Informed Prostate Cancer Support Group Inc.
"A 501 C 3 CORPORATION ID # 54-2141691"

August 2020 NEWSLETTER

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Phone: 619-890-8447 Web: http://ipcsg.org

Wednesday, August 12,

Volume 13 Issue 08

Live-Stream Event, Saturday, August 15th,10:00am PT

Social Security and Supplemental Plans

As the enrollment period for Social Security nears, Richard Russell a licensed sales agent will be discussing Social Security and supplemental plans. Richard will focus on Medicare enrollment, what each of the parts A, B, C & D mean, the differences between only having original Medicare verses private insurance plans, and when it makes the most sense to compliment/supplement Original Medicare. He will also discuss options people have, when to make changes and why. Another important topic, special election periods, what and when they are.

Richard can answer general questions as to the presentation and other items that may come to mind. If Richard feel it is private in nature he will defer to contacting him directly for the answer. Richard can be reached via phone at (760) 214-8715 or email at rarffg@gmail.com, or via his web site http://www.myuhcagent.com/richard.russell

Due to COVID-19, no in-person meetings at the Sanford Burnham Prebys Medical Discovery Institute will take place until further notice. This meeting will be live-streamed and will also be available on DVD.

- **For further Reading: https://ipcsg.blogspot.com/**
- **For Comments, Ideas and Questions,** email to Newsletter@ipcsg.org

July 2020 Informed Prostate Cancer Support Group Online Presentations

Personal Experiences: GENE VAN VLEET; DICK HOWARD; RALPH HUGHES

Summary by Bill Lewis

Gene Van Vleet's first-person account:

Many of you have heard my story over the years, but to quickly recap: I was first diagnosed 18 years ago. I am now 81 years old. I had retropubic surgery January 2003. The pathology of the removed prostate showed the cancer was already outside. Imaging available at that time was not good enough to show that, before I chose surgery. These days it would have shown on a multiparametric MRI or Axumin scan. Two years later in 2005, the PSA began moving upwards, so I had salvage radiation of the prostate area.

In 2007 my PSA was rising again. Fortunately, I learned of The Informed Prostate Cancer Support Group and through knowledge available from this group, I have been able to maintain control of my cancer – albeit not easily. I also have become very involved in the management of the support group, which has been very rewarding to me. Through them I learned of Dr. Lam at Prostate Oncology specialists who has successfully guided my treatments since 2007. You can see details of these events on this website:

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Organization

a 501c3 non-profit organization - all positions are performed gratis

IPCSG

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Gene Van Vleet

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Bill Bailey, ...Librarian
Jim Kilduff, ...Greeter
John Tassi .....Meeting Set-up
Stephen Pendergast ..... Editor

NEWSLETTER
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PROSTATE CANCER—*2 WORDS, NOT A SENTENCE*

What We Are About

Our Group offers the complete spectrum of information on prevention and treatment. We provide a forum where you can get all your questions answered in one place by men that have lived through the experience. Prostate cancer is very personal. Our goal is to make you more aware of your options before you begin a treatment that has serious side effects that were not properly explained. Impotence, incontinence, and a high rate of recurrence are very common side effects and may be for life. Men who are newly diagnosed with PCa are often overwhelmed by the frightening magnitude of their condition. Networking with our members will help identify what options are best suited for your life style.

Be your own health manager!!

Meeting Video DVD's

DVD's of our meetings are available through our website: https://ipcsg.org/purchase-dvds

The DVD of each meeting will be available by the next meeting date.

From the Editor

Due of COVID-19, our usual meeting place, the ***Sanford Burnham Prebys Medical Discovery Institute*** is not available. We will keep you updated as to when these facilities are once again open and our in person meetings can resume. Until then, we will be live-streaming our monthly presentations on the third Saturday of each month, starting promptly at 10:00 PT (San Diego California time).

We will continue to post and distribute the newsletter in the interim. In order to include more articles of interest in this issue, we have included extra pages in the web distributed version of the newsletter. The mail version is limited to ten pages.

Join the IPCSG TEAM

If you consider the IPCSG to be valuable in your cancer journey, realize that we need people to step up and HELP. Call **President** Lyle LaRosh @ 619-892-3888; or **Director** Gene Van Vleet @ 619-890-8447.

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ipcsg.org/personal-experience, or in the August 2019 newsletter.

Medications taken:

AVODART (started due to BPH – prostate enlargement – but still taking it because it blocks the conversion of testosterone to dihydrotestosterone, the more active form of the hormone)

CASODEX (an "anti-androgen" that worked for a while; no longer using)

LUPRON (blocks testosterone production; used it for eight years, then moved on)

XGEVA (helps prevent bone density loss: still taking)

PROVENGE (helps build up your immune system; no longer being treated with it)

METFORMIN (originally used by diabetics; found to improve cancer treatments; still using it)

XTANDI (a "super Casodex" – still taking a low dose)

KEYTRUDA (helps build up your immune system; no longer being treated with it)

ZYTIGA (a "super Lupron" – still taking a low dose)

PREDNISONE (taking to minimize side effects of the Zytiga)

PROVIGIL (helps overcome fatigue; I call it my "happy pill")

LYNPARZA (a new drug that my genetic tests showed may be helpful)

Also had external radiation on spots three times, and internal radiation (Xofigo (radium 223 dichloride).

You may contact me at 619-890-8447 to discuss my experience.

It has been my belief that once PCa is outside the prostate, it is circulating in your system waiting for a place to happen. Therefore, constantly test.

One of the most beneficial things to help me deal with all the various drugs and treatments is routine exercise, which I have done diligently since I met Dr. Lam. Essentially, I do cardio and resistance exercises six days a week, until lately at a local YMCA, to help me overcome muscle and bone loss caused by many of the drugs. Since the onset of the corona virus, I have obtained equipment to do this at home.

In conclusion, I do have a relatively good lifestyle, although more limited due to all the treatments I have endured as well as to neuropathy which has limited my mobility more each year.

Ralph Hughes

At age 63, Ralph had a biopsy when his PSA was about 4-5, and he was offered robotic surgery "in two weeks." A friend encouraged him to attend the IPCSG – the next day! – and the speaker was Dr. Mundt, talking about radiation as an alternative to surgery. In contrast, a retired surgeon friend recommended surgery, non-robotic. He went to Prostate Oncology Specialists, and talked with Dr. Turner, who recommended radiation. He chose surgery (at UCSD), because he didn't like the 4% chance of a secondary cancer from radiation treatment. But an mpMRI a week before the scheduled surgery showed the cancer had escaped the capsule. Dr. Kane assured him he could still perform an effective surgery, which was done the following Monday in December 2014. Not surprisingly, his cancer recurred, with his PSA rising to 0.16 by June 2015. A Decipher (Genomic) test showed he had "High risk prostate cancer," with a 43% risk of metastasis in 5 years.

He had radiation starting in October 2015, along with Lupron shots starting a little earlier. Unfortunately, by mid-2016, his PSA was rising again. He then got very helpful information through the IPCSG. In October, Dr. Almeida spoke about how there could be isolated spots when the PSA was in the range of 0.2 to 0.5 (right where Ralph's numbers were), and the importance of PSA doubling time. The next month, Dr. Lam spoke about radiation to isolated spots – the earlier the better. So he went to Dr. Almeida for a C-11 acetate scan, which showed one definite spot and two likely spots.

Hormone therapy was started in May 2017 in advance of targeted radiation. After both Drs. Kane and Mundt mentioned the possibility of microscopic cancer not seen in the C-11 scan, he went back to Prostate Oncology Specialists (despite embarrass-

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ment at having rejected Dr. Turner's 2014 recommendation for radiation vs. surgery), and learned that a new approach just discussed in a conference was to simultaneously add Zytiga, radiation and chemo to the ADT he had recently started, with the idea that each contributes to fighting/eliminating the cancer. Coincidentally, he and his wife had already concluded that chemo would be their best next treatment.

He had targeted IMRT (intensity-modulated radiation treatment) for about a week starting at the end of August 2017, four infusions of chemo (Docetaxel) starting in October, Zytiga from July through April 2018, and continued his ADT (Trelstar) until December 2017. He tolerated the chemo fairly well, though with significant fatigue, and a little neuropathy that gradually resolved. Although his surgery had almost no long-term effects on his urinary continence or sexual performance, these later treatments did have negative effects on the latter, due to low testosterone.

He went back to work as a lawyer in January 2018, but the case was settled early, so he went on a skiing vacation to Colorado, and then on a trip to Mexico, where he had to get his Zytiga locally (actually, from Canada, via Mexico City) due to customs problems at the border.

Since these last treatments, his PSA has stayed consistently at <0.01, with his testosterone remaining very low.

Surprisingly, though he told his doctors he is an avid, high-level skier, they never encouraged him to check his bone density. When he and his wife recently wondered about it and checked, it was confirmed that he has osteopenia, so he now takes a medicine for it. He also started 500 mg calcium with Vitamin D3 last week.

Lessons learned:

1. Don't keep your cancer a secret. Talk to people. Learn from them.
2. Take someone with you.
3. Create a notebook.
4. Prepare questions. Ask "What else could we do, that we haven't talked about?"
5. You are your own case manager.
6. You are the center of a team.
7. Keep records.
8. Don't let up.

Dick Howard

Lessons emphasized:

1. Always get a second opinion (or a third or 4th)
2. Get all the info and help you can get. The IPCSG was key for him.

Last year, he had "symptoms." His doctor gave him a PSA test, and then it went up to 16 in a short time. A biopsy gave 3+4's and a 4+5 Gleason score. After the biopsy, he had an explosive bleed on the way home, losing 3 pints of blood in the entrance to his home. He went into shock and lost consciousness. He was in the emergency room at Scripps La Jolla for two days, and the bleed mysteriously resolved on its own.

On Nov 22, seed implants were scheduled to be placed prior to radiation. He was uneasy about his doctors, because of the biopsy aftermath – particularly since the same doctor was going to do the implants (Not a happy thought!). But on the previous Friday, his wife found the newspaper ad for the IPCSG meeting that was being held the next day. He went, and was blown away by all the info provided by Dr. Mundt about radiation treatment. He was advised to call Gene Van Vleet, and did so. In just twenty minutes, Gene got him an appointment with Dr. Mundt that Thursday. Two hours, face to face! Dr. Mundt said #1, they don't do implants any more, as of 5 years ago. #2, he would not be a candidate for such implants (due to age, diabetes and 5 stents in his heart). #3, X-ray radiation is not the way to go for him, but rather proton therapy would be best, since his cancer was contained within the prostate. Dick said, "Thank you, doctor. You're my new doctor!"

In Jan-Feb 2020, he had 28 proton treatments. Six weeks later, his PSA was 0.09. He had substantial side effects, but he was "happy to suffer them." His treatment seems to have to have worked. If you have any interest in details, email him with your phone number and he will call you -- Dick-how83@gmail.com.

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The proton therapy side effects were minimal until the last few treatments. Then he had intestinal problems – explosive diarrhea every few hours, 24 hours a day for a couple of months. It was radiation proctitis. He was not offered the SpaceOar gel, which might have protected the rectum. A balloon was used, which was very uncomfortable.

On the lighter side

"If you need help, press the button. Quit calling 911."

"Hi, honey. Good news... we can afford the new car."

"He's taken a turn for the worse."

"They're for anxiety. Take one before I tell you about the side effects."

Crosstalk between COVID-19 and prostate cancer

Can PCa treatments serve as potential therapeutic options for COVID-19 patients?

Wassim Abou-Kheir

nature.com

Abstract

A new coronavirus, named SARS-CoV-2, emerged in Wuhan city, China, in December 2019 causing atypical pneumonia and affecting multiple body organs. The rapidly increasing numbers of infected patients and deaths due to COVID-19 disease necessitated declaring it as a global pandemic. Efforts were combined since then to rapidly develop a treatment and/or a vaccine to combat the deadly virus. Drug repurposing approach has been pursued as a temporary management tactic to treat COVID-19 patients. However, reports about the efficacy of many of the used drugs had been controversial with a dire need to keep the ongoing efforts for rapid development of new treatments. Promising data came out pointing to a possible hidden liaison between prostate cancer (PCa) and COVID-19, where androgen-deprivation therapies (ADT) used in PCa had been shown to instigate a protective role against COVID-19. Delving into the possible mechanisms underlying the crosstalk between COVID-19 and PCa alludes a potential association between SARS-CoV-2 targets on host epithelial cells and PCa genetic aberrations and molecular signatures, including *AR* and *TMPRSS2*. The question remains: Can PCa treatments serve as potential therapeutic options for COVID-19 patients?

Perspective

In December 2019, a new coronavirus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in Wuhan city, Hubei Province, in China causing severe acute respiratory distress syndrome and atypical pneumonia outbreak. Due to the increasing number of infected patients across the globe, the World Health Organization (WHO) made the assessment that COVID-19 can be characterized as a pandemic on March 11, 2020, and announced a state of global health emergency to combine efforts to contain the spread of the virus and rapidly develop a treatment and/or a vaccine for it. As of mid-July 2020, the virus has infected more than 14 million people around the world, killing more than 600,000 and affecting 216 countries globally [1]. Drug repurposing approach has been pursued as a temporary management tactic to treat COVID-19 patients. However, the efficacy of many of the clinically approved drugs tried had been controversial. Therefore, it is still a global priority to keep the efforts ongoing for rapid development of new treatments against SARS-CoV-2.

Recently, studies have been coming out pointing to a possible hidden liaison between prostate cancer (PCa) and COVID-19. Indeed, a study revealed that PCa patients receiving androgen-deprivation therapy (ADT) had a significantly lower risk (fourfold) of SARS-CoV-2 infection compared with patients not receiving ADT or even patients with any other cancer type [2]. Delving deep into the possible mechanisms underlying the protective role of PCa therapies against COVID-19 reveals a potential association between SARS-CoV-2 targets on host epithelial cells on one hand, and PCa genetic aberrations and molecular signatures, such as androgen receptor *(AR)* and transmembrane protease, serine 2 (*TMPRSS2)*, on the other hand [3] (Fig. 1). So far, two main genes have been associated with entry of the COVID-19 virus into host alveolar epithelial cells, namely angiotensin-converting enzyme 2 *(ACE2)* and *TMPRSS2*, via binding of spike (S) glycoprotein of coronaviruses to specific cellular ACE2 receptors and its subsequent cleavage (priming) by cellular TMPRSS2 proteases in *TMPRSS2+* cells or cysteine proteases cathepsin B or L (cathepsin B/L) in *TMPRSS2−* cells [4].

Fig. 1: Schematic representation of the crosstalk between COVID-19 and prostate cancer.

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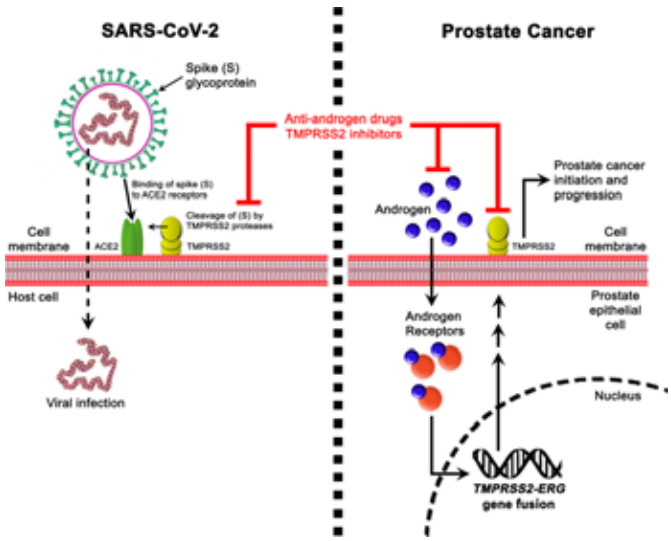

Potential association is present between SARS-CoV-2 targets on host epithelial cells on one hand, and prostate cancer genetic aberrations and molecular signatures, such as *AR* and *TMPRSS2*, on the other hand. Antiandrogen drugs and *TMPRSS2* inhibitors used in prostate cancer might hence serve as common therapeutic options for COVID-19 patients.

Reports have lately emerged contemplating the possible role of AR sensitivity in increasing susceptibility of patients to SARS-CoV-2 infection via regulating *TMPRSS2* transcription [5], which is in turn crucial for SARS-CoV-2 entry into its target cells and initiation of the infectious process [3]. The central role of *TMPRSS2* in provoking viral entry into the host lung cells also extends to other respiratory viruses wherein infecting *Tmprss2−/−* mice with H1N1 influenza virus failed to cause serious infection and protected them from lung disease compared with wild-type mice [6]. In COVID-19, it has been hypothesized that higher androgen levels and hence sustained *TMPRSS2* expression among males might explain their predominance in numbers of deaths from the disease versus females [2, 3]. Another key player in the pathogenesis of COVID-19 is *ACE2*, which is expressed on epithelial cells of the lungs and is used as a cell receptor for SARS-CoV-2 entrance into the host cell [7]. Interestingly, this gene is also highly expressed in the male urogenital system organs, including the prostate, and indeed it has been postulated that patients with chronic urinary diseases might be more susceptible for SARS-CoV-2 infection than others [8].

In the prostate gland, upon activation of AR by androgen binding, it undergoes conformational change instigating transcription of target genes, such as prostate-specific antigen and *TMPRSS2*. The latter androgen-regulated *TMPRSS2* gene fuses to *ERG* driving PCa initiation and progression in almost 50–70% of PCa patients [9]. Therefore, in androgen-sensitive PCa, the standard first-line therapy is still ADT ever since 1941 until today. In addition to ADT, an alternative approach to directly target and modulate *TMPRSS2* expression is via protease inhibitors that impair the activity of *TMPRSS2*, such as Camostat, Nafamostat, and Bromhexine [10]. Many of those drugs are currently under investigation in clinical trials on COVID-19 patients. Moreover, we hypothesize that any drug which downregulates *TMPRSS2* expression through targeting AR, AR co-regulatory factors, or AR downstream transcription factors might be potentially effective against COVID-19 and is worth investigating under a clinical trial. Noteworthy mentioning that a phase III clinical trial will be started soon to assess the efficacy of 13-cis-retinoic acid (isotretinoin)—a retinoid used in severe acne due to hyperandrogenism—in the treatment of COVID-19 (ClinicalTrials.gov; NCT04353180; estimated study start date June 2020).

Collectively, these pieces of evidence suggest that a crosstalk indeed exists between COVID-19 and PCa at a subcellular genetic level. The high expression of *TMPRSS2* and its role in the pathogenesis of both diseases paves the way for identifying novel therapeutic approaches to treat COVID-19 that are based on androgen suppression and *TMPRSS2* protease inhibition. What is really promising about PCa treatments being repurposed to target SARS-CoV-2 is that many of those drugs have low risk of serious side effects and thus can be used solely or in combination with other potential repositioned drugs to study their efficacy against COVID-19.

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COVID-19 and prostate cancer management

Posted on July 27, 2020 by Sitemaster

Do you live in the USA and believe that your prostate cancer care may have been ***seriously*** affected by the COVID-19 pandemic? For example:

- Might you have an elevated PSA level and a high-risk form of prostate cancer but your biopsy/diagnosis has been delayed because of the pandemic?
- Might you have been already diagnosed with a high-risk form of prostate cancer but your first-line treatment has been delayed because of the pandemic?
- Might you have a progressive or recurrent form of prostate cancer after first-line treatment, but second-line treatment has been delayed because of the pandemic?
- Might your intravenous chemotherapy for advanced prostate cancer have been interrupted or deferred as a result of the pandemic?

If you are a US-based patient who thinks that your prostate cancer care may have been ***seriously*** affected by the COVID-19 pandemic, please text the sitemaster at +1 267 250 5087. We are trying to find two or three patients who might be willing to talk to a highly respected healthcare reporter from a major media outlet about such risks.

Switching from Abiraterone Plus Prednisone to Abiraterone Plus Dexamethasone Can Extend Its Effectiveness — Cancer ABCs

cancerabcs.org

There has been evidence that the effectiveness of Abiraterone Acetate (Zytiga) along with prednisone (P) can be extended by switching the P to another steroid, dexamethasone (D) in certain men who are castrate resistant and still without symptoms and who start experiencing a rise in their PSA scores.

Ninety-three (93) men treated with Zytiga + P who experienced biochemical progression (rise in their PSA while still taking Zytiga + P) were switched from 10 mg/day of P to 0.5 mg/day of D until they experienced radiological and/or clinical progression in order to evaluate the effectiveness of substituting the P with D.

The primary endpoint of the study was progression-free survival (PFS).

Results

The median time to PSA progression (the time at which PSA scores increased despite taking Zytiga +P) was 8.94 months. The median PFS on Zytiga +D and Zytiga+corticosteroids (P then D) was 10.35 and 20.07 months.

A total of 56.25% of men showed a decrease or stabilization in their PSA levels after the switch. The researchers then wanted to understand which men who made the switch from P to D had the best response.

In univariate analysis, three markers of switch efficiency were significantly associated with a longer PFS from the switch: long hormone-sensitivity duration (≥5 years; median PFS 16.62 vs. 4.17 months,); low PSA level at the time of switch (<50 ng/mL; median PFS 15.21 vs. 3.86 months; and a short time to PSA progression on Zytiga+P (<6 months; median PFS 28.02 vs. 6.65 months).

In multivariate analysis, hormone sensitivity duration and PSA level were independent prognostic factors.

Conclusion

A steroid switch from P to D appears to be a safe and non-expensive way of obtaining long-term responses to Zytiga in selected men with mCRPC. A longer PFS has been observed in men with previous long hormone sensitivity duration, and/or low PSA level and/or short time to PSA progression on Zytiga+P.

https://bjui-journals.onlinelibrary.wiley.com/doi/epdf/10.1111/bju.14511

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Adding carboplatin to chemotherapy regimens for metastatic castrate-resistant prostate cancer in postsecond generation hormone therapy setting: Impact on treatment response and survival outcomes

Mohamed E. Ahmed MB, BCh

onlinelibrary.wiley.com

ORIGINAL ARTICLE

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First published: 31 July 2020

Abstract

Background

The clinical course in metastatic castrate-resistant prostate cancer (mCRPC) can be complicated when patients have disease progression after prior treatment with second generation hormone therapy (second HT), such as enzalutamide or abiraterone. Currently, limited data exist regarding the optimal choice of chemotherapy for mCRPC after failing second generation hormone therapy. We sought to evaluate three common chemotherapy regimens in this setting.

Methods

We retrospectively identified 150 mCRPC patients with disease progression on enzalutamide or abiraterone. Of these 150 patients, 92 patients were chemo-naïve while 58 patients had previously received docetaxel chemotherapy before being started on second HT. After failing second HT, 90 patients were assigned for docetaxel-alone (group A), 33 patients received carboplatin plus docetaxel (group B), while 27 patients received cabazitaxel-alone (Group C). A favorable response was defined by more than or equal to 50% reduction in prostate -specific antigen from the baseline level after a complete course of chemotherapy. Survival outcomes were assessed for 30-month overall survival.

Results

Patients in group (B) were 2.6 times as likely to have a favorable response compared to patients in group (A) (OR = 2.625, 95%CI: 1.15-5.99) and almost three times compared to patients in group (C) (OR = 2.975, 95%CI: 1.04–8.54) (P = .0442). 30-month overall survival was 70.7%, 38.9% and 30.3% for group (B), (A), and (C), respectively (P = .008). We report a Hazard Ratio of 3.1 (95% CI, 1.31-7.35; P = .0037) between patients in group (A) versus those in group (B) and a Hazard Ratio of 4.18 (95% CI, 1.58-11.06; P = .0037) between patients in group (C) compared to those in group (B)

Conclusion

This data demonstrates improved response and overall survival in treatment-refractory mCRPC with a chemotherapy regimen of docetaxel plus carboplatin when compared to docetaxel alone or cabazitaxel alone. Further investigations are required.

Acute exercise has beneficial effects on the immune system during prostate cancer

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by The Physiological Society

medicalxpress.com

New research published this week in *Experimental Physiology* found that in prostate cancer survivors, a moderate bout of exercise kept the cell count of certain type of immune cells at a normal level, suggesting the exercise is safe for prostate cancer survivors. After 24 hours after a moderate bout of cycling, the immune cell count of natural killer (NK) cells, part of the body's first line of defence, had returned to resting levels.

Prostate cancer treatments, including androgen deprivation therapy (ADT), have numerous adverse effects that reduce physical function and quality of life. Exercise is recommended for cancer survivors to reduce the side effects of treatment and has shown to have many benefits.

However, the effects of prostate cancer treatment and acute exercise on the immune system have only been briefly examined. Exercise oncology guidelines were initially based on the responses seen in healthy, older adults. But individuals with cancer have different physiological responses to exercise, many of which we are only just beginning to understand.

Exercise helps the immune system mobilise by causing NK cells to move into the blood and be transported them to areas of need, such as sites of infection or tumours. At the tissues, these cells move out of circulation and in cancer patients they can the infiltrate the tumour and potentially slow the tumour's rate of growth. This has been shown very elegantly in animal models but the exercise and immune response in cancer survivors is limited, with only a few studies in prostate cancer.

The researchers, based at Victoria University in Australia, had volunteers (11 cancer survivors currently receiving ADT treatment, and 14 men with prostate cancer not on ADT, and 8 healthy controls) completed a cycling task to determine their maximal aerobic fitness.

The researchers chose to use a moderate intensity exercise session that was consistent with current exercise oncology guidelines but was also a bout that would be practical for prostate cancer survivors to perform on their own.

To ensure that the exercise bout used to stimulate the immune system was the same degree of difficulty for everyone, they standardised based on their maximal effort.

To determine immune function, they obtained blood samples before exercise, immediately after and 2h after they finished cycling. The participants then came back the next day (24h) after exercise, and immune function was assessed again after one night of recovery. They also measured several key hormone levels, including adrenaline and noradrenaline, as they play a role in activating and mobilising the NK immune cells.

The researchers found that 24 hours after a moderate bout of cycling, the immune cell count of natural killer (NK) cells, part of the body's first line of defence, had returned to resting levels.

They also showed that the immune cell mobilisation with exercise does not appear to be significantly altered during prostate cancer treatment, which provides direct evidence that acute exercise that falls within current oncology guidelines also appears to be beneficial for the immune system.

A limitation of the study is the modest sample size, and also that they examined cytokines and proteins that are related to NK cell function but did not directly assess the killing capacity of the NK cells.

Erik D Hanson, first author on the study said,

"One of the most enjoyable aspects of working with these men is how willing these men are to help their fellow prostate cancer survivors. Many of them realise that these studies are not likely to benefit them directly. However, they do not hesitate to volunteer and are willing to do just about whatever is asked of them for the collective good."

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More information: Erik D. Hanson et al, Natural killer cell mobilization and egress following acute exercise in men with prostate cancer, *Experimental Physiology* (2020). DOI: 10.1113/EP088627

Citation: Acute exercise has beneficial effects on the immune system during prostate cancer (2020, July 29) retrieved 2 August 2020 from https://medicalxpress.com/news/2020-07-acute-beneficial-effects-immune-prostate.html

July 7, 2020

MRI Alone Cannot Replace Prostate Cancer Active Surveillance Biopsies

Jody A. Charnow

In a study of men on active surveillance for low-risk prostate cancer, multiparametric magnetic resonance imaging by itself missed about one-fifth of men who had pathologic upgrading on subsequent biopsies.

Multiparametric magnetic resonance imaging (mpMRI) helps improve detection of clinically significant prostate cancer (PCa), but by itself cannot replace confirmatory or surveillance prostate biopsies, investigators concluded.

In a single-center study, 21.5% of men on active surveillance (AS) for low-risk (Grade Group 1) PCa and a negative mpMRI scan were found to have Grade Group 2 or higher cancer on subsequent prostate biopsies.

"These findings suggest that there is a persistent subset of men on AS with grade reclassification undetected by mpMRI," Carissa E. Chu, MD, and colleagues at the University of California, San Francisco, reported online in *European Urology*.

The study included 344 men on AS who had at least 1 mpMRI scan and biopsy after their PCa diagnosis. The men had 408 mpMRI scans during a median 71 months on AS. The median time between prostate biopsies was 16.5 months. The overall negative predictive value (NPV) of a negative mpMRI scan was 79.5%. The NPV ranged from 74.4% at the confirmatory (second) biopsy to 84.6% for all subsequent biopsies up to the fourth surveillance biopsy, according to the investigators.

Further, among men with a PSA density (PSAD) of 0.15 ng/mL/cm^3 or higher, the overall NPV of mpMRI was 65.5% and ranged from 57.1% to 73.3% across serial mpMRI scans, according to the investigators.

"This is the first study reporting the NPV of mpMRI at multiple time points during AS," the investigators wrote. "It supports previous findings that a percentage of clinically significant prostate cancers remain undetectable by mpMRI."

The authors concluded that mpMRI alone is insufficient to rule out grade reclassification among men on AS, especially among those with a PSA density of 0.15 ng/mL/cm^3 or higher, and, in particular, mpMRI should not replace confirmatory biopsy.

Reference

Chu CE, Lonergan PE, Washington SL, et al. Mutiparametric magnetic resonance imaging alone is insufficient to detect grade reclassification in active surveillance for prostate cancer [published online July 3, 2020]. *Eur Urol*. doi: 10.1016/j.eururo.2020.06.030

ADT for Prostate Cancer: Concern That Injections Often Given Late

Pam Harrison

medscape.com

The objective of androgen deprivation therapy (ADT) in men with prostate cancer is to maintain very low levels of testosterone so that the hormone does not promote tumor growth. But a new

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analysis found that drugs commonly used to achieve this are administered later than the recommended 28-day regimen, and this late dosing was associated with ineffective suppression of testosterone.

"Evidence suggests achieving and sustaining T levels <20 mg/dL with ADT is desirable and correlates with improved disease-specific survival in patients with advanced prostate cancer," lead author David Crawford, MD, professor of urology, University of California, San Diego, and colleagues point out.

They looked at administration schedules for luteinizing hormone-releasing hormone (LHRH) agonists and found that they were frequently (84%) administered later than the recommended schedule of every 28 days. Nearly half of the late testosterone values for the extended month were greater than 20 ng/dl, and mean testosterone was almost double the castration level, they report.

"Considering the presumed clinical benefits of maintaining effective T suppression throughout the course of ADT, clinicians should administer treatments within approved dosing instructions, monitor T levels, and consider prescribing treatments with proven efficacy through the dosing interval to maintain T below castration levels," they emphasize.

The analysis was published in the *Journal of Urology* and was presented during the virtual American Urological Association 2020 annual meeting.

The study was done before the current pandemic, which canceled the in-person gathering of AUA 2020. Now, in the COVID-19 era, the interval between when men are scheduled for their next injection and when they actually get it may well be growing longer. Crawford says he recently saw one patient who waited 3 months before getting his next "monthly" injection.

28-day Injection Cycle

For the review, Crawford and colleagues examined electronic health records (EHRs) and associated insurance claims for a total of 85,030 injections to evaluate the frequency of late dosing.

When the pivotal registration trials for LHRH agonist were done, a 1-month injection of an LHRH formulation was defined as every 28 days, and not 30 or 31 days as per calendar months.

The current analyses were done using 2 definitions of a month: a 28-day month with late dosing defined as injections given after day 28, and an "extended" month with late dosing defined as injections given after day 32, for products that are dosed once-monthly. The analyses also looked at products that are dosed once every 3-months, once every 4 months, and once every 6 months.

The team also evaluated how often testosterone exceeded the castration level of 20 ng/dL, as well as mean T levels and frequency of T tests and prostate specific antigen (PSA) tests taken by physicians prior to administering the injection.

Results showed that 84% of the 28-day dosing interval and 27% of the extended-month dosing administrations were late.

Furthermore, "when LHRH agonist dosing was late, both the proportion of T tests with T >20 ng/dL and mean T were higher compared to when the dosing was early or on-time," Crawford and colleagues point out.

"Synthetic lethality" kills cancer by blocking DNA repair mechanism

By Michael Irving

newatlas.com

“Synthetic lethality” is a phenomenon where genetic mutations that normally don’t harm a cell suddenly become deadly when paired up. Now, scientists have found a way to use this method to selectively kill off cancer that results from genetic mutations, without harming healthy cells.

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The study focused on two particular genes called BRCA1 and BRCA2, that when mutated, boost a person's chance to develop certain types of cancer. Specifically, these mutations are associated with a higher risk of breast and ovarian cancer in women, and breast and prostate cancer in men.

That means that these if certain synthetic lethal relationships are found in these mutations, activating them would kill only the cancer cell lines and not healthy cells. So for the new study, scientists from the University of California San Diego and the Ludwig Institute for Cancer Research explored these possibilities, studying a species of yeast called *Saccharomyces cerevisiae.*

One particular enzyme stood out – Flap Endonuclease 1 (FEN1) – due to its key role in DNA replication and repair. The researchers blocked FEN1 in human cell cultures, using either a drug inhibitor or genetically knocking it out, and in both cases found that it killed more of the BRCA1 and BRCA2 mutant cancer cell lines. Healthy cells, on the other hand, were found to recover from having FEN1 inhibited.

Next, the researchers tested the method in mice which had human cancers. Sure enough, blocking FEN1 in these animals also worked to reduce the growth of the tumors.

The team says that the study shows that FEN1 inhibitors could be a new avenue for future research to explore, as potential cancer therapies.

The research was published in the journal *Proceedings of the National Academy of Sciences*.

Source: University of California San Diego

Reconsidering the Trade-offs of Prostate Cancer Screening

Sounding Board

New England Journal of Medicine

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Article

After the widespread adoption of prostate-specific antigen (PSA) screening in the early 1990s, prostate cancer diagnoses increased rapidly while death rates halved over the course of the next quarter century.[1] Initial results from randomized trials and recommendations against screening from professional societies, which were recently moderated, probably contributed to screening's falling out of favor over the past decade.[2-4] Decreased screening has been associated with a sustained fall in prostate cancer diagnoses.[1] Although not necessarily reflective of a change in the number of men in whom metastatic disease will ultimately develop, some evidence suggests that the incidence of metastatic disease at diagnosis, which had been decreasing until 2010, may now be rising.[1,5-8] The decline in PSA screening has a number of contributing factors but appears to have been precipitated in part by misinterpretation of existing randomized data and lack of attention to follow-up time when the calculus of harms and benefits is evaluated. Here, we present a reevaluation of the plausible long-term effects of PSA screening using the most up-to-date data available.

A prevailing opinion regarding PSA screening is that "two large, randomized, controlled trials of PSA screening showed equivocal or no benefit."[9] This view is problematic. One of these trials — the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial — was not useful for evaluating the efficacy of screening relative to no screening, be-

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cause nearly 90% of the men in the control group had undergone PSA testing.[10-13] The other widely cited trial of screening is the European Randomized Study of Screening for Prostate Cancer (ERSPC), in which the rate of screening in the control group was substantially lower than the rate in the control group of the PLCO trial.[14] The most recent update of the ERSPC estimated that 570 men from 55 to 69 years of age would need to be screened to prevent one death from prostate cancer with 16 years of follow-up.[15,16] This benefit is qualitatively similar to recommendations supporting breast cancer screening, with the need to screen 1250 women from 50 to 59 years of age, 476 women from 60 to 69 years of age, and 769 women from 70 to 74 years of age to prevent one death from breast cancer at 10 years.[17]

Given the natural history of prostate cancer, 16 years of follow-up from randomization may not provide a sufficient time horizon to examine the mortality benefit from screening, because men often begin screening in their 50s and the median age at death from prostate cancer is 80 years.[1] Conflation of the long-term benefits of screening that are needed to inform policy and patient decisions and the short-term results available from clinical trials is highly problematic. Among men with clinically detected prostate cancer (usually a more advanced form than screening-detected cancer) who were followed for 21 years, mortality from prostate cancer tripled from 15 per 1000 person-years during the first 15 years to 44 per 1000 person-years thereafter.[18] Thus, the absolute benefit of screening over the longer term may be greater than that observed over the 16-year horizon in the ERSPC as deaths from prostate cancer continue to accrue.

The benefits of screening cannot be measured only in mortality reduction and should also reflect the diminished morbidity from avoidance of advanced disease. Metastatic prostate cancer is incurable and, if symptomatic, can be painful and debilitating. Its treatment (i.e., androgen deprivation and chemotherapy) is costly and associated with long-term toxic effects. Relatively short-term (12-year) data from four centers participating in the ERSPC have shown that screening results in an absolute risk reduction of metastatic disease of 3.1 per 1000 men who underwent randomization.[19] The Prostate Testing for Cancer and Treatment (ProtecT) trial, which compared monitoring, surgery, and radiotherapy for localized, largely low-risk prostate cancer, also clearly showed a reduction in prostate cancer metastases with definitive treatment at 10 years of follow-up.[8]

In light of the oncologic benefits of screening, patients, providers, and policymakers need to weigh the value of these benefits against the harms of screening. Perhaps the greatest of these harms is the detection of cancers that would not cause deaths or complications in a patient's lifetime ("overdetection") and consequent treatment-related long-term adverse effects. Although screening is certainly associated with excess detection, many prostate cancers that would present clinically may simply be found earlier with screening. For instance, the cumulative incidence of prostate cancer in the ERSPC was 13.3% among men in the screening group and 10.3% among men in the control group at 16 years, and the relative risk of prostate cancer diagnosis in the screening group as compared with the control group diminished with longer follow-up time.[16] Thus, this discrepancy in rates probably represents the upper limit of excess detection associated with screening, because the control group may continue to "catch up" to the screening group with additional follow-up.

Since many policymakers now advocate for "shared decision making" regarding PSA screening, it is imperative for patients and providers to have a clear understanding of the harm–benefit calculus for screening. Available decision aids for prostate cancer screening, such as those developed by the U.S. Preventive Services Task Force and the American Academy of Family Physicians,[20,21] are limited by their reliance on relatively short-term follow-up (i.e., 13 years) in their calculations of the benefit of screening. This reliance on short-term follow-up is

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rooted in an unsupported presumption that additional benefit will not continue to accrue over a man's lifetime. The presentation of data in the above decision aids also implies that only lethal prostate cancer would be diagnosed in the absence of PSA screening. The resultant suggestion is that screening prevents one death from prostate cancer per 1000 men screened at the expense of diagnosing 100 cancers.

Table 1. Estimates of the Number Needed to Screen and the Number of Excess Prostate Cancer Diagnoses to Prevent One Death from Prostate Cancer during the Indicated Follow-up Interval.*

Variable	No. Needed to Screen (95% CI)	No. of Excess Diagnoses (95% CI)
16 Yr of follow-up: empirical estimate from ERSPC	570 (380–1137)	18 (12–35)
25 Yr of follow-up: conservative model estimate	385 (273–687)	11 (8–20)

* Model estimates are based on extrapolation of deaths from prostate cancer among men who received a diagnosis of prostate cancer during the first 16 years of follow-up of the European Randomized Study of Screening for Prostate Cancer (ERSPC), under the assumption that the relative mortality reduction would continue with additional follow-up. Confidence intervals are based on 95% confidence limits of the 16-year empirical estimates of mortality. (For model assumptions and details, see the Supplementary Appendix.) ERSPC protocols varied among sites. Men underwent randomization between the ages of 55 and 69 years and at most centers were screened every 4 years, with referral to biopsy when prostate-specific antigen levels were more than 3.0 ng per milliliter. The stopping age varied from 67 to 78 years of age.

Table 1.

Table 1. Estimates of the Number Needed to Screen and the Number of Excess Prostate Cancer Diagnoses to Prevent One Death from Prostate Cancer during the Indicated Follow-up Interval.

Using a formal, transparent model, we provide alternative estimates of the long-term effects of PSA screening (Table 1). The model projections are based on long-term survival of patients with prostate cancer and competing mortality in the United States. The projections assume that the relative mortality reductions observed in clinical trials continue to hold, as deaths resulting from cases diagnosed during the first 16 years of follow-up continue to accrue (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The model projects that 11 additional cases need to be diagnosed to prevent one death from prostate cancer at 25 years in the United States. Although the preservation of the relative reduction in mortality among men in whom prostate cancer was diagnosed over 16 years of screening in the ERSPC is uncertain, other assumptions that underpin these projections are conservative (see the Supplementary Appendix). Even though other screening programs are likely to have different magnitudes of harms and benefits,[22] limited data on other programs are available from randomized trials. We believe that these projections provide a more complete picture of the plausible long-term effects of PSA screening.

Important considerations are not reflected in these estimates. These include the *benefit of preventing advanced prostate cancers, associated costs of screening and detection, as well as the ways in which detection and a cancer diagnosis affect a man's quality of life.* Perhaps chief among these quality-of-life concerns is that screen detection exposes men to the risks of treatment, which can have long-lasting effects on urinary and sexual function. Contemporary data on these treatment-related side effects show that the burden of erectile dysfunction and urinary incontinence caused by treatment is of somewhat similar magnitude as the modeled prostate cancer–specific mortality benefit presented here.[23-26] For instance, the ProtecT trial showed that treating 4 men with prostatectomy or 8 with radiotherapy rather than active monitoring would cause one additional case of erectile dysfunction at 2 years. Similarly, treating 5 men with prostatectomy or 143 men with radiotherapy would cause one additional case of urinary incontinence.[25] These data also show that, in contrast to metastatic prostate cancer, these therapies do not affect overall health-related quality of life, with no clinically significant declines in physical functioning or emotional well-being or worsening in energy or fatigue scores.[23,27,28] It must be acknowledged, though, that these patient-reported outcomes may not reflect the full effect of treatment on these men's lives.

Also not included in our analysis are more recent changes to prostate cancer diagnosis and management strategies that have the potential, albeit as yet

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unproven, to refine screening for the better. Previous work has suggested that the trade-offs of screening can potentially be improved by stopping testing or testing less frequently, and using more conservative biopsy criteria, in older men and by using longer screening intervals for men with low PSA levels.[22] Magnetic resonance imaging (MRI) continues to be evaluated as a triage tool before biopsy, with the PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) trial indicating that more than a quarter of men with an elevated PSA level may safely avoid prostate biopsy by undergoing a prebiopsy MRI.[29,30] Although the data are not yet mature, supplemental biomarkers and polygenic risk scores also show promise in further risk stratification of patients.[31,32] The harms of overdetection have also been attenuated in the United States in recent years by divorcing radical therapy from detection. Almost 50% of U.S. men who receive a diagnosis of low-risk prostate cancer now opt for active surveillance, in which cancers are closely monitored rather than immediately treated.[33-35] If U.S. practice patterns follow those observed in the U.K. ProtecT trial, more than 50% of men on active surveillance will ultimately cross over to definitive therapy.[36] Although surveillance has harms, it avoids or delays the risk of erectile dysfunction, which affects many aging men at baseline.[37]

Evidence from randomized trials shows that PSA screening reduces prostate cancer mortality and prevents metastatic disease. Overdetection and associated treatment-related complications remain substantial disincentives. Greater acceptance and adoption of active surveillance and newer diagnostic pathways may already be mitigating some of these harms. It is nevertheless true that despite three decades of PSA screening in the United States, the long-term magnitude of benefit balanced against the harms of screening remains uncertain. Here, we integrate relevant data under transparent assumptions to evaluate the trade-offs of PSA screening. As clinicians who screen, diagnose, and treat patients with prostate cancer and as statisticians who are devoted to understanding the effects of cancer screening, we suggest that the balance of benefits and harms of screening may be more favorable than is generally appreciated.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Drs. Shoag and Nyame contributed equally to this article.

medpagetoday.com

CTC Count Can Predict Outcome in Prostate Cancer

by Greg Laub, Director, Video, MedPage Today June 18, 2020

6-7 minutes

Meeting Coverage > ASCO Video Pearls MM

— Amir Goldkorn describes the valuable biomarker that will help guide treatment

Baseline circulating tumor cell (CTC) count was found to be significantly predictive of clinical outcome in a phase III trial of metastatic castration-sensitive prostate cancer (mCSPC) presented at the 2020 American Society of Clinical Oncology virtual scientific meeting.

In this exclusive MedPage Today *video, lead researcher Amir Goldkorn, MD, of the Keck School of Medicine and Norris Comprehensive Cancer Center at the University*

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of Southern California, explains that the results suggest that CTC count could be used as a noninvasive biomarker to help guide treatment decisions.

Following is a transcript of his remarks:

Hi, my name is Amir Goldkorn. I'm a medical oncologist and an associate professor at University of Southern California Keck School of Medicine. I want to tell you briefly about the results of our study looking at circulating tumor cells, or CTCs, in metastatic castrate-sensitive prostate cancer that we just presented as an oral abstract at the ASCO 2020 meeting.

So currently in metastatic castrate-sensitive prostate cancer, the standard of care for therapy is combination of androgen deprivation therapy, or ADT, usually plus another drug, sometimes abiraterone or enzalutamide or chemotherapy. But we have very few biomarkers to guide the way that we treat patients to tell us who will respond and for how long. The FDA-cleared CELLSEARCH platform has been looked at extensively in metastatic castration-resistant prostate cancer, a more advanced disease state. So we asked them for this study whether we could also use it as a biomarker, the CTC counts, to tell us how patients will respond and for how long in metastatic castrate-sensitive prostate cancer.

We did this in a large phase III clinical trial, SWOG S1216, a study run by the NCI Southwest Oncology Group. The PI on the clinical trials is Neeraj Agarwal of the University of Utah. What we did in our CTC study was we obtained baseline CTC counts for men going on trial. These men, 1,200 men, were randomized to receive ADT with either bicalutamide or orteronel, which is a CYP17 inhibitor in a class like abiraterone. And what we looked at for readouts is a response to hormonal therapy, which we defined as the 7-month PSA. That means after the 6 months of treatment, at month seven, had the PSA fallen to less than 0.2, 0.2-4.0, or >4.0, which has been previously shown to be an intermediate endpoint actually for overall survival as well. And the other thing we looked at is progression, 2-year progression-free survival.

And what we found was actually pretty significant. There was a very big difference between men who had versus did not have CTCs. For example, comparing a man who had zero CTCs at baseline versus a man who had five or more CTCs, the man who had zero CTCs had more than a six-fold odds ratio of having a complete response in terms of a 7-month PSA on hormonal therapy, relative to the man who had five or more CTCs. And conversely, the man who had five or more CTCs had an almost four-fold odds ratio for progression 2 years on therapy relative to the man who had zero CTCs. And these sorts of relationships held across different cut points. We also looked at men with fewer than five versus greater than five, which is a cut point often used in castrate-resistant disease. We also looked at having any CTCs versus no CTCs, and all of these had statistically significant differences.

So, we conclude from this study that baseline CTC counts were indeed highly prognostic of PSA response and progression in this cohort of men with metastatic castrate-sensitive prostate cancer who were just starting their therapy with hormonal treatment. And the implications for this in the clinical setting is that, hopefully even at this stage, it might give us a little bit more information about our patients when they come through the door. For example, if we have a gentleman coming in to begin therapy who is older or more frail, but has zero CTCs, we may feel that he would do quite well with standard hormonal therapies and feel comfortable knowing that he would have favorable outcomes. Versus another gentleman who comes in the door, but maybe has many more CTCs, we may consider him to have a less likely chance of having favorable outcomes with just hormonal therapies. And someone like that we may be more likely to try to use more intensified therapies or even trials of new combination therapies for more aggressive treatment. Ultimately we want to get the final overall survival data from this trial and all the data com-

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piled. We would look at this also to look at CTC counts as a predictive factor, meaning can they help us select between different types of treatments, so we will do that analysis by treatment arm of this trial. And ultimately we may be able to build on this with new trials, where CTC counts could be taken into account to help us predict who will respond and who will not respond to particular treatments such as ADT plus chemo versus abiraterone or enzalutamide. So ultimately we hope that this will tell us not only how patients will do overall, but perhaps be useful to help guide specific choice of treatment.

Last Updated June 18, 2020

sciencedaily.com

Study sheds light on how cancer spreads in blood: Analysis of particles shed by tumors points to new, less invasive way to diagnose malignancies

A new study sheds light on proteins in particles called extracellular vesicles, which are released by tumor cells into the bloodstream and promote the spread of cancer. The findings suggest how a blood test involving these vesicles might be used to diagnose cancer in the future, avoiding the need for invasive surgical biopsies.

The research is a large-scale analysis of what are known as palmitoylated proteins inside extracellular vesicles, according to Dolores Di Vizio, MD, PhD, professor of Surgery, Biomedical Sciences and Pathology and Laboratory Medicine at Cedars-Sinai. Di Vizio is co-corresponding author of the study, published online June 10 in the *Journal of Extracellular Vesicles*.

Extracellular vesicles have gained significant attention in the last decade because they contain proteins and other biologically important molecules whose information can be transferred from cell to cell. They are known to help cancer metastasize to distant sites in the body, but exactly how this happens is not clear.

To learn more about this process, the research team looked into a process called palmitoylation, in which enzymes transfer lipid molecules onto proteins. Palmitoylation can affect where proteins are located within cells, their activities and their contribution to cancer progression.

The investigators examined two types of extracellular vesicles, small and large, in samples of human prostate cancer cells. Using centrifuges, they separated the extracellular vesicles from the other cell materials and analyzed the levels of palmitoylation and the types of proteins present.

The team found extracellular vesicles derived from the cancer cells contained palmitoylated proteins that are associated with the spread of cancer. Further, when the team chemically suppressed the palmitoylation process, the level of some of these proteins went down in the extracellular vesicles.

"Our results suggest that protein palmitoylation may be involved in the selective packaging of proteins to different extracellular vesicle populations in the body," Di Vizio said. "This finding raises the possibility that by examining these proteins in extracellular vesicles in the bloodstream, we may be able to detect and characterize cancer in a patient in the future without performing a surgical biopsy."

Di Vizio said the next step in the research is to conduct a study in collaboration with her Cedars-Sinai colleagues and industry partners that will use advanced technologies, including mass spectrometry and flow cytometry, with the goal of identifying clinically significant prostate cancer at diagnosis.

In addition to Di Vizio, Wei Yang, PhD, associate professor of Surgery at Cedars-Sinai, and Andries Zijlstra, PhD, are co-corresponding authors for the study. Zijlstra completed the research while working at Vanderbilt University Medical Center in Nashville. Javier Mariscal, PhD, a postdoctoral scientist in Di Vizio's laboratory, is the study's first author.

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Story Source:

Materials provided by **Cedars-Sinai Medical Center**. *Note: Content may be edited for style and length.*

redjournal.org

Interim results of a prospective PSMA-directed focal stereotactic re-irradiation trial for locally recurrent prostate cancer

Abstract

Purpose

To report the feasibility, toxicity, and preliminary outcomes (metabolic and biochemical) of ^{68}Ga-PSMA PET/CT directed focal prostate re-irradiation using linear accelerator (LINAC) based stereotactic body radiation treatment (SBRT).

Methods and Materials

From March 2016 to March 2019 25 patients were enrolled in a prospective single institution trial (XXX). Eligibility criteria included patients with biopsy proven isolated prostate recurrence following definitive irradiation, with concordant multiparametric MRI and ^{68}Ga-PSMA PET/CT findings, and a PSA of less than 15ng/mL at the time of recurrence. The study included a sequential dose escalation component with the first 18 patients receiving 36Gy in 6 fractions on alternate days with subsequent patients receiving 38Gy in 6 fractions assuming acceptable toxicity.

Results

Median age was 72 years (range 62-83) with a median time between first RT and salvage SBRT of 8.3 years (range 4.5- 13.6 years). Median PSA at re-irradiation was 4.1 (range 1.1 to 16.6). The median follow-up was 25 months (range 13-46 months). Acute grade 1 and 2 genitourinary (GU) toxicity occurred in 6 (24%) and 1 (4%) men respectively. Acute grade 1 gastrointestinal (GI) toxicity occurred in 8% with one acute grade 3 GI toxicity (4%) due to a rectal ulcer overlying the hydrogel. Late grade 1 and 2 GU toxicity occurred in 28% and 4%. Late grade 1 GI toxicity occurred in 8% with no grade 2 or greater toxicity. Twenty-four patients have undergone per-protocol 12 month ^{68}Ga-PSMA PET/CT, of which 23 (92%) demonstrated a complete metabolic response. Biochemical freedom from failure was 80% at 2 years with 3/4 of the biochemical failures exhibiting recurrent local disease.

Conclusions

PSMA-directed salvage focal re-irradiation to the prostate using LINAC-based SBRT is feasible and safe. Toxicity was low, with very favourable short term local and biochemical control in a carefully selected cohort of patients.

nature.com

Risk of erectile dysfunction after modern radiotherapy for intact prostate cancer

Bridget F. Koontz

Abstract

Background

Erectile dysfunction (ED) is a prevalent side effect of prostate cancer treatment. We hypothesized that the previously reported rates of ED may have improved with the advent of modern technology. The purpose of this project was to evaluate modern external beam radiotherapy and brachytherapy techniques to determine the incidence of radiotherapy (RT) induced ED.

Methods

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A systematic review of the literature published between January 2002 and December 2018 was performed to obtain patient reported rates of ED after definitive external beam radiotherapy, ultrafractionated stereotactic radiotherapy, and brachytherapy (BT) to the prostate in men who were potent prior to RT. Univariate and multivariate analyses of radiation dose, treatment strategy, and length of follow-up were analyzed to ascertain their relationship with RT-induced ED.

Results

Of 890 articles reviewed, 24 met inclusion criteria, providing data from 2714 patients. Diminished erectile function status post RT was common and similar across all studies. The median increase in men reporting ED was 17%, 26%, 23%, and 23%, 3DCRT, IMRT, low dose rate BT, and SBRT, respectively, at 2-year median follow-up.

Conclusion

ED is a common side effect of RT. Risk of post-RT ED is similar for both LDR brachytherapy and external beam RT with advanced prostate targeting and penile-bulb sparing techniques utilized in modern RT techniques.

medpagetoday.com

New Focus on ADT in Prostate Cancer Guideline

by Charles Bankhead, Senior Editor, MedPage Today June 30, 2020

Meeting Coverage > AUA

— AUA, SUO, ASTRO offer 38 recommendations across categories of advanced disease

For the first time in its long and storied history, hormonal therapy for advanced prostate cancer has received broad and detailed attention in a clinical practice guideline.

The new American Urological Association (AUA) guideline provides direction for the use of hormonal therapy (or androgen-deprivation therapy, ADT) for men with multiple categories of advanced and metastatic prostate cancer.

"[ADT] is a mainstay of management that we've known about since the Nobel Prize-winning work in the 1940s," said guideline co-chair Michael Cookson, MD, of the University of Oklahoma Health Sciences Center in Oklahoma City. "It's taken a long time to get there, and that's partly due to the fact that a lot of what we did was empiric. There weren't many trials designed to show the true benefit."

Another guideline first reflects the growing recognition of the different stages of disease evolution before the emergence of metastatic castration-resistant prostate cancer (mCRPC).

"There's a lot of excitement in the field about newly diagnosed metastatic disease," Cookson told *MedPage Today*. "Most of the early trials were in men who failed hormonal therapy. Now the trials have moved back to earlier in the disease, looking at conventional hormonal therapy, *plus*. That 'plus' initially included chemotherapy, which showed survival advantages of 12 to 18 months. That was big.

"Then additional androgen-active therapies, such as abiraterone (Zytiga) and then oral agents such as enzalutamide (Xtandi) and now apalutamide (Erleada). That translated into a year or more of additional cancer control and survival when the disease was treated earlier with the combination," he said.

The guideline also addressed the evolutionary period before emergence of radiographically confirmed mCRPC, often associated with a rapid rise in prostate-specific antigen (PSA). Now known as nonmetastatic CRPC, the disease state has three FDA-approved options in the androgen receptor antagonist drug class: darolutamide (Nubeqa), in addition

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to enzalutamide and apalutamide. The drugs' approval was based primarily on the newly recognized endpoint of metastasis-free survival and relatively limited overall survival data, said Cookson. Subsequently, a survival advantage was reported for enzalutamide.

"That's been a real area of controversy," he continued. "Many clinicians were hesitant to fully embrace the therapy because they didn't really understand the true benefit of this new endpoint called metastasis-free survival. The 'purists' among oncologists, and maybe just the purists in general, want an overall survival benefit. Now we're starting to see that happen. There are three studies in that category, and as the data matures, I think we'll see more of that, since the drugs are pretty similar."

Frontline standard of care for mCRPC remains docetaxel for men with no prior exposure to the drug. Cabazitaxel (Jevtana) or a novel anti-androgen agent is appropriate in the setting of docetaxel failure.

New to guideline history -- and to many clinicians who treat prostate cancer -- is genetic testing. About a fourth of CRPC harbors germline or somatic mutations, said Cookson. New drugs that target the mutations continue to emerge on a regular basis, affording opportunities for precision-medicine approaches to treatment of CRPC. The most common mutation is *BRCA2*, and the FDA has already approved two drugs to treat CRPC harboring *BRCA2* mutations, the PARP inhibitors olaparib (Lynparza) and rucaparib (Rubraca).

"There are instances in which men have been on conventional therapy -- chemotherapy or hormonal therapy -- and they've also failed the newer antiandrogens, such as abiraterone and enzalutamide," said Cookson. "In the past, we didn't have much hope for them. Now there is a class of drugs that if they have the right genetic makeup in their tumor, they're going to have a better chance to respond to the therapy."

Immunotherapy may also have a role for some men with CRPC. The PD-1 inhibitor pembrolizumab (Keytruda) has tumor-agnostic approval for treatment of heavily mutated solid tumors (microsatellite instability-high). The field of prostate cancer is "still in its infancy" with regard to use of drugs that target genetic alterations in tumors.

The key message in the guideline is for prostate cancer specialists to be aware of recommendations for genetic testing, particularly for men with aggressive disease that progresses rapidly through conventional therapies, Cookson added. Moreover, testing for germline mutations has implications for genetic counseling, including family members who might be at increased risk for several types of cancer.

The guideline was developed in collaboration with the Society of Urologic Oncology and the American Society for Radiation Oncology. The guideline panel made a total of 38 recommendations pertaining to the prostate cancer continuum of care:

- Early evaluation and counseling
- Nonmetastatic biochemical recurrence after exhaustion of local treatment options
- Metastatic hormone-sensitive prostate cancer
- Nonmetastatic CRPC
- mCRPC
- Bone health

The complete guideline is available on the AUA website. Cookson and the other guideline co-chair, William Lowrance, MD, of the University of Utah School of Medicine and the Huntsman Cancer Institute in Salt Lake City, summarized the key points of the guideline during the AUA virtual meeting.

"For the past several years, the prostate cancer landscape has been rapidly evolving due to changes in PSA screening standards, as well as the approval of new classes of treatment options for use in various prostate cancer disease states," Lowrance said in a statement. "This guideline is comprised of clinical recommendations based on this new evidence and aims to further support the medical community and patients as they navigate through the various stages of this disease."

NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Lyle LaRosh, and Gene Van Vleet are available to speak to organizations of which you might be a member. Contact Gene 619-890-8447 or gene@ipcsg.org to coordinate.

Member and Director, John Tassi is the webmaster of our website and welcomes any suggestions to make our website simple and easy to navigate. Check out the Personal Experiences page and send us your story. Go to: https://ipcsg.org/personal-experience

Our brochure provides the group philosophy and explains our goals. Copies may be obtained by mail or email on request. Please pass them along to friends and contacts.

Ads about our Group are in the Union Tribune the week prior to a meeting. Watch for them.

FINANCES

We want to thank those of you who have made special donations to IPCSG. Remember that your gifts are tax deductible because we are a 501(c)(3) non-profit organization.

We again are reminding our members and friends to consider giving a large financial contribution to the IPCSG. This can include estate giving as well as giving in memory of a loved one. You can also have a distribution from your IRA made to our account. We need your support. We will, in turn, make contributions from our group to Prostate Cancer researchers and other groups as appropriate for a non-profit organization. Our group ID number is 54-2141691. Corporate donors are welcome!

While our monthly in-person meetings are suspended, we still have continuing needs, but no monthly collection. If you have the internet you can contribute easily by going to our website, http://ipcsg.org and clicking on "Donate" Follow the instructions on that page. OR just mail a check to: IPCSG, P. O. Box 420142, San Diego CA 92142