The Clinical Problem of Persistent Cancer Pain

In 2008, in the United States, more than 1.4 million individuals were diagnosed with cancer and more than 550,000 patients died from cancer.1 Pain is the first symptom of cancer in 20–50% of all cancer patients, and 75–90% of advanced or terminal cancer patients must cope with chronic pain syndromes related to chemotherapy, failed treatment, and/or tumor progression.2,3 Cancer patients can experience pain with varying degrees of intensity and frequency at multiple anatomical locations. Cancer pain is multifaceted, with clinical descriptors including acute, chronic, nociceptive (somatic), visceral, and neuropathic.4 It consists of complex mixtures of nociceptive and neuropathic types of pain that are likely to be driven through different mechanisms.6

The most commonly diagnosed cancers—lung, prostate, and breast cancers2—often metastasize to bone, and in advanced states, they are associated with bone remodeling and eventual bone fracture that contributes to incapacitating pain and limited or total loss of daily activity.17 Excessive bone destruction is correlated with ongoing pain in the area of the tumor and is characterized as dull in character, constant in presentation, and generally showing a time-dependent increase in intensity.17 As bone destruction progresses, breakthrough pain—an intermittent episode of extreme pain—may occur spontaneously or, more commonly, by weight bearing or movement of the affected bone.19,23 Breakthrough pain is very difficult to control, and it represents one of the most serious and highly debilitating cancer-related events.19,23 Pain limits daily activity in 41% of patients reporting mild to moderate pain and in 94% of patients reporting moderate to severe pain, leading to greatly diminished quality of life in these patients.7 Advances in cancer therapies have drastically improved survival times of patients with prostate cancer, including those with bone metastases. The lifespan of patients diagnosed with metastatic prostate cancer has increased to an average of 55 months (4.5 years).10 However, these patients still experience pain from the bone metastases that can be severe and unpredictable and can greatly limit daily activities.6,10,18 This situation highlights the need for effective treatment that can be given over long periods of time without the side effects associated with current treatments.

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Successful opioid treatment of any duration depends on achieving a favorable balance between analgesia and adverse effects. Importantly, there is great interindividual variability in opioid effects; even with a similar type or severity of pain, the effective opioid dose as well as the relative toxicity ratios may vary greatly across patients. Critical for effective management of cancer pain is appropriate knowledge of analgesic (primarily opioid) pharmacology with respect to dosing, timing, alternative routes of administration (such as rectal, subcutaneous, epidural, and intrathecal), and converting from intravenous to oral therapies. The American Pain Society proposes several important considerations for appropriate pain management, including: (1) the source of the patient’s pain; (2) the patient’s age, general health, and comorbidities; (3) the potential for medication-related adverse effects; (4) potential drug interactions; (5) comorbidities that may be relieved by nonanalgesic effects of the medications (e.g., sleep disturbances, depression, or anxiety); (6) comorbidities that may be exacerbated by the nonanalgesic effects of the medications (e.g., hypertension, ulceration, renal impairment, or cognitive impairment); (7) costs associated with therapy; (8) potential risks for medication abuse; and (9) risks of overdose. It is argued that although no single opioid is optimal for all patients, an optimal opioid can generally be found for each patient.

Long-Term Opioid Administration

Opioids are recommended for treatment of moderate to severe cancer pain, with morphine being used most frequently. Although opioids have good efficacy with acute treatment, it has been argued that analgesic efficacy for chronic pain conditions, although initially good, is not always sustained during continuous and long-term treatment (months to years). Importantly, the chronic nature of cancer pain often requires prolonged opioid administration through controlled-release tablets, repeated bolus injections, or transdermal patches. Another potential problem with the use of opioids in treating cancer pain is decreased analgesic efficacy, which can potentially arise from multiple mechanisms, including the development of receptor desensitization, opioid-induced hyperalgesia, subtle and intermittent withdrawal, and psychological factors. In addition, increased doses of opioids may be required because of advancement of the disease, resulting in greater pain. Clinical studies have reported that opioids administered by different routes of administration (transdermal, oral, intrathecal, and intravenous) can unexpectedly produce hyperalgesia and allodynia, particularly during rapid dose escalation.

Preclinical studies have demonstrated that opioids can paradoxically enhance pain. Structurally distinct opioids, including nonpeptidic agonists (e.g., morphine, oxymorphone, and fentanyl) as well as peptides acting at mu-opioid receptors (e.g., DAMGO), have been shown to produce hyperalgesia in preclinical models. Recent research has demonstrated that sustained morphine administration for several days induces neuroplastic adaptations in rodents that paradoxically enhance pain. In rodents, sustained morphine administration has been demonstrated to: (1) upregulate excitatory neurotransmitters, such as substance P and calcitonin gene-related peptide (CGRP) in primary afferent fibers and the spinal cord; (2) increase evoked release of excitatory neurotransmitters within the spinal cord; (3) upregulate spinal dynorphin levels, promoting enhanced input from afferent nociceptors; and (4) activate descending pain facilitation from the rostral ventromedial medulla.

The above studies exploring preclinical mechanisms of opioid-induced hyperalgesia have focused on opioid-induced pronociceptive changes in uninjured animals. However, the effects of prolonged, sustained opioid administration in the presence of a persistent pain state, such as cancer-induced bone pain, have only recently begun to be examined. Single bolus injections of morphine were shown to effectively block behavioral measures of cancer-induced bone pain in mice. Similar efficacy was observed with daily bolus morphine injections, with no tolerance to morphine’s antinociceptive effects. In contrast, sustained delivery of morphine through osmotic minipumps, designed to maintain stable blood plasma levels for several days, enhanced cancer-induced pain in a murine model of sarcoma-induced bone pain. Moreover, sustained morphine infusion increased the expression of excitatory neurotransmitters (substance P and CGRP) in primary afferent fibers, suggesting the potential for enhanced nociceptive signaling in the...
morphine-treated animals. In addition, sustained morphine administration surprisingly enhanced sarcoma-induced bone loss and fracture, as well as expression of activating transcription factor 3 (ATF3, a marker of neuronal damage) in cell bodies of primary afferent fibers. These data indicate that sustained morphine infusion may result in "add-on" mechanisms of pain beyond those engaged by the sarcoma alone. In addition, both the enhanced cancer-induced bone pain and bone loss were dose dependent and were reversed by coadministration of naloxone, suggesting that these effects are dependent on the mu-opioid receptor.

Sustained morphine exposure has also been suggested to alter cancer growth in vitro and in vivo. However, results are conflicting as to whether morphine enhances or inhibits tumor cell proliferation. Several studies have shown that morphine inhibits tumor cell proliferation. However, others have found that morphine promotes tumor cell proliferation as well as metastasis and mortality. The discrepancies between these results may be due to a number of factors, including the use of different cell lines, different doses of morphine, and different durations of morphine exposure across experiments.

While it is unknown whether these effects will generalize to other cancers or opioids, it is clear that there is a need for increased understanding of the neurobiological consequences of prolonged opioid exposure in chronic pain conditions. Such an understanding may allow improvements in the use of opioids and enhance the effective management of patients with chronic cancer pain. The debilitating side effects of opioids and chronic opioid treatment required in most patients with bone metastases, together with the increase in survival time of prostate cancer patients with bone metastases, call for better pain management options.

**Opioid Switching and Rotation**

Responses to opioids vary significantly among patients and even in an individual patient at different stages of treatment, leading to difficulties in finding long-term analgesia with minimum side effects. Changes in opioids are likely (1) when the selected opioid has failed to provide adequate analgesia at doses below those that produce adverse side effects (opioid switching); or (2) following a period of chronic treatment with the selected opioid when it appears that the analgesic benefits are diminishing (opioid rotation). For both opioid switching and opioid rotation, sequential trials may be required to find the optimal opioid for effective pain management. No single mechanism adequately explains the intraindividual or interindividual variability observed with opioids. Available evidence suggests that a constellation of neurobiological, demographic, medical, and patient-specific factors all contribute to determining a patient's response to a particular opioid. Moreover, several factors may contribute to the diminished analgesic efficacy of opioids given in chronic pain conditions, including pharmacological tolerance, possible development of opioid-induced hyperalgesia, and progression of the disease. The recommended practice for opioid switching and rotation is to use an "equianalgesic table" to estimate the dosing equivalence for the new opioid relative to the previous opioid. Given that the potency and bioavailability of opioids vary dramatically and are dependent on route of administration, the conversion ratios must be carefully considered during opioid switching or rotation.

Effective pain management with opioids is dependent on understanding of opioid pharmacology, including different formulations, the impact of route of administration, and the potential for interactions with concurrent medications. These concepts are important for selection of the initial opioid, as well as for opioid switching and rotation, to maintain effective pain management.

**Potential Benefits of Coanalgesics**

Coanalgesics are drugs administered in conjunction with NSAIDS and opioids that may enhance the analgesic activity of the NSAIDs or opioids, have independent analgesic activity in certain pain states, such as neuropathic pain, or may counteract some of the adverse side effects associated with NSAIDS or opioids. Several preclinical studies indicate that combination therapies may prove beneficial in improving the analgesic efficacy of opioids as well as diminishing adverse side effects and disease progression. Coadministration of selective cyclooxygenase-2 (COX-2) inhibitors with morphine has been demonstrated to diminish tumor growth in vitro as well as in vivo. Moreover, COX-2 inhibitors were found to block morphine-induced enhanced tumor growth, angiogenesis, and metastases in preclinical studies. Other studies have shown that COX-2 inhibitors block development of opioid-induced hyperalgesia. Moreover, coadministration of COX inhibitors with morphine provided synergistic antiallodynic effects in a rat model of neuropathic pain.

As neuropathic pain is a recognized component of cancer-induced bone pain that is resistant to opioids, coadministration of COX inhibitors may prove a useful strategy for effective pain management that limits the adverse side effects of opioids.

**The use of coanalgesics that target neuropathic pain may be particularly important because such pain is resistant to opioids**

Clinically, coanalgesics consist of a diverse range of drug classes, including anticonvulsants (e.g., gabapentin,
pregabalin), antidepressants (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors), N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine), corticosteroids, skeletal muscle relaxants, local anesthetics, and alpha-2 adrenergic agonists (e.g., clonidine). Coanalgesics are frequently administered with opioids in efforts to diminish the dose required for effective pain management and reduce adverse effects. The American Pain Society states that the proper use of coanalgesics is critical to successful pain management, and that it depends on evaluation of risks (adverse effects and drug interactions) versus benefits (improved pain relief, sleep, and quality of life). Moreover, the use of coanalgesics that target neuropathic pain may be particularly important because such pain is resistant to opioids, and it occurs in 40–50% of patients with cancer pain.

**Combination therapies may prove beneficial in improving the analgesic efficacy of opioids as well as diminishing adverse side effects and disease progression**

Overall, multimodal therapy for pain management is recommended for two main reasons: (1) coadministration of adjuvants that block adverse effects such as nausea, constipation, and opioid-induced hyperalgesia will improve pain management and decrease adverse side effects, thus improving the patient’s quality of life; and (2) combination pharmacotherapy is often better than opioids alone due to multiple mechanisms of action, particularly given the multifaceted nature of cancer pain regarding neuropathic, inflammatory, and mechanical qualities. In combination with traditional analgesics, patients also receive therapies designed to diminish tumor burden, such as radiation therapy, or bone remodeling, such as bisphosphonates. As stated above, issues of potential interactions between analgesics and nonanalgesic medications must be taken into account to optimize disease treatment and pain management for these patients.

**Conclusion**

Opioids are currently the most effective and most appropriate treatment for moderate to severe cancer-induced pain, and they remain the best front-line treatment for cancer pain patients. However, care must be taken to closely monitor patients for potential adverse effects of opioids. Alternatives such as co-therapies and opioid rotation must be considered and appropriately used to minimize opioid-induced adverse side effects and to maintain the analgesic efficacy of opioid treatment. Focusing on the impact of the disease as well as that of the therapeutic strategies becomes particularly important as chemotherapeutic treatments advance and extend the lifespan of patients. Important advances are increasing the therapeutic options for patients with metastatic bone pain. New drugs, such as anti-nerve growth factor antibodies, are currently undergoing clinical trials for cancer-induced bone pain. In addition, preclinical studies indicate that agents such as COX inhibitors, neurokinin-1 antagonists, and serotonin (5-HT3) antagonists may be considered as adjuncts in ameliorating opioid side effects such as opioid-induced induced hyperalgesia and analgesic tolerance, thus increasing the therapeutic potential of the opioids in these patients. Further study on the effects of prolonged opioid exposure on pain processing and on disease progression will provide important insights as to potential improvements in long-term pain management in cancer patients with chronic tumor-induced pain.
References


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