Cancer remains the second most common cause of death in the United States despite advances in prevention, early detection, and newer treatment protocols. Pain continues to be the most feared complication of this diagnosis. Numerous studies have shown that when the World Health Organization treatment guidelines are followed, 90% of patients are pain-free. Although evidence is convincing that opioids are effective in the treatment of patients with cancer pain, reluctance to use them continues. Barriers to opioid use are multifactorial, but with education of healthcare providers and patients, treatment to manage pain will be more effective.

Despite treatment advances, cancer remains the second leading cause of death in the United States. The incidence of cancer continues to rise as the result of increases in population and average life expectancy. Mortality rates for certain cancers (colon, prostate, female breast) continue to decrease as the result of screening guidelines that allow early detection and advances in treatment.

Pain continues to be a major problem in patients with cancer, affecting 25% to 30% of patients with recently diagnosed cancers. The incidence of pain in advanced stages of cancer approaches 70% to 80%. One of the major fears of patients with cancer is pain, which can occur as a result of the cancer itself or its treatment, or from other causes. Cancer can spread by metastasis or direct invasion, and 90% of patients with metastasis to osseous structures report pain. Patients with cancer can have neuropathic pain due to direct compression of nerves or plexus or spinal cord involvement.

Chemotherapeutic drugs such as vinca alkaloids or radiation therapy have also been associated with neuropathic pain. Postsurgical pain commonly occurs in patients who have had thoracotomy, mastectomy, or amputations to manage their neoplastic disease. Steroids used in treatment of patients with cancer have been associated with avascular necrosis of the hip and subsequent fracture.

Inadequate treatment and under-treatment are associated with increased pain scores, decreased functional ability, and increased depression and anxiety. The American Pain Society and the Joint Commission of Accreditation of Healthcare Organizations recently placed emphasis on this problem. A campaign is under way to have pain become a “fifth vital sign” because it, like other vital signs such as blood pressure, heart rate, respiratory rate, and body temperature, needs frequent assessment. Visual analog and 11-point (0 to 10) numeric scales are used to measure pain, a process that allows frequent reassessment and therefore adequate treatment.

The World Health Organization (WHO) in 1986 established a stepladder approach for treatment of patients with cancer pain (Figure). The goal was to provide treatment guidelines that healthcare practitioners could easily follow. The initial step consisted of acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) with or without adjuvant therapy. If pain is not controlled, medications combining mild to moderate opioids with acetaminophen are added to step one. If pain persists, stronger opioids such as morphine are added and titrated to pain relief. Around-the-clock dosing schedules are used to minimize the frequent use of breakthrough medications. Most cancer patients’ pain can be controlled by morphine oral doses of less than 200 mg/d. Greater than 80% of cancer patients can be pain-free when physicians follow WHO guidelines and use higher doses as needed to obtain relief.

This article reviews major classes of medications, mechanisms of action, and doses used in WHO guidelines. Adjuvant medications such as ketamine, antidepressants, anticonvulsants, steroids, biphosphonates, topical, anxiolytics, laxatives, hormones, antihistamines, and antiemetics will be reviewed in detail.

**NSAIDs, COX-2 Inhibitors, ASA, and Acetaminophen**

It is now established that prostanoids play important roles in many cellular responses and pathophysiologic processes, including modulation of inflammatory reactions, erosion of cartilage and...
juxta-articular bone, gastrointestinal cytoprotection and ulceration, angiogenesis and cancer, hemostasis and thrombosis, renal hemodynamics, and progression of kidney disease. Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase type 2 (COX-2) inhibitors, and acetylsalicylic acid (ASA) prevent formation of prostanoids from arachidonic acid. This synthesis of prostaglandins from arachidonic acid is controlled by two separate cyclooxygenase enzymes (COX-1 and COX-2).

Traditional nonselective NSAIDs inhibit both COX-1 and COX-2, a nonselective inhibition that results in not only an anti-inflammatory response but also reduced gastrointestinal cytoprotection; this latter effect causes gastric mucosal ulceration and bleeding. Newer COX-2 inhibitors were designed to selectively inhibit only this enzyme, thus maintaining an anti-inflammatory response with low risk of side effects that occur with nonselective inhibitors of COX enzymes. Recently, however, COX-2 inhibitors have received attention because of an increased incidence of stroke and myocardial infarction when used in high doses to decrease the incidence of cancerous polyps (in familial polyposis). Two COX-2 inhibitors (rofecoxib and valdecoxib) marketed in the United States have been removed from the market because of the increased rate of stroke and myocardial infarction associated with their use.

The entire class of NSAIDs is now under increased scrutiny as this unwanted side effect may not be class-specific. Despite these concerns, NSAIDs and COX-2 inhibitors are promising as anticancer drugs because they inhibit tumor angiogenesis and induce tumor cell apoptosis.

NSAIDs play a key role in the first step of the WHO guidelines for management of cancer pain. Nearly 90% of patients with bone metastasis present with pain. NSAIDs are the most effective agents for treatment of patients with this condition as prostaglandins appear to play an important role. A recent review showed NSAIDs are more effective than placebo for cancer pain and that they all are comparable in safety profile and effectiveness. Comparison of opioid combination preparations with NSAIDs alone showed no or at most only a slight difference which was not statistically significant (Table 1).

**Opioids**

In treating patients with cancer pain, opioids (in particular morphine) remain the gold standard with which other treatment modalities are compared. The second step of the WHO guidelines involves use of mild to moderate opioids in combination with acetaminophen or ASA. Administration of medications used in step one is continued because NSAIDs, COX-2 inhibitors, and acetaminophen have been shown to be effective even with the addition of opioids. Adjuvant medications are also indicated in this step as well as all the steps of the WHO ladder.

In 1973, several teams of researchers found the presence of an “opioid receptor” in the nervous system. It was believed that endogenous substances were present in the body which when released were bound to the opioid receptor and provided analgesia. This receptor binding was reversed by naloxone. These endogenous substances were later identified as enkephalins, β-endorphins, and dynorphin. Three separate opioid receptors were identified and labeled: mu (μ), kappa (κ), and delta (δ). The major receptor associated with analgesia is μ, and opioid development has centered on targeting this site, which provides intense analgesia without binding other opioid receptors that are commonly associated with unwanted side effects (eg, nausea and dysphoria).

Oral morphine is the primary opioid used in the United States for treatment of patients with severe pain in advanced stages of cancer. In the United Kingdom, diamorphine (heroin) is used secondarily because of its greater solubility, but it has no clinical advantage over morphine. Methadone hydrochloride, a drug commonly prescribed to prevent withdrawal in recovering drug users, is used in hospices in the United Kingdom and Canada. It is also being used in the United States for the treatment of patients with refractory or neuropathy-associated pain.
Numerous opioid preparations are now available (Table 2). Currently, morphine can be obtained in an immediate-release (IR) form (eg, oxycodone IR, fentanyl IR) and a sustained-release (SR) form (eg, oxycodone SR) with dosing of every 8, 12, or 24 hours. Never sustained-release technology allows for sprinkling pellets in applesauce, which was not possible with the previously available preparations. Other sustained-release preparations could not be given via gastrostomy tube because of problems with uncontrollable and variable release if pills are crushed or cut.

Fentanyl, an analgesic commonly used in anesthesia, is now widely used throughout hospitals via the intravenous route. Fentanyl is now also available via transdermal or transmucosal delivery systems with predictable drug concentration comparable to that achieved via the intravenous route.

In terms of efficacy, one opioid formulation offers no advantage over another for pain control. Experience of the healthcare provider and cost seem to be the determining factors in choosing one preparation over another.

Long-term use of opioids is associated with physical dependence and tolerance. These two physiologic processes have nothing to do with addiction, which is psychological. Tolerance is defined as a physiologic phenomenon of progressive decline in the potency of an opioid with continued use, manifested by the requirement of increasing opioid dose to achieve the same therapeutic effect.

Tolerance may occur in any patient taking narcotics for more than 1 or 2 weeks, though the degree to which tolerance occurs in patients with cancer-related pain is uncertain.

Increased doses can continue to provide adequate analgesia as there appears to be no ceiling, but escalating doses can increase side effects (eg, nausea, vomiting, constipation, abdominal pain, pruritus) that may limit their use. Tolerance occurs due to:

- Increased activation and/or upregulation of the N-methyl-D-aspartate (NMDA) receptor because of repeated exposure of mu receptors to opioids; use of an NMDA-receptor antagonist can diminish or reverse tolerance.

- Downregulation and/or possible conformational changes in opioid receptors that is thought to occur with long-term opioid exposure.

N-methyl-D-aspartate receptors are present in the periphery as well as the central nervous system (CNS). Activation of these sites is associated with memory, learning, neural development, plasticity, and acute and chronic pain states. Acute and chronic stimulation of peripheral pain fibers (A-delta and C) can result in activation and recruitment of NMDA receptors; when this activation and recruitment occurs, symptoms of both allodynia and hyperalgesia commonly occur, especially in patients with neuropathic pain.

Rotating opioids reduces tolerance. Rapid switching from one opioid to another can be easily accomplished with minimum periods of inadequate analgesia. A standard equianalgesic table for conversions from one to another is used only as a guide because incomplete or decreased cross-sensitivity may play a part in the conversion process. In switching from one opioid to another, 60% to 70% of the total daily dosage of the current opioid calculated from an equianalgesic conversion table should be used and accompanied by frequent supplementation with as-needed rescue dosing.

Because dosing and conversion of opioids are complex processes requiring knowledge of opioid properties, professional skill, and caution, this article does not include a conversion table. Readers should refer to prescribing information and available resources for calculating opioid conversion.

Dependence is a physiologic process that is independent of tolerance and characterized by withdrawal symptoms on abrupt discontinuation or reduction of a chronically administered drug. Addiction is a process believed to be a psychological and behavioral syndrome manifested by drug-seeking behavior, loss of control over drug use, and continued use despite adverse effects. In 1980, Porter and Jack reported that addiction is rarely seen in patients with cancer pain when use is appropriate; however, patients with a history of previous addiction may be at an increased risk for this behavior.

Adjuvant Analgesia Ketamine

Ketamine, a derivative of phencyclidine, has been used in anesthesia for more than 40 years. Ketamine provides both amnesia and intense analgesia to produce “dissociative anesthesia.” Dissociative anesthesia resembles a state of catalepsy in which the patient is unable to respond or communicate, yet appears awake. Use of ketamine has been limited because of emergence delirium, which can be partially inhibited by preoperative doses of a benzodiazepine.

The mechanism of action is noncompetitive blockade of the NMDA receptor. Ketamine has been shown to attenuate and reverse morphine tolerance by inhibition of NMDA receptors.

Ketamine has been used in a variety of pain conditions that are refractory to high-dose opioid and other conventional modes of therapy. Low-dose continuous intravenous administration of ketamine can provide analgesia with a minimum incidence of associated cardiovascular or neurologic side effects. Infusion rates of 0.1 to 5.0 milligrams per kilogram of body weight per hour (mg/kg/h) titrated to sedative effects have been used to treat patients with refractory pain resistant to opioid therapy. During titration, opioid consumption can be slowly reduced by 10% to 90%. Ketamine can provide analgesia without the sedation of high-dose opioid administration. Tachyphylaxis can develop with prolonged use of either intravenous or oral ketamine, and bioavailability from oral administration can also limit long-term effectiveness.

Antidepressants

Tricyclic antidepressants (TCAs) have efficacy in treatment of patients with neuropathic pain and patients with pain syndrome and comorbid depression. The doses effective for neuropathic pain are usually lower than those used for depression. The TCAs have no differences in their effectiveness. In this group, both tertiary amines (amitriptyline hydrochloride, imipramine, doxepin hydrochloride, and clomipramine hydrochloride) and secondary amines (nortriptyline hydrochloride and desipramine hydrochloride) have analgesic effects in cancer.
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The JAOA also advises readers to refer to the current edition of the Physicians’ Desk Reference for prescribing information for nonopioid analgesics and and to keep current with US Food and Drug Administration advisories and alerts regarding COX-2 inhibitors and nonselective NSAIDs via documents posted to the FDA Web page at www.fda.gov/cder/drug/infopage/COX2.
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The JAOA also advises readers to refer to the current edition of the Physicians' Desk Reference for prescribing information for opioid analgesics and to keep current with possible future US Food and Drug Administration advisories and alerts regarding opioids.
patients, especially for concurrent neuropathic pain syndrome.23 The major mechanism of the analgesic effect was believed to be related to inhibition of norepinephrine or serotonin reuptake or of both. Common side effects include sedation, confusion, orthostatic hypotension, weight gain, tachycardia, arrhythmia, anticholinergic effects (dry mouth, blurred vision, and urinary retention).

Tricyclic antidepressants should be administered cautiously in the elderly and in patients with angle-closure glaucoma, benign prostatic hypertrophy, urinary retention, constipation, cardiovascular disease, or impaired liver function. These agents should be avoided in patients with severe liver disease, second- or third-degree heart block, arrhythmias, QT prolongation and/or in patients with a history of recent myocardial infarction.

In general, secondary amines have fewer sedative and anticholinergic effects than tertiary amines; therefore, the secondary amines may be more desirable in the elderly.24 In this latter population, the starting dose is usually 10 mg every night, then gradually titrated to therapeutic level. Trazodone hydrochloride is as effective as amitriptyline in cancer-related neuropathic pain syndrome.13 Recent clinical trials demonstrate that the selective serotonin and norepinephrine reuptake inhibitor duloxetine hydrochloride, an antidepressant, is also effective for neuropathic pain.25

Anticonvulsants
Anticonvulsants have been used in the treatment of neuropathic pain for many years. The mechanism of the analgesic activity of carbamazepine, phenytoin, and valproic acid is thought to be associated with blocking sodium channels and increased membrane stability. Clonazepam increases γ-aminobutyric acid (GABA) levels and also activates the benzodiazepine receptor; this receptor activation cause an increase in chloride ion which inhibits neuronal activity. Gabapentin is designed to be an analog of GABA, but its true mechanism of action is still not known. The most common adverse effects are dizziness, somnolence, ataxia, and lethargy.

Caution should be taken when administering carbamazepine, phenytoin, or valproic acid because of their severe adverse effects such as bone marrow depression and liver toxicity. Baseline evaluation of liver function and a complete blood cell count should be done before initiating use of these medications.

At present, gabapentin is the most commonly used adjuvant analgesic for neuropathic pain.26 It is not metabolized, has no known drug-drug interaction, and has the most acceptable safety profile for side effects. Treatment usually starts with 100 mg/d to 300 mg/d. Gradual dose titration continues until benefit occurs, side effect supervenes, or the total daily doses reach 3600 mg. Occasionally, patients receive benefits at even higher doses. An adequate trial should include 1 to 2 weeks at the maximum tolerated dose.

Like gabapentin, levetiracetam and pregabalin have proven efficacy for neuropathic pain. Dunteman27 reported a greater than 70% reduction of opioid use with the administration of levetiracetam, as well as improved pain relief in patients with neoplastic plexopathies previously resistant to standard analgesic approaches.

Corticosteroids
Corticosteroids are given as adjunctive therapy for cancer-related neuropathic pain, especially for metastatic spinal compression, pain associated with soft tissue infiltration, and visceral distension. Mechanisms of action include:
- inhibiting prostaglandin production and reducing inflammation;
- decreasing capillary permeability and reducing peritumor edema; and
- directly affecting membrane stabilization, which decreases neuronal excitability.

Administering these drugs can produce significant adverse effects such as hypertension, hyperglycemia, immunosuppression, gastrointestinal ulceration, and psychiatric disorders. Dexamethasone is the corticosteroid most commonly used for spinal cord compression because of a decreased tendency for salt and fluid retention.28 The doses range from 10 mg to 20 mg administered intravenously (IV) every 6 hours. Corticosteroids are also used to improve appetite, reduce nausea and malaise, and improve overall quality of life.

Adjuvant Analgesia for Bone Pain
Bone pain secondary to tumor expansion and inflammation is a common symptom of some cancers. Radiation therapy with corticosteroids is highly effective for the treatment of patients with focal bone lesions. Some medications useful for treating bone pain by inhibiting osteoclast activity include bisphosphonates, calcitonin, and radionuclides.

The analgesic efficacy of bisphosphonates, particularly the second-generation bisphosphonate pamidronate disodium, has been well established.29 For tumor-related bone pain, 60 mg to 90 mg of pamidronate injected intravenously is recommended every 3 to 4 weeks. Adverse effects include hypocalcemia, and a flulike syndrome. Zoledronic acid, a new bisphosphonate, is approximately two to three times more potent than—and as effective as—pamidronate.24

Calcitonin is usually administered subcutaneously and intranasally. The initial dose is 200 IU in one nostril a day, alternating nostrils every day. Apart from infrequent hypersensitivity reactions associated with subcutaneous injections, the main side effect is nausea.

Radionuclides that are absorbed at areas of high bone turnover have been assessed as potential therapies for metastatic bone pain.13 Strontium-89 chloride and samarium-153 are available in the United States.

Local Anesthetics
Evidence has been presented showing a higher density of Na⁺ channels following nerve damage and subsequent spontaneous firing.30 By inhibiting sodium channels, local anesthetics are effective in treating patients with nonmalignant and cancer-related neuropathic pain syndrome. These agents should be considered once trials of anticonvulsants or antidepressants have failed. Common adverse effects are paresthesias (fingers), abnormal taste, tinnitus, blurred vision, drowsiness, dysarthria, or local skin rash secondary to topical application of the anesthetic.
Severe systemic toxicity due to high plasma levels can cause seizure or result in cardiotoxicity with cardiac arrest. For intravenous lidocaine infusion, the dose is either 1 mg/kg or 5 mg/kg over 2 hours. When administered topically, 5% of lidocaine gel or patch is placed directly on skin over painful regions. Mexiletine hydrochloride, an antiarrhythmic with structural similarity to lidocaine, has been used off label to treat patients with neuropathic pain from numerous etiologies and is the preferred oral local anesthetic. Topical capsaicin, a peptide that depletes substance P in small primary afferent neurons, has been shown to significantly decrease cancer-related neuropathic pain. A major side effect, localized irritation that causes a burning sensation, limits use of capsaicin.

Miscellaneous Adjuvants

Other medications are sometimes used as adjuvants for pain or symptom management related to cancer treatment.

- Baclofen is used in treatment of spasticity, trigeminal neuralgia, and central pain secondary to spinal cord lesions; its mechanism of action is activation of GABA receptors.
- Benzodiazepines are anxiolytics that help to reduce cancer pain by reducing patients' fear, apprehension, and anxiety related to their disease.

In cancer patients, psychostimulant drugs (dextroamphetamine, methylphenidate) can reduce opioid-induced somnolence, improve cognition, treat depression, and alleviate fatigue. For breast or prostate cancer pain, hormonal therapy (eg, tamoxifen citrate or leuproide acetate, respectively) can provide beneficial effects.

Antihistamines, anticholinergic drugs, antipsychotics, and laxatives are sometimes used to treat patients for cancer-related symptoms or complications of cancer treatment, such as dizziness, vertigo, nausea and vomiting, confusion and delirium, and constipation. This group of medications should be used cautiously, with precautions taken to reduce side effects and drug-drug interactions.

Comment

The management of pain is an important goal in the holistic care of patients with cancer. Studies have shown effective pain control can be achieved in 90% of patients by following the WHO step ladder system. Major obstacles still exist that prevent reduction of pain in cancer patients. Education of patients, families, healthcare providers, legislators, and law enforcement agencies is needed to improve the treatment of patients with cancer pain with all the pharmacologic therapeutic modalities available.

References