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Optimal Pain Management for Patients With Cancer in the Modern Era

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Abstract

Pain is a common symptom among patients with cancer. Adequate pain assessment and management are critical to improve the quality of life and health outcomes in this population. In this review, the authors provide a framework for safely and effectively managing cancer-related pain by summarizing the evidence for the importance of controlling pain, the barriers to adequate pain management, strategies to assess and manage cancer-related pain, how to manage pain in patients at risk of substance use disorder, and considerations when managing pain in a survivorship population

Discussion

A recent review of 40 years of literature revealed that 64% of patients with advanced or metastatic cancer report pain; 59% of patients currently receiving anticancer treatment report pain, and one-third of patients have pain even after completing curative treatment.1 Although in some areas of the world the major barrier to pain control is adequate access to opioids,2 even in areas where opioids are available, pain remains prevalent in patients with cancer and has a significant impact on clinical outcomes. The presence and severity of pain has important clinical implications, for pain as a variable contributing to health-related quality of life (HRQOL) provides prognostic information for survival.3,4 In addition, the experience of pain can either positively or negatively influence patient outcomes. Poor communication between providers and patients regarding pain control can decrease patient satisfaction.5 Poor pain control is also associated with more psychological distress and decreased social activities and social support.6 Inversely, increased symptom monitoring and patient self-reporting of pain has been shown to improve HRQOL, decrease unexpected health care utilization, and improve adherence to antineoplastic treatment.7 Despite understanding the influence of pain on clinical outcomes, pain is often undertreated in patients with cancer. Studies examining the frequency and quality of pain management show room for improvement—a systematic review revealed that, despite a 25% decrease in undertreatment of cancer pain between 2007 and 2013, approximately one-third of patients living with cancer still have pain that is inadequately treated.8 Although the prevalence of pain varies by malignancy and disease stage,1 studies have shown no significant difference in pain severity between solid and hematologic malignancies,9,10 reflecting that the burden of pain is not limited to specific subsets of patients living with cancer but remains widespread. Consequently, all clinicians caring for patients with cancer must know how to effectively manage pain. Given the prevalence and impact of pain, it is vital to understand the principles of pain management and the barriers that prevent these strategies from being effectively implemented.

Pain Management

After a comprehensive pain assessment is completed, a multimodal management plan can be implemented. One of the first steps in managing pain is setting appropriate expectations for patients. The etiology of pain influences the expected outcome and improvement in intensity of pain and functional status. For example, pain from local tumor burden or an acute fracture may be expected to improve in a predictable manner as the disease is treated, whereas chronic neuropathy has a very different trajectory over time. Setting appropriate expectations is linked to better patient satisfaction 5 and treatment adherence. A framework for managing pain often starts with the World Health Organization (WHO) Analgesic Ladder. The WHO ladder (Fig. 1)66 consists of a stepwise approach in which the choice of analgesic is determined by the severity of pain; as the level of pain increases, so does the strength of recommended analgesic. Step 1 on the WHO ladder consists of using over-the-counter analgesics to manage pain. Step 2 escalates to using medications traditionally considered "weak" opioids (eg, codeine), and Step 3 advocates for use ofstronger opioids. A final Step 4 reminds clinicians to consider the use of interventions for nonpharmacologic management
options for pain.67 The WHO ladder was originally developed to guide clinicians through a systemic approach to pain management. Although it has been found
to be effective in treating cancer pain in a majority ofpatients, there is ongoing debate about whether these guidelines remain the optimal way of treating pain in all
patients.68 Newer evidence indicates that patients with moderate pain secondary to cancer are more likely to respond to low-dose morphine than they are to codeine,
calling into question whether it is necessary to try "weak" Step 2 opioids before initiating morphine for the control of moderate pain, especially because there were no differences in adverse effects between the 2 groups.69 Although they are not included on the WHO ladder, adjuvant analgesics, integrative therapies, and interventions can and should be considered at any step in pain management. Finally, recent evidence suggests that interventions may be more beneficial when offered earlier in the disease trajectory rather than reserving these for when pain is considered refractory to standard pharmacologic management.70,71 There are several acceptable treatment options that can be offered to patients. These include over-the-counter analgesics, nonopioid prescription medications, interventions, complementary therapies, and systemic opioids.

Pain Management: Nonopioid

Although opioids are the mainstay of moderate-to-severe cancer-related pain, there are several nonopioid treatment modalities available to patients. These include both pharmacologic and nonpharmacologic strategies.

Acetaminophen

Acetaminophen can be used as a first-line treatment in patients with mild cancer pain who may not require an opioid or may be hesitant to use an opioid. Peak plasma concentrations occur in approximately 30 to 60 minutes, and daily dose limits depend on age and underlying hepatic function.68 Acetaminophen can be used in combination with opioids; some prescription formulations contain acetaminophen plus an opioid in the same pill for ease of administration. However, a systematic review of the evidence for acetaminophen plus an opioid found no benefit to the addition of acetaminophen in 4 of 5 studies. Of note, the study that found a benefit to acetaminophen used a daily
dose of 5 grams, which is higher than the recommended daily dose, and followed patients for only 4 days.72 Consequently, although patients may start with the use of acetaminophen for mild pain, clinicians should consider promptly changing the regimen to an opioid for more optimal

pain control if adequate analgesia is not achieved with acetaminophen alone. In addition, use of acetaminophen in the oncologic population is limited by hepatotoxicity, particularly in patients with liver disease, as well as the need for close monitoring for fevers in patients with neutropenia.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDS) have anti-inflammatory, analgesic, and antipyretic properties. This class of medications has a maximum daily dose and multiple safety considerations (eg, bleeding, preexisting renal impairment, risk of precipitating renal impairment in patients with multiple myeloma, increased risk of hypertension). NSAIDs may be used alone or in combination with an opioid. There is conflicting evidence on the benefits of adding an NSAID to an opioid, with some studies showing a benefit to the combination,73 whereas other studies have shown minimal to no difference when comparing the use of an NSAID plus an opioid versus using either class of drug alone.

Antidepressants

The pathophysiology of neuropathy is complex and involves receptors for norepinephrine, serotonin, opioids, and Nmethyl- D-aspartic acid. Consequently, some antidepressants with activity at these receptors can be effective in treating neuropathic pain.80

Duloxetine

Duloxetine has been shown to be superior to placebo in treating CIPN. One study demonstrated that 59% of patients who received duloxetine reported “any decrease” in pain compared with 38% of patients who received placebo; the relative risk of a 30% reduction in pain was 1.96 with duloxetine versus placebo. In addition, the authors found that patients with oxaliplatin-related neuropathy had more benefit than patients with taxane-related neuropathy. Secondary outcomes (decrease in pain interfering with daily
function, decrease in numbness/tingling, and improvement in pain-related quality of life) were better for patients who received treatment with duloxetine.81 Although it can be difficult to decrease the numerical pain score when treating neuropathy, the improvement in secondary outcomes may be clinically significant in improving quality of life for patients.

Anticonvulsants

Gabapentin

The efficacy of gabapentin has been demonstrated in a variety of nonmalignant neuropathic pain states.85 Studies evaluating its effectiveness in treating CIPN show poor to no effect.86,87 Despite this, ASCO notes that it is “reasonable” to try it in certain populations, as there are limited treatment options available.77 In addition, some insurers still require documentation of a trial of gabapentin before approving coverage for pregabalin.

Pregabalin

Pregabalin has been shown to be superior to gabapentin and amitriptyline in managing neuropathic cancer pain. In a randomized, double-blind, placebo-controlled study, patients who received pregabalin had less pain, needed less PRN morphine, and had improved functional status compared with those who received gabapentin or amitriptyline.86

Radiation Therapy

Radiation therapy can be an integral component of cancer pain management. Because malignancy-specific indications are part of the oncologic care plan and are coordinated jointly between the medical and radiation oncologists, the details of radiation therapy indications for each specific malignancy are not discussed in detail here. Across all cancer types, approximately 50% of radiation therapy is considered to be palliative rather than curative in

nature. Treatment duration is determined after considering multiple clinical factors, although there is some observed variability based on geographic region, income level, and race that parallels disparities seen in other areas of health care. Another worthwhile consideration is that studies have shown that approximately 20% to 25% of patients die within 2 weeks of completing radiation, and nearly 20% of patients who received radiation in the last 30 days of life spent more than 10 of those days receiving radiation treatment

Nerve blocks

Although historically nerve blocks are Step 4 on the WHO analgesic ladder, more recent evidence shows that interventions may be more effective when considered earlier in the disease course. A randomized controlled trial of early versus later neurolytic sympathectomy for pain from an abdominal or pelvic cancer showed that patients who received the intervention earlier used less oral analgesics and reported improved pain control and quality of life.71 Therefore, nerve blocks can be considered earlier in management, if appropriate.

Integrative Therapies

Although some integrative therapies may not be the firstline treatment of cancer-related pain, patients may be interested in nonpharmacologic management strategies either in addition to or in lieu of pharmacologic therapy. A full listing is not included here, because options may vary across medical centers, but are outlined in brief below.

Cannabis or "Medical Marijuana"

To date, 29 states in the United States, the District of Columbia, Guam, and Puerto Rico allow for a medical marijuana program.97 When discussing the use of cannabis for medicinal purposes with patients, it is important to separate the broader movement to decriminalize the recreational use of marijuana from the evidence regarding its efficacy for medicinal purposes in patients living with a serious illness. Clinicians should differentiate between plant-based phytocannabinoids and synthetic cannabis products, because it is believed that the former contain multiple substances that create a synergistic entourage effect, which may not be replicated in synthetic products.98 The studies evaluating the use of cannabis in treating symptoms also often include a mix of cancer and noncancer symptoms, and many include formulations that are not available in the United States. One consistency across studies is that there is often some form of methodological flaw, including design quality and/or risk of bias. Most studies can clearly document the adverse effects; the increased risk of dizziness, nausea, fatigue, somnolence, disorientation, drowsiness, and confusion99 may be particularly important when considering the frailty, baseline symptom burden, and complicated comorbidities of many patients receiving antineoplastic treatment. One study of uncontrolled, cancer-related pain comparing tetrahydrocannabinol (THC) with cannabidiol (CBD) (THC:CBD), THC alone, and placebo showed that THC:CBD significantly improved pain compared with placebo.100 A review published in 2017 specifically evaluated cannabinoid use in treating cancerrelated pain; only 8 studies of "low-to-moderate quality" (which were conducted from the 1970s through 2014) were able to be included. These studies compared cannabinoids with placebo or codeine and found it was "not possible to demonstrate a clear therapeutic benefit" to using cannabinoids and that therapeutic effects were limited by adverse effects.101 In conclusion, there is a paucity of high-quality evidence on using cannabinoids to treat cancer-related pain, and clinicians should thoroughly discuss the side effect profile and current lack of evidence when discussing marijuana for the management of cancer-related pain.

Summary and Conclusions

Inadequate pain management continues to plague patients with cancer despite multiple safe and effective options for managing pain in this population. Although there are many barriers to pain management, clinicians must be armed with the knowledge to dispel myths and misconceptions about cancer-related pain and the use of opioids in this population. Pain should be assessed at every visit and, although patients may not become completely pain-free, clinicians and patients can work together to determine a plan that will allow a patient to live an independent, functional life with a

tolerable level of pain. A multimodal approach of opioids, adjuvant medications, and interventional or complementary therapies may be used in conjunction with disease-directed treatment. Given the current regulatory climate toward opioid use, it is more important than ever for oncology teams to proactively, safely, and effectively manage pain within the framework of patients who are living with cancer.

References:

1. Scarborough B, Smith C. Optimal pain management for patients with cancer in the modern era. CA Cancer J Clin. 2018.

2. Furrow BR. Pain management and provider liability: no more excuses. J Law Med Ethics. 2001

3. D'Arcy Y. Pain management standards, the law, and you. Nursing. 2005