Bone metastases are associated with considerable morbidity and can result in skeletal-related events (SREs), including pathologic fractures, the need for palliative radiotherapy, spinal cord compression, the need for surgery to bone to prevent or treat a pathologic fracture or spinal cord compression, and hypercalcemia of malignancy. Such SREs have been associated with decreases in survival and increases in healthcare costs. Skeletal morbidity and bone pain from metastases can also reduce patients’ functional capacity and undermine their quality of life. Patients who develop bone metastases from advanced cancers commonly receive bisphosphonates to not only delay the onset of SREs and reduce their frequency but also provide clinically meaningful palliative effects for bone pain. Ongoing research may lead to improvements in skeletal health monitoring and management for patients with malignant bone disease.

At a Glance
- Bone metastases place patients at risk for considerable morbidity and can result in skeletal-related events (SREs).
- Bisphosphonates can prevent and delay the onset of SREs.
- Bisphosphonates can reduce bone pain from metastases.

In large-scale clinical trials, SREs occurred in about 50% of patients with bone lesions (Berenson et al., 1998; Lipton et al., 2000; Rosen et al., 2004; Saad et al., 2004; Yarbro, O’Kelly, de Mattos Pimenta, Caponero, & Aranda, 2003) (see Figure 1), and patients experienced an average of 1.5–5.7 SREs per year, depending on the primary cancer: 1.5 for prostate cancer, 2.2 for...
multiple myeloma, 2.7 for lung cancer and other solid tumors, and 3.7 for breast cancer (Berenson et al., 1998; Lipton, 2003; Lipton et al., 2000; Rosen et al., 2004; Saad et al., 2004). Each type of SRE has been associated with decreases in patients' quality of life (QOL), and fractures have been associated with decreased survival (Oefelein, Ricchiuti, Conrad, & Resnick, 2002; Saad et al., 2007). SREs decrease patients' functional independence and thus limit their autonomy (Weinfurt, Anstrom, Castel, Schulman, & Saad, 2006; Weinfurt et al., 2004). In addition, SREs are associated with increases in healthcare costs (Botteman et al., 2006; Groot, Boeken Kruger, Pelger, & Uyl-de Groot, 2003). For example, in the United States, the average cost increase was $44,442 (2006 dollars) in patients with SREs versus no SREs for all tumor types with metastatic bone disease (Schulman & Kohles, 2007).

The introduction of bisphosphonates has provided an important tool to prevent or delay skeletal morbidity from bone metastases. Bisphosphonates, which inhibit osteoclast-mediated osteolysis, are the current standard of care for patients with bone metastasis from breast, prostate, or lung cancer or other solid tumors, or bone lesions from multiple myeloma (Heidenreich et al., 2009; Hillner et al., 2000; National Comprehensive Cancer Network, 2008). In clinical trials, bisphosphonates have been shown to not only delay the onset of SREs and reduce their frequency but also reduce bone pain and improve QOL in patients with advanced cancer (Pavlakis, Schmidt, & Stockler, 2005). This article presents the clinical implications of bone metastases in patients with advanced cancer, reviews pharmacologic treatment options, and provides practical guidance for the optimal management of patients with bone metastases.

### Pathophysiology and Disease Burden From Bone Metastases

The human skeletal system provides structural support for movement and is necessary for hematopoiesis (Reich, 2003). All bone surfaces must undergo periodic bone remodeling to maintain skeletal integrity through the processes of osteoclast-mediated osteolysis and new bone formation by osteoblasts (as described in the introduction), which are tightly regulated (Berenson, Rajdev, & Broder, 2006). The intricate bone remodeling cycle is maintained by growth factors and cytokines embedded in the local bone matrix. The bone’s abundant supply of growth factors, easily accessible supply of blood, and porous nature create an ideal microenvironment for tumor cells to metastasize.

Figure 1 illustrates bone resorption.

If patients are left untreated, the vicious cycle of tumor growth and bone destruction can undermine skeletal integrity, and about half of all patients with bone metastases will develop an SRE. In addition to their effects on overall QOL, these events can result in substantial costs and increased risks for further complications. Bone metastases can result in severe pain, which may become refractory to standard pain medications. One of the most common SREs, and typically the first one experienced, is bone pain requiring palliative radiotherapy (Lipton, 2007). Palliative radiotherapy is costly and inconvenient to patients and can lead to usually temporary pain flares in some patients, in which bone pain intensifies rather than abates. Spinal cord compression, often presenting initially as back pain, may cause irreversible paraparesis or paraplegia if not detected and treated at an early stage. Patients with bone metastases also may experience pathologic fractures, which are associated with shorter survival compared with patients without a fracture (Lipton, 2007). A retrospective study of 123 patients with a solid tumor or multiple myeloma who experienced a long bone fracture revealed extended healing time, with fracture healing occurring in only 26% of patients who survived for more than six months after the event (Gainor & Buchert, 1983). Patients with a pathologic fracture may have to undergo surgery to stabilize the bone, which can lead to prolonged hospital stays and increased mortality from surgery-associated complications such as emboli (Choong, 2005). Additionally, in a study of older adult patients with hip fractures, patients with lower postfracture physical function are at increased risk for being institutionalized compared with patients who have higher physical function after a fracture (Cree et al., 2000). Hypercalcemia of malignancy, another serious SRE, can lead to heart failure or coma if not diagnosed and treated.

The negative impact of SREs on patients with bone metastases underscores the importance of bone-targeted therapies, such as bisphosphonates. Indeed, by breaking the cycle of tumor

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**Figure 1. Skeletal-Related Events Among Patients With Bone Lesions (Trials of Approximately Two Years’ Duration)**

*Note.* Based on information from Berenson et al., 1998; Lipton et al., 2000; Rosen et al., 2004; Saad et al., 2004.

growth and bone destruction, normalizing the bone remodeling process, and preventing or delaying SREs, bisphosphonates provide a means to preserve functional independence and maintain QOL for patients with bone metastases.

**Prevention of Skeletal Complications**

Bisphosphonates significantly reduce the rate or risk of SREs in patients with malignant bone disease from advanced cancer (Coleman, 2004). Nitrogen-containing bisphosphonates, including zoledronic acid, pamidronate, and ibandronate, have demonstrated the most consistent efficacy compared with non-nitrogen-containing bisphosphonates, such as clodronate. The approved dosing schedules for the IV agents are summarized in Table 1 (Hoffmann-La Roche, 2004; Novartis Pharmaceuticals Corporation, 2008a, 2008b; Roche Products Ltd., 2007). Ibandronate has been approved for treatment of bone metastases from breast cancer only in Europe; clodronate has been approved only in Europe for treatment of bone metastases from breast cancer and bone lesions from multiple myeloma. Only pamidronate and zoledronic acid have received worldwide regulatory approval for treatment of bone metastases from breast cancer and bone lesions from multiple myeloma. In addition, zoledronic acid has received widespread regulatory approval for treatment of bone metastases from prostate cancer, lung cancer, and other solid tumors. Because of the approval of IV pamidronate and zoledronic acid in the United States, the American Society of Clinical Oncology consensus treatment guidelines specifically recommend IV bisphosphonates for patients with breast cancer and plain radiographic evidence of bone destruction (Hillner et al., 2003).

Among bisphosphonates evaluated in a review of randomized, placebo-controlled trials investigating skeletal events in women with bone metastases from breast cancer, zoledronic acid yielded the largest reduction in skeletal morbidity (Body et al., 2003, 2004; Hortobagyi et al., 1996, 1998; Kohno et al., 2005; Kristensen et al., 1999; Paterson et al., 1993; Pavlakis et al., 2005; Tubiana-Hulin et al., 2001) (see Figure 3). Zoledronic acid is the only bisphosphonate that has been compared head-to-head with pamidronate in a double-blind, randomized, controlled, phase III trial; zoledronic acid produced benefits beyond those of pamidronate in patients with bone lesions from breast cancer or multiple myeloma (Rosen et al., 2005). After 25 months of follow-up, multiple-event analysis showed that the risk of SREs was reduced by a relative 20% (p = 0.03) with zoledronic acid compared with pamidronate (Rosen et al., 2003). The safety profiles of zoledronic acid and pamidronate were similar, with the most commonly reported adverse events for each treatment group being bone pain (58% and 57%, respectively), nausea (48% for both), and fatigue (43% for both). Grade 3 or 4 increases in serum creatinine occurred in 0.4% of patients treated with zoledronic acid (4 mg via 15-minute infusion) and in 1.9% of patients treated with pamidronate (90 mg via two-hour infusion).

Osteonecrosis of the jaw (ONJ) is an uncommon adverse event that has been reported in patients with cancer receiving complex treatment regimens, including bisphosphonates. Patients with ONJ have exposed bone in the maxillofacial area that occurs in association with dental surgery or spontaneously, with no evidence of healing after six weeks of appropriate dental care in the absence of metastatic disease in the jaw or osteoradionecrosis. In the largest database study to date of ONJ in patients with solid tumors or multiple myeloma treated with
bisphosphonates (N = 4,019), the overall frequency of ONJ was approximately 0.8% (Hoff et al., 2008). Longer-term follow-up of ongoing trials and additional prospective studies will provide further information on the outcomes of ONJ. Recent investigations have shown that implementation of proactive dental surveillance and completion of necessary dental work prior to bisphosphonate therapy can decrease the incidence of ONJ, and that early identification and management of this condition may improve healing (Dimopoulos et al., 2009; Ripamonti et al., 2009).

Zoledronic acid is the only bisphosphonate to significantly reduce the risk of SREs (p ≤ 0.05) versus placebo in patients with bone metastases from a broad range of solid tumors (Kohno et al., 2005; Lipton, Seaman, & Zheng, 2004; Major, 2007; Major, Cook, Chen, & Zheng, 2005; Rosen et al., 2004; Saad et al., 2004) (see Figure 4). Although several bisphosphonates have been studied in patients with bone metastases from hormone-refractory prostate cancer, only zoledronic acid has demonstrated significant, objective, long-term benefits at two years of treatment (Dearnaley et al., 2003; Elomaa et al., 1992; Ernst et al., 2003; Kylmala et al., 1997; Saad, 2002; Saad et al., 2004; Small, Smith, Seaman, Petrone, & Kowalski, 2003; Smith, 1989; Strang et al., 1997). Zoledronic acid not only reduced the proportion of patients who had an SRE (38% versus 49% with placebo; p = 0.03) (Saad et al., 2004) but also consistently reduced the proportion of patients who experienced each type of SRE (Saad et al., 2002). At 15 months, the safety profile of zoledronic acid 4 mg was comparable with that of placebo. The most commonly reported adverse events for each treatment group were bone pain (51% and 61%, respectively), nausea (36% and 37%, respectively), and constipation (34% and 35%, respectively). Grade 3 increases in serum creatinine occurred in 15.2% of patients treated with zoledronic acid (4 mg via 15-minute infusion) and in 11.5% of patients in the placebo group. Because earlier treatment may be more effective, studies in patients with hormone-sensitive disease are ongoing. Despite the differences in established efficacy among the bisphosphonates tested in the prostate cancer...
setting, analyses have pooled all of the data, resulting in changes in healthcare policies. For example, zoledronic acid may be difficult to acquire in the United Kingdom because of National Health Service reimbursement issues in the urology setting, and many patients with prostate cancer may now go untreated or receive treatment with alternative bisphosphonates whose efficacy has not been established for tumors other than breast cancer.

Zoledronic acid also is the only bisphosphonate that has demonstrated significant benefits and received widespread regulatory approval in patients with bone metastases from lung cancer and other solid tumors. In a randomized, placebo-controlled trial of zoledronic acid (4 mg) every three weeks for 21 months in patients with lung cancer and other solid tumors, zoledronic acid reduced the number of patients with any SRE (including hypercalcemia of malignancy) compared with placebo (39% versus 48%, respectively; p = 0.04) (Rosen et al., 2004) (see Figure 5). In addition, zoledronic acid significantly delayed the median time to first SRE (236 versus 155 days with placebo; p = 0.009) and significantly reduced the skeletal morbidity rate (1.74 versus 2.71 SREs per year with placebo; p = 0.01). The safety profile of zoledronic acid (4 mg via 15-minute infusion) was comparable with that of placebo. The most commonly reported adverse events for each treatment group were bone pain (51% and 61%, respectively), nausea (49% and 36%, respectively), and anemia (38% and 35%, respectively). Grade 3 or 4 increases in serum creatinine occurred in 1.8% of patients who received that zoledronic acid regimen or placebo.

**Bone Pain and Quality of Life**

Bone metastases are the most common source of chronic pain in the advanced cancer setting, yet they may remain undetected and undertreated in many patients (Coleman, 1997; Peng, Wu, Sun, Chen, & Huang, 2006). Indeed, bone metastases have been identified as a source of pain that typically is not adequately treated, and the side effects associated with management of bone pain can impair patients’ QOL above and beyond the effects of the pain itself (Coleman, 1997).

Treatment of bone pain typically involves the concomitant use of focal radiotherapy and analgesic drugs, especially steroids and nonsteroidal anti-inflammatory drugs (often in combination with opioids) (Payne, 1989). Nonpharmacologic interventions can include heat and cold applications, therapeutic mattresses, massage, and relaxation exercises (Reich, 2003). Radiotherapy to bone is standard therapy for palliation of malignant bone pain that has become refractory to pharmaceutical interventions, and the need for palliative radiotherapy is one of the most prevalent SREs (Rosen et al., 2003, 2004; Saad et al., 2002, 2004). For example, in the placebo-control arms of long-term clinical trials of zoledronic acid and pamidronate in patients with malignant bone disease, 33%-37% of patients with bone metastases from solid tumors (breast, prostate, and non-small cell lung cancers) or bone lesions from multiple myeloma required palliative radiotherapy (Berenson et al., 1998; Lipton et al., 2000; Rosen et al., 2004; Saad et al., 2004). In a retrospective review of data from a clinical trial of zoledronic acid versus placebo in patients with prostate cancer (N = 248), radiation to bone reduced the extent to which bone pain interfered with patients’ daily activities (Weinfurt et al., 2005). However, having received radiotherapy also was associated with decreases in scores on the Functional Assessment of Cancer Therapy–General (FACT-G) for physical, functional, and emotional well-being at the patient’s subsequent FACT-G assessment, potentially because of adverse events from radiotherapy (Weinfurt et al., 2005). Therefore, palliative radiotherapy not only is a surrogate endpoint for bone pain but also is associated with decreases in health-related QOL (Weinfurt et al., 2005).

An additional class effect of bisphosphonates is clinically meaningful palliation for patients with refractory bone pain. In a randomized, placebo-controlled trial in patients with bone metastases from breast cancer (N = 144), the addition of the early-generation bisphosphonate clodronate (1,600 mg per day) to standard therapy for as long as 12 months was shown to significantly decrease pain according to visual analog scale pain scores (p = 0.01) and to reduce the need for analgesics (p = 0.02) (Tubiana-Hulin et al., 2001). Newer-generation nitrogen-containing bisphosphonates (e.g., pamidronate, ibandronate, risedronate, zoledronic acid) also decrease pain. Patients with bone metastases from breast cancer treated with pamidronate (90 mg; n = 185) had a smaller increase in bone pain compared with placebo (n = 195) after 12 months (p = 0.05) (Hortobagyi et al., 1996). In an open-label trial of zoledronic acid (4 mg) every three to four weeks for as many as six infusions in patients with breast cancer, prostate cancer, or multiple myeloma (N = 260), mean visual analog scale pain scores were significantly reduced after treatment compared to baseline in all patients overall and in each tumor type subset (p < 0.001) (Wiktor-Jedrzejczak, 2005). In the phase III trials, zoledronic acid significantly reduced the incidence of palliative radiotherapy to bone by 33% compared with placebo in men.
with prostate cancer ($n = 422$; $p = 0.03$), by $32\%$ compared with placebo in patients with lung cancer or other solid tumors ($n = 501$; $p = 0.01$), and by $18\%$ beyond the benefit of pamidronate in patients with breast cancer ($n = 766$; $p = 0.05$) (Major et al., 2005). The incidence of palliative radiotherapy also was reduced in a randomized, placebo-controlled trial in patients with advanced breast cancer ($N = 227$) treated with zoledronic acid ($8.8\%$ versus $17.7\%$ with placebo) (Kohno et al., 2005).

In a Cochrane meta-analysis of bisphosphonates for relief of bone pain secondary to bone metastases, their use was recommended for patients with diffuse, painful metastases, especially when analgesics (with or without radiotherapy) failed to provide adequate pain relief or produced unacceptable adverse drug reactions (Wong & Wiffen, 2002). Considering that pain is a symptom of bone metastases, healthcare professionals should consider therapies that are both palliative and able to treat the underlying source of the pain. Therefore, bisphosphonates should be considered for pain management in all patients with bone metastases because they are the only class of supportive therapy agents that has been demonstrated to not only relieve pain but also affect the underlying pathophysiology of bone metastases (malignant osteolysis).

**Practical Implications**

The role of nurses in the management of patients with metastatic bone disease is multi-faceted, involving administering anticancer therapy, conducting pain assessments, and counseling patients and caregivers about potential SREs and how to prevent and manage them (Reich, 2003). Nurses provide important ongoing support to patients by monitoring progress, side effects, and therapeutic outcomes. In addition to ensuring the safety of bisphosphonate administration (Berenson, 2005; Maxwell, 2007; Maxwell, Swift, Goode, Duane, & Rogers, 2003), nurses also can educate patients with regard to monitoring pain status and reducing fracture risk by incorporating changes in lifestyle and environment to prevent falls (Maxwell; Maxwell et al.) (see Figure 6). Assessments at baseline and throughout therapy are necessary to monitor how patients are responding to therapy and whether changes in treatment regimens are needed. Additionally, QOL assessments allow nurses to monitor patients’ well-being and ability to function in daily activities. Any changes in QOL or decreases in performance status during treatment may necessitate changes in disease management.

**Bone-Specific Quality-of-Life Assessment**

A newly developed QOL assessment specific to symptoms of bone metastases is being evaluated in phase III trials (Chow et al., 2007). The tool was developed to capture morbidity and effects not currently included in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (also known as the EORTC QLQ-C30). The new assessment tool consists of 22 questions rated on a scale from 1 (not at all) to 4 (very much) that are based on a patient’s experiences during the previous week. Most questions concentrate on pain, such as where and when pain occurred and the nature of the pain. The remaining questions address how the symptoms may interfere with daily activities and any worries that a patient may have about loss of mobility or decreased health. When validated, the tool should enable the accurate recording of QOL in patients with bone metastases and assist with appropriate treatment decisions (Costa, Badia, Chow, Lipton, & Wardley, 2008).

**Patient Diary**

Use of a patient diary for recording assessment results such as pain scores, new bone events, or adverse events may facilitate monthly interactions between nurses and patients (Schumacher et al., 2002). A diary can be filled out at each visit and provides an ongoing record of a patient’s progress. The diary allows a patient to record events and symptoms as they are experienced, on an ongoing basis, and gives the patient a sense of control over his or her symptoms (Reich, 2003). The diary also may assist the patient in recognizing early and more subtle benefits of therapy, which may improve adherence. Diaries promote discussion between patients and healthcare professionals about what has been recorded, help nurses motivate patients to continue therapy, and establish connections with patients. Diaries also may help nurses to identify when interventions are necessary to enhance QOL.

**Adherence to Therapy**

Adherence to an approved bisphosphonate dosing schedule can have a direct effect on treatment efficacy. Given that bisphosphonates are administered as a preventive intervention, patients might not appreciate the ongoing benefits of therapy because no direct effects can be observed. Therefore, patients may lose their motivation to take medication as prescribed during long-term treatment, especially if they do not have regularly scheduled follow-up visits. In an analysis of two U.S. health-claims databases comparing fracture rates among postmenopausal women with osteoporosis who were either persistent or nonpersistent with their oral bisphosphonate therapy ($n = 6,391$), only $20\%$ of patients were persistent with their therapy during 24 months, as indicated by no refill gaps of more than 30 days for their prescriptions. Fracture rates were significantly lower over 24 months among persistent versus nonpersistent patients ($p < 0.001$) (Siris et al., 2006). Although the analyses were in the benign setting, they illustrate that nonpersistence with bisphosphonate therapy may reduce treatment efficacy (Siris et al.). Moreover, in the overall patient population ($N = 35,537$), better adherence correlated with lower fracture risk. However, adherence with oral bisphosphonates may be poor because of administration requirements such as fasting before a dose and remaining upright after a dose to reduce gastrointestinal toxicity (Mangiapano, Hoefer, Gothe, Barghout, & Haeussler, 2006; Roche, 2006). For example, a retrospective analysis of German health insurance claims found that $50\%$ of patients with cancer who initiated oral bisphosphonate therapy stopped treatment within three to four months and that $65\%$ of patients stopped treatment within six months (Göl, Höer, Schifflhorst, Brandman, & Häussler, 2005). By providing education on the benefits of bisphosphonate therapy and enacting established supportive care protocols to
ensure patient safety and comfort during therapy, nurses may increase patients’ persistence and adherence to bisphosphate therapy to avoid SREs.

In general, patients receiving IV bisphosphonates have high adherence to their treatment. A retrospective analysis of a German health-claims database found that only 8% of patients with cancer who initiated IV bisphosphonate therapy stopped treatment within six months compared with 64% of patients with cancer receiving oral bisphosphonate therapy (Mangiapane et al., 2006). Clinical outcomes could be maximized through patient adherence to and persistence with bisphosphonate regimens. For example, persistent treatment with zoledronic acid reduced the incidence of monthly SREs compared with untreated patients (Hatoum, Lin, Smith, Barghout, & Lipton, 2008). Additionally, zoledronic acid (4 mg every three to four weeks) correlated with a reduction of at least 48% in the first six weeks) correlated with a reduction of at least 48% in the first six weeks) correlated with a reduction of at least 48% in the first six months of treatment compared with less frequent administration or no administration.
Conclusions

Bone metastases are common in patients with advanced malignancies, especially those with breast or prostate cancer, and are associated with bone pain and SREs. Because SREs and bone pain are associated with decreases in QOL and functional independence, any therapy that can reduce the number or severity of SREs also should reduce the negative effects of skeletal complications on QOL. Nurses can enact management strategies to ensure patient safety and comfort and to maximize adherence with effective treatment regimens.

Bisphosphonates prevent or delay potentially debilitating SREs and reduce bone pain. Further research may allow improvements in skeletal health monitoring and management for patients with metastatic bone disease. Such improvements may enable patients to better maintain their QOL and functional independence throughout the course of their disease. Nurses play an important role in assessing, administering treatment, and monitoring responses to therapy for patients with metastatic bone disease to reduce SREs in this population.

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References


Wong, R., & Wiffen, P.J. (2002). Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database of Systematic Reviews, 1*, CD002068.