The Use of Adjuvant Bisphosphonates in the Treatment of Early-Stage Breast Cancer

Aju Mathew, MD, MPhil, and Adam M. Brufsky, MD, PhD

Aju Mathew, MD, MPhil, is the chief fellow in hematology and medical oncology at the University of Pittsburgh Cancer Institute and Adam Brufsky, MD, PhD, is a professor of medicine at the Magee-Womens Hospital of the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania.

Address correspondence to:
Aju Mathew, MD, MPhil
University of Pittsburgh Cancer Institute
5150 Center Avenue
UPMC Cancer Pavilion, Room 463
Pittsburgh, PA 15232
E-mail: mathewa@upmc.edu
Fax: 412-648-6579

Abstract: Adjuvant treatment of breast cancer has resulted in significant improvement in breast cancer–related outcomes. In addition to chemotherapy and endocrine therapy, the bone-protective agents known as bisphosphonates have been extensively investigated for their putative antitumor effect. Backed by strong preclinical data from in vitro and in vivo models, several randomized clinical trials have evaluated the role of bisphosphonates in an adjuvant setting. The recent NSABP B-34 (National Surgical Adjuvant Breast and Bowel Project protocol B-34) and AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) studies found no disease-free survival benefit with clodronate and zoledronate, respectively, whereas the ABCSG-12 (Austrian Breast and Colorectal Cancer Study Group trial 12) study found improvement in disease-free survival with zoledronate. Data from these trials suggested a beneficial effect of bisphosphonates in older, postmenopausal women and in premenopausal women treated with ovarian suppression. Given the acceptable toxicity profile of bisphosphonates, these agents could be a useful adjunct to adjuvant chemotherapy or endocrine treatment for early-stage breast cancer in a carefully selected subset of patients. This review aims to critically synthesize the results of clinical trials of adjuvant bisphosphonates in early-stage breast cancer, and to provide guidelines for the use of these agents in early-stage breast cancer.

Keywords
Adjuvant, bisphosphonates, breast cancer, clodronate, zoledronate, zoledronic acid

Introduction

The goals of adjuvant treatment in early-stage breast cancer are to decrease the risk for local recurrence, prevent distant metastasis, and prevent breast cancer–related mortality. In light of these goals, adjuvant chemotherapy and endocrine therapy have been able to significantly improve outcomes following early-stage breast cancer. Despite advancements in adjuvant therapy, the breast cancer recurrence rate following adjuvant chemotherapy and endocrine therapy for estrogen receptor–positive, node-positive early-stage disease has

been estimated to be approximately 36% at 10 years of follow-up.[1] In addition to adjuvant chemotherapy and endocrine treatment, the role of adjuvant bisphosphonate therapy in decreasing the risk for breast cancer recurrence has undergone extensive investigation. This review aims to summarize the clinical trials evaluating bisphosphonate treatment in early-stage breast cancer.

Bisphosphonates: How They Work, Types, and Formulations

Bisphosphonates are synthetic analogues of pyrophosphate that bind to the hydroxyapatite in bone, which accounts for their significant antiresorptive properties.[2] The active remodeling process in bone is mediated by osteoblasts and osteoclasts, which work in equilibrium to ensure normal bone function through bone formation and resorption. When metastases occur within bone, the tumor cells secrete growth factors and cytokines, causing the disproportionate activation of osteoclasts. Bisphosphonates are concentrated in areas with intense osteoclastic activity and are internalized by osteoclasts, eventually resulting in apoptosis of bone-resorptive cells.

Bisphosphonates can be classified into 2 types, based on the presence or absence of a covalently bonded nitrogen atom. Aminobisphosphonates, such as alendronate, pamidronate, risedronate, ibandronate, and zoledronate, contain nitrogen. The mechanism of action of these drugs is thought to be mediated by inhibition of the farnesyl pyrophosphate synthase enzyme in the mevalonic acid pathway of cholesterol synthesis, and resultant inhibition of protein prenylation (posttranslational modification of guanosine triphosphate–binding proteins), causing apoptosis of osteoclasts.[3-5] Zoledronate and risedronate are among the most potent inhibitors of the mevalonate pathway.[3] Non-aminobisphosphonates, such as clodronate and etidronate, are internalized by osteoclasts and metabolized into hydrolysis-resistant analogues of adenosine triphosphate, resulting in apoptosis of bone-resorptive cells.[6]

Alendronate, risedronate, and etidronate are administered orally, and pamidronate and zoledronate are given intravenously. Ibandronate and clodronate are available in both oral and intravenous formulations, although clodronate is not available in the United States.

Preclinical Studies

Initially approved for use in patients with osteoporosis, bisphosphonates are valuable in the care of cancer patients. The inhibition of osteoclasts in patients with bone metastatic disease initially was hypothesized to improve outcomes related to skeletal events, such as fractures, bone pain, and hypercalcemia of malignancy,[7] and several clinical trials confirmed a bone-protective role for bisphosphonates in cancer. As a result, bisphosphonates now are approved for use for the prevention of skeletal-related events in patients with bone metastatic disease, the treatment of hypercalcemia of malignancy, and the prevention of therapy-induced bone loss in patients being treated with aromatase inhibitors.[7]

The role of bisphosphonates as adjuvant therapy for early-stage breast cancer is an area of intense clinical research, based on extensive preclinical data that have shown antitumor action. Furthermore, various case-controlled observational studies have suggested a use for bisphosphonates in the prevention of cancer.[8-11] Recent post hoc analysis of 2 large, randomized, placebo-controlled clinical trials using alendronate or zoledronate in women with osteoporosis did not find a difference in the incidence of breast cancer, which brings doubt to the hypothesis that bisphosphonates have direct antitumor properties.[12] Whether the observed antitumor effect of bisphosphonates is related to a direct or an indirect effect on tumor cells is at the moment uncertain. Increasingly, it is thought that the primary mechanism of action is alteration of the bone microenvironment, thereby manipulating the "soil" in which tumor cells remain dormant.[13,14] Osteoclasts, immune cells, and stromal cells secrete cytokines and growth factors, which in turn stimulate more osteoclast production—a vicious circle.[15] Bisphosphonates may reduce the production of these growth factors by their inhibitory effect on osteoclasts, thereby inhibiting cancer cell growth. Such an effect on the tumor microenvironment also may inhibit tumor cell adhesion to bone marrow, thereby preventing a nidus for tumor growth and metastases. By their effect on osteoclasts in the bone microenvironment, bisphosphonates may delay the incidence of bone metastases or distant metastatic disease and thus improve breast cancer–related outcomes.

Although clinical trial observations favor an indirect effect, several preclinical studies have demonstrated a direct antitumor effect. When aminobisphosphonates were used against tumor cell lines in in vitro models, antitumor effects were observed.[16,17] Similar effects on delaying or preventing metastasis were noted in animal models across a variety of cancers.[18-22] Additionally, bisphosphonates were found to have synergistic interactions when used in combination with chemotherapy agents, enhancing the antitumor effect of cytotoxic agents.[23-25]

In summary, studies of bisphosphonates have demonstrated an antitumor effect that is both direct and indirect. Impaired tumor cell adhesion to bone, inhibition of tumor migration, induction of tumor cell apoptosis, and inhibition of angiogenesis may mediate the antitumor effect in a complementary manner.[16,17,26]

Table 1. Adjuvant Bisphosphonate Trials in Early Breast Cancer

Study Details	Study Population	Primary Endpoint	Conclusions	Comments
Clodronate				
Diel et al,[30] 1998	Pre- and postmenopausal	Distant metastases	Lower distant metastasis rate (P<.001)	All women had tumor cells in bone marrow at study entry
Powles et al,[33] 2002	Pre- and postmenopausal	Bone metastases	No difference	Lower mortality in clodronate group (P=.047) Placebo-controlled
Saarto et al,[34] 2004	Pre- and postmenopausal	DFS	Inferior outcomes in clodronate group	Possible effect modification by menopausal status
Paterson et al,[32] 2012 NSABP B-34 trial	Pre- and postmenopausal	DFS	No difference	Adherence to the drug was 56% Beneficial effect in older women on subgroup analysis Placebo-controlled
Ibandronate				
von Minckwitz et al,[35] 2013 GAIN study	Pre- and postmenopausal	DFS	No difference	Only 17% women were older than 60 years All women received chemotherapy
Zoledronate				
Gnant et al,[31] 2011 ABCSG-12 study	Premenopausal	DFS	32% relative risk reduction and 4% absolute risk reduction for recurrence	Factorial design No interaction between endocrine therapy and zoledronate
Brufsky et al,[27] 2012 Z-FAST trial	Postmenopausal	Lumbar spine BMD	No difference	Up-front vs delayed therapy 25% in delayed group got zoledronate DFS was secondary endpoint
Coleman et al,[29] 2013 ZO-FAST trial	Postmenopausal	Lumbar spine BMD	No difference	Up-front vs delayed therapy DFS was secondary endpoint Beneficial effect in older, postmenopausal women on subgroup analysis
Coleman et al,[28] 2014 AZURE trial	Pre- and postmenopausal	DFS	No difference	Beneficial effect in older, postmenopausal women on subgroup analysis Decreased incidence of bone metastases ONJ rate of 1.7%

ABCSG-12, Austrian Breast and Colorectal Cancer Study Group trial 12; AZURE, Adjuvant Zoledronic Acid to Reduce Recurrence; BMD, bone mineral density; DFS, disease-free survival; GAIN; German Adjuvant Intergroup Node-Positive; NSABP B-34, National Surgical Adjuvant Breast and Bowel Project protocol B-34; ONJ, osteonecrosis of the jaw; Z-FAST/ZO-FAST, Zometa-Femara Adjuvant Synergy Trial (in North American and Europe, respectively).

Clinical Studies

A systematic search of published clinical trials relating to adjuvant bisphosphonate therapy for early-stage breast cancer was conducted in MEDLINE for studies published until July 31, 2014. We identified 9 clinical trials that reported data on adjuvant bisphosphonate use for early-stage breast cancer (Table 1).[27-35] Zoledronate and clodronate were the most-studied drugs. There were 4 trials each using clodronate and zoledronate and one using ibandronate. Most of these trials used disease-free survival (DFS) as either a primary or a secondary endpoint. We did not include an adjuvant pamidronate trial because it used an oral formulation that is no longer available.[36]

Clodronate Trials

Clodronate was first investigated in a cohort of 302 patients with primary breast cancer who had tumor cells in their bone marrow.[30] People in the study population, consisting of 63% postmenopausal women, were randomly assigned to receive clodronate 1600 mg per day orally for 2 years or standard-of-care follow-up. At a median follow-up of 3 years, the incidence of distant metastases was 13% in the clodronate group and 29% in the control group (P<.001). Similar risk reductions for bone and visceral metastases were noted that favored the clodronate group. This randomized clinical trial in a group of patients who were at high risk for distant recurrence demonstrated a beneficial effect with adjuvant use of clodronate. Adjuvant systemic

chemotherapy or endocrine therapy was used in 81% of the study population, of whom more than half received adjuvant chemotherapy.

A similar dose of clodronate was tested for its role in decreasing the incidence of bone metastases in a large, double-blind, multicenter trial of 1069 patients with early-stage breast cancer.[33] At a median follow-up of 5.5 years, no significant difference in the incidence of bone recurrence was found (hazard ratio [HR], 0.77; 95% CI, 0.56-1.08; *P*=.1). However, there was a significant reduction in mortality in the clodronate group compared with the control group (*P*=.047). Similarly as in the earlier trial by Diel and colleagues, approximately 50% of patients in this study were postmenopausal and 60% were hormone receptor–positive. The study drug was found to be well tolerated; diarrhea was the only significant adverse event that was more frequent in the clodronate group than in the control group.

A trial of adjuvant clodronate in Finland investigated various breast cancer recurrence–related endpoints in 299 women with early-stage breast cancer.[34] After a 10-year follow-up period, the incidence of bone metastases did not differ between those who received adjuvant clodronate and those who did not. Contrary to the hypotheses of a beneficial role for adjuvant clodronate, there were more nonskeletal recurrence events in the clodronate group than in the control cohort. In a subgroup analysis of patients who were premenopausal and hormone receptor–negative, it was noted that the 10-year DFS rate was inferior in the clodronate group compared with the control group. No difference in DFS rate was seen in the subgroup of postmenopausal women who were hormone receptor–positive, thereby suggesting an effect modification by menopausal or hormone receptor status.

The conflicting results from these 3 adjuvant clodronate trials prompted a multicenter investigation by the National Surgical Adjuvant Breast and Bowel Project (NSABP) group. The NSABP B-34 trial investigated the use of adjuvant clodronate 1600 mg daily by mouth for 3 years for improving DFS in early-stage breast cancer.[32] After a median follow-up of 7.5 years, the study failed to find a beneficial effect for clodronate in increasing DFS or increasing the bone metastasis–free interval. No overall survival (OS) benefit was found. However, a prespecified subgroup analysis of patients older than 50 years demonstrated a significant difference in recurrence-free interval, bone metastasis–free interval, and non-bone metastasis–free interval favoring the clodronate group compared with placebo. Within this subgroup, there was a nonstatistically significant trend for improvement in OS in patients receiving adjuvant clodronate. In summary, the NSABP B-34 trial observed an antitumor effect for adjuvant clodronate in older postmenopausal women.

Ibandronate Trial

The GAIN (German Adjuvant Intergroup Node-Positive) study is the only clinical investigation using adjuvant ibandronate.[35] GAIN was conceptualized as a phase 3, open-label, randomized, controlled trial with 2 × 2 factorial design, in which node-positive women with early-stage breast cancer received 2 different regimens of dose-dense chemotherapy and ibandronate 50 mg per day orally for 2 years, or observation. After a median follow-up of 3 years, the study failed to detect a significant difference in DFS or OS. In a post hoc subgroup analysis defined by age, however, women younger than 40 years or at least 60 years of age seemed to benefit from adjuvant ibandronate therapy compared with women between the ages of 40 and 59 years (test for interaction, *P*=.093). Unlike in most other adjuvant trials, just 17% of the women in the GAIN study were aged 60 years or older. Any possible benefit for adjuvant ibandronate may have been nullified with the use of dose-dense adjuvant chemotherapy. Nevertheless, the study noted that adjuvant ibandronate has an acceptable toxicity profile.

Zoledronate Trials

There are 4 zoledronate trials in the adjuvant setting. The Z-FAST and ZO-FAST (Zometa-Femara Adjuvant Synergy Trial [in North America and Europe, respectively]) studies included only postmenopausal women, the ABCSG-12 (Austrian Breast and Colorectal Cancer Study Group trial 12) study included only premenopausal women, and the AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) trial included both pre- and postmenopausal women.[27-29,31]

The ABCSG-12 study was a randomized, controlled, open-label, 2 × 2 factorial trial in premenopausal women with hormone receptor–positive early-stage breast cancer.[31] Patients were randomly assigned to receive tamoxifen or anastrozole—both in combination with ovarian suppression using goserelin (Zoladex, AstraZeneca)—plus either zoledronate 4 mg intravenously every 6 months for 3 years, or observation. After a median follow-up of 5 years, zoledronate reduced the risk of DFS events (HR, 0.68; 95% CI, 0.51-0.91; *P*=.009) and noted a nonsignificant trend toward an improvement in OS (*P*=.09). The absolute risk reduction for DFS events was 4%, suggesting a number needed to treat of 25 to prevent 1 DFS event. In addition, the study did not find an interaction between endocrine therapy and zoledronate. Women receiving zoledronate experienced a higher incidence of bone pain, arthralgia, and fevers compared with those not receiving zoledronate. It must be noted that only 5% of women in this trial received adjuvant chemotherapy. The ABCSG-12 trial suggested a significant DFS benefit for adjuvant zoledronate therapy in premenopausal women with hormone receptor–positive early-stage breast cancer.

In contrast to the ABCSG-12 trial, in which DFS was a primary endpoint, the Z-FAST and the ZO-FAST trials primarily investigated the bone-protective effect of zoledronate in postmenopausal women taking the aromatase inhibitor letrozole (Femara, Novartis).[27,29] Women receiving aromatase inhibitors as adjuvant endocrine therapy were randomly assigned to receive zoledronate either up front or in a delayed manner. The delayed-use group received the drug when the patient became osteopenic, developed pathologic fracture, or had an asymptomatic vertebral fracture at 3-year follow-up. Zoledronate was administered at a dose of 4 mg intravenously every 6 months for 5 years. In the Z-FAST trial, there was no difference in the secondary endpoint of DFS rates between the up-front and delayed-start groups after 5 years of follow-up.[27] The larger ZO-FAST trial found a decrease in incidence of DFS events for women receiving up-front therapy compared with those receiving delayed-start zoledronate (HR, 0.66; 95% CI, 0.44-0.97; *P*=.037).[29] In these trials, 47% to 53% of participants received adjuvant chemotherapy (46.8% in Z-FAST, 53.3% in ZO-FAST) and 25% to 27% of those in the delayed-start group received zoledronate (24.6% in Z-FAST, 26.9% in ZO-FAST).[27,29] In the ZO-FAST study, an exploratory analysis based on menopausal status at study entry found improvement in both DFS and OS rates with up-front zoledronate therapy in older women.[29] Similar to the findings of the NSABP B-34 and GAIN (German Adjuvant Intergroup Node Positive) trials, a greater benefit with adjuvant bisphosphonates was noted in women older than 60 years or more than 5 years after menopause.[29,32,35]

Recent updated results from the AZURE trial only serve to heighten the controversy about adjuvant bisphosphonate therapy.[28] An open-label, randomized, controlled, parallel-group phase 3 trial in women with stage II or III breast cancer, the AZURE (BIG [Breast International Group] 01/04) study investigated an adjuvant role for zoledronate therapy, at a dose of 4 mg given intravenously every 3 to 4 weeks for 6 cycles, followed by every 3 months for 8 doses, followed by every 6 months for 5 cycles over 5 years, in combination with standard adjuvant systemic therapy, vs standard therapy alone.[37] Forty-four percent of women in the AZURE trial were premenopausal at study entry. After a median follow-up of 7 years, the trial failed to find a difference in DFS rate between the group that received zoledronate and the control group (HR, 0.94; 95% CI, 0.82-1.06; *P*=.30). However, in a prespecified subgroup analysis based on menopausal status, zoledronate improved invasive DFS in women who were more than 5 years postmenopausal compared with the control group (test for heterogeneity by menopausal status, *P*=.03). In addition, zoledronate reduced the risk of developing bone metastases in the study population. There was no relation between zoledronate effects and hormone receptor status; 78% of the study cohort was hormone receptor–positive. In the AZURE trial, 95% of women received neoadjuvant or adjuvant chemotherapy, compared with only 5% in the ABCSG-12 study.[28,31]

Table 2. Baseline Characteristics in the ABCSG-12 and AZURE Trials

Characteristics	ABCSG-12 Trial[31]	AZURE Trial[37]
Study population	Premenopausal	All women
Adjuvant chemotherapy use	5%	95%
Endocrine therapy	50% had combined antiestrogen and ovarian suppression	Standard-of-care antiestrogen therapy
Maximum no. of zoledronate doses	7	19
No. of years of adjuvant therapy	3	5
No. of participants	1803	3360
Stage of disease	Stage I in 70% of patients	Stage II or III

ABCSG-12, Austrian Breast and Colorectal Cancer Study Group trial 12; AZURE, Adjuvant Zoledronic Acid to Reduce Recurrence; no., number.

In summary, a role for adjuvant zoledronate in early-stage breast cancer remains unclear. A differential improvement in outcomes based on menopausal status was noted in the ZO-FAST and AZURE trials.[28,29] The conclusions of the Z-FAST trial may have been affected by the small sample size of the study.[27] The key differences in baseline characteristics between the ABCSG-12 study and the AZURE study (Table 2) may have further influenced the contradictory conclusions from these trials; in the primary analysis, ABCSG-12 found a DFS benefit and AZURE noted no difference in DFS rates in the groups treated with zoledronate vs without zoledronate. Beyond these differences, the trials demonstrated a similar trend toward a DFS benefit for women who were in a low-estrogen state: older, postmenopausal women in the AZURE study and premenopausal women receiving combination antiendocrine therapy (antiestrogen therapy and ovarian suppression) in the ABCSG-12 trial. In summary, none of the 4 zoledronate trials described in this review proved an adjuvant role for the drug in early-stage breast cancer in improving DFS or OS. Therefore, other than identifying a subgroup of patients who may benefit from the drug, these trials failed to meet their desired conclusions. But the results of these clinical investigations support the use of zoledronate in a subset of patients, selected by menopausal status or the use of combination endocrine therapy.

Adverse Events

The side effects of bisphosphonates have been studied extensively. Bisphosphonates are considered to have an acceptable toxicity profile, with fever and infusion reactions being the most commonly noted adverse events. The NSABP B-34 trial observed an adverse event profile for clodronate similar to that with placebo, except for a more frequent incidence of grade 3 or 4 liver dysfunction or diarrhea.[32] The GAIN study also found a higher frequency of gastrointestinal toxicity with ibandronate.[35] Interestingly, the adverse event profile was similar in the group receiving zoledronate vs the control group in the more dose-intensive AZURE trial, with the exception of the incidence of osteonecrosis of the jaw (ONJ).[28]

More women in the AZURE trial developed ONJ than in all the other zoledronate trials combined. The incidence of ONJ in the zoledronate group of the AZURE trial was 1.7% (95% CI, 1.0-2.4).[28] There were no cases of ONJ in the control group. The ZO-FAST and the Z-FAST trials noted 5 cases of confirmed ONJ. In fact, a pooled analysis of zoledronate trials estimated the incidence of ONJ at approximately 1%.[38] The rates of ONJ can be further decreased by careful selection of patients and proper dental care, and most cases of ONJ can be managed conservatively.

Although renal failure is reported (rarely) in bisphosphonate trials in metastatic breast cancer, this has not been observed with adjuvant bisphosphonates and therefore is not a cause for concern in this setting. Hypocalcemia and hypophosphatemia may rarely occur in patients receiving bisphosphonates, which can be prevented to a great extent by the use of supplemental vitamin D and calcium.

Clinical Practice Guidelines

Based on trial data, adjuvant bisphosphonates certainly are not ready for use in all patients with early-stage breast cancer. Although the results of the clodronate trials were contradictory, the recent large NSABP B-34 study revealed a possible beneficial role in older postmenopausal women.[32] The results are more convincing for the potent aminobisphosphonate zoledronate, especially in the postmenopausal subgroup—although none of the trials were definitive.[28,29] A literature-based meta-analysis of adjuvant zoledronate trials noted a 19% risk reduction for death with zoledronate use compared with no use or delayed use of the medication (P=.007).[39] However, this analysis did not demonstrate a risk reduction for bone metastases or improvement in DFS rates between the 2 groups. A meta-analysis of data from individual participants in bisphosphonate trials may provide more power for subgroup analysis, especially pertaining to menopausal status.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) is currently conducting such a meta-analysis, pooling individual patients' data from a variety of adjuvant bisphosphonate trials. Preliminary results presented at the 2013 San Antonio Breast Cancer Symposium suggested a beneficial effect for adjuvant bisphosphonate therapy in decreasing breast cancer–related mortality in postmenopausal women.[40] The meta-analysis pooled individual patient-level data from nearly 18,000 women with early-stage breast cancer who were treated with bisphosphonates, regardless of the type of drug or dosing schedule. The overall analysis found beneficial effects for bisphosphonate use in decreasing breast cancer–related mortality (P=.03) and decreasing recurrence in bone (P=.0009).[40] The study included nearly 11,000 postmenopausal women and a subgroup analysis in this cohort observed similar benefits in breast cancer–related mortality and bone metastases. There was no difference in the premenopausal subgroup in breast cancer–related outcomes between patients receiving bisphosphonates and those not receiving the drug. Interestingly, the pooled data meta-analysis failed to show a difference in the incidence of contralateral breast cancer between the 2 groups, which probably suggests the lack of a direct antitumor effect of bisphosphonates.[40]

How will the results of the EBCTCG meta-analysis alter the management of patients with early-stage breast cancer? We believe that a drug with an acceptable toxicity profile that provides an absolute benefit comparable to that obtained through the use of significantly more toxic adjuvant chemotherapy will be a useful weapon in the armamentarium of oncologists when used in a carefully selected subset of patients. Bisphosphonates such as clodronate and zoledronate have demonstrated a clinically meaningful benefit in older, postmenopausal women and in premenopausal women treated with ovarian suppression.[28,29,31,32] Based on the results of the individual patient data meta-analysis from the EBCTCG group, potent bisphosphonates such as zoledronate and clodronate could be considered as adjuvant treatment options for women with early-stage breast cancer who are either postmenopausal or premenopausal and treated with ovarian suppression.[40] Furthermore, several randomized clinical trials have demonstrated improvement in bone mineral density with bisphosphonate use in women who are being treated with aromatase inhibitors or those who have osteoporosis.[27,29,41] Their use in women with osteopenia or osteoporosis may be beneficial for both bone health and antitumor effect, and therefore well justified.

Areas of Uncertainty

Regardless of the results of the meta-analysis, several questions remain. For instance, we do not know the type of bisphosphonate, the dosing schedule, or the duration of treatment that will be most effective for adjuvant therapy.

Because clodronate is unavailable in the United States, zoledronate remains the only option. A dosing schedule that reflects that used in the ABCSG-12 trial may be easier to administer and may have fewer adverse effects than the more intense schedule used in the AZURE study.[37,42] However, the duration of therapy will remain an area of uncertainty. Our recommendation is to treat for at least 3 years on an every-6-month schedule if a decision has been made to use zoledronate in the adjuvant setting and if the patient tolerates the drug. Furthermore, the existence of a predictive biomarker that can be used to identify a subset of patients who may maximally benefit from adjuvant bisphosphonate use remains unclear; bone turnover markers and hormonal assays were shown to be inadequate as biomarkers in the AZURE trial.[28]

Conclusions

Bisphosphonates may have a role in the treatment of high-risk, early-stage breast cancer, particularly in low-estrogen environments, such as in postmenopausal women or in premenopausal women receiving combined antiestrogen therapy and ovarian suppression. The data from the adjuvant bisphosphonate trials in breast cancer suggest a beneficial effect for potent bisphosphonates such as clodronate and zoledronate. Given the acceptable toxicity profile for bisphosphonates, these drugs could be a useful adjunct to adjuvant chemotherapy or endocrine treatment for early-stage breast cancer in a carefully selected subset of patients. In summary, the decision to use adjuvant bisphosphonate therapy in early-stage breast cancer should be individualized and made after a careful discussion of the side effects and judicious interpretation of clinical trial data.

Disclosures

Dr Mathew has disclosed no conflicts of interest. Dr Brufsky has received consulting fees from Novartis.

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