



Philip Pearlstein. *Jerusalem, Kidron Valley* (detail), 1988. Heliorelief with roulette on wood, 40" × 119".
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Bisphosphonates are effective in reducing skeletal-related complications associated with metastatic breast cancer.

The Use of Bisphosphonates in Patients With Breast Cancer

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Background: Bone is the most common site of breast cancer metastases. Skeletal metastases may be associated with harmful and painful events such as fractures, spinal cord compression, and hypercalcemia. By inhibiting osteoclasts and bone resorption, bisphosphonates can interrupt the process of bone destruction and decrease the risk of skeletal complications.

Methods: A review of the literature was undertaken regarding the use of bisphosphonates in breast cancer management, with particular attention to prospective, randomized clinical trials that have influenced the treatment of bone metastases.

Results: Large prospective, randomized trials have demonstrated that bisphosphonates are effective in reducing skeletal-related complications from metastatic breast cancer.

Conclusions: For many patients with osseous lesions from breast cancer, bisphosphonate therapy is a useful intervention in managing their disease. Bisphosphonates are the treatment of choice for hypercalcemia of malignancy and bisphosphonates reduce the risk of pathologic fractures, spinal cord compromise, the need for radiation or surgery to bone, and bone pain.

Introduction

Breast cancer incidence in the United States in 2002 is expected to account for approximately 30% of all new cancer cases among women, and mortality due to breast cancer is estimated to comprise 15% of all cancer-related deaths.¹ When managing metastatic disease, the treatment objectives are to optimize treatment response, improve survival, and balance these goals while maintaining the highest possible quality of life. Approximately 65% to 75% of patients with metastatic breast cancer develop osseous metastases.² Skeletal

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metastases are often associated with harmful and painful events such as spontaneous fractures, spinal cord compression, or hypercalcemia.³ Thus, managing skeletal metastases is an important component of treating patients with metastatic breast cancer.

Risk of Bone Metastases and Skeletal Complications of Malignancy

Studies to identify risk factors associated with relapse in bone have been performed. Colleoni et al⁴ evaluated breast cancer patients from the International Breast Cancer Study Group, adjuvant trials I through VII, for pattern of recurrence among 6,792 patients. The cumulative incidence of bone metastases was highest among patients with more than four axillary lymph nodes involved, tumor size greater than 2 cm, estrogen receptor-positive tumors, and age less than 35 years at diagnosis. Similarly, Smith et al⁵ reported their assessment of 14,614 women from seven National Surgical Adjuvant Breast and Bowel Project (NSABP) trials where involved axillary lymph nodes and estrogen receptor positivity correlated with subsequent development of bone recurrence. In a smaller study, Solomayer et al⁶ reported a retrospective analysis of 648 patients with metastatic breast cancer. Bone as the first metastatic lesion correlated with positive estrogen and progesterone receptor status, tumor grade, and S-phase fraction, but not tumor size, nodal status, or menopausal status.

Domchek et al³ evaluated the incidence rate of bone complications and sought to identify predictors of skeletal complications in 718 patients who had developed metastatic breast cancer between 1981-1991, a time period that predated the use of bisphosphonates. This study demonstrated that approximately 50% of patients developed bone complications (hypercalcemia, spinal cord compression, surgical intervention to bone, radiation therapy to bone, or pathologic fracture). Predictors of skeletal complications included bone involvement at the time of diagnosis of metastatic disease, abnormal alkaline phosphatase, and a disease-free interval of less than 3 years since primary therapy.

Methods of reducing the impact of breast cancer are actively being sought, and paramount in this effort is the identification of patients at increased risk of visceral and/or skeletal metastases. Active investigation is underway to help define prognostic factors beyond tumor size, hormonal receptor status, and conventional analysis of lymph node status. At present, the importance of cytokeratin positive lymph nodes and bone marrow are being investigated; it is anticipated that these findings will impact treatment decisions for adju-

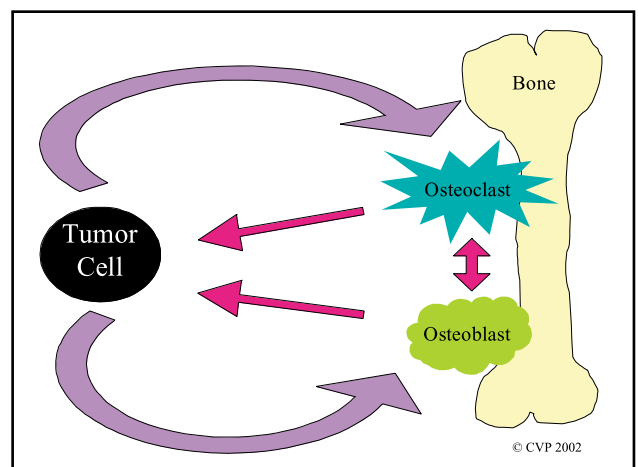
vant therapy.⁷ Breast cancer cells have been found in the circulation of patients, but the significance of this has yet to be realized.⁸ Research is ongoing to identify new prognostic and predictive factors.

Pathophysiology of Bone Metastases

Normal bone is comprised of both organic and cellular elements. The bone matrix serves as a reservoir for minerals, cytokines, and growth factors. The cellular component contains both bone and hematopoietic cell lines.

Normal bone is constantly remodeling, and this healthy bone metabolic activity is characterized by two opposite actions: the formation of new bone by osteoblasts and the resorption of old bone by osteoclasts. The normal balance between resorption and deposition is disturbed by cancer. When the tumor has metastasized to bone, it can directly alter the bone and cause lesions that may be lytic (due to increased resorption), blastic (due to increased deposition) or a combination of both, causing a mixed lesion.

When the osteoclast resorbs bone, growth factors and cytokines are liberated to interact with the tumor cells. In turn, the tumor cell may express cell signals that then stimulate the osteoclast and a "vicious cycle" of cell signaling is established. In the development of osteolytic lesions, these signals include parathyroid hormone-related protein (PTHrP) and transforming growth factor beta (TGF- β).⁹ Tumor cells in the bone micro-



Signaling between the breast cancer metastases and the bone microenvironment involves parathyroid hormone-related protein (PTHrP), transforming growth factor beta (TGF- β), receptor activator of NF κ B (RANK), receptor activator of NF κ B Ligand (RANK-L), and insulin-like growth factor 1 (IGF-1). Other factors believed to be involved in tumor to bone signaling include (but are not limited to) platelet-derived growth factors, plasminogen activator, gonadal steroids, bone morphogenic proteins, tumor necrosis factors, vascular endothelial growth factor, epidermal growth factor, interleukins, prostaglandins, and fibroblast growth factor. Copyright 2002, Catherine Van Poznak.

environment may produce PTHrP, thereby stimulating osteoclastic bone resorption that in turn results in the release of active TGF- β . TGF- β can then act on the tumor cells, stimulating their metastatic capacity and their ability to produce of PTHrP. Other cell signaling occurs through receptor activator of nuclear factor κ B (NF κ B) (RANK), its ligand (RANKL), and its soluble decoy receptor osteoprotegerin as well as signaling through insulin-like growth factors (Figure). The net results are tumor growth and the development of osseous lesions.

Treatment of Bone Metastases

Both antineoplastic therapy and bone supportive therapy may be used in the treatment of bone metastases. Antineoplastic interventions include hormonal therapy or chemotherapy for systemic treatment and radiation therapy or surgery for site-specific treatment. Supportive therapies include analgesics and bisphosphonates. Bisphosphonate therapy has demonstrated the ability to reduce the incidence of skeletal complications,¹⁰⁻¹⁵ and novel therapeutics, including small molecules and monoclonal antibodies, are being developed to target bone and tumor signaling pathways.

Bisphosphonate therapy alters the “vicious cycle” by changing the bone microenvironment. Bisphosphonates decrease the number of osteoclasts by inhibiting the recruitment of osteoclasts, inhibiting osteoclast activity, and activating osteoclast apoptosis. Both the non-nitrogen-containing and the nitrogen-containing bisphosphonates act by inhibiting cell function and by

inducing apoptosis. The non-nitrogen-containing bisphosphonates can be incorporated into adenosine triphosphate-containing compounds.¹⁶ The nitrogen-containing bisphosphonates can inhibit the mevalonate pathway and thereby inhibit the prenylation of guanosine triphosphate-binding proteins that control cytoskeletal reorganization, vesicular fusion, and apoptosis, thereby effecting processes involved in osteoclast activation and function (Table 1).^{17,18}

Preclinical data have shown that bisphosphates enhance apoptosis in breast cancer cells¹⁹ and bisphosphonates can inhibit the attachment of breast and prostate cancer cells to bone matrix.²⁰ Preclinical data have also suggested that bisphosphonates may decrease tumor cell proliferation and increase the efficacy of antineoplastic therapy with paclitaxel.²¹ In addition to a direct effect on tumor cells, bisphosphonates may also affect angiogenesis²² and immunomodulation.²³ The inducement of apoptosis in tumor cells by the bisphosphonates may be a result of direct antitumor effect or indirect antitumor effect secondary to changes produced in the bone microenvironment. Although bisphosphonates have been shown to exert an apoptotic effect preclinically,¹⁹ it is unclear whether bisphosphonates can clinically alter the volume of a patient’s tumor burden.

Bisphosphonate Therapy

The addition of bisphosphonates to standard chemotherapy or hormonal therapy has been shown to produce a reduction in skeletal complications in breast cancer patients. Presently within the United States, two bisphosphonates — pamidronate and zoledronic

Table 1. — Comparison of the Nitrogen-Containing and Non-Nitrogen-Containing Bisphosphonates

| | Non-Nitrogen-Containing Bisphosphonate | Nitrogen-Containing Bisphosphonate |
|---|---|---|
| Pharmacologic Effects | Inhibition of bone resorption and stimulation | Inhibition of mevalonic pathway, inhibition of of apoptosis of osteoclasts osteoclast activation and function; promotes osteoclast apoptosis |
| Mechanism of Action | Form adenosine triphosphate analogs that inhibit enzymatic activity | Inhibition of prenylation of proteins involved in signal transduction pathways |
| Gastrointestinal Side Effects (Oral Administration) | Mild to moderate nausea, vomiting, and diarrhea in <10%; no severe gastrointestinal effects have been reported | Moderate to severe nausea, vomiting; endoscopic evidence of erosive esophagitis and gastritis in some patients |
| Other Side Effects | No acute phase response has been reported | Renal toxicity; proinflammatory properties that are thought to underlie an acute phase response (fever, malaise, myalgia, and transient decrease in lymphocytes) |
| Effects on Survival | No survival benefit but a suggestion of possible increased survival in breast cancer in one small study ¹⁸ | No survival benefit but in subset analysis one study suggested that women aged <50 years with breast cancer on hormonal therapy had a longer survival ¹⁴ |

acid — are approved for the treatment of skeletal metastases from breast cancer. Three large randomized clinical trials have directed the use of bisphosphonates for metastatic breast cancer patients in the United States.¹²⁻¹⁵ These studies investigated the effect of intravenous bisphosphonates on skeletal-related events, an aggregate of bony complications that include pathologic fractures, spinal cord compression or collapse, radiation for pain relief or treatment of pathologic fracture, surgery to bone, and hypercalcemia. Two randomized, placebo-controlled studies investigated pamidronate 90 mg infused over 2 hours every 3 to 4 weeks in patients with lytic metastases greater than 1 cm in size and demonstrated the ability of pamidronate to reduce the risk of skeletal-related events. The third study investigated zoledronic acid in a randomized clinical trial where zoledronic acid was shown to be not inferior to pamidronate (Table 2 and Table 3).

Pamidronate in Conjunction With Chemotherapy

Three hundred eighty-two women with stage IV breast cancer and at least one osteolytic metastatic lesion who were receiving chemotherapy were randomized to receive either a 2-hour infusion of pamidronate 90 mg every 3 to 4 weeks or placebo.^{12,13} The study drug was administered 12 times. Patients were evaluated for skeletal complications, including pathologic fractures, spinal cord compression with vertebral compression fracture, the need for surgery to treat or prevent pathologic fractures or spinal cord compression, or the need for radiation therapy to bone. Patients were also assessed for hypercalcemia. The pamidronate group demonstrated a significantly longer median time to the first skeletal complication than the placebo group (13.1 vs 7.0 months, $P=.005$) with the

Table 2. — Pivotal Trials Investigating Intravenous Bisphosphonates in Patients With Metastatic Breast Cancer

| Trial | Intervention | Patients | Skeletal Complications | Toxicity |
|--------------------------------------|---|---|--|--|
| Hortobagyi et al, ¹² 1996 | Pamidronate 90 mg IV every 3-4 weeks vs placebo × 12 cycles | MBC with lytic bone lesion on chemotherapy (N = 382) | <ul style="list-style-type: none"> • Median time to first SRE: 13.1 vs 7.0 months ($P=.005$) favoring pamidronate • Proportion of patients with any SRE: 43% vs 56% ($P=.008$) favoring pamidronate | Incidence of adverse clinical the 2 study groups |
| Hortobagyi et al, ¹³ 1998 | Pamidronate 90 mg IV every 3-4 weeks vs placebo × 12 cycles | MBC with lytic bone lesion on chemotherapy (N = 382) | <ul style="list-style-type: none"> • The odds ratio of having SRE during placebo treatment compared to pamidronate: 2.3 (95% CI, 1.5-3.5) | No new tolerability or safety issues arose in the second treatment year |
| Theriault et al, ¹⁴ 1999 | Pamidronate 90 mg IV every 4 weeks vs placebo × 24 cycles | MBC with lytic bone lesion on hormonal therapy (N = 372) | <ul style="list-style-type: none"> • Median time to first SRE: 10.4 vs 6.9 months ($P=.049$) favoring pamidronate • Proportion of patients with SRE: 56% vs 67% ($P=.027$) favoring pamidronate • At 24 cycles of treatment, the odds ratio of having SRE during placebo treatment compared to pamidronate was 1.6 (95% CI, 1.1 to 2.5) | Pamidronate was well tolerated; pamidronate arm experienced slightly more vomiting, fatigue, leukopenia, injection site reactions, and hypocalcemia than placebo arm |
| Rosen et al, ¹⁵ 2001 | Zoledronate 4 or 8/4 mg vs pamidronate 90 mg every 3-4 weeks IV | MBC with lytic or mixed bone metastases and multiple myeloma with lytic lesions (N = 1,648) | <ul style="list-style-type: none"> • Primary endpoint: proportion of patients with at least 1 SRE (not including hypercalcemia of malignancy) was similar among all treatment groups (44-46%). • Secondary endpoints: pain score, analgesic score, and performance status were similar among treatment groups | Both the 5-minute infusion and the 8-mg dose of zoledronic acid were associated with increased renal toxicity; the 4-mg zoledronic acid dose over 15 minutes has a safety profile similar to 90 mg of pamidronate infused over 2 hours |

MBC = metastatic breast cancer
SRE = skeletal-related event (pathologic fractures, spinal cord compromise, radiation therapy to bone, surgery to bone, and hypercalcemia of malignancy)

time to first non-vertebral pathologic fracture, first radiation therapy, first bone surgery, and first episode of hypercalcemia showing statistical significance. The pamidronate arm also demonstrated a decrease from baseline in bone pain and marker of bone metabolism. The incidence of adverse clinical side effects and toxic effects was similar in the two study groups. Overall survival was not statistically different between the two study groups, with a median estimate of survival of 14.8 months in the pamidronate group and 14.2 months in the placebo group.

To assess the long-term tolerability and safety, effects on survival and durability of the skeletal protection, the above study was continued for a second year.¹³ All patients who entered the second year of the trial had received 12 doses of study drug (pamidronate or placebo) and remained on the same treatment. The proportion of patients with any skeletal complication was less in the pamidronate arm than in the placebo group (odds ratio 2.3, 95% confidence interval [CI], 1.5 to 3.5). Laboratory findings with anemia, thrombocytopenia, and hyperphosphatemia were slightly more common in the pamidronate group than in the placebo

group. The requirements for treatment of hematologic and mineral disturbances were similar for placebo and pamidronate. Symptoms of myalgias, arthralgias, and influenza-like symptoms were slightly more common in the pamidronate arm. There was no difference in survival between the two treatment groups.

Pamidronate in Conjunction With Hormonal Therapy

To investigate the use of intravenous pamidronate in women with osteolytic breast cancer metastases who were receiving hormonal therapy, a parallel study to the above-mentioned chemotherapy trial was performed.¹⁴ In this study, pamidronate 90 mg was administered intravenously over 2 hours vs placebo administered monthly for 24 cycles. The first 12 months of study focused on safety and efficacy. The second 12 months focused on the assessment of the safety of long-term administration of pamidronate. Double-blind administration of the study drug continued throughout the study. A total of 372 patients were randomized to pamidronate or control. The median time to first skeletal complication was 10.4 months for the pamidronate group vs 6.9 months for the placebo group ($P=.049$). At 24 cycles of treatment, the odds ratio of having a skeletal event on placebo to pamidronate was 1.6 (95% CI 1.1 to 2.5). Fatigue, vomiting, leukopenia, and injection site reactions were slightly more common in the pamidronate group. An exploratory subgroup analysis demonstrated that women 50 years of age or younger experienced a median survival of 26 months in the pamidronate group vs 18 months in the placebo group. However, for the entire study, the median estimate of survival was approximately 23 months for both groups, demonstrating no overall survival difference between the pamidronate and placebo groups.

Zoledronic Acid vs Pamidronate in Patients With Metastatic Breast Cancer and Multiple Myeloma

Zoledronic acid is a new, high-potency, nitrogen-containing bisphosphonate developed on the hypothesis that a more potent inhibitor of osteoclast-mediated bone resorption would have greater clinical activity. A large international, randomized phase III clinical trial compared zoledronic acid (4 or 8 mg) to pamidronate 90 mg infused over 2 hours every 3 to 4 weeks in patients with multiple myeloma and metastatic breast cancer who had at least one bone lesion, which could be osteolytic or mixed.¹⁵ The study was designed to directly compare the efficacy and safety of the two intravenous bisphosphonates in these two patient populations. A total of 1,648 patients were enrolled, 69% of whom had breast cancer. During the course of the

Table 3. — Most Common Side Effects of Intravenous Bisphosphonates

| |
|---|
| <p>Transient pyrexia (10%-41%)</p> <ul style="list-style-type: none"> • Nitrogen containing bisphosphonates are associated with an acute phase reaction • Self limiting and the incidence decreases with subsequent doses • Consider premedication with acetaminophen, dilute with greater quantity of infusate, or a longer infusion time |
| <p>Phlebitis at injection site (erythema/pain: 18%)</p> <ul style="list-style-type: none"> • Utilize central venous catheter if available, if not, then alternate site of infusion • Consider increasing the volume of infusate or a longer infusion time |
| <p>Transient myalgia, arthralgia, bone pain, malaise (10%)</p> <ul style="list-style-type: none"> • Analgesics as needed • Consider premedication with acetaminophen, a larger volume of infusate, or a longer infusion time |
| <p>Hypocalcemia (5%-17% usually asymptomatic)</p> <ul style="list-style-type: none"> • To decrease the incidence of hypocalcemia, patients should use 500 mg of calcium supplement and daily dose of 400-500 IU of vitamin D daily unless contraindications to these supplements exist • If symptomatic, short-term treatment with intravenous calcium supplementation may be required |
| <p>Bisphosphonate: Warnings</p> <ul style="list-style-type: none"> • Bisphosphonates are not to be given during pregnancy • Serial monitor of serum creatinine is required • Renal insufficiency may require a change in dosing interval or dose given • Serial monitor of complete blood count and biochemical profile is required • Fracture healing or a new orthopedic implant is not a contraindication to bisphosphonate therapy |

study and other zoledronic acid studies, the data monitoring safety board noted evidence of renal toxicity in some patients receiving zoledronic acid. This renal impairment was related to the dose and infusion duration of zoledronic acid. To avoid excess renal toxicities, the protocol underwent two modifications. The initial zoledronic acid infusion rate of 5 minutes was extended to 15 minutes and the 8-mg dose was changed to a 4-mg dose, making this group the 8/4-mg arm. Approximately 60% of patients completed 12 months of therapy. Rosen et al¹⁵ published the study with the three arms defined as 4-mg zoledronic acid, 8/4-mg zoledronic acid, and pamidronate.

The primary efficacy endpoint was the proportion of patients with at least one skeletal-related event (not including hypercalcemia of malignancy) during the 13-month trial. The proportion of patients experiencing at least one skeletal-related event (44% to 46%) was similar between treatment groups and disease process. The median time to first skeletal-related event was similar between treatment groups (range 353–373 days from study entry). In subgroup analysis the proportion of patients receiving radiation therapy to bone was statistically significantly lower overall in the 4-mg zoledronic acid group than the pamidronate group (15% vs 20%, $P=.031$) and among breast cancer patients receiving hormonal therapy (16% vs 25%, $P=.022$). In addition, the zoledronic acid group demonstrated a statistically significant decrease in the markers of bone metabolism. Analysis of skeletal morbidity rate (ie, the ratio of the number of skeletal complications experienced by a patient divided by the time on the trial by the end of the specified time period, for all skeletal-related events, including hypercalcemia of malignancy) was lower in the 4-mg zoledronic acid group than in the pamidronate group. No statistically significant difference among treatment groups was noted with respect to the secondary endpoints of change in pain score, analgesic score, and performance status. To date, there has been no statistically significant difference in bone lesion response, time to disease progression, or overall survival.

In all treatment groups, the most commonly reported adverse events were bone pain, fatigue, and fever. The frequency of renal impairment associated with zoledronic acid was related to the dose and infusion rate. The proportion of patients with renal toxicity in the 8/4-mg zoledronic acid arm (18% to 29%) was greater than that of the 4-mg zoledronic acid arm and the pamidronate arm. After the protocol amendments, the proportion of patients with deterioration of renal function in the 4-mg zoledronic acid group resembled that of the pamidronate group. In the 4-mg zoledronic acid group, 9% of patients with normal baseline serum

creatinine levels experienced an increase in serum creatinine of 0.5 mg/dL or more compared with 8% in the pamidronate group. In patients with abnormal baseline serum creatinine values, 4% of patients in the 4-mg zoledronic acid group experienced a rise of 1.0 mg/dL or more from baseline serum creatinine compared with 9% in the pamidronate group. At a dose of 4 mg via a 15-minute infusion in 100 mL of infusate, zoledronic acid demonstrated a renal tolerability profile similar to pamidronate 90 mg via 2-hour infusion in 250 mL of infusate. Due to the risk of renal changes with intravenous bisphosphonates, monitoring for changes in serum creatinine is to be performed as outlined in the packet inserts. For both pamidronate and zoledronic acid, the serum creatinine should be measured before each dose, and treatment should be withheld for renal deterioration. In the clinical study, renal deterioration was defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine and an increase of 1.0 mg/dL for patients with abnormal creatinine. In the clinical study, the intravenous bisphosphonate was resumed only when the creatinine returned to within 10% of the baseline value.

Zoledronic acid had demonstrated superiority over pamidronate in the treatment of hypercalcemia of malignancy.²⁴ The study by Rosen et al¹⁵ demonstrated non-inferiority of 4-mg zoledronic acid infused over 15 minutes when compared with 90-mg pamidronate infused over 2 hours in the treatment of osteolytic or mixed bone metastases in patients with metastatic breast cancer or myeloma. The question of whether the high-potency nitrogen-containing bisphosphonates yield an increased efficacy in treating bone metastases warrants further exploration.

Long-term Use of Intravenous Bisphosphonates

To assess for safety and efficacy of long-term intravenous bisphosphonate therapy, Ali et al²⁵ studied cancer patients receiving pamidronate or zoledronic acid for longer than 2 years. Of the 22 patients identified, 5 were men with multiple myeloma and 17 were women with metastatic breast cancer. The median duration of follow-up was 3.6 years (range 2.2 to 6.0 years). During the first 2 years of treatment with either pamidronate or zoledronic acid, 6 of the 22 patients developed a pathologic fracture or received radiation therapy. Skeletal events that occurred after the first 2 years of bisphosphonate therapy included fractures in 4 of the 22 patients. There was no clinically relevant change in complete blood cell counts, platelet counts, calcium and electrolyte analysis, or kidney function for these patients receiving long-term intravenous bisphos-

phonate therapy. Long-term use of pamidronate and zoledronic acid appears to be well tolerated.

Bisphosphonates Guidelines

The American Society of Clinical Oncology (ASCO) guidelines for use of bisphosphonates in patients with metastatic breast cancer aids in directing bisphosphonate therapy.²⁶ The guidelines were created before the publication of the zoledronic acid studies and before the FDA approval of zoledronic acid; therefore, the recommendations focus on pamidronate. The ASCO guidelines are outlined in Table 4. However, questions remain regarding maximizing bisphosphonate use and the selection of patients for bisphosphonate therapy: When is the optimal time to start or stop bisphosphonate therapy? What is the best drug, route of administration, and dosing schedule? Who are the patients most like to benefit (or not) from bisphosphonate therapy? It has been suggested that either a scoring system for rating risk of pathologic fracture²⁷ or monitoring markers of bone catabolism²⁸ may direct patient-specific therapy. However, neither of these approaches has been validated to date. The ASCO guidelines advocate that intravenous bisphosphonate therapy, once begun, be continued in conjunction with systemic therapy until there is evidence of substantial decline in the

patient's performance status. At the point of significant clinical deterioration, goals of treatment generally focus on best supportive care.

Palliative Bone Pain Therapy

Randomized, controlled trials evaluating intravenous pamidronate, clodronate, ibandronate, and zoledronate have demonstrated that these bisphosphonates aid in the relief of bone pain.^{12,14,29-32} Prolonged administration of oral clodronate (1,600 mg daily) reduces the frequency of morbid skeletal events by more than 25%, although compliance can be a limiting factor with the high oral dose required for this compound.^{33,34} Although bisphosphonates have not had an impact on overall survival, they have reduced skeletal complications of breast cancer. In addition, intravenous bisphosphonates have clinically relevant analgesic effects in patients with metastatic bone pain. The current standards of care for cancer pain — analgesics and local radiation therapy — should not be displaced by bisphosphonates²⁶; bisphosphonates may complement other treatment modalities. Pamidronate has been shown to reduce pain even in patients in whom conventional antineoplastic therapy fails.³⁵ Bisphosphonates also provide treatment for patients with widespread, poorly localized bone pain and in patients experiencing recurrence of pain in previously irradiated skeletal sites. The pain relief obtained from bisphosphonates can play a role in maintaining patient comfort during palliative care.^{36,37} The role of bisphosphonates in the hospice setting needs to be further defined.

Hypercalcemia of Malignancy

Hypercalcemia of malignancy is the most common metabolic complication of breast cancer. The bone destruction occurring in the osseous metastatic lesions can result in elevated serum calcium levels and the associated symptoms of hypercalcemia: fatigue, nausea, vomiting, dehydration, and mental status changes. Hypercalcemia of malignancy is also associated with an increase in renal tubular resorption and a decrease urinary calcium excretion that further increases the serum calcium level. The mechanism of hypercalcemia of malignancy involves production of tumoral parathyroid hormone-related protein (PTHrP) as well as bone-resorbing cytokines, vitamin D metabolites, and prostaglandins.³⁸ The key to long-term control of hypercalcemia of malignancy is to treat the underlying malignancy. In patients with moderate to severe hypercalcemia of malignancy, aggressive hydration, and anti-resorptive therapy with intravenous bisphosphonates are instrumental in regaining normocalcemia. The bis-

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phosphonate reduces osteoclast activity, thereby decreasing the osteolytic process and the associated release of calcium from bone.

Two identical, concurrent, randomized, double-blind, parallel clinical trials were conducted to study hypercalcemia of malignancy in Europe and North America, and the results were pooled for analysis.²⁴ A total of 287 patients were enrolled to compare the efficacy and tolerability of a single dose of zoledronic acid, 4 or 8 mg, given as a 5-minute infusion vs a single 90-mg dose of pamidronate as a 2-hour infusion. The primary endpoint was complete response, defined as corrected serum calcium level <10.8 mg/dL by day 10, and the secondary endpoints included time to relapse and duration of complete response. Patients refractory to the initial treatment were eligible for a second phase of the trial and treatment with a single dose of 8 mg of zoledronic acid. Two hundred seventy-five patients were eligible for efficacy analysis. Patients treated with zoledronic acid had a significantly faster normalization of corrected serum calcium compared with the pamidronate group. The 4-mg zoledronic acid arm demonstrated a significantly longer therapeutic effect than the pamidronate arm, with a single dose of 4-mg zoledronic acid normalizing the corrected serum calcium level for 30 days vs 17 days for the 90-mg pamidronate arm. The complete response rate at day 10 was greater for the 4-mg zoledronic acid arm, with 88% of patients obtaining a complete response vs 70% of patients in the pamidronate group. Although the 8-mg zoledronic acid dosage appeared to be as effective as the 4-mg dose, the higher dosage is not recommended due to associated increased risk of renal toxicities. The 4-mg zoledronic acid dose demonstrated an improved efficacy over pamidronate in treating hypercalcemia of malignancy, has received FDA approval for hypercalcemia of malignancy, and may be considered as first-line therapy for this condition when intravenous bisphosphonates are indicated.

Oral Bisphosphonates for Breast Cancer Bone Metastases

In the United States, only the intravenous pamidronate and zoledronic acid are approved by the FDA for treatment of osseous metastases. However, oral bisphosphonates have been clinically studied in the treatment of breast cancer metastases.³⁹ Where available, the oral bisphosphonate, clodronate, is efficacious in the treatment of breast cancer osseous metastases lesions.⁴⁰ A recent report of a phase III clinical trial of oral ibandronate demonstrated efficacy in the treatment of skeletal complications of malignancy in patients with osseous metastases from breast cancer.⁴¹

Diel et al⁴² compared oral clodronate, intravenous clodronate, and intravenous pamidronate in patients with osteolytic breast cancer lesions and demonstrated that the best pain reduction was obtained with intravenous pamidronate, followed by intravenous clodronate and then oral clodronate. The optimal bisphosphonate drug, route of administration, and schedule is yet to be defined; however, the intravenous route appears to be necessary to obtain optimal effects on bone pain.

Potential Use of Bisphosphonates for Prevention of Bone Metastases

Based on the observation that bisphosphonates reduce the release of bone-derived growth factors and cytokines associated with bone resorption, which have the potential to attract cancer cells to bone and facilitate tumor growth and proliferation, it is possible that bisphosphonate therapy may be able to help prevent the development of bone metastases. To explore this concept, clinical trials of adjuvant bisphosphonate therapy have been performed. Two studies have suggested a decrease in the development of osseous metastases and an improvement in survival with the use of adjuvant oral clodronate after primary treatment for operable breast cancer.^{43,44} However, Saarto et al⁴⁵ reported results to the contrary. To shed light onto these conflicting results, two large, multicenter, randomized clinical trials are investigating the use of adjuvant bisphosphonates (NSABP B-34 and SWOG S9905). Until additional data are generated, starting bisphosphonate therapy for the purpose of preventing bone metastases in patients at any stage of nonosseous disease is not recommended outside of a clinical trial.²⁶

Osteopenia and Osteoporosis in Breast Cancer Patients

Osteoporosis, primary or secondary, is often a comorbid condition in patients with breast cancer. The antineoplastic therapy for breast cancer can itself have adverse effects on bone.⁴⁶ Chemotherapy can have direct negative effects on bone mineral density, as can the glucocorticoids used as antiemetics and premedications. Adjuvant chemotherapy can cause premature menopause and increased risk for osteoporosis. Hormonal replacement therapy is commonly used for prevention and treatment of osteoporosis. However, this intervention is controversial in women with a history of breast cancer and is generally not an accepted option in this patient population.⁴⁷ Osteoporosis can be both prevented and treated with bisphosphonates. In conjunction with calcium, vitamin D, and weight-bearing exercise, bisphosphonate therapy may be con-

sidered in women who are at risk for osteopenia or osteoporosis. Selecting interventions for the treatment of osteoporosis is influenced by the patients' prior history of breast cancer, as well as the conflicting data on adjuvant use of bisphosphonates. Agents to consider in the treatment of low bone mineral density in patients with breast cancer include selective estrogen receptor modulators, bisphosphonates, calcitonin, or clinical trials exploring novel therapies such as parathyroid hormone and monoclonal antibodies targeting signaling through osteoprotegerin or its ligand.

Pharmacoeconomics

Bisphosphonates have been shown to decrease the frequency of hypercalcemia of malignancy, the need for radiation to bone, and the rate of vertebral fractures. Theoretically, this clinical benefit would be expected to translate into a cost benefit for patients receiving bisphosphonates; however, this potential cost benefit has not yet been documented. There is a lack of prospective cost effectiveness studies, and much of the data have been generated through modeling. In a model based on the pivotal phase III pamidronate trials, the cost associated with pamidronate use exceeded the cost of avoiding skeletal-related events.⁴⁸ In a separate study, the costs associated with pamidronate vs zoledronic acid were examined. This microcosting analysis demonstrated the potential for zoledronic acid to result in a reduction in the patient visit time and in nurse labor costs⁴⁹; cost effectiveness was not investigated in this study.

The existing cost effectiveness data are difficult to apply across different healthcare systems. Also, the existing data do not take into account pain or quality of life, which are key endpoints when treating for palliation. In spite of the questionable cost effectiveness, bisphosphonates remain an integral part of the treatment of lytic breast cancer metastases. Prospective studies to identify subgroups of patients most likely to benefit (or not) from bisphosphonate treatment are needed to tailor therapy to the individual patient.

Conclusions

Both metastatic breast cancer and bone are involved in cell signaling, and this "vicious cycle" can lead to progression of disease in bone. Bisphosphonates are able to inhibit osteoclast activity and alter the signaling between tumor and bone. Bisphosphonates are the treatment of choice in hypercalcemia of malignancy and provide proven clinical benefit in reducing the skeletal complications of breast cancer and reduc-

ing bone pain. For many patients with osseous lesions from breast cancer, bisphosphonate therapy is an important component in the management of their disease. Attention is now being focused on how to optimize the use of bisphosphonates and the identification of patient and tumor-specific characteristics to predict response to therapy. Clinical trials are needed to answer questions such as when is the optimal time to initiate or stop therapy, how best to monitor treatment, and how to use bisphosphonates in a cost-effective manner. New drugs, including small molecules and monoclonal antibodies, are under clinical investigation and may eventually become treatment options, either in conjunction with or as an alternative to bisphosphonate therapy. State-of-the-art care requires that the therapies be as targeted as the present technology will allow. With bone metastases from breast cancer, there are two targets to approach, the tumor and the bone.

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