Bisphosphonates: Expanded Roles in the Treatment of Patients With Cancer

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Bisphosphonates are a class of drugs originally developed for and used in the treatment and prevention of osteoporosis; they are now known to be instrumental in the treatment of bone metastases and hypercalcemia of malignancy. Several oral agents have been used for osteoporosis, and, although side effects are associated with oral bisphosphonates, their advantages in the treatment of this often debilitating illness have been a therapeutic boon to patients with osteoporosis. In particular, since the advent of new warnings about the use of hormone replacement therapy in menopausal women, bisphosphonates may carry an even more important role in the prevention of osteoporosis-related fractures.

Although bisphosphonates first were used in osteoporosis, these agents are effective in treating bone metastases, reducing skeletal-related events, and decreasing risk of spinal cord compromise (Ali et al., 2001; Van Poznak, 2002). Many patients with cancer develop metastases to bone, which affects quality of life and contributes to the morbidity of the disease. Bisphosphonates are useful in the treatment and prevention of fractures related to metastatic disease and are the treatment of choice for hypercalcemia of malignancy; researchers currently are looking at these agents in the treatment of cancer as well.

Bisphosphonates are important inhibitors of osteoclastic bone resorption seen in patients with bone metastases associated with malignancy. Bisphosphonates are used in the treatment of patients with bone metastases and have been shown to reduce skeletal-related events and symptoms, contributing to improved patient outcomes and quality of life. These agents first were approved in the treatment of patients with osteoporosis and have been used for the past two decades in this role. Because bisphosphonates inhibit osteoclast-mediated bone resorption, the bone remodeling cycle slows down and an increase in bone mineral density occurs. These agents are useful in treatment for both hypercalcemia and pain, although they have not definitively shown improvement in survival time. Considerable interest exists in the use of bisphosphonates for prevention of bone metastases and their potential antitumor activity. These drugs are well tolerated and have minimal side effects, but they are not inexpensive. This article discusses the role of bisphosphonates in patients with cancer and future directions for further research.

Key Words: neoplasms, metastases, bone; hypercalcemia; osteoporosis

Bisphosphonates in the Treatment of Osteoporosis

Osteoporosis is characterized by low bone mass and deterioration of bone, leading to bone weakness and an increased susceptibility to fractures. Bone density correlates with bone strength and is a major determinant of fracture risk. Osteoporosis is responsible for 1.5 million low-trauma fractures per year, and the incidence is much higher in women than in men. One of every two women and one in eight men older than 50 will have an osteoporosis-related fracture in their lifetimes. Risk factors for osteoporosis include Caucasian race, low weight or history of weight loss, and history of previous fracture or family history of fracture (Messinger-Rapport & Thacker, 2002).

The World Health Organization has defined low bone mass, osteopenia, as bone mineral density (BMD) 1.0–2.5 standard deviations below the mean for a young adult woman. Osteoporosis is defined as BMD equal to or greater than 2.5 standard deviations below the young adult mean (Miller & Lane, 2001).

The indications for bone mass measurement are to diagnose osteopenia or osteoporosis, predict fracture risk, and monitor the response of BMD to therapy. The dual-energy x-ray absorptiometer is the examination most commonly used because it depicts early bone loss (see Figure 1).
A dual-energy x-ray absorptiometer scan shows the lumbar spine of a 32-year-old man on prednisone for juvenile rheumatoid arthritis. The gradients of color are a visual representation of bone density; green represents more dense bone, and red indicates severe bone thinning. The red line through the graft is the mean average bone density score, and the black lines represent two standard deviations above and below the mean measurement. This patient’s measurements of his lumbar spine are represented by the white box, which falls below the standard deviation. The patient’s T score is –3.4, and he was diagnosed with osteoporosis.

**FIGURE 1. DUAL-ENERGY X-RAY ABSORPTIOMETER SCAN OF LUMBAR SPINE**

(Messinger-Rapport & Thacker, 2002; Miller & Lane, 2001). Plain radiologic films may not show evidence of bone loss until 30%–50% of the bone is gone (Struthers, Mayer, & Fisher, 1998). Measurement devices are categorized by whether they measure the central skeleton (hip and spine) or the peripheral skeleton (finger, heel, tibia, and wrist or forearm).

The prevention of osteoporosis may involve adequate intake of vitamin D, oral calcium, and exercise (see Figure 2). Treatment of osteoporosis involves intake of oral calcium, vitamin D, calcitriol, and bisphosphonates; until recently, hormone replacement therapy played a significant role in the prevention of osteoporosis as well as other conditions related to menopause (Messinger-Rapport & Thacker, 2002). Both alendronate and risedronate are approved for the prevention and treatment of osteoporosis. The evidence to date supports the effectiveness of bisphosphonates in the treatment of women with severe osteoporosis; however, oral bisphosphonates must be dosed carefully to increase patient tolerance and absorption (Hodsman, Hanley, & Josse, 2002). Certain foods and medications can inhibit absorption (Berenson & Lipton, 1999). Researchers recently have been interested in IV bisphosphonates for patients with osteoporosis, although they are not yet approved for this use.

Patients with cancer receiving agents that promote osteoclastic bone activity (e.g., corticosteroids, heparin, anticonvulsants) or those who have chemotherapy-induced ovarian failure are at risk for osteoporosis. Women receiving aromatase inhibitors have been shown to have an increased risk for fracture (Munster & Horton, 2001). About 22% of women with breast cancer are premenopausal at diagnosis, and 63% or more of these patients experience chemotherapy-induced ovarian failure within one year of receiving chemotherapy with cyclophosphamide (Mincey, 2003). These patients have a higher risk of accelerated bone loss, possibly increasing their fracture risk (Mincey). Oral bisphosphonates are not well absorbed (1%–10% of the oral dose actually is absorbed), they must be taken on an empty stomach, and the patient must remain in an upright position for 30 minutes after the dose. Gastrointestinal toxicity, especially esophagitis and ulcer formation, can occur (Berenson & Lipton, 1999). These agents are much more effective when given via IV (Wade, 2001).

Osteoporosis also plays a significant role in patients with prostate cancer. Postmenopausal women have been studied extensively with regard to osteoporosis, but the condition has not been researched well in men (Gholz, Conde, & Rutledge, 2002). Many men receive androgen deprivation therapy for treatment of prostate cancer; both bilateral orchiectomy and gonadotropin-releasing hormone agonist treatment can cause a decrease in BMD, thus increasing fracture risk (Dawson, 2002; Gholz et al.). When patients with prostate cancer receive androgen therapy, osteoblastic bone formation activity is decreased and osteoclastic activity increased, creating an opportunity for osteoporosis to occur (Gholz et al.). Bisphosphonates are useful in prevention of this side effect and should be considered for patients with prostate cancer who are at risk for osteoporosis.

Two specific pharmacologic classes of bisphosphonates exist: nitrogen-containing and non-nitrogen–containing compounds. The non-nitrogen–containing agents include etidronate, clodronate, and tiludronate and have a relatively low potency (Major, 2002). The nitrogen-containing drugs include pamidronate and zoledronic acid and are considerably more potent; zoledronic acid is the most potent bisphosphonate available (Major).

**Patients With Cancer and Bone Metastases**

Patients with advanced cancer may develop metastases to bone; breast, lung, prostate, kidney, and thyroid cancers account for more than 80% of metastatic bone disease (Elomaa, 2000; Maisano, Pergolizzi, & Cascini, 2001). Patients with multiple myeloma usually develop osteolytic lesions that are present at the onset of the diagnosis of the disease, with about 30% of those patients suffering from...
Pathophysiology of Bone Metastasis in Patients With Cancer

Normal bone formation is a process that usually involves three steps: producing the extracellular organic matrix, mineralizing the matrix to form new bone, and bone remodeling by resorption and reformation (Mellors, 2003). Osteoblasts are the precursors of bone matrix and regulators of mineralization. Osteoclasts (derived from hematopoietic stem cells) are attracted to areas of fatigue or old bone and break it down, leaving osteoblasts to fill in cavities; both are essential in the process of bone remodeling (Mellors). Osteoblasts manufacture and lay down the precursors of collagen, which accounts for 90%–95% of the organic matrix of bone (Gholz et al., 2002). As the body begins to form bone, osteoblasts lie in lacunae, which are small spaces within the mineralized matrix. When they come to rest in the lacunae, the osteoblasts are called osteocytes (Mellors).

Osteoclasts are thought to be activated by signals from osteoblasts. The process of bone remodeling usually is self-regulated in response to the needs of the body, but in the case of patients with multiple myeloma, bone resorption by osteoclasts increases and excess bone reformation, with osteoclast activity responding to osteoclastic activating factors (OAFs) (Berenson & Lipton, 1999; Shipman et al., 2000). Cancer cells basically increase osteoclast differentiation, and bone biopsies in women with breast cancer have shown an increase in number of osteoclasts, whether in bone next to tumor cells or directly in the affected bone (Body & Mancini, 2002). Inhibition of osteoclasts may be initiated by calcitonin, estrogen, some interleukins (both 4 and 13), interferon-gamma, prostaglandin E, transforming growth factor-beta, and insulin growth factor (Gholz et al., 2002).

Osteoblastic lesions are believed to be caused by tumor-induced stimulation of factors that create proliferation of the osteoblasts (Dawson, 2002). Bone lesions related to metastatic breast cancer and multiple myeloma are thought to be primarily osteolytic lesions; metastatic prostate cancer produces mostly osteoblastic lesions; however, morphologic examination usually reveals a mix of both lesions in most patients with bone metastases (Dawson).

Bone metastases occur more frequently in areas of the skeleton with a higher proportion of trabecular bone, such as the axial skeleton (Diel et al., 2000). The spine is affected most often, then the pelvis, hip, upper leg bones, and skull. Cancer cells are attracted to bone surfaces by the products of resorbing bone and then destroy bone with stimulation of the osteoclasts (Body & Mancini, 2002). Osteoclasts are released locally to resorb bone in response to tumor-induced factors or OAFs (Dawson, 2002). These factors include parathyroid hormone-related protein, interleukin-6, interleukin-1, tumor necrosis factor-a, and macrophage inflammatory protein-1a (Dawson). The growth factors and cytokines that are secreted by the turnover of bone also may increase the rate of micrometastases, leading to a detrimental cycle of interactions that characterize the process of tumor osteolysis (Diel et al., 2000). The goal of bisphosphonate therapy is to interrupt the interactions between the tumor cells and bone processes.

Diagnosis of Bone Metastasis

Patients with bone metastases frequently complain of pain, which usually is the presenting symptom; for some patients, the initial presentation of bone metastases may be a pathologic fracture. Fractures from bone metastases usually are preceded by a period of increasingly severe pain, although some patients may deny their symptoms or attribute the pain to muscle pulls or strains (Benjamin, 2002). Diel et al. (2000) reported that 80% of patients with breast cancer with bone metastases had at least one episode of severe bone pain requiring treatment. Some patients with breast cancer reported a period of intense bone pain prior to an actual fracture (Diel et al., 2000).

Both nuclear medicine bone scans and plain radiographic films are used to diagnose bone metastases; computerized tomography and magnetic resonance imaging scans also are sensitive indicators of metastasis (Struthers et al., 1998) (see Figures 3, 4, 5, and 7). Bone scans depict the metabolic reaction of bone to the disease process, which may be caused by tumor, inflammation, or trauma. Bone scans usually reflect bone metastases earlier than plain radiographic films because the reactive bone produces a focal increase in tracer uptake. Plain radiographic films of the symptomatic area still should be taken because pure lytic lesions may not always present on bone scans; if a film is positive, a full body nuclear medicine scan should be ordered (Kori, LaPerriere, Kowalski, Rodriguez, & Dinwoodie, 2002).

In patients without a diagnosis of cancer, the diagnosis must be made by biopsy to determine tissue type and pathologic diagnosis. Although bone metastasis is common in advanced cancer, some patients present with solitary bone pain and are found to have metastatic disease without a history of cancer. In one unusual case, a woman was found to have heel pain as her initial presenting symptom and ultimately was diagnosed with a rare metastatic calcaneal lesion from a primary endometrial adenocarcinoma (Manolitsas, Fowler, Gahbauer, & Gupta, 2002). Persistent bone pain in patients without cancer and no history of precipitating factors should be evaluated thoroughly.

After a diagnosis of metastatic disease is made, palliative treatment is offered. Although treatment may involve surgery to stabilize or treat fractured bones, radiation, hormone therapy, or chemotheraphy (Struthers et al., 1998), this article will focus on the role of bisphosphonates.

Activity of Bisphosphonates in Patients With Cancer

Bone Metastasis

IV bisphosphonates pamidronate and zoledronic acid, as well as oral clodronate and ibandronate, have been shown to reduce skeletal-related events in patients with cancer and bone metastases (McCloskey, Dunn, Kanis, MacLennan, & Drayson, 2001; Mundy, 2002). Bisphosphonates are chemical analogues of pyrophosphate, which bind to bone.
at sites of active bone remodeling (Diel et al., 2000; Theriault & Hortobagyi, 2001). Pyrophosphate is a natural inhibitor for bone demineralization (Maisano et al., 2001). Because bisphosphonates act as osteoclast inhibitor drugs, they are ideal in the treatment of increased osteoclastic activity in patients with bone metastases (Maisano et al.). When bisphosphonates bind to bone, they help to stabilize the bone mineral and inhibit breakdown (Maisano et al.). Bisphosphonates seem to prefer sites of active bone remodeling, localizing in these areas of increased activity (Body & Mancini, 2002).

Pamidronate’s efficacy was determined in a large study of 380 women with stage IV breast cancer who were receiving chemotherapy and had at least one lytic bone lesion (Hortobagyi et al., 1996). The women were randomized into two groups receiving either 90 mg of pamidronate or placebo. The women in the pamidronate group had a longer median time to occurrence of first skeletal complication (13.1 versus 7.0 months, respectively), and the number of patients who experienced skeletal complications was lower (43 percent versus 56 percent, respectively) (Hortobagyi et al.). Pamidronate also experienced less bone pain and better performance status than the placebo group, and the researchers concluded that monthly infusions of pamidronate as a supplement to chemotherapy can help to protect women with stage IV breast cancer and bone metastases (Hortobagyi et al.).

Another trial looked at women with breast cancer receiving hormonal therapy and found similar results (Theriault et al., 1999). The study randomized 372 women with bone metastases to pamidronate 90 mg or placebo. Time to first skeletal-related event was longer for the pamidronate group (10.4 versus 6.9 months, respectively), and the total number of skeletal complications was reduced (56% versus 67%, respectively) (Theriault et al.). These studies and others led to pamidronate’s approval for use in patients with breast cancer or multiple myeloma with osteolytic lesions associated with bone metastasis (Cohen et al., 2002).

Zoledronic acid is the most recently approved bisphosphonate for bone metastasis (Berenson et al., 2002). Its indication is broader than that of pamidronate, and it is a highly potent bisphosphonate (Berenson et al., 2001). In a phase I trial of 59 patients with cancer and bone metastases, zoledronic acid was determined to be an effective inhibitor of bone resorption and was well tolerated. The studied dose was 8 mg, and the infusions were given over five minutes; however, in subsequent trials, renal toxicity was seen in patients receiving the same dose and infusion.
Bisphosphonates have been shown in some studies to reduce bone complications in breast cancer with improvement in quality of life but without a definitive improvement in survival (Hillner et al., 2000). Three European trials studied the role of bisphosphonates, specifically oral clodronicate (not yet available in the United States), as adjuvant therapy for patients with breast cancer (Diel et al., 1998; Powles et al., 2002; Saarto, Blomqvist, Virkkunen, & Elomaa, 2001). The results of the trials were conflicting. The American Society of Clinical Oncology (ASCO) guidelines on the role of bisphosphonates in breast cancer concluded that these agents provide an important supportive but not life-prolonging benefit to many patients with cancer, identifying the need for further study of their use for patients with bone metastases (Hillner et al.). Recently, ASCO provided new guidelines for the use of bisphosphonates in patients with multiple myeloma (Berenson et al., 2002). The expert panel also concluded that the class of drugs was useful in providing a meaningful and supportive benefit to patients with multiple myeloma (Gordon et al., 2002). Sixteen newly diagnosed patients were given a single infusion of pamidronate, and the researchers found a significant increase in the amount of apoptosis of plasma cells in 10 of the 16 patients (Gordon et al.). Both zoledronic acid and pamidronate were shown to have activity in apoptosis in plasma cells in vitro as well. This finding creates interest in the antitumor activity of these agents (Gordon et al.). Kondo and Mori (2002) published a case report of a patient with multiple myeloma who was treated with pamidronate disodium every three weeks for 18 months; no additional chemotherapy agents were given. The patient exhibited a marked reduction of marrow plasmacytosis and serum paraprotein levels, along with an increase in BMD, suggesting an antitumor effect of the agent (Kondo & Mori). Researchers also have seen an increase in survival in some patients with multiple myeloma receiving pamidronate, although definitive evidence that bisphosphonate therapy was the cause has not been proven (Musto, 1998; Shipman et al., 2000).

Animal models showed that bisphosphonates actually impaired the progression of bone metastasis through the enhancement of apoptosis in osteoclasts and breast cancer cells colonized in bone (Yoneda et al., 1999). Preclinical studies also showed a reduction in the tumor volume of bone by zoledronic acid, with increase in tumor cell apoptosis in a murine model of mammary carcinoma metastasis (Mundy, Yoneda, & Hiraga, 2001). In 1995, three bisphosphonates—risedronate, clodronate, and pamidronate—were found to promote apoptosis in osteoclasts in mice (Hughes et al., 1995). Researchers also found that pamidronate promoted apoptosis in human melanoma cells in vitro, suggesting a direct antitumor effect, as well as an effect on osteoclasts and bone metastasis (Riebeling, Forsa, Raisova, Orfanos, & Geilen, 2002). The bisphosphonate ibandronate induced apoptosis on human breast cancer cells as well as osteoclast cells in bone metastasis (Hiraga, Williams, Mundy, & Yoneda, 2001). Because these agents have been found to have antitumor activity in breast and other cancer cells in vitro, more research is needed to determine their further inhibitory role in patients with cancer (Body & Mancini, 2002).

A recent article described pamidronate as having a role in inducing apoptosis of plasma cells in vivo in patients with multiple myeloma (Gordon et al., 2002). Patients received either 4 mg or 8 mg of zoledronic acid, and the pamidronate dose was 90 mg. The trial was not designed to show superiority of zoledronic acid over pamidronate (Rosen et al.). The findings helped to lead to approval of zoledronic acid in a 4 mg dose with an infusion time of 15 minutes to lessen the risk of renal toxicity.

Zoledronic acid is indicated for patients with multiple myeloma and those with documented bone metastases from solid tumors, in conjunction with antineoplastic therapy. Unlike pamidronate, zoledronic acid also has shown activity in osteoblastic metastasis, the dominant lesion seen in metastatic prostate cancer to bone. In a randomized, placebo-controlled trial of 643 patients with prostate cancer and hormone-refractory disease, patients in the zoledronic acid group showed reduced pain and analgesic scores compared to the placebo group (Saad et al., 2002). Although no difference was found in disease progression or quality-of-life scores, the researchers concluded that zoledronic acid reduced skeletal-related events in patients with prostate cancer and bone metastases (Saad et al.). Zoledronic acid is indicated for patients with prostate cancer who experience progressive disease after at least one hormonal therapy (Cohen et al., 2002).

**Cancer Cell Effects**

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**Figure 6. X-Ray of Left Humerus**

Patient with multiple myeloma with prior spinal cord compression and surgical intervention (the same patient seen in Figure 4) sustained a fractured clavicle when he reached for the phone on his bedside table and felt his collar bone snap.

**Figure 7. Left Humerus Following Orthopedic Intervention**

Same patient seen in Figures 4 and 5 presented with pain in his arm with large lytic lesions visible on x-ray.
patients with multiple myeloma (Berenson et al., 2002). However, the panel also believed that further research was needed to determine additional factors: when to start and stop therapy, integration of bisphosphonates with other treatments, and their role in patients without lytic involvement (Berenson et al., 2002). After treatment is initiated for metastatic bone disease in patients with breast cancer, therapy usually is given for the remainder of the patients' lives (Diel et al., 1998).

### Bisphosphonates and Hypercalcemia

Tumor-induced hypercalcemia is considered to be an oncologic emergency and must be treated promptly to improve patient outcomes and prevent morbidity and mortality. About 10%–20% of patients with cancer develop hypercalcemia; patients with breast and lung cancers are among the most frequently affected (Chisholm & Taylor, 2002). Although ionized calcium levels are the best measure of active calcium, some institutions may not be able to perform the test; therefore, total serum calcium assays (with correction of albumin) may be used to determine serum calcium levels (Chisholm & Taylor). Patients with severe hypercalcemia (serum concentrations above 14 mg/dl) may exhibit symptoms of fatigue, gastrointestinal disturbances, bone pain, confusion, and lethargy (Chisholm & Taylor). Dehydration may occur if patients have polyuria or polydipsia.

Bisphosphonates now are the mainstay of treatment for hypercalcemia because they are efficacious and well tolerated (Maisano et al., 2001). Both pamidronate and zoledronic acid are approved by the U.S. Food and Drug Administration (FDA) for treatment of hypercalcemia; parenteral clodronate also has been studied in Europe and Canada in patients with hypercalcemia. In a dose-finding study, researchers discovered that both the 60 mg and 90 mg doses of pamidronate were effective in treating hypercalcemia (Nussbaum et al., 1993). In 1995, a study showed superiority of pamidronate compared to clodronate in reducing the level of calcium in the serum (Purohit, Radstone, Anthony, Kanis, & Coleman, 1995). Forty-one patients were randomized to receive pamidronate 90 mg infusion or 1500 mg of clodronate. All of the patients in the pamidronate group (n = 19) developed normal calcium levels compared to 16 of 20 patients in the clodronate group, with duration of normal calcium for the pamidronate group 14 days longer than the clodronate group 14 days longer than the clodronate patients (Purohit et al.). Pamidronate is indicated for both moderate and severe hypercalcemia related to malignancy, with or without skeletal metastasis.

Although patients with hypercalcemia can be treated with pamidronate or zoledronic acid, zoledronic acid is the most potent nitrogen-containing bisphosphonate to date and was approved by the FDA in the treatment of hypercalcemia in 2001. Two large, randomized phase III trials established the superiority of zoledronic in comparison to pamidronate (Major et al., 2001). A total of 287 patients were enrolled in the study. Results showed that the complete response (CR) rates for patients treated with zoledronic acid (4 mg) were 88.4% compared to the pamidronate (90 mg) group at 69.7% (Major et al.). Patients receiving the 8 mg dose of zoledronic acid showed CR rates of 86.7%. Two patients in the 8 mg zoledronic acid group and one in the 90 mg pamidronate group developed grade 4 serum creatinine values. Researchers recommended the lower dose of 4 mg of zoledronic acid as initial therapy for most hypercalcemic patients, leaving the 8 mg dose as a consideration for patients not responsive to the first treatment. In addition, the median time to relapse and median duration of response were longer in the group of patients receiving zoledronic acid (Major et al.). Therefore, based on these results, zoledronic acid may become the treatment of choice for patients with hypercalcemia of malignancy (Major, 2002).

### Administration of Bisphosphonates

Pamidronate infusion for hypercalcemia should be preceded by vigorous hydration with normal saline to rehydrate; urine output should be increased to two liters a day throughout treatment. If patients are hypovolemic, diuretic therapy should be avoided.

The recommended infusion time is two hours. Side effects are similar to those experienced by patients being treated for bone metastases. Patients receiving zoledronic acid for hypercalcemia should receive pre-treatment IV hydration with saline, and then the drug should be infused over at least 15 minutes. Zoledronic acid is given at a dose of 4 mg via IV. Repeat administration may be indicated if serum calcium does not normalize with zoledronic acid; however, clinicians must wait at least seven days to allow for full response of the drug (Osborne, 2002).

When treating patients with bone metastases, infusion rates remain the same. Baseline laboratory values should include complete blood count, serum or ionized calcium levels, blood urea nitrogen, electrolytes, magnesium, and phosphate (Novartis Pharmaceuticals, 2003a, 2003b; Osborne, 2002). Bisphosphonates have been associated with impairment of renal function; serum creatinine should be monitored prior to each dose of zoledronic acid and pamidronate.

If an increase of more than 0.5 mg/dl occurs in a patient with baseline creatinine of 1.4 mg/dl, or if a patient with a starting creatinine higher than 1.4 mg/dl develops a level higher than 1.0 mg/dl baseline, these medications should be held until adequate renal function returns (Major, 2002; Novartis Pharmaceuticals, 2003b). Renal dysfunction may lead to renal failure. Therefore, to minimize renal effects, nurses must strictly adhere to both dose and infusion times while monitoring appropriate electrolytes. Hypophosphatemia and hypocalcemia also can occur with bisphosphonate therapy (Osborne). Some patients may require calcium replacement.

Both agents can cause influenza-like symptoms and mild fever reaction (Body, 2001; Osborne, 2002). The fever reaction usually is one or two degrees higher than normal body temperature but may last as long as 48 hours. Occasional, transient bone pain can occur; body aches, malaise, rigor, or flush may be seen in patients on parenteral bisphosphonate therapy (Body; Osborne). Education of patients should include information about side effects of these medications and significance of fever activity.

### Cost of Bisphosphonates

Bisphosphonates are not inexpensive; they add a considerable cost to treatment regimens for patients with cancer and bone metastases. However, when compared to the cost and morbidity of treating patients with pathologic fractures, the use of these agents in treatment and prevention of bone metastases is important. Because these medications affect budgets for cancer drugs, clinicians and hospital formulary groups need to better determine cost-benefit consequences for the use of bisphosphonates compared to the consequences of skeletal-related events (Hillner, 2001). In a hypothetical model, researchers studied the effects of pamidronate in a cohort of women. The study examined assigned costs per skeletal event and quality-of-life and utility values over one month (Hillner). The results showed that the total costs associated with pamidronate therapy exceeded the savings from prevention of adverse events, leading researchers to conclude that pam-
idronate is effective in supportive care for metastatic breast cancer but that it is associated with a high financial cost per adverse event avoided (Hillner). Although the model was hypothetical, researchers should further examine the cost of including bisphosphonate therapy in the total financial picture for patients with breast and other cancers.

Pamidronate’s two-hour infusion time versus a 15-minute infusion time for zoledronic acid is a factor to consider. Additionally, two generic formulations of pamidronate are available to hospital formularies, which should make the drug less expensive for patient use (Hillner et al., 2000).

A time and motion study of zoledronic acid and pamidronate infusion was reported in 2001 (DesHarnais et al., 2001). The researchers found that the average visit time for patients receiving the study dose of zoledronic acid was one hour and six minutes compared to two hours and 52 minutes for the pamidronate group. In the analysis of the data, the total direct costs were $728 per patient receiving zoledronic acid compared to $776 in the pamidronate group (DesHarnais et al.). These results led the researchers to conclude that the shorter infusion time for zoledronic acid created a substantial time savings for patients, as well as the opportunity to treat more patients in the facility (DesHarnais et al.).

Nursing Care of Patients With Bone Metastases

Patients with bone metastases usually have pain as a presenting symptom. Once metastasis is established and a treatment plan determined (i.e., radiation, chemotherapy, hormonal, or bisphosphonate treatment), management of patient discomfort is a priority. Pharmacologic management of pain may include bisphosphonates. Indeed, studies indicate that bisphosphonates have been used in the treatment of acute pain related to bone metastases (Groff et al., 2001; Johnson, 2001). As early as 1988, researchers reported lower pain ratings in patients with breast cancer and bone metastases who received oral clodronate (Elomaa et al., 1988). Similar results were seen in patients with prostate cancer (Elomaa et al., 1992).

Other analgesic agents are recommended for pain control. Although opioids certainly can be useful in the management of bone pain related to metastasis, nonsteroidal anti-inflammatory drugs (NSAIDs) also have been documented as having increased efficacy in this symptom complex (Struthers et al., 1998). Because bone metastases induce an inflammatory reaction, using NSAIDs can relieve some of the pain caused by inflammation.

Surgical or orthopedic intervention in the treatment of fractures related to bone metastasis also is a crucial factor. If patients are at risk for fractures (see Figures 8 and 9), then surgical intervention by pinning or stabilizing the bone may be necessary to further reduce patient morbidity and improve quality of life. Early identification of impending fracture and stabilization are important to improve patient outcomes.

Because patients with bone metastases may live for years after initial presentation, providing equipment to help them maneuver safely and prevent further complications is important (see Figure 2). Corsets or devices to help stabilize the spine are helpful; patients may help to increase their mobility safely by using walkers and crutches (Struthers et al., 1998). Evaluations by physical and occupational therapists also may be appropriate in patients with skeletal metastases and fractures.

In addition to bisphosphonate therapy, patients with skeletal metastases also may consider oral calcium and vitamin D as supplemental medications.

Conclusion

Early intervention with bisphosphonate therapy and appropriate supportive measures can help to improve quality of life (see Inset 1). Oncology nurses should be aware of bisphosphonates and prepared to administer these agents to patients with bone metastases and hypercalcemia. Monitoring appropriate laboratory values helps to identify early renal effects of bisphosphonates. Patients with bone metastases may live for several years after diagnosis. Bisphosphonate treatment can reduce skeletal-related events and contribute to improved quality of life; increased survival has not yet been proven. Although initial data exist on the effects of bisphosphonates on cancer cells and apoptosis, further research on the action of these agents in patients with cancer is needed. Additional research should address the question of when clinicians should begin and cease bisphosphonate therapy. The role of bisphosphonates in adjuvant therapy needs to be further evaluated.
Inset 1. Case Study

A 58-year-old woman was diagnosed with stage III lung cancer by computerized tomography scan. She underwent a thoracotomy with removal of her left lung and began chemotherapy with carboplatin and gemcitabine. The patient tolerated the chemotherapy well except for occasional complaints of constipation. After about two months of therapy, the patient came to her clinic visit complaining of lower abdominal pain and constipation. She did not report a history of nausea or vomiting, although her oral intake was less than usual. On examination, her abdomen was slightly distended and mildly tympanic. She did not exhibit rebound or other signs of an acute abdomen. The healthcare provider sent the patient for an x-ray of the kidneys, ureter, and bladder (i.e., KUB) to rule out bowel obstruction. The physician performing the wet reading reported that the patient did not have a bowel obstruction but that she did have several large sclerotic lesions in the pelvis from probable lung cancer metastatic to bone. The lower abdominal pain was thought to be caused by metastatic bone disease, and the patient was started on zoledronic acid 4 mg IV over 15 minutes monthly along with a nonsteroidal anti-inflammatory drug. Her pain resolved, and she has not developed fractures related to her bone metastasis. The patient still is receiving maintenance zoledronic acid therapy 18 months after her original diagnosis.

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References


Bisphosphonates have been associated with renal impairment; therefore, serum creatinine levels should be monitored prior to each dose of pamidronate and zoledronic acid.

Bisphosphonate administration has become the mainstay of treatment for malignancy-induced hypercalcemia because this class of drugs is effective and well tolerated by patients.

Rapid Recap

**Bisphosphonates: Expanded Roles in the Treatment of Patients With Cancer**

- **Bisphosphonates** are a class of drugs originally used to treat osteoporosis and now are used to treat bone metastases and hypercalcemia of malignancy.
- Patients with cancer receiving agents that promote osteoclastic bone activity, such as corticosteroids, therapeutic doses of hepamin, or anticonvulsants; women who have treatment-induced ovarian failure; and men who have received androgen deprivation therapy for prostate cancer are at risk for osteoporosis.
- Patients with bone metastases often experience pain, which usually is the presenting symptom. For some patients, the initial presentation of bone metastases may be a pathologic fracture.
- The bisphosphonates pamidronate and zoledronic acid (both administered via IV), as well as the oral drugs clodronate and ibandronate, reduce skeletal-related events in patients with cancer with bone metastases.
- Bisphosphonate administration has become the mainstay of treatment for malignancy-induced hypercalcemia because this class of drugs is effective and well tolerated by patients.
- Bisphosphonates have been associated with renal impairment; therefore, serum creatinine levels should be monitored prior to each dose of pamidronate and zoledronic acid.