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REVIEW ARTICLE

Pain in Cancer Survivors

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ABSTRACT

Pain is a common problem in cancer survivors, especially in the first few years after treatment. In the longer term, approximately 5% to 10% of survivors have chronic severe pain that interferes with functioning. The prevalence is much higher in certain subpopulations, such as breast cancer survivors. All cancer treatment modalities have the potential to cause pain. Currently, the approach to managing pain in cancer survivors is similar to that for chronic cancer-related pain, pharmacotherapy being the principal treatment modality. Although it may be appropriate to continue strong opioids in survivors with moderate to severe pain, most pain problems in cancer survivors will not require them. Moreover, because more than 40% of cancer survivors now live longer than 10 years, there is growing concern about the long-term adverse effects of opioids and the risks of misuse, abuse, and overdose in the nonpatient population. As with chronic nonmalignant pain, multimodal interventions that incorporate nonpharmacologic therapies should be part of the treatment strategy for pain in cancer survivors, prescribed with the aim of restoring functionality, not just providing comfort. For patients with complex pain issues, multidisciplinary programs should be used, if available. New or worsening pain in a cancer survivor must be evaluated to determine whether the cause is recurrent disease or a second malignancy. This article focuses on patients with a history of cancer who are beyond the acute diagnosis and treatment phase and on common treatment-related pain etiologies. The benefits and harms of the various pharmacologic and nonpharmacologic options for pain management in this setting are reviewed.

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INTRODUCTION

According to the National Coalition for Cancer Survivorship, an individual is considered to be a cancer survivor from the time of diagnosis through the balance of his or her life. Family members, friends, and caregivers are included in this definition, because the survivorship experience also has an impact on them. However, for the purposes of this article, we will use the survivorship definition promulgated by the National Cancer Institute's Office of Cancer Survivorship, which focuses on patients with a history of cancer who are beyond the acute diagnosis and treatment phase.[1] The number of cancer survivors in the United States increased to 13.7 million in 2012 (not including carcinoma in situ or basal cell and squamous cell skin cancers), with nearly two thirds diagnosed more than 5 years ago and 40% alive more than 10 years after diagnosis.[2]

Although these survivors may have beaten cancer, many have poor outcomes across multiple burden-of-illness measures, including pain, for years after diagnosis. For them, pain shifts from being a short-term problem during active treatment to a chronic problem that may last months, years, or even a lifetime.[3] As a result, oncologists and others who provide pain management to survivors may need to use chronic pain management strategies and an interdisciplinary approach to optimize rehabilitation as well as pain relief (Table 1). But this population is different from people with chronic pain who do not have a history of cancer because they usually have identifiable tissue damage as the basis of their pain complaint. In addition, the survivor is at risk for recurrent disease or second malignancies, so new or worsening pain must be carefully evaluated, which requires an approach that is specifically tailored to this population. The use of opioids also shifts from the routine prescribing during active treatment to a more measured and thoughtful approach when pain is expected to persist for years.

EPIDEMIOLOGY OF PAIN IN SURVIVORS

The categorization of pain etiology used for patients with cancer—tumor-related, treatment-related, or pain due to debility or unrelated to cancer or its treatment—remains relevant, but there is a major shift in the prevalence away from tumor-related to treatment-related etiologies. This article primarily focuses on chronic pain related to cancer treatments.

Table 1. Outpatient Chronic Pain Management in Cancer Survivors: A Framework for Evaluation and Management

1. Define who is responsible for comprehensive pain management program and prescribing.
Providers who may provide chronic pain management
Medical or radiation oncologist
Survivorship clinic provider
Primary care provider
Palliative or supportive oncology provider
Chronic pain specialist (anesthesia, neurology, rehabilitation medicine, internist)
If plan involves co-management, define and communicate to other providers who is responsible for prescription management.
Opioids should be prescribed by only one provider.
2. Evaluation
Perform comprehensive history and physical examination with attention to functional and psychosocial issues related to pain.
If opioids are being considered, a standard opioid risk assessment tool may be useful, such as the Screener and Opioid Assessment for Patients with Pain (SOAPP-R) or Opioid Risk Tool (ORT).[4,5]
For new or changing pain syndromes, always evaluate for recurrence or second primary, as well as development of late effects of treatment.
For new or changing pain syndromes, consider imaging and referral back to oncology (if the oncologist is no longer involved).
3. Management
Pharmacologic
Co-analgesics: antidepressants, anticonvulsants, nonsteroidal anti-inflammatory drugs, acetaminophen, others.
Opioids: prescribing should be undertaken within the following universal precautions framework:
Assessment of risk for opioid misuse
Stratification for location of pain care based on risk assessment (primary care, occasional specialty consultation, or specialist management)
Structuring of therapy commensurate with assessment of risk (weekly versus monthly prescriptions; regular versus sporadic urine drug screens)
Establishment of functional goals to guide dose titration
Maintenance of ongoing monitoring for opioid misuse, abuse, or diversion
Management of emerging problems consistent with medical best practices and existing laws and regulations
Nonpharmacologic: Refer for the following behavioral and therapeutic interventions:
Exercise program
Cognitive-behavioral therapy
Physical medicine and rehabilitation, physical therapy, transcutaneous electrical nerve stimulation, scrambler therapy
Integrative medicine approaches (acupuncture, massage)
Interventional approaches

Table 2 lists the pain syndromes associated with cancer treatments. Table 3 describes the systems affected, incidence and prevalence data, and potential treatments. However, as cancer survivors live longer, chronic noncancer pain of aging such as osteoarthritis becomes common and may interact with post-treatment pain such as arthralgias.

Comprehensive estimates of the prevalence of persistent pain in cancer survivors are currently lacking, although several large prospective cohort studies are now underway.[21,22] Clinical factors that may be associated with pain complaints by survivors include the type and invasiveness of the tumor, modalities of anticancer treatment received, time since completing treatment, comorbid conditions, and initial pain management. Racial and sex disparities in the incidence of chronic pain and its impact on the quality of life (QOL) in cancer survivors have also been identified in some studies.[21]

Reviews suggest that up to 40% of cancer survivors are in pain,[23] but the timing of pain surveys is important because many treatment-related pains diminish over time as injured tissues heal and regenerate. For example, only 21% of more than 10,000 adult survivors of childhood cancer participating in the Childhood Cancer Survivor Study (mean interval from cancer diagnosis, 16.5 years) reported pain in the previous week that they attributed to their previous cancer or cancer therapy.[24] In addition to the raw prevalence data, pain severity and interference with function are also important. In the Childhood Cancer Survivor Study, only 11% reported medium or higher pain intensity.[24] Likewise, a survey of Australian adult cancer survivors 5 to 6 years postdiagnosis found that only 6% reported pain intensity as "quite a bit-very much," and only 4% rated pain interference at this level.[25] In certain subgroups of patients, such as breast cancer survivors, the prevalence of pain may be much higher, with more than 30% of patients reporting above-average pain 10 years after treatment.[26]

Pain rarely occurs in isolation, and survivors have many other troublesome symptoms.[27,28] Approximately 1 year after diagnosis, more than 90% of patients being observed in the American Cancer Society's Study of Cancer Survivor-I reported symptoms related to their cancer and/or its treatment.[22] Approximately one quarter of patients fell in the "high symptom burden" category, and pain, depression, and fatigue had the greatest impact on QOL in this group. In the Australian survivorship survey, the most prevalent symptoms were insomnia (13.1%), tiredness (12.9%), and memory difficulties (8.8%). Two or more symptoms were reported by 18%.[25] Adding to these multiple symptoms, the diversity of pain syndromes as indicated in Table 2 can make treatment a challenge.

TREATMENT-RELATED PAIN SYNDROMES IN CANCER SURVIVORS

Surgery

Surgery has long been known to produce painful persistent postsurgical syndromes, such as postmastectomy pain and phantom limb pain. Risk factors include inadequate postoperative pain control, radiation therapy to the affected area, neurotoxic chemotherapy, and

Table 2. Chronic Pain Syndromes Related to Cancer Treatment[6]

Surgery
Intercostal neuralgia
Lymphedema
Neuroma pain
Pain related to breast implants/reconstruction
Phantom pain
Postmastectomy pain
Postsurgical neck dissection pain
Post-thoracotomy pain
Radiation
Chest pain/tightness
Cystitis
Enteritis/proctitis
Fibrosis of skin or myofascia
Fistula formation
Myelopathy
Osteoradionecrosis
Pelvic insufficiency fractures
Peripheral nerve entrapment
Plexopathies
GI, abdominal, other adhesions in the radiation field
Hormonal therapy
Arthralgia/myalgia
Muscle cramps/spasms
Carpal tunnel syndrome
Trigger finger
Chemotherapy
Arthralgia/myalgia
Osteoporosis
Osteonecrosis
Chemotherapy-induced peripheral neuropathy
Muscle cramps
Steroids
Osteoporosis
Osteonecrosis (avascular necrosis; typically femoral head, knee, humeral head)
Bisphosphonates
Osteonecrosis of jaw
Hematopoietic stem-cell transplantation (chronic graft-versus-host disease)
Abdominal, GI adhesions, pain
Arthralgia/myalgia
Contractures with pain and decreased range of motion
Corneal ulcerations with pain, dryness, and burning in eyes
Cystitis
Erythema
Esophageal structures and ulcers leading to retrosternal pain
Fibrosis/scleroderma with contractures, pain and decreased range of motion
Infection
Inflammation/edema
Mucous membrane inflammation, thinning, strictures, ulcers (mouth, GI tract, vagina)
Muscle cramps
Peripheral neuropathy
Osteonecrosis of joints

psychosocial characteristics such as anxiety, depression, and catastrophizing.[7,29,30] Genetic predisposition may contribute to these risks. Although modern, less invasive surgical techniques may result in less postsurgical pain, this is not always the case. For example, lumpectomy and axillary dissection and/or reconstruction may result in more pain than a standard modified radical mastectomy.[31,32] In addition to these classic postsurgical syndromes, patients may also develop chronic postoperative pain as a result of complications such as adhesions, collections, fistulae, and so on.

Radiation Therapy

Radiation therapy can produce an array of persistent painful syndromes, most notably plexopathies and osteoradionecrosis.[33] These are generally late effects, but the onset varies. For example, in one case series of 33 women with breast cancer, plexopathies developed anywhere from 6 months to 20 years after treatment.[34] Because most patients have received radiotherapy along with other modalities, it can be difficult to discern the precise cause of persistent pain. As radiotherapy techniques become more targeted, late-occurring radiation-induced pain syndromes may become less common.

Chemotherapy-Induced Peripheral Neuropathy

The most common pain syndrome resulting from chemotherapy is chemotherapy-induced peripheral neuropathy (CIPN). A comprehensive list of agents, incidence, and characteristics of CIPN is presented in Table 4. The pain is usually a symmetrical, distal painful neuropathy described as tingling, burning, or numbness.[41] CIPN is generally dose-dependent and only partially reversible. The phenomenon of "coasting" (worsening symptoms weeks or months after the last dose of chemotherapy) has been described.[42] Risk factors for CIPN include pre-existing neuropathies, older age, and genetic polymorphisms.[43,44] Patients who experienced acute paclitaxel pain syndrome immediately after treatment have been shown to be more likely to develop chronic CIPN.[45] Animal models are enabling better understanding of the mechanisms of CIPN,[46] raising the prospect of targeted treatments in the future. For example, oxaliplatin, paclitaxel, and vincristine increase abnormal spontaneous discharges in A-beta and C fiber nociceptors, leading to painful peripheral neuropathies.[47-50] These agents and bortezomib appear to disrupt mitochondrial function, altering the sodium-potassium pump that maintains the normal neuronal resting potential.[51] Cytokine-mediated inflammation and a deficiency in neurotrophic factors, such as nerve growth factor and brain-derived neurotrophic factor, have also been implicated.[52-54]

Hematopoietic Cell Transplantation

In addition to chronic pain syndromes related to chemotherapies or radiation therapy, chronic graft-versus-host disease (GVHD) is an additional source of chronic pain in hematopoietic cell transplantation recipients. Allogeneic transplantation recipients are at greater risk if they have histocompatibility disparities with their donor, receive stem cells from peripheral blood rather than marrow, are a male recipient receiving stem cells from a female, have a donor that is of older age, and have had acute GVHD.[55] Notably, treatment of GVHD includes immunosuppressive agents that can themselves lead to persistent pain syndromes (Table 3).

Hormonal Therapy

Aromatase inhibitors prescribed for many years after completion of treatment to prevent recurrence of breast cancer can produce arthralgias[56] characterized by joint pain and stiffness in up to 40% of women, usually occurring within the first 3 months of therapy.[57] Affected joints include the hands, arms, knees, ankles, hips, and back.

Table 3. Chronic Pain Syndromes in Cancer Survivors, by System[7-20]

System Affected	Pain Syndrome	Incidence
Neurologic	Chemotherapy-induced peripheral neuropathy	Up to 100%
	Postoperative pain syndromes	Post-thoracotomy pain: 25%–60%
		Postmastectomy pain: 50%; lumpectomy with axillary node dissection: 39%
		Phantom-breast pain: 13%–24%
		Postamputation pain: 30%–80%
		Radical neck dissection: 40%–52%
	Brachial or lumbar plexopathy, secondary to radiation, brachytherapy, or surgery	Brachial: 18% radiation-induced pain; onset may be delayed by decades Lumbar: radiation-induced is uncommon
	Postherpetic neuralgia	35%, after stem-cell transplantation (retrospective medical records review). May also develop at site of radiation therapy or surgery. More common in patients older than 50 years. Risk of postherpetic neuralgia developing is no greater than in general population.
	Complex regional pain syndrome after axillary node or neck dissection	Rare (case reports)
Rheumatic	Migratory noninflammatory myalgias and arthralgias from tamoxifen, aromatase inhibitors, radiation, deconditioning, steroids, and steroid taper	Common
Integumentary	Graft-versus-host disease with pain in skin, mucous membranes, and musculoskeleton	30%–80% of those who survive 6 months after transplantation with graft-versus-host disease
Lymphatic	Pain or discomfort from lymphedema, secondary to breast surgery, axillary or inguinal node dissection, or radiation	Upper extremity: 20%–56%; of those, 30%–60% have pain; lower extremity: 10%–15%
Skeletal	Osteoporosis	10%–38% (arthritis/osteoporosis)
	Osteonecrosis of femoral head, knee, humeral head	3.7% at 5 years; 5% at 10 years after hematopoietic cell transplantation
	Pelvic insufficiency fracture after whole pelvic radiation	8.5%–32%
	Osteonecrosis of the jaw from bisphosphonates, denosumab, or radiation to the head and neck	Bisphosphonates: 3%–11%. Radiation: small incidence. More common after prolonged exposure (36 months or more) to pamidronate and zoledronic acid, age > 65 years and with pre-existing dental problems
Myofascial	Rotator cuff tendonitis, adhesive capsulitis (frozen shoulder), neck and back pain	70% shoulder pain after radical neck dissection
GI/urinary/pelvic	Chronic pelvic pain, chronic enteritis, proctitis, cystitis, tenesmus	Cervical cancer: 38%
	Associated urinary or fecal urgency/incontinence is common	
	Radiation-related adhesions	
Genital	Dyspareunia: secondary to menopause, decreased vaginal lubrication from radiation, vaginal stricture/fibrosis from radiation	34%–58%; women experience more of an impact than men

Symptoms are worse in the morning and improve somewhat with movement. Risk factors include prior exposure to paclitaxel, previous hormone replacement therapy, and obesity.[57-59] Symptoms associated with estrogen deprivation also occur as a result of aromatase inhibitors, including night sweats, vaginal dryness, and sexual dysfunction. Along with pain, these contribute to the decreasing QOL experienced by women receiving this class of medication. Nonadherence is a common result of these adverse effects, thus increasing the risk of recurrent disease. A study of 12,000 pharmacy records revealed adherence to therapy after 3 years of only 62% to 79%.[60]

APPROACHES TO TREATMENT

Guidelines for managing pain during survivorship released by the National Comprehensive Cancer Network in 2013 demonstrate the rarity of clinical trials for pain management in this population other than for neuropathy and phantom limb pain.[61] Chronic pain management guidelines recommend a multidisciplinary approach that uses multiple modalities focused on both comfort and function and that is delivered by a multidisciplinary program whenever it is available.[62] A combination of pain medicines, physical therapy, regular exercise, psychosocial interventions, and complementary and alternative modalities may be used (Table 1). This is especially helpful for the disabled survivor with chronic pain and comorbidities such as a depressive disorder or sleep disorder. The far more common condition of chronic pain with limited impact on function and mood can typically be managed in the oncologist's office or the primary care environment. Whether multiple or single modalities are used, the treatment goal should not only be pain relief but also improved function.

Pharmacologic Approaches

Just as when they were being treated for cancer, survivors with pain may benefit from pharmacotherapy with opioids and other agents such as antidepressants, anticonvulsants, and nonsteroidal anti-inflammatory drugs. The safety and effectiveness of long-term opioids in survivors has not been well studied, but there is only weak evidence that long-term continuation of opioids provides clinically significant pain relief in chronic noncancer pain.[63] The evidence base for nonopioid analgesics in survivors is growing,

Table 4. Agents Associated with Chemotherapy-Induced Peripheral Neuropathy[16,35-40]

Chemotherapy Class	Example Drugs	Incidence (%)	Comments
Vinca alkaloids	Vincristine	30-57	Typically sensorimotor neuropathy, with autonomic features in 20%–30%. Dose dependent. "Coasting" (worsening symptoms weeks or months after the last dose of chemotherapy) may occur. May resolve within 3 months but more likely to persist with vincristine.
	Vinblastine	25-40	
	Vinorelbine	7-40	
	Vindesine		
Platinum compounds	Cisplatin	30-100	Sensory or sensorimotor neuropathy, autonomic features less common; ototoxicity may occur. Cumulative dose-dependent. Coasting is common.
	Carboplatin	6-42	
	Oxaliplatin	7-20	
Taxanes	Paclitaxel	57-83	Painful symmetrical distal sensory neuropathy. Motor effects less common. Paclitaxel protein-bound neuropathy is clinically less severe than paclitaxel. Symptoms may wax and wane. May ascend the limbs from distal site. Cumulative, dose-dependent. Coasting is common.
	Paclitaxel protein-bound	73 overall; 10-15 severe	
	Docetaxel	11-64 overall; 3-14 severe	
Proteasome inhibitors	Bortezomib	31-55 overall; 9-22 severe	Small-fiber sensory neuropathy, leading to therapy discontinuation in 4%. Motor and autonomic features common. Dose-dependent. Often resolves in 3-6 months but may persist.
Other	Thalidomide	25-83 overall; 15-28 severe	Sensory or sensorimotor neuropathy, with autonomic features in 56%. Dose-dependent. Persists for 1 year or longer.
	Lenalidomide	10-23 overall 1-3 severe	Similar to thalidomide.
	Ixabepilone	63 overall; 14 severe	Painful burning paresthesias, usually resolves within 4-6 weeks.
	Etoposide	1-2	Sensorimotor polyneuropathy with autonomic dysfunction.
	Cytarabine	Rare	Severe sensorimotor neuropathy, greater risk with high dose or in combination with daunorubicin or asparaginase. High dose: acute irreversible cerebellar syndrome.
	Ifosfamide	8	Neuropathy
	Suramin (investigational drug)	30 sensory; 5-10 motor	Distal sensorimotor polyneuropathy, subacute demyelinating polyradiculoneuropathy.

especially for CIPN. For example, 5 weeks' treatment with duloxetine has been shown to be more effective than placebo.[64] Venlafaxine has also been shown to reduce acute oxaliplatin neurotoxicity.[65] Conversely, gabapentin was shown to be no better than placebo for CIPN,[66] although pregabalin had some efficacy in an uncontrolled phase II study.[67]

Opioids do not need to be automatically stopped in a cancer survivor who is at low risk for pain medicine abuse, has been compliant with the medications during treatment, and has stable, well-controlled treatment-related pain that is opioid-responsive. Opioids may be considered for initiation in a survivor with moderate to severe pain that has been unresponsive to nonopioid therapies and nonpharmacologic approaches and when the chronic opioid therapy is likely to possess equivalent or better risk-to-benefit ratios.

Therefore, oncologists and other clinicians prescribing opioids in cancer survivors should be knowledgeable about the risk factors for opioid abuse (eg, young age, personal or family history of alcoholism or illicit drug use, psychiatric disorder) and methods for assessing risk, including the patient self-report questionnaires that have been developed for this purpose.[4,68]

Once the decision is made for a trial of opioid therapy in a survivor, the same general approach to prescribing them in patients with cancer-related pain should be followed,[69] with two caveats. First, the pain crises that may occur in patients with cancer who have advanced disease are not expected in survivors. Therefore, rapid escalation of the opioid dose to high levels should not be needed. Second, the role of as needed rescue doses of immediate-release opioids for breakthrough pain is currently controversial in chronic pain. The premise for not offering as needed doses to patients with chronic pain is that time-scheduled, extended-release preparations result in more stable opioid blood levels and provide better pain relief, with fewer adverse effects, less reinforcement of pain behaviors, and lower addiction risk. More recently, however, surveys of patients who are given time-scheduled doses have found typically higher dosage levels and higher levels of patient concerns about opioid use.[70] It is the authors' opinion that unless there are particular concerns about addiction, oncologists should continue to prescribe immediate-release opioids to most cancer survivors for rescue dosing for breakthrough pain. New long-term pain treatment goals should also be established for the survivor on opioids. These goals include maintenance of analgesic efficacy with improved function; minimalization of adverse effects, including long-term effects such as, hypogonadism, which may not be fully appreciated[71]; and the absence of evidence of abuse or misuse of the pain medicine. Close monitoring and regular follow-up is mandatory. The frequency of return visits to assess the response to chronic opioid therapy is not defined in the survivor population; however, follow-up at least every 3 to 6 months is recommended.

If pain subsides or a survivor prefers to stop taking opioids, a slow taper to prevent opioid withdrawal symptoms is recommended. There are currently no standard protocols for tapering opioids in patients with chronic pain. Limited guidance is available outside the drug rehabilitation literature and is provided by professional groups or government agencies such as the Veterans Administration.[72,73] The speed of tapering will be determined by the reason for reducing the dose. When dose reduction is not emergent, a slow taper is preferred. One schedule recommends reductions of 10% every 2 to 4 weeks, slowing to reductions of 5% once a dose of one third of the initial dose is reached.[72] The end point of successful tapering may also vary from no opioid to a moderate dose of a time-scheduled opioid that provides effective analgesia with minimal withdrawal symptoms.

Medicines such as diphenhydramine, acetaminophen, or a clonidine patch may be used to treat withdrawal symptoms. In some patients, it may take several months to taper and discontinue even small opioid doses, such as 5 mg of oxycodone taken twice daily. Predictors for the outcome of attempts to wean opioids are currently poorly understood but are affected by genetic polymorphisms and are probably similar to those for opioid abuse[74]; much more research in this area is needed.

Strong Opioids and Abuse Issues

The assessment and management of chemical coping by patients with cancer and the under- and overtreatment of cancer are covered elsewhere in this series, but opioid abuse needs some discussion here because the growth in the population of cancer survivors and chronic post-treatment pain parallels growing concerns regarding opioid-related morbidity and mortality in patients with chronic pain.[75] How much this concern should envelope the cancer survivor population is unclear. Iatrogenic addiction in patients with cancer has long been held to be uncommon,[76] and patients with most cancers who stop opioids do so without developing craving. However, a subset of patients with cancer and survivors will be at risk for abuse of and dependence on their pain medicines, since 10% of the US population currently abuses or is dependent on substances,[77] and there is an association between drug abuse and certain types of cancer (eg, hepatocellular carcinoma). In one study, 29% of patients with cancer had high-risk scores on an opioid risk assessment tool.[5]

All patients should be regularly evaluated, with the intensity of the evaluation determined by risk stratification at the start of treatment and behavior during prior treatment. Evaluation includes clinical assessments, urine toxicology when appropriate, and prescription monitoring where available. Survivors also need education about responsible opioid use, storage, and disposal, since almost 80% of opioid-related deaths occur in nonpatients who took opioids prescribed to pain patients by a single prescriber.[78,79] Drug diversion may be occurring without the patient's knowledge, but intentional drug diversion by pain patients is significantly more harmful than other aberrant behaviors and must be dealt with immediately. In the United States, prescribing when diversion is known to be occurring, or should have been known to be occurring, could be prosecuted as a felony under federal law. It is the one situation in which a clinician should stop prescribing unless this would place a patient under imminent risk of harm.

When high-risk behaviors are detected, such as self-escalation of doses, or taking opioids in an attempt to manage anxiety, they need to be evaluated within a medical context, and a broad differential diagnosis should be considered.[80] Opioids, like any other intervention, should be tapered and discontinued if ineffective or harmful. Discontinuation is not synonymous with abandoning the patient or their pain treatment. If complex opioid misuse issues develop, including potential abuse or diversion, the oncologist should consider referral to or collaboration with a chronic pain expert, palliative care specialist, addiction specialist, or substance abuse treatment center.

Exercise and Cognitive-Behavioral Methods

Meta-analysis confirms that cognitive behavioral treatments are effective in reducing pain and related symptoms across the cancer continuum into survivorship.[81] Similarly, strength training and aerobic exercises are effective in improving pain along with other symptoms that frequently co-occur with pain such as physical dysfunction, fatigue, and distress.[82] The safety and efficacy of strength training for women with lymphedema after breast cancer and in other cancer survivors is now well established. Effectiveness has been demonstrated in community-based programs using trainers who have received specialized, brief preparation in adapting their training to the needs of cancer survivors.[83,84] Consequently, all survivors with chronic musculoskeletal pain should be considered for a program that establishes a regular exercise routine, particularly group programs that provide a supportive environment. Pain that is unrelieved by medical treatment alone or occurs with multiple other symptoms including fatigue and emotional distress warrants referral for cognitive-behavioral treatment as well.

Physical Medicine and Rehabilitation

The key to the success of rehabilitative interventions for chronic pain in cancer survivors is an accurate and specific diagnosis that is supported by a thorough and comprehensive clinical evaluation. This clinical assessment includes not only a detailed history, but also a physical examination that may involve specialized diagnostic maneuvers.[85] Electrodiagnostic testing, imaging, and/or laboratory testing are often necessary to confirm and support the clinical impression.

A variety of noninvasive pain management approaches are used by the rehabilitation physician in the management of chronic postcancer pain. Perhaps the most commonly prescribed modality is physical therapy (PT). Progressive resistance training is more effective than standard PT for treating shoulder pain and dysfunction in patients with head and neck cancer.[86] PT is also effective in reducing pain and improving shoulder function and QOL following axillary dissection for patients with breast cancer.[87,88] PT combined with massage can reduce pain and improve mood in patients with terminal cancer but has not been tested in survivors post-treatment.[89] A variety of techniques are often used in PT, such as myofascial release (including areas affected by radiation fibrosis), visceral therapy, neuromuscular re-education, and craniosacral manipulation. Although there is little scientific evidence to support the use of these techniques, they are commonly practiced with sufficient anecdotal efficacy to bolster their ongoing use.

Pain may be reduced during PT by increasing blood flow, decreasing muscle spasm, and decreasing inflammation among other effects. Modalities producing these effects include superficial heat (heating pads, moist compresses, hydrocollator packs, paraffin baths, whirlpool baths), deep heat (ultrasound, moist heat, laser), and cryotherapy.[90] Kinesio taping is a therapeutic modality that has become popular in recent years to treat a wide variety of neuromuscular disorders and lymphedema, producing an immediate reduction in pain for some musculoskeletal disorders, but there is no evidence for a long-term effect.[91]

Orthotics may be useful in the adjunctive management of chronic pain for select disorders such as median mononeuropathies at the wrist, medial and lateral epicondylitis, and a variety of shoulder, hip, knee, ankle, and foot disorders. A properly used straight cane can have significant beneficial effects on the pain associated with knee or

hip osteoarthritis by decreasing the weight on the affected painful joint.

Integrative Medicine

Two of the most useful integrative medicine techniques for chronic pain in cancer survivors are acupuncture and manual therapies, or massage. Acupuncture can assist cancer survivors with postsurgical pain and postradiation syndromes, even pain that has persisted for years. A 1-month course of acupuncture has been shown to provide significant pain relief in patients with head and neck cancer with moderate to severe pain a median of 39 months after neck dissection and radiation therapy.[92] Case studies have further demonstrated improved neuropathic pain in cancer survivors receiving acupuncture.[93,94] Manual therapy can be helpful in the control of various types of pain in survivors. Techniques include Swedish massage, light touch massage, and foot massage. One session of massage that used any combination of these techniques reduced mean pain scores by 47%, with postmassage pain relief persisting through 48 hours of follow-up.[95]

Interventional Approaches

Survivors suffering from focal pain may be amenable to interventional approaches for improved pain control, as may those who have inadequate pain control or significant adverse effects from pharmacotherapy. One can target the pain generator either peripherally or centrally. Options include injection therapies (myofascial, joint, and vertebroplasty/kyphoplasty), neural blockade, interventional neurostimulation therapies, and neuraxial analgesia (Table 1).[96] Regardless of the cause of neural injury, injured primary sensory nerves (eg, intercostal, ilioinguinal, lateral femoral cutaneous) can be targeted for diagnostic blockade with local anesthetic such as lidocaine.[97] If the pain symptoms are abated, after careful consideration of the patient population, neurolysis can be performed under image guidance (eg, ultrasonography) by using cryoablative, thermal, or chemical techniques.[98]

However, if the pain syndrome involves mixed motor and sensory nerves, multiple nerves, or complexity for which peripheral nerve destruction would not be possible, then neuraxial or neuromodulation may be options.[99] Injuries that involve plexuses may better respond to intrathecal drug delivery or spinal cord stimulation.[100] A trial of intrathecal drug delivery may be undertaken, with various techniques being evaluated before implantation.[101] Once the catheter has been implanted, guidelines may be followed to infuse opioids, local anesthetics, and other medications which are not as easily infused systemically, such baclofen and clonidine.[101]

Spinal cord stimulation uses devices implanted in the epidural space to stimulate sections of the spinal cord, commonly the dorsal columns or radicular nerves.[102,103] This may interfere with pain signal processing, and perhaps create a functional sympathectomy. Once the device is implanted, patients can control levels of electrical stimulation that interfere with their sensation of pain, thereby reducing their pain symptoms.[104]

A noninvasive neuromodulation technique that may be considered is transcutaneous electrical nerve stimulation (TENS). Used as a goal-directed therapy, TENS may improve peripheral pain syndromes from surgery and radiotherapy.[105] Newer TENS modalities that modify the shape of the electric waveform may provide pain relief in CIPN survivors by changing the action potential of the neurons involved in pain transmission.[106] Other novel neuromodulation devices such as peripheral nerve field stimulation and cortical stimulation may be used in rare instances.[100] If noninvasive modalities are not adequately treating the patient's pain, neurolysis may be considered. For visceral pain, especially of abdominal and pelvic origin, the sympathetic chain may be targeted.[100] Abdominal and pelvic ganglia and plexi can be targeted with diagnostic blockade and possible subsequent neurolysis for relief of pain symptoms.[105] Similar techniques have been performed for complex pain syndromes of the extremities (eg, stellate ganglion blockade for brachial plexopathy and complex regional pain syndrome),[107] although the risks may be unacceptable in a patient with normal life expectancy.

In summary, pain is a common problem in cancer survivors, especially in the first few years after treatment. Longer term, some 5% to 10% of survivors have chronic severe pain that interferes with functioning, and managing this pain may be a challenging clinical problem. Strong opioids may be indicated for survivors with moderate to severe pain, but most survivors will not require them. In addition, more than 40% of cancer survivors now live longer than 10 years, and the evidence for the long-term safety and effectiveness of chronic opioid therapy in this population is lacking. A "universal precautions" approach to opioid abuse is recommended. Greater emphasis should be placed on nonopioid analgesics and nonpharmacologic therapies in this population, with the aim of restoring functionality as well as providing comfort. Oncologists and community providers should have access to state-of-the-science education on the management of chronic pain in cancer survivors. They also should collaborate or consult with pain management specialists when their survivorship patients have complex pain problems.

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