Original Article

The Role of Bisphosphonates in Breast Cancer

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Key Words

Breast neoplasms, bisphosphonates, chemotherapy, osteoclast activity, metastases, pamidronate, zoledronic acid

Abstract

Breast cancer frequently metastasizes to bone. Metastases result in skeletal morbidity including pathologic fractures, the need for radiation or surgery to bone, spinal cord compression and hypercalcemia. The pathophysiology of bone destruction is related to activation of osteoclasts by tumor-derived and bone marrow microenvironmental factors. One prominent osteoclast–activating factor associated with breast cancer is parathyroid hormone-related peptide (PTHrP). Bisphosphonates have been shown to impair osteoclast activity by decreasing recruitment from the monocyte macrophage cell line, inhibiting osteoclast function at the bone site and causing osteoclasts to undergo apoptosis. Clinical studies with bisphosphonates show an improvement in the control of hypercalcemia and a reduction in skeletal related morbidity with administration of pamidronate and zoledronic acid. Bisphosphonates have become the standard of care for osteolytic metastases associated with breast cancer. Recent data with zoledronic acid found that skeletal related morbidity may be reduced regardless of the radiographic picture of skeletal metastases. Thus, zoledronic acid may be valuable in osteolytic and osteoblastic disease as well as in disease with an osteolytic or osteoblastic radiographic appearance. In breast cancer with osteolytic disease, zoledronic acid may be more effective than pamidronate in reducing skeletal morbidity and prolonging the time to first skeletal event. (*JNCCN* 2003;1:232–241)

Breast cancer is an osteotropic tumor with a predilection for metastasizing to bone.[1] Consequently, patients with metastatic breast cancer are at risk for morbidity related to bone metastasis. Bone pain is common, and often the initial symptom of metastatic disease. Treatment for bone disease has included systemic therapies, chemotherapy, and hormone therapy as well as local or regional therapies, radiation, and surgery. Chemotherapy and hormone therapy frequently palliate symptoms and induce tumor regression; they may positively impact survival.[2] Because at clinical presentation bone disease usually is not bidimensionally measurable, it is difficult to assess objective response to treatment. Bone disease has a protracted clinical course, and patients are at risk for symptoms and skeletal complications over a long period of time.[3–5] As the biology of bone metastases is being clarified, therapeutic interventions directed specifically at bone and attendant bone-related complications have been developed and are being used in patient care. This article reviews some of the pathophysiology of bone metastases, alterations in bone remodeling associated with metastases, and the clinical presentation and morbidity of bone metastases.

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Bone Metastases

Bone metastases from primary breast cancer are a substantial clinical problem, and the prevalence is extraordinarily high. Evidence from clinical and postmortem studies suggests that 47% to 85%[6] of breast cancer patients with metastases will have bone disease. Bone metastases are the most frequent first site of metastatic disease.[5,7] Frequent anatomic sites of involvement are the pelvis, ribs, thoracic and lumbar spine, skull, cervical spine, and long bones.[3,8–11]

The prognosis of bone metastases from different primary tumor sites varies. Survival for patients with bone-only metastasis from breast cancer is longer than that for patients with visceral metastases. A median survival of 24 to 34 months has been reported for bone-only disease.[4,11] Prolonged survival is associated with a substantial time at risk for skeletal morbidity. Scheid et al[3] reviewed

morbidity with bone-only metastases and found that of 180 patients with disease, 102 had fractures. Fracture sites included ribs, spine, long bones, and pelvis. Twenty-four of 180 patients had multiple fractures. Spinal cord compression occurred in 10% of patients, and hypercalcemia was frequent, with 35 of 180 patients having at least one episode.

A more recent review by Domchek et al[4] examined the incidence of skeletal complications in an unselected population of women with metastatic breast cancer and determined the predictors of skeletal complications. In 718 women, at a median follow-up of 107 months, skeletal complications included pathologic fracture, hypercalcemia of malignancy, spinal cord compression, surgery to bone, and radiation to bone. Fifty-one percent of the patients developed skeletal complications, and more than half of the patients had multiple complications. For all patients, the median time to first skeletal complication from time of diagnosis of metastases was 27 months, while the time was 11 months for patients with bone-only metastases.[4] Radiation therapy to bone was frequent: 40.8% incidence. Pathologic fracture was not as frequent as reported in the Scheid et al[3] study, 7.8% incidence. Domchek et al[4] reported a median survival of 26 months for patients with bone–only metastases and 21 months for those with bone plus another site of disease.

Breast Cancer Cells and Osteotroposim

The factors responsible for the proclivity of breast cancers to metastasize to bone are not known; however, tumor-derived and bone marrow microenvironmental factors are involved.[1] One factor associated with breast cancer bone metastasis is parathyroid hormone-related peptide (PTHrP), which is produced in cultured breast cancer cells as well as in fresh tumor specimens.[12,13] mRNA and immunohistochemical expression of PTHrP have been reported to be more common in cells metastasized to bone.[14–16] Localization of PTHrP has been reported more frequently in bone metastases than in other organ sites, suggesting that PTHrP plays a role in the osteotropism of breast cancer metastases.[14,15,17–19] PTHrP expression in breast cancer cells is up–regulated by transforming growth factor–beta (TGF-β). TGF-β is released from bone as a consequence of increased osteolysis associated with breast cancer bone metastasis.[16]

Bone Remodeling in Cancer Metastases

Bone remodeling is defined as osteoblast-mediated bone formation equal to and occupying the space established by osteoclast-mediated bone resorption. There are two processes underway simultaneously and these are linked activities.[20] Osteoclast degradation of bone is followed by new bone formation by osteoblasts. Ordinarily this process is coupled and balanced, but perturbations in bone remodeling occur as a consequence of metastases in bone.[21] Excessive osteoclastic activity is accompanied by inadequate osteoblastic restoration of bone in either quantity or location.

A variety of factors activate osteoclasts, including PTHrP, interleukin-1 (IL–1), IL–6, and TGF-α.[22-26] Osteoclast formation is induced by receptor activator of nuclear factor–kappa β (RANK) ligand. RANK ligand is a tumor necrosis factor (TNF) family cytokine produced by bone marrow stromal cells and osteoblasts.[27-29] RANK ligand binds to receptors on osteoclasts and osteoclast precursors, inducing osteoclast genesis. The inhibitor of RANK ligand, osteoprotegerin (OPG), is also a TNF family cytokine;[30] it is produced by many cell types and acts as a soluble inhibitory receptor in circulation. The relative activity of RANK ligand is controlled by OPG. In breast cancer, PTHrP enhances RANK ligand production, enhancing osteoclastic activity in bone.[31]

The interaction among these cytokines is probably not as simple as stated (Fig. 1). Continuous activation of osteoclasts by tumor-derived and bone marrow[32,33] microenvironmental factors leading to osteoclastic destruction of bone is the end result. The final common pathway for bone destruction due to breast cancer metastasis is activation of osteoclastic function with increases in the number and functional activity of osteoclasts in the region of metastatic disease sites.[32]

Bisphosphonates and Breast Cancer

Bisphosphonates, analogues of pyrophosphate (Fig. 2), are natural inhibitors of bone demineralization.[34] Modification of the pyrophosphate molecule with the substitution of carbon for a central oxygen results in bisphosphonates being resistant to hydrolysis by endogenous phosphatases. Bisphosphonates bind to hydroxyapatite crystals of bone, resulting in stabilization of bone matrix. In experimental systems, bisphosphonates have decreased bone turnover by exerting a

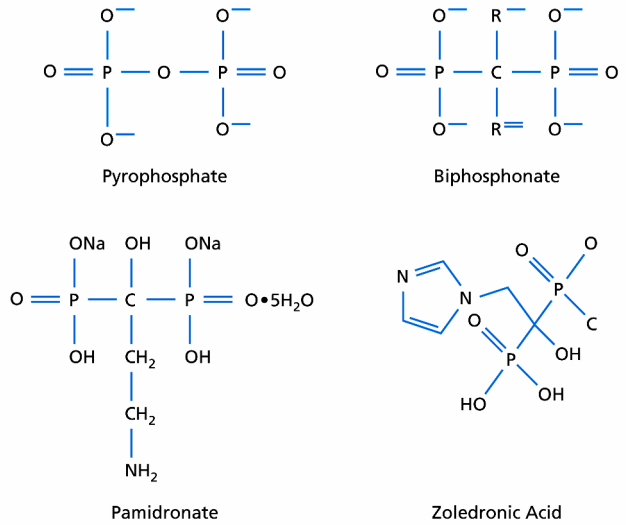

Figure 1 Pyrophosphonate, bisphosphonate, aminobisphosphonate, (pamidronate), and heterocyclic bisphosphonate (zoledronic acid) structures are shown.

positive effect on the bone-remodeling unit. They also decrease the depth of resorption cavities at osteoclastic binding sites on bone, inhibit osteoclastic osteoclast function, alter morphology of the osteoclast ruffled border, and inhibit maturation and recruitment of osteoclasts from the monocyte macrophage cell line.

Preclinical data indicate that bisphosphonates enhance apoptosis of osteoclasts and breast cancer cells.[35,36] Experimental systems also have shown bisphosphonates to reduce metastatic human breast cancer burden in bone. Sasaki et al,[37] reporting on the use of risedronate in an MDA-MB231 mouse model, showed that risedronate given subcutaneously before or simultaneously with inoculation of the breast cancer cells slowed the progression or completely inhibited the development of bone metastases. They further showed that there was a marked decrease in osteoclast number at metastatic sites and a marked decrease in metastatic tumor burden in bone.[37]

Similar effects were reported by Sasaki et al[38] using the experimental bisphosphonate YH529, again in a nude mouse mode. In a myeloma model, ibandronate reduced the occurrence and extent of lytic bone metastases.[39] Zoledronic acid has been shown to induce apoptosis in breast cancer cells and inhibit prostate cancer cell growth.[40] Bisphosphonates also inhibit breast and prostate cancer cell invasion, suggesting a potential use for bisphosphonates in bone metastases prevention.[41–43] Inhibition of osteoclastic activity as demonstrated by the preclinical models led to trials demonstrating the

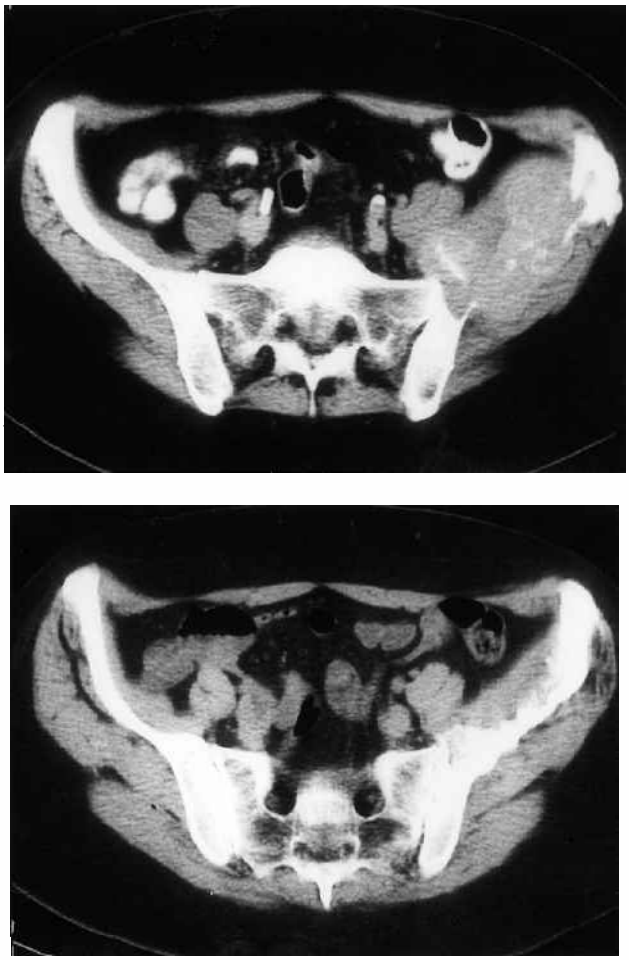

Figure 2 (A) Pretreatment computed tomography of pelvis showing large lytic bone destruction in the iliac area with substantial soft tissue component. (B) Post-treatment scan (approximately 6 months after chemotherapy and pamidronate) shows a decrease in soft tissue mass and partial reconstitution of iliac bone.

efficacy of bisphosphonates for treating hypercalcemia of malignancy.[44–49]

Bisphosphonates vary in their ability to inhibit osteoclast function. The non–amino-containing agents etidronate and clodronate are less potent than the amino-containing compounds alendronate, risedronate, and pamidronate. Zoledronic acid, the most potent osteoclast inhibitor, has a complex imidazole ring. The potency of bisphosphonates is assessed by in vivo rat model system.[50]

Amino bisphosphonates inhibit the mevalonate pathway, which is essential for cholesterol synthesis and protein prenylation. Lipid modification of G-proteins, Ras, and Rho, is essential for functional activity, including signaling functions for cell growth and differentiation.[51,52]

Osteoclast morphology and function is modified by inhibition of prenylation, and apoptosis of osteoclasts is induced by inhibition of prenylation. Dunford et al[53] showed a correlation between inhibition of farnesyl diphosphate synthase and inhibition of bone resorption. Bisphosphonate structure influences farnesyl diphosphate inhibition and apoptosis. Of the bisphosphonates tested, zoledronic acid was the most potent inhibitor of prenylation. Bisphosphonates also activate caspases, which are involved in apoptotic cell death.[54]

In addition to the anti–osteoclast cellular effects, Viereck et al[55] showed that zoledronic acid and pamidronate up–regulate OPG production by osteoblasts. Enhancement of OPG production would be expected to inhibit osteoclastogenesis.

Bisphosphonate and Clinical Bone Metastasis

The effects of bisphosphonates on skeletal morbidity due to bone metastases from breast cancer have been assessed in randomized clinical trials. A study of oral clodronate concluded that clodronate reduced fracture risk and hypercalcemia and had a salient effect on bone pain.[56] Skeletal benefits were confirmed in a larger study of 173 patients with breast cancer bone metastases treated with oral clodronate.[57] In addition to reducing fracture risk, hypercalcemia and bone pain, the need for radiation therapy for bone was reduced.

Oral and intravenous administrations of pamidronate were assessed in randomized studies of breast cancer bone metastases. Reductions in bone pain, pathologic fractures, radiation to bone, and hypercalcemia were reported.[58,59] Delay in the time to first skeletal event and a decrease in number of events were noted in a randomized placebo–controlled trial of intravenous pamidronate.[60]

Intravenous pamidronate was compared with placebo in two large, double-blind, randomized clinical trials for patients with metastatic breast cancer.[61,62] Hortobagyi et al[61] reported a benefit with pamidronate for patients treated with chemotherapy for metastatic breast cancer with lytic disease radiographically demonstrable in bone. Skeletal related events included bone pain and analgesic scores, fractures, radiation to bone, surgery to bone, spinal cord compression, and hypercalcemia of malignancy. The proportion of total events at 12 months in each treatment group was the trial endpoint.

The results showed that pamidronate had a beneficial effect on the course of bone metastases. The time to first skeletal related event was longer in the pamidronate group than placebo (13.1 vs 7 months; $P = .005$). The proportion of patients with any skeletal related event was lower with pamidronate than placebo (43% vs 56%; $P = .008$). Reductions in bone pain and maintenance of performance status were noted with pamidronate.[9] Metabolic markers of bone turnover were improved with pamidronate. Urinary hydroxyproline/creatinine ratio, urinary calcium/creatinine ratio, and bone alkaline phosphatase were all significantly improved compared with placebo treatment. This occurred in patients being treated with antineoplastic chemotherapy.[61]

A parallel study of similar design reported by Theriault et al[62] involved 372 patients treated with hormone therapy for lytic bone metastases. Patients were randomized to receive pamidronate or placebo in a double-blinded fashion. The endpoint for the initial phase of the study was skeletal related events at 13 months[62] and patients were followed for 24 months for safety and efficacy. The results showed that the skeletal morbidity rate, that is, the number of skeletal complications experienced by a patient divided by the time on the trial by the end of each specified time period, was reduced at 12, 18, and 24 months in the patients treated with pamidronate ($P = .028$, .023, .008, respectively). The proportion of patients with any skeletal event was reduced at 24 months with pamidronate (56% vs 67% placebo; $P = .027$). Time to first skeletal event was also longer with pamidronate (10.4 vs 6.9 months; $P = .049$). For the pamidronate-treated patients, bone pain scores improved significantly at the 12-month follow-up ($P = .002$).[62]

An update of these combined studies was reported by Lipton et al,[63] who reviewed the skeletal morbidity rate, proportion of patients with skeletal complications, and time to first skeletal event in the 751 patients treated in the hormone and chemotherapy pamidronate trials. Analysis indicated the proportion of skeletal events in the pamidronate arm to be 51% and the placebo arm 64% ($P < .001$). Time to first event was 12.7 months for pamidronate and 7 months for placebo ($P = .001$), while the time to a new pathologic fracture was 25.2 months in the pamidronate group and 12.8 months in the placebo group ($P = .003$). The median

time to radiation therapy was "not reached" for pamidronate and 16 months for placebo (P = .001). Differences in pain and analgesic scores substantially favored the pamidronate group (P = .015 for pain score and P = .001 for analgesic score).[63] Based on these data, pamidronate was approved by the U.S. Food and Drug Administration for palliation of bone metastases for patients with lytic bone disease from primary breast cancer. Pamidronate use for lytic metastases from breast cancer has been included in the NCCN Breast Cancer Guidelines (this issue).[64]

The most recent bisphosphonate of clinical value is zoledronic acid, which has a heterocyclic imidazole side chain on the pyrophosphate backbone (Fig. 2). The relative potency of zoledronic acid using the hypercalcemic TPTX rat model shows it is approximately 850 to 1,000 times more potent than pamidronate.[65] Zoledronic acid has been shown to inhibit osteoclast formation and osteoclastic bone resorption, interfere with osteoblast and osteoclast signaling, and inhibit mevalonate pathway and protein prenylation.[66] It also induces apoptosis in osteoclasts. Zoledronic acid has been shown to decrease the viability of human MDA-MB231 breast cancer cells[67] and to induce apoptosis in human HS578T breast cancer cells.[43,68–71] Synergistic apoptotic effects of zoledronic acid have been found on MCF-7 breast cancer cells in culture treated with paclitaxel, and it had a synergistic effect with tamoxifen in a similar in vitro system with MCF-7 cells.[40] In preclinical in vitro models, it decreased cancer cell adhesion to mineralized and nonmineralized matrices, and decreased cancer cell invasion into extracellular matrices. Boissier et al[43] showed that invasion of human breast cancer cells into matrigel was inhibited by zoledronic acid.[40,41,71,72]

Zoledronic Acid and Pamidronate: Clinical Comparison

Compared with pamidronate in studies of cancer-related hypercalcemia, zoledronic acid had a more rapid onset of hypocalcemic effect and a statistically significantly longer duration of action than pamidronate.[16] Using 4 mg and 8 mg doses of zoledronic acid over five minutes and 90 mg of pamidronate over two hours, researchers found a higher response rate (normalization of serum calcium by day 10) with the 4 mg zoledronic acid (88.4%, 86.7% vs 69.7%) than with pamidronate.

Berensen et al[73] examined the efficacy of zoledronic acid at three different dose levels in patients with bone metastasis compared with pamidronate at the standard dose of 90 mg intravenously every four weeks using a two-hour intravenous infusion. Zoledronic acid doses of 0.4, 2, or 4 mg were given on a four-weekly schedule with a 10-month observation period. Zoledronic acid at a dose of 0.4 mg was not effective; however, doses of 2 and 4 mg significantly reduced the need for radiation therapy to bone, the primary study endpoint. These two doses were as effective as 90 mg of intravenous pamidronate. Increases in bone mineral density and decreases in the bone resorption marker, N-telopeptide, were noted for zoledronic acid as well as pamidronate. The infusion time of zoledronic acid was five minutes and for pamidronate was 120 minutes.[73]

Rosen et al[74] reported on the efficacy of zoledronic acid and pamidronate in addition to antineoplastic therapy in a large randomized study of patients with multiple myeloma and breast cancer bone metastasis. The study endpoint was proportion of skeletal events at 13 months. Two doses of zoledronic acid were tested, 4 mg and 8 mg, and compared with pamidronate 90 mg as the "standard." The 8 mg zoledronic acid dose was reduced to 4 mg, and the intravenous infusion time lengthened from 5 minutes to 15 minutes because of unexpected renal toxicity.

Patients could have any systemic therapy for malignant disease, hormone or chemotherapy for breast cancer, at the discretion of the attending oncologist. This study demonstrated the equivalency of zoledronic acid compared with pamidronate. Forty-four percent of patients treated with zoledronic acid 4 mg compared with 46% in the 8 to 4 mg and 46% in the pamidronate 90 mg group had skeletal related events. Equivalency was confirmed for the proportion of patients developing fractures or needing radiation to bone, surgery to bone, and spinal cord compression. The mean skeletal morbidity rate for the zoledronic acid 4 mg dose was not different whether patients were treated with chemotherapy or hormonal therapy for metastatic disease.

In a subsequent subset analyses, the benefit of zoledronic acid was examined in women with at least one lytic bone lesion. This radiographic requirement had been a prerequisite to participate in the original pamidronate studies.[61–64] One hundred ninety patients in the zoledronic acid 4 mg group had a radiographi-

cally–confirmed lytic lesion, and they were compared with 162 patients in the previously reported pamidronate group. The proportion of patients with skeletal related events was 48% for zoledronic acid and 58% for pamidronate (P = .058). The time to first skeletal related event was 310 days in the zoledronic acid group versus 174 days in the pamidronate group (P = .013).[75] Overall, zoledronic acid at a dose of 4 mg intravenously every four weeks by 15–minute intravenous infusion appears to be equivalent to pamidronate 90 mg intravenously every four weeks by two–hour intravenous infusion, and better than pamidronate in the subset of patients with osteolytic disease.

Bisphosphonates as Adjuvant Therapy

Bisphosphonates also have been assessed as adjuvant therapy in primary breast cancer. In a study reported by Diel et al,[76] 302 patients with primary breast cancer and tumor cells demonstrable in the bone marrow by immunohistochemical analyses for cytokeratin were randomized to receive oral clodronate 1600 mg per day for two years or standard care for breast cancer. No placebo was used. The authors reported a decrease in frequency of visceral and bone metastases (21 in the clodronate group vs 42 in the standard care group), a decreased frequency of bone metastases (12 vs 25), and a decrease in mortality (6 deaths in the clodronate group vs 22 in the standard care group).[76] A later report with a median follow-up of 53 months included 288 patients with follow-up data.[77] The number of patients with bone disease was still reduced, 20 in the clodronate group vs 34 in the no treatment group (P = 0.044), while mortality also was reduced, 13 deaths in the clodronate group vs 32 in the no treatment group (P = 0.002). The original conclusions, that metastases were reduced in bone and visceral sites and an improved survival, were modified. There was no effect on visceral metastases prevention.

Powles et al[78] reported on 1,069 patients with primary breast cancer randomly assigned to oral clodronate or placebo. The patients received 1,600 mg of clodronate daily or placebo for two years with treatment beginning within six months of breast cancer diagnosis. At the initial report, the frequency of bone metastases was 20 in the clodronate group and 39 in the placebo group. In a recent update with a median follow-up of 5.5 years, 63 patients in the clodronate group and 80 in the placebo group showed bone metastases (P = ns). There was no effect on mortality or bone metastases development after cessation of clodronate administration. The authors concluded that clodronate did not affect visceral metastases, had no effect on overall survival, and reduced bone metastases incidence.[79] Saarto et al[80] also reported on the adjuvant use of oral clodronate in a randomized, controlled clinical trial. In this trial, 299 women with node-positive breast cancer received oral clodronate 1,600 mg per day for three years or no treatment. Adjuvant breast cancer treatment included CMF for six cycles for premenopausal women and tamoxifen or toremifene for postmenopausal women.

The authors noted an increased risk of bone and visceral metastases and poorer survival in the clodronate-treated patients.[80] At five years, the frequency of bone metastases in the clodronate group was 21% and 17% in the control group (P = .27). The rates of non-bone metastases were 43% in the clodronate group and 25% in the control group (P = .0007). Disease-free survival was substantially less in the clodronate group than the control group (56% vs 71%; P = .007) and overall survival was also negatively impacted in the clodronate group (70% vs 83%; P = .009).[81]

Oral Bisphosphonates

A review of oral bisphosphonate use for patients with bone metastasis concluded that oral agents are not as effective as intravenous agents in reducing skeletal complications of bone metastasis.[82] Because of reduced efficacy, oral agents "should not be substituted for intravenous administration."[82]

A Cochrane review concludes that oral clodronate reduced the risk of skeletal events by 16% in women with breast cancer and evident bone metastases.[83] The only oral agent with data from randomized clinical trials is clodronate. Randomized trial data are not available for tiludronate, alendronate, or risedronate.

Pain Relief

Bisphosphonate use in breast cancer bone metastasis results in decreases in bone pain and analgesia use.[61,62] Analysis of randomized controlled trials of bisphosphonates reported improvements in pain and quality of life from 4 (pain) and 2 (quality of life) of 19 randomized studies analyzed.

Analysis of costs

Prospective cost-benefit studies of bisphosphonate use have not been completed. An analysis of resource use for zoledronic acid used time study methodology to assess the impact of zoledronic acid use in three outpatient facilities. Because of a shorter infusion time compared with pamidronate, there were time savings for patients. The authors concluded that "opportunity benefits" favored zoledronic acid.[84]

In a cost-effectiveness analysis of pamidronate use in breast cancer bone metastasis, Hillner et al[85] concluded that the costs of pamidronate use exceeded the cost savings of prevention of skeletal events. They noted that their analysis was "most sensitive" to the costs of pamidronate and treatment of pathologic fractures. Prospective data on cost, benefits, and quality-adjusted life year are not available.

Toxicities

Clinical toxicities associated with bisphosphonate use include systemic and end organ toxic effects. Transient increases in bone pain, myalgias, and acute febrile reactions occur in more than 5% of patients. Fatigue and nausea may occur. Anemia and neutropenia have been reported, but increased need for packed red blood cell transfusion has not been seen. Bisphosphonates may affect electrolytes and renal function. However, hypocalcemia has been reported rarely.

Renal toxicity has been seen with pamidronate and zoledronic acid use. In the breast cancer study comparing zoledronic acid and pamidronate, the 8 mg dose of zoledronic acid was reduced to 4 mg due to renal toxicity manifest by increases in serum creatinine.[75] Increasing the length of infusion time from 5 minutes to 15 minutes and increasing infusion volume from 50 to 150 mL brought the incidence of renal toxicity with zoledronic acid close to that of pamidronate.[74] This also was reported for the prostate cancer patient bisphosphonate study.[86]

Conclusions

Bisphosphonate use has been shown to be of clinical value with level-1 evidence in reducing skeletal morbidity due to metastases from primary breast cancer.[87,88] Benefits include decreases in bone pain and analgesic requirements, reductions in skeletal related events, including fractures, and the needs for radiation or surgery to bone, and hypercalcemia. In addition, prolongation of time to first skeletal event was seen consistently. Future studies are needed to clarify the role of bisphosphonates in breast cancer metastasis prevention.

The American Society of Clinical Oncology published guidelines on bisphosphonate use in breast cancer. They correctly identified the questions that remain unanswered. These include when to initiate or stop bisphosphonate therapy, what patients are likely to benefit from bisphosphonate use, and what is the cost-benefit analysis for bisphosphonate use.

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