

Bisphosphonate Therapy for Metastatic Bone Disease: The Pivotal Role of Nurses in Patient Education

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Purpose/Objectives: To describe the role of bisphosphonate therapy for metastatic bone disease and skeletal-related events associated with some of the most common malignancies, and to highlight the importance and untapped potential of nurses intervening in the education and treatment of patients with these issues.

Data Sources: Contemporary evidence-based studies on the prevalence and impact on quality of life in metastatic bone disease and skeletal-related events, and all major clinical trials describing the efficacy of bisphosphonates for the treatment of metastatic bone disease.

Data Synthesis: Metastatic bone disease is a common consequence of cancer that impairs patient quality of life. Bisphosphonate therapy is effective in preventing or delaying complications associated with metastatic bone disease.

Conclusions: Bisphosphonate therapy can help preserve functional independence and improve the quality of life for many patients with cancer. Poor adherence to bisphosphonate therapy frequently is caused by patients not understanding how the drug works or why they need it. Premature discontinuation of bisphosphonate therapy leaves patients at risk for painful and debilitating skeletal-related events, which reduces their functional independence and impairs their activities of daily living.

Implications for Nursing: Nurses are uniquely positioned to educate patients and their caregivers about the need to begin or continue taking bisphosphonates for treatment of metastatic bone disease and associated skeletal-related events. Nurses often are the most appropriate healthcare providers for counseling patients with metastatic cancer about personal and family issues and for communicating the needs and concerns of patients to their physicians.

Metastatic bone disease can occur with most solid tumors and multiple myeloma and signals significant progression of the underlying cancer (Coleman, 1997; Sabino & Mantyh, 2005). Skeletal-related events are caused by metastatic bone disease and refer to episodes of bone pain requiring the use of opioid analgesics or palliative radiation therapy, bone fractures and the surgery required to stabilize the fractures, spinal cord compression, and hypercalcemia of malignancy. Metastatic bone disease and associated skeletal-related events are the most common causes of pain in patients with cancer and are associated with a measurable decrease in quality of life and increased mortality (DeVita, Hellman, & Rosenberg, 2001; Lipton, 1997; Weinfurt, Anstrom, Castel, Schulman, & Saad, 2006). Bisphosphonate therapy prevents or delays the occurrence of skeletal-related events in patients with cancer (Hillner et al., 2000) and, as a result, directly improves patient quality of life (Rosen, Gordon, Dugan, et al., 2004; Rosen, Gordon, Tchekmedyian, et al., 2004; Saad et al., 2002). However, many

Key Points . . .

- Nurses should have a thorough understanding of the mechanisms of action and the adverse-event profile of bisphosphonates so they are comfortable educating patients about the drugs and the need for continued treatment.
- Programs developed for nurse-facilitated patient education must be applicable to a variety of nursing settings and complement existing patient oncology care programs.
- A nursing consensus guideline regarding the use of bisphosphonate therapy for patients with metastatic bone disease is needed.

patients who could benefit from bisphosphonate therapy do not receive treatment or they prematurely discontinue treatment because of a lack of information on why they should begin or continue to receive the drug. Because their healthcare providers may not have had the time to carefully explain how the drug works and what the common side effects are, the patient may decide to stop taking the medication when mild or expected and transient side effects do occur.

Prevalence and Affect of Metastatic Bone Disease and Skeletal-Related Events

Metastatic bone disease and associated skeletal-related events are common during the later stages of cancer (Coleman, 1997; Lipton, 2005; Saad, Olsson, & Schulman, 2004)

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Table 1. Prevalence of Bone Metastasis Across Tumor Types

Variable	Breast	Myeloma	Prostate	Lung and Other
Study	Lipton, et al., 2000	Berenson et al., 1998	Saad 2003	Rosen et al., 2004
Observation (months)	24	9	24	21

Variable	Patients Affected in Placebo Arm (%)			
Total skeletal-related events (excluding hypercalcemia)	64	51	49	46
Radiation to bone	43	34	33	34
Fractures	52	37	25	22
Hypercalcemia	13	9	1	4
Surgery to bone	11	5	4	5
Spinal cord compression	3	3	8	4

(see Table 1). Bone is the third-most common metastatic site after lung and liver, and as many as 90% of patients who die from breast cancer have bone metastasis (Mundy & Yoneda, 1995). The types of cancer that most commonly metastasize to the bone are breast, prostate, kidney, thyroid, and multiple myeloma. One of the most distressing skeletal-related events associated with metastatic bone disease is pathologic fracture, which has been reported in as many as 53% of patients with breast cancer and bone metastasis (Petrucci, Trinkaus, Simmons, & Clemons, 2008). The most common life-threatening skeletal-related event is hypercalcemia of malignancy, usually caused by hormones secreted by some of the most common tumors and/or cytokines, that stimulate the excessive resorption of calcium from bone (Gobel, 2005; Halfdanarson, Hogan, & Moynihan, 2006). One of the most common hormonal mediators is parathyroid hormone-related protein, which is associated with the hypercalcemia seen in a variety of common solid tumors and multiple myeloma (Horiuchi et al., 1997; Lee et al., 1997; Sriussadaporn et al., 2007). Although less common, hypercalcemia of malignancy also can result from calcium mobilization caused by lytic bone lesions (DeVita et al., 2001).

Symptomatic Treatment of Metastatic Bone Disease and Skeletal-Related Events

Hypercalcemia of malignancy is characterized by lethargy, anorexia, nausea, thirst, dehydration, constipation, confusion, and unsteady consciousness. Because the appearance of metastatic bone disease signals advanced disease, it also is associated with significant psychological consequences that may, in turn, limit functional capabilities (Saad et al., 2004; Weinfurt et al., 2005). Metastatic bone disease often is seen as an indication that the disease is no longer curable and the therapeutic focus changes from life preservation to function preservation. Patients may experience anxiety or depression from the realization that they may soon die. The need for opioid analgesics to treat the pain also carries negative emotional consequences. Some patients may feel like they are addicted to the drugs or that others will perceive them to be (National

Cancer Institute [NCI], 2008). In addition, opioids can have physical side effects that can negatively affect the patient's functional independence. Most skeletal-related events are associated with loss of functional independence, reduced physical capacity, and diminished quality of life (Coleman, 1997; Cooper, 1997; Weinfurt et al., 2005). Because of the need to medically manage the pain and, in some cases, surgically stabilize fractures, skeletal-related events also are associated with increased care costs (Delea et al., 2005; McKiernan et al., 2004).

The focus during disease progression should be on preserving the emotional and functional well-being of the patient. Nurses can play a pivotal role through education and reassurance. Functional independence often can be prolonged through effective exercise and other activity-related programs that can help decrease fatigue and mood disturbance and improve sleep (Coleman et al., 2003). A study of 52 women with breast cancer by Mock et al. (2001) found that a home-based exercise program was an effective and low-cost intervention that managed fatigue and improved quality of life during chemotherapy and radiation therapy. Patients who regularly exercised before being diagnosed with cancer are most inclined to maintain a regular exercise program after the diagnosis; therefore, nurses should pay particular attention to individuals who lead a sedentary lifestyle and provide nursing support and education regarding the importance of exercise routines (Pickett et al., 2002). However, exercise and simple activities, such as getting out of bed or getting up from a chair, can be difficult because of the severe pain associated with bone metastases. Effective pain treatment is, therefore, a key component of any program that is successful in maintaining mobility in these patients. Nonsteroidal anti-inflammatory medications would ideally be all that is needed for pain relief. Indeed, some recent evidence suggests that COX-2 may be involved in the development of bone metastases from breast cancer and that COX-2 inhibitors may therefore play a role in helping to prevent bone metastases and, therefore, bone pain (Singh et al., 2007). But the pain associated with bone metastases often is so severe that narcotic pain medications are needed. Continuous or high-dose narcotic therapy causes constipation and lethargy side effects.

Bisphosphonates

Bisphosphonates are the most common drugs used for the medical management of skeletal-related events in patients with cancer and metastatic bone disease (DeVita et al., 2001). Extensive evaluation in multiple clinical trials has shown bisphosphonates to be effective in reducing pain and limiting the occurrence of fractures. Bisphosphonates are categorized as bone resorption inhibitors in that they interfere with the metabolic activity of osteoclasts and inhibit calcium released from the bone. Bisphosphonates, therefore, effectively limit lytic activity of bone metastases and delay or prevent occurrence of skeletal-related events (Saad et al., 2002). At least five different bisphosphonates are available, although most have limited indications. Only zoledronic acid has been proven effective for skeletal-related events associated with prostate cancer and other solid tumors (see Table 2). As a result, zoledronic acid also is the only bisphosphonate approved for treatment of bone metastases associated with solid tumors.

The route of administration (oral or IV) varies depending on the compound. Some preparations, such as ibandronate and clodronate, can be given either orally or IV, whereas others, such as zoledronic acid and pamidronate, are given IV. Common side effects of oral bisphosphonate therapy include nausea, constipation, and dyspepsia (Vogel et al., 2004), events which can be severe enough to discontinue treatment (Wu, Dahut, & Gulley, 2007). Alternatively, switching to IV bisphosphonate therapy should be considered. Adverse events are much less common with IV therapy, but do include fever, arthralgias, and anemia. Transient, flu-like symptoms are not uncommon following the first dose of IV bisphosphonates. Renal adverse events, characterized by elevated serum creatinine, also have been reported with IV bisphosphonate therapy (Berenson, 2005; Major, 2004). Osteonecrosis of the jaw is an uncommon event that has been reported in patients with cancer receiving complex treatment regimens including radiation, chemotherapy, and other treatments. Reports also have surfaced of osteonecrosis of the jaw in patients with cancer who use an IV bisphosphonate treatment regimen (Weitzman et al., 2007). Invasive dental procedures and poor oral health are among the suspected risk factors for this issue (Novartis Pharmaceuticals, 2006b; Sambrook, Olver, & Goss, 2006). Patients are encouraged to have a dental examination and complete any necessary surgical dental procedures before they start bisphosphonate therapy (Novartis Pharmaceuticals, 2006b; Weitzman et al.). Patients who are taking bisphosphonates and exhibit exposed bone in the oral cavity should be referred to a dental professional for appropriate evaluation as soon as possible (Weitzman et al.). Advocacy for oral health and follow-up on oral symptomology is an opportunity for nursing intervention and education regarding bisphosphonate therapy.

Patients may survive for many years after they develop bone metastasis (Weinfurt et al., 2005). Therefore, they also may develop skeletal-related events, become disabled, or struggle with diminished quality of life for many years. Bisphosphonates, particularly zoledronic acid, limit the development of skeletal-related events and improve patient quality of life (Hillner et al., 2000). In a Cochrane Database of Systematic Reviews study of nine randomized clinical trials of women with breast cancer and clinically evident bone metastases ($N = 2,189$), bisphosphonates were found to reduce the risk of developing skeletal-related events by 17% (Pavlakakis, Schmidt, & Stockler, 2005). However, the risk reduction varied substantially among the available bisphosphonate formulations. The largest risk reduction was 41%, seen with zoledronic acid therapy at a dose of 4 mg IV; pamidronate 90 mg IV resulted in a 23% risk reduction; and ibandronate and clodronate were associated with risk reductions of 18% or less.

Table 2. Uses of Available Bisphosphonate Therapies

Drug	Hypercalcemia of Malignancy	Breast Cancer	Multiple Myeloma	Prostate Cancer
Clodronate	X	X	X	
Etidronate	X			
Pamidronate	X	X	X	
Ibandronate	X			
Zoledronic acid	X	X	X	X

Note. Based on information from DeVita et al., 2001.

Medications cannot be effective if they are not taken as prescribed and evidence suggests that poor adherence to bisphosphonate therapy is associated with increased medical complications. In a study of 35,537 women who were prescribed bisphosphonates for osteoporosis, a significant relationship was found between bisphosphonate prescription refill adherence and fracture risk reduction (Siris et al., 2006). After 24 months, a 45% relative risk reduction for fractures was seen in patients who took their medication. According to a Kaiser Permanente study, dosing frequency was the strongest predictor of medication adherence and persistence (Cramer, Amonkar, Hebborn, & Altman, 2005). Patients receiving weekly dosings had significantly higher adherence and longer persistence with the treatment compared to those on daily dosings. In addition to the side effects and other difficulties associated with oral bisphosphonate therapy, another reason for poor bisphosphonate adherence may be that treatment benefits, particularly a reduction in bone pain, are often not realized until several weeks or months after the start of therapy. As a result, one study of patients with cancer receiving oral bisphosphonates found that 65% of patients stopped taking the drug within six months of therapy initiation (Hoer et al., 2005). Others also have found that oral bisphosphonate therapy is associated with poor adherence compared with IV administration (Reid et al., 2002). Although oral ingestion might otherwise be considered preferable, it is associated with uncomfortable gastrointestinal side effects, such as nausea, dyspepsia, acid indigestion, diarrhea, and constipation; all symptoms that are not an issue with IV treatment (Heatley, Lothman, & Major, 2006; Heidenreich, Hofmann, & Engelmann, 2001; Major et al., 2001). In addition, proper absorption of the oral formulation requires that the patient fast both before and after taking the medication and remain upright for a period of time after ingestion.

Critical Role of Nurses as Educators and Healthcare Providers

Oncology nurses can take on several roles, such as educator, patient advocate, compassionate caregiver, and insightful listener, that can help educate patients regarding bisphosphonate treatment and enhance patient adherence and improve outcomes. The benefits of treatment with bisphosphonates are well-established, but the various types of bisphosphonates and their indications, administration methods, and safety profiles require decisions that must be made regarding not only the advisability of bisphosphonate treatment, but also which drug and administration route is appropriate for the patient. A lack of understanding on the part of nurses regarding bisphosphonates was identified by nurses as the main barrier to providing education to patients (Novartis Pharmaceuticals, 2006a). Participants agreed that an educated patient is most likely to adhere to bisphosphonate therapy recommendations.

In most oncology clinics, the nurse is the most appropriate person to provide primary education regarding the need for treatment. Because of this, nurses should have a clear understanding of the indications for bisphosphonate therapy, the mechanism of action of these drugs, and possible treatment side effects. Patients have varying educational needs and should be individually assessed on how to best communicate details regarding their disease treatment. Gender or social or educational status may determine a patient's inclination to

ask questions about the disease or therapy. Unfortunately, patients often believe that they will be labeled as “bad” patients or that their questions will impede the quality of care they receive if they ask too many questions (NCI, 2008). Other patients actively avoid discussions about their disease because they do not want to be reminded of it. As a result, some patients will avoid going to support groups and choose instead to trust what the doctor is telling them without question. It often falls to the nurse to initiate a dialogue about pain or other issues that have a significant affect on the patient’s quality of life.

Most patients with cancer are not aware of the signs and symptoms of metastatic bone disease or the consequences of the complication. Other patient education needs may be broadly characterized as a need for reassurance, a need for an explanation of treatment benefits, and a need for details about the treatment mode. A need to reassure patients that bisphosphonate therapy will be effective and that they are receiving the latest and best-studied formulations is specifically needed. Bisphosphonate treatment is not chemotherapy and the difference should be explained to the patient. Likewise, the benefits of bisphosphonate treatment also should be emphasized, such as limiting or preventing the development of skeletal-related events or delaying their occurrence. The ability of bisphosphonate therapy to restore function, in part through reducing pain, also should be emphasized. A final but important component of patient education programs should be practical details about the therapy itself. Patients should clearly understand how and how often the drug should be administered, how long they should expect to be treated, and what side effects they might expect. If patients are forewarned about the possibility of gastrointestinal side effects with an oral bisphosphonate, they are less likely to discontinue therapy if such symptoms occur.

Guidelines for bisphosphonate therapy in treating patients with metastatic bone disease and skeletal-related events are needed and should be developed to assist nurses caring for patients with cancer. Nurses are uniquely positioned to communicate the importance of bisphosphonate therapy and are more likely than other healthcare providers to spend the necessary time educating and listening to the patient’s concerns and questions. Nurses typically establish a relationship with the patient that involves a level of comfort and trust that is sometimes not possible in the doctor-patient relationship. Because of this, the nurse can greatly influence the likelihood that the patient will understand the need for bisphosphonate therapy, resulting in better treatment adherence. The patient’s quality of life will improve and he or she will be far less likely to prematurely discontinue therapy. However, to fulfill this role, the nurse must be comfortable with the details of bisphosphonate therapy, including the mechanism and duration of action of the drug, how the drug is administered, common side effects, and how to assist the patient in managing those side effects.

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