Advances in the Treatment of Bone Metastases

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Bone metastases are common in many cancers. They are the most common cause of cancer-related pain (Mercadante, 1997) and a major cause of morbidity in patients with cancer (Rubens, 1998). Malignancies that most frequently metastasize to the bone are breast, prostate, and lung cancers. Multiple myeloma, osteosarcoma, and Ewing’s sarcoma are primary skeletal tumors but nonetheless have the same destructive effect on bone as metastatic disease (Mercadante). Although metastases are the focus of this article, from a standpoint of therapeutic interventions, similar principles of treatment apply to primary skeletal malignancies.

Nurses play a vital role in the assessment and management of metastatic bone disease. Early identification of skeletal lesions not only aids in early intervention and better pain control but also can prevent complications, such as hypercalcemia, myelosuppression, pathologic fractures, and spinal cord compression.

This article reviews bone physiology, the pathophysiology associated with bone metastases, strategies of medical management, and nursing implications for managing patients with metastatic bone lesions. Areas of future research in bone metastases also are described.

Physiology of Bone

The human skeletal system consists of bones and articulations that provide structural support and movement. Bone also is essential in maintaining hematopoiesis and mineral homeostasis (Fisher, Mayer, & Struthers, 1997). Bone is composed of minerals (cortical portion) and collagen (cancellous portion). Cortical bone is very dense and compact and constitutes about 85% of the total skeletal mass. Cancellous bone (15%) is more porous and spongy, and thereby is more susceptible to disease processes such as osteoporosis and malignant metastases (Mundy, 1995). It is found in the metaphysis of long bones such as the femur and inside of flat bones such as the ilium, cranium, and ribs.

Once the skeleton has reached maturity, regeneration (referred to as remodeling) occurs on a continuous basis (Body, 2000). At the cellular level, bone remodeling is regulated by an intricate balance of varying levels of simultaneous osteoblastic and osteoclastic activity (see Figure 1). Osteoblasts (bone-forming cells) are responsible for the production of collagen and other proteins to synthesize the bone matrix. Osteoclasts (bone-eroding cells) mediate resorption of the bone matrix by binding to the bone surface, secreting citric and lactic acids, then dissolving and digesting bone minerals and collagen (Body). Osteocytes, another type of bone cell, are transformed osteoblasts that are believed to participate in supplying nutrients to the bone matrix (McCance & Huether, 1998).

Many hormones and cytokines are involved in the modulation of bone formation and resorption. These modulators work at either a local or systemic level and may increase or decrease the activity of osteoclasts (resorption) and osteoblasts (formation).

Pathophysiology of Bone Metastases

The cortical (calcified) matrix stores many growth factors. These can nourish cancer cells that have settled in the bone, thus providing a fertile microenvironment for the continued growth of cancer cells. Because cancellous
Metastatic bone lesions consist of three types.
- Osteolytic lesions are areas of eroded bone as seen in multiple myeloma. Myeloma cells excrete excessive protein (called M protein) that directly stimulates osteoclastic activity. On radiographs, these erosions appear as multiple, rounded, punched-out areas on the ribs, skull, vertebrae, pelvis, and long bones (Barlogie, 1997).
- Osteoblastic lesions are new bone growths on top of existing bones. These lesions weaken the underlying bone structure and increase the risk of fracture. They are observed frequently in patients with prostate cancer with bone metastasis.
- Mixed osteoblastic and osteolytic lesions often are seen in patients with breast cancer. Although osteolytic and osteoblastic lesions both weaken bone, the former are more prone to pathologic fractures.

Metastatic bone lesions lead to many complications, several of which can be prevented if detected early. Prophylaxis of these potential complications is important because they are major causes of morbidity in patients with cancer (Rubens, 1998).

**Pain:** Pain is the hallmark symptom of malignant skeletal metastases. The mechanisms involved in pain may be attributed to (a) stimulation of nerve endings in the endostium resulting from the release of prostaglandins, bradykinin, substance P (a proinflammatory hormone that inhibits adrenocorticotropic hormone), or histamine as bone tissue is destroyed, (b) stretching of the periosteum as tumor size increases, (c) fractures, and (d) tumor growth into surrounding nerves and tissues (Nielsen, Munro, & Tannock, 1991). The pain usually is described as dull and constant, with increased intensity at night or with weight bearing. Pain usually develops gradually and becomes more severe within weeks to months (Mercadante, 1997). Percussion tenderness commonly is noted over the affected area (Mayer, Struthers, & Fisher, 1997).

**Pathologic fractures:** Fractures occur most commonly in long bones and most often with multiple myeloma (lytic lesions) and breast cancer (mixed lesions). The pain of a pathologic fracture is characterized as acute and sharp with a specific focal point. Rubens (1998) wrote that an important goal in the management of metastatic bone disease is prophylaxis, that is, surgical fixation (or radiation) of an at-risk bone before a fracture can occur. Mirels (1989) developed a practical scoring system that uses the factors of lesion size and extent of bone destruction to help guide patient selection for surgical fixation (see Table 1).

**Spinal cord compression:** Spinal cord compression may occur from direct pressure from an enlarging tumor, spinal angulation after vertebral collapse, vertebral dislocation after a pathologic fracture, or pressure from intradural metastases (rare) (Rubens, 1998). It is an oncologic emergency that necessitates prompt diagnosis and treatment because progressive and irreversible neurologic damage may occur. Early detection and intervention significantly improve the outcome of spinal cord compression. At presentation, back pain is the most common symptom. Motor weakness, sensory loss, and autonomic (bowel and bladder) dysfunction also may be present (Flouders & Ott, 2003; Schiff, 2003).

**Hypercalcemia:** Increased serum calcium is associated more often with osteolytic lesions than with osteoblastic lesions. Tumor-induced bone breakdown releases calcium into the bloodstream. This overwhelms the kidney’s capacity to filter calcium to maintain homeostasis (Maxwell, Givant, & Kowalski, 2001). High serum calcium levels also may be seen in patients with cancer without skeletal involvement if a tumor produces parathyroid hormone-related protein that, in turn, stimulates calcium release (Rubens, 1998). Hypercalcemia often is severe enough to constitute an oncologic emergency that requires prompt treatment. As serum calcium levels rise (generally greater than 10.8 mg/dl), symptoms may be gradual or a patient’s condition may deteriorate rapidly. The symptoms of hypercalcemia include anorexia, nausea and vomiting, constipation, lethargy, weakness, confusion, dehydration, and eventually stupor leading to coma (Rubens). Aggressive hydration often is used to help lower serum calcium levels.

**Myelosuppression:** Bone marrow depression occurs when extensive infiltration of the bone marrow causes impaired hematopoiesis. Associated anemia, leukopenia, and...
The diagnosis of malignant bone lesions is established through clinical presentation, laboratory analysis, and radiography. Clinical presentation may include any or all of the previously addressed complications or symptoms: pain, pathologic fractures, spinal cord compression, hypercalcemia, and myelosuppression. Serum calcium, complete blood count, and alkaline phosphatase level (increased in the presence of osteoblastic activity) are laboratory tests that may aid in differential diagnosis.

**Evaluation and Management of Bone Metastases**

Plain radiographs (i.e., x-rays) usually are the first step in evaluating bone metastases. They are specific (i.e., have a low false-positive rate) and can detect osteolytic and osteoblastic lesions. At the same time, x-rays are not very sensitive because a lesion must be rather large (greater than 1 cm with at least 30%–50% loss of bone matrix) to be visible (DeVita, Hellman, & Rosenberg, 2001; Gradisher, Mundy, & Harvey, 2001). Scintigraphy (i.e., bone scan) is a very sensitive technique for detection of bone metastases. It shows skeletal involvement much earlier than a plain radiograph (DeVita et al.) and uses radiolabels (e.g., technetium) that accumulate at sites of osteogenic activity and then light up as “hot spots” on film (Gradisher et al.). Scintigraphy can detect lesions as small as 2 mm, but it is not specific. Lesions that are detected may be caused by other processes such as trauma, infection, or arthritis (Nielsen et al., 1991; Strohl, 2000). Computed tomography (CT) or magnetic resonance imaging (MRI) are very sensitive and specific tools but have a substantially greater expense. If bone scans or x-rays are inconclusive, they should be correlated with CT or MRI (DeVita et al.).

The goals of treatment for bone metastases are to control pain, restore mobility, prevent pathologic fractures and neurologic complications, and prevent (or administer early intervention) hypercalcemia or myelosuppression. Palliative interventions include analgesia, hormone therapy, chemotherapy, surgery, radiation therapy including radiopharmaceuticals, and bisphosphonate therapy.

**Analgesia:** The Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guidelines for the pharmacologic management of pain associated with bone metastases are simple to follow and well validated. They are effective in relieving cancer pain for about 90% of patients (AHCPR, 1994). Individualized regimens beginning with nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended to decrease the release of prostaglandins (inflammatory mediators) at the site of injury by inhibiting the enzyme cyclooxygenase. NSAIDs relieve mild to moderate pain. If pain persists, a mild opioid (e.g., codeine, hydrocodone) may be added but not substituted. If pain still persists, stronger opioids (e.g., morphine, hydromorphone) should be added. At this point, around-the-clock dosing with supplemental breakthrough dosing is indicated to maintain constant drug levels for pain control (AHCPR). Coanalgesics such as corticosteroids may help patients by blocking the synthesis of cytokines that can contribute to inflammation and nociception (Mercadante, 1997).

Nonpharmacologic approaches may complement pharmacologic interventions and include behavioral or cognitive interventions, heat and cold applications, therapeutic mattresses, massage, immobilization, relaxation exercises, and transcutaneous electrical nerve stimulation (Struthers, Mayer, & Fisher, 1998).

**Hormone therapy:** Hormone blockade is used with the intention of depriving hormonally dependent tumors of their stimulus, thus slowing tumor growth (Mercadante, 1997).

**Chemotherapy:** Various chemotherapy regimens are used to treat the primary malignancy with the goal of eradicating metastatic disease, including bone metastasis. Assessing the independent impact of chemotherapy on quality of life and actual pain relief of bone metastases is difficult because other concurrent treatments generally are administered (Nielsen et al., 1991).

**Surgery:** Surgical stabilization of the spine and extremities may be necessary to avoid or treat pathologic fractures. Prophylaxis of fractures has many benefits, including cost effectiveness, improved quality of life, decreased pain and suffering, and prolonged survival (Mercadante, 1997). Once a pathologic fracture occurs, the bone must be stabilized. Morbidity and mortality are greater, recovery is slower, and procedures generally are more aggressive. Recent advances in surgical options include vertebral body reconstruction, kyphoplasty (i.e., inflation of a balloon into the collapsed vertebral body), arthroplasty (i.e., construction of a new joint), and vertebroplasty (i.e., using cement to stabilize vertebral bodies) (Fourney & Gokaslan, 2003). These surgical procedures are used to alleviate pain, restore mobility, and prevent neurologic complications.

Sometimes a patient is a poor surgical candidate or the expected life span is too short to benefit from surgical fixation. Other approaches for these situations may be more appropriate, such as radiation therapy or immobilization (Struthers et al., 1998).

**Radiotherapy:** External beam radiation directly kills tumor cells and also may have an effect on the chemical mediators of pain (such as substance P) at the bone site (Gradisher et al., 2001; Mercadante, 1997; Struthers et al., 1998). This is the first treatment used for a solitary bone metastasis. For most patients, a single dose or a short course of one to two weeks is sufficient for pain relief with minimal side effects. Multiple lesions may be treated with wide-field irradiation (i.e., hemibody radiation, treating the upper or lower half of the body), although an increased incidence of side effects exists with this method. Prophylactic radiation may be used to prevent an impending fracture with or without surgery. Radiation in conjunction with high-dose steroids is the noninvasive treatment of choice for spinal cord compressions because of its rapid results (Mercadante).

Radiopharmaceuticals are bone seeking (site-selective radioisotopes). They can offer

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**Table 1. Proposed Scoring System for Diagnosing Impending Pathologic Fractures**

<table>
<thead>
<tr>
<th>Variable/Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Upper limb</td>
<td>Lower limb</td>
<td>Peritrochanter</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
<td>Blastic</td>
<td>Functional</td>
</tr>
<tr>
<td>Lesion</td>
<td>&lt; 1/3</td>
<td>1/3–2/3</td>
<td>&gt; 2/3</td>
</tr>
<tr>
<td>Size of bone diameter**</td>
<td>&lt; 1/3</td>
<td>1/3–2/3</td>
<td>&gt; 2/3</td>
</tr>
</tbody>
</table>

*Rate each item with a score of 1, 2, or 3. The lowest possible total is 4; the highest possible is 12.  
** Proportion of bone lesion

very effective pain relief for multiple sites of malignant bone lesions. They are convenient and generally less toxic than external beam radiation. Strontium 89 is chemically similar to calcium, has a preferential affinity for osteoblastic lesions, and delivers therapeutic amounts of beta radiation. Samarium 153, once taken up by the target bone lesions, emits amounts of beta radiation. Samarium 153, because it is less penetrating, makes it the radiopharmaceutical of choice (Weinberger, 2000). Occasionally, radiation may cause an exacerbation or flare of a patient’s symptoms within 48 hours of treatment. This phenomenon (which also can occur after bisphosphonate administration) is caused by an inflammatory response with subsequent irritation of the nerves in the periosteum. It is managed effectively with NSAIDs, steroids, or opioids, depending on severity.

Bisphosphonates: This class of drugs is used to inhibit calcification (e.g., bisphosphonates are used in toothpaste to prevent dental calculus) and bone resorption in diseases such as osteoporosis and Paget’s disease, as well as tumor bone diseases such as hypercalcemia, multiple myeloma, and bone metastases. Bisphosphonates were developed in the early 1900s for industrial use as corrosion inhibitors. They also were used in the textile, fertilizer, and oil industries. They helped to prevent calcium deposits (i.e., scaling) because of their ability to inhibit calcium carbonate precipitation. Since the 1970s, bisphosphonates have been developed into drugs for use in a variety of diseases (Fleisch, 1998). These drugs have a high affinity for bone minerals and can chelate calcium ions, thus binding readily to areas of exposed bone minerals. Osteoclasts surround the calcium-bisphosphonate complexes. Once inside osteoclasts, bisphosphonates cause either an inhibition of bone resorption or osteoclastic apoptosis (Rogers, Watts, & Russell, 1997).

Bisphosphonates inhibit myeloma cell proliferation and induce apoptosis in vitro, but further investigation is needed to confirm these observations in vivo (Shipman, Rogers, Apperley, Russell, & Croucher, 1997). Growing evidence shows that bisphosphonates may modulate the local bone concentration of growth factors and cytokines that are important for the proliferation and survival of tumor cells (Coleman et al., 2001). Therefore, by inhibiting bone resorption, these drugs correct hypercalcemia and reduce pain, the risk of fractures, and the development of new osteolytic lesions (Mercadante, 1997). The side effects of bisphosphonates include low-grade fever, nausea, myalgias, bone pain, and renal toxicity.

Bisphosphonates are the current standard therapy for the treatment of hypercalcemia and osteolytic bone involvement from multiple myeloma and breast cancer (Rosen et al., 2001). Despite the efficacy of chemotherapy or steroids in reducing the tumor burden of multiple myeloma, these drugs have little effect on the progression of underlying bone destruction. For this reason, bisphosphonates are used synergistically with these other therapies (Berenson et al., 1998; Hussein, Juturi, & Lieberman, 2002). In breast cancer research, pamidronate was found to be superior to placebo for the treatment of bone metastases. Researchers found a decrease in the number of patients requiring radiation therapy, decreased incidence of pathologic fractures, and prolonged time to first skeletal-related event and first fracture. The study also documented significantly less bone pain, less narcotic use, and a slower decline in performance status in the pamidronate group. However, no differences in survival rates were found between the two patient treatment groups (Gradisher et al., 2001). Bisphosphonates used for bone metastases are listed in Table 2.

Zoledronic acid is the newest bisphosphonate (third generation) and has been shown to induce more cytotoxic effects on myeloma cells than pamidronate (Kyle, 2000). It also is more effective than pamidronate in normalizing hypercalcemia (Gradisher et al., 2001). In the treatment of bone metastases (in patients with myeloma and breast cancer), it was as effective and as well tolerated as pamidronate. An additional benefit of zoledronate is that its administration time is 15 minutes versus two hours for pamidronate (Rosen et al., 2001).

**Bone growth markers:** N-telopeptide (NTX), pyridinoline, deoxypyridinoline, and alkaline phosphatase are bone markers used to measure bone resorption activity. Lipton et al. (1998) proposed using NTX to monitor the efficacy of bisphosphonate therapy. The goal is to normalize the excretion of NTX. In a study by Rosen et al. (2001), NTX was the most sensitive of the four serum bone markers and was reduced to a greater extent in patients treated with zoledronate versus pamidronate.

### Implications for Practice

Nurses play a very important role in identifying and managing patients with malignant bone lesions. The ability to recognize early signs and symptoms of these lesions can prevent complications and irreversible sequelae. The areas of focus for nursing care are:

- Administration of chemotherapy or hormonal therapy to treat the underlying primary malignancy
- Administration of bisphosphonates to treat or prevent skeletal events
- Early recognition of hypercalcemia, spinal cord compression, or other skeletal-related events
- Patient and family education related to recognizing and reporting early signs and symptoms, pain management, bisphosphonate therapy, treatment options, and safety issues to decrease fracture risk. In addition, other areas of nursing focus include rehabilitation, pain management, and promotion of psychosocial adaptation.

**Rehabilitation:** Patients with bone metastases can survive for years after diagnosis. Rehabilitation strategies should incorporate safety as well as strengthening and mobility measures. The use oforthotics such as walkers, braces, and collars; exercises that focus on bone protection and increasing muscle strength; and home environment modifications can assist in reaching these goals (Struthers et al., 1998).

**Pain assessment:** The importance of effective pain assessment cannot be overemphasized. The many components of pain can affect patients with bone metastases in every aspect of life, thus affecting the quality of survival. The physiologic component of pain is the actual process that is causing the pain (e.g., a bone lesion). The sensory component of pain is perceived as deep within the body, ranging from mild to severe, and described as dull, aching sensations that intensify at night or with actions resulting in stress on the affected bone. The affective components are the emotional aspects and include fear, grief, despair, anger, anxiety, and depression. Cognitive components of pain are a patient’s beliefs and attitudes toward the cancer, pain, and measures for pain relief. Behavioral components are actions used by a patient to express, prevent, or reduce pain (Coward & Wilkie, 2000). Research-based evidence supports the importance of using a patient diary for the assessment of pain (Schumacher et al., 2002). A diary heightens a patient’s awareness of pain, guides behaviors in pain management, gives a sense of control over pain, and facilitates communication with health-care professionals.

**Psychosocial issues:** To promote psychosocial adaptation, areas to be addressed include assessment of spiritual, sexual, and psychosocial needs. Roles and relationships may change and cause caregiver burden. Participation in support groups can be very helpful to some patients and their families. Other areas to be assessed are patients’ hobbies and leisure activities. These may be encouraged if they are safe. Establishing culturally sensitive communication with patients and
families and respecting their beliefs and values in decision making also promote adaptation to a difficult situation. The ultimate goals of intervention are to maintain a maximum level of independence and optimize quality of life.

Areas of Research

New areas of medical management for bone metastases are being studied. They will affect the nursing care of this population of patients and include

- The optimum timing, dosing, scheduling, and potency of bisphosphonate therapy
- Adjuvant use of bisphosphonates in bone lesion prophylaxis (Coleman et al., 2001; Gradisher et al., 2001)
- Use of serum markers of bone resorption to individually monitor bisphosphonate therapy (Rosen et al., 2001)
- Use of zoledronate in postmenopausal women with osteoporosis to reduce bone turnover (Reid et al., 2002)
- Evaluation of bisphosphonates in preventing bone loss in men with prostate cancer who are on androgen deprivation therapy; these men are at increased risk for osteoporosis and, therefore, fractures (Smith, 2003)
- Endothelin 1 (produced by some cancer cells), which may contribute to an osteoblastic bone response; targeted therapy with an endothelin 1 inhibitor called atrasentan is showing promising results in men with prostate cancer (both in decreasing tumor marker levels and slowing the progression of metastatic bone lesions) (Nelson et al., 2003)
- Radiofrequency ablation that uses heat energy to destroy the tumor, now being studied in metastatic bone lesions. This is a localized treatment that does not require general anesthesia and has been effective in treating liver metastases and primary liver cancers (Neeman & Wood, 2002).

Conclusion

Malignant bone lesions cause considerable morbidity in patients with cancer. Many studies have addressed management of these lesions, and treatment strategies are improving gradually. The addition of therapies such as bisphosphonates and radiochemicals in the 1990s was a big step forward, and treatment of malignant bone lesions continues to improve with newer generations of drugs.

Nurses are instrumental in promoting positive outcomes for patients with bone metastases. An understanding of the physiology of bone and the pathophysiology of bone metastases guides nurses through accurate assessment. Once bone metastases are identified, nurses play a key role in management. This role includes not only pain and medical management but also patient and family education and psychosocial interventions. Pain scales and quality-of-life measurement tools then may measure the impact of these interventions. Nurses can and do make a difference in the success of bone metastases management for patients and their families.

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Rapid Recap

Advances in the Treatment of Bone Metastases

- Malignant skeletal lesions usually are seen in multiple myeloma and metastatic cancer of the breast, prostate, and lung.
- Malignant skeletal lesions may be osteolytic, osteoblastic, or mixed. Of these three types, bones with osteolytic lesions are the most susceptible to pathologic fractures.
- Complications of these bone lesions include pathologic fractures, spinal cord compression, hypercalcemia, and myelo-suppression.
- Treatment includes analgesics, hormonal therapy, chemotherapy, surgery, radiation, and bisphosphonate therapy.
- Nurses must be able to recognize the signs and symptoms of malignant skeletal lesions and implement pharmacologic and nonpharmacologic treatment strategies.

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