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REVIEW ARTICLE

Pain in cancer survivors; filling in the gaps

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Abstract

Cancer survivorship represents a growing clinical challenge for pain clinicians. The population of cancer survivors is rapidly expanding and many of these patients experience pain as a sequelae of their disease and its treatment. The features, pathophysiology and natural history of some painful conditions observed in cancer survivors, such as direct tumour effects, cancer induced bone pain (CIBP) or chronic post-surgical pain have received extensive exposure elsewhere in the literature. In this narrative review, we attempt to 'fill in the gaps' in the knowledge, by providing a succinct outline of a range of less well known pain states encountered in the cancer survivor population. These include neuropathies as a result of graft versus host disease (GVHD), novel chemotherapeutic agents and monoclonal antibodies (mAb), and radiation induced pain states. The increasing prevalence of visceral post-surgical pain and aromatase inhibitor-induced arthralgia (AIA) is also detailed. Additionally an overview of suggested approaches to the assessment of pain in cancer survivors is provided and potential treatment strategies, with a focus on novel approaches are discussed.

Key words: cancer; pain; therapy, pain management; cancer-related pain; pain, intractable

The understanding and treatment of cancer has made huge progress, resulting in an expansion of therapeutic options available to clinicians, and marked improvements in the survival rates of patients. Great advances are often accompanied by novel clinical challenges, and cancer management is no exception. We are now observing the rapid expansion of a population of cancer survivors, patients who, as a group, possess their own unique pathological, social and psychological profile.

This era of the cancer survivor is of particular importance as a number of pain states encompassing a broad range of pain phenotypes are commonly encountered within this cohort of patients.[1] Pain in cancer survivors has been reported on recently,[2–4] however this narrative review will focus on aspects that have not been widely disseminated including a treatise of some of the newer causes of treatment-related pain. We will examine previously disregarded facets of the burden of survivorship; pain from aromatase inhibitors and visceral chronic post-surgical pain being two notable absentees from the pain literature. We will also appraise the contemporaneous evidence and attempt to synthesise a pragmatic synopsis of approaches to pain management in this population, 'filling in the gaps' of the reader's knowledge.

Survivorship

The concept of a cancer 'survivor' is relatively novel, and represents a somewhat contentious term, both as a result of a lack of consensus regarding the precise definition of a cancer survivor and because of connotations of combat and warfare with the term 'survivor'.[5]

A range of alternative definitions of cancer survivorship have been suggested. The National Coalition for Cancer Survivorship (NCCS) (in the United States) defines a cancer survivor as a patient 'from the time of diagnosis and for the balance of life'.[6] In the United Kingdom (UK), the National Cancer Survivor Initiative defined a survivor as someone 'living with and beyond cancer'[7] whilst the European Organisation of Research and Treatment of Cancer (EORTC) Survivorship Task

Force has defined a cancer survivor as 'any person who has been diagnosed with cancer, has completed his or her primary treatment (with the exception of maintenance therapy), and has no evidence of active disease'.[8]

From a pain perspective, the first two definitions of survivorship encompass the stage of disease from first diagnosis (when the tumour itself may be causing pain) through treatment (commonly resulting in pain) to a state of disease quiescence or cure (where more persistent forms of pain are often encountered).

Early detection and progress in treatment has improved and over the last four decades the number of cancer survivors has increased, with over 2 million cancer survivors estimated to be living in the UK.[9] The transformation in cancer survival has been striking; patients diagnosed with all cancer types in 1971-72 had survival of 50% one year after diagnosis, in 2014, the one year post-diagnosis survival for all cancer types had increased to 70.4% and the 10 year post-diagnosis survival was 50%.[10 11] It should be emphasised that marked variations between tumour types persist, with five year relative survival rates for pancreatic, liver, oesophagus and lung cancer remaining below 20%.[12]

Interest amongst clinicians and health policy makers in this group of patients has grown rapidly because of an appreciation of the current and future volume of significant unmet clinical need within survivors. This health and social burden includes pain, fatigue, psychological comorbidity and the negative impact of these after-effects on societal engagement such as the ability to work.[13]

Causes of pain in cancer survivors (see Fig. 1)

Pain from tumours

Given the definition of a 'survivor' encompasses the journey from diagnosis to death, tumour-related pain is relevant. However we have focused on other less extensively discussed areas of pain in the context of cancer survivors. Suffice to say that pain caused directly by a growing tumour is the archetype of cancer pain, embodied by the construct of an expanding tumour eroding into normal tissue, resulting in pain.

A tumour is not solely formed from primary cancer cells but includes a host-derived stroma[14] containing an array of immune, mesenchymal and endothelial cells. Mediators produced by both the tumour and its stroma facilitate the dynamic relationship which exists between the neoplasm and surrounding tissues.[15] The development of many tumour types appears to be linked to their successful exploitation of host neuronal tissue, several neurotrophic factors including nerve growth factor (NGF) are produced by tumour types.[16–18] Independently to the increase in neuronal density observed in the tumour vicinity, a slew of pain-modulating agents such as hydrogen ions, Tumour Necrosis Factor-alpha (TNF-α),Transforming Growth Factor-beta (TGF-β), prostaglandins, Interleukin-1 (IL-1) and IL-6 are released into the tumour microenvironment, sensitising and stimulating sensory fibres resulting in pain.[19–21] Central effects are also observed, leading to neuronal hyperexcitability and pain.[22]

Cancer induced bone pain

Cancer induced bone pain (CIBP) manifests as a triad of constant, dull background pain, spontaneous pain flare-ups and movement-induced (incident) pain[23] and is especially important in metastatic breast cancer where survival is often prolonged.

CIBP is a complex entity whose pathophysiology encompasses tumour induced periosteal anatomical disruption, local tissue destruction, changes in sensory innervation and the release of pro-inflammatory mediators.[23] Tumour cells effectively 'hijack' normal bone homeostatic processes by releasing an array of signalling molecules such as IL-1, IL-6, TGF-β and receptor activator of nuclear factor kappa B ligand (RANKL).[24] Osteoclasts are recruited, activated and stimulated by these factors leading to abnormal bone destruction and remodelling.

Developing bone metastases inflame and disrupt neighbouring periosteum,[25] which, along with the marrow and cortex, is densely innervated by sensory and autonomic fibres.[26 27] Release of nerve growth factor (NGF) from tumour stromal cells[28] leads to pathological sprouting of sensory fibres, and the formation of microneuromas.[29] These abnormal sensory fibres are sensitised by pro-hyperalgesic mediators produced by tumour and stromal cells leading to lower excitatory thresholds.[30] Additionally some tumour lines have been shown to secrete the excitatory neurotransmitter glutamate.[31]

Significant reorganisation of both neuronal and supporting cell populations in the dorsal root ganglion (DRG) and dorsal horn of the spinal cord occur in response to bone metastases.[32] Mirroring primary tumours, the dorsal horn changes observed in CIBP are peculiar to the condition[33] and include neuroplastic remodelling of substantia gelatinosa excitatory fibres, raised concentrations of calcitonin gene related peptide (CGRP)[34] and increased expression of Na_v 1.8 sodium channels,[35] resulting in central sensitisation and alterations in sensory modulation and transmission.[36] These changes combined with the pathophysiology of bone metastases explains the differing clinical manifestations of cancer induced bone pain, although our knowledge remains incomplete.[37]

Treatment-related causes of pain

Chronic post-surgical pain (CPSP) (see Fig. 2)

Features of general CPSP

For many cancers, surgery is a principal treatment. Persistent or chronic pain may occur after any surgical insult and is encountered in and is hugely relevant to cancer survivors as a result of its impact on poor recovery outcomes and reduced quality of life.[38]

There remains no standardised definition of chronic post-surgical pain (CPSP) but there is general consensus that it represents pain which; 1) develops after or increases in intensity after a surgical procedure, 2) has a duration of at least three to six months after surgery and impacts on quality of life, 3) represents either a continuation of acute post-surgical pain or develops after an asymptomatic period, 4) is localised in either the surgical field or present in the territory of a nerve associated with the surgical field and 5) has had other causes such as infection or recurrence of malignancy excluded.[39]

The development of CPSP is strongly associated with thoracotomy (30-50%), herniorrhaphy (20-60%), limb amputation (30-85%) and breast surgery (15-25%),[40 41] although it can occur after any surgery.[42] In a Norwegian cohort of over 2,000 patients, approximately 20% were experiencing moderate to severe pain at a time point greater than three months post-surgery.[43]

Commonly, CPSP possesses many of the features of a neuropathic pain state, with positive and negative sensory changes including hypoesthesia, hyperesthesia and allodynias.[44] The presence of these features results in more intense pain and a greater impact on quality of life.[45] However, in a proportion of patients with CPSP a neuropathic component is not detected[46] and sensory

changes are not demonstrated with quantitative sensory testing (QST).[47]

The transitional period from acute to chronic pain is a fundamental process in this condition but remains poorly understood,[48] however genetic factors may influence peripheral and central changes.[49]

Risk factors for CPSP

A number of risk factors for the development of CPSP have been identified and predictive tools subsequently developed. Chronic post-breast surgery pain represents a considerable burden to the cancer survivor population[50] and occurs in approximately 15-25% (although variable) of patients after breast surgery.[41] The condition manifests as pain with neuropathic features localised to the axilla, breast/thoracic wall and medial aspect of the upper arm ipsilateral to the breast surgery.[51]

Risk factors for the development of any CPSP include patient and surgical or procedural factors and those identified for breast surgery are in general common to all CPSP. Preoperatively anxiety, depression and traits such as pain catastrophisation, pre-existing chronic pain states, young age and raised BMI have all been shown to predict the development of CPSP.[52–56] For other patient-specific factors such as conditioned pain modulation (the human correlate of diffuse noxious inhibitory control – the ability of descending pathways to inhibit transduction of pain signals[57]) the evidence currently remains unclear.[58 59]

Perioperatively, transition to CPSP is increased by a longer duration of operation, the division or retraction of nerves, open versus laparoscopic approaches, the use of drains and surgery in low-volume centres.[60 61] After surgery, the presence of moderate to severe acute pain is an important risk factor.[62] Using these predictive factors, validated risk-stratification tools have been developed to provide an individualised indication of risk, potentially enabling targeting of resources or early intervention.[63]

Mechanism based treatments

Prevention or attenuation of the transition from acute to chronic pain is a key therapeutic target. Reducing the initial nociceptive barrage at the time of surgery, either through regional anaesthesia or different pharmacological agents has been studied but evidence is by no means conclusive. A Cochrane review examining the use of epidurals or paravertebral blocks in thoracotomy and breast surgery respectively, demonstrated a beneficial reduction in CPSP rates, although small numbers and poor data quality eroded the strength of the findings.[64] The terms pre-emptive, preventive and protective analgesia are a source of much confusion, leading to flawed study design and the drawing of erroneous conclusions regarding putative agents (see Katz *et al.*'s[65] review).

Small study size and the heterogeneity of both outcomes and the analgesic regimens used limit the applicability of these data. Gabapentinoids may reduce acute postoperative pain (with increased sedation and other side-effects)[66] but there is contradictory evidence for its amelioratory effect on CPSP.[67–69] Similarly results of perioperative administration of ketamine, is ambiguous but suggestive of limited effectiveness in reducing CPSP.[68]

The processes leading to the development of CPSP make the discovery of a 'silver bullet' intervention highly unlikely. Implementation of complex interventions comprising a number of evidence based or 'best practice' approaches during the perioperative period (termed 'transitional pain services') may provide a more productive approach.[70] These include the use of a multidisciplinary team to ensure: pain education, optimisation of pre-existing pain states before surgery, the deployment of 'bite-sized' psychological interventions,[71] preventive analgesic approaches in the perioperative period, attention to acute pain management postoperatively, and the ability to review patients once discharged.

Visceral chronic postsurgical pain

There are data on many aspects of CPSP exploring risk factors, prevalence and underlying pathophysiological mechanisms. Investigation has focussed on the somatic domain with relatively little research on visceral chronic postsurgical pain. What evidence is available has largely concerned prevalence and risk factors but with minimal information regarding natural history or mechanisms meaning that visceral chronic postsurgical pain is not well-defined.

Epidemiology

As for other CPSP, the incidence appears to be relatively high.[72] In a prospective cross-sectional study in 911 patients, 33% had abdominal or visceral surgery with an estimated incidence of chronic pain (>3 on NRS) of 7%. Some of this pain was described as scar pain.[73]

After radical prostatectomy, CPSP was identified in 14.3% of patients after three months, reducing to 1.2% at six months.[74] At three months all patients with CPSP had worse physical and mental function scores and greater disability. A similar study after nephrectomy highlighted a three month incidence of CPSP as 28.6% and 8.6% at six months.[75]

CPSP was described in 25.1% 4 months after abdominal hysterectomy compared with 11.8% after vaginal hysterectomy.[76] At one yr and two-yr follow up the incidences had reduced to 9.9% and 6.7% respectively for abdominal hysterectomy and 4.1% and 2.2% after vaginal hysterectomy. Preoperative pain and poor mental and physical health were predictive of visceral CPSP. Of note, these studies all show high attrition rate from three to six months potentially indicating the time point at which visceral CPSP may be accurately diagnosed.

Although arguably less compared with open, laparoscopic visceral surgery still has a significantly high incidence of CPSP. One retrospective study reported an incidence of 17% in the 199 patients who had undergone laparoscopic colorectal surgery.[77] This was reported at the median of just over three yr and the majority had negative effects on quality of life. Previous inflammatory bowel disease, preoperative pain and repeat surgery, were independent risk factors. Notwithstanding, less invasive surgery may be a strategy for reduction of visceral CPSP.

Risk factors

From the above studies several risk factors can be identified.

- Acute postoperative pain.[78]
- Pre-existing pain in surgical domain[74 77 79]
- Pre-existing pain in remote site[74 78 80]
- Preoperative anxiety[75]
- Comorbidity and disability[75]

Prevalence of neuropathic pain in visceral CPSP

Although post-breast surgical pain seems to be pain of a predominantly neuropathic origin, post thoracotomy pain, for example, has a relatively low incidence (30%) of neuropathic

pain.[45 81] However, visceral CPSP has been shown to be predominantly neuropathic after abdominal hysterectomy,[82] with an incidence of approximately 50% using the DN4 questionnaire and sensory changes around the scar were identified in approximately 20% of patients. The GENDOLCAT study found pain was neuropathic in 44% after abdominal hysterectomy (but 24.5% neuropathic after vaginal hysterectomy).[76] In patients with chronic pain (NRS of greater than 4) reported after hysterectomy, neuropathic pain was described in 48% at three months and 42% at 12 months. Therefore visceral CPSP appears to be neuropathic in just under half of the patients.[83]

Potential mechanisms and treatments

Knowledge of visceral hyperalgesia may be extrapolated and used to inform potential treatment options.[84] For example, the $Na_v1.9$ voltage-gated sodium channel is also integral to inflammatory activating mechanisms important in visceral pain states.[85] The presence of A118A (SNP of OPRM1) seemed to be protective of visceral chronic post-surgical pain.[86]

Reducing acute postoperative pain could potentially attenuate the development of visceral CPSP. The GENDOLCAT prospective cohort study found the use of perioperative neuraxial blockade was associated with less chronic pain.[76] Epidural and intrathecal anaesthesia in addition to a general anaesthetic (GA) for major abdominal surgery reduced chronic pain and early changes of wound hyperalgesia, although this was retrospective data from previous trials.[87] Less CPSP was reported after combining an epidural with GA compared with GA alone (17.6% *vs* 34%) after open abdominal surgery, albeit in a case control study.[88] Neuraxial blockade may be considered as an option to reduce visceral CPSP putatively by reducing acute pain. However, these studies are of mixed methodology and did not consistently report differences in acute pain. Just as for the use of paravertebral block in reduction of breast CPSP, is the important therapeutic aspiration reduction of acute pain rather than the means used to attain it? Notably, the use of patient-controlled analgesia after major abdominal surgery showed a reduction in moderate to severe acute pain and subsequent visceral CPSP.[89] In this large study ($n = 1215$), incidence of CPSP was 34.2% in the non-patient controlled analgesia (PCA) group compared with 27% in those who had a PCA.

Chemotherapy induced peripheral neuropathy (CIPN) and other treatment related causes of sensory neuropathies

Chemotherapy-induced neuropathy has been well described and reasonably well represented in the literature. However, this review will examine causes of neuropathy that to date have not been widely considered.

Neuropathy associated with newer myeloma treatments

Bortezomib is a proteasome inhibitor that is used for the treatment of refractory or relapsed myeloma and has a high incidence of causing peripheral neuropathy.[90] The route of administration of bortezomib has changed from i.v. to subcutaneous (s.c.), and although anecdotally this has resulted in less bortezomib induced neuropathy, a recent trial did not bear this out.[91] Peripheral neuropathy of any grade was present in 48% of the patients receiving i.v. treatment and in 41% in the s.c. group.

Some of the newer treatments of myeloma include lenalidomide and pomalidomide (thalidomide analogues acting by reducing tumour angiogenesis and immunomodulators). In a trial of 221 patients receiving pomalidomide with or without low-dose dexamethasone, no grade 3-4 neuropathy was observed.[92] Moreover treatment with pomalidomide plus low-dose dexamethasone or high-dose dexamethasone alone resulted in 12.3% peripheral neuropathy with pomalidomide.[93]

In a direct comparison of patients receiving thalidomide or lenalidomide, thalidomide was associated with an incidence of peripheral neuropathy of 35% compared with 29% with lenalidomide.[94] Lenalidomide administered as a single agent for the treatment of refractory myeloma was associated with an incidence of neuropathy of 23% and severe (grade 3-4) in only 3%.[95] Therefore these agents appear to be associated with less peripheral neuropathy. However, lenalidomide might not be protective for CIPN when combined with bortezomib and dexamethasone as demonstrated by the 80% incidence of sensory neuropathy, of which 32% had neuropathic pain.[96]

Carfilzomib is another proteasome inhibitor used for refractory myeloma. Preclinical data suggested potentially less neurotoxic action corroborated by the incidence of 13.9% (of 526 subjects) experiencing peripheral neuropathy after single-agent carfilzomib.[97] In only 1.3% was this more severe than grade 2.

Specific neuropathies in patients with haematological malignancy

Graft versus host disease (GVHD), after allogeneic stem cell transplant can cause neuropathic pain by a number of mechanisms,[98] and many neuropathies have been described.[99] These neuropathies are becoming more common but may not always be recognised and have attracted little research interest. In the archetypical demyelinating neuropathy of Guillan-Barre, motor and autonomic nerves are more likely involved but some variants involve sensory nerves and can cause neuropathic pain symptoms.[100] Chronic inflammatory demyelinating polyradiculoneuropathies and axonal polyneuropathies have also been described and may have a higher preponderance of sensory symptoms.[101]

There is minimal evidence to support specific approaches, but treatment of the underlying GVHD is indicated. The situation is potentially complicated by multifarious other neurotoxic assaults, including chemotherapies, and other immunomodulatory drugs such as cyclosporin and thalidomide (used in treatment of myeloma).[102]

Monoclonal antibodies (mAbs) and neuropathy: evidence and pathology

Antibodies and neuropathy in disease

Major advances in the understanding of the mechanisms of oncogenesis have revealed a myriad of potential therapeutic targets.[103] Parallel developments in antibody technologies has allowed production of 'magic bullet'-like tools in quantity, quality and cost that render their clinical use feasible. These monoclonal antibodies can kill tumour cells either directly or by, invoking an immune response and interference with cancer supporting stromal cells and vascular neogenesis. The success of these strategies in many different types of cancer have seen a dramatic increase in the number of patients receiving these agents. Although many potential side-effects are recognised, we continue to learn about emergent adverse effects, such as neuropathy.

An *a priori* indicator of the potential for mAbs to cause neuropathies was demonstrated in patients with monoclonal gammopathy

of undetermined significance (MGUS), a pre-malignant disorder where plasma cells produce high concentrations of monoclonal paraproteins.[104] Waldenstrom's macroglobinaemia is also associated with a 47% incidence of peripheral neuropathy.[104] Myeloma itself may impact on potential peripheral neuropathy caused by anti-myeloma treatments, contributing to the observation of a high incidence of pre-existing neuropathy in myeloma patients naïve to these neurotoxic agents.[105]

One rare, but important similar entity is POEMS syndrome, a constellation of Polyneuropathy, Organomegaly, Endocrinopathy, M-protein (such as immunoglobulins) and Skin changes. Sensorimotor neuropathy is often the dominant symptom.[106] These paraneoplastic neuropathies foretell the possibility of neuropathy arising from the therapeutic use of monoclonal antibodies.

mAbs and neurotoxicity

So to what extent are mAbs neurotoxic? Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, is used to enhance the action of paclitaxel in treating breast cancer. 19% of patients taking bevacizumab with paclitaxel had grade 2 or greater neuropathy compared with 8% on paclitaxel alone after 6 cycles and 74% and 40% respectively after 12 cycles.[107] Similarly Miller found an increased incidence of grade 3/4 neuropathy of bevacizumab with paclitaxel of 23.6% compared with paclitaxel alone (17.6%,) in patients treated for metastatic breast disease.[108] However in 462 patients with metastatic breast cancer receiving either single-agent capecitabine or combined with bevacizumab, no neuropathy was recorded, implying a requirement of the presence of other neurotoxic agents to realise the neurotoxic action of bevacizumab.[109]

The anti-CD30 (a member of the tumour necrosis factor receptor family) mAb, brentuximab vedotin (conjugated with a microtubule disrupter), was used in Hodgkin lymphoma.[110] The overall incidence of sensory neuropathy related to brentuximab was 48% of which 54% exhibited some recovery one year later. In another study 69% developed peripheral neuropathy (50% grade 2 or more) occurring at a median time of 15 weeks after first dose.[111] Similar to other neurotoxic agents, 74% displayed evidence of some recovery at two years. Other mAbs have been described as potentially neurotoxic, such as ipilimumab (for melanoma).[112]

Use of these agents remains novel, but reports suggest that neuropathy of multiple mechanistic types may be associated with the use of some monoclonal antibodies. Nevertheless neuropathy probably occurs at lower incidence than that observed with chemotherapy and biological agents. Detailed natural history and specific treatment options are still unclear but as for any form of neuropathic pain an individualized and potentially mechanistic assessment is warranted.

Radiation induced pain

Radiotherapy is a key element of cancer treatment. The potentially damaging effects depend not only on dose and volume of tissue affected, but also susceptibility of the tissue to radiation. Nervous tissue is vulnerable to damage from ionising radiation but also secondary and longer term effects mediated by fibrosis can contribute to neuropathy and neuropathic pain with reactive oxygen species and certain cytokines implicated.[113] Some of the neuropathic changes are secondary to fibrosis but the nerves are sensitive to direct damage causing acute electrophysiological changes and later effects, in part mediated by vascular changes.[114] Several radiation induced neuropathic pain states have been described.[115]

Radiation induced brachial plexopathy (RIBP) and other plexopathies

Progressive brachial plexopathy is the best described and arguably the most notorious pain consequence of radiotherapy. Over time, reductions in total radiation dose and per fraction dose for the treatment of breast cancer has reduced the incidence of RIBP. Current incidence is described as less than 2% if total dose is less than 55Gy.[116] A less common presentation with rapid, acute onset, known as early transient RIBP, is thought to be mediated by reversible oedema which often resolves within a year.[117] So called 'positive' symptoms of paraesthesia are superseded with the 'negative' symptoms of numbness and often a later delayed progressive motor weakness. The timing of the process is variable and can take years. Although neuropathic pain is repeatedly reported as being uncommon, in a series of pilot clinics of RAGE members, 70% reported pain and 46% had hand/arm paralysis (Personal communication PFS). Lymphoedema can exacerbate symptoms of pain and limb dysfunction and indeed is itself associated with pain after axillary dissection.[118] A key differential diagnosis is brachial plexopathy as a result of direct tumour involvement or paraneoplastic brachial plexopathy, and although pain and progressive sensory *and* motor dysfunction (as opposed to progressive motor dysfunction in RIBP) is suggestive of this, diagnosis should not be made on clinical grounds alone.

Lumbosacral plexus neuropathy is less commonly reported but can occur after radiotherapy for testicular cancer and pelvic radiotherapy. Although less well characterised, symptoms and signs can be more insidious, develop later and have fewer sensory symptoms.[119]

Other causes of neuropathic pain associated with radiotherapy

Radiation can cause pain through other modalities such as mucositis, osteonecrosis[120] and myelopathy.[121] More difficult to define and characterise is less well circumscribed neuropathic pain either after radiotherapy in isolation or after radiotherapy with other anti-cancer treatments. Anecdotally some neuropathic pains of undefined aetiology are often ascribed to radiotherapy even if after non-neurotoxic doses and not clearly within the treatment field. To what extent these patients' neuropathic pain is as a result of exacerbation of direct tumour effects, radiation-induced bystander effects[122] or are related to systemic and atypical manifestations of chemotherapy or paraneoplastic-induced pain is unclear.

Aromatase inhibitors and pain

It has long been recognised that post-menopausal women develop joint pain related to decreased oestrogen levels. The hormonal treatment of oestrogen dependent breast tumours targets either a direct anti-oestrogen effect (tamoxifen) or inhibits oestrogen biosynthesis (Aromatase inhibitors (AI)), either reversibly ('non-steroidal' - anastrozole, letrozole) or irreversibly ('steroidal'- exemestane). AIs have been associated with many side-effects, the most prevalent of which being aromatase inhibitor-induced arthralgia (AIA).[123]

Prevalence, risk factors and compliance

Prevalence can be as high as 74%, although there is some heterogeneity of reporting of joint arthralgia or joint 'stiffness'. Crew *et al.*[124] identified 47% with joint pain whilst 44% reported joint stiffness. AIA was less likely with a BMI of 25-30 (compared with BMI of greater than 30) but four times more likely if patients had received taxane chemotherapy therapy. In a study of 300 patients, 47% reported arthralgia of which three quarters developed this within three months and 67% reported pain as moderate or severe.[125] Joints affected were: wrist/hand 60%, knee 60%, back 54%, ankle/foot 52%. In one study, of the 23 out of 100 of patients who discontinued AIs, 13 were as a result of arthralgia.[126] Comparative data shows little difference between AIs. Arthralgia was reported by 47.9% with anastrozole and 48.2% on letrozole with grade 3/4 toxicity described in 3.3% and 3.9% respectively.[127]

Side-effect related non-compliance of AIs appears to be more common in clinical settings compared with trials. Approximately 20% (of 185) non trial patients stopped AIs because of arthralgia and interference with activities of daily living.[128] Another study estimated a non-compliance of 31% with anastrozole compared with 20% with tamoxifen.[129]

AIs seem to be associated with more arthralgia compared with tamoxifen. Joint problems were reported by 34% with anastrozole compared with 29% with tamoxifen.[130] Interestingly those who described joint problems within three months of treatment were less likely to develop recurrent breast cancer. Moreover, higher BMI (greater than 30) was associated with more arthralgia (37%) compared with BMI 25-30 (31%).

Aetiology of AIA

Several theories have been expounded including a direct effect of oestradiol on pain pathways.[131] However, this does not fit with reports that the highest pain tolerance during the menstrual cycle is when oestradiol is at its nadir.[132] Nevertheless, oestrogen receptors are found in synovia and expression is increased in joints affected with osteoarthritis.[131] Other proposed mechanisms include (auto)-immune modulation and cytokine activity (although not necessarily the classical inflammatory mediators) associated with oestrogen changes.[131]

Vitamin D may be important. In a study of 60 women taking letrozole, only 48% of women with concentrations greater than 66 ng/mL had disabling joint pain compared with 81% with vitamin D concentrations less than 66 ng/mL.[133] However a randomised trial looking at high and low doses of vitamin D supplementation did not show any significant differences in the incidence of AIA.[134]

Imaging techniques may give insight not only into diagnosis but also aetiology. A relatively robust finding on ultrasound and MRI is the observation of fluid and frequent thickening in tendon sheaths.[135] These tenosynovial changes, especially marked in the digital flexor tendons were also associated with a reduction in grip strength. Some have suggested grip strength be used a part of the AIA assessment. Grip strength shows a non-linear correlation with BMI, with greater reduction in high BMI and low BMI patients.[136] This led the authors to propose a link with insulin-like growth factor-1 (IGF-1) as lowering of oestrogen levels has been shown to reduce IGF-1 and cause joint pain.[137]

Treatment of pain in cancer survivors

As a result of the complex nature and the sheer variety of pain states encountered in cancer survivors, a 'one size fits all' management approach is unlikely to prove effective. Patients have reported that they prefer their pain to be managed by pain specialists working in conjunction with other professionals including their oncologist in a multidisciplinary team.[138]

A comprehensive initial assessment of the patient focusing on their cancer history and treatment should be conducted and include concurrent medical conditions, the presence of previous or existing pain states and current and previous pain therapies trialled. Attention should be paid to the associated psychological and social facets of cancer pain, neglect of this multidimensional process may result in suboptimal treatment.[139]

Examination should delineate the anatomical relationships of the pain and identify and demarcate areas of abnormal sensory function such as numbness, allodynia or painful or sensitive scars; results of recent imaging may help. The psychosocial impact of the pain and evidence of psychological morbidity such as anxiety and depression are also paramount.

In pain medicine there is often a deficiency of robust clinical evidence. The pain specialist must be clinically nimble and demonstrate a degree of ingenuity in the adaption of therapies from other similar chronic pain states. Pharmacological management may involve the use of agents outwith their license. In these cases, full discussion with and consent from the patient and compliance with the regulatory and judicial restrictions relevant to the practitioner are essential.

Pharmacological management

Opioids

Cancer-associated pain has traditionally been treated with opioid analgesics, often in escalating doses. This approach is embodied in the World Health Organisation's cancer pain ladder for adults,[140] which whilst often entirely appropriate for the successful control of pain in patients with advanced, and terminal disease, does not synergise quite so well with the rehabilitative aims of pain management in a survivor population. Here, there exists a therapeutic quandary between the potential detrimental impact of opioids such as sedation, tolerance, potential immunomodulation[141] and endocrine dysfunction[142] which can impede rehabilitation and the fact that cancer survivors may experience 'opioid responsive' pain. Opioid use should occur under the auspices of a multi-disciplinary pain management team with discussion of the risks and benefits of the medication with the patient and regular review to assess for efficacy and side-effects. Guidance on best practice opioid prescribing are available from a number of sources.[143 144]

Neuropathic pain: topical and systemic treatments

Many of the pain states encountered in cancer survivors have neuropathic features[115] and assessment is pivotal to commencing appropriate agents, either systemic or topical. As for many pain phenotypes in cancer survivors, evidence is sparse and a pragmatic approach is advised.

For patients with localised neuropathic pain (LNP), allodynia or hyperalgesia, topical agents may be appropriate.[145] Compared with systemic anti-neuropathic drugs, these medications are generally well tolerated, with minimal side-effects resulting in improved compliance. Efficacy is empirical and requires regular reassessment of the pain state. Potential topiceuticals which may be applied to areas of focal pain include 5% lidocaine patches, 2% menthol in aqueous cream, clonidine, ketamine and topical tricyclic antidepressants.[146]

Large, well conducted RCTs supporting the use of Lidocaine patches are lacking.[147] However the patches may in some circumstances demonstrate equivalence to systemic anti-neuropathic agents with superior tolerability.[148] Their use is recommended for consideration in frail patients, a physical state common to many cancer survivors.[149 150] A Cochrane review of low-concentration capsaicin cream found insufficient data to recommend its use in neuropathic pain,[151] whilst the high-concentration patch form also suffers from a deficiency of evidence sufficient to make confident pronouncements on its efficacy.[152]

The use of topical menthol,[153] clonidine,[154] ketamine[155] and tricyclic antidepressants[156] have only been investigated in small studies or case series, often in non-cancer related LNP and whose findings are often contradictory. Trialling these agents in LNP encountered in cancer survivors should be the judgement of the clinician managing the patient; close monitoring of efficacy and for potential adverse events is advised. Further well conducted studies in cancer-related LNP are undoubtedly warranted.

In non-localised neuropathic pain states, systemic anti-neuropathic agents are indicated. Consideration of the risk-benefit of commencing these agents is required. Strategies for the selection and commencement of systemic agents are provided by the guidelines detailed above,[149 150] and specifically for painful chemotherapy-induced peripheral neuropathy.[157]

There is burgeoning interest in the use of novel biological agents to control the pain arising from bone metastases. Tanezumab, a nerve growth factor (NGF) sequestering agent[158] and denosumab a monoclonal antibody to receptor activator of nuclear factor κB ligand (RANKL)[159] have been shown to be effective in controlling cancer-induced bone pain[158 160] and the efficacy and long-term safety profile continue to be actively investigated.[161]

Treatment of radiation induced pain

Rationalisation and reduction of radiotherapy has already resulted in huge reduction in incidence of RIBP. Hyperbaric oxygen has little evidence to support its use in reduction of RIF and symptoms associated with it.[162] Pentoxifyllin-tocopheral potentially reduces fibrosis after radiotherapy has shown mixed but potentially promising results.

Management of AIA

There is some evidence that switching AIs may be beneficial[131] however, there is little data regarding prevention or treatment of AIA pain. Pilot data demonstrated a 30% improvement in average pain score with duloxetine up to a dose of 60 mg/day.[163] Although not evidence based, in our experience the pain of AIA is often opioid sensitive whilst acknowledging the caveats of instigating opioid therapy in cancer survivors outlined above.

50% of patents report rapid alleviation of symptoms on cessation of treatment but the incidence of persistent pain after discontinuation of AI is unknown. Persistence of AIA was noted with exemestane treatment[164] which could be related to activation of autoimmune processes that persist after cessation of treatment.[165] The observation that short course low-dose prednisolone (5mg) can be potentially analgesic supports this.[166]

Interventional approaches

A variety of different approaches exist, and the choice of which intervention to offer depends both patient and institutional factors. For some evidence-based interventions such as vertebral augmentation (vertebroplasty and kyphoplasty) myeloma,[167 168] referral to other specialities may be required.

Implantable devices: Spinal cord stimulators and intrathecal drug delivery systems

The implantation of spinal cord stimulators (SCS) is an established and recognised treatment for chronic pain.[169] For painful diabetic peripheral neuropathy, symptomatologically comparable with CIPN, significant reductions in pain scores and improvements in quality of life have been demonstrated,[170] however evidence for CIPN is limited to a single case report.[171] A recent (2015) Cochrane review of spinal cord stimulation for cancer-related pain in adults concluded that the existing evidence base was insufficient to establish the role of SCS in cancer-related pain and more studies are needed.[172]

For cancer survivors treated with opioids experiencing side-effects or treatment refractory pain, an intrathecal drug delivery system (IDDS) may be considered.[173] By targeting the spinal cord, many systemic opioid-related side-effects can be avoided. A range of different agents[174] can be used intrathecally and can reduce pain scores, systemic analgesic requirements and toxicity whilst potentially prolonging duration of survival.[175]

High intensity focused ultrasound (HIFU)

Bone metastases represent a major cause of morbidity in cancer survivors. The use of image guided HIFU represents a developing and novel therapeutic option for these lesions.[176] HIFU involves the generation of an ellipse of focused ultrasound energy where temperatures transiently increase to around 80 °C. Localised tissue ablation can lesion specific targets, guided by MRI thermometry which allows near-real time visualisation of heat production. Thermal lesions can be made with relative precision minimising collateral damage, in contrast to the potential toxicity to surrounding tissues caused by radiotherapy. A number of studies have reported HIFU effectively reducing pain from bone metastases non-responsive to radiotherapy or analgesia,[177 178] and consensus guidelines have been published.[179] Ongoing research is focusing on additional safety and efficacy of bone metastases treatment and the effect of lesioning peripheral to reduce pain.

Acupuncture

In cancer survivors acupuncture is currently used in the control of persistent pain,[180] additionally it can also target other symptoms encountered in this patient group such as fatigue, vasomotor symptoms as a result of hormonal manipulation[181] and chemotherapy induced peripheral neuropathy.[182] A meta-analysis of five trials suggested a possible role for acupuncture in the management of AIA.[183] Conducting high-quality studies that include inert controls or sham interventions prove methodologically challenging.[184] Acupuncture potentially represents a useful component of a multi-modal approach to improving the quality of life in cancer survivors and is popular with patients.

Conclusion

Cancer survivorship represents a growing area of unmet pain need. As our understanding of the causes and mechanisms of pain in this population grows, so the commonality between

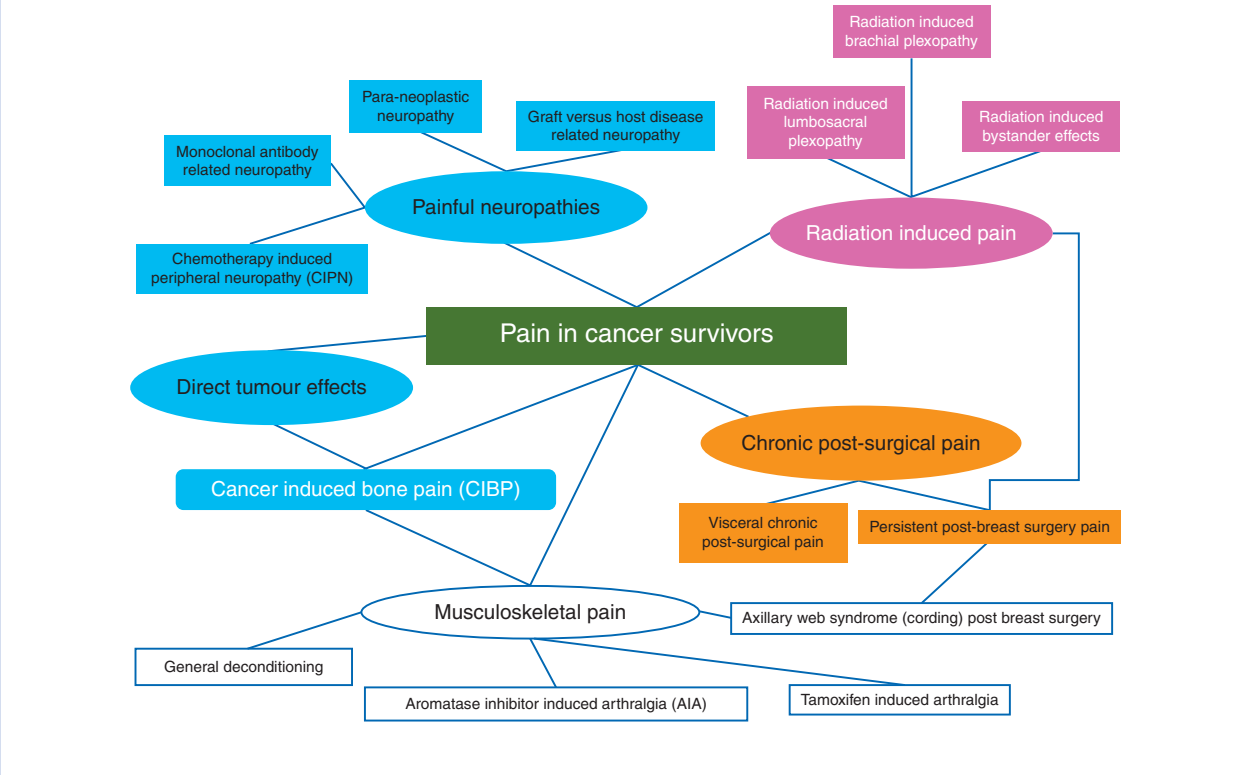

Fig 1 An outline of the different causes of pain in patients surviving cancer, related both to the disease itself, and the oncological treatment.

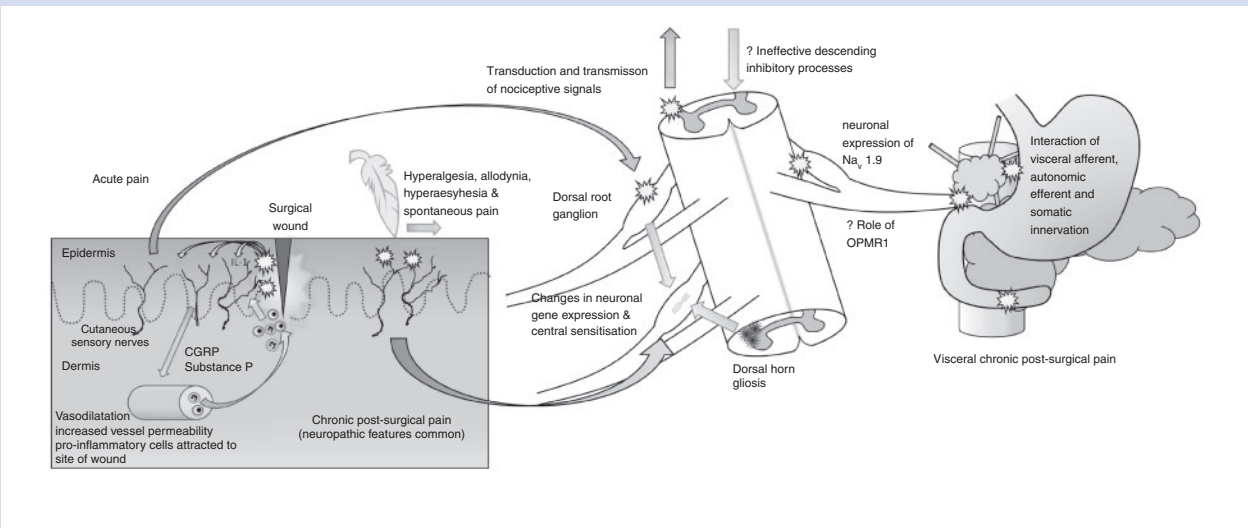

Fig 2 An overview of the pain syndromes (acute and chronic) occurring after cancer surgery, with potential mechanisms.

these pain states becomes apparent, both in mechanisms and treatment approaches. This review has focused on areas not routinely discussed in other published literature but it is clear that cancer treatments, novel and established, may be associated with a significant long term pain burden. We propose that this constellation of pain phenotypes be collectively referred to as 'chronic cancer-related pain' (CCRP). This alignment of the cancer survivor population with patients with non-cancer 'chronic' pain reflects the growing awareness that these cohorts of patients should be treated similarly. Additionally we suggest that the term 'chronic post-surgical pain' reflects this resonance with other chronic pain states. Whatever the nomenclature, we

must invest time and resources into understanding and consequently treating this growing pain epidemic.

Authors' contributions

The authors (M.R.D.B., P.F-S) contributed equally to the development, drafting and final review of the manuscript. M.R.D.B. produced Figures 1 and 2

Declaration of interest

M.R.D.B, none declared. P.F.-S. has previously undertaken paid consultancy work for Astellas, Napp, Pfizer and Grunenthal and has received expenses for contributing to a British Journal of Anaesthesia hosted workshop at the 6th International congress on neuropathic pain (2017).

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