The Role of Bisphosphonates in the Adjuvant Setting for Breast Cancer

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Bone health is a critical issue in the management of women with breast cancer. Many women who develop breast cancer are postmenopausal, which already predisposes them to osteoporosis. Systemic treatments for breast cancer, including chemotherapy and endocrine therapy, decrease circulating levels of estrogen in both pre- and postmenopausal women, further accelerating the natural process of bone loss. The primary concern in breast cancer patients is that this accelerated bone loss, known as cancer treatment–induced bone loss (CTIBL), will lead to an increase in fractures, chronic pain, and loss of mobility. Bisphosphonates are highly effective at slowing the rate of bone loss in postmenopausal women with osteoporosis and at preventing skeletal-related events in women with metastatic breast cancer. Many studies are now focusing on the role of bisphosphonates in preventing CTIBL in the adjuvant setting. Both oral and intravenous bisphosphonates have shown promising activity in preventing CTIBL in patients receiving chemotherapy or hormonal therapy. In addition, emerging data indicate that the use of bisphosphonates in the adjuvant setting may prevent disease recurrence and prolong survival. Data from a number of ongoing trials will further elucidate the role of bisphosphonates in the adjuvant setting over the next few years.

Most women with early-stage breast cancer are treated with systemic therapy following surgery in order to prevent disease recurrence. Depending on the individual characteristics of her tumor, a patient may receive chemotherapy, endocrine therapy, or a combination of both.[1] Endocrine therapies, which include gonadotropin-releasing hormone (GnRH), luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogens (eg, bicalutamide, flutamide), and aromatase inhibitors (AIs), decrease circulating levels of estrogen. Lower levels of estrogen lead to an increase in bone resorption and a slowing of bone formation, resulting in overall loss of bone mass.[2] Chemotherapy also lowers estrogen levels by inducing premature ovarian dysfunction in the majority of premenopausal women.[3,4] A second mechanism of chemotherapy-induced bone loss involves a direct nonhormonal toxic effect on bone cells.[2] The combination of both chemotherapy and endocrine therapy places women at a high risk of cancer treatment–induced bone loss (CTIBL).

CTIBL exposes breast cancer patients to increased skeletal morbidity which can lead to chronic pain, decreased mobility, and ultimately, a shorter survival time.[5] Early identification of patients who are at risk for CTIBL is critical to improving their outcome with preventive therapy. Bisphosphonates are the standard of care for reducing the risk of skeletal-related events (SREs) in patients with metastatic bone disease, but no guidelines have yet been established for the use of bisphosphonates in the adjuvant setting. In this review, we will discuss the evolving role of bisphosphonates in the adjuvant setting, including a focus on data indicating that bisphosphonates not only promote bone health, but also may prevent disease recurrence and prolong survival.

Pathogenesis of Bone Loss

Bone remodeling is the normal process by which bone health is maintained. Bone remodeling involves the balanced turnover of bone elements, which includes resorption of existing bone by osteoclasts and formation of new bone by osteoblasts. The activity of osteoclasts and osteoblasts is regulated by both local factors and systemic hormones, including estrogen. The active form of estrogen, estradiol, appears to have a stimulatory effect on osteoblasts, which is believed to contribute to the maintenance of bone mass in healthy adult females.[6] Bone mineral density (BMD) loss occurs when an imbalance develops in the normal process of bone remodeling. The imbalance may be the result of increased activity of osteoclasts or decreased activity of osteoblasts, which causes disruption of the microarchitecture of the bone. The structural integrity of the bone is thus compromised, leading to fragility and an increased risk of fracture.[7] Adjuvant breast cancer treatments that alter estrogen levels may lead to a decrease in the
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Cancer Treatment-Induced Bone Loss (CTIBL)

Chemotherapy-Induced Bone Loss

More than 60% of breast cancer patients undergoing adjuvant chemotherapy will experience ovarian failure within 1 year of beginning their treatment.[2] The rate of ovarian dysfunction in premenopausal women aged > 50 years is > 90%, and remains substantially higher for women aged > 40 years compared with those < 40 years of age.[4] Chemotherapy-induced menopause, either temporary or permanent, has been associated with significant bone loss; on average, women experience a > 7% decrease in BMD within the first year.[3] In addition to inducing menopause, cytotoxic chemotherapy is also believed to cause CTIBL by a direct toxic effect of the chemotherapy on bone cells. This toxic effect can decrease BMD by another 1% in the first year following treatment.[2,3]

Aromatase Inhibitor–Associated Bone Loss

All of the endocrine therapies can significantly affect bone health, but aromatase inhibitors (AIs) are perhaps of the greatest concern because of their ability to almost completely eliminate circulating estrogen. The Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial has demonstrated the superiority of AIs over tamoxifen in postmenopausal women with early-stage breast cancer,[8,9] leading to a significant increase in women taking AIs. Although anastrozole (Arimidex) had a better overall safety profile than tamoxifen, anastrozole was associated with a greater fracture incidence (11% vs 7.7%, respectively).[8,9] Aromatase inhibitors are now also being studied in premenopausal women in combination with ovarian ablation or suppression, which is likely to contribute to the growing concern about AI-associated bone loss (AIBL).

Another important clinical concern with AIBL is the duration of exposure to endocrine therapy. AIBL is more rapid than bone loss associated with menopause (with total hip BMD loss of 1.7% and lumbar spine BMD loss of 2.6% during the first year, ATAC investigators reported).[8] and the severity increases with treatment duration. AI therapy was initially approved for 5 years, but several studies are now evaluating treatment duration of more than 5 years. In the MA 17 trial, patients were treated in the adjuvant setting with 5 years of letrozole (Femara) after completing 5 years of tamoxifen. Two years into treatment with the AI, women experienced a decrease of 3.6% in total hip BMD, compared with 0.71% for placebo ($P = .044$), and a BMD decrease of 5.3% at the lumbar spine, compared with 0.70% for placebo ($P = .008$).[10] As the duration of AI therapy lengthens, the importance of minimizing the risks of AIBL becomes even more critical.

The Role of Bisphosphonates in Preventing CTIBL

Bisphosphonates are antiresorptive agents that prevent bone loss by interfering with normal osteoclast activation and function and by inducing osteoclast apoptosis. They have been shown to prevent bone loss in the postmenopausal setting, and are now used extensively in women with a diagnosis of osteoporosis or osteopenia. Both oral and intravenous forms of bisphosphonates have been studied in patients with breast cancer. In patients who already have bone metastases, intravenous bisphosphonates have been shown to decrease pathologic fractures, bone pain, hypercalcemia, spinal cord compression, and the need for palliative radiation to bone.[11] These observations have led researchers to investigate the role of bisphosphonates in prevention of bone loss in the adjuvant setting.

Oral Bisphosphonates

The oral bisphosphonates, clodronate and risedronate (Actonel), have both been shown to decrease bone loss associated with chemotherapy-induced ovarian failure.[12,13] One study randomized women who had received six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to either 3 years of oral clodronate at 1,600 mg daily or placebo. At 2 years of follow-up, patients who took clodronate and were amenorrheic experienced 38% less of a decrease in mean lumbar spine bone loss compared with the control group.[12] The benefit persisted at 5 years of follow-up, when patients who received clodronate were found to have a 5.8% decrease in BMD from baseline at the lumbar spine, compared with a 9.7% decrease in the placebo arm ($P = .008$). Clodronate was generally well-tolerated, with no significant difference in the adverse events reported between
treatment groups. A recent 10-year update of this trial reported that patients who received clodronate continued to have less BMD loss, indicating the importance of initiating bisphosphonate treatment at the time of chemotherapy.[14]

In the similar study of oral risedronate in premenopausal women, mean BMD of the lumbar spine and femoral neck was significantly reduced by 2.5% ($P = .041$) and 2.6% ($P = .029$), respectively, compared with women who received placebo.[13] After 3 years, differences in BMD remained significant at the lumbar spine ($P = .024$), femoral neck ($P = .011$), and trochanter ($P = .008$). Risedronate was also well-tolerated; adverse events were reported to be mild and similar between the treatment groups, with no evidence of laboratory abnormalities.

Risedronate has also been evaluated in postmenopausal women with breast cancer. In one study, 87 postmenopausal women received chemotherapy followed by either risedronate at a dosage of 35-mg weekly for 2 years or placebo. Nearly 70% of patients had estrogen receptor (ER)-positive disease, and thus also required concomitant endocrine therapy. These ER-positive patients who took risedronate had a 2.4% decrease in BMD at the lumbar spine, compared with a 4.8% decrease in patients taking placebo.[15] All of these studies demonstrate that oral bisphosphonates appear to reduce CTIBL, although bone integrity is still somewhat compromised.

**Intravenous Bisphosphonates**

Although oral bisphosphonates clearly reduce the amount of bone loss in patients undergoing chemotherapy, they do not completely eliminate the risk. Intravenous bisphosphonates have been studied in several types of solid tumors to determine if they could further reduce or even eliminate bone loss associated with cancer therapies. Pamidronate (Aredia) and zoledronic acid (Zometa) have both shown clinical benefit in the treatment of bone metastases among patients with breast, lung, and prostate cancer. Several phase III studies showed that zoledronic acid reduced the risk of developing SREs by 31%–41% compared with placebo ($P < .02$ for all studies).[16-18] Zoledronic acid was found to be superior to pamidronate in patients with breast cancer, with a relative risk reduction of an SRE by an additional 16% ($P = .03$).[19] A review that compared all oral and intravenous bisphosphonates that were approved for breast cancer treatment in 2005 demonstrated a 41% risk reduction in SREs with zoledronic acid vs placebo, compared with a 14%–23% risk reduction for ibandronate (Boniva), clodronate, and pamidronate.[20]

In the past 2 years, several trials have reported results of the use of zoledronic acid in premenopausal women who develop ovarian failure in the adjuvant setting. In one trial, 101 premenopausal women with early-stage breast cancer were randomized to receive either zoledronic acid or placebo after completion of chemotherapy.[21] Patients who did not receive zoledronic acid experienced a 4.4% and 2.1% decrease in BMD at the lumbar spine and total hip, respectively, at 12 months. Women who did receive zoledronic acid at a dosage of 4-mg intravenously every 3 months had stable BMD at both the spine and hip at 12 months.

The ongoing Cancer and Leukemia Group B (CALGB) 79809 trial is also evaluating the efficacy of zoledronic acid in preventing bone loss in women who develop ovarian suppression while undergoing chemotherapy. Premenopausal women with early-stage breast cancer who became amenorrheic with chemotherapy were randomized to receive zoledronic acid at 4-mg intravenously every 3 months, either beginning with chemotherapy (immediate) or 1 year after chemotherapy (delayed).[22] At the first analysis at 12 months, patients in the delayed-therapy arm, who had not yet initiated zoledronic acid treatment, had a decrease in BMD of 6.4% at the lumbar spine. Patients in the immediate-therapy arm had a 2.6% improvement in their lumbar BMD ($P < .0001$), demonstrating the significant benefit of initiating bisphosphonate therapy upfront. Follow-up from this trial will provide insight regarding the optimal timing of bisphosphonate therapy.

*(ABCSG) trial ABCSG-12.*
The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial was conducted to determine if zoledronic acid could also be effective at preventing endocrine therapy–induced bone loss in premenopausal women. In this large randomized, open-label, phase III study, premenopausal women with early-stage hormone receptor (HR)-positive breast cancer were randomized to receive goserelin (Zoladex) at 3.6-mg monthly combined with tamoxifen at 20-mg daily or anastrozole at 1-mg daily with or without zoledronic acid at 4-mg intravenously every 6 months for 3 years[23,24] (Figure 1). At a median follow-up of 3 years, women receiving goserelin and anastrozole had greater bone loss than patients receiving goserelin plus tamoxifen (17.3% vs 11.6% decrease in BMD, respectively). The addition of zoledronic acid to either treatment regimen effectively prevented bone loss, with a BMD of 1.032 g/cm2 after 3 years of treatment, compared with a BMD of 1.018 g/cm2 at baseline.

With additional follow-up at 5 years, zoledronic acid was shown to actually improve BMD in patients continuing to receive endocrine therapy, with an increase in BMD of 4.0% ($P = .02$).[24] Zoledronic acid combined with endocrine therapy was well tolerated, and there was no observed additive toxicity between zoledronic acid and either of the endocrine therapy regimens. Adverse events associated with zoledronic acid included mild to moderate flu-like symptoms consisting of nausea, vomiting, fever, and myalgias. There were no cases of renal failure or osteonecrosis of the jaw reported.

**FIGURE 2** Design of the Zometa-Femara Adjuvant Synergy Trial (Z-FAST).

In the postmenopausal setting, women with HR-positive breast cancer typically receive AIs. As previously mentioned, AIs have been associated with a higher risk of BMD loss than tamoxifen,[9] underscoring the growing concern about AIBL in postmenopausal women. The Zometa/Femara Adjuvant Synergy Trial (Z-FAST) evaluated the efficacy of immediate vs delayed administration of zoledronic acid in postmenopausal women with early-stage HR-positive breast cancer who were receiving adjuvant letrozole.[25] Women randomized to the immediate arm received upfront zoledronic acid at 4-mg intravenously every 6 months. Patients in the delayed arm of the trial received zoledronic acid only if T-scores at the lumbar spine or total hip decreased below – 2.0 SD or if they had a clinical fracture or asymptomatic vertebral fracture at 36 months (Figure 2). Women in the immediate arm experienced an increase in BMD at the lumbar spine and total hip of 2.0% and 1.4%, respectively, after 1 year of zoledronic acid treatment.[25] In contrast, BMD of the lumbar spine decreased by 2.6% and total hip BMD decreased by 2.1% among women in the delayed arm. Adverse events were similar between treatment groups, although bone pain was more common with upfront (11.3%) vs delayed zoledronic acid (4%).[25] ZO-FAST is a similarly designed trial, conducted in Europe, with almost twice the number of patients enrolled in Z-FAST. An integrated analysis of the 1,667 patients participating in these two trials demonstrated improvements in BMD at both the lumbar spine and total hip of 5.2% and 3.5%, respectively.[26] At 24 months of follow-up, the fracture rates remained similar in the immediate and delayed arms of the trial. Taken together, these trials demonstrate that zoledronic acid is a safe and effective method for preventing AIBL in postmenopausal women, but the effect of this benefit on SREs remains to be seen.

**Denosumab**

Denosumab (Prolia) is a fully humanized monoclonal antibody against receptor activator of nuclear factor-κB ligand (RANKL) that is emerging as a possible alternative to bisphosphonate therapies for the prevention of CTIBL. The binding of RANKL to its receptor, RANK, is critical for osteoclast differentiation, function, and survival. The inhibition of RANKL by denosumab has been hypothesized to preserve bone integrity by preventing osteoclasts from breaking down bone. In one study, 252 patients with early-stage breast cancer and osteopenia were randomized to placebo or denosumab at 60-mg subcutaneously every 6 months for 2 years. At 2 years of follow-up, denosumab improved BMD from baseline, with a difference of 7.6% at the lumbar spine compared with placebo.[27] The results of more studies of denosumab in the adjuvant setting are eagerly awaited.
The Role of Bisphosphonates in Preventing Disease Recurrence

Antitumor Effects of Bisphosphonates

TABLE 1

Clodronate Trials Evaluating Disease Recurrence

Breast cancer that has metastasized to bone is primarily an osteolytic process. Tumor cells that have settled in the bone are believed to release local factors that activate osteoclasts, promoting osteolysis. Bisphosphonates interfere with normal osteoclast differentiation and function, and therefore may also play a role in preventing the initiation and propagation of skeletal metastases. A growing body of evidence supports the concept that bisphosphonates may prevent disease recurrence by inhibiting the migration and invasion of tumor cells, as seen in preclinical models.[28] Additionally, bisphosphonates have demonstrated antiproliferative, proapoptotic, and antiangiogenic properties in cell lines and animal models of human breast cancer.[28,29]

FIGURE 3

Zoledronic acid increased BMD at the lumbar spine and total hip in the Zometa-Femara Adjuvant Synergy Trial (Z-FAST)

The promising data from preclinical studies have led to a number of studies evaluating the antitumor and antimetastatic potential of bisphosphonates in breast cancer. Studies investigating the oral bisphosphonate clodronate have produced encouraging but conflicting results (see Table 1). Three trials investigated the role of clodronate in the adjuvant setting by randomizing patients to placebo or oral clodronate at 1,600 mg daily for 2 or 3 years. All patients also received standard adjuvant treatment, which could include surgery, radiation, or endocrine therapy as deemed appropriate. Two of the trials demonstrated a statistically significant improvement in overall survival in the patients who received adjuvant clodronate.[30,31] The third trial revealed a nonsignificant trend in the opposite direction for overall survival, but it did show a significant increase in the number of nonskeletal metastases with clodronate therapy[32] (Table 1). A recent meta-analysis summarized the data from these clodronate trials and demonstrated that oral clodronate in patients with early-stage breast cancer did not show a benefit in terms of disease-free or overall survival.[33] The antitumor potential of intravenous bisphosphonates has also been studied. As previously mentioned, the ABCSG-12 trial studied the effect of adding zoledronic acid to endocrine therapy in 1,800 premenopausal women (Figure 1). At a median follow-up of 47.8 months, zoledronic acid plus endocrine therapy improved disease-free survival by 36% ($P = .01$) and recurrence-free survival by 35% compared with endocrine therapy alone ($P = .015$).[34] Although the overall number of recurrences has been small, subset analyses did reveal a reduction not only in distant recurrences but also in locoregional and contralateral breast recurrences.REFERENCE GUIDE
Interim results from the Z-FAST and ZO-FAST studies demonstrated a significant decrease in disease recurrence with immediate vs delayed zoledronic acid at 12 months (0.84% vs. 1.9%; \( P = .0401 \)).
These results were confirmed after 24 months of follow-up, with fewer patients experiencing disease recurrence in the immediate-treatment arm (3.6% vs 5.5%; \( P = .0183 \)). At 36 months of follow-up, the relative percentage change of BMD continued to increase (Figure 3). Several other ongoing prospective, randomized clinical trials are evaluating the effects of bisphosphonates on disease-free and overall survival in early-stage breast cancer patients. The results of these trials, including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B34 study, the AZURE trial (Adjuvant Zoledronic acid to Reduce Recurrence), and Southwest Oncology Group study 0307, are eagerly awaited, as we will learn whether they validate the preliminary results.

**Conclusion**

In summary, the mechanism of accelerated bone loss in women undergoing treatment for breast cancer is multifactorial. Adjuvant chemotherapy can lead to premature ovarian failure, and adjuvant AI therapy further suppresses circulating estrogen levels. Breast cancer treatments therefore place women at increased risk for osteoporosis, which can lead to significant morbidity from fractures, bone pain, and loss of mobility. Both oral and intravenous bisphosphonates have been shown to mitigate CTIBL in pre- and postmenopausal women. Additionally, growing evidence suggests that bisphosphonates may protect against disease recurrence. Ongoing and recently closed clinical trials will likely expand the role of bisphosphonates in maintaining bone health and preventing disease recurrence in the adjuvant setting.

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