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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