Aromatase Inhibitors: How much it Bites the Bone?

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Abstract- Tamoxifen in treatment of breast cancer is replaced by aromatase inhibitors (AI's) which blocks and prevent estrogens by inhibiting aromatase enzyme. Treatments in breast cancer, such as oophorectomy, gonadotropin-releasing hormone (GnRH) agonists, chemotherapy and AIs, all decrease endogenous estrogens and cause significant decrease in bone mineral density (BMD) leading to bone loss and increase the risk of fractures. There is evidence to suggest that various musculoskeletal issues (pains) may be associated with low circulating estrogen levels. The most important and efficient step in preventing AI induced fracture risk is to assess for other clinical risk factors for osteoporosis before initiating AIs. The most robust non-BMD risk factors are age and prevalent fracture. The various steps in prevention of AIs induced fracture are.
1. Healthy and active lifestyle.
2. Regular Vitamin D and Calcium supplements.
3. Vigilant Monitoring of affected areas.

Index Terms- aromatase inhibitors, bone metastasis, fracture.

I. INTRODUCTION

Breast cancer is the most common malignancy in women. It is estimated that in 1999, 30% of new cancer cases arose in this site, 176,300 cases were diagnosed and almost 44,000 women died. Bone is the most common site of metastasis in patients with breast cancer.[1] Fisher et al examined the site of first metastasis lesion in women undergoing radical mastectomy and found that bone was the initial site in 26% however; a substantially larger proportion of patients will ultimately develop metastasis to bone.[2] Median survival with metastatic breast cancer varies widely depending on the site(s) of involvement. In the past twenty years the role of tamoxifen has been greatly challenged by aromatase inhibitors. AI(s) block or prevent estrogens from stimulating the growth of cancer by inhibiting Aromatase from converting androgens into estrogen.[3]

They induce an increase in gonadotropin secretion secondary to the reduced negative feedback of estrogen to the pituitary, leading to ovarian stimulation and a potential increase in ovarian size which may result in ovarian cysts. The primary source of estrogen in premenopausal women is the ovaries; the primary source in postmenopausal women is the adrenal gland, where aromatase converts adrenal androgens to estrogens. AI(s) prevent conversion of androgens to estrogens leading to rapid decrease in circulating estrogen.[4]

Etiology of AIs induced bone loss: All modalities of Breast cancer treatments, such as surgical oophorectomy, hormonal therapy like GnRH agonists, chemotherapy and aromatase inhibitors (AIs), all decrease endogenous estrogens and cause bone loss and increase the risk of fractures.[5] The more sudden and severe the estrogen deprivation occurs, the greater the magnitude of bone loss.[6] Boneloss is most rapid in premenopausal women receiving both ovarian suppression therapy (GnRH agonist) and an AI.

Incidence of musculoskeletal events and fractures in patients using AI(s): Musculoskeletal issues, including joint pains, are a very significant issue for patients taking AIs and can result in non-adherence. The incidence of joint complaints ranged from 20% to more than 30% in the pivotal AI trials, and was significantly higher in patients receiving AIs compared with those treated with tamoxifen.[8] Almost 50% of the patients using AI(s) complained of vague musculoskeletal issues which were often under-reported in several trials. The IES [Intergroup Exemestane Study] trial more precisely defined the musculoskeletal events as arthritis, osteoarthritis, arthralgias, carpal tunnel syndrome, or musculoskeletal pain.[9] These effects may be contributed to decreased levels of circulating estrogens. A retrospective analysis of the ATAC trial suggested that the presence of joint symptoms may be associated with a decreased risk for recurrence,[10] although such an association was not confirmed in an analysis of the MA.27 trial.[11]

In several of the AI trials, fracture data has been reported.[12] In a meta-analysis of seven trials comparing AIs to tamoxifen in postmenopausal women with early stage breast cancer, use of AIs significantly increased the risk of bone fractures (OR 1.47, 95% CI 1.34-1.61).[13] The major drawback of these trials were that fracture outcomes were not the primary endpoints; therefore, fracture and other skeletal events were collected as adverse events as part of a long-term safety and tolerability assessment. With exception of the MA-17 trial, all adjuvant AI trials demonstrated a significant increase in the rate of overall fractures compared with tamoxifen. The MA-17 trial examined the efficacy of letrozole versus placebo in postmenopausal women who had completed five years of tamoxifen therapy. Of 5149 women, 256 had a clinical fracture (5.3 percent of patients assigned to letrozole compared with 4.6 percent assigned to placebo).[14] In the ATAC trial comparing anastrozole with tamoxifen described above, the annual incidence of fractures was higher in women receiving anastrozole (11 versus 7.7 percent) throughout the five years of treatment.[15] However, beginning in the sixth year, the fracture rate decreased in the women previously assigned to anastrozole treatment such that in years seven to nine the fracture rates with both treatments were similar.[16] This suggests that AI-related fracture rates will decrease upon cessation of the drug.

Prevention: The most easy and effective tool to assess bone loss and increased fracture risk in patients before starting AI(s) is a routine BMD (bone densitometry). The American Society of Clinical Oncology (ASCO) recommends BMD testing (DXA) for postmenopausal women taking AIs and for premenopausal women who develop treatment-related premature menopause following treatment.[19] In several of the AI trials, BMD and bone turnover markers were evaluated in a subset of women. BMD of the lumbosacral (LS) and total hip (TH) were significantly reduced in postmenopausal women receiving AIs versus tamoxifen or placebo.[7] Recommendations for Aromatase Induced Bone Loss (AIBL)[17]:

1. All patients initiating AI therapy should receive calcium and vitamin D supplements.
2. Any patient initiating or receiving AI therapy with a T-score ≥−2.0 and no additional risk factors should be monitored every 1–2 years for change in risk status and bone mineral density (BMD).
3. Any patient initiating or receiving AI therapy with a T-score <−2.0 should receive bisphosphonate therapy.
4. Any patient initiating or receiving AI therapy with any two of the following risk factors—T-score <−1.5, age >65 years, low BMI (<20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use >6 months, and smoking—should receive bisphosphonate therapy.
5. BMD should be monitored every 2 years, and treatment should continue for at least 2 years and possibly for as long as AI therapy is continued.
6. To date, the overwhelming majority of clinical evidence supports zoledronic acid 4 mg every 6 months to prevent bone loss in women at high risk. Although there is a trend towards fewer fractures with zoledronic acid, studies completed to date have not been designed to capture significant differences in fracture rate, and longer follow-up is needed

Thus, fracture risk assessment should include evaluation of the following:

- Clinical risk factors for osteoporosis
- Bone mineral density (BMD) measured by dual energy x-ray absorptiometry (DXA)
- Several groups have published recommendations for the evaluation of fracture risk in women initiating AIs.

These guidelines for evaluating bone density were developed largely from guidelines for screening, monitoring, prevention, and treatment of osteoporosis in postmenopausal women.[18] Apart from AIs there are various other factors which lead to enhanced bone loss in postmenopausal breast cancer patients, some of them are listed below:

- Advancing age
- Prior history of fragility fracture
- Chronic glucocorticoid use
- Low BMI
- Parental history of hip fracture
- Cigarette smoking, and excess alcohol

A thorough check should be made regarding these factors and if found should be corrected.

Management of AIBL: (DO's and DON'T's)

1. Laboratory evaluation — All women being initiated on AIs should have a serum calcium level and serum Vitamin D3 levels checked routinely, as most of the women may have one of these deficiencies as the secondary cause of bone loss which might need primary correction. In a retrospective study of women (64 with breast cancer) referred to a bone health clinic during a six-year interval, 78 percent of the women with breast cancer had at least one secondary cause of bone loss, other than cancer or cancer-related therapies.[20] The most common finding was vitamin D insufficiency (38 percent with vitamin D <30 ng/mL [74.9 nmol/L]). Suggested intake of elemental calcium is 1200 mg (total diet plus supplement) and 800 international units of vitamin D daily. In women with low vitamin D levels (25-hydroxyvitamin D level <20 ng/mL), vitamin D supplementation should be provided prior to therapy with bisphosphonates. Other causes of bone loss included idiopathic hypercalciuria and normocalcemic hyperparathyroidism. Women with low bone mass (T-score below -2.5) who are initiating or already taking AIs should have the following basic tests.

- Biochemistry profile (especially calcium, phosphorous, albumin, total protein, creatinine, liver enzymes including alkaline phosphatase, electrolytes)
- 25-hydroxyvitamin D
- Complete blood count

2. Non-pharmacologic intervention: Women are encouraged to adopt lifestyle changes that promote not only bone health but overall health as well. These include increasing physical activity including weight bearing exercise, reducing or stopping smoking and taking calcium and vitamin D supplements.[21]
3. Pharmacologic intervention: The pharmacologic agents available for the prevention of aromatase inhibitor (AI)-induced bone loss in postmenopausal women are bisphosphonates and denusumab.

- Bisphosphonates— Bisphosphonates are specific inhibitors of osteoclast-mediated bone resorption.[22] They are considered first-line pharmacologic therapy for postmenopausal women with osteoporosis. In several randomized trials, bisphosphonates prevented or reduced bone loss in women receiving AIs.[23] In a meta-analysis of six trials evaluating bisphosphonates in women with breast cancer receiving AIs, bisphosphonates did not significantly decrease the number of fractures compared with placebo or no treatment (OR 0.79, 95% CI 0.53-1.17).[24] The wide confidence interval fail to emphasize the impact of bisphosphonates on prevention of AI induced fractures. The two largest randomized trials were the Zometa-Femara Adjuvant Synergy Trials (Z-FAST and ZO-FAST). In both trials, zoledronic acid (4 mg every six months) was evaluated for prevention of AI-induced bone loss. Postmenopausal women with estrogen receptor-positive early-stage breast cancer who were

receiving adjuvant letrozole were randomly assigned to immediate treatment with ZA for five years or to delayed administration (when spine or hip T-score decreased to <-2.0 or the occurrence of fracture).[25] All patients received 500 mg of calcium and 400 to 800 international units of vitamin D. The SABRE trial was designed to evaluate the effect of weekly oral risedronate on bone loss in postmenopausal women receiving anastrozole. In the SABRE trial, postmenopausal women receiving anastrozole were stratified by their baseline T-scores into low risk (T-score of ≥-1.0), moderate-risk (T-score between -1.0 and -2.0), and high risk (T-score <-2). The women with moderate risk were randomized in a double-blind fashion to receive oral risedronate 35 mg/week or placebo, whereas women at low risk received anastrozole alone and women at high-risk received anastrozole and risedronate.[26] After 24 months, there was a significant difference in the change in LS and TH BMD from baseline in moderate risk women, favoring risedronate (2.2 versus -1.8 percent and 1.8 versus -1.1 percent, respectively). LS and TH BMD increased significantly (2 to 3 percent) in women in the high risk group and LS decreased significantly (-2.1 percent) in the low risk group.

Choosing a candidate for bisphosphonate therapy should be based upon a combination of BMD and clinical risk factors which quantify the fracture risk probability.

- Denosumab is a fully human monoclonal antibody for the treatment of osteoporosis and treatment-induced bone loss. Denosumab is designed to target RANKL (RANK ligand), a protein that acts as the primary signal for bone removal. Bone remodeling (or bone metabolism) is a lifelong process where mature bone tissue is removed from the skeleton (a process called bone resorption) and new bone tissue is formed (a process called ossification or new bone formation). These processes also control the reshaping or replacement of bone following injuries like fractures but also micro-damage, which occurs during normal activity. Remodeling responds also to functional demands of the mechanical loading. In the first year of life, almost 100% of the skeleton is replaced. In adults, remodeling proceeds at about 10% per year.[27] An imbalance in the regulation of bone remodeling's two sub-processes, bone resorption and bone formation, results in many metabolic bone diseases, such as osteoporosis.[28] To summarise all patients initiating AIs should be thouroughly screened for other clinical risk factors leading to osteoporosis and fracture. The most robust non-BMD risk factors are age and prevalent fracture. All women should be encouraged to adopt lifestyle changes that promote not only bone health but overall health as well.

Not all women receiving AIs require treatment with pharmacologic therapy. Risk stratification based upon baseline BMD T-scores and clinical risk factors justifies the use of bisphosphonates. Denosumab is an alternative option for women who do not tolerate bisphosphonates. The choice of bisphosphonates depends upon patient preference and cost. Oral therapy with risedronate or alendronate should be favored as initial therapy. However, zoledronic acid is an option if the patient does not tolerate oral bisphosphonates. The optimal schedule and duration of ZA has not been defined for AI-induced bone loss.

Screening for AIBL is still an evolving area which should be taken care of diligently in all patients who are administered AIs. More and more emphasis should be placed on clinical examinations and laboratory evaluations and scans should be reserved for symptomatic patients.

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