesophageal cancer, and lung cancer. The value of trastuzumab therapy, as measured in a cost-effectiveness framework, varies greatly across these indications. However, drug payments for trastuzumab are the same regardless of indication. In indication-specific pricing, the payment for a specified drug is allowed to vary by indication. Pharmaceutical companies could garner higher payments in settings in which the drug has a high proven efficacy, such as adjuvant trastuzumab therapy for *HER2*-positive breast cancer (34% reduction in the risk of death at 2 years after completion of therapy).[48] In situations in which trastuzumab has a lower efficacy, such as metastatic esophagogastric cancer (2.7-month improvement in median overall survival),[49] a lower price would be required to maintain cost-effectiveness. The incentive structure of this system would encourage pharmaceutical companies to develop drugs in a way that maximizes efficacy for distinct targeted populations, rather than a way that seeks the lowest efficacy threshold achievable in the largest possible patient population.

Indication-specific pricing and other forms of value-based payment would require specific reimbursement system changes to permit implementation[47] and likely would require a governmental mandate. Legislative price controls are considered politically challenging in the United States, although implementation of controls in developed countries around the world attests to their widespread acceptability. Nevertheless, finding ways to restrain uncontrolled growth in the prices of cancer therapies is imperative at the societal level to maintain access to treatment for patients. The efforts of ASCO and other societies to call attention to the cost and value of cancer therapies are an important step toward moderating drug costs and delivering on the promise of high-value, highly targeted cancer therapies.[2-4,50]

CONCLUSION

It is exhilarating to practice oncology with the current and rapidly expanding ability to deploy effective and well-tolerated molecularly targeted therapies to prevent, control, and sometimes cure malignant diseases. Challenges remain, however, in applying principles of value-based care in this rapidly evolving landscape. These challenges are compounded by the fragmentation of classic diagnostic categories into a

greater number of molecularly defined disease entities. In clinical research, key questions include which and how many molecular targets are needed, and whether they are needed alone or in combination. In clinical practice, best practices are emerging for the development and deployment of the integrated tools, teams, and processes to provide value-based care. At the societal level, increasing costs associated with cancer treatment threaten access to therapies, and strategies are needed to ensure that costs are commensurate with benefits at the individual and societal levels.

To meet these challenges and achieve true value-based care will require the support of government, industry, and health systems for continued research and development of effective therapies. We need investments in real-time decision support, expanded access to clinical trials, and new payment and team-based care models. The scientific advancements that have enabled the genomic revolution are truly remarkable; however, the promise of this new era cannot be fully realized for our patients until the implementation of value-based care is accomplished.

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G. A. Brooks and L. D. Bosserman contributed equally to this article.

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