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Pain in Cancer Survivors: How to Manage

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Opinion statement

Managing pain in cancer survivors requires that oncologists understand the common painful syndromes that can occur from treatment or disease. Assessment no longer singularly focuses on pain characteristics (e.g., intensity, quality, location), now incorporating a strong focus on functional impairment and potential improvement that might occur with adequate treatment. Improvement in function is now the goal used to measure success. In addition, assessment must incorporate risk factors that might predispose patients to substance use disorder so that interventions can be implemented to mitigate this risk. Universal precautions are measures that help assess and ensure adherence to the treatment plan and may include the use of agreements, urine toxicology, and review of dispensing information derived from state prescription drug monitoring program (PDMP). These are generally obtained annually for all individuals, although some states have instituted mandatory review of the PDMP whenever prescribing an opioid. For patients at moderate to high risk for misuse of opioids, where opioids are warranted for the treatment of their pain syndrome, universal precautions are instituted more frequently. Other measures may include prescribing a 1- to 2-week supply of medications if compulsive use leads the patient to running out of drug early, and in some cases, family members may be employed to dispense daily allotments of the medication. When opioids are no longer indicated, gradual tapering of the drug by approximately 10% per month is generally sufficient to prevent withdrawal symptoms and ensure patient acceptance.

Introduction

Currently, there are 15.5 million cancer survivors in the USA, close to 5% of the population, and this number is expected to increase to more than 26 million people by the year 2040. This increase in cancer survivorship is largely due to improved early detection techniques and newer, highly effective cancer therapies. Although these figures demand celebration, an unfortunate result of cancer and its treatment in these survivors is a higher risk

of persistent pain. The majority of these chronic pain syndromes occur as a result of cancer treatment, although ongoing pain related to the tumor can also occur. Optimal management of chronic cancer-related pain requires a multimodal approach that incorporates pharmacologic, non-pharmacologic, interventional, and integrative therapies [1••]. Although these are all integral to pain management across the disease trajectory, the emphasis in long-term survivors with persistent pain is weighed more heavily towards non-drug therapies. This may represent a shift in focus for many oncologists and oncology providers more accustomed to treating acute cancer pain or pain associated with advanced disease [2].

Challenges to the provision of multimodal therapy include inadequate education of professionals about pain management in cancer survivors, along with poor reimbursement, particularly for physical or occupational therapy and integrative treatments [3]. Medication shortages and limits on opioid dosing or numbers of pills dispensed further hamper the provision of effective pain control. The current epidemics of opioid-related deaths and substance use disorder further complicate perceptions about the use of opioids and access to this therapy [2]. Oncologists and oncology providers must be aware of guidelines designed to safely and effectively manage chronic pain in adult survivors of cancer.

Defining "Survivor"

One challenge to better understanding pain in this population is the lack of consensus regarding the definition of "cancer survivor." Some definitions encompass a broad time frame, such as "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life." This definition is supported by the National Cancer Institute (NCI), the National Comprehensive Cancer Network (NCCN) Survivorship Panel, and the National Coalition for Cancer Survivorship (NCCS) [4].

Although this definition appropriately normalizes living well throughout the course of cancer diagnosis and treatment, it may be too encompassing when attempting to describe the unique pain experience of those who have undergone cancer treatment. 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" [5]. This more closely captures the population of interest, those with chronic pain due to cancer or its treatment, yet excludes many who may have continued disease. For example, some women with primary breast cancer and bone metastasis are surviving for years with serious pain, yet they might be excluded from discussion by this definition. Although clarity is lacking regarding the most effective and valid definition of cancer survivor, it is clear that these individuals experience late adverse treatment effects, including pain, that can seriously impair quality of life [6••].

Prevalence of pain in cancer survivors

The prevalence of pain in cancer survivors has been reported to be as high as 40% [7, 8, 9•, 10, 11]. Important predictive factors include the type and invasiveness of the tumor, along with the treatment regimen used. Other factors include the time since cancer therapy and the efficacy of the initial pain treatment. The presence of pain frequently leads to physical, emotional, and financial burden and is associated with overall impaired quality of life [6••, 12].

Causes of pain in cancer survivors

Pain in cancer survivors usually arises from the tumor or from treatment [13]. Direct tumor effects can include the erosion of the tumor into neighboring tissues. While this formerly was associated with advanced disease and a limited prognosis, due to effective therapies, people with invasive or metastatic disease have improved survival rates. Examples include pain as a result of bone metastases in people with breast or prostate cancer, who are now living many years with these potentially painful lesions. Those with multiple myeloma may also experience pain associated with bone lesions, while living many years during treatment.

Cancer treatment is a primary cause of pain in those who have completed treatment with no current evidence of disease. Table 1 lists selected examples of persistent pain syndromes that can occur as a result of treatment [1••, 13–16, 22, 23]. Understanding these causes is a bit of a moving target with the almost daily introduction of new treatments (e.g., immunotherapies), while older treatments undergo refinement that may limit the development of persistent pain. Examples of these enhanced treatments include three dimensional conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or stereotactic radiosurgery, all of which limit exposure of normal tissue while increasing the dose and precision of radiation delivered to the tumor [24].

Management of pain in cancer survivors

Management of pain in cancer survivors includes the same principles used to treat all persistent pain, including conducting a full assessment and incorporating the use of multimodal therapies (see Table 2) [1••]. Unique among this population, however, is that the identification of new pain in cancer survivors may raise the possibility of recurrence or the development of secondary malignancies, warranting aggressive evaluation.

Table 1. Common persistent pain syndromes associated with cancer therapies

Chemotherapy	Hormonal therapy
• Bony complications of corticosteroids • Chemotherapy-induced peripheral neuropathy (CIPN)	• Arthralgia/myalgia associated with aromatase inhibitors
Radiation therapy	Stem cell transplant
• Lymphedema • Osteoradionecrosis • Plexopathies	• Graft versus host disease can affect most systems, including skin, eyes, mucous membranes
Surgery	Immune checkpoint inhibitor therapy
• Phantom pain after amputation • Post-surgery pain after mastectomy, radical neck dissection, thoracotomy	• Arthralgia/myalgia

References [1••, 13–21]

Table 2. Management of pain in cancer survivors

Assess pain, function, and risk of misuse
Develop a multimodal pain plan of care that incorporates adjuvant analgesics and non-opioids if feasible, along with non-pharmacological, integrative, and interventional therapies
Stratify risk if opioids are considered part of the plan of care
Weigh the potential risks and benefits of prescribing opioids
If prescribing opioids, use the lowest dose to achieve function goals
Employ universal precautions and monitor for aberrant use
Avoid the use of other sedating drugs, particularly benzodiazepines
Taper opioids gradually when feasible

Reference [1••]

Screening and assessment

Given the significant prevalence of pain in survivors of cancer, and the numerous potential causes, oncology providers should screen all patients for the presence of pain. If pain exists, a full assessment is warranted. Whereas the focus on pain assessment previously emphasized intensity, quality, location, and other factors, comprehensive assessment now also stresses functional impairment resulting from pain. This awareness similarly guides the development of goals for pain therapy, rather than focusing on a pain intensity number as a desired outcome. A guiding question may be: "if your pain were better managed, what could you do that you cannot now." Specific examples may be needed to assist patients as they shift their goals towards functional outcomes, such as return to work or improved recreational activities. Physical examination complements the comprehensive assessment and imaging or other diagnostic testing may be warranted to further investigate the underlying etiology of pain if unclear.

In addition to assessing pain and function, risk factors for substance use disorders should be determined. Specific questions may include current or past smoking, alcohol, and prescription or recreational drug use, as well as family history and a history of sexual abuse or other significant trauma [25, 26]. There are a variety of tools available, although more research is warranted regarding their role in the oncology setting [27–29].

Stratification

Taking the results of the comprehensive pain, function, and risk assessment, the clinician will formulate a multimodal treatment plan that may or may not include opioids. If opioids are being considered after careful evaluation of the risks and benefits, patients are then stratified by their level of risk for misuse. Levels may be "low," "medium," or "high" risk, although limited data exist to support the clinician in developing a strict algorithm for this stratification. The strength of the risk will dictate the frequency of efforts designed to mitigate misuse. These efforts are often referred to as universal precautions.

Universal precautions

Universal precautions are measures employed to mitigate risk when using opioids. Based on similar principles advanced by the Centers for Disease Control (CDC) and the Occupational Safety and Health Administration (OSHA) to treat all blood or body fluids as potentially infectious, universal precautions in the context of opioid use acknowledge that anyone might be at risk for misuse. Alternate approaches that target those perceived to be "at risk," rather than screening all patients, will be liable to expose the patient to the clinician's implicit bias (i.e., assumptions about misuse based on age, socio-economic status, or race) [30].

Universal precautions may include the use of urine toxicology [27, 31•, 32, 33], standardized agreements [34], and review of the data derived from the state prescription drug monitoring program (PDMP) [35, 36]. Little data are available to guide oncology providers regarding which of these components are most beneficial or cost and time effective. There are risks that if the results of the urine toxicology are not accurately interpreted, patients may be inappropriately accused of inadequate adherence or even misuse. There are two primary urine toxicology tests conducted, an enzyme-mediated immunoassay (EIA) or gas chromatography/mass spectroscopy (GC-MS) or high-performance liquid chromatography (HPLC). Immunoassays are less expensive, quick, and generally available, yet can yield false positives. GC-MS is more accurate although less widely available, pricier, and more time consuming. As a result, GC-MS or HPLC may be used to confirm questionable findings on the immunoassay test. Examples of agents that can lead to false positives for opioids include fluoroquinolones or rifampin. And more synthetic agents, such as fentanyl patches, may not be detected on immunoassays, which has led some clinicians to assume the patient is non-adherent. Several excellent reviews can assist providers as they interpret the findings from urine toxicology testing [27, 31•, 32].

Optimal agreements are designed to be educational, alerting patients to their shared responsibilities in ensuring safe opioid use and reducing risks of misuse or diversion [34]. Storage, appropriate use, and eventual disposal strategies may work to limit diversion, and despite constant media attention to the opioid epidemic, patients are often surprised when advised to lock up their medications [37, 38]. An advantage regarding the use of agreements is the educational opportunity and patient-provider shared sense of responsibility in safe opioid management. One danger in our current climate is to simply have the patient "sign another form" or to use these tools to "fire" patients or stop prescribing opioids.

State prescription drug monitoring programs (PDMPs) provide information about controlled substance prescribing for individual patients within a state [36, 39]. Some PDMPs allow access to data from multiple states. Although often considered to be used for pejorative reasons (i.e., to detect doctor shopping), PDMPs can also assist prescribers in understanding when and where an agent was dispensed and how many tablets were actually filled (in the case of a partial fill due to shortages or insurance requirements). Integration of PDMPs within the electronic medical record is imperative to streamline access to these data.

Abnormal findings from any of these tools should not immediately lead to cessation of opioid prescribing for that patient. Unexpected findings should

elicit a conversation between the clinician and patient to better understand the issues and restate the goals of care. If aberrant drug-related behaviors are identified, several strategies can be employed. Weaning or tapering the opioid may be appropriate. Referral to addiction specialists may also be warranted.

Weaning opioids

Long-term opioid use is associated with endocrinopathies, sleep-disordered breathing, and neurotoxicities [1••, 40–42]. When no longer indicated, very gradual reduction of the opioid dose, supported by strong, supportive encouragement, can generally be achieved without difficulty. Although doses may be reduced as rapidly as 10% per week, this author finds 10% reduction per month in cancer outpatients is better tolerated and more predictive of successful weaning. There may be times when the dose is plateaued (e.g., holidays or special family events) but downward dose adjustment will then be resumed. Avoid adding other controlled substances, such as benzodiazepines. To address any symptoms of withdrawal, such as sleeplessness, tricyclic antidepressants and sleep hygiene education may be of benefit.

The goal for most long-term survivors with no evidence of active disease will be to completely stop the opioid, although some patients may continue to require small amounts, decided upon by the provider and patient in collaboration. To enhance this process, again consider other non-opioid and non-pharmacologic therapies to supplement analgesia and build strong coping mechanisms. An important resource is the network of cancer wellness centers that offer mindfulness, gentle exercises, and various forms of psychological support through individual counseling or group efforts. Most of these services are provided at no or reduced cost.

Conclusion

The numbers of cancer survivors in the USA will be expanding greatly in the near future. Many of these individuals will experience chronic pain syndromes that occur as a result of cancer treatment. Screening and comprehensive assessment of pain will emphasize essential aspects of pain evaluation, along with awareness of functional limitations due to pain and risk for substance use disorder. Optimal management of chronic cancer treatment-related pain requires a multimodal approach that incorporates pharmacologic, non-pharmacologic, interventional, and integrative therapies, with the emphasis weighed more heavily towards non-drug therapies. Oncologists and oncology providers must be aware of guidelines designed to safely and effectively manage chronic pain in adult survivors of cancer.

Compliance with Ethical Standards

Conflict of Interest

The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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