Maintaining Bone Density in Patients Undergoing Treatment for Breast Cancer: Is There an Adjuvant Benefit?

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Abstract

Women undergoing treatment for breast cancer often experience a marked decrease in bone mineral density. This decrease is observed with chemotherapy as well as endocrine therapy and is more pronounced and rapid than normal postmenopausal bone loss. Pharmacologic intervention is, therefore, necessary in many cases to preserve bone health and prevent fractures. Many small studies have demonstrated that cancer therapy–induced bone loss (CTIBL) is effectively prevented by bone-targeted therapies, such as bisphosphonates and other inhibitors of bone resorption. Recently, several trials have confirmed the efficacy of bisphosphonates in the prevention of CTIBL in both premenopausal and postmenopausal women with early-stage breast cancer. In addition, concomitant treatment with zoledronic acid 4 mg every 6 months and standard adjuvant endocrine therapy has been reported to significantly improve disease-free survival and decrease disease recurrence in bone as well as other sites compared with standard therapy alone. Zoledronic acid treatment has also decreased residual tumor volume in the neoadjuvant setting. Furthermore, long-term follow-up of a single study in patients with bone marrow micrometastases from breast cancer revealed overall survival benefits for patients receiving clodronate 1600 mg/day compared with placebo; however, combined results from several trials of clodronate are inconclusive. Overall, a large body of evidence is accumulating to support the potential adjuvant benefits of bisphosphonates in the treatment of early-stage breast cancer. Results from ongoing studies are expected to further elucidate the benefits of bisphosphonates in maintaining bone health and improving clinical outcomes in patients with breast cancer.

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Introduction

Breast cancer is the most common cancer and the leading cause of cancer-related deaths among women worldwide.[1] The annual global incidence of breast cancer is estimated to be > 1.3 million cases, and approximately 465,000 women die of this disease every year. Advances in technologies for early diagnosis and therapies for breast cancer have substantially improved survival and clinical outcomes in recent years, especially in the United States and other developed countries.[2] Treatment of breast cancer includes surgical resection and systemic therapy; chemotherapy is used extensively in the metastatic setting and in the treatment of hormone receptor–negative breast cancer, whereas hormonal (endocrine) therapy has become the standard adjuvant treatment option for hormone receptor–positive breast cancer.[2,3]

Patients and Methods

A systematic survey of published literature, recent reports at scientific congresses, and clinical trial registries was performed to identify key data pertaining to cancer therapy–associated bone loss

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This article includes the discussion of investigational and/or unlabeled use of drugs, including the use of clodronate, ibandronate, pamidronate, risedronate, zoledronic acid, denosumab, and toremifene in early-stage breast cancer.

and therapeutic approaches to the prevention or mitigation of such bone loss. Based on these data, a detailed review of bone-directed therapies in nonmetastatic breast cancer and analysis of their potential adjuvant benefits were generated.

Cancer Therapy–Associated Bone Loss

Estrogen action profoundly influences bone health, and postmenopausal women are at greater risk for osteoporosis and fractures (eg, hip and vertebra) compared with healthy premenopausal women.[4] The early years after menopause are characterized by rapid decrease in bone mass; although the exact magnitude of such bone loss varies between reports, it is typically around 2.5% per year and has been reported to be as high as 4% per year.[5-9] This accelerated bone loss lasts for 3-5 years after menopause, and cumulative bone loss during this period approaches 15%.[7] The rate of bone loss decreases approximately 5 or 6 years after menopause,[7,8] and annual bone loss thereafter is approximately 0.7%-1% compared with ≤ 0.4% in premenopausal women.[10] Endocrine therapies for breast cancer, such as ovarian ablation and aromatase inhibitors (AIs), profoundly decrease circulating estrogen levels in both premenopausal and postmenopausal women and are associated with profound and rapid decreases in bone mineral density (BMD); the exception is tamoxifen, a selective estrogen receptor modulator (SERM) that exerts bone-protective effects in the postmenopausal setting. Ovarian suppression (eg, with a luteinizing hormone-releasing hormone agonist) or ablation (eg, by oophorectomy, radiation therapy, or cytotoxic chemotherapy) in premenopausal women results in immediate artificial menopause accompanied by postmenopausal levels of circulating estrogens. Despite the bone-protective activity of tamoxifen in postmenopausal women, the past decade has seen a switch toward the use of AIs as the adjuvant endocrine therapy of choice in this setting.[3] These agents offer better clinical outcomes, such as disease-free survival (DFS), and safety, particularly in regard to endometrial cancer, uterine polyps, and thromboembolic adverse events, compared with tamoxifen[3]; however, AIs suppress estrogen production in peripheral tissues and further reduce estrogens in circulation to below normal postmenopausal levels.[11] Consequently, women receiving AI therapy for breast cancer have accelerated bone loss (AI-associated bone loss [AIBL]) of approximately 2.6% annually throughout therapy (typically ≥ 5 years) compared with the long-term annual bone loss of approximately 1% in untreated postmenopausal women.[10,12]

Chemotherapy for breast cancer is also associated with detrimental effects on bone health. Some chemotherapeutic agents, such as doxorubicin, methotrexate, and cyclophosphamide, exert direct nonhormonal effects on bone cells, thereby undermining skeletal integrity and resulting in an annual decrease in BMD of up to 1%.[13,14] In addition, chemotherapy induces ovarian dysfunction in premenopausal women; the incidence of impaired ovarian function varies from approximately 45% to approximately 70% depending upon the chemotherapeutic agent or combination being used.[14-17] The incidence of ovarian dysfunction after chemotherapy is > 90% in premenopausal women aged > 50 years and is substantially higher in women aged > 40 years compared with those aged ≤ 40 years.[15] Chemotherapy-induced ovarian dysfunction is accompanied by rapid decrease in BMD (> 7% decrease within 12 months).[14] Although the significance of early menopause in determining the long-term risk of osteoporosis has been debated and advanced age has been found to be the larger risk factor,[18] these findings were in women who underwent natural menopause and did not receive subsequent treatment with agents detrimental to bone health. Moreover, that report predated the advent of AIs as adjuvant therapy for postmenopausal breast cancer, and the data are, therefore, based on smaller decreases in circulating estradiol levels than those seen with AI therapy. Overall, cancer therapy–induced bone loss (CTIBL) occurs more rapidly and is of greater magnitude compared with postmenopausal osteoporosis. Pharmacologic intervention might be necessary to prevent such bone loss and subsequent fractures and to preserve patients' quality of life (QOL).

Bone Remodeling

Physiologic remodeling of bone is characterized by balanced and coupled resorption of existing bone by osteoclasts and formation of new bone by osteoblasts (Figure 1).[19] Several local and systemic factors, including estrogen, regulate these processes. Receptor activator of nuclear factor-κB (RANK) is a cell surface receptor expressed by immature and mature osteoclasts that plays an important role in osteoclast maturation and activation. Binding of RANK to RANK ligand (RANKL), which is produced locally by osteoblasts and other stromal cells in response to systemic signals, is necessary for osteoclast fusion, differentiation, and maturation. During breast cancer therapy, except with tamoxifen in the postmenopausal setting, osteoclast-mediated osteolysis is increased, resulting in net bone loss. Prevention of such bone loss requires antiresorptive agents, such as bisphosphonates or RANKL inhibitors.

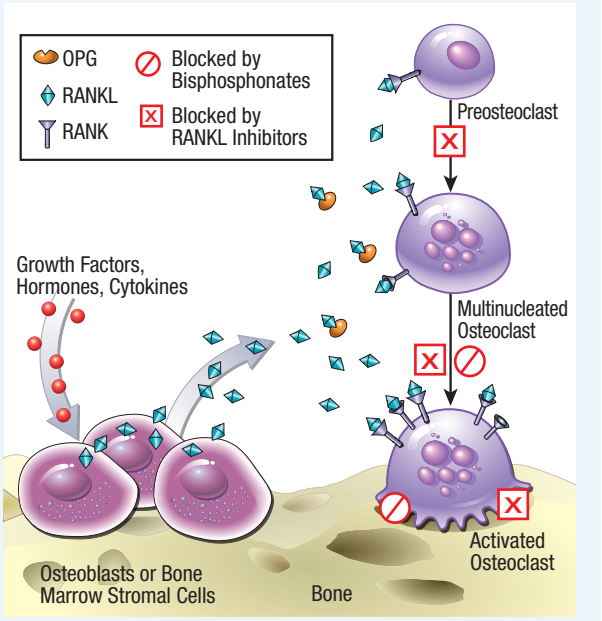
Several studies evaluating various bone-targeted therapies for the prevention of CTIBL in the adjuvant setting conducted in recent years will be reviewed here. This article will also discuss the evidence on potential adjuvant benefits from the addition of bisphosphonates to standard therapy for breast cancer and will present an overview of ongoing trials of bisphosphonates for the prevention of disease recurrence.

Results and Discussion

Therapies to Prevent Bone Loss and Maintain Bone Mineral Density During Treatment of Breast Cancer

Bisphosphonates. Bisphosphonates are antiresorptive agents that induce osteoclast apoptosis and are divided into 2 categories based on their chemical structure.[20] Early-generation non–nitrogen-containing bisphosphonates, such as clodronate and etidronate, are small-molecule pyrophosphate analogues that bind to the bone surface via their carbon-phosphate P-C-P backbone. These agents are internalized by osteoclasts during bone resorption, resulting in the accumulation of cytotoxic levels of bisphosphonate metabolites in osteoclasts. Nitrogen-containing bisphosphonates, such as pamidronate, ibandronate, risedronate, and zoledronic acid, also accumulate in bone and are preferentially taken up by osteoclasts. In addition, these agents inhibit the mevalonate pathway of posttranslational protein modification, leading to impaired osteoclast activation and function. In patients with bone metastases, intravenous nitrogen-containing bisphosphonates have proven efficacious in preventing skeletal-related events (SREs), such as

Figure 1 Mechanism of Action of Antiresorptive Agents



Abbreviations: OPG = osteoprotegerin; RANKL = receptor activator of nuclear factor-κB ligand

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pathologic fractures, spinal cord compression, hypercalcemia of malignancy, and the need for palliative radiation or surgery to bone.[21] These agents can also palliate bone pain and improve QOL in patients with bone metastases from breast cancer. Moreover, in a meta-analysis of patients with bone metastases and elevated levels of osteolysis from 3 large trials, zoledronic acid improved survival among the patients who normalized the rate of osteolysis within 3 months of zoledronic acid therapy; the observed benefits were proportional to the rate of decrease in osteolysis.[22] Recent data support the efficacy of bisphosphonates in the prevention of CTIBL.[23] Some bisphosphonates, such as clodronate and zoledronic acid, have also demonstrated antitumor activity in the preclinical and preliminary clinical settings[24] and might, therefore, provide benefits that extend beyond the prevention of bone loss.

RANKL Inhibitors. Osteoclast maturation and activation are dependent upon the RANK/RANKL pathway. Under physiologic conditions, RANKL function is regulated by its soluble competitive (decoy) receptor, osteoprotegerin.[19] Perturbations in the RANKL: osteoprotegerin ratio (eg, during cancer therapy) result in unbalanced bone turnover. Inhibitors of RANKL would, therefore, decrease bone resorption and prevent bone loss. Denosumab is an investigational monoclonal antibody that inhibits RANKL and, in preliminary studies, suppressed bone resorption marker levels in patients with bone metastases from a variety of solid tumors.[25] Several trials evaluating the efficacy of denosumab in the early-stage and metastatic cancer settings are ongoing, and emerging evidence in a small cohort of patients with breast cancer indicates that denosumab prevents CTIBL.[26]

Adjuvant Studies of Bone-Targeted Therapies to Prevent Cancer Therapy–Induced Bone Loss in Breast Cancer: Premenopausal Setting

Efficacy of Oral Bisphosphonates. Oral bisphosphonates have demonstrated some efficacy in the prevention of CTIBL in premenopausal women with breast cancer. In a study in 113 premenopausal women receiving 6 cycles of adjuvant cyclophosphamide/methotrexate/5-fluorouracil (CMF) chemotherapy, patients were randomized to receive either placebo or clodronate 1600 mg/day orally for 3 years.[27] At a 2-year follow-up, lumbar spine BMD had decreased substantially compared with baseline in the control arm (overall: –5.9%; amenorrheic patients: –9.5%); this BMD decrease was partially prevented in the clodronate arm (overall: –2.2%, $P = .0005$; amenorrheic patients: –5.9%). Clodronate also preserved BMD at the femoral neck, with a change in BMD from baseline of –2.0% in the control arm and +0.9% in the clodronate arm ($P = .017$). At a 5-year follow-up (2 years after completion of clodronate therapy), the patients who received clodronate continued to receive protective benefits against BMD loss, with a change from baseline in lumbar spine BMD of –9.7% in the control arm compared with –5.8% in the clodronate arm ($P = .008$).[28] Recently, 10-year follow-up data from this trial confirmed that the bone-protective effects of clodronate persisted for a long time after clodronate was discontinued,[29] indicating that bisphosphonate treatment at the initiation of chemotherapy is a key factor in mitigating long-term bone loss and preventing subsequent osteoporosis in premenopausal women with breast cancer.

In a similar study of risedronate, 53 premenopausal women with breast cancer and chemotherapy-induced ovarian failure were randomized to receive either placebo or 8 cycles of risedronate 30 mg/day orally for 2 weeks on and 10 weeks off over 2 years; patients were followed for an additional year without any bisphosphonate treatment.[30] Risedronate prevented CTIBL in these patients, with lumbar spine BMD maintained at or above baseline during the 2 years of treatment. At a 2-year follow-up, the mean BMD difference between the treatment groups was 2.5% ± 1.2% ($P = .041$) at the lumbar spine and 2.6% ± 1.1% ($P = .029$) at the femoral neck. However, BMD in the patients who received risedronate started to decrease after completion of therapy, indicating that continuous treatment with risedronate is required to effectively prevent bone loss in this setting.

Intravenous Bisphosphonates. Pamidronate has been evaluated in the prevention of CTIBL in a small trial in 40 premenopausal women receiving adjuvant CMF or anthracycline-based chemotherapy for breast cancer.[31] Patients were randomized to receive either placebo or 4 doses of pamidronate 60 mg intravenously (I.V.) every 3 months. At a 12-month follow-up, lumbar spine BMD was increased compared with baseline in the patients receiving pamidronate (+1.9%) but substantially decreased in the placebo arm (–3.2%; $P = .002$ between groups). Although total hip BMD decreased in all patients, the effect was larger with placebo compared with pamidronate (–2.8% vs. –0.3%; $P = .08$). Similar BMD trends were noted in the subset of patients who developed amenorrhea during chemotherapy.

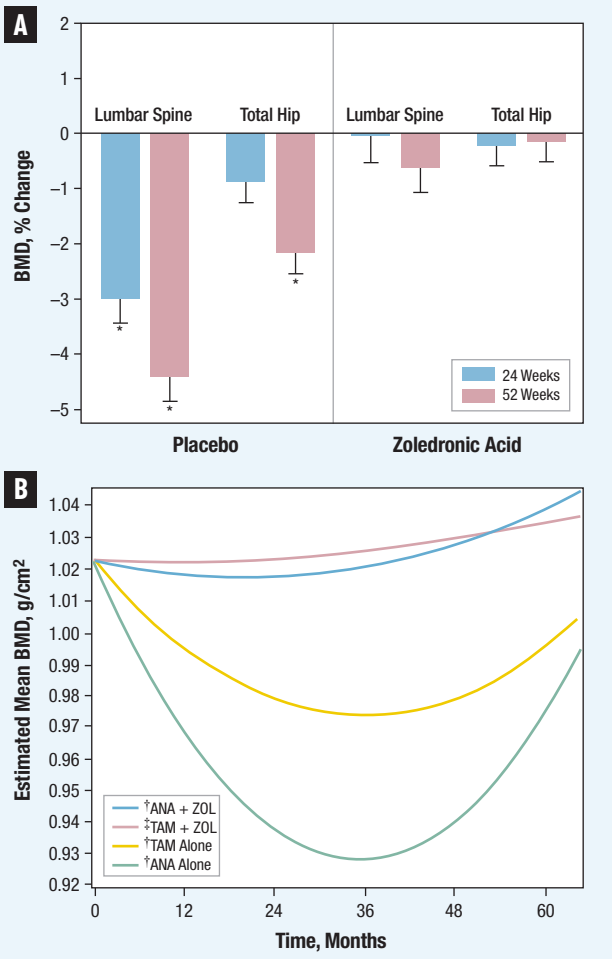
Zoledronic acid is a member of the most recent generation of bisphosphonates that has demonstrated equal or superior efficacy to

pamidronate in the metastatic breast cancer setting[32] and has established efficacy in the treatment of postmenopausal osteoporosis.[33] In the HORIZON trial, annual treatment with zoledronic acid 5 mg substantially improved BMD, reduced the risk of vertebral fracture by 70%, and reduced the risk of hip fracture by 41% over a 3-year period compared with placebo. Recently, a small trial evaluated the efficacy of a single dose of zoledronic acid 4 mg in treating osteopenia in 66 patients who had received anticancer therapies.[34] In this study, 1 dose of zoledronic acid resulted in sustained improvement in BMD for up to 36 months in the patients who were osteopenic > 1 year after curative therapy for cancer. Although these results are highly promising and indicate that infrequent treatment with zoledronic acid might be adequate for improving BMD in some patient populations, it is important to note that the majority of patients in this study were not receiving concomitant anticancer therapy and their estradiol levels were substantially higher than were the levels seen during AI therapy. Only 8 patients, all with breast cancer, were receiving endocrine therapy during the trial; of these, 5 were receiving tamoxifen and 3 were receiving AIs. Therefore, results from this trial provide little insight into the efficacy of single-dose zoledronic acid for preventing CTIBL or preserving BMD during ongoing adjuvant therapy for breast cancer, which could result in higher ongoing rates of bone loss.

In the adjuvant setting, zoledronic acid 4 mg I.V. every 3 months effectively prevented CTIBL in 101 women (96 evaluable for primary outcome) receiving chemotherapy for early-stage breast cancer.[35] Chemotherapy included CMF, anthracycline-based regimens, and taxane-based regimens. The patients receiving chemotherapy plus placebo experienced a substantial decrease in lumbar spine and total hip BMD compared with baseline at both 6 (–2.9% and –0.9%, respectively) and 12 months (–4.4% and –2.1%, respectively; $P < .05$ for each measurement; Figure 2A),[35] whereas the patients receiving chemotherapy plus zoledronic acid had stable BMD at both sites at 6 and 12 months, which was a significant improvement compared with placebo (lumbar spine: $P = .0001$; hip: $P = .02$).

Zoledronic acid has also been evaluated in the prevention of endocrine therapy–associated bone loss in premenopausal women with early-stage breast cancer. The bone substudy of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial enrolled 404 premenopausal women with a mean age of 45 years with hormone-responsive, early-stage breast cancer.[36] Patients received 3 years of endocrine therapy consisting of ovarian suppression with goserelin 3.6 mg subcutaneously every 28 days plus either tamoxifen 20 mg/day orally or the AI anastrozole 1 mg/day orally either alone or with zoledronic acid 4 mg I.V. every 6 months. At a median follow-up of 3 years, endocrine therapy alone resulted in significant overall bone loss compared with baseline (–14.4%; $P < .001$). In contrast, BMD remained constant in the patients receiving zoledronic acid concomitant with endocrine therapy compared with baseline (1.032 g/cm^2 vs. 1.018 g/cm^2; $P < .0001$ compared with endocrine therapy alone).[37] Loss in BMD was more pronounced in the patients receiving goserelin/anastrozole compared with those receiving goserelin/tamoxifen (–17.3% vs. –11.6%; $P < .001$). At a median follow-up of 5 years (2 years after cessation of therapy), BMD had improved compared with the 3-year time point but remained significantly lower than baseline in the patients who received endocrine therapy alone (lumbar spine: –6.3%; $P = .001$; Figure 2B).[36] Although BMD at 5 years had recovered to within the normal range (0.99 g/cm^2) in the goserelin/tamoxifen arm, the patients in that arm experienced a window of low BMD during and immediately after the completion of endocrine therapy (Figure 2B). In addition to the potential increase in fracture risk during this period, the long-term implications of this period of osteopenia for bone microarchitecture and fracture risk are not known, but should become evident with longer follow-up data from this trial. In contrast, zoledronic acid significantly increased lumbar spine BMD in the patients receiving concomitant endocrine therapy (+4.0%; $P = .02$). Similar results were obtained for trochanter BMD. Long-term follow-up from this study will provide insights into the importance of preventing bone

Figure 2 Zoledronic Acid Prevents Ovarian Suppression–Associated Bone Loss in Premenopausal Women with Breast Cancer



Zoledronic acid 4 mg every 3 months prevents chemotherapy-associated bone loss (**A**).[35] Zoledronic acid 4 mg every 6 months prevents bone loss associated with ovarian suppression using goserelin (**B**).
*$P < .05$ for comparison between treatment groups at specific times.
†$P < .0001$ versus baseline.
‡$P < .05$ versus baseline.
Abbreviations: ANA = anastrozole; BMD = bone mineral density; TAM = tamoxifen; ZOL = zoledronic acid
(**B**) *Adapted from Lancet Oncol, vol. 9, Gnant M, et al. Adjuvant therapy plus zoledronic acid in premenopausal women with early-stage breast cancer, 840-9, © 2008, with permission from Elsevier.*[36]

loss during breast cancer treatment in the reduction of the incidence of subsequent fractures. Zoledronic acid therapy for 3 years was well tolerated in this study; there were no significant safety problems attributable to zoledronic acid at this dose and frequency.

Ongoing Trials of Zoledronic Acid. The ongoing large Cancer and Leukemia Group B 79809 trial is evaluating the efficacy of zoledronic acid 4 mg every 3 months in the prevention of bone loss in women with early-stage breast cancer who developed chemotherapy-induced ovarian failure.[38] In this study, women with stage I-III breast cancer were randomized to receive adjuvant chemotherapy with or without tamoxifen plus zoledronic acid 4 mg I.V. every 3 months either initiated with chemotherapy (up front) or after 12 months of chemotherapy (late). Interim results from this study revealed that up-front zoledronic acid prevented CTIBL and increased BMD above baseline levels. Patients in the late treatment cohort will initiate zoledronic acid during the second year of the study. Therefore, the 24-month analysis is expected to provide insight into the efficacy of zoledronic acid in reversing CTIBL that has occurred during the first 12 months. In the 166 patients who developed ovarian failure, change in lumbar spine BMD from baseline at 12 months was –6.6% in those receiving chemotherapy alone compared with +2.2% in those receiving chemotherapy plus up-front zoledronic acid ($P < .0001$). The addition of tamoxifen to chemotherapy decreased but did not prevent bone loss compared to chemotherapy alone (BMD change: –4.3% vs. –9.5%). Concomitant treatment with zoledronic acid was equally effective in both groups. Future analyses from this trial, including data on the late treatment group, will address the optimal timing of zoledronic acid in premenopausal patients undergoing adjuvant chemotherapy for breast cancer.

Adjuvant Studies of Bone-Targeted Therapies to Prevent Cancer Therapy–Induced Bone Loss in Breast Cancer: Postmenopausal Setting

Oral Bisphosphonates. A small trial of clodronate in postmenopausal women receiving oral antiestrogen therapy (tamoxifen or toremifene) for 3 years demonstrated limited efficacy in the prevention of cancer therapy–associated bone loss.[39] In this study, 61 postmenopausal women with operable breast cancer were randomized to receive antiestrogen therapy plus either placebo or clodronate 1600 mg/day orally for 3 years. After 3 years, lumbar spine BMD deteriorated in the patients receiving antiestrogen therapy alone but improved in those receiving clodronate (–1.7% vs. +1.0%; $P = .01$). At a 5-year follow-up (2 years after completion of clodronate therapy), although patients in both groups experienced BMD loss, lumbar spine BMD remained higher than baseline in the patients who received clodronate compared with those who did not (–1.0% vs. –3.2%; $P = .06$). Recently, a 10-year follow-up from this study confirmed the reduced incidence of osteoporosis in the clodronate arm[29]; however, it is important to qualify that the endocrine therapies used in this study were SERMs (tamoxifen in 20 evaluable patients and toremifene in 14 evaluable patients at 10 years) and not AIs, which are the current standard of care for postmenopausal women eligible for adjuvant endocrine therapy. Because AIs have a more profound effect on BMD compared with SERMs, which protect BMD in the postmenopausal setting, it is not known whether clodronate 1600 mg/day orally will prove efficacious in preventing AIBL.

Risedronate has also been evaluated in the prevention of bone loss in the postmenopausal breast cancer setting. In a study of risedronate in 118 postmenopausal women receiving the AI anastrozole, bone loss in the total study population was significant compared with age-matched controls (mean BMD change: –3.3%; $P < .0001$).[40] In the 15 osteoporotic patients in this study, risedronate prevented further bone loss at the hip and improved BMD at the spine compared with baseline (+4.1%; $P = .008$). In a separate study of risedronate in 87 postmenopausal patients who had undergone chemotherapy for breast cancer, patients were randomized to receive either placebo or risedronate 35 mg/week orally for 2 years, with concomitant endocrine therapy if required.[41] Approximately 70% of the patients received tamoxifen, toremifene, or fulvestrant during the course of the study. At the end of 2 years, BMD measurements at the spine and hip were 1.6%-2.5% lower in the placebo arm compared with the risedronate arm ($P < .05$). In this study, the patients receiving placebo and no AI had stable BMD at the spine and a small decrease in BMD at the hip. In contrast, the women receiving placebo plus AI experienced a mean BMD decrease of 4.8% at the spine and 2.8% at the hip compared with baseline ($P < .001$ for each). Risedronate partially protected BMD in all subgroups. Lumbar spine BMD decreased by 2.4% with risedronate plus AI; hip BMD remained stable with risedronate plus AI and improved by 2.2% in the risedronate without AI arm. Although these results are promising, the numbers of patients included in these studies are very small, and the findings need confirmation in larger patient populations.

Intravenous Bisphosphonates. The largest trials of bisphosphonates in the prevention of bone loss in the postmenopausal breast cancer setting involve zoledronic acid. The Z-FAST, ZO-FAST, and E-ZO-FAST trials are 3 parallel companion trials evaluating the efficacy of zoledronic acid 4 mg I.V. every 6 months in the prevention of AIBL in postmenopausal women receiving adjuvant endocrine therapy for hormone-responsive, stage I-IIIA breast cancer.[42,43] In these trials, patients with baseline BMD T-score ≥ –2.0 (normal or osteopenic) were randomized to receive letrozole 2.5 mg/day orally plus zoledronic acid either up front (initiated ≤ 14 days after start of letrozole therapy) or delayed (initiated in patients with postbaseline BMD T-score < –2.0 or nontraumatic fracture). Integrated analysis of the Z- and ZO-FAST studies in a total of 1667 patients demonstrated significant differences in the percentage change in lumbar spine (5.2%; $P < .0001$) and total hip (3.5%; $P < .0001$) BMD between the up-front and delayed groups at 12 months (Figure 3).[43] At a 24-month follow-up, fracture rates were similar between the 2 treatment arms; however, a substantial proportion of fractures occurred in the osteopenic women who received up-front zoledronic acid, whereas fractures were more common among the women with normal BMD who received delayed zoledronic acid.[44] Similar differences were observed at a 12-month follow-up in the E-ZO-FAST trial in 522 patients; the patients who received up-front zoledronic acid had a mean lumbar spine BMD increase of 2.7% over baseline compared with a mean decrease of 2.7% in those who received delayed zoledronic acid ($P < .0001$).[42] Total hip BMD was also significantly improved with up-front zoledronic acid compared with sub-

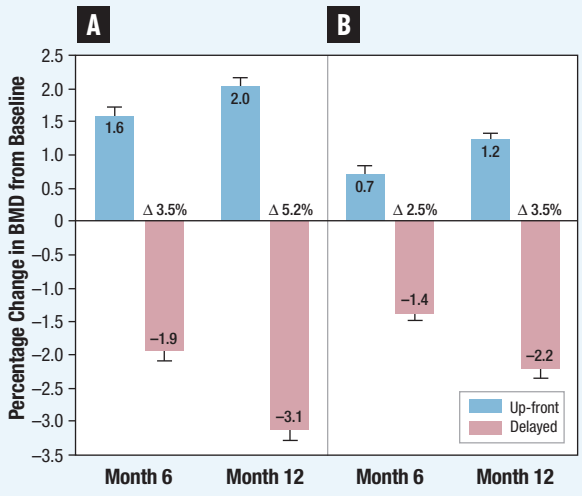
stantial deterioration with delayed zoledronic acid ($P < .0001$ between groups). Thus, the Z-, ZO-, and E-ZO-FAST trials in > 2000 women with early-stage breast cancer demonstrate that twice-yearly zoledronic acid treatment prevents AIBL and consistently improves BMD.

Other Planned/Ongoing Trials

Oral Bisphosphonates. Several trials evaluating oral bisphosphonates, such as risedronate and ibandronate, in the prevention of CTIBL have been initiated. The N02C1 study randomized 220 women undergoing adjuvant or neoadjuvant chemotherapy for stage I-IIIB breast cancer to receive either placebo or weekly oral risedronate.[45] After 1 year, change in BMD (lumbar spine, hip, and femoral neck) was similar between the risedronate and placebo treatment groups ($P > .1$ at all sites), demonstrating that risedronate 35 mg/week orally does not prevent CTIBL. In the ongoing SABRE (Study of Anastrozole With the Bisphosphonate Risedronate) trial, patients undergoing AI therapy (anastrozole) for breast cancer with baseline BMD < –1.0 at either hip or spine but ≥ –2.0 at both sites were randomized to receive either placebo (n = 65) or risedronate 35 mg/week orally (n = 73).[46] At a 12-month follow-up, BMD was significantly increased in the patients receiving anastrozole/risedronate compared with those receiving anastrozole alone (lumbar spine: +1.71% vs. –0.41%, $P < .0001$; hip: +1.29% vs. –0.09%, $P = .002$). Levels of biochemical markers of bone turnover reflected the observed BMD changes, indicating that risedronate treatment suppresses elevated bone metabolism in women receiving AI therapy for breast cancer. A third study of risedronate in women undergoing AI therapy for breast cancer, IBIS (International Breast Cancer Intervention Study)-II, enrolled 613 women in the bone substudy.[47] In the 162 women with normal baseline BMD, anastrozole treatment for 12 months significantly decreased BMD compared with placebo at the lumbar spine (–2.5% vs. –0.97%; $P = .002$) and hip (–1.34% vs. –0.37%; $P = .02$); risedronate was not investigated in this cohort. In the women who were osteopenic at baseline, concomitant risedronate significantly decreased anastrozole-associated bone loss at the hip compared with anastrozole/placebo (+0.67% vs. –2.27%; $P = .01$). Similar changes were observed in lumbar spine BMD but the differences did not attain statistical significance. Thus, concomitant treatment with risedronate prevents AIBL in women with baseline osteopenia.[46,47] The efficacy of risedronate in the prevention of AIBL in women with normal baseline BMD is yet to be determined.

The ARIBON trial is evaluating the efficacy of ibandronate 150 mg/month orally in the prevention of AIBL in postmenopausal women receiving adjuvant anastrozole therapy for hormone-responsive breast cancer.[48] In this study, 50 women with baseline osteopenia were randomized to receive anastrozole plus either placebo or monthly ibandronate. At 12- and 24-month follow-ups, BMD was decreased compared with baseline in the placebo arm and substantially increased in the ibandronate arm. Changes in lumbar spine BMD at 12 and 24 months were +3.11% and +2.98%, respectively, in the patients receiving ibandronate concomitant with anastrozole compared with –2.35% and –3.22%, respectively, in those receiving anastrozole with placebo ($P < .01$ at each time point). Ibandronate also effectively reduced bone turnover marker levels at 12 months, indicating that ibandronate suppresses elevated bone metabolism in patients undergoing AI therapy.

Figure 3 Zoledronic Acid Prevents Aromatase Inhibitor–Associated Bone Loss in Postmenopausal Women with Breast Cancer



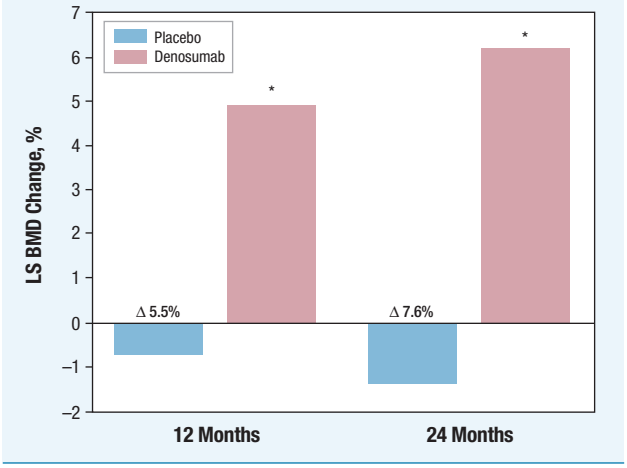
Zoledronic acid 4 mg every 6 months prevents aromatase inhibitor–associated bone loss at the lumbar spine (**A**) and hip (**B**) in postmenopausal women with breast cancer ($P < .0001$ for up-front compared with delayed zoledronic acid at both sites and time points).
Abbreviation: BMD = bone mineral density
Adapted with permission from Brufsky A, et al, Oncologist, © 2008 vol. 13, 503-14, Alphamed Press.[43]

Denosumab. Denosumab is a fully human monoclonal antibody against RANKL that is being evaluated in the prevention of AIBL.[26] The double-blind phase III HALT-BC trial randomized 252 patients with breast cancer and low baseline BMD (T-score ≤ –1.0 but ≥ –2.5) undergoing adjuvant AI therapy for breast cancer to receive either placebo (n = 125) or denosumab 60 mg subcutaneously every 6 months (n = 127) for 2 years. In the placebo arm, lumbar spine BMD decreased substantially during 2 years of AI therapy. Denosumab prevented AIBL and substantially improved BMD compared with baseline. Between-group differences in lumbar spine BMD were 5.5% at 12 months and 7.6% at 24 months ($P < .0001$ for each; Figure 4).[26] Similar improvements in BMD were observed at the hip, femoral neck, and trochanter. These results with denosumab appear promising and warrant further safety and efficacy investigation in larger patient populations. A second, larger ongoing phase III trial (ABCSG-18) of denosumab in postmenopausal women undergoing AI therapy for breast cancer has a target accrual of 2800.[49] First results from this study are expected in 2012.

Rationale for the Use of Bone-Targeted Agents in the Prevention of Disease Recurrence

Breast cancer has a high rate (approximately 70%) of metastasis to bone and gives rise to predominantly osteolytic lesions.[50] Breast cancer cells that lodge in bone are thought to activate osteoclasts via local production of paracrine factors, including parathyroid hormone-related peptide and interleukins, which can stimulate osteoclast differentiation and osteolytic activity. In turn, osteolysis releases factors, including insulin-like growth factor-1 and transforming growth factor-β, which can enhance tumor cell survival, proliferation, and invasion. This sets up a "vicious cycle," resulting in enhanced growth and spread of bone metastases.

Figure 4 Denosumab Prevents Aromatase Inhibitor–Associated Bone Loss in Postmenopausal Women with Breast Cancer[26]



Abbreviations: BMD = bone mineral density; LS = least squares
*P = .0001 for comparison between treatment groups.

Bisphosphonates are antiresorptive agents that markedly reduce osteoclast viability and activity.[20] These agents suppress osteolysis and delay the onset of SREs in patients with metastatic bone disease.[21] Bisphosphonates can, therefore, render the bone microenvironment less supportive of tumor cell proliferation through their antiosteolytic activity, potentially leading to fewer and smaller metastatic lesions.[50]

Antitumor Activity of Bisphosphonates

Preclinical Evidence. A large body of preclinical evidence shows that nitrogen-containing bisphosphonates possess inherent antitumor activity.[24] Studies in cell lines as well as animal models of human breast cancer have demonstrated antiproliferative and proapoptotic efficacy of bisphosphonates alone as well as synergistically with cytotoxic agents.[24,50] Bisphosphonates also inhibit tumor cell migration and invasion in preclinical models.[24] In addition, zoledronic acid has demonstrated antiangiogenic properties and activates the immune system against cancer cells, which might contribute to its overall antitumor actions.

Early Clinical Evidence. Zoledronic acid has demonstrated promising antitumor activity in several small pilot trials. In a recent study, 40 patients with bone metastases from bladder cancer were randomized to receive either placebo or zoledronic acid 4 mg I.V. every 28 days for 6 months.[51] At a median follow-up of 183 days, zoledronic acid significantly reduced the incidence of SREs and bone pain compared with placebo ($P \leq .015$ for each). In addition, zoledronic acid significantly improved the 1-year overall survival (OS) rate compared with placebo (30% vs. 5%; $P = .02$).

Zoledronic acid 4 mg I.V. every 28 days has also demonstrated anticancer efficacy in 94 patients undergoing chemotherapy for previously untreated multiple myeloma.[52] At a median follow-up of 49.6 months, 5-year OS estimates improved from 46% with chemotherapy to 80% with chemotherapy plus zoledronic acid ($P < .01$). In addition, zoledronic acid reduced the incidence of SREs. Thus, the addition of zoledronic acid to conventional chemotherapy not only reduced skeletal morbidity in patients with multiple myeloma but also improved OS.

In a third pilot study, 40 patients with advanced solid tumors and no evidence of bone metastases were randomized to receive either monthly zoledronic acid or no treatment (control) and followed until bone metastases were detected.[53] At 12 months, the rate of bone metastases–free survival was 60% in the zoledronic acid arm compared with 10% in the control arm ($P < .0005$). This difference was still detectable at 18 months, at which time 20% of the patients in the zoledronic acid arm were free of bone metastases compared with only 5% in the control group ($P = .0002$).

Emerging data also indicate that zoledronic acid effectively reduces the prevalence and persistence of disseminated tumor cells (DTCs) in the bone marrow of women with early-stage breast cancer.[54,55] One study treated women with detectable DTCs in bone marrow at baseline with zoledronic acid 4 mg/month I.V. for 2 years and concomitant endocrine therapy.[54] At a 1-year follow-up, 69% of the patients had a decrease in DTCs compared with baseline ($P = .013$), and 71% had reduced DTCs at 2 years ($P = .01$).[56] In another study, 172 patients with detectable tumor cells in bone marrow were randomized to receive adjuvant chemotherapy alone (control; n = 141) or in combination with zoledronic acid 4 mg I.V. every 28 days (n = 31) for 6 months.[55] After treatment, DTCs in bone marrow were detected in 27% of the patients in the control group compared with 13% of those in the zoledronic acid group ($P = .099$).

In a small trial in 42 patients with advanced breast cancer, a single dose of zoledronic acid administered before chemotherapy reduced circulating levels of vascular endothelial growth factor (VEGF), a key stimulator of angiogenesis, by ≥ 25% compared with baseline in 59.5% of the patients.[57] Further analysis revealed that zoledronic acid–mediated reduction in VEGF levels was associated with significant increases in times to first SRE ($P = .0002$), progression of bone disease ($P = .0024$), and deterioration of performance status ($P = .0352$) compared to lack of reduction in VEGF level.

Overall, the combined preclinical and early clinical data suggest that the addition of bisphosphonates to conventional cancer therapy might provide tangible antitumor and antimetastatic benefits for patients with primary cancers that have a high frequency of metastasis to bone.[50] As a result, numerous studies are investigating the antitumor potential of bisphosphonates in the breast cancer setting.

Using Bone-Targeted Agents to Prevent Disease Recurrence: Emerging Evidence from Adjuvant Studies of Oral Bisphosphonates

Trials of Clodronate. The potential antimetastatic efficacy of clodronate has been evaluated in 3 trials. In a study in 1069 patients with stage I-III breast cancer randomized to receive standard adjuvant therapy either alone or with concomitant clodronate 1600 mg/day orally for 2 years, oral clodronate significantly reduced the risk of bone metastases (Figure 5A) in the overall study population (hazard ratio [HR], 0.692; $P = .043$) at a median follow-up of 5.6 years.[58] Benefits were more pronounced in the patients with stage II/III breast cancer (HR, 0.592; $P = .009$). The addition of clodronate also improved OS by approximately 23% compared with standard therapy alone ($P = .048$).

Clodronate was also found to reduce the risk of distant metastases in patients with breast cancer and tumor cells in bone marrow.[59] A total of 302 patients were randomized to receive standard adjuvant therapy either alone (control; n = 145) or with clodronate 1600 mg/day orally (n = 157) for 2 years. At a 36-month follow-up, the number of patients with distant metastases was significantly smaller in the clodronate arm compared with the control arm (21 vs. 42; $P < .001$). The incidences of skeletal and visceral metastases were significantly lower in the clodronate arm compared with the control arm ($P = .003$ for each), and fewer patients receiving clodronate died during the 36-month period (6 vs. 22; $P = .001$). Long-term follow-up of this trial revealed that the OS rate at 8.5 years was 79.6% in the clodronate group compared with 59.3% in the control group ($P = .049$).[60]

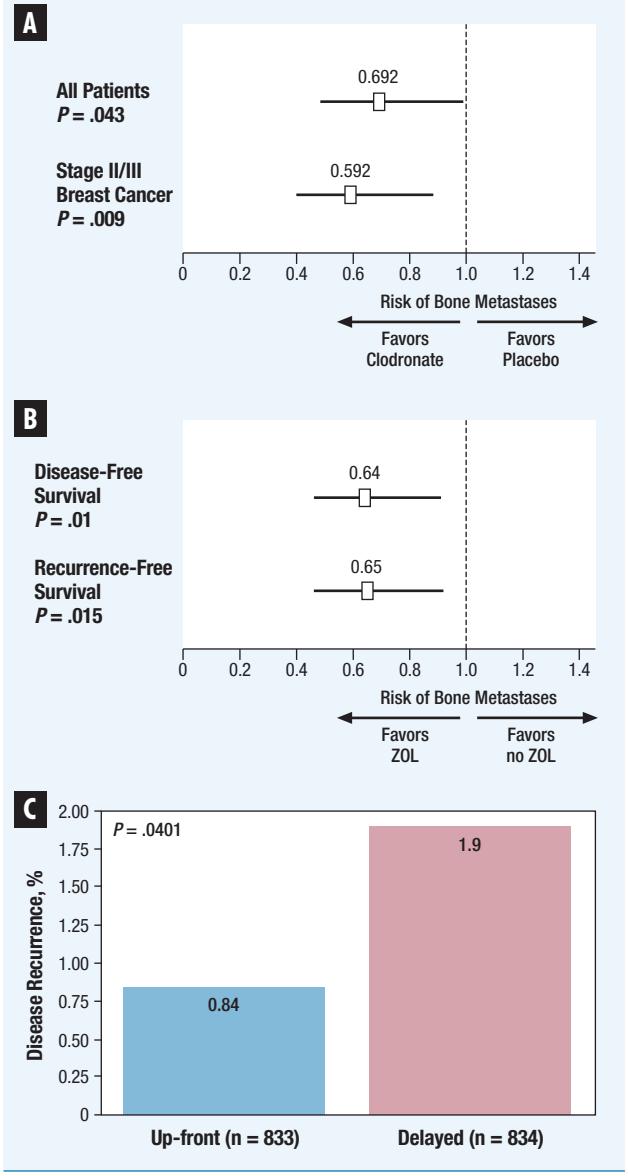
However, a third trial of clodronate in women with primary node-positive breast cancer yielded conflicting results.[61] The study randomized 299 patients to receive adjuvant therapy either alone (control; n = 150) or with clodronate 1600 mg/day orally (n = 149) for 3 years and initially followed the patients for 5 years. The incidence of bone metastases was similar in the clodronate arm compared with the control arm (21% vs. 17%; $P = .27$); however, 43% of the patients in the clodronate arm developed visceral metastases compared with 25% of those in the control arm ($P = .0007$), resulting in significantly lower rates of DFS (56% vs. 71%; $P = .007$) and OS (70% vs. 83%; $P = .009$) in the clodronate group. A 10-year follow-up of this trial confirmed significantly higher rates of nonskeletal metastases (visceral or local) in the clodronate arm compared with the control arm (50% vs. 36%, $P = .005$).[62] At 10 years, the DFS rate remained lower in the clodronate arm compared with the control arm, particularly in the patients with hormone receptor–negative disease (25% vs. 58%; $P = .004$), but OS rates were similar between treatment groups.

Overall, trials of clodronate in the adjuvant setting provide promising but inconclusive results. A meta-analysis of these studies revealed no significant benefit from clodronate treatment in patients with early-stage breast cancer (OS: HR, 0.75 [95% CI, 0.31-1.82).[63] As discussed in preceding sections, the benefits of adding bisphosphonates to standard adjuvant therapy for maintaining skeletal health are now well established through several studies. Recent trials using more active bisphosphonates in the adjuvant setting in breast cancer are providing better insight into the potential benefits from bisphosphonates that might extend beyond skeletal health.

Using Bone-Targeted Agents to Prevent Disease Recurrence: Emerging Evidence from Adjuvant Studies of Intravenous Bisphosphonates

ABCSG-12 Results. The ABCSG-12 trial compared tamoxifen with anastrozole and endocrine therapy alone with endocrine therapy plus zoledronic acid 4 mg I.V. every 6 months in premenopausal women with endocrine-responsive, early-stage breast cancer.[64] The first efficacy results from this study revealed that DFS outcomes at 47.8 months median follow-up were similar with tamoxifen and anastrozole (HR, 1.096; $P = .593$) in the 1803 women receiving ovarian suppression therapy with goserelin. However, the addition of zoledronic acid to adjuvant endocrine therapy significantly improved DFS by 36% ($P = .012$) and recurrence-free survival (RFS) by 35%

Figure 5 Addition of Bisphosphonates to Standard Therapy Improves Clinical Outcomes in the Adjuvant Breast Cancer Setting



Daily oral clodronate reduces the risk of bone metastases in patients with breast cancer (**A**).[58] Zoledronic acid 4 mg every 6 months improves disease- and recurrence-free survival in premenopausal women with hormone-responsive, early-stage breast cancer (**B**).[64] Up-front zoledronic acid 4 mg every 6 months reduces disease recurrence in postmenopausal women with hormone-responsive, early-stage breast cancer (**C**).[43]
Abbreviation: ZOL = zoledronic acid

($P = .014$) and produced a trend toward improved OS compared to endocrine therapy alone (Figure 5B).[64] In a multivariate analysis, zoledronic acid was a significant predictor of improved DFS (HR, 0.67; $P = .022$) and RFS (HR, 0.68; $P = .028$).[65] Interestingly, reduction in recurrences in the patients receiving zoledronic acid treatment was not limited to bone metastases; recurrences were reduced at all sites in the zoledronic acid groups.[64] Moreover, zoledronic acid treatment was well tolerated in this patient population; there were no confirmed cases of osteonecrosis of the jaw, and no renal toxicity was

noted. Therefore, the addition of zoledronic acid to adjuvant endocrine therapy proved a generally well-tolerated and effective means of improving clinical outcomes for premenopausal women with breast cancer. Overall, results from this large randomized trial indicate that the addition of zoledronic acid to adjuvant endocrine therapy not only prevents endocrine therapy–associated bone loss but also improves clinical outcomes in premenopausal women with early-stage breast cancer.[36,37,64,65]

Z-FAST/ZO-FAST Interim Results. The Z-FAST, ZO-FAST, and E-ZO-FAST trials were designed to evaluate the efficacy of zoledronic acid in the prevention of AIBL as well as disease progression in postmenopausal women with breast cancer.[43] Integrated analysis of the Z-FAST and ZO-FAST trials in a total of 1667 patients at a 12-month median follow-up demonstrated a significant decrease in disease recurrence with up-front compared with delayed zoledronic acid (0.84% vs. 1.9%; P = .0401; Figure 5C).[43] The 24-month integrated analyses support these data; disease recurrence rates were 3.6% with up-front zoledronic acid compared to 5.5% with delayed zoledronic acid (DFS: HR, 0.573; P = .0183).[44]

Conclusion

A large number of recent trials have demonstrated the efficacy of bisphosphonates (oral and I.V.) in the prevention of CTIBL in premenopausal and postmenopausal women with breast cancer. Long-term follow-up data from these trials will help address outstanding questions, including the consequences of increasing BMD in patients with normal baseline BMD and the effects of bisphosphonates on bone microarchitecture, strength, and fracture risk over time. Bisphosphonates as a class possess inherent antitumor activity, and recent trial results indicate that the addition of bisphosphonates to conventional adjuvant therapy at doses that prevent bone loss can significantly improve clinical outcomes in women with early-stage breast cancer. The evidence to date is strongest for zoledronic acid and suggests that the addition of zoledronic acid to standard adjuvant therapy will substantially improve DFS and RFS in women receiving adjuvant endocrine therapy for breast cancer. Indeed, the results from ABCSG-12 indicate that adjuvant treatment with zoledronic acid should be considered in order to improve the standard of care in premenopausal women with breast cancer. A large clinical trial program is ongoing to evaluate the potential efficacy of several bisphosphonates in this and related settings. Several ongoing trials (AZURE, National Surgical Adjuvant Breast and Bowel Project B-34, Southwest Oncology Group 0307, SUCCESS, NATAN, AZAC, ZEUS, RADAR, and Study 2419) are exploring the potential adjuvant benefits of bisphosphonates in breast and other cancers further and will enroll nearly 20,000 patients. These trials have been designed to investigate different doses and dosing intervals of bisphosphonates based on the anticipated disease burdens according to their inclusion criteria and, therefore, can provide important information regarding the best dosing regimens for different indications. For example, the AZURE trial has enrolled women with stage II/III breast cancer, and the residual disease burden after locoregional therapy (albeit lower than in the metastatic setting) is anticipated to be higher than in ABCSG-12, which included women with stage I/II breast cancer. As a result, the AZURE trial is evaluating the efficacy of more frequent treatment with zoledronic acid, particularly in the early months after locoregional therapy, compared with ABCSG-12. As data from these studies mature, the role of bisphosphonates in oncology, particularly the adjuvant therapy setting, is likely to expand.

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References

1. Garcia M, Jemal A, Ward EM, et al. *Global Cancer Facts & Figures,* 2007. Atlanta, GA: American Cancer Society; 2007.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365:1687-717.
3. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer: status report 2004. *J Clin Oncol* 2005; 23:619-29.
4. Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. *N Engl J Med* 1998; 339:733-8.
5. Bjarnason K, Hassager C, Ravn P, et al. Early postmenopausal diminution of forearm and spinal bone mineral density: a cross-sectional study. *Osteoporos Int* 1995; 5:35-8.
6. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab* 2008; 93:861-8.
7. Mazzuoli G, Acca M, Pisani D, et al. Annual skeletal balance and metabolic bone marker changes in healthy early postmenopausal women: results of a prospective study. *Bone* 2000; 26:381-6.
8. Pouilles JM, Tremollieres F, Ribot C. Effect of menopause on femoral and vertebral bone loss. *J Bone Miner Res* 1995; 10:1531-6.
9. Zhang HC, Kushida K, Atsumi K, et al. Effects of age and menopause on spinal bone mineral density in Japanese women: a ten-year prospective study. *Calcif Tissue Int* 2002; 70:153-7.
10. Warming L, Hassager C, Christiansen C. Changes in bone mineral density with age in men and women: a longitudinal study. *Osteoporos Int* 2002; 13:105-12.
11. Brodie A, Lu Q, Long B. Aromatase and its inhibitors. *J Steroid Biochem Mol Biol* 1999; 69:205-10.
12. Eastell R, Hannon RA, Cuzick J, et al. Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). *J Bone Miner Res* 2006; 21:1215-23.
13. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol* 2000; 18:1570-93.
14. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol* 2001; 19:3306-11.
15. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1996; 14:1718-29.
16. Bruning PF, Pit MJ, de Jong-Bakker M, et al. Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. *Br J Cancer* 1990; 61:308-10.
17. Lower EE, Blau R, Gazder P, et al. The risk of premature menopause induced by chemotherapy for early breast cancer. *J Womens Health Gend Based Med* 1999; 8:949-54.
18. Nordin BE, Need AG, Chatterton BE, et al. The relative contributions of age and years since menopause to postmenopausal bone loss. *J Clin Endocrinol Metab* 1990; 70:83-8.
19. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature* 2003; 423:337-42.
20. Rogers MJ, Gordon S, Benford HL, et al. Cellular and molecular mechanisms of action of bisphosphonates. *Cancer* 2000; 88(suppl):2961-78.
21. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer [published correction appears in *J Clin Oncol* 2004; 22:1351]. *J Clin Oncol* 2003; 21:4042-57.
22. Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. *Cancer* 2008; 113:193-201.
23. Aapro MS. Long-term implications of bone loss in breast cancer. *Breast* 2004; 13(suppl 1):S29-37.
24. Winter MC, Holen I, Coleman RE. Exploring the anti-tumour activity of bisphosphonates in early breast cancer. *Cancer Treat Rev* 2008; 34:453-75.
25. Lipton A, Jun S. RANKL inhibition in the treatment of bone metastases. *Curr Opin Support Palliat Care* 2008; 2:197-203.
26. Ellis GK, Bone HG, Chlebowski RT, et al. Randomized trial of denosumab in

patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol* 2008; 26:4875-82.
27. Saarto T, Blomqvist C, Välimäki M, et al. Chemical castration induced by adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy causes rapid bone loss that is reduced by clodronate: a randomized study in premenopausal breast cancer patients. *J Clin Oncol* 1997; 15:1341-7.
28. Vehmanen L, Saarto T, Elomaa I, et al. Long-term impact of chemotherapy-induced ovarian failure on bone mineral density (BMD) in premenopausal breast cancer patients. The effect of adjuvant clodronate treatment. *Eur J Cancer* 2001; 37:2373-8.
29. Saarto T, Vehmanen L, Blomqvist C, et al. Ten-year follow-up of 3 years of oral adjuvant clodronate therapy shows significant prevention of osteoporosis in early-stage breast cancer. *J Clin Oncol* 2008; 26:4289-95.
30. Delmas PD, Balena R, Confravreux E, et al. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. *J Clin Oncol* 1997; 15:955-62.
31. Fuleihan GE-H, Salamoun M, Mourad YA, et al. Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2005; 90:3209-14.
32. Rosen LS, Gordon DH, Dugan W Jr, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004; 100:36-43
33. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; 356:1809-22.
34. Brown JE, Ellis SP, Lester JE, et al. Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid. *Clin Cancer Res* 2007; 13:5406-10.
35. Hershman DL, McMahon DJ, Crew KD, et al. Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2008; 26:4739-45.
36. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol* 2008; 9:840-9.
37. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G, et al. Zoledronic acid prevents cancer treatment–induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol* 2007; 25:820-8.
38. Shapiro CL, Halabi S, Gibson G, et al. Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy. Presented at: 44th Annual Meeting of the American Society of Clinical Oncology; May 30-June 3, 2008; Chicago, IL. Abstract 512.
39. Saarto T, Vehmanen L, Elomaa I, et al. The effect of clodronate and antioestrogens on bone loss associated with oestrogen withdrawal in postmenopausal women with breast cancer. *Br J Cancer* 2001; 84:1047-51.
40. Confavreux CB, Fontana A, Guastalla JP, et al. Estrogen-dependent increase in bone turnover and bone loss in postmenopausal women with breast cancer treated with anastrozole. Prevention with bisphosphonates. *Bone* 2007; 41:346-52.
41. Greenspan SL, Brufsky A, Lembersky BC, et al. Risedronate prevents bone loss in breast cancer survivors: a 2-year, randomized, double-blind, placebo-controlled clinical trial. *J Clin Oncol* 2008; 26:2644-52.
42. Schenk N, Lombart A, Frassol[da]ti A, et al. The E-ZO-FAST trial: zoledronic acid (ZA) effectively inhibits aromatase inhibitor associated bone loss (AIBL) in postmenopausal women (PMW) with early breast cancer (EBC) receiving adjuvant letrozole (Let). *Eur J Cancer Suppl* 2007; 5:186 (abstract 2008).
43. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor–associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008; 13:503-14.
44. Frassoldati A, Brufsky A, Bundred N, et al. The effect of zoledronic acid on aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 24-month integrated follow-up of the Z-FAST and ZO-FAST trials. Presented at: 33rd Congress of the European Society for Medical Oncology; September 12-16, 2008; Stockholm, Sweden. Abstract 185 PD
45. Hines SL, Mincey BA, Sloan JA, et al. N02C1: a phase III randomized, placebo-controlled, double-blind trial of risedronate for prevention of bone loss in premenopausal women undergoing adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2008; 26(suppl):12s (abstract 525).
46. Van Poznak C, Hannon RA, Clack G, et al. The SABRE (Study of Anastrozole with the Bisphosphonate Risedronate) study: 12-month analysis. *Breast Cancer Res Treat* 2007; 106(suppl 1):S37 (abstract 502).
47. Singh S, Cuzick J, Edwards R, et al. Effect of anastrozole on bone mineral density after one year of treatment: results from bone sub-study of the International Breast Cancer Intervention Study (IBIS-II). *Breast Cancer Res Treat* 2007; 106(suppl 1): S9 (abstract 28).
48. Lester JE, Dodwell D, Purohit OP, et al. Use of monthly oral ibandronate to prevent anastrozole-induced bone loss during adjuvant treatment for breast cancer: two-year results from the ARIBON study. *J Clin Oncol* 2008; 26(15 suppl):19s (abstract 554).
49. Study to determine treatment effects of denosumab in patients with breast cancer receiving aromatase inhibitor therapy: ClinicalTrials.gov [Web site]. Available at: http://clinicaltrials.gov/ct2/show/NCT00556374. Accessed: April 30, 2009.
50. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2002; 2:584-93.
51. Zaghloul MS, Boutrus R, El-Hosieny H, et al. A controlled prospective randomized placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer patients. *J Clin Oncol* 2008; 26(suppl):257s (abstract 5033).
52. Avilés A, Nambo MJ, Neri N, et al. Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Med Oncol* 2007; 24:227-30.
53. Mystakidou K, Katsouda E, Parpa E, et al. Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline. *Med Oncol* 2005; 22:195-201.
54. Lin A, Park J, Melisko M, et al. Zoledronic acid as adjuvant therapy for women with early stage breast cancer and occult tumor cells in bone marrow. *Breast Cancer Res Treat* 2007; 106(suppl 1):S40 (abstract 510).
55. Rack BK, Jueckstock J, Genss E-M, et al. Effect of zoledronate on persisting isolated tumor cells in the bone marrow of patients without recurrence of early breast cancer. *Breast Cancer Res Treat* 2007; 106(suppl 1):S40 (abstract 511).
56. Lin AY, Park JW, Scott J, et al. Zoledronic acid as adjuvant therapy for women with early stage breast cancer and disseminated tumor cells in bone marrow. *J Clin Oncol* 2008; 26(suppl):20s (abstract 559).
57. Vincenzi B, Santini D, Dicuonzo G, et al. Zoledronic acid-related angiogenesis modifications and survival in advanced breast cancer patients. *J Interferon Cytokine Res* 2005; 25:144-51.
58. Powles T, Paterson A, McCloskey E, et al. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026] [published correction appears in *Breast Cancer Res* 2006; 8:406]. *Breast Cancer Res* 2006; 8:R13.
59. Diel IJ, Solomayer E-F, Costa SD, et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998; 339:357-63.
60. Diel IJ, Jaschke A, Solomayer EF, et al. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up. *Ann Oncol* 2008; 19:2007-11.
61. Saarto T, Blomqvist C, Virkkunen P, et al. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol* 2001; 19:10-7.
62. Saarto T, Vehmanen L, Virkkunen P, et al. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. *Acta Oncol* 2004; 43:650-6.
63. Ha TC, Li H. Meta-analysis of clodronate and breast cancer survival. *Br J Cancer* 2007; 96:1796-801.
64. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; 360:679-91.
65. Gnant M, Mlineritsch B, Schippinger W, et al. Zoledronic acid (ZOL) improved disease-free (DFS) and recurrence-free survival (RFS) in premenopausal women with early breast cancer (ERBC) receiving adjuvant endocrine therapy: multivariate analysis of efficacy data from the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12. *Ann Oncol* 2008; 19(suppl 8):44 (abstract 69O).