Published in final edited form as:

Community Oncol. 2008 November 1; 5(11): 625–626.

AIs: implications for fractures in perimenopausal women with breast cancer

Beatrice J. Edwards, MD, MPH¹, Athena Samaras, BA^{2,3}, June M. McKoy, MD, MPH, JD^{1,2,3,4}, Simone Boyle, BA^{2,3}, and Charles L. Bennett, MD, PhD, MPP^{2,3,4}

¹Bone Health and Osteoporosis Program and Division of Geriatric Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

²Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL

³The Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

⁴VA Midwest Center for Management of Complex Chronic Care, Jesse Brown VA Medical Center, Chicago, IL

Aromatase inhibitors (AIs) prevent the conversion of adrenal androgens into estrogens by the enzyme aromatase and thus impede the majority of estrogen production in peri- and postmenopausal women. By lowering estrogen levels, AIs inhibit tumor progression. Unlike other hormonal therapies, AIs produce no clinically relevant suppression of cortisol or aldosterone. Additionally, several large randomized trials comparing AIs with tamoxifen as first-line treatment of metastatic breast cancer have demonstrated similar or slightly superior clinical efficacy. Because of these attributes, AIs have become a widely popular breast cancer treatment in postmenopausal women.

Recent instances of increased fracture risk have been reported among perimenopausal women using AI treatment. The use of AIs in perimenopausal women can decrease estrogen levels by approximately 90%, leading to the onset of premature menopause, increased bone turnover, and accelerated bone loss.¹ The effects of AI-induced estrogen loss are less severe among pre- and postmenopausal women. Because estrogen is vital for maintaining bone health, perimenopausal women with breast cancer, like their menopausal counterparts, have demonstrated an increased risk of fractures while using AIs. In this article, investigators affiliated with RADAR (Research on Adverse Drug events And Reports), an established pharmacovigilance program, reviewed clinical trial reports and one observational study to determine the frequency and clinical characteristics of AI-associated fractures in menopausal women with breast cancer.

Associated toxicities

In clinical trials, women using AIs have experienced accelerated bone loss, osteoporosis, and fractures. A retrospective analysis of 12,000 patients with breast cancer taking AIs found that the risk of bone loss was 27%, significantly higher (after adjusting for age and comorbidities) than in the non-AI group, where risk of bone loss was 21%.²

The Arimidex, Tamoxifen, Alone, or in Combination trial demonstrated that anastrozole was superior to tamoxifen in terms of disease-free survival, time to recurrence, and incidence of contralateral breast cancer. Safety analysis showed that musculoskeletal disorders and fractures were significantly more common in the anastrozole group (30.3% and 7.1%, respectively) versus the tamoxifen group (23.7% and 4.4%, respectively).³

We evaluated four cases of hip fractures in women (mean age, 54) undergoing therapy for breast cancer (stage 1/2B). Only one woman was on calcium, vitamin D, and bisphosphonate therapy. Chemotherapy-induced early menopause occurred in all women (mean age, 43 ± 2), all of whom had received doxorubicin and cyclophosphamide along with adjuvant therapy that included anastrozole. Bone mineral density (BMD) testing showed bone loss (osteopenia) with a mean spine BMD of 0.804 g/cm^2 and a T-score of -2.25 ; contralateral hip BMD was 0.674 g/cm^2 with a T-score of -2.1 . Notably, these patients on AIs experienced fractures at younger ages and at relatively higher BMDs, suggesting that AIs may be affecting the bone microarchitecture.

Fast Facts

Anastrozole (Arimidex) is the first aromatase inhibitor (AI) to be approved by the US Food and Drug Administration (FDA) for first-line treatment of estrogen-sensitive breast cancer in postmenopausal women. In 1996, anastrozole received FDA approval as second-line therapy for advanced breast cancer in postmenopausal women with disease progression after antiestrogen therapy (namely tamoxifen). Since then, several newer AIs have emerged and now include two third-generation agents: exemestane (Aromasin) and letrozole (Femara).¹ AIs may be used as primary therapy but are usually prescribed for women with breast cancer who have taken tamoxifen for 2–5 years. AIs should be considered in women who develop invasive estrogen-sensitive breast cancer while taking tamoxifen or who find tamoxifen's side effects intolerable.

Hip fractures result in functional impairment and physical disability in women aged 65 and older. In two of the four perimenopausal breast cancer survivors we evaluated, hip fractures resulted in difficulty ambulating, even 12 months later. Hip fractures may therefore result in long-term physical impairment among breast cancer survivors. Further research in this area is needed.

Recommendations

Management of long-term bone health is emerging as an important aspect of comprehensive cancer care. Considering that patients with cancer typically have several other risk factors for osteoporosis, screening for this bone disorder should be initiated, regardless of a patient's age or gender. Clinical risk factors for fractures among breast cancer patients include smoking, moderate alcohol use, glucocorticoid use, advanced age, and chronic illness (hyperthyroidism, inflammatory bowel disease, hyperparathyroidism). Familial history of fractures as well as height loss should also be monitored. Furthermore, because of the adverse impact of AIs on bone health, oncologists should recommend BMD evaluation to allow for early detection of low bone mass and osteoporosis.

Should low bone mass or osteoporosis be detected, supplementation with calcium and vitamin D and use of bisphosphonates are critical to obviating the deleterious effects of these important cancer agents on the bones of perimenopausal women. This recommendation is in concert with guidelines from the National Comprehensive Cancer Network⁴ and the American Society of Clinical Oncology.⁵ If a BMD test shows bone loss, or osteopenia with a T-score -2.0 (without additional clinical risk factors) or -1.5 (with clinical risk factors), therapy with bisphosphonates should be initiated.⁶

References

1. Eastell R, Hannon R. Long-term effects of aromatase inhibitors on bone. *J Steroid Biochem Mol Biol* 2005;95:151–154. [PubMed: 15970439]

2. Mincey BA, Duh MS, Thomas SK, et al. Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors. *Clin Breast Cancer* 2006;7:127–132. [PubMed: 16800971]
3. Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003;98:1802–1810. [PubMed: 14584060]
4. Theriault RL, Biermann JS, Brown E, et al. NCCN Task Force Report: Bone Health and Cancer Care. *J Natl Compr Canc Netw* 2006;4 suppl 2:S1–S20.
5. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: status report 2002. *J Clin Oncol* 2002;20:3317–3327. [PubMed: 12149306]
6. Chien AJ, Goss PE. Aromatase inhibitors and bone health in women with breast cancer. *J Clin Oncol* 2006;24:5305–5312. [PubMed: 17114665]

Biography

Dr. Bennett is Associate Director of the VA Center for Management of Complex Chronic Care, Jesse Brown VA of the Chicago Healthcare System, Chicago, IL. He is also affiliated with the Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, and the Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL. He can be reached at cbenne@northwestern.edu.