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REVIEW ARTICLE/BRIEF REVIEW

Brief review: Pain management for cancer survivors: challenges and opportunities

Bref exposé: Prise en charge de la douleur chez les survivants du cancer: défis et opportunités

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Abstract

Purpose *As the number of cancer survivors continues to increase due to advances in medicine, many cancer survivors remain on their same pain management regimen long after their cancer treatment has been completed. Thus, the purpose of this review is to encourage awareness of the challenges and opportunities of pain management in cancer survivorship. It is our expectation that these patients will be referred to pain medicine specialists so their pain management can be optimized during the period of survivorship and ultimately improve their quality of life.*

Principal findings *Cancer and its treatment can cause significant pain which requires multidrug therapy, including strong analgesics such as opioids. Optimal pain management has been shown to improve the quality of life of cancer patients, and that is also true for cancer survivors. Nevertheless, the appropriate use of pain medications, especially opioids, must be re-evaluated and adjusted during treatment as the patient transitions into survivorship care and thereafter. This may otherwise result in unnecessary opioid use or may even lead to abuse. Fortunately, as cancer treatment is completed and the survivorship period begins, pain improves gradually and the need for pain medication should decrease. Unfortunately, some patients continue to take their potent analgesics during the period of survivorship although it may not be necessary. It is a challenge for pain practitioners who do not see these patients early in their disease or in the recovery period. Nevertheless, this challenge presents an opportunity for pain management providers to educate oncologists to refer cancer survivors to pain centres early during the period of their survivorship. Cancer survivors could then receive optimal care and maintain a better quality of life without having to take unnecessary pain medications.*

Conclusions *It is clear that there is a need to improve pain management in cancer patients, particularly in cancer survivors. Pain physicians should play a critical role as part of a multidisciplinary team that cares not only for cancer patients but also for cancer survivors. Optimizing pain management during the cancer survivorship period results in a better quality of life.*

Résumé

Objectif *Avec l'augmentation du nombre de patients survivant à un cancer grâce aux progrès de la médecine, nombre d'entre eux conservent le même protocole de gestion de la douleur longtemps après la fin de leur traitement. L'objectif de cet exposé était donc d'encourager la sensibilisation aux défis et opportunités de la gestion de la douleur chez les survivants du cancer. Nous nous attendons à ce que ces patients soient adressés à des spécialistes du traitement de la douleur de façon à ce que la prise en charge de la douleur soit optimisée pendant la période de survie et, finalement, améliore leur qualité de vie.*

Constatations principales *Le cancer et son traitement peuvent causer des douleurs significatives qui nécessitent une multithérapie incluant des analgésiques puissants tels*

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que les opioïdes. Il a été montré que la gestion optimale de la douleur améliore la qualité de vie des patients cancéreux, ce qui est également vrai pour ceux qui ont survécu à un cancer. Néanmoins, la bonne utilisation des médicaments de la douleur, notamment des opioïdes, doit être réévaluée et adaptée au cours du traitement lorsque le patient entre dans la phase des soins de survie à la maladie et au-delà. Faute de quoi, une utilisation inadéquate des opioïdes pourrait même déboucher sur des abus de ces médicaments. Heureusement, avec la fin du traitement du cancer et le début de la période de survie, la douleur s'améliore progressivement et le besoin de médicaments contre la douleur devrait baisser. En revanche, certains patients continuent à prendre leurs analgésiques puissants au cours de la période de survie bien que cela puisse ne pas être nécessaire. C'est un défi pour les médecins de la douleur qui ne voient pas ces patients précocement au cours de leur maladie ou pendant la phase de convalescence. Néanmoins, pour les spécialistes du contrôle de la douleur, ce défi offre l'opportunité d'expliquer aux oncologues qu'ils doivent adresser les patients survivant à des cancers à des centres de la douleur tôt dans leur période de survie. Les patients survivant à un cancer pourraient alors recevoir des soins optimaux et maintenir une meilleure qualité de vie sans devoir prendre inutilement des médicaments contre la douleur.

Conclusions *Il existe un net besoin d'améliorer le contrôle de la douleur chez les patients cancéreux, en particulier chez les patients survivant au cancer. Les spécialistes de la douleur jouent un rôle essentiel dans l'équipe multidisciplinaire qui traite non seulement les patients atteints de cancer, mais aussi ceux qui y survivent. L'optimisation du contrôle de la douleur au cours de la période de survie au cancer aboutit à une meilleure qualité de vie.*

In the last several decades, we have seen a marked rise in the population of cancer survivors. Novel chemotherapeutic agents, advanced radiation treatments, sophisticated surgical techniques, as well as advances in genetic modelling have all contributed to improved treatment for a wide variety of malignancies. Subsequently, the proportion of patients who are cancer survivors continues to increase. Not surprisingly, the demand for oncology services is expected to rise tremendously by the year 2020.[1]

In addition to the disease itself, many of the treatment modalities utilized in the treatment of cancer may lead to various types of chronic pain. Chronic pain entities, such as post-thoracotomy pain syndrome, chemotherapy-induced peripheral neuropathy, and radiation fibrosis, have been well documented as sources of pain in cancer survivors. The tumour itself, whether or not it is stable in nature, may also contribute to pain based on various characteristics such as size, type, and location. The treatment process is often long and arduous and often leads to psychosocial stresses that, in turn, affect the patient's perception of pain. During the treatment process, patients often have their pain managed by their oncologist or primary care physician. While certain pain management options may be appropriate during the active phase of treatment, the same options require frequent adjustment during and after the completion of cancer treatment. Unfortunately, this is seldom the case; consequently, many cancer survivors remain on the same pain management regimen long after their treatment has been completed.

These patients are often referred to a pain medicine specialist only after failing the "standard" options offered by their oncologist or primary care physician. These "standard" options can have significant variability based on training and community-based standards of care. Pain medicine specialists can offer tailored medical management, advanced interventional techniques in the treatment of cancer, as well as the potential sequelae of treatment. The purpose of this review is to encourage awareness of the issues surrounding pain management in cancer survivorship. The goal is to ensure that these patients are referred to pain medicine specialists early in their diagnostic and therapeutic course so that appropriate and timely pain care can lead to a better quality of life with fewer adverse effects.

Survivorship

There has been a marked shift from the previously utilized model of the traditional "cure" to the modern definition of cancer survivor. Dr. Fitzhugh Mullan, a physician and cancer survivor, highlighted this in his 1985 article in the *New England Journal of Medicine* entitled "Seasons of Survival".[2] In his article, Dr. Mullan does not attempt to define a time when the patient is considered "cured"; rather, he emphasizes the evolution of disease. The cancer survivor, then, becomes someone in whom the disease process is sufficiently controlled. The committee members of The National Coalition for Cancer Survivorship, founded in 1986, state that an individual diagnosed with cancer is a survivor "from the time of diagnosis and for the balance of life". Since that time, the definition of survivor has been expanded and now encompasses a wider spectrum of individuals that includes family and caregivers.[3] This broader definition has definite implications for health care. To this end, the National Cancer Institute (NCI) established

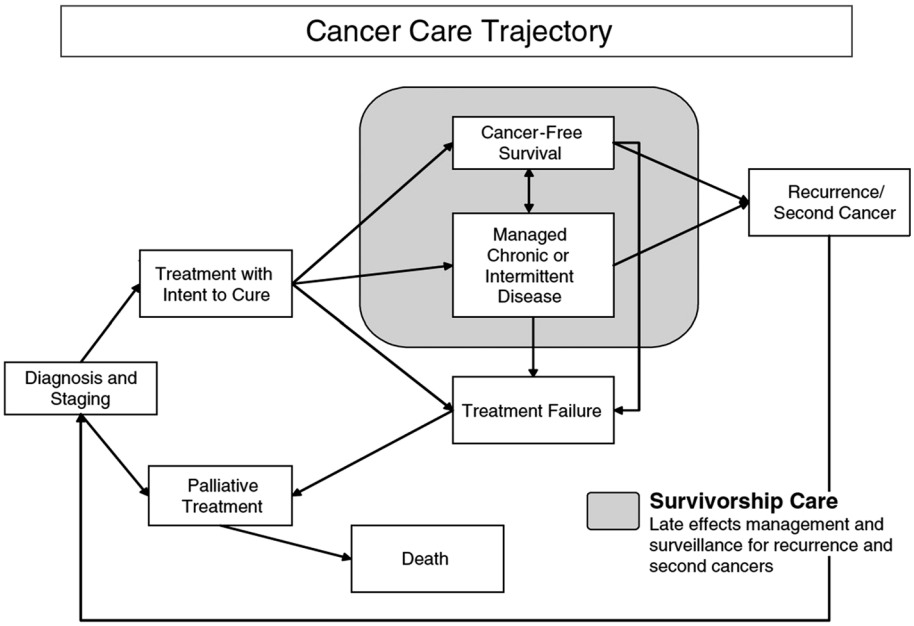

Fig. 1 Cancer Care Trajectory. Reproduced with permission from: *Hewitt ME, Greenfield S, Stovall E.* From Cancer Patient to Cancer Survivor: Lost in Transition. National Academy Press 2006[5]

the Office of Cancer Survivorship (OCS) in 1996. The OCS was established to help address the issues faced by "the large number of individuals now surviving cancer for long periods of time. … [as well as] their unique and poorly understood needs".[4]

One of the most challenging needs of cancer survivors is appropriate transition of care. Each patient's course through the disease process is unique. After initial diagnosis and staging is established, the patient may undergo either palliative treatment or "curative" treatment. Further down the road, the patient's disease process may go into remission, become chronically managed in nature, or progress. At any point during this process, disease recurrence or a second primary disease process may occur. Furthermore, each patient's coexisting medical problems may complicate the issue. Disease-related treatments may also have their own complications. All of these lead to an inevitably complex journey for patients, their families, their caregivers, and their healthcare providers. The Institute of Medicine released a "Cancer Care Trajectory" in 2006 (reproduced in Fig. 1) which outlines many facets of this journey.[5]

For the pain medicine physician, the shift of a patient to survivorship carries numerous implications. These include challenges as well as unique opportunities to advance patient care, discussed below. Communication with the patient's primary healthcare provider and oncologic teams is critical. The Institute of Medicine recommends that each patient should have a survivorship care plan. This plan should include treatment history of the disease process, potential adverse effects of the treatments, and surveillance guidelines for disease recurrence or the occurrence of a second primary cancer.[6] Just as surgeons detail their treatment of cancer with operative reports, it has been suggested that medical oncologists should also adhere to this type of plan.[7] The care plan is important not only for the patient but also for secondary healthcare providers such as pain medicine physicians. The care plan outlines important details about the patient's status in the treatment process, as each stage has its own specific challenges and opportunities.

Epidemiology

The NCI's Surveillance, Epidemiology, and End Results (SEER) program has been collecting data on cancer incidence and survival in the United States since 1973. The NCI collaborates with the North American Association of Central Cancer Registries (NAACR) in order to incorporate all state registries.[8] An annual report detailing epidemiological data is published. These reports include the most recent data on incidence, mortality, prevalence, lifetime risk, and survival statistics.

Nearly 14 million Americans are currently living with a history of cancer, excluding basal cell and squamous cell skin cancers. There is no doubt that cancer survivors are increasing in number.[9] Figure 2 illustrates the steadily increasing relative survival over the past 34 years, as reported to the National Cancer Institute.[10]

Although overall survival rates have been increasing, they still vary considerably amongst varying cancer diagnoses. While some diagnoses carry five-year survival rates approaching 100%, others are still less than 10%. Figure 3 depicts the five-year relative survival percentage for the most common cancer diagnoses.[11]

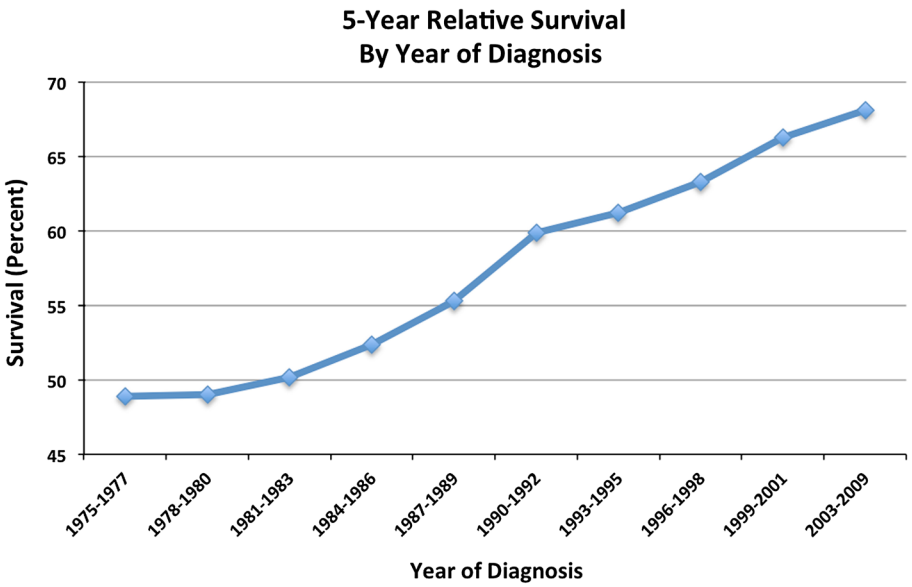

Fig. 2 Five-year relative survival (in percentage of diagnosed patients) by grouped years Data source: Surveillance, Epidemiology, and End Results Program, National Cancer Institute, 1975-2009[10]

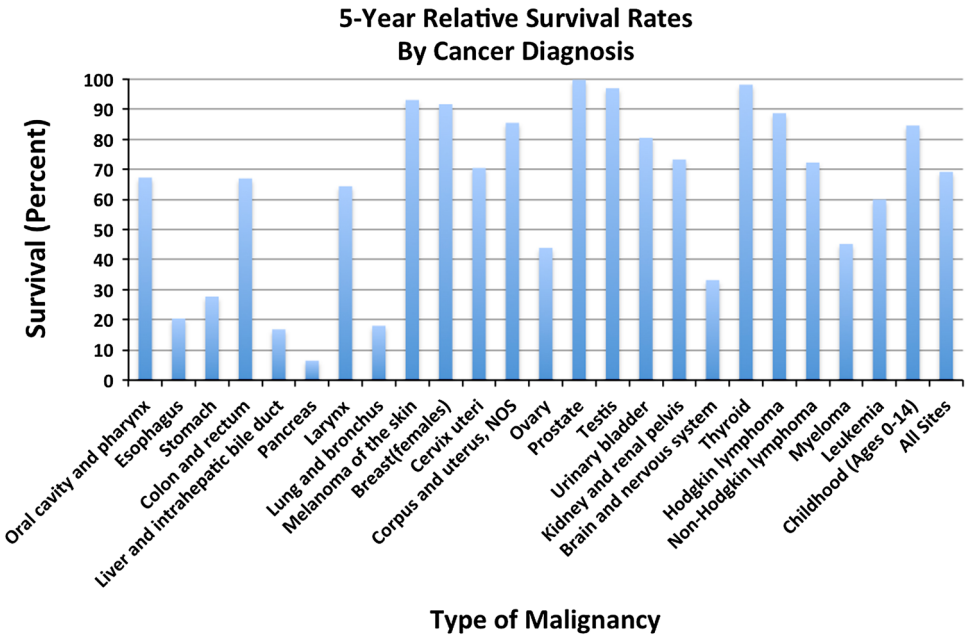

Fig. 3 Five-year relative survival (in percentage of diagnosed patients) by type of malignancy Data source: Surveillance, Epidemiology, and End Results Program, National Cancer Institute, 1950-2010[11]

Another discrepancy lies in survival between ethnic groups. Figure 4 shows the five-year relative survival percentage for various types of cancer by ethnicity.[10] Only data from black and white ethnic groups were available on the SEER database website.

Sex differences continue to exist in survivorship statistics; although, in recent years, the five-year relative survival gap between the two groups appears to be closing. This is shown in Fig. 5.[10]

The issue of cancer pain has gained more attention in the past two decades. The World Health Organization (WHO) pain ladder, established in 1986, provided guidelines for appropriately treating cancer pain.[12] More recently, advanced strategies for effective management have become available. These strategies include adjuvant medications and techniques for image-guided interventional pain medicine. Nevertheless, cancer pain remains a potentially undertreated entity. A 2007 meta-analysis of 52 studies revealed the prevalence of pain to be 33% in patients after curative treatment, 59% in patients on anticancer treatment, and 64% in patients with metastatic or advanced stage disease. More than one-third of patients were reported to have moderate to severe pain (visual analogue scale > 4).[13]

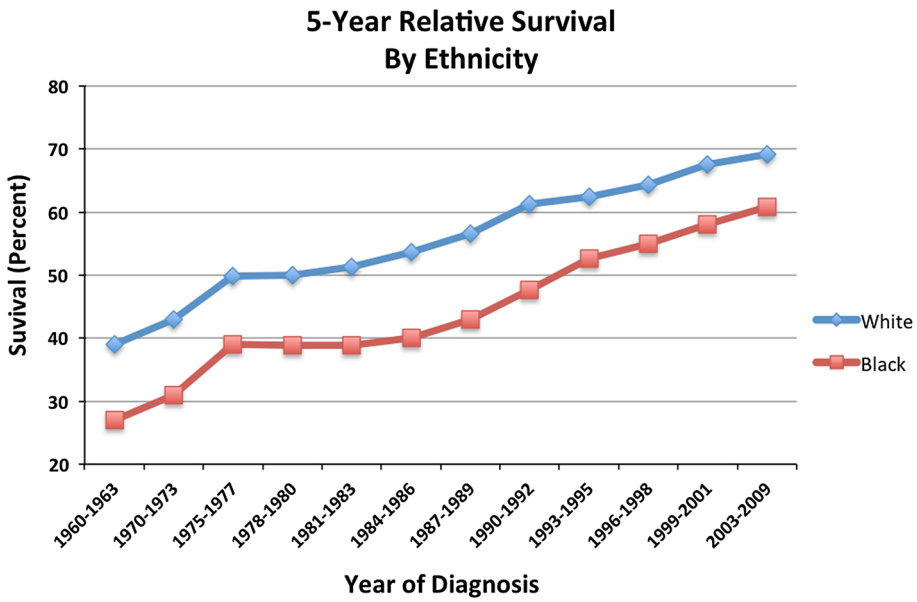

Fig. 4 Five-year relative survival (in percentage of diagnosed patients) by ethnicity and grouped years (as reported in the referenced database). Data source: Surveillance, Epidemiology, and End Results Program, National Cancer Institute, 1975-2009[10]

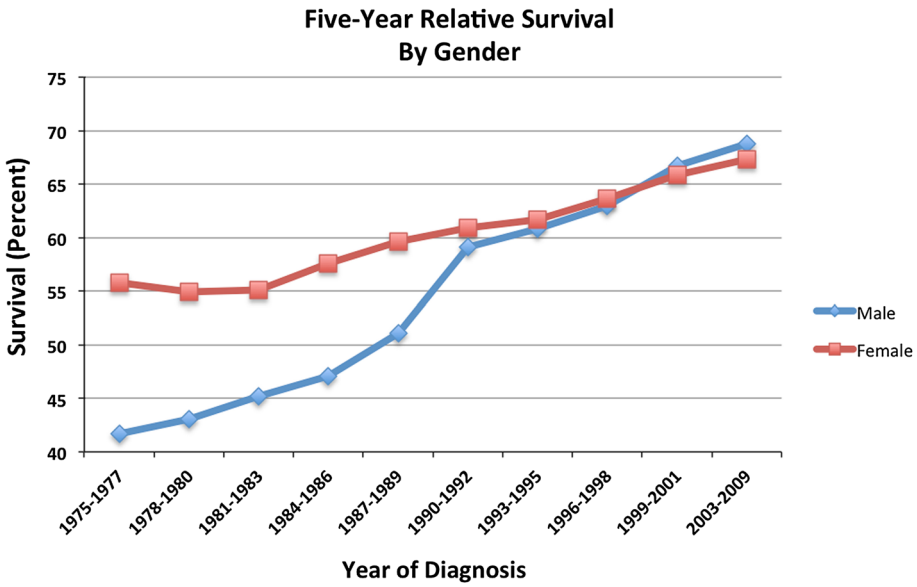

Fig. 5 Five-year relative survival (percentage of diagnosed patients) by sex and grouped years. Data source: Surveillance, Epidemiology, and End Results Program, National Cancer Institute, 1975-2009[10]

The most common types amongst male survivors are prostate, colorectal, and melanoma of the skin. For female survivors, the most common types are breast, uterine corpus, and colorectal.[14] The prevalence of pain and common pain generators varies by disease process and associated treatment modalities. For example, in prostate cancer, the pain may be from the cancer itself (77%), treatment-related (19%), or unrelated (3%).[15] Nevertheless, undertreatment is the common thread among all cancer and treatment-related pain entities. Risk factors for uncontrolled pain in cancer patients include age older than 65 yr, female sex, lack of higher education, and minority cultural groups. Recommendations for resolving undertreatment have included optimizing patient assessment, adopting a holistic treatment approach, and utilizing opportunities for education.[16]

Challenges

Cancer survivors present unique challenges to the pain medicine physician. The pain generators for these patients are often multifactorial and fluid in nature. Challenges related to the cancer itself are complex, especially in the setting of advanced disease. Rates of pain in patients with advanced disease have been reported as high as 90%.[17] With widespread disease, narrowing the site of pain generation becomes difficult. Treatment of the underlying disease may significantly improve pain.

Treatment-related pain generators may significantly contribute to complaints in cancer survivors. Surgical intervention is often utilized in treatment plans. For example, mastectomy has been utilized in approximately

Table Chronic pain diagnoses associated with antineoplastic treatments

Pain Diagnosis	Associated Treatment
Chemotherapy-induced peripheral neuropathy	Vinca alkaloids, platinum compounds, taxanes, thalidomide
Painful fibrosis, restriction	Radiation therapy
Persistent post-mastectomy pain	Mastectomy, breast reconstruction
Post-thoracotomy pain syndrome	Video-assisted thoracoscopic surgery, thoracotomy
Post-radical neck dissection pain	Neck dissection, flap reconstruction
Phantom limb pain, stump pain	Amputation, hemipelvectomy
Lymphedema-associated pain	Lymph node dissection
Generalized myalgias, arthralgias	Aromatase inhibitors, corticosteroids, cyclophosphamide, stem cell transplantation
Postherpetic neuralgia	Immunosuppression
Vertebral compression fractures	Radiation therapy, corticosteroids
Avascular necrosis	Stem cell transplantation, corticosteroids
Mucositis	Radiation therapy
Osteonecrosis	Corticosteroid therapy

41% of women with breast cancer.[18] This may lead to persistent post-mastectomy pain. Similarly, resection of other types of cancer may lead to postsurgical pain syndromes, such as post-thoracotomy pain syndrome, post-neck dissection pain, and phantom pain from amputation, etc. This type of pain often has a neuropathic component as nerves suffer trauma during surgical intervention. Hypothetically, further treatment modalities, such as chemotherapy and radiation therapy, may further injure neural structures, potentially leading to a larger neuropathic pain generator. Interestingly, a recent study of persistent post-mastectomy pain showed that neither surgical factors (such as total mastectomy, lymph node dissection, and reconstruction) nor treatment exposures (radiation and chemotherapy) were associated with persistent post-mastectomy pain. This may be partially due to the time elapsed after surgery, as many of the inflammatory and neuropathic components of post-surgical pain syndromes may resolve over time.[19]

Chemotherapy-induced peripheral neuropathy remains a major source for pain in cancer survivors. It is associated with commonly used chemotherapeutic agents, including platinum-based agents, taxanes, and vinca alkaloids. Its incidence has been reported to be as high as 40%.[20] Agents that target cancer cells and exert their action by disrupting microtubules may also affect axonal transport in the peripheral nervous system. Such effects are often related to treatment duration, dose, and predisposing factors and may be partially reversible. Unfortunately, they may persist and cause chronic pain in some survivors. The mainstay of treatment for chemotherapy-induced peripheral neuropathy has been pharmacotherapy with antiepileptics, tricyclic antidepressants, and local anesthetics. Advanced techniques such as neurostimulation may be utilized.[21]

Radiation therapy can have both acute and chronic manifestations leading to painful states. Radiation-induced mucositis is a common pain complaint for patients with head and neck cancer. Long-term, survivors may suffer from painful fibrosis, peripheral neuropathy, and nerve entrapment.[22] The Table lists common sources of pain related to cancer treatment.

Cancer pain is unique in that the patient may experience a higher level of pain during initial diagnosis and treatment and experience a decrease in pain as the disease goes into remission or is surgically removed.[23] Patients often present with uncontrolled pain during the diagnostic stages of the disease process, and the initial treatment may include strong opioid analgesia. As treatment is initiated, pain related to the disease process may begin to subside. Unless significant treatment-associated morbidity occurs, overall pain should begin to decrease and subsequent tapering of analgesic therapy should begin. Nevertheless, the tapering process in the cancer survivor population is more complex than for patients with chronic non-cancer pain. The incidence of anxiety and depression reported in cancer patients has a wide range, but the average for both disorders has been reported at 25-30%.[24] Patients experiencing psychosocial stress from anxiety or depression have been shown to report higher levels of pain as well as collateral symptoms.[25] When coupled with the psychosocial stress of a cancer diagnosis, this leads to higher levels of pain reported, which may not directly correlate with nociceptive input. This is true not only of cancer but also of many types of painful chronic illness. The most robust data in this field appear to be for sickle cell disease in which genuine analgesic dependence and pseudoaddiction are prevalent.[26] In cancer survivors, chemical coping also contributes significantly to opioid misuse and the problems encountered when tapering medications. Research in this field is rapidly expanding as the cancer survivor population continues to grow.[27] Further complicating this matter is the issue of preexisting or developing substance abuse. Although traditionally thought to have a relatively low prevalence in the cancer patient population, inconsistency in the studies behind this theory indicates the need to re-evaluate prevalence in this specialized patient population.[28]

Through the course of survivorship, other sources of chronic pain may surface. This includes the same etiologies of chronic pain experienced by the non-cancer population,

such as degenerative disc disease and osteoarthritis. As previously mentioned, treatment-related chronic pain sequelae may also contribute. Given the underlying anxiety, depression, and other psychosocial stressors associated with cancer, treatment of these pain sources may be difficult. This will be especially true if the patient has unrecognized or untreated psychosocial disorders which, as highlighted above, may lead to issues with opioid tapering.

Short-term side effects of opioid therapy are well studied and include constipation, nausea, sleep disturbances, respiratory depression, and cognitive impairment. Data are lacking on the long-term side effects of enteral opioid therapy, specifically in the cancer survivor population.[29] Long-term intrathecal opioids have been shown to be associated with endocrine abnormalities, including hypogonadotropic hypogonadism in both sexes.[30] Tolerance, physical dependence, and addiction potential are problems that are not unique to cancer survivors when it comes to opioid therapy. Tapering opioids in this population can be challenging, however, as the degree of tolerance and physical dependence may be quite high. Additionally, any increase in pain may cause patients and caregivers significant psychosocial stress, as they may see increased pain as a sign of disease recurrence or treatment failure.

For cancer patients, pain is initially a symptom of a disease process or, in some cases, the treatment-related consequences of a disease process. Over time, continuing pain may lead to secondary pathology,[31] including but not limited to central sensitization, psychosocial distress, and opioid tolerance, and this can lead to a more complex picture of chronic pain. Unfortunately, during the early phases of cancer, control of pain with therapies other than opioid analgesics may be compromised by the need for surgery and the effects of chemotherapy on various organ systems. This leads to potentially high-dose opioid therapy, which may be difficult to taper later on.

Further complicating the issue is each patient's use of coping strategies. Unlike patients with chronic non-malignant pain, cancer survivors have the added burden of fear of disease recurrence or the chance of developing a second primary neoplasm. Patients utilizing effective active coping strategies have been shown to report less chronic pain.[32]

Opportunities

Management of the chronic pain patient can be challenging, with or without an underlying cancer diagnosis. As the number of cancer survivors in the population increases, so does the number of opportunities available to help our patients manage their chronic pain more effectively.

Cancer survivors are unique in the chronic pain population. While many practitioners are now moving away from opioid use in non-cancer pain, opioids have a defined role in treating pain during the active phase of cancer. Unfortunately, the transition of patients from the active phase to survivorship may be riddled with complexity. While the patient's pain from an active neoplasm may be resolved, the aforementioned treatment-related complications may cause pain that is equal to or greater in intensity than that of cancer. Treating such pain with judicious use of interventional pain techniques is an opportunity not only to relieve pain but also to aid in our long-term goal of weaning patients from opioids to the maximal extent possible.

An increase or change in the character of pain presents both a challenge and an opportunity for the pain medicine physician. Recurrence or the development of a second primary malignancy should always be in the differential diagnosis when treating a cancer survivor. As these patients often visit the pain clinic more often than the once-yearly surveillance clinic, should suspicion of malignancy arise, appropriate diagnostic testing must be undertaken in coordination with the primary oncologic team. The pain medicine physician is in a unique position to help evaluate survivors when their symptoms take a turn for the worse.

As many cancer patients undergo surgical intervention, prevention or attenuation of the common postoperative pain syndromes (persistent post-mastectomy pain, post-thoracotomy pain syndrome, post-radical neck dissection pain, amputation, etc.) appears to be an ideal opportunity to reduce the incidence of chronic pain in this subgroup of cancer patients and survivors. Early work on the "injury discharge" phenomenon[33] sparked interest in the field of preemptive analgesia. The theory that controlling pain perioperatively could potentially reduce the development of chronic pain gained further ground with studies on the plasticity of the nervous system.[34] Unfortunately, studies on preemptive analgesia have had mixed results. Nevertheless, there have been some promising results regarding the effect of certain perioperative pharmacologic and interventional techniques and the development of chronic pain after surgery. Although these techniques have been largely limited to non-cancer patients, the basic scientific principles behind them can likely be applied to any patient population.[35]

Future research should focus on the relationship between various risk factors in the development of chronic pain as well as the causality of such risk factors.[36] There are numerous factors to consider when studying this phenomenon. Individual patient genetics and susceptibility undoubtedly play a role in the development of chronic pain. As many oncologic medical and surgical treatments are now individualized to patient genetics, so

should pain medicine treatments. Identifying patients at higher risk for certain pain syndromes may help pain medicine physicians treat these patients more effectively, beginning from the date of diagnosis. Biomarkers have been implicated in individuals genetically susceptible to abnormal inflammatory cytokine release. This may lead to an increase in inflammatory response and potential central and peripheral sensitization.[37] Investigation of further diagnostic and therapeutic biomarkers can help identify susceptible patients and perhaps even predict their response to certain pharmacologic and interventional therapies.

Conclusions

Pain management for cancer survivors can be fraught with challenges. This unique patient population is growing as evidenced by the increased five-year survival rates for many types of cancer. Their pain generators are often multifactorial and may be related to the tumour itself, treatment-related toxicities, and other pain etiologies that are not cancer or treatment-related. Furthermore, any change in character or increase in pain must always be evaluated with the possibility of recurrence or a second primary malignancy. Psychosocial factors are considerably different in this population as well, leading to an even more complex interaction between psychology and pain perception.

Cancer survivors often present late in the course of treatment and sometimes even after treatment has been completed. Pain management utilized during active cancer and subsequent treatment is seldom changed or tailored as the patient approaches the transition of care associated with survivorship. This may lead to significant opioid tolerance, dependence, and even signs of addiction in select patients. At each juncture in the cancer diagnosis, treatment, and survivorship continuum, opportunities exist to optimize pain management for these patients – whether through medication management or interventional therapies. Regardless of the modalities employed, early referral to a pain medicine specialist can facilitate prompt appropriate utilization of pain management options in order to provide patients with better quality of life and potentially decreased adverse effects.

Conflicts of interest None declared.

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