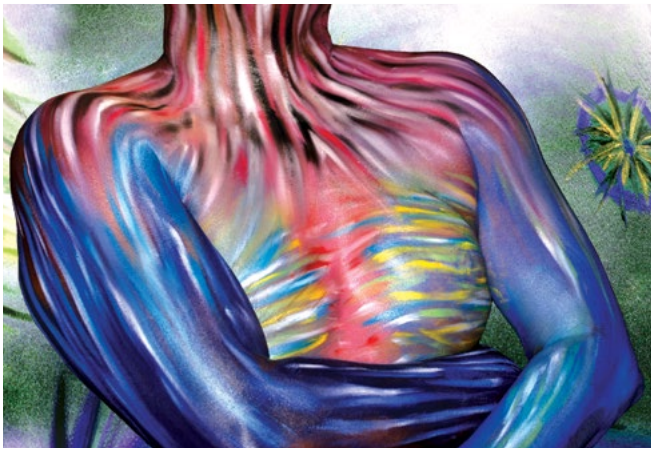

Photo courtesy of Lisa Scholder. *Solid Stance.* 16" × 24".

It is important that clinicians assess opioid responsiveness to determine whether adjuvant analgesics should play a role in the treatment plan.

Pharmacological Management of Cancer-Related Pain

Eric E. Prommer, MD

Background: *Pain occurs in 50% of patients with cancer at the time of diagnosis, and nearly 80% of patients with advanced stage cancer have moderate to severe pain. Assessment of pain requires the health care professional to measure pain intensity, delineate opioid responsiveness, and clarify the impact of pain on a patient's psychological, social, spiritual, and existential domains. To this end, the World Health Organization (WHO) has developed a 3-step pain ladder to help the health care professional effectively manage pain, classifying pain intensity according to severity and recommending analgesic agents based on their strength.*

Methods: *Health care professionals should follow the WHO guidelines to manage cancer-related pain in their patients. With regard to opioids, dosing, equianalgesic conversions, the management of adverse events, and the identification of new agents are discussed. Integrating adjuvant analgesics and interventional pain techniques into the management of cancer-related pain is also discussed.*

Results: *The WHO analgesic ladder is an effective tool for managing cancer-related pain. Successful pain management in patients with cancer relies upon the health care professional to pay attention to detail, especially during the introduction of new drugs and in identifying potential adverse events. Health care professionals must assess opioid responsiveness to determine whether adjuvant analgesics should also play a role in a patient's treatment plan.*

Conclusion: *Adherence to the WHO pain ladder and understanding proper use of interventional pain techniques complement the pharmacological management of cancer-related pain.*

Introduction

Pain occurs in 50% of patients with cancer at the time of diagnosis, and approximately 80% of patients with advanced stage cancer have moderate to severe pain.[1] Pain can impact quality of life, limit function, and affect mood. Untreated pain may sometimes lead to requests for physician-assisted suicide or unnecessary visits to the emergency department and hospital admissions.[2,3] Opioids are the cornerstone of treatment for moderate to severe pain associated with cancer because they decrease pain and improve function.[4] Strong opioids are the initial choice for moderate to severe pain associated with cancer, and the World Health Organization (WHO) recommends a pain ladder, which is a step-by-step approach for the management of chronic pain based on pain intensity.[5,6]

Epidemiology

Pain occurs at diagnosis in 20% to 50% of patients with cancer.[7] Cancer-related pain may be the result of the

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cancer itself, oncology treatment, and coexisting nonmalignant pain.[8] Cancer types determine pain prevalence; for example, patients with head and neck cancer have the highest prevalence of cancer pain.[9] Age has also been show to affect cancer pain; younger patients experience more pain and more pain flares than older patients.[10] In addition, elderly patients receive less opioids than their younger counterparts.[11] Patients with cancer most commonly experience pain in the back — prompting health care professionals to exclude spinal cord metastasis — as well as in the abdomen, shoulders, and hips.[12]

World Health Organization Pain Ladder

WHO guidelines form the basis of cancer pain management, recommending a step-by-step approach to managing cancer pain based on pain intensity.[2] The pain ladder starts with nonopioid analgesics, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), for mild pain, then adds a so-called weak opioid if pain persists or increases, and then replaces the weak opioid with a step 3 opioid for severe pain. Morphine is recommended as a first-line opioid to relieve cancer-related pain; however, the evidence level for morphine as a first-line opioid is not particularly strong.[3,6] Other step 3 options for moderate to severe pain include methadone, oxycodone, fentanyl, and hydromorphone. Successfully using the WHO pain ladder can help manage pain/provide effective analgesia in 90% of patients in certain settings, although results from randomized control trials show success rates of 70% to 80%.[13-15]

Step 1

Step 1 analgesics include acetaminophen and NSAIDs, which are both analgesic and anti-inflammatory; acetaminophen is only analgesic.[16,17] Dosing of acetaminophen and NSAIDs is limited by a ceiling effect, meaning that further dose escalation will not improve analgesia. Acetaminophen dosing is limited by concerns of hepatic toxicity at a total dose of more than 4 g/day.[18] Acetaminophen has several postulated mechanisms of action, including central inhibition of the cyclooxygenase system, nitric oxide synthetase, the endocannabinoid system, and the descending serotonin pathways.[17] NSAIDs inhibit the enzyme cyclooxygenase, which produces inflammatory prostaglandins that cause sustained nociceptive responses by lowering pain thresholds in nociceptive, neuropathic, and possibly visceral pain through a process called peripheral sensitization.[19] One major action of NSAIDs is the prevention of peripheral sensitization.[20] When considering the use of NSAIDs, choices should be based on experience and the toxicity profile, which depends on the cyclooxygenase 1:2 ratio. There is no ideal NSAID. NSAIDs are orally administered, with the exception of ketorolac. Thus, loss of the oral route with advanced illness eliminates NSAIDs from consideration for analgesia in patients at the end of life.

At the end of life, NSAIDs are typically replaced by stronger analgesics in the setting of moderate to severe pain. It may be important to continue NSAIDs as long as possible, because clinical trials show additive analgesia when combined with opioids as well as an opioid-sparing effect.[21] Ketorolac, diclofenac, and ibuprofen are parenteral NSAIDs, and ketorolac is useful for the treatment of cancer pain syndromes not uniformly responsive to opioid therapy.[22] Ketorolac use in the advanced patient with cancer is not recommended for more than 1 week.[23] Acetaminophen has not been shown to work synergistically with opioids but has not been shown to be opioid-sparing with opioid doses of more than 200 mg of morphine equivalents.[22] NSAIDs are useful for pain originating in tissues such as connective tissue, joints, serous membranes, and the periosteum; in addition, visceral pain may also respond to NSAIDs.[24]

Step 2

Step 2 on the WHO pain ladder is for mild to moderate cancer pain and includes recommendations for acetaminophen products containing hydrocodone, oxycodone, codeine, and tramadol, as well as propoxyphene and dihydrocodeine (not available in the United States).[2] Propoxyphene is not recommended for use in cancer pain.[25]

Hydrocodone: Hydrocodone is structurally similar to morphine, differing only in having a single bond at carbons 7 and 8 and a keto (=O) group at 6-carbon. Hydrocodone is metabolized by both cytochrome P450–dependent oxidative metabolism and glucuronidation. CYP3A4 and CYP2D6 play a role in the generation of hydrocodone metabolites: norhydrocodone and hydromorphone, respectively.[26] Polymorphisms of CYP2D6 potentially affect hydrocodone metabolism and therapeutic efficacy.[27] Hydrocodone has equivalent potency as morphine on a milligram-for-milligram basis.[27] Adverse events of hydrocodone are similar to other opioids.

Rodriguez et al[28] evaluated 118 study patients with chronic cancer pain and compared hydrocodone/acetaminophen with tramadol in a double-blind, randomized controlled trial. A total of 62 study patients received hydrocodone/acetaminophen and 56 received tramadol.[28] Hydrocodone/acetaminophen decreased pain in 57% of participants at a starting dose of 25 mg/2500 mg/day (5 doses per day).[28] Analgesic responses increased by 15% with dose doubling.[28] Pain did not respond to hydrocodone/acetaminophen administration in 29% of study patients.[28]

Another multicenter, double-blind, randomized, parallel group study compared codeine/acetamino-

phen phosphate with hydrocodone/acetaminophen for moderate to severe pain.[29] Study patients had chronic moderate to severe cancer pain (> 3 on a 10-cm visual analog scale and > 1 on a 4-point verbal intensity scale).[29] A total of 88% of study patients had moderate pain and 12% had severe pain; 121 participants received either 1 tablet of codeine/acetaminophen 30/500 mg or hydrocodone/acetaminophen 5/500 mg orally every 4 hours (total daily doses, 150/2500 and 25/2500 mg, respectively) for 23 days.[29] Dose escalation occurred after 1 week if participants experienced severe pain.[29] The primary end point was the percentage of study patients achieving a decrease in their pain score by 1 point on a 5-point verbal intensity scale.[29] The secondary end point was the percentage of study patients whose pain decreased by at least 3 cm on the 10-point scale.[29] Of the 121 participants, 59 received codeine/acetaminophen and 62 received hydrocodone/acetaminophen.[29] Of the total number of cases, 59 had ages ranging from 60 to 89 years.[29] A total of 58% of patients in the codeine/acetaminophen arm of the study experienced pain relief, and an additional 8% achieved pain relief with a doubling of the dose.[29] Approximately one-third had unresponsive pain.[29] In the hydrocodone/acetaminophen arm of the study, 56% experienced pain relief with a starting dose of 25/2500 mg/day.[29] A total of 15% more achieved pain relief doubling of the initial dose, and one-third of patients did not respond to hydrocodone/acetaminophen.[29]

Tramadol: Tramadol is a synthetic opioid from the aminocyclohexanol group. Tramadol has opioid-agonist properties and prevents the uptake of norepinephrine and serotonin, making it useful for neuropathic pain.[30] Tramadol possesses low affinity for opioid receptors, with an affinity to μ receptors 10 times weaker than codeine, 60 times weaker than dextropropoxyphene, and 6,000 times weaker than morphine.[31] Tramadol requires conversion to an active metabolite by CYP2D6. This metabolite has affinity for opioid receptors, but less so than step 3 opioids.[31] Patients who are poor metabolizers of CYP2D6 may experience poor analgesia.[32] Adverse events of tramadol include constipation, dizziness, nausea, sedation, dry mouth, and vomiting.[33]

Rodriguez et al[28] evaluated 118 participants with chronic cancer pain and compared hydrocodone/acetaminophen and tramadol in a double-blind, randomized controlled trial. In addition, Wilder-Smith et al[34] compared tramadol with morphine in a randomized, crossover, double-blind study for severe cancer pain (N = 20). Initially, participants received either tramadol 50 mg or morphine 16 mg every 4 hours, with dose titration to achieve pain control.[34] After 4 days, pain intensities did not differ between the groups, although adverse events appeared to differ, with less-intense nausea and constipation noted in the tramadol group.[34] The authors estimated equianalgesic doses of morphine and tramadol and found a ratio of morphine to tramadol of 1:4.[34]

Tawfik et al[35] compared oral tramadol with sustained release morphine for cancer pain in 64 participants with severe cancer pain in a randomized, double-blind study. Tramadol worked best in participants with lesser pain intensity, and morphine worked more effectively and was preferred for participants experiencing severe pain intensity.[35] Good analgesia was achieved in 2 weeks of treatment in 88% of study patients receiving tramadol and 100% of study patients receiving sustained-release morphine. Participants receiving tramadol experienced fatigue (15%), nausea (8%), and sweating (8%).[35] In those receiving morphine, adverse events included constipation (35%), rash (14%), and drowsiness (14%).[35]

Bono and Cuffari[36] compared tramadol with buprenorphine in a randomized, crossover trial in study patients with cancer pain. All 60 study patients received either drug for 1 week and then, after a 24-hour wash-out period, were switched to the other drug.[36] The tramadol dose was 300 mg/day and the buprenorphine dose was 0.2 mg 3 times a day.[36] Tramadol was associated with better analgesia ($P < .05$) and was associated with higher acceptance among study patients.[36] Tramadol was better tolerated than buprenorphine and caused less frequent and milder adverse events, and more study drug withdrawals occurred in the buprenorphine arm.[36]

Tapentadol: Tapentadol is structurally related to tramadol.[37] Opioid receptor–binding studies show that tapentadol is a strong opioid with high-affinity binding to μ, δ, and κ opioid receptors. In human μ opioid receptor ^{35}S GTPγS–binding assays, tapentadol shows agonistic activity, with an efficacy of 88% relative to morphine; tapentadol provides potent inhibition of norepinephrine uptake and its bioavailability is lower than tramadol.[31] T_{max} is achieved in 1.25 to 1.5 hours, the half-life is 24 hours, and the plasma protein binding is 20%.[38] Tapentadol metabolism is mainly by glucuronidation, with some contribution from CYP enzymes, especially CYP2D6.[39] Tapentadol is not an inducer of CYP3A4.[39] Tapentadol has no active metabolites. There is chiefly renal excretion. Tapentadol causes adverse events such as nausea, dizziness, vomiting, headache, and somnolence.[40] The manufacturer recommends against using tapentadol in severe hepatic or renal failure, and dosing above 600 mg/day should be avoided.[41] Equianalgesic dosing studies are unavailable but information from its use in non–cancer-related pain studies suggest morphine 60 mg is equivalent to tapentadol 100 to 200 mg.[42] The current dosing recommendations is 50, 75, or 100 mg every 4 to 6 hours.[40] Tapentadol does

not affect the QTc interval.[43] Prolonged-release tapentadol (100–250 mg twice daily) is effective compared with placebo for managing moderate to severe, chronic, malignant tumor-related pain.

Codeine: Codeine is a prodrug whose analgesia is mediated through the μ receptor by its metabolite, morphine. A total of 10% of codeine is broken down to morphine by CYP2D6, an enzyme lacking in 5% to 10% of white populations.[44] Codeine use is not recommended in the setting of renal failure.[45] One placebo-controlled study has evaluated codeine for cancer pain involving a sustained-release formulation.[46] Thirty study patients with chronic cancer pain completed the study and received either sustained-release codeine every 12 hours or placebo in a double-blind study.[46] Crossover occurred after 7 days.[46] Pain intensity was measured using a visual analog scale as well as a 5-point categorical scale. Rescue analgesia (acetaminophen/codeine 300 mg/30 mg every 4 hours as needed) was recorded. The median doses of controlled-release codeine doses were 277 ± 77 mg (range, 200–400 mg). Pain intensity scores on a visual analog scale, categorical pain intensity scores when assessed by day of treatment and by time of day, and need for breakthrough pain were significantly lower in the codeine arm ($P < .0001$).[53]

Step 3

The WHO pain ladder recommends the use of step 3 opioids as first-line therapy for moderate to severe pain (morphine, oxycodone, hydromorphone, fentanyl, levorphanol, methadone).[47] Step 3 opioids differ from those in step 2 medications in terms of potency and dosing. Although many step 2 medications often have a ceiling dose due to fixed formulations with acetaminophen, step 3 opioids do not have this ceiling. Dosing can increase to achieve adequate analgesia as long as adverse events are tolerated. Step 3 opioids interact with opioid receptors found throughout the central nervous system and peripheral tissues, resulting in analgesic effects, as well potential adverse events, including sedation, respiratory depression, and dependence. Opioid receptors exist throughout the intestinal tract and, when activated, slow bowel motility.[48] Varying degrees of activation and affinity for each receptor subtype may account for the differences in efficacy and activity between opioids. In addition, interindividual variation is significant in analgesic response and toxicities based on genetic disparities.[49] However, a reliable method to predict an individual patient's response does not exist and a paucity of evidence suggests superiority of one opioid over another in terms of efficacy or tolerability.

Morphine: WHO considers morphine the drug of choice for moderate to severe cancer pain.[50] The liver is the principal site of morphine glucuronidation.[51] There is a minor contribution (30%) to glucuronidation from the kidneys.[52] First-pass metabolism of oral morphine determines its systemic bioavailability. Three major metabolites are produced: normorphine, morphine-3-glucuronide, and morphine-6-glucuronide. The metabolites are principally eliminated by the kidney and accumulate in renal failure.[53] The elimination half-life of morphine is approximately 2 hours and is independent of route of administration or formulation.[54] Morphine administered by sublingual and buccal routes has a delayed onset of action compared with oral morphine (smaller peak plasma levels, lower bioavailability, and larger interpatient variability).[54] Intrathecal morphine is 100 times as potent as its oral form, and epidural morphine is 10 times as potent (0.5 mg intrathecally equals 5 mg epidurally).[54] Morphine dosing is minimally affected by hepatic failure but is greatly affected by renal failure. There is a linear relationship between creatinine clearance and renal clearance of morphine, morphine-3-glucuronide, and morphine-6-glucuronide.[55] Kidney failure impairs glucuronide excretion more than morphine excretion, increasing the duration of action of morphine-6-glucuronide and morphine-3-glucuronide, thus leading to adverse events.[56] Glucuronidation is largely unaffected by cirrhosis. Morphine doses must be carefully titrated or avoided when creatinine clearance is less than 30 mL/minute.[54] Morphine continues to be considered the standard medication for the treatment of cancer pain partly due to familiarity with the product as well as cost effectiveness. However, it may not always be the ideal product due to issues associated with its metabolism and adverse-event profile.[11] Almost all randomized controlled comparisons of potent opioids have shown equivalence (ie, noninferiority) to morphine.[6,11,57-59]

Methadone: Methadone has features that make it unique: It works at 3 levels to provide analgesia. It is a potent opioid with strong interactions with the μ-opioid receptor, and it is an N-methyl-D-aspartate (NMDA) receptor antagonist, a receptor that is activated in chronic pain states and, when blocked, can enhance analgesia and reverse opioid tolerance. Methadone also works on neurotransmitters, such as norepinephrine and serotonin, which play a role in descending pain modulation.[59,60]

Methadone is a second-line analgesic for pain that is poorly responsive to other opioids.[59] It shows promise as a first-line analgesic for cancer pain, neuropathic pain, and as a breakthrough agent. Methadone is available in oral, sublingual, and intravenous formulations. Methadone has different pharmacokinetics from other opioids. Methadone has a long half-life that varies between 60 and 120 hours.[59] High-dose intravenous methadone is associated with QT prolongation and torsades de pointes.[61] In fact, a retrospective study found

that oral methadone can cause QT prolongation in 16% of patients.[62] Dosing of methadone is complicated. Methadone shows an inverse relationship of its starting dose to the total morphine equivalent daily dose (MEDD). As the MEDD increases, the equianalgesic dose of methadone progressively decreases.

Clinical trials comparing methadone to morphine have not shown superiority of methadone; in fact, 3 studies have compared morphine and methadone as first-line therapy for cancer-related pain.[6,63,64] Ventafridda et al[63] compared methadone with morphine for moderate to severe cancer pain in 54 study patients who had previously been taking step 2 opioids. Patients received either morphine or methadone by mouth for 14 days.[63] Both therapies provided clear reductions in pain intensity, there was less stability in analgesia in the morphine arm, and study patients receiving morphine had a higher incidence of dry mouth.[63] Otherwise, no other differences in toxicities or the ability to achieve pain relief were seen.[63] Mercadante et al[64] conducted a prospective randomized study in 40 study patients with advanced cancer who required strong opioids for their pain management and receiving home hospice care. Study patients were treated with sustained-release morphine or methadone in doses titrated to pain relief and administered 2 or 3 times daily according to clinical need.[64] Results suggested that methadone more quickly achieved analgesia and methadone analgesia was more stable than that achieved with morphine.[64] Bruera et al[6] compared the effectiveness and adverse events of methadone and morphine as first-line treatment with opioids for cancer pain. In this multicenter, international study, 103 participants with pain requiring strong opioids were randomly assigned to receive either methadone or morphine for 4 weeks. Participants with 20% or more reductions in pain scores were equal in both groups. Those in both arms reported satisfaction with their therapies. The methadone arm had a higher number of dropouts and required fewer dose adjustments to achieve analgesia than those in the morphine arm.[6,11]

Hydromorphone: Hydromorphone is similar in structure to morphine and is available as parenteral and oral products. It is the best opioid for subcutaneous administration.[65] The oral formulation is available in an immediate-release formulation, and a single, daily dose, extended-release formulation has been shown to be effective in patients with cancer.[66] Administered orally, hydromorphone has a bioavailability of 50% and its plasma elimination half-life is 2.5 hours.[67] Metabolism in the liver produces hydromorphone-3-glucuronide, which has no analgesic properties but can cause neurotoxicity.[68] Hydromorphone is effective in treating pain in patients with renal impairment. Hydromorphone metabolites accumulate in patients receiving chronic infusions.[69] A double-blind, randomized comparison of sustained-release hydromorphone with sustained-release morphine showed equivalence in pain relief.[70] Systematic reviews involving 11 studies and 645 study patients show that hydromorphone equals morphine in analgesic effect.[71]

Oxycodone: Oxycodone is available as immediate-release and sustained-release formulations. (Intravenous formulations are available in Europe.) The immediate-release formulation has a half-life of approximately 2 to 4 hours and a bioavailability of 50% to 60%.[72] The primary difference between oxycodone and morphine is its bioavailability: its half-life is longer than normal in renal failure and liver failure.[45,73] Several trials comparing oxycodone with morphine show equal efficacy.[72,74] Minor differences in adverse events have been described.[74] Hallucinations and nausea are less common with oxycodone treatment.[75] However, because of its cost and lack of versatility, morphine remains the preferred analgesic.[76] Bruera et al[74] demonstrated that oxycodone is 1.5 times as potent as morphine when comparing analgesic potency.

Oxymorphone: Oxymorphone is a semisynthetic μ-opioid agonist 1.2 times as potent as morphine.[77] Until recently, oxymorphone was available as parenteral injection and in suppository form; however, immediate-release and long-acting oral formulations were developed that make oxymorphone another option for treating moderate to severe pain. Trials in malignant and nonmalignant pain confirm its potential as another step 3 option.[77] Oxymorphone is more lipid soluble than morphine. The oral bioavailability of oxymorphone is approximately 10%, which is the lowest of the oral step 3 opioids.[77] In healthy volunteers, the half-life ranges from 7.2 to 9.4 hours. The half-life of immediate-release oxymorphone is longer than that of morphine, hydromorphone, and oxycodone.[78] Immediate-release oxymorphone tablets may be given at 6-hour intervals, whereas the extended-release formula is dosed twice daily. Steady-state conditions are achieved after 3 to 4 days. Oxymorphone is subject to hepatic first-pass effects and is excreted by the kidneys. Oxymorphone accumulates in renal failure. Oxymorphone has a prolonged half-life in renal failure.[79] In the setting of hepatic insufficiency, increasing the dosing interval is recomended.[80]

Sloan et al[81] conducted a pilot study comparing extended-release oxymorphone and controlled-release oxycodone in 86 study patients with moderate to severe cancer pain. The tolerability and safety profiles (eg, nausea, drowsiness, somnolence) were similar between the 2 drugs, and no significant differences in daily pain intensity scores were seen between extended-release oxymorphone and oxycodone.[81]

Fentanyl: Fentanyl, a lipid-soluble, synthetic opioid, is available as parenteral, transdermal, and transmucosal products. Its lipophilic properties allow it to

cross both the skin and oral mucosa.[82] The transdermal formulation delivers fentanyl from the reservoir into the stratum corneum where it then slowly diffuses into the blood. Another formulation on the market is a matrix-delivery system in which fentanyl is dissolved in a polyacrylate adhesive. This formulation can be cut.[83] Both the reservoir and matrix-based patches have similar kinetics and clinical effectiveness.[83] Fentanyl is metabolized to norfentanyl under the influence of CYP3A4.[84] The concomitant use of fentanyl with potent CYP3A4 inhibitors (eg, ritonavir, ketoconazole) may affect its metabolism. Fentanyl is safe to use in patients with renal failure.[60] The elimination half-life of transdermal fentanyl is approximately 12 hours. Conversions to fentanyl are made by calculating the MEDD and the using the ratio of 2 mg:1 µg to reach the starting fentanyl dose.[82] Most experts do not recommend using transdermal fentanyl for acute titration.[85,86] Compared with morphine, constipation is less frequent with fentanyl.[87] Comparisons between morphine and transdermal fentanyl have shown equal analgesic efficacy.[88] When compared with morphine, daytime drowsiness and interference with daytime activity occur at lower rates.[88]

The oral transmucosal administration of fentanyl has been extensively explored. In 1 study, 25% of the delivered drug was transmucosally absorbed, with another 25% delivered through the gastrointestinal tract.[82] Randomized controlled trials of oral transmucosal fentanyl citrate show increased analgesic efficacy and patient preference over placebo and morphine.[89,90] Administration of fentanyl is being explored through other routes (eg, intranasal).[91] Rapid intravenous administration of fentanyl in the emergency department can result in rapid improvement in pain control.[92]

Buprenorphine: Buprenorphine is emerging as another option for cancer pain. Well-known as a strong analgesic, the development of a transdermal formulation makes it a possible option for cancer pain.[93,94] Buprenorphine is also available in intravenous and sublingual formulations, with the sublingual formulation having a bioavailability of 50% to 65% and a half-life of more than 24 hours.[95] After application of the transdermal formulation, plasma concentrations steadily increase. The larger-dose transdermal formulations achieve the minimum effective therapeutic dose sooner.

Open-label, randomized, parallel-group, multiple-dose pharmacokinetic studies show that the minimum effective concentrations are reached after 31, 14, and 13 hours, respectively, with the 35, 52.5, and 70 mg/hour patches (not available in the United States).[96] Patches reach steady state after the third consecutive application.[97] Bioavailability of the transdermal formulation is 60% compared with the intravenous route.[98] Effective plasma levels occur within 12 to 24 hours and last for 72 hours. It takes 60 hours to reach C_{max}. After patch removal, concentrations decrease to one-half in 12 hours, then more gradually decline.[96]

Metabolism by CYP3A4 and CYP2C8 converts buprenorphine to an active metabolite, norbuprenorphine, which is a weaker but full-opioid agonist. Buprenorphine and its metabolite later experience glucuronidation.[99] Liver disease affects buprenorphine metabolism. With involvement of both cytochrome oxidase system and glucuronidation in metabolism, severe liver disease potentially inhibits formation of norbuprenorphine through effects on the cytochrome oxidase system. Liver disease does not affect glucuronidation as much. Buprenorphine is safe to use in the presence of mild to moderate liver failure as well as in the setting of renal insufficiency and dialysis.[94,100]

Buprenorphine produces adverse events similar to other step 3 opioids and include constipation, urinary retention, sedation, and cognitive dysfunction. Buprenorphine causes less nausea than transdermal fentanyl.[101]

Three phase 3, placebo-controlled studies of mixed study populations with cancer evaluated transdermal buprenorphine for cancer pain.[102-104] In these studies, buprenorphine acted as an opioid agonist. There was no dose ceiling or opioid antagonist activity.

Levorphanol: Levorphanol is a potent opioid considered to be similar to methadone.[105] Morphologically similar to morphine, levorphanol has strong affinity for µ, δ, and κ opioid receptors.[106] Levorphanol is a noncompetitive NMDA receptor antagonist and blocks NMDA with the same potency as ketamine.[107] Levorphanol can be orally, intravenously, subcutaneously, and intramuscularly administered.[108] Levorphanol has poor absorption via the sublingual route compared with other opioids such as morphine sulfate (18%), buprenorphine (55%), fentanyl (51%), and methadone (34%).[109] The pharmacokinetics of levorphanol are similar to methadone with a duration of analgesia ranging from 6 to 15 hours and a half-life as long as 30 hours.[110] First-pass metabolism produces a 3-glucuronide metabolite, which may have neurotoxicity.[110] Metabolites of levorphanol are renally excreted. The high volume of distribution and increased protein binding suggest that levorphanol should not be dialyzable. In the setting of renal disease, the dosing interval should be increased. This differs from methadone. The predominant mode of metabolism is hepatic. In the setting of hepatic insufficiency, it is advisable to consider an increased dosing interval.[108] Experience and clinical trial results suggest that the type and incidence of adverse events are similar to those seen with strong opioids.[108] Levorphanol has been studied as a treatment for chronic neuropathic pain and has been shown to be effective.[111]

Interventional Pain Modalities

Clinicians consider "step 4" of the WHO pain ladder when there is an inadequate response to step 3 agents, adjuvants, or both.[112] Treatment options include use of nerve blocks, as well as spinal administration of local anesthetics, opioids, and other adjuvants. Abdominal pain may be controlled by a blockade of the celiac plexus, which, if successful, can block nociceptive input from many structures in the upper abdomen, in particular the pancreas.[113] Use of the superior hypogastric ganglion block for the treatment of malignant pelvic pain was first described by Plancarte et al.[114]

Opioids

Receptor Interactions

Opioids interact with opioid receptors to produce analgesia (as well as adverse events).[115,116] Opioids interact with receptors, leading to receptor phosphorylation by G protein-coupled receptor kinases. Arrestin then binds with the activation of distal pathways.[117] Opioids intracellularly drive receptors by endocytosis, with the receptors ultimately resurfacing.[117] Opioids differ in their G protein coupling and in their propensity to drive receptors into the cell. For example, compared with other strong opioids, morphine is inefficient in its ability to promote receptor internalization.[117] Some postulate that noninternalized receptors continue to signal and promote adaptive responses, thus causing cellular tolerance.[117]

Responsiveness

Opioid responsiveness is the "degree of analgesia achieved as the opioid dose is titrated to an endpoint, defined either by intolerable side effects or the occurrence of acceptable analgesia."[118] Pain poorly responsive to opioids exists when intolerable adverse events, inadequate analgesia, or both continue despite opioid escalation. Pharmacodynamic and nonpharmacodynamic factors affect opioid responsiveness. Identifying pain poorly responsive to opioids should lead the health care professional to consider using adjuvant analgesics or opioid switching, changing the route of administration, using NMDA antagonists, or interventional pain techniques.[113,119-121]

Routes of Administration

Opioids are available in many dosage forms, including via the oral, rectal, subcutaneous, intramuscular, intravenous, transdermal, transmucosal, and intraspinal routes of administration. Oral administration is simple, cost effective, and is the preferred route of delivery. Both immediate-release and extended-release preparations are available.

Clinicians use the subcutaneous, intravenous, rectal, transdermal, transmucosal, and intraspinal routes when patients cannot take oral medications. Intramuscular administration is contraindicated as it does not confer any pharmacokinetic advantages and is painful for patients.[122] Subcutaneous delivery is relatively easy, effective, and safe.[123] Intravenous routes are useful when pain is severe or pain levels have acutely increased. Transdermal fentanyl preparations are effective for patients unable to take oral medications and have stable pain control. Other short-acting opioids are used to control pain when transdermal fentanyl is used, because levels of fentanyl gradually increase during a 12- to 24-hour period until reaching steady state.[124] Transmucosal fentanyl is similar to intravenous administration in its rapid onset, and it can be used for acute breakthrough pain. Historically, dosing of transmucosal fentanyl was not thought to be based on dose proportionality, but this consideration has been challenged.[125] Intraspinal administration of opioids can either be epidural or intrathecal. This method is the most invasive technique and requires a specialist for initiation. This delivery confers advantages in patients with significant dose-limiting adverse events as systemic involvement is circumvented. Intraspinal delivery allows the addition of adjuvant medications to opioids that can be directly administered to the spinal cord.[126]

Dose Titration

Clinicians adjust opioid analgesics to balance adequate pain control with their respective adverse events. Dosage requirements change with cancer progression. Most patients with cancer have chronic daily pain, so analgesics should be given on a scheduled basis.[121] Breakthrough analgesics are ideally given according to the time it takes to reach C_{max}. The C_{max} depends on the route of administration. C_{max} is 1 hour for the oral route, 30 minutes for the subcutaneous route, and 6 minutes for the intravenous route.[127,128] Once C_{max} is reached, another dose should be given if pain is not adequately controlled.

Multiple approaches to opioid initiation and titration exist. The European Association for Palliative Care recommends dose titration with immediate-release oral morphine every 4 hours, with breakthrough dosing of the same dose given every hour as needed.[129] The scheduled dose should then be adjusted to account for the oral MEDD. Several studies have shown acceptable pain control and adverse-event profiles with use of 5 mg every 4 hours in study patients naive to opioids and 10 mg every 4 hours in patients previously using a step 2 drug.[129-131] After acceptable pain control occurs, patients can use extended-release preparations as this is convenient and improves compliance.[132] Breakthrough dosing is 10% to 20% of the MEDD.[133]

Opioid titration with sustained-release formulations is slower than titration with immediate-release formulations.[129] Titration with intravenous medications

is effective and tolerated.[134] In patients on established opioid regimens, dosing adjustment should be made according to the level of pain. Adult cancer pain guidelines recommend an increase of 25% to 50% in the total MEDD for moderate pain (4–6 out of 10) and 50% to 100% for severe pain (7–10 out of 10).[133]

Equianalgesic Conversions

When converting between opioids, equianalgesic guidelines should be followed, although they may be modified according to clinical judgment with regard to adequacy of a patient's current pain medication regimen.[135] Opioid rotation may be secondary to poor analgesia, excessive adverse events, convenience, or patient preference.[136] Incomplete cross tolerance is a phenomenon that has been empirically observed.[135] For various reasons, patients may develop less of a response (eg, poor analgesia, adverse events) to a particular opioid over time. Patients may not show these characteristics with a new opioid, despite similar action between opioids, and slight variations in opioid structures may account for this.[137] When calculating the dose of the new opioid, new doses should be reduced by 25% to 50% to account for non–cross tolerance.[133] This is not done for fentanyl or methadone, and equianalgesic guidelines should not to be used for these calculations.

Adverse Events

The development of adverse events varies between individuals based on age, comorbidities, stage of illness, and genetic differences.[116] Impaired renal function also increases the risk of adverse events due to accumulation of active metabolites.[116] The most common adverse events include constipation, nausea, vomiting, and altered cognition.[116] Other adverse events may include xerostomia, urinary retention, respiratory depression, myoclonus, pruritus, and hyperalgesia.[116] Most adverse events from opioid use subside within days to weeks, except for constipation for which patients do not develop tolerance and is not dose-related. For those symptoms that persist or are present during the initiation of opioid therapy, symptom management is a key element of care. Constipation is prophylactically managed. Opioids inhibit gastrointestinal peristalsis; thus, all patients should receive a stimulant laxative such as senna, which can be combined with a stool softener such as docusate sodium or polyethylene glycol. Dietary recommendations, such as increasing fiber in the diet, are unrealistic in patients with advanced disease because hydration is necessary to facilitate the action of fiber, often something difficult to achieve in ill patients.[126] Constipation is exacerbated by metabolic abnormalities, including diabetes, hypercalcemia, hypokalemia, and hypothyroidism, that should be corrected if possible.[116] Increased physical activity is often helpful if possible. Use of quaternary opioid antagonists may be needed.[116] The quaternary agents do not cross the blood–brain barrier and do not reverse the analgesic effects of opioids. Nausea frequently occurs at the start of opioid therapy but seldom persists. Ongoing nausea may occur with advanced disease or as a complication of disease treatments. Opioids can cause nausea through several mechanisms, either through direct stimulation of the chemoreceptor trigger zone, increased sensitivity of the vestibular apparatus, or delayed gastric emptying.[116] Management consists of therapies targeting these processes. Dopamine antagonists, such as prochlorperazine or haloperidol, work on the chemoreceptor trigger zone. Antihistamines or anticholinergics can be used in patients who have nausea associated with movement. Metoclopramide is both a dopamine antagonist and promotility agent commonly used for the treatment of nausea in palliative care. Ondansetron, a serotonin receptor antagonist, is also a first-line agent for the management of nausea.[116,138] If sedation and altered sensorium are present, then management should include evaluation for other sources such as dehydration, drug interactions, or disease progression. Studies have investigated use of stimulants such as methylphenidate and modafinil with varying results.[139,140]

If excessive adverse events limit pain control or impair quality of life, opioid rotation is often effective at achieving greater pain control with less adverse events.[136] In addition, this method of adverse-event management is preferable in patients for whom polypharmacy is a concern. Based on pharmacodynamic studies, dose-response relationships exist for central nervous system effects, such as sedation, myoclonus, and delirium, and may improve with dose reduction.[116]

Treating Neuropathic Pain

Although adjuvant analgesics are often used in neuropathic pain, health care professionals should consider opioids as another option for neuropathic pain. Opioids are recommended as part of neuropathic pain algorithms.[141]

Adjuvant Analgesics

Adjuvant analgesics are drugs with a primary indication other than pain that have analgesic properties.[142] The group includes drugs such as antidepressants, anticonvulsants, corticosteroids, neuroleptics, and other drugs with narrower adjuvant functions. Adjuvant analgesics are particularly useful when evidence of decreased opioid responsiveness is present.

Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors

The tricyclic antidepressants have been studied for use in neuropathic pain syndromes, although study results are conflicting about their analgesic effectiveness.[143-145]

Use in the elderly may also be problematic due to adverse events, including orthostatic hypotension and sedation.[146] Tricyclic antidepressants should also be cautiously used in patients with coronary artery disease or cardiac rhythm disorders, as well as those with a history of narrow anterior eye chambers or glaucoma. The anticholinergic properties of these drugs contribute to delirium in the elderly or anyone at risk for delirium such as patients whose cancer has metastasized to the central nervous system. These drugs should be started at the lowest dose with cautious escalation. Dose escalations are made every 3 to 4 days if analgesic response is suboptimal.

Selective serotonin reuptake inhibitors (SSRIs) have a limited role as adjuvants, although paroxetine and citalopram have been evaluated for nonmalignant neuropathic pain.[147,148] No studies have been performed on cancer pain. Some SSRIs have unique mechanisms of action that may make them useful for cancer pain; for example, venlafaxine, which inhibits the uptake of serotonin and norepinephrine (important in the regulation of descending pain pathways), is effective for painful neuropathy and neuropathic pain associated with therapy used in breast cancer.[148,149] Newer drugs, such as duloxetine, can be used to inhibit the uptake of norepinephrine, which is also effective in neuropathic pain, especially related to chemotherapy.[150] Bupropion, a noradrenergic compound, has both analgesic and activating properties and can be effective in patients with depression- and significant neuropathic pain.[151]

Corticosteroids

Corticosteroids can be used for patients with bone pain and to decrease swelling in the brain and spinal cord due to metastatic disease. Nerve root inflammation responds to corticosteroids. Corticosteroids are often considered for painful liver metastasis and obstruction of the ureter, although the evidence base for this use is not strong.[152] The most commonly used corticosteroid is dexamethasone, which has low mineralcorticoid properties. Optimal dosing for palliation may be 8 mg as this dose has no more adverse events than placebo.[153] In the case of spinal cord compression, recommendations exist for either high-dose (96 mg/day) or low-dose (16 mg/day) dexamethasone.[154] The challenge with the higher dose of steroids is the occurrence of adverse events.[155] The management of edema associated with brain metastasis can be treated with dexamethasone 4 to 6 mg every 6 hours with a taper during the last phases of palliative radiation therapy. The minimal effective dose for brain metastasis is 8 mg/day.[156] Steroids can be useful to counteract the phenomenon of radiation "flare," which can occur with radiation therapy when radiation is applied to painful bony sites.[157]

Anticonvulsant Drugs

Anticonvulsants can be used for managing neuropathic pain.[158] The most often used anticonvulsant for neuropathic pain is gabapentin. Gabapentin is effective for cancer-related neuropathic pain.[159] Gabapentin can have significant adverse events if it is started at too high a dose or titrated too fast. Dosing begins at 150 mg to 300 mg at bedtime, with escalations every 3 days if pain control is suboptimal. The maximum dose is 3600 mg/day. The chief adverse event is somnolence.[160] Gabapentin must be dose adjusted for renal insufficiency. Anoother anticonvulsant that may be useful for cancer pain is phenytoin.[161] Agents such as lamotrigine, oxcarbazepine, pregabalin, topiramate and levetiracetam have been used for nonmalignant neuropathic pain and are considerations in the refractory case, but they have not been studied in the cancer pain population. Levetircetam requires further study for cancer-related neuropathy.[162] Lamotrigine is not effective in chemotherapy-related neuropathy.[163]

Oral and Parenteral Local Anesthetics

The most common parenteral anesthetic used for symptom management is lidocaine.[164] Studies suggest its efficacy in refractory cases of neuropathic pain. One study in patients with cancer with refractory pain showed improved analgesia with a single dose of lidocaine.[165] The recommended starting dose is 1 to 5 mg/kg infused for 20 to 30 minutes. In patients who are frail, lower doses may be needed. Lidocaine should be avoided in patients with coronary artery disease. One potential benefit of lidocaine is prolonged pain relief that occurs following its infusion. Lidocaine can be given subcutaneously in the home or hospice setting.[166] Mexililetine, an oral cogener of lidocaine, has been used after lidocaine infusions.[167] Clinical trial results suggest that mexiletine has a distinct adverse-event profile and may not be tolerated by all patients.[168]

Transdermal Analgesics

Transdermal lidocaine (5% patch) provides another route for local anesthetics. It can be used to treat postherpetic neuralgia, but use in other settings requires further study to clarify its role in cancer-related neuropathy. The patch has minimal systemic absorption, and it can be applied 12 hours per day; evidence suggests that increasing the number of patches and extended dosing periods may be safe.[169,170] It may take several weeks to observe a maximal effect. The most frequently reported adverse events are mild to moderate skin redness, rash, and irritation at the patch application site.[105]

Ketamine

Chronic pain is associated with central nervous system

changes, including activation of the NMDA receptor, and can lead to opioid tolerance and the development of opioid resistance.[171] Pharmacological blockade of the NMDA receptor offers a therapeutic approach in the setting of opioid resistance. Ketamine is a useful NMDA antagonist to consider in the management of cancer pain and its use often leads to reduced opioid requirements.[172] Given at subanesthetic doses (< 1 mg/kg), ketamine is an effective analgesic in cancer-related neuropathic pain.[172] Multiple routes exist for administration and include the oral, intravenous, subcutaneous, and topical routes. Ketamine is metabolized via CYP3A4. No significant drug interactions have been reported.[173] Ketamine is recommended by the WHO for the management of refractory pain.[174] The oral bioavailability is 17%, and onset of action of ketamine is 15 to 20 minutes. The half-life of ketamine is 2.5 to 3 hours. Ketamine has protein binding of 20% to 30%.[175] Pharmacologically, no major differences exist in the characteristics between the isomers.[176] Its intravenous onset of action is within seconds and, subcutaneously, the onset of action is 15 to 20 minutes. The half-life is 2 to 3 hours for both routes.[173] The results of 1 trial of subcutaneous ketamine as an add-on option to opioids showed no efficacy in cancer-related nociceptive pain.[177]

Cannabinoids

Formulations of cannabinoids, the cannabinoid extracts, have been studied for cancer-related pain.[178] Johnson et al[179] evaluated tetrahydrocannabinol (THC)/cannabidiol (CBD) in a 2-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial of 177 study patients with cancer whose pain was inadequately controlled despite them being on opioid therapy. The cannabinoid extract contains THC 2.7 mg and CBD 2.5 mg per dose.[179] It is formulated in ethanol/propylene glycol with peppermint flavoring and is designed as a pump spray for self-administration and titration via the oromucosal route.[180] The study patients received THC/CBD, THC extract, or placebo and continued their previous analgesics.[179] The THC/CBD extract arm achieved a statistically significant improvement in pain when compared with placebo ($P < .024$) as measured on a numerical rating scale, a primary end point of the study.[179] The THC extract showed no significant changes from baseline compared with placebo.[179]

Neuroleptics

Second-generation (atypical) agents, such as olanzapine, have been shown to have antinociceptive activity in animal models.[181] Clinical evaluation of its analgesic effects has been limited. Khojainova et al[182] evaluated the analgesic activity of olanzapine in 8 study patients with severe cancer pain who did not respond to increased opioid dosing and who also received olanzapine for the treatment of associated anxiety and mild cognitive impairment. Participants did not meet diagnostic criteria for delirium and the cognitive impairment was classified as not otherwise specified.[182] Study patients received 2.5 to 7.5 mg of olanzapine daily, and their pain intensity, sedation, and opioid consumption measurements were made before administering olanzapine and 2 days after olanzapine was given.[182] Cognitive function was assessed daily.[182] All participants experienced reduced pain scores, and the average daily opioid use significantly decreased in all study patients.[182] Cognitive impairment and anxiety resolved within 24 hours of initiating olanzapine.[182] The authors suggested that olanzapine may have an intrinsic analgesic action, but they also suggested that pain scores and opioid requirements may have resulted from improvement in cognitive function and the known anxiolytic effect of olanzapine.[182]

Agents Specifically Used for Bone Pain

Bone pain is a common problem in the palliative care setting. Radiation therapy can be effective with localized pain. Systemic therapies with NSAIDs, corticosteroids, bisphosphonates, and radiopharmaceuticals can be useful for patients with multifocal lesions.

Bisphosphonates: Bisphosphonates are analogues of inorganic pyrophosphate that inhibit osteoclast activity and can be useful in many types of cancer in which bone resorption leads to complications. Bisphosphonates bind to calcium on bone, become ingested by osteoclasts, and then subsequently kill osteoclasts, thus preventing bone resoprtion.[183] The end result of decreased osteoclast activity is increased bone stability and reduced pathological fractures. The most potent bisphosphonate is zoledronic acid, which has been shown to reduce pain and the occurrence of skeletal-related events in breast and prostate cancers, multiple myeloma, and a variety of solid tumors, including lung cancer.[184-187] Denosumab is useful when renal insufficiency precludes the use of bisphosphonates.[188]

Radiopharmaceuticals: Radionuclides are agents absorbed in areas of metastatic cancer activity. Strontium-89 and samarium-153 are effective for diffuse bony metastatic disease, such as in the case of prostate cancer.[189]

Muscle Relaxants

Pain originating from connective tissue injury is common in patients with cancer. However, use of muscle relaxants as adjuvant agents has not been evaluated in patients with cancer.

Use for Malignant Bowel Obstruction

Pain, along with nausea and vomiting, is a common symptom associated with malignant bowel obstruction. Nonsurgical management of malignant bowel ob-

struction focuses on the management of pain and other obstructive symptoms, such as distension, nausea, and vomiting. The use of parenteral opioids, antiemetics, and antisecretory agents, such as octreotide, are common methods of pharmacological symptom control. Octreotide has anecdotally been shown to have analgesic properties.[190]

Combination Use

The treatment of neuropathic pain frequently requires several adjuvants. For example, it is not unusual for a patient with severe, cancer-related neuropathic pain to require an opioid or several additional adjuvants. When this occurs, the clinician should monitor the patient for potential drug interactions.[191]

Conclusions

Successful cancer pain management requires close attention to detail, particularly when introducing the drug; in addition, health care professionals must be watchful for the presence of adverse events. Assessing opioid responsiveness will help determine the role of adjuvant analgesic use. Adherence to the World Health Organization pain ladder and understanding proper use of interventional pain techniques complements the pharmacological management of cancer-related pain. New drugs are being introduced into the market and their roles in cancer-related pain control are being evaluated.

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