Bisphosphonates in Breast Cancer: Antitumor Effects

Rebecca Aft, MD, PhD

Dr. Aft is a Professor of Surgery in the Division of General Surgery at the Washington University School of Medicine in St. Louis, Missouri.

Address correspondence to:
Rebecca Aft, MD, PhD
Professor, Surgery
Division of General Surgery
Surgical Oncology and Endocrine Surgery Section
Washington University School of Medicine
660 S. Euclid Avenue, Campus Box 8109
St. Louis, MO 63110
Phone: (314) 747-0063
Fax: (314) 454-5509
E-mail: aftr@wudosis.wustl.edu

Abstract: Bone metastases add to the burden of breast cancer, with patients experiencing severe bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy. Nitrogen-containing bisphosphonates have become the standard treatment for skeletal-related events and bone pain, as well as for bone loss associated with chemotherapy and aromatase inhibitors. Emerging preclinical and clinical evidence indicates that bisphosphonates negatively affect multiple processes that support tumor growth and proliferation and formation of metastases. Several small clinical trials suggest that bisphosphonates can modify angiogenic factors, immune surveillance, and disseminated tumor cells detected in bone marrow. Emerging data suggest that bisphosphonates used for osteoporosis prevention may inhibit breast cancer development. Three large prospective studies have shown improved outcomes with the addition of zoledronic acid to conventional neoadjuvant or adjuvant therapy. This article focuses on current clinical trials examining the use of bisphosphonates in patients with breast cancer.

Keywords
Breast cancer, bisphosphonate, zoledronic acid, bone metastases

Introduction

This article is the second of a 2-part series on bisphosphonates (BPs) in breast cancer. The first part of this series was published in the March 2011 issue of *Clinical Advances in Hematology & Oncology*.

Clinical Studies

Antiangiogenic Effects

Preclinical data demonstrating inhibitory properties of BPs on endothelial cell proliferation, adhesion, and capillary formation strongly support an antiangiogenic mechanism, although translation to anticancer activity in the clinical setting is just beginning to emerge. Several studies were designed to quantitate changes in circulating angiogenic cytokines after single or multiple doses of BPs. In an early study, 25 cancer patients (11 with breast cancer) with bone metastasis were treated with a single infusion of pamidronate 90 mg.[1] Vascular endothelial growth factor (VEGF) levels decreased significantly from baseline (-19.2%; P=.019) after 1 day, continued

to decline on day 2 (-25.2%; *P*=.001), and persisted through day 7 (-25.2%; *P*=.03). In contrast, the levels of interferon γ and interluekin (IL)-6 decreased significantly from baseline (*P*=.003 and *P*=.007, respectively) on day 1, but were not significantly different from baseline on day 7. In a similar study, 30 cancer patients (17 with breast cancer) with metastatic bone disease were treated with a single infusion of zoledronic acid 4 mg.[2] An increase in the number of patients with reduced circulating VEGF levels was observed, from 36.7% (11/30) on day 1 to 63.3% (19/30) on day 21. This was associated with a decrease in VEGF levels from baseline that was significant by day 2 (-23%; *P*=.0298) and long lasting, reaching a 34% decrease by day 21 (*P*=.001). Interestingly, a study of 18 breast cancer patients with bone metastasis who were treated with a single dose of zoledronic acid 4 mg had slightly different results.[3] An 11.8% decrease (*P*=.03) in VEGF levels was observed 2 days after treatment. However, 7 days after BP infusion, VEGF levels rose to 11.9% above basal levels, though the increase was not statistically significant (*P*=.07). Changes in blastic fibroblast growth factor (bFGF), interferon γ, and interleukins were not significant at any time point. Longer term metronomic therapy was also investigated in 26 patients with solid tumors (4 with breast cancer) and bone metastasis.[4] Zoledronic acid 1 mg weekly was administered for 4 weeks followed by 4 mg every 28 days for 3 cycles. VEGF levels were 29.7% lower (*P*=.038) than baseline 7 days after a single dose of zoledronic acid. The decreased levels persisted throughout the remainder of the study period and remained statistically significant. Thus, it appears that the antiangiogenic effects of BPs may be long lasting. However, the ability of BPs to modulate various angiogenic factors appears to vary, and how this differential activity translates into anticancer activity remains to be elucidated.

Modulation of Immune Surveillance (γδ T Cells)

As in the preclinical setting, the anticancer activity of BPs associated with γδ T-cell activation/proliferation in the clinical setting has been investigated mainly in nonbreast or solid tumors. One study enrolled 19 patients with low-grade non-Hodgkin lymphoma or multiple myeloma with the goal of determining the effective dose for γδ T-cell proliferation.[5] The first 10 patients received a single dose of pamidronate 90 mg followed by increasing doses of IL-2 (0.25 to 3×10^6 IU/m^2) from day 3 to day 8. Since none of the patients showed a measurable γδ T-cell response and since stable disease in 1 patient was the best response, the subsequent 9 patients were selected by positive in vitro proliferation of γδ T cells. Treatment was similar to that for the first group, though IL-2 was administered on days 1–6. In vivo proliferation of γδ T cells was observed in 5 of 9 patients, 3 of whom achieved a partial response and 1 of whom achieved stable disease. In line with this, another study evaluated the effect of low-dose zoledronic acid on Vγ9Vδ2 cells in 9 patients (3 with breast cancer) with metastasis to the bone who showed positive in vitro proliferation of Vγ9Vδ2 T cells.[6] Peripheral blood mononuclear cells were collected at various time points for analysis. After IL-2 treatment in vitro, zoledronic acid induced an expansion of effector Vγ9Vδ2 T cells and a decrease in naïve and memory Vγ9Vδ2 T cells from peripheral blood mononuclear cell (PBMCs) collected at 1 month, and more so at 3 months. Thus zoledronic acid appears to induce maturation of Vγ9Vδ2 T cells toward an effector phenotype, which may enhance antitumor response. A third study examined the effects of zoledronic acid on immunologic parameters of therapeutically terminal advanced breast cancer patients.[7] Ten patients received low-dose IL-2 followed by zoledronic acid 4 mg every 21 days for 1 year and PBMCs were obtained at various time points. Differentiation of Vγ9Vδ2 T cells toward an effector/memory-like phenotype was observed in all patients and remained robust at 12 months in 3 of 10 patients. Of these 3 patients, 1 achieved a partial response and 2 achieved stable disease. Thus, while these data indicate anticancer activity associated with the activation of Vγ9Vδ2 T cells, it appears that prescreening for proliferation may be useful if not necessary to identify potentially responsive patients.

Effects on Disseminated Tumor Cells

The first step in the metastatic process is the early dissemination of cells from the primary tumor. Although disseminated tumor cells (DTCs) in the bone marrow may remain dormant for prolonged periods, their presence is an independent prognostic indicator for increased risk of distant metastasis and death.[8,9] Preliminary clinical data support the hypothesis that antineoplastic effects of BPs may occur through a reduction in DTCs. In a phase II trial, 120 women with newly diagnosed stage II/III breast cancer were randomized to receive 4 cycles of neoadjuvant epirubicin/docetaxel and 2 cycles of adjuvant epirubicin/docetaxel concomitantly with zoledronic acid 4 mg every 3 weeks or no zoledronic acid for 1 year.[10] The primary endpoint was the number of patients with detectable DTCs after 3 months. At baseline, DTCs were detected in 43.3% (26/60) of patients in the zoledronic acid group and 48.3% (28/58) of patients in the control group. At 3 months, 30.4% (17/56) of patients receiving zoledronic acid versus 47.2% (25/53) of patients in the control group had detectable DTCs (*P*=.054). Patients with no initial detectable DTCs were also more likely to remain negative for DTCs at 3 months when treated with zoledronic acid (87.1%) than without zoledronic acid (60.0%; *P*=.03). Disease-free survival and overall survival (OS) were assessed at a median follow-up

of 61.9 months, and no differences were observed between trial arms in the overall population. However, there was a significant improvement in disease-free survival (DFS) and OS among patients with estrogen receptor (ER)–negative, human epidermal growth factor receptor 2 (HER2)-negative disease (*P*=.013).[11] In another study, 45 patients with stage I–III breast cancer who were positive for DTCs and had completed neoadjuvant or adjuvant therapy received zoledronic acid 4 mg monthly for 2 years.[12] The primary endpoint was the reduction in DTCs. An analysis of 32 patients demonstrated a reduction in DTCs from a mean of 25.4/mL at baseline to 8/mL (*P*=.0017) after 1 year of therapy. A third study was conducted in 96 stage I–III breast cancer patients who were positive for DTCs.[13] Patients were randomly assigned to receive monthly zoledronic acid 4 mg or no zoledronic acid for 2 years in conjunction with adjuvant chemotherapy with or without hormone therapy or hormone therapy alone. The aim of the study was to evaluate the reduction in DTCs. Results showed that 66.7% of patients treated with zoledronic acid were DTC negative after 12 months, whereas only 35.1% of those who did not receive zoledronic acid had a DTC-negative status (*P*=.0009). A nonsignificant trend for a reduction in the number of DTCs in the zoledronic acid group compared with the control group (*P*=.066) was also observed. These studies clearly demonstrate that zoledronic acid affects reduction in DTCs. It remains unclear how this translates into a reduction in the risk of distant metastasis and death; however, it appears that zoledronic acid may benefit a subset of difficult-to-treat patients.

Metastatic Breast Cancer

There are limited data on the ability of BPs to delay disease progression and improve survival in the metastatic setting. In a randomized trial conducted by the Aredia Multinational Cooperative Group, patients with bone metastasis were randomized to receive chemotherapy plus pamidronate 45 mg every 3 weeks (n=143) or chemotherapy alone (n=152).[14] Patients remained in the active phase of the trial until disease progression in bone. Chemotherapy was administered at the discretion of the investigator. Results showed that the addition of pamidronate increased the time to disease progression (TTP), a primary endpoint, by 48% (249 days for chemotherapy plus pamidronate vs 168 days for chemotherapy alone; *P*=.02). Another study compared the safety and efficacy of pamidronate and zoledronic acid in 1,130 patients with bone metastasis secondary to stage IV breast carcinoma or stage III multiple myeloma.[15] Patients were randomized to receive zoledronic acid 4 mg or 8 mg or pamidronate 90 mg every 3–4 weeks for 24 months. During the course of the trial, the 8-mg dose of zoledronic acid was reduced to 4 mg for safety reasons. A retrospective subset analysis was undertaken to determine the correlation between normalization of elevated baseline levels of N-telopeptides of type I collagen (NTX) at 3 months and OS at 24 months. The analysis included 328 patients who received zoledronic acid and for whom bone resorption marker data were available. Results demonstrated that at 3 months, NTX levels had normalized in 149 of the 196 patients, with elevated NTX levels at baseline. Of the remaining patients, 31 had persistently elevated NTX levels and 16 had died. Patients with normalized NTX levels at 3 months had a significantly lower risk of death at 24 months than those with persistently elevated NTX levels. Median survival was 790 days for patients whose NTX levels normalized, compared with 446 days for patients whose NTX levels remained elevated. In contrast to these studies, a meta-analysis of 4 advanced breast cancer trials showed no significant benefit in OS (hazard ratio [HR], 0.71; confidence interval [CI], 0.40–1.26), bone metastasis–free survival (HR, 0.68; CI, 0.34–1.36), or nonskeletal metastasis–free survival (HR, 0.95; CI, 0.31–2.91) in patients receiving clodronate therapy compared with those who received no active treatment, as demonstrated by the CIs that crossed 1.0.[16]

The above studies provide preliminary clinical evidence for anticancer activity in the metastatic setting. Studies to date indicate that anticancer activity may be limited to nitrogen-containing BPs (N-BPs) and that biomarkers for response may provide a useful tool for assessing potential response. A number of ongoing studies should clarify possible anticancer activity of the N-BPs in the metastatic setting. These studies include an assessment of the ability of zoledronic acid to delay disease progression and prolong OS in patients with metastatic breast cancer (NCT01129336, NCT00458796, NCT00365105). In particular, the Z-ACT trial (NCT01129336) is evaluating the antitumor effects of zoledronic acid in patients with newly diagnosed HER2-negative metastatic breast cancer, with progression-free survival (PFS) as the primary endpoint. Secondary endpoints include TTP, time to bone metastases, and OS.

Adjuvant Treatment of Breast Cancer

Three large prospective studies have shown improved outcomes with the addition of zoledronic acid to conventional neoadjuvant or adjuvant therapy (Figure 1).[17-19] The randomized Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial (NCT00295646) evaluated the effect of adding zoledronic acid to endocrine therapy.[20] In this 4-arm trial, 1,803 premenopausal women with hormone-responsive stage I/II breast cancer were randomized to receive goserelin 3.6 mg every 28 days plus either tamoxifen 20 mg daily or anastrozole

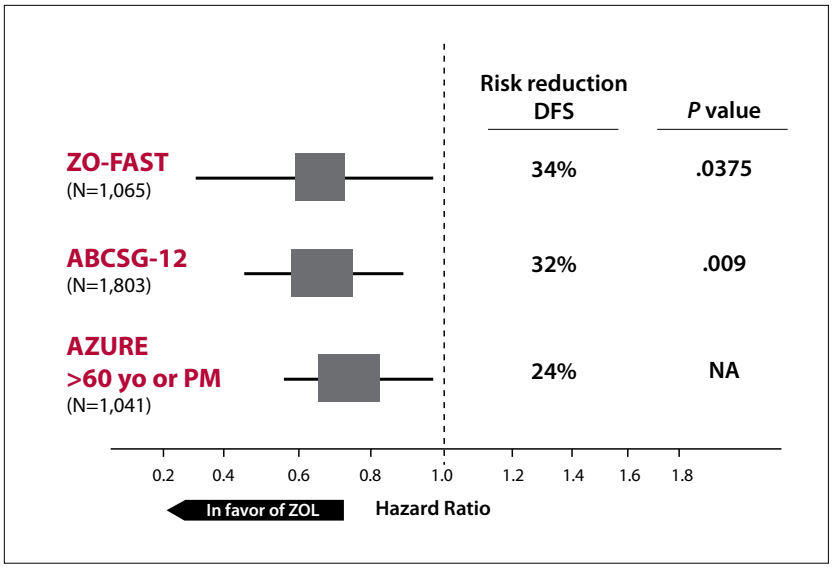

Figure 1. Improvement in disease-free survival with the addition of zoledronic acid to conventional therapy.[17-19]

DFS=disease-free survival; PM=postmenopausal; yo=year old; ZOL=zoledronic acid.

1 mg daily, with or without zoledronic acid 4 mg every 6 months for 3 years (7 total doses). The addition of zoledronic acid resulted in a 36% reduction in the risk of disease progression, the primary endpoint, compared with endocrine therapy alone (*P*=.01) after a median follow-up of 47.8 months. At a median follow-up of 62 months, the risk of disease progression was maintained (32% reduction; *P*=.008).[21] The reduction in recurrence was observed locally and distantly both in and outside the bone. The risk of death was also reduced but did not reach statistical significance, although it approached significance in women older than 40 years (*P*=.057). The AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) trial (NCT00072020) evaluated the addition of zoledronic acid to adjuvant or neoadjuvant chemotherapy or endocrine therapy in 3,360 patients with stage II/III breast cancer.[17] Patients received chemotherapy with or without zoledronic acid 4 mg every 3–4 weeks for 6 doses, every 3 months for 8 doses, and every 6 months for 5 doses (19 doses in 5 years). The primary endpoint was DFS, defined as recurrent locoregional or distant disease. In an interim analysis, zoledronic acid was not associated with a significant improvement in DFS in the overall population. However, in a subgroup analysis, zoledronic acid improved OS by 29% (*P*=.017) and reduced DFS events in and outside the bone in women who were more than 5 years postmenopausal. A subset of 195 patients who received neoadjuvant therapy with zoledronic acid for up to 6 doses were also assessed for pathologic tumor response, specifically residual invasive tumor size (RITS), at surgery.[22] By multivariate analysis, the adjusted mean RITS was 12 mm lower in the zoledronic acid group (15.5 mm) than in the group not receiving zoledronic acid (27.4 mm; *P*=.006). In the Zometa-Femara Adjuvant Synergy Trials (Z-FAST/ZO-FAST/E-ZO-FAST), which were designed to investigate the bone-protective effects of zoledronic acid, an exploratory analysis was conducted to assess the anticancer potential of zoledronic acid. A total of 2,194 postmenopausal women with hormone-responsive early breast cancer received letrozole 2.5 mg daily.[23] Patients were randomized to receive zoledronic acid 4 mg administered every 6 months for 5 years starting either upon randomization (up-front) or upon a predetermined measure of bone loss (delayed start). After 36 months of follow-up, a 34% reduced incidence of DFS events with up-front zoledronic acid treatment compared with delayed treatment was observed in the ZO-FAST trial (*P*=.0375).[18] These studies show a DFS benefit or OS benefit in postmenopausal women or women who have chemical ovarian suppression.

Pamidronate has also shown anticancer efficacy. In a small nonrandomized trial, patients with primary breast cancer and 4 or more positive nodes receiving adjuvant therapy were assigned to receive pamidronate 45 mg every 2 weeks for 4 cycles (n=33) or no additional therapy (n=57).[24] The primary endpoints were the reduction or delay of bone metastasis. Results showed that pamidronate significantly reduced the incidence of bone metastases (*P*=.005) and significantly improved bone metastasis–free survival (*P*=.029). In another study, 429 perimenopausal women with primary operable stage I–III breast cancer were assigned to receive pamidronate (n=258) or no BP therapy (n=171) concomitantly with adjuvant chemotherapy.[25] The incidence of bone metastasis was 2.3% in the pamidronate group and 8.7% in the control group. The incidence of metastasis at other sites was lower in the

Table 1. Ongoing Trials Evaluating Anticancer Activity of Antiresorptives in Breast Cancer

Study	Agent	Region	Planned Accrual (Closed/Open)
Adjuvant			
NSABP B-34 (NCT00009945)	Clodronate	Canada/US	3,400 (Closed)
SUCCESS	Zoledronic acid	Germany	3,754 (Closed)
SWOG 0307 (NCT00127205)	Clodronate vs ibandronate vs zoledronic acid	US	6,097 (Closed)
AZAC	Zoledronic acid	France	600 (Open)
HOBOE (NCT00412022)	Zoledronic acid	Italy	1,050 (Open)
NATAN (NCT00512993)	Postoperative zoledronic acid	Germany, Austria	693 (Closed)
GAIN (NCT00196872)	Ibandronate	Germany	3,024 (Open)
ICE (NCT00196859)	Ibandronate	Germany	1,500 (Open)
Metastatic			
Optimize 2 (NCT00320710)	Zoledronic acid	US	705 (Open)
BisMARK (NCT00458796)	Zoledronic acid	UK	1,500 (Open)
CALGB 70604 (NCT00869206)	Zoledronic acid	US	1,538 (Open)
Z-ACT (NCT01129336)	Zoledronic acid	US	300 (Open)

pamidronate group than in the control group, but the difference was not statistically significant. Rates of OS and DFS were equivalent in the 2 groups.

A meta-analysis of 3 early breast cancer trials examining the effect of clodronate on OS has been conducted.[16] No significant benefit in OS (HR, 0.75; CI, 0.31–1.82), bone metastasis–free survival (HR, 0.68; CI, 0.38–1.23), or nonskeletal metastasis–free survival (HR, 0.89; CI, 0.40–1.98) was observed in patients who received clodronate therapy compared with those who received no active treatment.

As in the metastatic setting, N-BPs appear to have greater anticancer potential than non–N-BPs in the adjuvant setting. Zoledronic acid and pamidronate have demonstrated efficacy in the bone. Outside the bone, zoledronic acid is efficacious, though pamidronate may be less so. Current evidence from clinical trials suggests that N-BPs have anticancer activity in the subpopulation of breast cancer patients who are 5 years or more postmenopausal or older than 40 years with ovarian suppression (Figure 1). Several large studies to further assess the anticancer effects of BPs in breast cancer patients are ongoing. Among them, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-34 trial (NCT00009945) will determine whether clodronate administered for 3 years, alone or in addition to adjuvant chemotherapy and/or hormone therapy, will improve DFS. The Southwest Oncology Group 0307 study (NCT00127205) is comparing zoledronic acid with clodronate and ibandronate in terms of improving DFS and OS. In the HOBOE (A Study of Hormonal Adjuvant Treatment Effect on Bone Mineral Density in Early Breast Cancer Patients) study (NCT00412022) comparing tamoxifen (or triptorelin in premenopausal patients), letrozole, and letrozole plus zoledronic acid, DFS in premenopausal patients is a primary endpoint (Table 1).

Breast Cancer Risk

Three studies have investigated whether BPs are able to reduce breast cancer risk. A retrospective analysis examined the association between oral BP use and invasive breast cancer in postmenopausal women enrolled in the Women's Health Initiative.[26] In this study, 18.2% (2,816/154,768) of participants were oral BP users at entry. After an average of 7.8 years of follow-up, invasive breast cancer incidence was significantly lower, by 32%, in BP users (P<.01), as was the incidence of ER-positive invasive cancers (P=.02). A similar but nonsignificant trend was seen for ER-negative invasive cancers. The incidence of ductal carcinoma in situ was higher in BP users (HR, 1.58; 95% CI, 1.08–2.31; P=.02), suggesting that BPs may interfere with the progression of breast cancer development. A second population-based case-control study comprising 2,936 patients with incident-invasive breast cancer and 2,975 controls older than 70 years was conducted to evaluate the association between BPs and breast cancer.[27] Results showed a 33% reduction in breast cancer risk among BP users compared with nonusers (odds ratio 0.67; CI, 0.51–0.89). Risk reduction was greatest with increasing duration of BP use (P-trend=.01)

and in women who were not obese (*P*-interaction=.005). Another population-based case-control study, the Breast Cancer in Northern Israel Study, evaluated 4,039 postmenopausal patients with breast cancer and age-, clinic-, and ethnic-group matched controls.[28] BP use for at least 1 year before diagnosis was associated with a significant 39% reduction in breast cancer risk (odds ratio 0.61; CI, 0.50–0.76). In this study, breast cancer risk did not change with longer duration of BP use, and breast tumors that developed during BP therapy tended to have a more favorable prognosis (more ER-positive and well differentiated).

Implications of Clinical Data

Taken together, clinical studies support the notion that BPs have antitumor properties. Data from several small clinical trials suggest that BPs can modify angiogenic factors, immune surveillance, and disseminated tumor cells detected in bone marrow, which provide possible mechanisms for the favorable effects observed on recurrence and survival observed in early and late stage breast cancer. Moreover, emerging data suggest that BPs used for osteoporosis prevention may inhibit breast cancer development.

The development of metastatic disease is a complex multi-step process. Recent data suggest that there is cross-talk between tumor cells and the bone marrow, which results in the release of growth factors as well as bone marrow–derived cells, which play critical roles in both tumor growth and metastases development.[29] Interference with this process by alteration of the bone marrow microenvironment with BP treatment may provide an explanation for the effects of BP treatment on tumor development, local-regional recurrence, and metastases. Future experiments directed at understanding the tumor-bone marrow interaction will lead to new insights into the effects of BPs.

Safety of BPs

In clinical trials, therapy with N-BPs has been associated mainly with mild to moderate adverse events; severe adverse events have been rare.[30,31,32,33] The most common adverse effects associated with N-BPs (>25%) were nausea, fatigue, anemia, bone pain, constipation, fever, vomiting, and dyspnea. Noteworthy adverse reactions to N-BPs are renal toxicity, hypercalcemia of malignancy, acute-phase reactions, mineral/electrolyte abnormalities, injection-site reactions, and ocular abnormalities (uveitis/scleritis). As reviewed by Ruggiero and Mehrortra, osteonecrosis of the jaw is a rare adverse reaction, with a reported incidence of 0.8–12%.[34]

Beyond BPs

Improvements in our understanding of the molecular and cellular basis of metastasis have resulted in the development of novel therapies. Normal bone remodeling is tightly balanced between bone resorption by osteoclasts and bone formation by osteoblasts. The formation of bone metastases alters the balance of bone remodeling.[35] Denosumab is a fully human monoclonal antibody that targets the receptor activator for nuclear-factor-κB ligand, one of the principal regulators of osteoclast differentiation, function, and survival.[36] Denosumab has demonstrated beneficial effects on skeletal-related events (SREs).[37] No PFS or OS advantage compared with zoledronic acid has been observed. Further investigation into the mechanisms of its potential anticancer effects, as has been demonstrated with BPs, as well as its safety profile compared with BPs, is warranted. The D-CARE (Study of Denosumab as Adjuvant Treatment for Women With High Risk Early Breast Cancer Receiving Neoadjuvant or Adjuvant Therapy) trial (NCT01077154) is investigating the effect of adjuvant denosumab in women at high risk for disease recurrence. Src is a positive regulator of osteoclasts and a negative regulator of osteoblasts. Src inhibitors (dasatinib [Sprycel, Bristol Myers-Squibb], bosutinib [Wyeth], and saracatinib [AstraZeneca]) are in early stages of clinical testing for breast cancer. Preliminary data from studies in patients with advanced breast cancer suggest clinical benefits with dasatinib as a single agent in ER-positive[38] and triple-negative tumors,[39] as well as in combination with paclitaxel[40] and capecitabine.[41] Studies with saracatinib have shown very little activity.[42,43]

Conclusion

Bone metastases add to the burden of breast cancer, with patients experiencing considerable skeletal morbidity, including severe bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy, all of which substantially reduce the patient's quality of life. Non–N-BPs inhibit bone resorption, thereby reducing the risk of skeletal complications. Consequently, N-BPs have become the standard treatment for SREs and bone pain, as well as for chemotherapy-associated and aromatase inhibitor–associated bone loss.

Emerging preclinical and clinical evidence indicates that BPs negatively affect multiple processes that support tumor growth and proliferation and formation of metastases. The data suggest that these effects can occur directly through inhibition of farnesyl diphosphate synthase and indirectly by release of cytokines such as IPP.

BP treatment likely leads to an alteration of the bone marrow microenvironment, which not only affects the lodging of DTCs, but interrupts the interaction between the host tumor and the bone marrow, which appears to play an important role in release of growth factors and bone marrow–derived cells, which ultimately provide support for local tumor progression, metastatic niche formation, tumor self-seeding, and metastases development. However, the process of tumor growth and metastasis is complex, and BPs may be effective in some but not all pathways and may depend on the host environment.

Clinical benefit in OS, DFS, and TTP has been demonstrated with BP treatment in the adjuvant setting (Figure 1). Zoledronic acid administered during adjuvant therapy significantly reduces the risk of disease progression and recurrence locally and systemically in premenopausal women with ovarian suppression, in women who are 5 years or more postmenopausal, and in postmenopausal women receiving treatment with an AI. Pamidronate has been shown to reduce bone metastasis. Additional studies to confirm the antitumor activity of N-BPs are warranted, and results from a number of large trials with DFS as the primary endpoint are expected in the next few years (Table 1).

In the metastatic setting, N-BPs have been shown to significantly improve TTP and OS. However, there have been only a limited number of small trials, and large randomized studies with disease progression, if not OS, as primary the endpoint are needed. In the neoadjuvant setting, zoledronic acid has been shown to significantly reduce residual tumor size. Emerging data suggest that BP treatment for osteoporosis leads to a reduction in breast cancer risk.

Ongoing clinical trials will further elucidate the patient populations most likely to benefit from BP treatment, optimal BP dosing, combination therapy, treatment duration, and markers of response. Current evidence suggests that with appropriate safety considerations, the addition of BPs, particularly N-BPs, to standard therapy may provide anticancer benefits. To date, the combination of zoledronic acid and standard therapy has been the most widely investigated combination of an N-BP and standard therapy.

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