Prostate Cancer and Malignant Bone Pain

Prostate cancer is the second most prevalent cancer diagnosis among men worldwide, with an estimated 782,000 new cases in 2007 that will lead to over 253,000 deaths [1].

Diagnosis
Most patients worldwide are diagnosed above the age of 65; in developed countries, the mean age of diagnosis is approximately 59 years [7]. Earlier diagnosis is partly due to greater awareness about prostate cancer and increased screening, especially with the use of the prostate-specific antigen (PSA) test. The highest incidence rates are in the United States, while parts of Asia and Africa have the lowest incidence, with a 50-fold difference between the lowest and highest incidence rates.

The 5-year survival rates for all stages of prostate cancer vary from 40% to over 90% in developed countries. Men with early-stage or localized prostate cancer have a cure rate ranging from 50% to 85%, depending on certain features of their cancer. Those with low-grade features and comorbidities are considered for active surveillance, while those with more aggressive tumors who are otherwise healthy may choose definitive local treatment. These treatments include prostatectomy (radical retropubic or robotic-assisted prostatectomy), external-beam radiotherapy, and low-dose brachytherapy [5]. Those diagnosed with metastatic disease are usually started on systemic hormonal therapy that leads to medical castration (reduction of testosterone levels) and often causes remission of prostate cancer.

Symptoms
Patients with early-stage prostate cancer may present with bladder symptoms related to local obstruction of the urinary outflow tract. After primary therapy, patients often report irritable bladder and bowel symptoms, urinary incontinence, and sexual dysfunction.

Metastatic disease most commonly occurs in the bones (90%), lungs (46%), and liver (25%) [4]. Similar to the pattern of disease spread, pain is usually related to bone metastases, and a bone scan is helpful to screen for these lesions. Prostate cancer usually leads to blastic lesions that cause sclerotic bone formation. Paradoxically, these lesions appear denser on radiographic images, but the bone formation is abnormal in architecture and inherently weak.

Patients may experience direct pain at the site of metastases, often a dull and constant pain that gradually increases in intensity over time. Patients commonly describe worsening of symptoms with activity or when pressure is applied to the affected area [8]. Close examination of the bone may show microfractures and disruption of the periosteum. Other patients report no pain until a secondary complication occurs, such as structural instability leading to pathological fractures or vertebral collapse. Such events may cause reactive muscle spasms, nerve compression, and most seriously, spinal cord compression.

Therapy

1) **Anticancer Treatments**
   Initial therapy for pain related to prostate cancer should always include anticancer treatments. Gonadotrophin-releasing hormone (GnRH) agonists (e.g., goserelin and leuprorelin acetate) will cause a decline in PSA in over 85% of patients, and thus will commonly relieve symptoms. Initial therapy is sometimes associated with a luteinizing hormone surge, and patients should be temporarily started on an antiandrogen (e.g., bicalutamide or flutamide) prior to initiation of a GnRH agonist to prevent a “flare” of symptoms. For individuals found to be refractory to hormonal treatments, chemotherapy is a standard approach. Docetaxel with prednisone given every 3 weeks has been found to improve survival as well as decrease pain symptoms [10].

2) **Analgesics**
   Nonsteroidal anti-inflammatory drugs (NSAIDs) are a cornerstone of treatment for many mild to moderate pain syndromes, and they are particularly useful in bone pain. They are usually combined with opioids for moderate and

severe pain. Usually an immediate-release opioid should be made available for breakthrough pain, which is particularly common with bone metastases. Rapid-onset opioids are preferred because they can quickly resolve breakthrough pain associated with bone metastases. Depending on nerve involvement, neuropathic agents such as antidepressants and anticonvulsants may be considered.

3) Bisphosphonates

Initial studies of first- and second-generation bisphosphonates showed that these drugs can help prevent skeletal events such as fractures, but their role in pain relief was unclear. However, more recent use of zolendronate, a third-generation bisphosphonate, in prostate cancer has shown benefit in relieving pain from bone metastases as well [9]. Evidence for acute pain relief is lacking.

4) Radiotherapy and Radiopharmaceuticals

For localized bone pain, external beam radiotherapy should be considered. External beam radiotherapy, using either single or multiple fractions, produced 50% pain relief in 41% of patients and yielded complete pain relief at 1 month in 24% of patients [6]. Relief often begins within several days, but the maximum effect may not be felt for several weeks. Overall, these treatments are well tolerated and usually have limited side effects, depending on the location.

When patients present with multiple affected areas or diffuse bone pain, radiopharmaceuticals have an important role. Strontium-89 and samarium-153 are two agents that have been studied in the prostate cancer population with positive results [2]. Significant pain relief has been reported in more than two-thirds of patients, with 20–30% having complete relief. Toxicities primarily consist of anemia, neutropenia, and nausea; thus, careful patient selection is important to avoid any serious side effects.

5) Other Therapies and Procedures

When a pathological fracture occurs, splinting and immobilization are simple first steps prior to urgent evaluation by an orthopedic surgeon. Surgical stabilization should be considered in these patients, or if it is not appropriate, neuraxial analgesia should be considered. A common site of metastases is the vertebral bodies, especially in the lumbar spine. If vertebral collapse occurs, with associated pain, vertebroplasty (injection of cement through a needle into the vertebrae to restore the height and stabilize the bone) may be a good minimally invasive option.

The most serious and urgent pain syndrome is spinal cord compression [3]. This diagnosis should be considered for any patient with known bone metastases presenting with back pain and neurological symptoms. The gold standard for evaluation is a full-spine magnetic resonance imaging (MRI) scan. Steroids are usually started empirically if suspicion of cord compression is high. If cord compression or impending cord compression is confirmed, immediate consultation with surgery and radiation oncology is warranted.

References

1. American Cancer Society. Global cancer facts and figures 2007. American Cancer Society; 2007.
2. Bauman G, Charette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radiother Oncol 2005;75:258–70.
3. Benjamin R. Neurologic complications of prostate cancer. Am Fam Physician 2002;65:1834–40.
4. Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, Gasser TC, Mihatsch MJ. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol 2000;31:578–83.
5. Jani AB, Hellman S. Early prostate cancer: clinical decision-making. Lancet 2003;361:1045–53.
6. McQuay HJ, Collins SL, Carroll D, Moore RA. Radiotherapy for the palliation of painful bone metastases. Cochrane Database Syst Rev 2000;CD001793.
7. Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. BJU Int 2002;90:162–73.
8. Reale C, Turkiewicz AM, Reale CA. Antalgic treatment of pain associated with bone metastases. Crit Rev Oncol Hematol 2001;37:1–11.
9. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Zheng M, Zoledronic Acid Prostate Cancer Study Group. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004;96:879–82.
10. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.

© 2009 International Association for the Study of Pain®