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REVIEW

Pain management in cancer survivorship

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ABSTRACT

Background. The number of patients surviving cancer disease has increased in last decades. Consequently, an emerging population with different needs due to long-term or late effects of cancer disease and/or treatment, e.g. chronic pain, is of major concern.

Epidemiology. Chronic pain is one of the main problems in this population and prevalence varies between 16% and 50%. Most information derives from breast cancer patients assessed by surveys from national or local institutional databases. A Danish population-based survey estimated that 41.5% of all cancer survivors reported chronic pain.

Pain etiology. Neuropathic pain seems to be the major pain etiology in cancer survivors and therefore adjuvant analgesics should be the first choice of analgesic treatment.

Context. This article addresses the central aspects of pain epidemiology, mechanisms and the frequent pain syndromes met in cancer survivors. Pain management strategies are discussed according to the biopsychosocial model and with the rapidly growing number of cancer survivors the establishment of multidisciplinary clinics as a part of comprehensive cancer centers are proposed.

The advance in the medical field has provided more sophisticated tools for earlier cancer diagnosis and successful treatment options. As a result, an increasing number of patients survive the cancer disease; however, cancer survivorship may be followed by long-term/late effects of disease and/or treatment, e.g. chronic pain. In this context, the rational for pain treatment may follow the same principles of chronic non-cancer pain management, but keeping surveillance to the possibility of new or recurrent malignancy.

According to the National Cancer Institute at the National Institutes of Health [1], a cancer survivor "is anyone from the moment of the diagnosis until the end of life". In this article we will focus on those patients who had cancer in the past and have no current active cancer disease. Pain prevalence, syndromes and causes, etiology, pathophysiology and treatment of cancer survivors will be discussed.

Epidemiology

Despite increasing attention to cancer survivors, studies regarding prevalence of chronic pain in this population are sparse. According to a review study, 25–50% of breast cancer women experience chronic pain after treatment and the prevalence varies according to the different operational definitions for survivors, characteristics and study designs [2]. Most information derives from breast cancer patients assessed by surveys from national or local institutional databases.

Three examples of national surveys derived from databases are Danish [3–5] and Norwegian [6]. Those surveys investigated self-reported chronic pain in nationally representative samples of breast cancer survivors. A Danish cross-sectional survey was conducted in women who had breast cancer treatment 2–3 years before the study and did not present new occurrence

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of cancer. Response rate was 87% (3253/3754). The over-all prevalence of chronic pain was 47%, [3]. Another Danish study analyzed data from breast cancer survivors after at least five years from primary surgery without recurrence. Response rate was 79% (1413/1783) and 1316 questionnaires of women > 40 years and without recurrence of cancer were analyzed. Prevalence of chronic pain related to breast cancer (pain lasting six months or more) was 29%; however, the over-all prevalence of chronic pain was 42% in this population [4]. The Norwegian study analyzed data of women submitted to surgery and adjuvant therapy for breast cancer in the previous 2–6 years before their study. Response rate was 63% (832/1332). Prevalence of chronic pain (pain lasting three or more months and reported as a result of operation and/or treatment for breast cancer) was 41%; out of these 41% reported moderate pain and 33.8% reported characteristics of neuropathic pain [6].

The Danish National Cohort Study of 2010 collected information regarding health status and behavior of a representative sample of the total Danish population consisting of 25 000 individuals (at least 16 years old). Of them, 6380 individuals with age equal or higher than 50 years were analyzed regarding the occurrence of over-all pain lasting for at least six months. In total 536 individuals were cancer survivors (had previous history of cancer) and 41.5% of them reported chronic pain, while 33.0% (n = 5685) of the individuals without cancer history reported chronic pain [5].

Other studies with institutional breast cancer databases reported similar figures. In an Australian longitudinal study 1205 women that had breast cancer, but no recurrent disease or new primary tumor, were analyzed regarding presence of persistent breast pain and reduced wellbeing. Almost 45% (n = 540) reported breast pain lasting at least three months after first surgery. Nearly 30% reported that initial pain was moderate or severely disabling. After five years, 80% of the 540 patients reported that they still had pain [7]. An US study evaluated 582 patients submitted to partial or total mastectomy due to cancer. Pain related to the mastectomy after two months to 10 years was reported by 47.4%; of them 32.5% had pain score above 2 (scale 0–10) [8]. Another US multicenter prospective study demonstrated that the prevalence of general pain in breast cancer patients after 40 months (N = 563) and five years (N = 522) post-diagnosis increased from 27.8% to 32.3%, respectively [9].

Treatment-related pain syndromes in cancer survivors

It is well known that surgery can produce chronic postsurgical pain syndromes, such as post-mastectomy pain and phantom limb pain. Risk factors involve insufficient postoperative pain control, radiation therapy, chemotherapy, and psychosocial characteristics, such as young age, short education, being single, anxiety and depression [10,11]. In addition, chronic postoperative visceral pain syndromes are common as a result of development of adhesions, collections and fistulae. The increasing use of less invasive surgical techniques may reduce chronic postsurgical pain. Radiation therapy can produce a number of persistent or chronic pain syndromes, most notably plexopathies and osteoradionecrosis. Further, radiotherapy has been demonstrated to be a major predictor for developing chronic pain in breast cancer survivors [4]; however, as radiotherapy becomes more targeted these pain syndromes may become less common. Chemotherapy-induced peripheral neuropathy (CIPN) is of increasing prevalence in spite of the development of more targeted therapies. CIPN due to treatment with oxaliplatin, paclitaxel, and vincristine is usually a dose-dependent, cumulative and only partially reversible side effect resulting in a symmetrical, distal painful neuropathy described as pricking, tingling, burning or numbness in hands and feet often followed by loss of proprioception and muscle weakness.

Pain etiology

Pain in active cancer disease involves a complexity, which is related to the presence of tumor and antineoplastic treatment. A distinctive feature of pain due to cancer is that the tumor and/or treatment independently of nerve damage causes local or generalized inflammation (e.g. pro-inflammatory cytokine responses), which in turn may produce or reinforce pain. In addition, tumor-related factors and responses to these factors may be responsible for many co-existing symptoms, such as cachexia, nausea, fatigue etc. This complexity is not found in non-malignant pain; however, in cancer survivors with chronic pain the pain etiology may consist of musculoskeletal and visceral pain conditions, but the presence of neuropathic pain (NP) conditions due to former treatments and lesions caused by tumor is paramount.

Clinical characteristics of neuropathic pain

The most recent definition of NP given by International Association for the Study of Pain (IASP) is "Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [12] and diagnostic criteria were also recently proposed by the IASP Special Interest Group on NP [13].

Unfortunately, the IASP NeuroPSIG recommendations can only to a limited extent be applied in cancer patients [14] and in cancer survivors NP can further deviate substantially. NP in cancer survivors is often chronic and may consist of background pain with acute flares of pain intensity, which may be spontaneous or evoked or both. Spontaneous and evoked pain is most often arising from areas of various sensory abnormalities (hyposensitivity, hypersensitivity, or both). Paraesthesia (abnormal sensation that is not painful or unpleasant) and dysaesthesia (unpleasant abnormal sensation) may often be present. Especially, touch-evoked allodynia (evoked pain that is elicited by a non-noxious stimulation), allodynia to cold/heat and hyperalgesia (increased response to a stimulus that is normally painful) are dominating findings in NP.

Fundamentals of pharmacological pain management in cancer survivors

Pain assessment in cancer survivors should be based on a systematic analysis of the pain cause, etiology, syndrome, pathophysiology and include other symptoms and problems. Pain induced by cancer treatments is often NP and the drugs commonly used for NP – anticonvulsants or antidepressants – have mainly been demonstrated to be effective in the management of post-herpetic neuralgia and/or diabetic polyneuropathy [15]. There exist a few controlled studies to support the use of adjuvant analgesics for treatment of NP in cancer, but no studies of the efficacy of adjuvant drugs in cancer survivors are available. In addition, NP in non-malignant diseases may be considerable different from NP in malignant diseases as inflammation is much more prevailing and dominant in the latter situation. Therefore, NP in cancer survivors may be quite different from NP in active cancer [16]. Long-term use of opioids may be advantageous in patients with opioid sensitive pain. However, opioids do have numerous side effects, serious long-term consequences and addiction [17], which are well described and prevalent in the chronic non-cancer pain population. The risk of long-term consequences and addiction to opioids in cancer survivors is not known. Based on this knowledge the authors of this article find that the analgesic strategy should be based on the assumption that the risks of long-term consequences and the risk of addiction may be of the same magnitude as in chronic non-cancer pain patients and therefore cautiousness should be exercised leaving opioids as the last analgesic treatment resort. Further, as NP seems to be the major pain etiology in cancer survivors adjuvant analgesics may be the first choice of analgesic treatment.

Non-opioid analgesics

Non-opioid analgesics are widely used in mild-to-moderate pain and NSAIDs and ASA are particularly efficient in inflammatory pain conditions, while paracetamol has weaker anti-inflammatory effects compared to NSAIDs [18], but is safer than the NSAIDs for long-term use. A Danish study in 2000 female breast cancer survivors at least five years after primary surgery without recurrence demonstrated that 47% used paracetamol, 17% ibuprofen and 9% acetylsalicylic acid regularly [4]. Paracetamol is generally well tolerated. However, a cautious approach should be taken to the use of all types of NSAIDs in high-risk patients, including elderly patients, those with *Helicobacter pylori* infection, peptic ulceration within the last year, patients being treated with corticosteroids or low-dose ASA and/or anticoagulants, those with advanced disease and excessive smoking and alcohol use. Some of these risks factors may be frequently met in cancer survivors and gastro-protective strategies as well as the cardiovascular risks should always be considered thoroughly [19].

Regarding the gastrointestinal risks, strategies should include interventions that precede oral NSAID and acetylsalicylic acid use, such as paracetamol, topical NSAIDs, adjuvant analgesics, and sometimes even weak or strong opioids. When treatment with NSAIDs is indicated and effective, it is recommended to use the lowest effective dose for the shortest period of time and combine the treatment with a gastro-protective agent or alternatively select a COX-2-inhibitor. Regarding the cardiovascular risks it seems increasingly likely that these are related to individual NSAIDs or coxibs rather than NSAIDs versus coxibs. The cardiovascular hazard of coxibs involves thrombosis and altered vessel wall reactivity, which are TXA2-driven; however, apparently some traditional NSAIDs, e.g. high dose ibuprofen and diclofenac have also been shown to present cardiovascular risks similar to that of coxibs. Based on current evidence, cancer survivors at high cardiovascular risks should be treated with either naproxen (plus proton pump inhibitors) or celecoxib. However, in general the lowest effective dose for the shortest possible duration of time should be used with both NSAIDs and coxibs [19].

Adjuvant analgesics

Adjuvant analgesics include gabapentinoids (gabapentin and pregabalin), antidepressants [tricyclic antidepressants (TCAs), duloxetine, and venlafaxine], corticosteroids, bisphosphonates, ketamine, and cannabinoids. However, in cancer survivors

gabapentinoids and antidepressants are most frequently used for treatment of NP [4]. The effects of gabapentin and pregabalin are well documented in non-malignant NP conditions (NNTs ranging from 4.2 to 6.4) [20], whereas the evidence for their use for NP in cancer is weak [21]. Onset of pain relief can be rapid during titration (within a week) and is often accompanied by improvements in sleep and mood. However, time to titrate and stabilize doses may be longer in order to obtain adequate balance between pain relief and side effects [22]. Central side effects like somnolence and dizziness are common; however, peripheral edema, increased appetite/weight gain, nausea, vertigo, asthenia, dry mouth, confusion and ataxia may also occur during dose titration and long-term treatment. Gabapentinoids undergo renal excretion and renal failure requires dosage decrement.

Antidepressants used in treatment of NP include primarily TCAs (e.g. amitriptyline, nortriptyline and imipramine). TCAs have been shown to be effective for especially different non-malignant NP conditions in randomized clinical trials (RCTs) (NNT values ranging from 2.1 to 2.8) [20]; however, it has also been suggested that they are effective in cancer patients with NP [21]. Central side effects like somnolence and confusion are common and an array of anticholinergic side effects are prevalent during TCA therapy (dry mouth, constipation, urinary retention, sexual dysfunction, sweating, and blurred vision). Selective SNRIs have been shown to have some efficacy in NP and recently duloxetine has demonstrated efficacy in a RCT of CIPN [23].

Combination therapies of different adjuvant analgesics have not yet been thoroughly investigated.

Opioids

The consumption of opioids by breast cancer survivors reporting cancer-related chronic pain was 12% in a Danish survey; however, the consumption of strong and weak opioids in the total population of breast cancer survivors (N = 2000) were 2% and 5%, respectively [4]. Despite not being the first line medication recommended for treating chronic non-malignant pain, opioids may be an option for selected patients with opioid responsive pain. There is a lack of data on the long-term use of opioids in cancer survivors. However, it is well known that common and immediate side effects are expected during short-term opioid treatment like nausea, itching, sedation, constipation and during long-term treatment more complex consequences may occur including physical dependence, tolerance, opioid induced hyperalgesia, cognitive dysfunction, addiction/abuse, and suppression of immune and endocrine systems [17]. Side effects and consequences like tolerance and opioid-induced hyperalgesia may be manageable with reduction of opioid dose, slow opioid dose tapering, and opioid rotation. Other effects, such as addiction and suppression of immune and endocrine systems, have higher potential of causing individual health problems and costs to society.

The prevalence of opioid addiction in chronic non-cancer pain patients in analgesic treatment varies among studies. Recent data showed a high prevalence of addictive behaviors to opioids when chronic pain patients treated with opioids were screened according to the International Classification of Diseases (ICD-10) and Portenoy criteria for addiction: 14.4% and 19.3%, respectively [24]. The factors that promote addiction in some people are not fully understood, although it is known that genetic factor and family history of substances abuse are risk factors, among others [17].

There is little evidence of effects of opioids on the immune system in humans; however, experimental studies in vitro and in animals have demonstrated differences in neuroimmunomodulation according to the different opioid receptors. Studies have demonstrated an enhanced sensitivity to viral and bacterial infections in opioid drug abusers and there is evidence that opioids affect the immune system function and induce a potential increased cancer risk due to angiogenesis, apoptosis, proliferation and invasion of tumor cells. However, whilst this is biologically plausible, clinical, in vitro and animal evidence is still mixed [25].

Regarding the endocrine system, hypogonadotroph hypogonadism is well reported with opioid use and it is suspected that it may also cause adrenocortical insufficiency [26]. Possible consequences of interference on endocrine system are osteoporosis, decreased libido, sexual dysfunction, fatigue and depression.

Non-pharmacological interventions

Depression, anxiety, post-traumatic stress disorder and reduction of physical functionality are very common in patients with chronic pain and also very frequent in cancer survivors. Non- pharmacological techniques can be used to enhance overall sensation of wellbeing, reduce pain hypervigilance and improve functionality in these patients. Non-pharmacological interventions are adjuvant strategies that can increment analgesic treatment effect and may reduce medication doses.

Physiotherapy/physical exercise, physical methods (heat, cold packs, massage, etc), transcutaneous electrical nerve stimulation, acupuncture, and

cognitive behavioral therapy are examples of non-pharmacological interventions. However, while some methods are very old techniques applied to patients with pain (e.g. heat/cold packs, and massage), there is limited evidence regarding effectiveness of many of these interventions (e.g. transcutaneous electrical nerve stimulation and acupuncture) [27].

Cognitive behavioral therapy has been one of the current strategies to strengthen patients' ability to live with chronic pain. It is based on the principle that pain has a social behavioral component, which has been captured in the society, and that it is possible to learn or re-learn a more positive adaptive behavior. The therapy aim is to help patients to understand that their thoughts are responsible for feelings and behaviors and that it is possible to manage the way they feel and behave by changing the way they think. Content of therapy includes educational activities regarding pain analysis and rethinking of behavior and thoughts, strategies to relieve emotional and psychological tensions (technics of relaxation and distraction, among others) and cognitive and physical exercise.

Perspectives

Cancer survivors are at increased risk for comorbid conditions including chronic pain and have reported a poor or fair health, psychological disability, limitations in daily life, and reduced ability to work after breast cancer compared to the general population. Nevertheless, we and others have found that health-related quality of life in breast cancer survivors was very similar to (or slightly better than) that reported by age-matched women of the general population [11]. Likewise The Danish National Cohort Study of 2010 showed no difference in the health-related quality of life in survivors of different cancer diseases and the general population without a history of cancer [5]. These findings may indicate that cancer survivors may deviate substantially from the population of chronic non-cancer pain patients, which in most surveys present with very low health-related quality of life. We find that this observation is important to bear in mind for a future clinical research agenda for studying chronic pain in cancer survivors. Findings in chronic non-cancer pain patients cannot readily and uncritically be transferred to cancer survivors – not even pharmacological research. Thus, when we advocate for cautiousness regarding long-term opioid therapy and state that analgesic strategy should be based on the assumption that the risks may be of the same magnitude as in chronic non-cancer pain patients it is merely based on a conservative attitude until more evidence is available. However, in terms of a general research agenda for pain in cancer survivors there is a lack of knowledge in several areas and important questions need to be clarified: Why do some people experience long-term problems after being exposed to a disease or symptom such as pain while others do not? Which general and procedure-/disease-specific factors are involved in the development of pain? Could we prevent the development of pain? How is acute pain transformed into a chronic pain condition after a procedure, disease or injury? Explanations may be manifold and presumably there are several risk factors due to the huge diversity regarding individual responses to painful stimuli. They probably include internal and external factors as gene expressions/biological functioning, social/environmental interactions, and psychological/emotional processes. Possibly internal and external factors interact and may produce different responses according to genetic variability. However, it may also be the case that a pure genetic factor may be responsible for a specific response [28]. However, there is as yet no consistent and compelling evidence for specific genetic factors playing a role in the transition from acute to chronic pain – not even when reviewing literature regarding perioperative pain [29]. Large, multisite genetic studies in cancer survivors developing specific chronic pain states will be necessary to address these issues definitively.

Thus, specific genes that characterize patients who are at risk of chronic pain, and the ability to identify these factors or genes, and to understand how they predispose individuals to chronic pain, might help us to prevent or even treat the condition.

The biopsychosocial model is a traditional but still highly relevant model that should be kept in mind when dealing with cancer survivors. According to the biopsychosocial model, future studies should consider all of the biological, psychological, existential and social dimensions. Further studies are needed across different cancer diagnoses to determine significant risk factors. The individual risk profile could then yield an estimate, which can assist in assessing the severity of health problems and potential consequences (e.g. chronic pain). This approach should be followed by prospective intervention studies. With the rapidly growing number of cancer survivors the establishment of multidisciplinary clinics as a part of comprehensive cancer centers may be a way forward in rehabilitation of cancer survivors according to the biopsychosocial model.

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