Aromatase Inhibitors and Bone Loss

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Abstract

The aromatase inhibitors (AIs) anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) are significantly more effective than the selective estrogen-receptor modulator (SERM) tamoxifen in preventing recurrence in estrogen receptor–positive early breast cancer. Aromatase inhibitors are likely to replace SERMs as first-line adjuvant therapy for many patients. However, AIs are associated with significantly more osteoporotic fractures and greater bone mineral loss. As antiresorptive agents, oral and intravenous bisphosphonates such as alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva), pamidronate (Aredia), and zoledronic acid (Zometa) have efficacy in preventing postmenopausal osteoporosis, cancer treatment–related bone loss, or skeletal complications of metastatic disease. Clinical practice guidelines recommend baseline and annual follow-up bone density monitoring for all patients initiating AI therapy. Bisphosphonate therapy should be prescribed for patients with osteoporosis (T score < −2.5) and considered on an individual basis for those with osteopenia (T score < −1). Modifiable lifestyle behaviors including adequate calcium and vitamin D intake, weight-bearing exercise, and smoking cessation should be addressed. Adverse events associated with bisphosphonates include gastrointestinal toxicity, renal toxicity, and osteonecrosis of the jaw. These safety concerns should be balanced with the potential of bisphosphonates to minimize or prevent the debilitating effects of AI-associated bone loss in patients with early, hormone receptor–positive breast cancer.

As a result of earlier diagnosis, more efficacious treatments, and longer survival, more patients than ever are receiving long-term treatment for breast cancer. Improved survival is due in part to the successful use of adjuvant hormonal therapies in estrogen and/or progesterone receptor—positive disease.[1] The increasing breast cancer survivor population—estimated at slightly over 2 million women in the United States in 2005[2]—may be at risk for long-term side effects of these beneficial treatments.
Recent randomized clinical trials have revealed the efficacy of aromatase inhibitors (AIs) as adjuvant therapy for early breast cancer in postmenopausal women.[3,4] However, the substantial benefits documented for this class of drug in the short term are associated with a significant, but manageable, increase in adverse events related to bone health. The cumulative incidence of AI-associated bone loss in patients with breast cancer in the long term is not known. The AIs anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) have been shown to be significantly more effective than the selective estrogen-receptor modulator (SERM) tamoxifen in preventing disease recurrence in estrogen receptor–positive early breast cancer. Aromatase inhibitors are likely to replace SERMs as first-line adjuvant therapy for many patients.[3–5] The growing use of AIs mandates vigilance about bone health in the oncology community. This article reviews the biology of AI-associated bone loss, summarizes recent safety data from clinical trials, and discusses options for preserving bone health in patients with breast cancer.

Pathophysiology of AI-Associated Bone Loss

The ongoing process of bone remodeling in the adult skeleton reflects a balance between the resorptive activity of osteoclasts and bone-forming action of osteoblasts, processes that are normally coupled and in equilibrium. Normal bone turnover is maintained through a complex regulatory system of both systemic and local factors. Molecular factors involved in bone resorption and remodeling include osteoprotegerin (OPG), receptor activator of nuclear factor kappa B (RANK) and RANK ligand (RANKL).[6] RANKL activates and binds to the RANK receptor on osteoclasts and their precursor cells, promoting osteoclast formation and prolonged osteoclast lifespan. Osteoprotegerin acts as a decoy receptor of RANKL and inhibits RANKL binding to RANK. Altering the relative biological availabilities of OPG and RANKL has direct consequences for the regulation of normal bone remodeling and in the pathogenesis of cancer-induced bone loss.[7,8]

Estrogen and Bone Physiology

Although the importance of the steroid sex hormones in bone metabolism has been recognized for many decades, their cellular and molecular mechanisms of action are still being elucidated. [3,9] Broadly speaking, estrogen has suppressive, antiresorptive effects on osteoclasts during bone remodeling. These pleiotropic effects are mediated through intracellular and cell surface estrogen receptors expressed by osteoclasts and osteoblasts and are largely indirect. For example, estrogen modulates osteoblast-derived cytokines, resulting in decreased differentiation and maturation of osteoclasts from precursors and increased osteoclast apoptosis (programmed cell death).[6,9] Estrogen may also induce direct effects on osteoblasts, further favoring bone formation over resorption.[9] In concert, these cellular responses have the net effect of dampening bone turnover under estrogen-replete conditions (Figure 1).

Estrogen deprivation that occurs with natural or treatment-associated menopause increases bone turnover and osteoclast activity, causing bone resorption and formation to become unbalanced.[9] This imbalance results in net bone loss as well as decreased bone quality, a term that encompasses both bone microarchitecture and degree of mineralization. Bone quality is increasingly recognized as an important determinant of overall bone health, and studies have shown that substantial deterioration of bone microarchitecture can occur before bone density is affected.[10]

Estrogen Blockade With AIs

In the postmenopausal state, the bulk of estrogen production switches from the ovaries to other sites such as adipose tissue, adrenal glands, smooth muscle, and bone.[3,9] Adrenally derived androgens circulate to peripheral tissues where they are converted to estrogen by the action of
the enzyme aromatase (also called estrogen synthetase). This residual postmenopausal estrogen, although substantially reduced, remains critical for bone health.[9]

The mechanism of action of the AIs is to block the peripheral conversion (aromatization) of estrogen from androgen precursors, effectively lowering tissue and circulating estrogen levels.[1,3] The AIs currently approved for adjuvant use in receptor-positive breast cancer in the United States belong to two distinct biochemical classes (Figure 2). The steroidal AI exemestane is a derivative of androstenedione that irreversibly occupies the aromatase substrate-binding site and may be considered an aromatase inactivator. Exemestane is approved as second-line treatment, after 2 to 3 years of tamoxifen, for early hormone receptor–positive breast cancer.

Nonsteroidal inhibitors such as anastrozole and letrozole bind reversibly to the cytochrome P450 domain of aromatase. Anastrazole is approved as first-line adjuvant treatment of hormone receptor–positive early breast cancer. Letrozole is currently approved as second-line treatment, within 3 months of completion of 5 years of tamoxifen, for early hormone receptor–positive breast cancer. Because they do not inhibit estrogen synthesis in functioning ovaries, AIs are not indicated for use in premenopausal or perimenopausal patients with breast cancer. All of these third-generation AIs inhibit aromatase activity by more than 98% and are more potent than earlier drug entities.[1,3]

Unique Aspects of AI-Associated Bone Loss

Treatment-associated bone loss after cancer therapies such as oophorectomy, cytotoxic chemotherapies (eg, doxorubicin and cyclophosphamide)[11], and endocrine therapies may be distinct from normal postmenopausal bone loss. Estrogen deprivation that occurs after ovarian ablation or during AI therapy is generally abrupt compared with that occurring postmenopausally. In addition, treatment-related bone loss may occur at an accelerated rate. The rate of bone loss is estimated at 2% annually during the first years after the onset of menopause, leveling out to ~1% during the next decade and thereafter.[12] In contrast, compared with untreated postmenopausal women, patients with breast cancer who receive AIs experience a rate of bone loss estimated at 2.6% per year.[13] Premenopausal women who receive AIs in combination with a gonadotropin-releasing hormone (GnRH) agonist to effect complete ovarian suppression, or with ovarian failure secondary to chemotherapy, have even higher rates of bone loss—approximately 7% annually.[14,15]

Low bone mineral density (BMD) is a critical factor associated with pathologic fracture. The risk to patients inherent in bone loss is underscored by the exponential increase in vertebral and hip fracture with decreasing BMD, expressed as the T score (Figure 3 and Table 1).[16] Decreases in bone density of 10% to 15% have been shown to approximately double the risk of fracture, and even modest BMD increases can offer substantial preventative benefit.[16] Cumulative increases in BMD of at least 5% have been achieved with bisphosphonates in postmenopausal osteoporosis.[17] Increased BMD with bisphosphonates may result from the remineralization of established bone formation units, rather than from an increase in new bone.

Bone Turnover Markers and AIs

Bone turnover markers are biochemical products of osteoblasts and osteoclasts that reflect bone turnover in the whole skeleton (Table 2).[18,19] Clinically useful osteoblast-derived formation markers include the bone-specific isoform of the enzyme alkaline phosphatase (BALP), the C- and N-terminal propeptides of type 1 collagen (PICP, PINP), and osteocalcin (OC). Markers of osteoclast-mediated bone resorption include the collagen breakdown products, C- and N-telopeptide cross-links (CTX, NTX), pyridinoline (PYD), deoxypyridinoline (DPD), and tartrate-resistant acid phosphatase (TRACP). Assays for the measurement of bone formation
markers (BALP and OC) and bone resorption markers (NTX, PYD, and DPD) are commercially available and approved by the US Food and Drug Administration.

Increases in bone turnover markers approaching 100% may result from decreased estrogen levels at menopause. [18] Similarly, postmenopausal patients with breast cancer who are treated with AIs have significantly higher levels of the urinary bone resorption markers PYD and DPD.[20] Data from the placebo arms of two large randomized trials on the treatment of bone metastases secondary to prostate, non–small-cell lung cancer and other solid tumors with zoledronic acid found baseline levels of both NTX and BALP were highly predictive of subsequent skeletal complications.[21]

Suppression of bone resorption and formation markers has been correlated with clinical outcomes[22] and with clinical response to antiresorptive therapy.[23] A recent study in 328 breast cancer patients with bone metastases found zoledronic acid therapy for 3 months resulted in normalization of bone marker levels in 76% of patients with elevated levels at baseline. Patients with normalized markers had significantly unproved survival compared to patients whose bone marker levels were not normalized.[22] Although these recent data suggest that bone marker data may someday be useful in predicting clinical outcome for patients at risk for skeletal events, bone marker monitoring is not yet considered reliable for screening or diagnostic purposes.[24,25]

**Clinical Experience With AI-Associated Bone Loss**

Results from randomized clinical trials continue to document the disease-free survival, and in at least one study, overall survival benefits of AIs over tamoxifen, but also reveal the problem of bone loss associated with AIs, primarily as adjuvant therapy (Table 3). Studies of AIs in the neoadjuvant and prevention settings are limited to date and several trials are ongoing. AIs have also been evaluated in advanced metastatic disease; however, it is difficult to distinguish bone health–related AEs from those related to disease progression in patients who may already have bone metastases.[3]

**Adjuvant AI Therapy in Early Breast Cancer**

The large Arimidex, Tamoxifen Alone or in Combination (ATAC) study compared anastrozole, tamoxifen, and the combination of both drugs as first-line adjuvant therapy in over 9,000 women. This trial included self-reported fracture as a predefined endpoint.[26] Among the 6,185 patients randomized to either drug as monotherapy, there was a significantly higher incidence of fracture with anastrozole (7.1%) compared with tamoxifen (4.4%) ($P < .0001$) at the 40-month safety follow-up. By completion of this 5-year trial, patients treated with anastrozole had experienced significantly more fracture (11%), representing a hazard risk of 1.44 compared with tamoxifen ($P < .0001$).[27]

In a subprotocol analysis of the ATAC trial, lumbar spine and total hip BMD was measured at several intervals.[28] Bone density in anastrozole-treated patients was lower at 1 year relative to baseline and was further decreased after the second year (~4.0%). The increasing fracture rate and lower BMD at longer follow-up suggest that AI-associated bone loss may not level off but rather may continue to progress over time. These effects are in contrast to the bone-protective effect of the SERM tamoxifen, which has partial estrogen-receptor agonist activity.

Several sequential (“extended therapy”) trials examined the efficacy and safety of AIs after completion of adjuvant tamoxifen. In the large MA. 17 trial, more than 5,000 patients were randomized to letrozole or placebo after 5 years of tamoxifen.[29] When this trial was terminated early and un-blinded at 2.5 years, safety analysis of the entire study population showed a nonsignificant trend toward more frequent diagnoses of new-onset osteoporosis and
self-reported fracture in the letrozole group compared with placebo. Updated results subsequently reported that significantly more women in the letrozole group experienced self-reported new-onset osteoporosis (8%) compared with placebo (6%, \( P = .003 \)).[30] The lower fracture rate in this trial compared with nonsequential trials may be explained by the bone-protective effect of 5 years prior treatment with tamoxifen.

A planned bone substudy of the MA. 17 trial examined bone resorption markers and BMD in a subset of patients who received letrozole and placebo and whose baseline BMD was > −2.0. Letrozole therapy significantly increased urinary excretion of the bone turnover marker NTC at 6, 12, and 24 months. Of clinical importance, letrozole caused significantly larger decreases in total hip BMD (−3.6% from baseline) compared with placebo (−0.71%; \( P = .044 \)).

In the Breast International Group (BIG) 1–98 trial, patients were randomized to four arms: upfront letrozole or tamoxifen for 5 years, 2 years of tamoxifen followed by 3 years of letrozole, and vice versa.[32] After slightly more than 2 years of follow-up, 5.7% of letrozole-treated women had experienced fracture compared with 4% of women receiving tamoxifen, representing a significant increase in relative fracture risk (\( P = .001 \)).

Two treatment arms of the ongoing Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial are comparing combined endocrine blockade using anastrozole plus the GnRH agonist goserelin (Zoladex) vs tamoxifen plus goserelin in premenopausal women with receptor-positive breast cancer.[14] The bone density subprotocol of this trial reported much higher significant bone loss with anastrozole plus goserelin: −17.4% from baseline at 36-month follow-up, with a relative T score of −1.7 (\( P < .001 \)).[33]

The Intergroup Exemestane Study (IES) evaluated the efficacy of exemestane after 2 to 3 years of adjuvant tamoxifen therapy.[34] In this randomized study, there was a trend toward more self-reported fracture and osteoporosis with exemestane, although the differences did not reach significance at 1-year follow-up. However, 1-year results of the bone sub-protocol of IES showed a significant worsening of BMD at the lumbar spine (\( P < .0001 \)), total hip (\( P = .0001 \)), and femoral neck (\( P = .0003 \)). The onset of bone loss was rapid—within 6 months of discontinuing tamoxifen.[35]

Another randomized study comparing adjuvant exemestane with placebo in early breast cancer reported a significant reduction in femoral neck BMD after 2 years of exemestane (2.72% annually vs 1.48% with placebo, \( P = .024 \)).[36] Significant bone loss was not observed at the lumbar spine. An additional year’s follow-up after discontinuation of exemestane showed that spine BMD recovered to near placebo level and femoral neck BMD also increased slightly, but remained lower than with placebo.[37] There are no head-to-head trials comparing effects on bone metabolism of the steroidal vs nonsteroidal AIs.

**Bisphosphonate Treatment of Ai-Associated Bone Loss**

Several bisphosphonates are currently available for the treatment of age-related or menopausal osteoporosis, as well as treatment and prevention of skeletal metastases in solid tumors. Although not approved for bone loss associated with cancer treatments, bisphosphonates have shown significant benefits in clinical trials. The magnitude of prevention of BMD losses and even some increases in BMD achieved with bisphosphonates—at least 5% cumulatively[17]—suggest that a proactive approach with this drug class may decrease fractures among patients with breast cancer.
Structure and Mechanism of Action

The two major classes of bisphosphonate differ structurally according to their variable side chains, which determine their pharmacokinetics and mechanism of action (Figure 4). They vary in potency by several orders of magnitude, with the non–nitrogen-containing bisphosphonates (clodronate [Bonefos, available only outside the United States] and etidronate [Didronel]) less potent in general than the nitrogen-containing entities, or aminobisphosphonates (alendronate [Fosamax], ibandronate [Boniva], pamidronate [Aredia], risedronate [Actonel], and zoledronic acid [Zometa]).[38] Preclinical studies showed zoledronic acid to be more potent than all other bisphosphonates in blocking osteoclast-mediated bone resorption. In an animal model of hypercalcemia, zoledronic acid was 850-fold more potent than pamidronate, and in an in vitro assay of bone calcium release it was 40- to 100-fold more potent.[39]

After binding to mineralized bone matrix, bisphosphonates are taken up by osteoclasts during bone resorption and inhibit cell activity via several mechanisms.[38] Non-nitrogen-containing bisphosphonates exert their effects primarily by conversion into toxic metabolites, whereas nitrogen-containing agents also inhibit enzymes in the mevalonate pathway. This inhibits protein synthesis, disrupts the cytoskeleton, and induces osteoclast apoptosis, as well as blocks osteoclast-osteoblast signaling. The net result of death and less recruitment and maturation of osteoclasts is the suppression of active bone remodeling.

Bisphosphonates for Cancer Treatment-Associated Bone Loss

The efficacy of bisphosphonates in treating bone loss associated with cancer therapies has been demonstrated in completed studies and ongoing clinical trials. In an early study, premenopausal women receiving adjuvant chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF]) for operable breast cancer were randomized to the non–nitrogen-containing oral bisphosphonate clodronate at 1,600 mg/d or placebo for 3 years.[40] The subset of patients who experienced CMF-induced premature ovarian failure (amenorrhea) had significantly less bone loss at the lumbar spine ($P = .0005$) and femoral neck ($P = .017$) with clodronate compared with placebo. In contrast, in a subsequent study, short-term IV clodronate (seven intermittent infusions) failed to preserve BMD in similar patients with therapy-induced ovarian suppression, although it significantly reduced levels of the bone turnover marker PINP at 3 and 6 months.[41] These data suggest that short-term intervention with clodronate does not have the same bone-protective effect as longer-term therapy.

The oral bisphosphonate risedronate sodium, given as 30 mg/d for 2 weeks of a 12-week cycle, was evaluated in a randomized trial of patients who had undergone premature ovarian failure after chemo- or radiotherapy for early breast cancer. [42] Risedronate therapy for 2 years preserved BMD at the lumbar spine (0.3% annual increase from baseline) while bone mass was lost with placebo (1.4% annual decrease, $P = .018$). Bone loss began upon discontinuation of the bisphosphonate.

Alendronate sodium, a nitrogen-containing bisphosphonate that has been successfully used to treat age-related postmenopausal osteoporosis, was evaluated in a small number of premenopausal women being treated with a GnRH agonist.[43] In this trial, oral alendronate at 10 mg/d largely prevented femoral bone loss and slightly increased BMD at the lumbar spine (by 1%, $P = .35$). Although alendronate prevented treatment-related bone loss, the increase in BMD was less than expected. Together, data from trials of oral bisphosphonates of this potency suggest that these agents are effective in blunting bone loss associated with AIs and other cancer treatments, but do not actually increase BMD.
Two IV bisphosphonates, pamidronate and zoledronic acid, have been examined in large trials of treatment-associated bone loss. Pamidronate has been shown to prevent bone loss associated with androgen-deprivation therapy for prostate cancer.[44] No trials of pamidronate for AI-associated bone loss in women with breast cancer have been conducted.

The third-generation bisphosphonate zoledronic acid is the most potent bisphosphonate currently available, as determined in animal models and in vitro assays. In the ongoing four-arm ABCSG-12 study, zoledronic acid at 4 mg was administered every 6 months in two treatment arms combining goserelin or tamoxifen with the AI anastrozole in premenopausal women.[14] As expected, at the 3-year analysis anastrozole/goserelin induced the most severe bone effects (17% lower BMD, relative T score of −1.6). Zoledronic acid effectively prevented short-term severe losses in BMD (P < .001) in these patients on complete endocrine blockade.

Clinical trials are currently investigating the optimal timing and dosing of zoledronic acid in early breast cancer. The Zometa-Femara Adjuvant Synergy Trial (Z-FAST) is testing whether zoledronic acid can prevent bone loss associated with the AI letrozole. Patients are randomized to receive early zoledronic acid at 4 mg every 6 months, or to delay treatment until their T score falls below −2.0 or they experience a fracture. At the 12-month analysis, patients receiving upfront bisphosphonate had increased BMD at the lumbar spine and total hip.[23] This was significantly better (P < .001 at both sites) compared with rapid bone loss seen in patients in the delayed group who required treatment initiation (4% by 6 months and 8% by 12 months). In addition, the bone turnover markers NTX and BALP were significantly suppressed from baseline (P < .001) with zoledronic acid. These data suggest that early intervention with a bisphosphonate may be of value, although only 8% of patients in the AI alone arm met protocol BMD criteria to initiate zoledronic acid at the 1-year follow-up time.

The Cancer and Leukemia Group B 79809 trial is another ongoing prevention trial for premenopausal patients with premature ovarian failure secondary to adjuvant chemotherapy for breast cancer. In this 3-year study, patients were randomized to zoledronic acid every 3 months either for the first 2 years of adjuvant therapy or for years 2 to 3 after chemotherapy initiation. The primary endpoint of this trial, lumbar spine BMD at 12 and 36 months, is hoped to clarify the benefit of immediate bisphosphonate therapy in patients at known risk for bone loss.

The North Central Cancer Treatment Group is conducting two prospective trials incorporating bisphosphonates in the setting of adjuvant therapy for patients with early breast cancer (N02C1 and N03CC, BA Mincey principal investigator). The N02C1 trial is seeking to enroll 220 premenopausal women receiving adjuvant chemotherapy, with randomization to oral risedronate once weekly or placebo starting with chemotherapy. The N03CC trial is enrolling postmenopausal women eligible to receive AIs after tamoxifen therapy of variable duration. All patients receive letrozole, with zoledronic acid added up front or delayed until BMD has decreased to below −2.0. Calcium and vitamin D supplementation are standard for all participants.[45] In another prospective trial being initiated by the same investigators, patients with baseline T scores below −2.0 at initiation of letrozole will receive zoledronic acid concurrently. This trial is designed to determine the ability of this bisphosphonate to prevent further bone loss in patients with some baseline bone health problems.

**Safety and Tolerability of Bisphosphonates**

The safety and tolerability profiles of bisphosphonates differ according to their route of administration. Most side effects observed during clinical trials and after approval have been mild to moderate in severity. More common adverse events reported with the oral drugs alendronate and risedronate include infection, back or abdominal pain, arthralgia, nausea, dysphagia, dyspepsia, and diarrhea. Intravenous bisphosphonates such as zoledronic acid are
also generally well tolerated, although infusion may be associated with fever and a flu-like syndrome consisting of fever, chills, bone pain and/or arthralgias, and myalgias. Less common but important side effects include gastrointestinal (GI) effects, renal toxicity, and osteonecrosis of the jaw (ONJ). [17,46–49]

**Gastrointestinal Effects of Oral Bisphosphonates**

Because they have the potential for GI toxicity, such as esophagitis and esophageal ulcers or erosions, alendronate and risedronate require that the patient remain upright for varying periods after taking medication. [17,46,47] In addition, the oral bisphosphonates are poorly absorbed and must be taken on an empty stomach. These GI side effects and dosing protocols may pose barriers to compliance. A retrospective study of over 11,000 women reported that patients on bisphosphonates who were at least 80% compliant experienced a 16% lower rate of fracture. [50] Outside the controlled setting of a clinical trial, patient adherence to the prescribed regimen may be variable and should be addressed. Monthly dosing of ibandronate is designed to alleviate compliance barriers associated with oral bisphosphonates. [47]

**Renal Function and Bisphosphonates**

Because of their high affinity for bone, the effects of bisphosphonates are largely tissue-specific. However, unbound bisphosphonates are not metabolized in vivo and are excreted intact by the kidney, with renal clearance linearly related to creatinine clearance (CrCl). There is a greater risk of renal and other adverse reactions when these drugs are used in patients with impaired renal function; the IV bisphosphonates zoledronic acid and pamidronate have been linked with generally reversible renal adverse events. [24,48,49] Neither oral nor IV bisphosphonates are recommended for patients with severe renal impairment (CrCl < 30 mL/min) and CrCl should be measured before each dose of zoledronic acid is administered. In order to maintain constant drug exposure, dosing should be adjusted according to CrCl in patients with mild to moderate impaired renal function (CrCl 30 to 60 mL/min). [48]

**Osteonecrosis of the Jaw**

Other safety concerns became apparent after approval of bisphosphonates. Osteonecrosis of the jaw is a serious and painful condition that has been reported in patients taking both IV and chronic oral bisphosphonates. [51,52] Because these drugs disrupt the homeostatic balance between osteoclasts and osteoblasts, they are hypothesized to interfere with normal bone healing after infection or trauma. A prospective study of 252 patients with myeloma or cancer metastatic to bone found that the incidence of ONJ varied by site of primary cancer and increased with longer exposure to bisphosphonates: from 1.5% after 4 to 12 months to 7.7% after 37 to 48 months. [53] Osteonecrosis of the jaw was significantly more frequent with zoledronic acid than with pamidronate. Advanced cancer or other morbidities, chemotherapy, and corticosteroids have been identified as contributing factors. [51,53] Physicians should be alert to the early symptoms of ONJ, which include changes in periodontal and mucosal tissues, soft-tissue infection or swelling, oral mucosal lesions that fail to heal, oral or jaw pain or numbness, and loose teeth. Severe ONJ may manifest as exposed mandibular or maxillary bone in the oral cavity. [51]

Although there are currently no consensus guidelines on prevention or management, recommendations have been established to minimize the risk of developing ONJ. [51] These include a complete dental examination with preventative dentistry before initiating IV bisphosphonates, avoiding invasive dental procedures whenever possible, and maintaining excellent oral hygiene. Treating ONJ once it develops is conservative, consisting of minimal bony debridement to reduce sharp edges, in addition to antibiotic therapy. [51] Patients who develop severe ONJ may require interruption or discontinuation of bisphosphonate therapy. [48,51]
For a more detailed discussion of ONJ, see the article by Catherine Van Poznak and Cherry Estilo on page 1053 of this issue.

**Emerging Therapies for AI-Associated Bone Loss**

An agent currently under investigation for preserving BMD in patients with cancer is AMG 162 (denosumab), a fully humanized monoclonal antibody directed against RANKL. Studies in animal models have shown that blockade of RANKL signaling may prevent bone loss caused by osteoporosis and malignant tumors.[6] A small placebo-controlled trial with AMG-162 in 49 postmenopausal women found that a single subcutaneous dose resulted in an antiresorptive effect up to 6 months, as measured by decreased bone markers.[54] Phase III trials of AMG-162 for preserving BMD in patients receiving hormone-ablative therapy for breast and prostate cancer have recently completed patient accrual.

Results from a randomized phase II trial presented in 2006 demonstrated that comparable decreases in bone biomarkers could be achieved with denosumab and intravenous bisphosphonates in patients with breast cancer metastatic to bone (at an intermediary time point of approximately 3 months).[55,56]

**Diagnosing and Preventing AI-Associated Bone Loss**

Some clinical trials of AIs in breast cancer were not initially designed to evaluate bone health as a primary end-point and did so only as subanalyses. Taken together, however, results of all trials suggest that treatment-associated bone loss is a serious side effect that should be addressed proactively.[57]

**Bone Loss Screening and Monitoring**

An American Society of Clinical Oncology (ASCO) 2004 status report concludes that postmenopausal patients with breast cancer who are treated with AIs are at high risk for osteoporosis and fracture, and recommends close monitoring of BMD and consideration of proactive measures, including bisphosphonates, to preserve bone health (Table 1).[1,24] The National Comprehensive Cancer Network clinical practice guidelines for breast cancer and the National Osteoporosis Foundation also recommend frequent monitoring for women on AI therapy.[25,58]

Dual-energy x-ray absorptiometry I (DXA) provides a two-dimensional measure of BMD and remains the cornerstone of bone health evaluation. The most clinically useful DXA parameter is the T score: the number of standard deviations above or below the mean peak bone density of a comparator population: 30-year-old healthy women. Osteoporosis is defined as a T score $-2.5$ and osteopenia (borderline osteoporosis) encompasses T scores between $-1$ and $-2.5$. Severe osteoporosis is defined as the presence of one or more pathologic fractures and a T score $-2.5$. All patients receiving AI therapy should have a baseline DXA scan. At present, examination of bone turnover biomarkers is not recommended for routine screening or diagnosis of bone loss.[25]

Secondary causes of bone loss such as hyperparathyroidism or collagen metabolism disorder should be ruled out.[25] Other risk factors for fracture should be identified and modified whenever possible in patients receiving AIs. These include corticosteroid use for more than 3 months, current smoking, a lifelong low Ca$^{++}$ intake, excessive alcohol intake (> 2 drinks/d), and limited physical activity. Additional factors are associated with falls that may result in fracture: poor vision, dementia, poor health in general or frailty, and a history of recent falls.

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Lifestyle Interventions to Minimize AI-Associated Bone Loss

Lifestyle choices and dietary habits have a large impact on bone health. Patients should be advised to limit alcohol intake, avoid excess caffeine, and quit smoking. Adequate dietary Ca\(^{++}\) and vitamin D are critical, with current recommendations calling for a Ca\(^{++}\) intake of at least 1,200 mg/d (Table 3).[25,59] While foods high in Ca\(^{++}\) (eg, dairy products, green leafy vegetables, canned fish with bones, and nuts) may help to achieve this intake, most women will require supplements taken in divided doses.

Maintaining adequate vitamin D status is equally important. Vitamin D promotes intestinal absorption of Ca\(^{++}\) and suppresses parathyroid hormone (PTH) production. Women at risk for bone loss should consume 400IU to 800 IU/d (Table 3).[7,25,59] Foods with a high vitamin D content (eg, fatty fish and oils, liver, fortified milk, and cereal) should be encouraged; however, dietary supplementation (most easily combined with Ca\(^{++}\)) is recommended. Daily sun exposure of 15 to 30 minutes is recommended to promote endogenous vitamin D synthesis. Women having no sun exposure should consume at least 1,000 IU/d.[60] Determination of vitamin D levels is best accomplished by measurement of the circulating form—25(OH) vitamin D3—and PTH levels. Low 25(OH) D3 and elevated PTH indicate vitamin D deficiency and the need for additional supplementation.

A recent chart review study reported that very few patients receiving adjuvant hormone therapy for early breast cancer actually met current guidelines for Ca\(^{++}\) and/or vitamin D supplementation, highlighting a modification that may be easy to implement, with a large clinical benefit.[61]

Patients should also be encouraged to participate in weight-bearing physical activity tailored to the patient’s age and health status to increase bone density and muscle strength.[25] A novel nonpharmacologic strategy to improve bone density that is based on beneficial effects of weight-bearing exercise has been evaluated in a prospective randomized trial in postmenopausal women.[62]

This biomechanical therapy, consisting of a low-magnitude, high-frequency vibration applied for 20 minutes daily, was found to significantly reduce bone loss at the spine and femoral neck. It was most effective in subjects who were most compliant, and especially women of lighter weight. Such an approach might be useful in combination with drug therapy in patients undergoing AI therapy who are physically unable to participate in weight-bearing exercise.

Drug Therapy for AI-Associated Bone Loss

The ASCO clinical guidelines recommend that all patients on AI therapy with documented osteoporosis (T score ≤ −2.5) initiate antiresorptive therapy with a bisphosphonate (alendronate, risedronate, or zoledronic acid).[24] Recognizing that bone health spans a continuum, guidelines state that bisphosphonates are optional for patients with T scores between −1 and −2.5. Recommendations from NOF differ slightly, using a T score of < −2 (rather than −2.5) as a threshold for bisphosphonate therapy, and scores between −1.5 and −2.0 call for bisphosphonates if other risk factors are present. These include a history of corticosteroid use exceeding 3 months, smoking, low Ca\(^{++}\) or high alcohol intake (> 2 drinks per day), limited physical activity, and factors that predispose to falls such as frailty or poor vision.[25] All patients on AI therapy should be monitored annually with DXA.

Bisphosphonate treatment guidelines may be considered conservative because they do not take into account that many fragility fractures occur in women with T scores above these thresholds. In addition, guidelines do not consider deleterious effects on bone health such as altered microarchitecture that cannot be as easily assessed as BMD. It should be remembered that, in contrast to the AIs, the SERMs tamoxifen and raloxifene (Evista) have a protective effect on
bone health in postmenopausal women. This distinction should be considered along with the superiority of the AIs in preventing breast cancer recurrence. Differences in the side-effect profiles of antiestrogens vs AIs should be the individualized decision-making process for patients.

Conclusions

Increased risk of fracture in breast cancer survivors is an important result to emerge from the large Women’s Health Initiative.[63] Survivors experience significantly more fractures at all skeletal sites except the hip—even after controlling for factors such as age, time since menopause, weight, and ethnicity, and the detrimental effects observed with AIs will place additional burden on an already at-risk population. According to the American Cancer Society, more than 200,000 new cases of breast cancer were diagnosed in the United States in 2005. [2] More than two-thirds of patients have estrogen receptor-positive disease (> 75% of women over 70 years of age) and an increasing number will be prescribed hormonal therapy. With the 5-year survival rate for stage I breast cancer now exceeding 95%, many women can expect to be treated with adjuvant AIs, either after or in lieu of other drugs.

The encouraging survival statistics mandate a growing need for early recognition, accurate diagnosis, and effective management of treatment-associated bone loss. Increasing awareness of this problem, as well as age-related osteoporosis, is spurring clinical development of novel drugs to increase bone quality. With educational outreach, health-care providers can enlist patients to actively participate in their care. By using available medical therapies, the survival benefits conferred by AIs do not have to be compromised by debilitating bone loss.

Acknowledgments

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References


45. Mincey BA, personal communication.


Figure 1. Mechanism of Action

— Estrogen regulates physiologic bone remodeling by suppressing osteoclast-mediated bone resorption. During aromatase inhibitor–associated or postmenopausal estrogen deficiency, bone resorption and osteoblast-mediated bone formation are imbalanced, leading to net bone loss.
Figure 2. Steroidal and Nonsteroidal Aromatase Inhibitors
—Letrozole and anastrozole are nonsteroidal third-generation aromatase inhibitors. The steroidal aromatase inhibitor exemestane is an analog of androstenedione, the androgenic substrate of aromatase.
Figure 3. Vertebral and Hip Fracture Risk
The risk of both vertebral and hip fracture is exponentially increased with increasing age and decreasing bone mineral density. Adapted from Cummings et al.[16]
Figure 4. Bisphosphonate Structure
—Bisphosphonates are structurally related to the mineralized bone matrix component pyrophosphate and belong to two general classes. The more potent nitrogen-containing bisphosphonates possess one or more nitrogen atoms in their variable side chains around the central carbon atom. Adapted from Reszka et al.[38]
## Table 1

### Treatment Guidelines for Patients With Breast Cancer on Aromatase Inhibitor Therapy

<table>
<thead>
<tr>
<th>DXA T Score</th>
<th>Diagnosis</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;−1</td>
<td>Normal</td>
<td>Annual DXA screening Ca++ intake ≥1,200 mg/d Vitamin D intake 400 to 800 IU/d</td>
</tr>
<tr>
<td>−1 to −2.5</td>
<td>Osteopenia</td>
<td>Consider bisphosphonate therapy if other risk factors present Annual DXA screening Ca++ intake ≥1,200 mg/d Vitamin D intake 400 to 800 IU/d</td>
</tr>
<tr>
<td>≤ −2.5</td>
<td>Osteoporosis</td>
<td>Initiate bisphosphonate therapy Annual DXA screening Ca++ intake ≥1,200 mg/d Vitamin D Intake 400 to 800 IU/d</td>
</tr>
<tr>
<td>≤ −2.5 (with ≥1 fragility fracture)</td>
<td>Severe osteoporosis</td>
<td>Initiate bisphosphonate therapy Annual DXA screening Ca++ Intake ≥1,200 mg/d Vitamin D Intake 400 to 800 IU/d</td>
</tr>
</tbody>
</table>

---

*a* Information from References 1, 25, and 56.

*b* National Osteoporosis Foundation recommendation is to initiate bisphosphonate therapy at a T score of ≤ −2 rather than −2.5.

DXA = dual-energy x-ray absorptiometry.
# Clinically Useful Bone Turnover Markers

<table>
<thead>
<tr>
<th>Osteoclast-Derived Resorption Markers</th>
<th>Measured In</th>
<th>Osteoblast-Derived Formation Markers</th>
<th>Measured In</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX</td>
<td>Serum or urine</td>
<td>BALP</td>
<td>Serum</td>
</tr>
<tr>
<td>C-telopeptide crosslink (C-terminal crosslink degradation product of type 1 collagen)</td>
<td></td>
<td>Bone-specific isoform of alkaline phosphatase (involved in mineralization, from Immature cells)</td>
<td></td>
</tr>
<tr>
<td>NTX</td>
<td>Serum or urine</td>
<td>PICP</td>
<td>Urine</td>
</tr>
<tr>
<td>N-telopeptide crosslink (N-terminal crosslink degradation product of type 1 collagen)</td>
<td></td>
<td>C-terminal propeptide of type 1 collagen (from immature cells)</td>
<td></td>
</tr>
<tr>
<td>PYD</td>
<td>Urine</td>
<td>PINP</td>
<td>Urine</td>
</tr>
<tr>
<td>Pyridinoline (free crosslink degradation product of type 1 collagen)</td>
<td></td>
<td>N-terminal propeptide of type 1 collagen (from immature cells)</td>
<td></td>
</tr>
<tr>
<td>DPD</td>
<td>Urine</td>
<td>OC</td>
<td>Serum</td>
</tr>
<tr>
<td>Deoxypyridinoline (free crosslink degradation product of type 1 collagen)</td>
<td></td>
<td>Osteocalcin (most cell-specific protein, from mature osteoblasts)</td>
<td></td>
</tr>
</tbody>
</table>

*Data from Gamero[18] and Demers[19]*
Table 3
Bone Mineral Density and Fracture Risk With Aromatase Inhibitors and Tamoxifen

<table>
<thead>
<tr>
<th>Trial</th>
<th>Endpoint</th>
<th>AI vs Comparator</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anastrozole vs Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC[26-28]</td>
<td>Lumbar spine BMD, 24 mo Fracture, 40 mo Fracture, 60 mo</td>
<td>4.0% 1.9% 1.9%</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.1% 4.4% 4.4%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.0% 7.7% 7.7%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td><strong>Letrozole vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA17[29–31]</td>
<td>Total hip BMD, 24 mo Osteoporosis, 30 mo</td>
<td>−3.6% −0.71% −0.71%</td>
<td>.044</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.0% 6.0% 6.0%</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Letrozole vs Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIG1-98[32]</td>
<td>Fracture, 24 mo</td>
<td>5.7% 4.0% 4.0%</td>
<td>.0006</td>
</tr>
<tr>
<td><strong>Anastrozole vs Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG-8/ARNO-95[33]</td>
<td>Fracture, 28 mo</td>
<td>2.4% 1.2% 1.2%</td>
<td>.015</td>
</tr>
<tr>
<td><strong>Anastrozole vs Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG-12[33]</td>
<td>Lumbar spine BMD, 36 mo</td>
<td>−17.4% 11.6% 11.6%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Exemestane vs Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES[34,35]</td>
<td>Lumbar spine BMD, 12 mo Total hip BMD, 12 mo Fracture, 31 mo</td>
<td>−3.17% −.19% −.19%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.15% −.58% −.58%</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1% 2.3% 2.3%</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Exemestane vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lonning et al [36,37]</td>
<td>Femoral neck BMD, 24 mo</td>
<td>−2.72% −1.48% −1.48%</td>
<td>.023</td>
</tr>
</tbody>
</table>

*a Both plus the GnRH agonist goserelin.

*b Annual rate calculated after 2 years.

AI = aromatase inhibitor; BMD = bone mineral density.