Pain Management in Patients With Advanced Prostate Cancer

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Prostate cancer is the most commonly diagnosed cancer among American men. The majority of patients with advanced disease have metastatic bone lesions, which are frequently very painful. These lesions tend to respond well to treatment with both nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, although careful dose titration and individualized treatment plans may be needed to achieve maximal analgesia. Opioid side effects are often transient or well controlled with additional medication. Patients with intolerable side effects may experience fewer adverse reactions with a different opioid. Palliative radiation provides pain relief in up to 80% of prostate cancer patients with single or at most a few sites of localized bone pain. Bisphosphonates, powerful inhibitors of osteoclast-mediated bone resorption, are promising new agents for the treatment of painful bone lesions in prostate cancer patients. Radioisotopes, which deliver high-dose radiation to bone lesions without significantly affecting normal bone, are highly effective in providing some degree of pain relief in up to 80% of patients with diffuse, painful bone metastases. Also, chemotherapy shows promise in alleviating pain and possibly extending survival in patients with advanced prostate cancer.[ONCOLOGY 13(11):1537-1549, 1999]

ABSTRACT: Prostate cancer is the most commonly diagnosed cancer among American men. The majority of patients with advanced disease have metastatic bone lesions, which are frequently very painful. These lesions tend to respond well to treatment with both nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, although careful dose titration and individualized treatment plans may be needed to achieve maximal analgesia. Opioid side effects are often transient or well controlled with additional medication. Patients with intolerable side effects may experience fewer adverse reactions with a different opioid. Palliative radiation provides pain relief in up to 80% of prostate cancer patients with single or at most a few sites of localized bone pain. Bisphosphonates, powerful inhibitors of osteoclast-mediated bone resorption, are promising new agents for the treatment of painful bone lesions in prostate cancer patients. Radioisotopes, which deliver high-dose radiation to bone lesions without significantly affecting normal bone, are highly effective in providing some degree of pain relief in up to 80% of patients with diffuse, painful bone metastases. Also, chemotherapy shows promise in alleviating pain and possibly extending survival in patients with advanced prostate cancer.[ONCOLOGY 13(11):1537-1549, 1999]

Introduction

Prostate cancer is the most commonly diagnosed cancer among American men and the second leading cause of cancer death. An estimated 179,300 men will be diagnosed with this cancer in 1999 and 37,000 men will die from complications of prostate cancer.[1] Approximately 70% to 85% of patients with advanced prostate cancer have associated clinically apparent bone metastases, while another 20% to 25% have metastatic liver lesions. In addition to pelvic pain associated with primary tumor extension, these metastatic lesions cause pain that ranges from mild to very severe and may require extensive, highly individualized pain management. Pain is perhaps the one aspect of cancer that patients fear most, and effective pain control is a critical issue for patients and often a challenge for clinicians.

Numerous studies have shown that pain has a significant impact on multiple dimensions of quality of life. Patients with poorly controlled pain experience significant physical effects, such as decreased strength, limited mobility, and difficulty sleeping. In terms of psychological effects, patients with pain have increases in fear, anxiety, and depression and a decrease in their overall enjoyment of life. Socially, pain has an effect on the patient’s ability to form and maintain relationships with others and also places an increased burden on caregivers.[2] Pain needs to be continually reassessed in the prostate cancer patient since disease progression,
response to treatment, and response to pain control maneuvers all influence treatment strategies. The clinician needs to educate both patients and their families and caregivers about pain, its causes and treatments, and their active participation in pain management. Education should address pain assessment, dose titration, side effect management, and any fears and misconceptions regarding addiction and tolerance.

**Pain Syndromes in Prostate Cancer Bone Pain**

The majority of men with advanced prostate cancer have sclerotic bone metastases and associated bone pain. Prostate cancer is the most common source of osteoblastic metastases, and these lesions are most common in the skeleton where red bone marrow is located.[3,4] Although bone metastases from prostate cancer are primarily osteoblastic, there is increasing evidence that osteolysis also plays a key role in these sclerotic lesions and may be crucial to invasion from marrow into bone. Tumors may secrete proteases that cause bone cell lysis, and yet osteoclastic activity is required to break down the mineralized bone matrix; also, tumor cells secrete a number of factors that enhance osteoclastic activity. Tumor growth in bone may produce pain via multiple mechanisms. As the tumor expands outward from the marrow space, it may cause increased interosseal pressure, particularly if the growth is rapid. This may activate mechanoreceptive nociceptors in bone and stretch the highly innervated periosteum. Edema and inflammation may also contribute to pain, via both increased pressure and secreted mediators, which, in turn, activate pain receptors.

Extensive bone disease can also lead to fractures, and there is increasing evidence that tumors may synthesize prostaglandins, bradykinins, and other substances that both sensitize nociceptors and stimulate osteoclasts.[5] Adjacent nerves, vascular structures, and soft tissue may also be compressed by expanding bone tumors.

Chronic pain due to metastatic bone lesions generally develops gradually, is often described by patients as dull and aching, and tends to be well localized. The most common sites of bone metastases from prostate cancer are the pelvis, vertebrae, ribs, femora, and skull. Unlike arthritic pain, which tends to decrease during the course of the day, cancer-related bone pain tends to increase as the day goes on and is often most intense at night.

A significant number of patients have transient and often traveling bone pain, however, which at is not necessarily related to activity. Unlike visceral or neuropathic pain, bone pain generally responds well to pharmacologic maneuvers, although inconsistent pain (ie, sporadic and/or traveling pain) is more challenging to treat effectively.

**Neuropathic Pain**

Neurologic dysfunction often is also associated with metastatic bone disease, particularly when vertebral metastases encroach on the spinal cord or spinal nerves, or when metastatic lesions in the skull impinge on cranial nerves. Neuropathic pain is generally described as burning or shooting and may be accompanied by a sensation of numbness. Neurologic involvement may present as lower extremity pain, weakness, or paresthesias in a radicular pattern; less commonly, the upper extremities may be involved.

Patients may also present with cranial nerve palsies from metastatic disease in the skull. Clival metastases, for example, may compress the hypoglossal nerve, producing unilateral tongue weakness and protrusion. Disease in the middle cranial fossa may affect the facial nerve and cause ipsilateral weakness in the upper and lower face or numbness, particularly in the lower lip and jaw area.[5] Unilateral deafness, diplopia, and other visual disturbances may also occur as the result of cranial nerve damage from bony tumors.

Since small metastatic skull lesions may not be visible on plain film or bone scans, computed tomographic (CT) scans with bone window and “thin cuts” (5-mm sections) should be ordered to evaluate cranial neuropathies. Magnetic resonance imaging (MRI) may be necessary when CT scans fail to demonstrate an etiology for these conditions.

Neuropathic pain may also be caused by tumor growth in pelvic soft tissues near the prostate gland, particularly the psoas muscle, which contains the lumbosacral plexus. Compression of this nerve plexus can manifest as lower back pain radiating to the anterior thigh or into the posterolateral leg and buttock; the pain may be unilateral or bilateral depending on the location of the compression tumor.

Neuropathic pain often responds poorly to opioids but may be successfully treated with antidepressants or anticonvulsants. (See “Pharmacologic Management” below for a more extensive
Other Pain Syndromes

Enlargement and inflammation of the primary prostatic tumor may cause urethral, rectal, suprapubic, and penile pain. Less commonly, prostate cancer patients may have metastatic involvement of abdominal organs or extensive abdominal lymphadenopathy. Both can produce vague, colicky, poorly localized visceral pain, which may be referred to cutaneous areas and may also be accompanied by low-grade nausea. Metastatic liver disease may cause right upper quadrant pain that can radiate to the right shoulder. Abdominal pain in prostate cancer patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) may also be due to gastric irritation, ulceration, or severe constipation. Abdominal and pelvic pain from metastatic disease is often refractory to conventional opioid therapy but sometimes may be treated effectively with localized radiation therapy.

Pain Assessment

Careful assessment of pain in the prostate cancer patient is critical to an effective treatment plan. The primary source of information should be patient self-report obtained via a standardized reporting tool.[6] The individual perception of pain involves a complex interaction of physical, psychological, and emotional processes, and pain intensity often is not proportional to the type or extent of disease.

It is important for the clinician to address the issue of pain at every visit since patients may be reluctant to initiate such conversations on their own. A belief in stoicism, a desire to be seen as a “good” patient, denial, or the fear that pain is an ominous symptom of disease progression are all possible reasons for a patient’s reluctance to discuss pain issues with his clinician. Input from family members and caregivers should also be taken into consideration whenever possible since their relationships and daily interactions with patients may provide a valuable source of information.

Pain History

The initial assessment of pain should include a detailed history, including the location, intensity, frequency, temporal pattern, and specific characteristics of the pain. Knowledge of factors that aggravate and alleviate the pain is also critical to an effective treatment plan. The patient should be asked to grade the intensity of his pain at the time of evaluation, as well as at the times when it was least and most severe during the week prior to the examination. Three commonly used assessment scales are the Simple Descriptive Pain Intensity Scale, the 0-10 Numeric Pain Intensity Scale, and the Visual Analog Scale. Pain intensity usually can be reliably measured using a numerical rating scale, where 1 to 4 corresponds to mild pain; 5 to 6, to moderate pain; and 7 to 10, to severe pain.

A thorough assessment of pain must also include psychosocial issues, such as the patient’s attitude toward his diagnosis and treatment, his mechanisms for coping with pain and stress, his psychological responses to pain (such as anxiety and depression), and his attitude regarding controlled substances. These factors often play a role in both the patient’s experience of pain and his response to treatment. In addition, information regarding the patient’s support system and insurance plans often is crucial to the success of treatment.

Diagnostic Studies

Diagnostic evaluations may help determine the etiology of pain, as well as the extent of disease, and are useful to obtain at baseline, when pain progresses, and during treatment to monitor response. Radionuclide scintigraphy provides the most sensitive method for detecting early bone metastases and is a useful, accurate tool for documenting disease progression. Bone scans may detect lesions as small as 2 mm, but, due to low specificity, scintigraphic findings may require radiographic confirmation. The false-negative rate for bone scanning is approximately 8%, and the rate of false-positives may be as high as 40% to 50% when only a few lesions are visible.[6] Radiography is specific but insensitive; at least 50% of trabecular bone structure must be destroyed before bone metastases are detectable on plain films. Computed tomography provides good definition of both soft-tissue and bone disease and may be helpful in visualizing questionable areas on a bone scan. The clinician should keep in mind that patients may need analgesia in order to endure these intense side effects of pain management.
potentially uncomfortable evaluations.

**Evaluating Acute Pain**

Acute pain in the prostate cancer patient warrants immediate evaluation, as it may be due to fracture or impending spinal cord compression. Pathologic fractures are not as common in patients with prostate cancer as in those with other cancers that metastasize to bone, and generally develop in the vertebrae and the femora.

**Spinal cord compression** occurs as a result of extension of vertebral metastases into the epidural space. It occurs in 10% to 15% of prostate cancer patients and is one of the most severe potential sequelae of bone involvement.

Pain is the presenting symptom in over 90% of patients with cord compression and may manifest as either acute severe back pain, band-like chest or abdominal pain, or radicular pain. The pain is generally severe and unrelenting, and may increase when the patient is in a supine position. Patients with spinal cord compression generally complain of midline pain but may experience unilateral pain in the upper and/or lower extremities. Motor, sensory, and autonomic (bowel and bladder) dysfunction generally occur later.

If left untreated, the original pain will slowly increase and neurologic symptoms will develop. The mean duration from the onset of pain to the onset of neurologic deficit is 7 weeks, but this is highly variable.[7] Failure to promptly diagnose and treat spinal cord compression may result in permanent neurologic damage and paralysis. The severity of weakness at the time of presentation is an important prognostic factor. Approximately 90% of patients who are ambulatory at diagnosis will remain so after therapy, whereas only 13% of patients who present with paraplegia will regain function, particularly if symptoms have been present for over 24 hours.[8]

Patients with spinal suspected cord compression should be started immediately on dexamethasone (20-mg bolus immediately, followed by 4 mg every 6 hours until cord compression is ruled out), and scheduled for an urgent MRI of the spine. Since approximately 17% to 30% of prostate cancer patients who develop spinal cord compression have multiple sites of compression, the MRI should cover all known areas of the spine affected with metastatic disease.[9]

Localized radiation therapy is the treatment of choice in most patients with epidural compression; the most common regimen is 30 Gy in 10 fractions. More aggressive treatment in an otherwise healthy patient would consist of either laminectomy followed by radiation or anterior surgical decompression. With radiation alone, the response rate is approximately 80%; improvement of presenting symptoms occurs in 49% and stabilization, in an additional 31%. [8]

**Pharmacologic Management**

Pharmacologic management of cancer pain should always be individualized, based on a careful consideration of the patient’s pain pattern, as well as on psychosocial and economic factors. The treatment plan should start with the simplest dose schedules and the least invasive therapies.[10] The three-step analgesic ladder of the World Health Organization (WHO) is based on gradations of mild, moderate, and severe pain.[11] Patients with mild to moderate pain should be started initially on a nonopioid analgesic, such as acetaminophen, aspirin, or other NSAIDs. When pain persists despite maximum doses of these drugs, a weak opioid, such as codeine or hydrocodone, should be added (rather than substituted). Opioids at this step-two level are most often provided in fixed combinations with NSAIDs.

Patients who have moderate to severe pain despite the use of step-two opioids should be switched to step-three medications, which consist of opioids and NSAIDs administered separately. This allows for titration of the narcotic to maximally effective levels without exceeding the maximally recommended doses of acetaminophen, aspirin, and other NSAIDs, which can limit the use of step-two medications.

**NSAIDs**

Nonsteroidal anti-inflammatory drugs inhibit the cyclooxygenase pathway, thus blocking the production of prostaglandins and leukotrienes, which are important mediators of inflammation and may sensitize nerves to painful stimuli. The anti-inflammatory effect of these drugs may play a key role in alleviating pain from bone metastases. All NSAIDs have a ceiling effect on their analgesic potential, however, and severe renal and hepatic toxicity may result if patients exceed the recommended maximum doses of these agents.

Since NSAIDs do not activate opioid receptors, they can be used with opioids to provide more
analgesia than can be achieved with either drug class alone. Unless contraindications exist, prostate cancer patients with metastatic bone pain should be receiving regular doses of an NSAID with or without an opioid analgesic.

A number of both over-the-counter and prescription NSAIDs are available, with wide variations in cost and dosing schedules (Table 1). No single drug in this class has been shown to be superior to any other for relieving pain due to advanced prostate cancer.[12] Finding an effective NSAID medication and dose may take several manipulations. Once a particular drug is chosen, the dose should be increased until the patient experiences pain relief or reaches the maximal dose. If adequate analgesia is not achieved with the maximal dose, the patient should be switched to another NSAID. Ibuprofen is an economical, readily available medication that is often very effective in prostate cancer patients when used alone or in combination with other agents. Acetaminophen is often less effective in advanced prostate cancer patients since it has less anti-inflammatory activity than other nonsteroidal drugs. It does have an analgesic effect and does not affect platelet function, however, and therefore may be useful for select groups of patients. Doses of acetaminophen should not exceed 4 to 6 g/d to prevent liver toxicity.

Side Effects—Nonsteroidal anti-inflammatory drugs may produce a number of potentially serious side effects. Gastrointestinal (GI) irritation is the most commonly reported complication of NSAID therapy and encompasses a spectrum of symptoms, including gastritis, heartburn, nausea, vomiting, anorexia, diarrhea, constipation, bloating, flatulence, and abdominal pain or cramping. More serious side effects include the potential for GI bleeding, ulceration, and perforation.

Because of these complications, patients should be routinely asked about GI symptoms and advised to immediately report melena or blood in their stool. Clinicians may also need to prescribe an histamine-2 antagonist, sucralfate (Carafate), or a protective agent to ameliorate or prevent GI symptoms.[13] Misoprostol (Cytotec), 200 mg twice daily, has been shown in one study to be more effective than ranitidine, 150 mg twice daily, in preventing asymptomatic gastric ulcers in patients receiving NSAID therapy.[14]

Nonsteroidal drugs may also cause renal and hepatic dysfunction. This may develop during acute therapy but is more often associated with long-term use.[15] The risk of renal toxicity, in particular, increases with age, preexisting renal or hepatic dysfunction, congestive heart failure, hypovolemia, and concomitant diuretic use.

Nonsteroidal anti-inflammatory drugs also have an effect on platelet function that may, in certain cases, limit their use. Most NSAIDs cause a reversible inhibition of platelet aggregation, which is maintained as long as the drug is in the systemic circulation. Aspirin irreversibly inhibits platelet aggregation and may prolong bleeding time for several days after administration; this makes it a poor choice for patients with advanced disease and myelosuppression due to either extensive bony metastasis or chemotherapy. Nonacetylated salicylates, such as sodium salicylate and choline magnesium trisalicylate, have minimal effects on platelet function and may be acceptable alternatives for thrombocytopenic patients.

Prothrombin time or partial thromboplastin time should be monitored carefully in patients who are taking both NSAIDs and warfarin or other anticoagulants.

Cyclooxygenase-2 (COX-2) inhibitors, such as the recently approved agent celecoxib (Celebrex), have no effect on bleeding time and can be used safely in patients receiving warfarin. Since these agents are less likely to cause GI irritation, they may be useful as step-one medications for patients with advanced prostate cancer.

Potential Effects on Disease Progression—Recent data also have suggested that the regular use of NSAIDs may actually slow down the progression of prostate cancer. One study of 317 newly diagnosed prostate cancer patients and 480 age-matched controls showed a trend toward a reduced risk of advanced prostate cancer associated with regular use of NSAIDs and aspirin.[16] Studies have reported increased levels of prostaglandin E2 in human prostate cancer tissue,[17] and in vitro data suggest that NSAIDs may inhibit cell proliferation of human prostate cancer cell lines.[18,19]

Opioid Analgesics

When a prostate cancer patient continues to experience mild to moderate pain despite maximal doses of an NSAID given around-the-clock, he should also be given opioids, which are the mainstay of pain therapy for cancer patients. Both endorphins (endogenous morphine-like substances) and opioid drugs provide analgesia and other effects by binding to specific opioid receptors in the brain and spinal cord.

Pure opioid agonists, such as morphine, are particularly useful in treating cancer pain because they
have relatively straight-line dose curves; i.e., they fully occupy the opioid receptor, and increased doses provide increased analgesic effects. Full opioid agonists, such as morphine, hydromorphone, codeine, oxycodone, hydrocodone, methadone, levorphanol (Levo-Dromoran), and fentanyl, are most commonly used in the treatment of cancer pain. These drugs have no ceiling effects, and, therefore, dosage can be safely and predictably titrated upward as needed to achieve satisfactory analgesia (Table 2).

Partial agonists (buprenorphine) and mixed agonist/antagonists (pentazocine, butorphanol tartrate) do not have such straightforward effects, however, and for that reason are not commonly used in cancer pain management. Partial agonists bind to opioid receptors but do not fully activate them; thus, they have lower and flatter dose-response curves than the pure agonists and also have limited analgesic efficacy. Combination opioid agonist/antagonists have ceiling effects similar to partial agonists and can also reduce analgesia and even precipitate physical withdrawal symptoms in patients taking weak opioids.[20] Finally, meperidine is a very poor choice for treating chronic cancer pain since it has a short half-life and its metabolite, normeperidine, is toxic and can lead to central nervous system (CNS) stimulation and seizures.

**Step-two drugs**, including codeine, dihydrocodeine, hydrocodone, oxycodone, and propoxyphene, are short-acting opioids generally used in patients with moderate pain that has been inadequately controlled with around-the-clock NSAIDs. Many of these opioids, such as hydrocodone and oxycodone, are available in fixed combinations with aspirin or acetaminophen and the maximum daily dose is limited by the potential toxicity of the nonopioid. Others have dose-limiting side effects that make adequate titration impossible; codeine, for example, is associated with a high side effect profile at doses over 1.5 mg/kg of body weight.[21] Still, these so-called “weak” opioids provide adequate analgesia in a significant percentage of patients with advanced prostate cancer, either on around-the-clock schedules or with as-needed dosing.

**Step-Three Drugs**—Patients with moderate to severe pain that is not well controlled with step-two opioids require step-three opioids, which include morphine, hydromorphone, oxycodone, and fentanyl. These medications are pure opioid agonists; they have no ceiling effects, and, therefore, dosage can be titrated upward until adequate analgesia is achieved or the patient experiences unacceptable side effects. When pain is continuous, these analgesic medications should be administered around-the-clock.

There is tremendous variation in the dose needed to achieve adequate pain control, even in patients with similar pain profiles. Hence, the dose and frequency of administration need to be titrated to individual response. Although most cancer pain can be controlled with doses of ≤ 240 mg/d of oral morphine, patients with severe pain may require much higher doses. Some prostate cancer patients have very severe pain, particularly in the terminal stage of their disease, and the physician should not hesitate to increase opioid doses until adequate pain relief is achieved.

**Morphine and Oxycodone**—Morphine is the most common, most economical of the pure opioid antagonists; it is widely available in a variety of preparations and has a well-characterized pharmacologic profile. In addition to immediate release preparations, several controlled-release morphine preparations are available that can be dosed every 8 or 12 hours and can be easily titrated.[22] Oxycodone also is available in both short-acting and 12-hour, extended release formulations and may have fewer side effects than morphine.[23] Short-acting oral opioids start to exert an analgesic effect within a half hour of administration, and analgesia lasts approximately 4 hours. If pain returns sooner, the opioid dose should be increased until pain relief is achieved for 4 hours.[21]

The controlled-release preparations have the benefit of less frequent administration, which is often important to cancer patients. These medications usually begin to exert an analgesic effect 1 hour after administration, peak in 2 to 3 hours, and last for 12 hours. Controlled-release morphine may be given at lower doses every 8 hours, but long-acting oxycodone should be administered only every 12 hours, and doses should be increased if the analgesic effect wears off sooner. Patients need to be advised that controlled-release opioids should not be crushed or broken, as doing so makes the entire dose of the drug immediately available and may lead to toxicity.

**Transdermal fentanyl** (Duragesic) patches control pain for up to 72 hours. Because transdermal fentanyl bypasses GI absorption, it may be associated with less nausea than other long-acting opioids. These patches are available in 25-, 50-, 75-, and 100-µg/h sizes, and the maximum recommended dose is 300 µg/h. Plasma levels rise slowly over the first 12 to 18 hours after patch administration and peak between 24 and 48 hours.[24] When a patient first starts therapy with transdermal fentanyl or increases the dose by adding an additional patch, he should be advised that he will need to continue with oral breakthrough medication for the first 12 to 18 hours until plasma
levels of the new dose peak.
Since titration is not as simple as with oral medications, transdermal fentanyl is a good analgesic choice for patients with stable pain and infrequent episodes of breakthrough pain. When compared with oral morphine, studies suggest that transdermal fentanyl is preferred by cancer patients, improves sleep quality and morning vigilance, and is associated with decreased levels of nausea, vomiting, and constipation. The cost of transdermal fentanyl is significantly higher than that of morphine and other oral opioids, however, and this may clearly play a role in the choice of treatment.

Methadone is an inexpensive synthetic opiate receptor agonist that is infrequently used in the treatment of cancer pain but may be very useful for selected patients whose pain is poorly controlled with standard opioids. Methadone is rapidly absorbed from the GI tract, and plasma drug levels are measurable 30 minutes after administration.
There are tremendous interindividual variations in the pharmacokinetics of methadone, and its long elimination half-life requires up to 1 week to achieve steady-state plasma drug levels. These considerations make methadone a potentially difficult drug to titrate to acceptable analgesia, but it may prove to be a good alternative for patients whose pain is refractory to other oral step-three opioids.

Patients with moderate pain that is unrelieved with their current oral opioid dose may increase the dose by 25% to 50% every 24 hours until adequate analgesia is achieved. Patients with severe, unrelieved pain should increase the dose by 50% to 100% every day until they achieve a desired level of pain control.

Medications for Breakthrough Pain—Patients receiving long-acting step-three opioids often experience breakthrough pain or transient flares of otherwise well-controlled, persistent pain. These episodes may or may not be predictable (eg, occur with increased activity or stress), but all patients taking controlled-release medications should also be provided with immediate-release medications to treat breakthrough pain.
The effective dose of this as-needed medication may vary with each individual; however, in general, 10% to 20% of the total daily dose of a long-acting medication should provide pain relief in this setting. Immediate-release forms of morphine, hydromorphone, and oxycodone are all available in tablet form.
A transmucosal lozenge form of fentanyl citrate (Actiq) that is absorbed through the highly permeable, well-vascularized oral mucosa recently became available in the United States. This fentanyl lozenge produces more rapid pain relief than other immediate-release opioid tablets, with peak effect seen 15 to 20 minutes after oral administration.

Nonoral Administration Routes—Although the vast majority of patients with advanced prostate cancer can take oral medications and experience satisfactory analgesia with these formulations, a small subset of patients have pain that is much more difficult to control and may require different routes of administration. Transdermal fentanyl may be a good choice for these patients. Rectal morphine suppositories also are available, although these are not generally a popular choice with patients or caregivers.
Morphine and hydromorphone can be administered by continuous infusion, either subcutaneously or intravenously, in patients who cannot tolerate oral medications and in patients with acutely increasing pain that requires rapid dose escalation. Portable, easily programmable infusion pumps also are available, which allow patients to control analgesia in an outpatient setting.
A small subset of patients who require extremely large doses of oral, transdermal, or parenteral opioids, or who experience intolerable side effects from systemic administration of these drugs, may benefit from epidural or intrathecal infusion. Epidurally administered opioids are 5 to 10 times more potent than those administered parenterally; drug diffuses into the epidural space, through the dura into the CNS and then into the spinal cord. Intrathecal opioids are 10 times more potent than those administered epidurally, but these catheters for intrathecal drug administration must be placed by a neurosurgeon and are very costly.
Because the epidural and intrathecal routes deliver drug in close proximity to the dorsal horn of the spinal cord, patients require relatively small doses of opioids. This may decrease side effects associated with the drugs.

Side effects associated with opiates are frequent but may be limited or treatable. Constipation is almost universal with long-term opioid use due to decreased peristalsis (which may be compounded by decreased food and fluid intake from anorexia and progressive disease). Unless contraindications exist, all patients who are receiving around-the-clock opioid therapy should be started concomitantly on a bowel regimen.
Prevention may be adequately maintained with a stool softener plus a stimulant taken at bedtime (eg, Peri-colace, Ducolax, Senocot-S). Doses may be increased to two or three times per day as needed, up to eight tablets per day, and supplemented with lactulose or magnesium hydroxide. Patients should also be encouraged to stay as active as possible and consume adequate amounts of fluid and fiber.

Nausea and vomiting are experienced by about 30% of patients taking opioids, but these symptoms generally resolve within a week of initiating therapy. Unresolved nausea may be treated with neuroleptics, such as prochlorperazine, chlorpromazine, and haloperidol. Metoclopramide, at doses of 10 mg up to four times per day, may also successfully treat nausea.

Transient sedation often occurs during opioid dose titration or when doses are rapidly increased. Older adults are more likely to experience sedation with opioid use; initial doses in these patients should be lower and should be increased more slowly to avoid oversedation.

If sedation persists, it may be eased by decreasing the amount of opioid in each dose and increasing the dosing frequency. Persistent sedation also may be treated with CNS stimulants, such as dietary caffeine, methylphenidate (at doses of 5 to 10 mg in the morning and mid-afternoon and titrated upward as needed), dextroamphetamine (2.5 to 7.5 mg twice daily), or pemoline (Cylert; 18.5 to 37 mg orally every day).[28] Opioid-induced myoclonus may be treated with clonazepam (Klonopin; 0.25 to 0.5 mg orally three times daily).

Respiratory depression is relatively rare in patients receiving long-term opioid therapy. Acute respiratory depression may be treated with careful use of naloxone, which should be titrated to improve respiratory function without reversing analgesia and stimulating opioid withdrawal symptoms.

**Tolerance, Addiction, and Physical Dependence**—When a patient develops tolerance to large doses of an opioid or experiences intolerable side effects, the clinician should consider switching to another opioid. Because cross-tolerance among these drugs is incomplete, the new drug should be dosed initially at 50% of the calculated equianalgesic dose and then rapidly titrated upward to an acceptable level of analgesia.

Patients often have reservations about the use of narcotics based on fears of addiction and tolerance, and may need to be educated about the safety and efficacy of these drugs in treating cancer pain. Addiction, a psychological dependence on pain medications particularly for their euphoric effect, is extremely rare in cancer patients, with an estimated incidence of approximately 0.1%. Tolerance, which refers to the need to use increasing doses of an opioid to maintain adequate pain relief, is not a common problem in cancer patients. Usually, the need for increased analgesic doses in patients with advanced prostate cancer is due to disease progression.

Physical dependence, which is not the same as addiction, causes a physical reaction when an opioid is abruptly withdrawn or naloxone is administered. This is a common but not a worrisome phenomenon that occurs in virtually all patients who receive long-term opioids. Anxiety, irritability, chills, sweats, joint pain, rhinorrhea, diaphoresis, nausea, vomiting, diarrhea, abdominal cramping, and mild flu-like symptoms are all possible symptoms of this withdrawal syndrome, which can develop after as few as 2 weeks of opioid therapy. This possibility is an important consideration when effective therapies or pain changes warrant decreases in or discontinuation of opioids. Abrupt discontinuation of these drugs will often precipitate withdrawal symptoms; this may be avoided by carefully titrating the opioid dose downward over several days. The drugs may be gradually withdrawn by giving half the prior daily dose each day for 2 days and then decreasing the daily dose by 25% every 2 days until the total dose is the equivalent of 30 mg/d of morphine. After 2 days of this dose, the opioid may be safely discontinued.[29]

**Adjuvant Therapy**

Adjuvant medications may enhance the efficacy of opioids or independently treat pain of a different etiology, such as neuropathic pain.

**Tricyclic Antidepressants**

Tricyclic antidepressants are particularly effective in treating neuropathic pain, either in combination with opioids or alone; they potentiate the effects of opioids and appear to have analgesic properties themselves. Since they also elevate mood and cause sedation, tricyclics may also help with depression and insomnia in prostate cancer patients.

Amitriptyline is the most widely used tricyclic medication. It should be initiated at doses of 10 to 25 mg at bedtime and titrated upward as tolerated until desired analgesia is achieved (some patients
will require ≥ 150 mg to attain the full effect). Amitriptyline is frequently associated with anticholinergic side effects, such as urinary retention, constipation, and dry mouth, which can be a problem in the prostate cancer patient taking opioids, which produce similar side effects. Desipramine and nortriptyline also have been shown to be effective in treating neuropathic pain and may cause fewer side effects than amitriptyline. The analgesic effects of tricyclic antidepressants generally occur within a week or two, sooner than the occurrence of maximal antidepressant effects.

**Anticonvulsants**

Anticonvulsants are effective in treating lancinating, neuropathic pain and tic-like pain, and may be added to tricyclic antidepressants or used singly. Anticonvulsants may also effectively treat myoclonus linked to opioid therapy. Gabapentin (Neurontin) is the preferred agent for the treatment of refractory cancer-related neuropathy. Valproic acid and clonazepam enhance neuronal inhibition and are also effective in treating neuropathic pain. Although carbamazepine has been used to treat cancer-related neuropathies, it has the potential to cause marrow suppression and, thus, may not be a good choice for advanced prostate cancer patients with preexisting myelosuppression due to advanced disease or chemotherapy. Patients with well-localized nerve pain that does not respond well to medication may be referred to an anesthesiologist for nerve block therapy.

**Corticosteroids**

Corticosteroids are also useful in the treatment of advanced prostate cancer due to multiple effects, including mood elevation, appetite stimulation, and reduction of inflammation and nausea. They also decrease pain due to perineural edema and pressure on nerves, and are the standard treatment for suspected spinal cord compression. Prednisone (10 mg every day) or dexamethasone (4 mg twice daily) will generally achieve desirable effects. Megestrol acetate also is a potent appetite stimulant (at a dose of 800 mg/d) and may relieve hot flashes associated with androgen deprivation in prostate cancer patients.

**Local Therapy**

**Palliative Radiation**

Local palliative radiation is indicated in patients with advanced prostate cancer for painful bone metastases, impending fractures, nerve root compression, and spinal cord compression. The goals of this therapy are to alleviate symptoms, improve function, and prevent sequela of disease progression. Palliative radiation produces some degree of pain relief in 80% of prostate cancer patients with only a few sites of localized bone pain and completely abolishes symptoms in as many as 40%.

In general, the effects of this therapy are not immediate. Radiation therapy may produce an initial temporary pain flare, and one large study showed that only 50% of patients who will eventually respond to therapy experience symptomatic relief 2 to 4 weeks after initiating therapy. The interval to maximal response ranges from 2 to 12 weeks, and the median duration of pain relief is around 3 months.\textsuperscript{8}

Unlike definitive radiation therapy, which employs high-dose radiation with curative intent over long periods, palliative radiation uses a hypofractionated schedule, administering larger radiation doses over shorter periods. Several large studies examining various doses and fractionation schedules have shown that the onset and duration of pain relief are comparable with regimens ranging from 2.5 Gy fractions administered over 3 weeks to a single, 8-Gy dose. Most commonly, 30 Gy is administered over 2 weeks in 10 fractions. The one advantage of single-dose therapy is that retreatment is possible if pain returns in the treated area.

**Toxicity**—Hematologic toxicity associated with local radiation therapy is generally minimal, although patients with baseline myelosuppression are at increased risk of myelotoxicity. Other toxicities are specific to location: pelvic radiation may cause diarrhea; radiation to the cervical spine may produce dysphagia; and upper abdominal therapy may result in nausea and vomiting. In general, these side effects can be effectively treated prophylactically.

**Wide-Field Radiotherapy**

Although wide-field radiotherapy is seldom used in patients with advanced prostate cancer, it is
occasionally still an option that may be employed in patients with diffuse metastatic disease. It is
generally given as a single fraction of 6 to 10 Gy to the upper, middle, or lower body; alternatively, a
single dose of 6 to 7 Gy is administered to the upper or lower half of the body, followed by 5 to 7 Gy
to the other half of the body 4 to 6 weeks later.[8]
Response rates of prostate cancer patients to wide-field radiation therapy average around 80%. Pain
relief begins as early as 24 to 48 hours after treatment and lasts 3 months on average. Patients with
good performance status have better responses to this form of therapy. Wide-field radiation is used
primarily in patients with lytic lesions or low blood counts, since it generally has less associated
hematologic toxicity than does strontium treatment.

Physical Modalities

The regular application of either heat or cold to affected bony areas relieves pain in some patients
with advanced prostate cancer pain, although neither should be applied to previously irradiated
tissue. Acupuncture, which provides neurostimulation through the insertion of small needles at
various depths, has been reported by prostate cancer patients to relieve bone pain, although no
controlled studies have examined the efficacy of this alternative therapy in treating cancer pain.
Physical therapy may be helpful, particularly when localized pain or weakness from bone disease has
led to associated muscle atrophy and weakness. Although physical therapy does not specifically
treat pain, it can improve the discomfort associated with stiff joints and help patients regain mobility.
Exercise, as tolerated, also should be encouraged in all patients with advanced prostate cancer to
increase mobility.

Systemic Therapies

Bisphosphonates

Bisphosphonates effectively inhibit bone resorption by interfering with osteoclast activity through
mechanisms that are not fully understood. These drugs have a high affinity for calcium and, once
administered, are selectively concentrated in areas around resorbing osteoclasts, binding to
hydroxyapatite in areas of exposed bone mineral where active bone remodeling is occurring.
Bisphosphonates are then internalized by the osteoclasts, where they interfere with various critical
biochemical processes and may induce osteoclastic apoptosis.[30]
Several bisphosphonates have been used successfully to treat conditions associated with abnormal
osteoclastic activity such as hypercalcemia, Paget’s disease, and osteolytic skeletal metastases.
Bisphosphonate treatment in patients with these conditions is associated with decreased pain
scores, improved performance status, better quality of life, and a significant decrease in skeletal
events, such as fractures, cord compressions, and bony pain requiring palliative radiation therapy.
Since bisphosphonates relieve bone pain through inhibiting osteolysis, it seems surprising that they
should have an effect on pain due to advanced prostate cancer. Yet, despite the fact that the
majority of metastatic lesions in prostate cancer are osteoblastic, there is increasing histologic and
biochemical evidence of synchronous bone resorption in these lesions.[31,32] There seems to be a
symbiotic relationship between osteoclasts and osteoblasts in bone disease, although one type
generally predominates. Studies have demonstrated that the volume of normal, lamellar bone is
inversely related to the severity of tumor infiltration, and that as this lamellar bone is replaced with
an excess of woven bone, these lesions take on a sclerotic appearance.[33] There is increasing
evidence that this osteoclast-mediated bone resorption may be induced by substances released by
the tumor itself.
Bisphosphonates decrease indices of bone resorption that are above the normal range in 50% to
80% of prostate cancer patients.[34] Recent research indicates that these drugs may also inhibit the
adhesion of tumor cells to bone, thereby preventing or delaying the development of new bony
metastatic lesions.[35] Overall, studies of the bisphosphonates in metastatic prostate cancer have
yielded conflicting results: Some studies show considerable durable improvement in bone pain and
quality of life, some indicate only transient improvement, and others demonstrate no effect at
all.[36,37]
Older Agents—The two bisphosphonates used most commonly in prostate cancer to date are
clodronate (which is not currently available in the United States) and pamidronate (Aredia). Because
these drugs have very poor oral bioavailability, they are most effective when given as intravenous
infusions, although some studies have followed these infusions with high-dose oral maintenance
therapy.
Pamidronate is administered in doses ranging from 30 to 60 mg weekly to 90 to 120 mg every 3 or 4 weeks. In general, this bisphosphonate has been shown to reduce pain in 50% of patients.[38-40] Duration of response ranges from 4 to 24 weeks, and patients can be safely retreated with additional intravenous doses of the drug when pain symptoms recur.

All of the trials conducted to date seem to suggest the importance of continued bisphosphonate treatment to maintain low levels of osteoclastic activity, either through repeated infusions or with oral maintenance. Although animal studies show that pamidronate can cause renal damage, several studies of patients with normal renal function have failed to show any impairment in renal function with weekly pamidronate doses given over either 1 or 2 hours.[41,42] In general, bisphosphonates are well tolerated, although some patients experience pain flares 24 to 48 hours after administration, which may last for days or weeks. Fever may also been seen 12 to 24 hours after administration and is self-limiting.

New Agents—Several new, more potent bisphosphonates that are currently undergoing clinical trials show promising potential. Olpadronate was recently tested in 28 patients with prostate cancer and painful bony metastases. All patients received 4 mg/d intravenously for 5 days; the first 12 received no further treatment, and the last 16 were given oral maintenance doses of 200 mg/d. Overall, 76% of patients reported a decrease in pain after the infusion and this response was sustained in the groups on oral maintenance at 3 months.[43] Ongoing trials are assessing the efficacy of a single, 20-mg intravenous dose of olpadronate. Zoledronate, a bisphosphonate that is 100 times more potent than pamidronate, is being tested at low doses of 0.1 to 8.0 mg in 5-minute infusions and appears to be well tolerated.

Although neither of these drugs is currently available in the United States, these trials provide additional evidence that bisphosphonates are effective in treating prostate cancer and may become a standard therapy in the future.

Radioisotopes

Parenterally administered bone-seeking radioisotopes have been shown to provide significant relief in patients with painful bony metastases due to prostate cancer. These agents localize in the metabolically active bone surrounding osteoblastic lesions, delivering high-dose radiation therapy to involved bone without affecting normal tissues. Systemic radioisotopes are particularly beneficial for patients with multiple painful lesions since they target multiple sites simultaneously. These agents also have the advantages of relatively easy, single intravenous dose administration, and, with the exception of myelosuppression, they have relatively few side effects.

The primary goal of radioisotope therapy is palliative: to decrease pain and analgesic use and improve quality of life. Radioisotope therapy has not been shown to extend survival, but it may reduce or eliminate the need for subsequent localized palliative radiation.

Strontium-89

Strontium chloride-89 (Metastron) is a pure beta-emitter that imitates calcium in vivo and combines with the calcium component of hydroxyapatite in osteoblastic lesions. It has a half-life of 50.5 days, and, although it is cleared from healthy bone in approximately 14 days, it is retained in metastatic bone for as long as 90 days or more.

Since the beta-particle has a range of only 3 mm in bone, average marrow exposure is low, estimated at 2 to 50 times less than the dose to affected bone, which averages 20 to 24 Gy (range, 3 to > 300 Gy).[44,45] Patients with extensive preexisting metastatic bone marrow involvement may experience greater marrow exposure and subsequent myelosuppression, however. Clinically, the response to strontium-89 is equivalent to that of wide-field radiotherapy. Most studies show that approximately 80% of prostate cancer patients experience some degree of pain relief with strontium-89 therapy, and 10% to 15% experience complete relief.[46] Pain relief generally occurs 2 to 4 weeks after administration and peaks at 4 to 12 weeks; transient pain flares occur in 5% to 10% of patients 5 to 10 days after injection. It is important to advise patients that strontium-89 does not produce symptomatic relief immediately and that analgesics should not be tapered downward or stopped immediately after injection.

Response to strontium is increased in patients with less extensive disease, good performance status, and well-differentiated tumors. The presence of more than 20 lesions on bone scan is a predictor of poor response.[47] There is also evidence that, in addition to palliation of pain, radioisotope therapy may slow down the
progression of metastatic bone disease. In the phase III TransCanada study, patients first received localized radiotherapy and were then randomized to receive placebo or strontium-89. Although pain relief and survival were similar in the two groups, significantly fewer of the strontium-treated patients developed new sites of pain than did those in the placebo arm (41% vs 66%). Additional studies have confirmed that, in terms of overall duration of pain relief, strontium is similar to both local radiation therapy and hemibody radiation, but strontium delays the appearance of new sites of metastatic pain more than either of the other two therapies.[49,50]

**Toxicity**—Thrombocytopenia is the most common toxicity associated with strontium-89 therapy; in particular, platelet counts may decrease as much as 50% or more below pretreatment levels. Since prior chemotherapy and extensive marrow disease may potentiate myelosuppression, patients with baseline thrombocytopenia probably should not be treated with strontium. Blood counts reach nadir values 4 to 8 weeks after strontium administration and generally recover by 12 weeks. Since strontium is excreted in the urine, incontinent patients need to be catheterized. Patients may be retreated as necessary every 3 to 4 months, provided that hematologic toxicities have resolved; retreatment should be withheld in patients with white blood cell counts < 2.4 or a platelet count < 60,000. Some patients have received as many as 10 strontium injections.

**Newer Radioisotopes**

Several newer radioisotopes are currently undergoing investigation. These include samarium-153 ethylenedia-mine-tetramethylene phosphonic acid (Quadramet), tin-117, and rhenium-186. **Samarium-153** is a beta- and gamma-emitter with a much shorter half-life (1.9 days) than strontium, which permits the use of higher doses at shorter intervals. Myelosuppression occurs at about the same rate with samarium as with strontium but recovery is quicker and earlier retreatment is possible. Symptomatic relief is experienced by 60% to 90% of patients treated with samarium; relief occurs quickly (usually within 1 week) and is often durable (up to 16 weeks). In one recent Finish study, 35 patients with painful bone metastases were treated with a single intravenous dose of samarium-153 in doses ranging from 330 to 1,110 MBq (million becquerel [roughly 8-30 mCi]). Approximately 80% of treated patients experienced pain relief, and the duration of effect was between 2 and 17 weeks. The drug was well tolerated; only one patient experienced grade 3 myelosuppression.[51]

**Chemotherapy**

Although previous clinical trials using single-agent chemotherapy have shown poor results in advanced prostate cancer, newer studies suggest that multiagent chemotherapy may play an important role in relieving pain and other symptoms associated with progressive disease and may prolong survival. Subjective responses to chemotherapy, in terms of decreased pain and improved quality of life, have been documented in numerous studies. Objective measures of response, such as a decrease in tumor markers and stabilization or improvement of metastatic bone lesions, soft-tissue tumors, and adenopathy, have also been observed in patients treated with chemotherapy. Currently, the National Comprehensive Cancer Network (NCCN), a consortium of 17 major cancer centers, recommends five chemotherapeutic regimens for advanced prostate cancer (Table 3). Although most of these regimens have associated toxicities, such as fatigue, mild myelosuppression, and GI irritation, they are generally well tolerated by the majority of patients.

**References:**


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