Aromatase Inhibitor-Associated Bone Loss

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A 49-year-old postmenopausal Caucasian woman named M.A. was diagnosed with estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, HER2-negative breast cancer. Anthracycline and taxane-based adjuvant chemotherapy and radiation therapy were followed by adjuvant therapy with an aromatase inhibitor (AI). Before M.A. started adjuvant AI therapy, she was evaluated for any additional risks for bone loss or fractures. Her bone mineral density was measured by dual-energy x-ray absorptiometry of the lumbar spine and hip; follow-up bone evaluations were scheduled at 6, 12, and 24 months. M.A.'s age at the onset of menopause was 43, and she reported a family history of early menopause and osteoporosis with fragile hip fracture.

Considering M.A.'s early age of menopausal onset, baseline bone mineral density, and family history, the medical oncologist offered her the opportunity to participate in a clinical trial in which patients were randomized to receive an AI with or without concurrent bisphosphonate treatment. M.A. chose to participate in the trial (National Cancer Institute, Naples, 2010) and, after providing informed consent, was randomized to the study arm that included the addition of zoledronic acid therapy (4 mg via IV every six months) to letrozole (2.5 mg orally daily) for a planned duration of five years. Therapy was initiated after a dental examination to assess risk factors for osteonecrosis of the jaw, which yielded no pathology. The potential side effects of letrozole and zoledronic acid were discussed with M.A. She was advised to continue taking oral calcium (1 g per day) and vitamin D (400 IU daily) supplementation. The importance of adding a regular weight training exercise program, maintaining proper nutrition, and adhering to the treatment regimen also were reviewed with M.A.

Following six months of therapy, M.A. began an exercise program that included a weight-resistance training regimen. M.A. is now in her third year of adjuvant therapy, with no evidence of disease. She has received zoledronic acid every six months, and she continues to take letrozole daily. Of note, she has had no evidence of further AI-associated bone loss (AIBL). Bone mineral density T-score measurements by dual-energy x-ray absorptiometry scan of the lumbar spine and femur head remained stable in the two-year period following treatment with zoledronic acid.

Pathophysiology

Estrogen has growth-promoting effects in the majority of ER-positive and PR-positive breast cancers. Because of this, several approaches used to treat patients with these breast cancer subtypes involve blocking estrogenic effects or lowering estrogen levels (Burstein et al., 2010). Adjuvant endocrine therapy is designed to deprive tumor cells of the growth-promoting effects of estrogen (Perez, 2007) and, in the adjuvant setting, AIs have become the standard of care for postmenopausal women with ER-positive breast cancer (Cazzaniga et al., 2007). The AI-mediated mechanism of action involves blocking aromatase, an enzyme responsible for making small amounts of estrogen in postmenopausal women. AIs cannot block the synthesis of estrogen in the ovaries and, therefore, are most effective in postmenopausal rather than premenopausal women.

The third-generation AIs, which include the nonsteroidal formulations letrozole and anastrozole and the steroidal formulation exemestane, have demonstrated superior clinical efficacy when compared with the more traditional tamoxifen treatment, both as monotherapy and as sequential treatment (Burstein et al., 2010). In addition, all third-generation AIs have demonstrated almost complete suppression of plasma estrogen levels (Geisler, 2008).

Although AIs have improved survival in patients with breast cancer, they can have long-term detrimental effects on bone health (Clunie et al., 2009; Hadji et al., 2008, 2009). AI-induced estrogen depletion has been reported to result in musculoskeletal complications, including bone loss and osteoporotic fractures.

Bone tissue undergoes continuous resorption and formation cycles on a daily basis. Small amounts of bone mineral that are removed (resorption) by osteoclasts are balanced by equal deposition of new mineral (formation) by osteoblasts, preserving bone strength. Hormones, notably estrogen, are crucial modulators of bone formation. During menopause, natural decreases in estrogen are associated with perturbations in bone cycles, in which resorption typically exceeds formation, resulting in net bone loss, decrease in bone strength, and an increased fracture risk (Delaney, 2006).

Estrogen deprivation during AI therapy further enhances osteoclastic bone resorption. Bone loss associated with AI therapy is much more rapid than that seen in menopause, and a higher risk of fractures exists (Hadji, 2009). Bone loss seen during AI treatment appears to be similar for agents within this class of drugs, with the incidence of osteoporosis and fractures approximately 4% higher for patients receiving an AI compared to tamoxifen in primary adjuvant trials (Burstein et al., 2010).

Treatment and Management

Bone-related complications in patients undergoing AI therapy have received attention, resulting in an acknowledgment of the need for proper management and intervention to reduce bone loss and prevent fragility fractures (Bundred, 2009; Hadji et al., 2008). Despite evidence of AIBL, efficacy data, including reduced disease metastasis and a trend toward improved overall survival, outweighs bone fracture risk (Mouridsen et al., 2009).

Bisphosphonate treatment may prevent AIBL, although long-term follow-up studies are needed (Bundred et al., 2008; Hadji, 2009). Results from a combined trial

analysis evaluating the use of zoledronic acid for the prevention of AIBL indicate that zoledronic acid treatment initiated concurrently with the start of adjuvant therapy protects against AIBL and may improve clinical outcomes (Brufsky et al., 2006). A systematic review by Hadji et al. (2008) used an evidence-based medical approach to select risk factors for fracture in women with breast cancer, and eight risk factors were identified (see Figure 1).

Current guidelines advocate bone mineral density measurements (see Table 1) in all patients taking AIs and selective use of antiresorptive therapy in osteoporotic women (T score of –2.5 or lower) (Aapro et al., 2008; Bundred, 2009; Hadji, Ziller, Albert, & Kalder, 2010). Evolving data suggest that measuring biochemical markers of bone metabolism may provide additional information to help assess an individual's risk for fracture (Barginear, Clotfelter, & Poznak, 2009). Although bone loss and fractures are an important issue, strategies exist that may be combined with bisphosphonate therapy for effective management. These strategies may include lifestyle adjustments, such as muscle-strengthening exercises, reduced alcohol consumption, cessation of smoking, and dietary supplementation with calcium and vitamin D (Hadji et al., 2008). Given the significant benefits of AI therapy, including potential improvement in overall survival and reduction in disease metastasis, maintaining AI therapy and effectively managing adverse events are important. The benefits of superior disease control should always be considered in the context of the effective management of adverse events.

Table 1. World Health Organization Definitions Based on Bone Mineral Density Levels

Category	Bone Mineral Density Levels
Normal	Bone density is within 1 SD (1 or –1) of the young adult $\bar{X}$.
Low bone mass	Bone density is 1–2.5 SD below the young adult $\bar{X}$ (−1 to −2.5 SD).
Osteoporosis	Bone density is 2.5 SD or more below the young adult $\bar{X}$ (−2.5 SD or lower).
Severe osteoporosis	Bone density is 2.5 SD or more below the young adult $\bar{X}$, coupled with one or more osteoporotic fractures.

Note. From "Osteoporosis and Related Bone Diseases National Resource Center" by National Institutes of Health, 2009. Retrieved from http://www.niams.nih.gov/Health_Info/Bone/Bone_Health/bone_mass_measure.asp. Reprinted with permission.

Validated Risk Factors (Level of Evidence I)[a]
- Aromatase inhibitor therapy
- T score lower than −1.5
- Age older than 65 years
- Low body mass index (less than 20 kg/m^2)
- Family history of hip fracture
- Personal history of fragility fracture after age 50 years
- Oral corticosteroid use for more than six months
- Smoking (current and history of)

Possible Risk Factors[b]
- Chemotherapy
- Radiotherapy
- Low weight

[a] Validated in large clinical trials of healthy postmenopausal women (except aromatase inhibitor therapy)

[b] Could not be validated because of insufficient trial data

Figure 1. Risk Factors for Fracture in Women With Breast Cancer

Note. From "Practical Guidance for the Management of Aromatase Inhibitor-Associated Bone Loss," by P. Hadji, J.J. Body, M.S. Aapro, A. Brufsky, R.E. Coleman, T. Guise . . . M. Tubiana-Hulin, 2008, *Annals of Oncology, 19,* p. 1409. Copyright by Oxford University Press. Adapted with permission.

Implications for Nursing Practice

Because of the extended duration of adjuvant endocrine therapy, patient tolerability issues and their potential influence on adherence, therapeutic outcome, and quality of life are important concerns (Mortimer, 2010). Although AIs have improved survival in patients with breast cancer, they can have long-term detrimental effects on bone health (Clunie et al., 2009; Hadji et al., 2008, 2009). Estrogen has a negative regulatory effect on bone resorption; therefore, any therapy that depletes estrogen has the potential to cause bone loss. In addition, many patients with breast cancer already are at an increased risk for osteoporosis because of age and possible disease-related bone loss. Potential treatment-related bone loss may represent additional risk (Gralow et al., 2009).

Because AI therapy is recommended for postmenopausal women with breast cancer, screening for and managing bone complications in these women is important. A combination of risk factors (e.g., age, T score, body mass index, family and personal history, smoking) may be used to determine the optimal treatment plan to preserve bone integrity. Although no treatments are approved specifically for AIBL, patients at high risk for rapid bone loss may benefit from bisphosphonate therapy, along with adequate calcium and vitamin D supplementation. Renal toxicity and osteonecrosis of the jaw are potential complications for patients with cancer on bisphophonate therapy. Osteonecrosis of the jaw has a reported incidence of 4%–6% in patients with breast cancer receiving an IV or oral bisphosphonate (Gebara & Moubayed, 2009), and risk is increased for patients who undergo invasive dental procedures. Patients should have baseline dental evaluation and continue at six month intervals while receiving bishphophonates. Renal function should be evaluated at baseline at least every six months. In addition, nurses can educate patients on the importance of various healthy lifestyle changes, including muscle-strengthening exercises, reduced alcohol consumption, and cessation of smoking (Hadji et al., 2008). Managing bone health, in accordance with consensus clinical guidelines, is vital in patients receiving AI therapy so they can continue to receive the anticancer benefits of AIs. Patient assessment and education about the treatment plan, the risks, and the importance of adherence, conducted both before and during therapy, are key nursing responsibilities.

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Clinical Highlights: Aromatase Inhibitor-Associated Bone Loss

Definition and Pathophysiology

Aromatase inhibitor-associated bone loss is a potential risk for patients with breast cancer receiving aromatase inhibitor (AI) adjuvant therapy. AIs are recommended in adjuvant treatment for postmenopausal women with hormone-positive (estrogen receptor and progesterone receptor) breast cancer (Burstein et al., 2010). AIs deprive tumor cells of the growth-promoting effects of estrogen by blocking aromatase, an enzyme responsible for making small amounts of estrogen in postmenopausal women (Perez, 2007). Because estrogen has a negative regulatory effect on bone resorption, any therapy that depletes estrogen has the potential to cause bone loss. Many patients with breast cancer are already at an increased risk for osteoporosis because of age and possible disease-related bone loss. Although the mechanisms of action of the steroidal and nonsteroidal AIs are somewhat different, adverse effects on bone health have been observed with all AIs, with a higher incidence of osteoporosis and fractures compared to tamoxifen.

Clinical Presentation

All patients receiving AIs should be evaluated for potential bone-related complications at baseline and throughout therapy. Measuring baseline bone mineral density and identifying potential risk factors for fractures at baseline is key because bone loss is not usually symptomatic until it advances to frailty and a deformation or fracture occurs. A T score of –1.5 or less, age 65 years and older, low body mass index, family or personal history of hip fracture, and smoking are validated risk factors for fracture in this population (Hadji et al., 2008).

Diagnosis and Treatment

Aromatase inhibitor-associated bone loss differs from postmenopausal osteoporosis because it progresses much more rapidly and is more often associated with fractures. Regular bone mineral density measurements should continue throughout treatment, at least every two years, and patients also should be monitored for any other changes in risk factors. Vitamin D and calcium supplements should be given to all patients receiving AIs. Current guidelines advocate the use of antiresorptive therapy (bisphophonates) in osteoporotic women (T score of –2.5 or less). Emerging data is supporting a more comprehensive evaluation of bone health that incorporates risk factors and baseline T scores; and research is being conducted to determine whether patients with normal or low bone mass associated with two or more risk factors may benefit from upfront use of bisphosphonate therapy to prevent fractures (Hadji et al., 2008). Patients must have baseline renal and dental assessments before beginning therapy with a bisphophonate, and continue assessments at least every six months throughout therapy.

Implications for Nursing Practice

Because of the extended duration of adjuvant endocrine therapy, patient tolerability issues and their potential influence on adherence, therapeutic outcome, and quality of life are important concerns (Mortimer, 2010). Although AIs have improved survival in patients with breast cancer, they can have long-term detrimental effects on bone health (Clunie et al., 2009; Hadji et al., 2009). Screening for and managing bone complications in these women are important. A combination of risk factors (e.g., age, T score, body mass index, family and personal history, smoking history) may be used to determine the optimal treatment plan to preserve bone integrity. Nurses play an important role in educating patients on the importance of various healthy lifestyle changes, including muscle-strengthing exercises, reduced alcohol consumption, and cessation of smoking along with adequate calcium and vitamin D supplementation (Hadji et al., 2008; Thorne, 2007).

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