

How We Maintain Bone Health in Early-Stage Breast Cancer Patients on Aromatase Inhibitors

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We often confront the issue of advising otherwise healthy breast cancer survivors, who are likely to be long-term users of aromatase inhibitors (AIs), on the maintenance of bone health. Although our approach is largely based on the American Society of Clinical Oncology (ASCO) guidelines, we outline some practical considerations to this common problem.

Pathophysiology of Bone Loss

Bone construction and preservation are dynamic processes, given that bone is constantly formed by osteoblasts and resorbed by osteoclasts. Estrogens protect bone by stimulating osteoblasts and suppressing osteoclasts.¹ AIs decrease estrogen synthesis in postmenopausal women by suppressing aromatase activity, and this estrogen deprivation can be associated with bone loss. Tamoxifen can increase bone density because of its estrogen agonist effects in the postmenopausal bone. The consequences of bone loss can be measured through bone mineral density (BMD) and fracture rate. Measurement of BMD is used to establish the diagnosis of osteoporosis and to predict fracture risk.² The WHO defines osteoporosis as “a bone density that is 2.5 standard deviations (expressed as a *t* score) below peak bone mass or the mean bone density for young white adult women.”³ Of course the most clinically relevant end point of bone health is fracture rate because it is directly associated with morbidity and mortality.

Aromatase Inhibitors and Bone Health

Multiple clinical trials have demonstrated that all FDA-approved third-generation AIs (anastrozole, letrozole, and exemestane) can lower BMD and increase fracture rate.^{4–9} The two trials comparing AIs versus tamoxifen as initial adjuvant therapy (Arimidex, Tamoxifen, Alone or in Combination [ATAC] and BIG 1–98) demonstrated an absolute increase in fracture rate in the AI arm of 3.3% and 2.8%, respectively, compared with tamoxifen.^{4,5} Three trials comparing the strategy of five years of tamoxifen with a switch to AIs after 2 to 3 years of tamoxifen also revealed a significant increase in osteoporosis and fracture rate in the AI arm.^{6–8} For example, the IES trial showed that the exemestane switch arm had a 1.2% higher fracture rate than the tamoxifen arm.⁶ A negative effect on bone health was also noticed in the MA.17 trial, which compared letrozole versus placebo after 5 years of tamoxifen treatment. After median follow-up time of 30 months, 8.1% of women in the letrozole

arm versus 6% of women in the placebo arm were diagnosed with new onset of osteoporosis ($P = .003$), and 5.3% versus 4.6% patients suffered from clinical fracture ($P = .25$).⁹

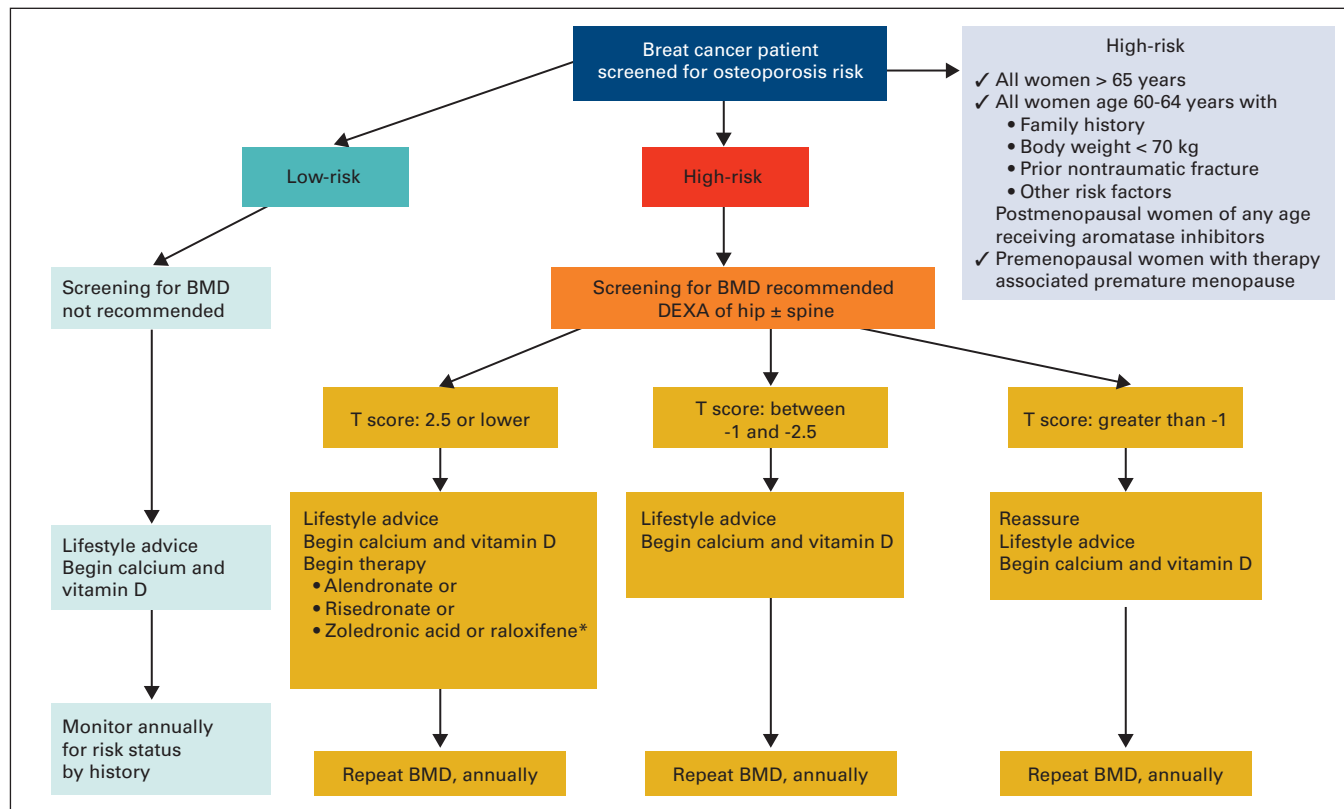
Our Approach to Bone Health Maintenance in AI Recipients

The 2003 ASCO guidelines on bisphosphonates and bone health identified AI therapy as a major risk factor for postmenopausal women to develop osteoporosis and fracture, and recommended a detailed and evidence-based algorithm to manage bone health of those women (Fig 1).¹⁰ When we are considering endocrine therapy in postmenopausal breast cancer patients, we evaluate fracture risk using prior fracture history, weight, smoking history, steroid use, and family history of osteoporosis and fracture. We obtain a dual energy x-ray absorptiometry (DEXA) scan to determine *t* scores in total hip (TH) and lumbar sacral (LS) regions. For all postmenopausal women breast cancer survivors, including those receiving AIs, we recommend a healthy bone lifestyle, which includes daily calcium intake of 1,200 to 1,500 mg, daily vitamin D intake of 800 units, avoidance of smoking and excessive alcohol intake, and weight-bearing activities at least three times weekly. We would also check their vitamin D level and initiate repletion as needed.

Risk Stratification Based on *t* Score

Initiation of bisphosphonate therapy is based on patients' risk factors and BMD. If the *t* scores are higher than -1.0 at all sites, we reassure patients that their fracture risk is currently low, encourage initiation or maintenance of a healthy bone lifestyle, and repeat DEXA scans periodically to reassess the risk of fracture. Conversely, if the *t* scores are lower than 2.5 at either site, we initiate bisphosphonate therapy and monitor BMD through annual DEXA scan. Our preference is to use one of the oral bisphosphonates such as alendronate, risedronate and ibandronate that cost about \$100/month. We rarely use intravenous (IV) bisphosphonate in these patients because of concern about potential renal toxicity, need for parenteral administration, lack of FDA approval for this indication, and higher price. With that being said, a recent randomized controlled trial has shown promise of once-yearly zoledronic acid in reducing fracture risk in postmenopausal women with osteoporosis.¹¹ We are watching with interest and may change our practice should FDA approve its use in osteoporotic patients. Although raloxifene is also used for management of osteoporosis in postmenopausal women, we do not use it in breast cancer survivors receiving AI because of

Figure 1. ASCO treatment algorithm for bone health in patients with history of breast cancer. BMD, bone mineral density; DEXA, dual energy x-ray absorptiometry.



its similarity to tamoxifen. Indeed the ATAC trial showed that the combination of tamoxifen with anastrozole produced inferior outcome compared with AI alone.⁴

The greatest challenge clinically is the management of patients receiving AIs with *t* scores between -1.0 and -2.5 . Whether to initiate bisphosphonate treatment in these women to prevent osteoporosis and fracture is an area of constant debate and active research. The ASCO guidelines recommend lifestyle alteration and yearly BMD evaluation, but do not recommend routine initiation of pharmacologic therapy for this population.¹⁰ We agree with these recommendations. Such therapy adds additional cost and adverse effects and the cost-effectiveness of initiating bisphosphonate therapy in this population has not been proved. Oral bisphosphonates are associated with GI symptoms and rarely osteonecrosis of the jaw, whereas IV bisphosphonates may cause renal failure, electrolyte imbalance, and jaw osteonecrosis. In the absence of evidence of clinical benefit in these women, we pursue the conservative course of watchful waiting. We are looking forward to the final results of two ongoing clinical trials, SABRE and Z-FAST trials that should refine our recommendations in the future.

Any postmenopausal woman with hormone receptor-positive, operable breast cancer who was to begin 5

years of anastrozole treatment was eligible for the SABRE trial. On the basis of screening DEXA scans, these anastrozole recipients were divided into three groups: high-risk group with *t* score less than -2.0 who will receive weekly risedronate for 2 years; low-risk group with *t* score more than -1.0 who will receive no bone agent, and the moderate-risk group with *t* score between -1.0 and -2.0 who are randomly assigned to risedronate or placebo. Initial results presented in 2006 demonstrated lower bone turnover and bone loss in patients receiving risedronate in the first 6 months. However, critical data regarding the difference in long-term effects, especially bone fracture, are not yet available.¹²

The Z-FAST/ZO-FAST study was designed to compare the effect of early versus delayed intervention with IV zoledronic acid in women with AI-associated bone loss. A total of 1,667 women with stage I to IIIA hormone-responsive breast cancer receiving letrozole with an LS or TH *t* score more than -2.0 were randomly assigned in an early-intervention arm that received zoledronic acid 4 mg IV every 6 months versus a delayed arm that started zoledronic acid only if the *t* score fell below -2.0 or a fracture was sustained. An interim analysis of this study in 2006 showed that, at 12 months, the early-start arm has a 2% increase in LS BMD and a 1% increase in TH BMD, whereas the delayed-start arm has a 3% decrease in LS BMD and a 2% decrease in TH BMD. The early-start arm

also experienced decreased bone turnover as evidenced by decreased bone turnover biomarkers, N-telopeptide, and bone-specific alkaline phosphatase. Among the 834 patients in the delayed-start arm, 89 patients have started taking zoledronic acid thus far. However, there is no difference in clinical fracture rate between the two arms at present, and more patients in the early arm (8% v 6%) experienced adverse effects associated with zoledronic acid treatment, such as renal failure, arthralgia, bone pain, and pyrexia.¹³

Finally, although there is little question that AIs are here to stay, we should recall that tamoxifen has a long and well-established track record in breast cancer and is known to reduce fracture rates. In our view, it remains a valuable

alternative to AIs in breast cancer patients with poor bone health or other significant adverse effects from AIs. Its significant antitumor and bone-preserving effects should not be forgotten.

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