Journal of Osteoporosis & Physical Activity

Razaq et al., J Osteopor Phys Act 2015, 3:3
DOI: 10.4172/2329-9509.1000155

Review Article Open Access

Aromatase Inhibitors and Osteoporosis - Risk, Prevention and Treatment Review

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Abstract

Breast cancer is the most common cancer diagnosed and second leading cause of death among women in United States. Surgical resection with or without radiation remains the cornerstone of treatment for early stage breast cancer. Systemic adjuvant therapy with Tamoxifen or Aromatase Inhibitors (AIs) is indicated for Estrogen/Progesterone receptor (ER/PR) positive non metastatic breast cancer, depending upon their menopausal status. AIs are the drug of choice in postmenopausal women. They block or prevent estrogens from stimulating the growth of cancer by inhibiting aromatase from converting androgen into estrogen. According to an updated 2004 assessment from the American Society of Clinical Oncology, AIs are recommended to be used in adjuvant therapy initially or after Tamoxifen use for postmenopausal women with ER/PR positive breast cancer.

Keywords: Early breast cancer; Hormonal therapy; Bone loss; Osteoporosis; Risk prevention; Treatment

Abbreviations: AIs: Aromatase Inhibitors; ER/PR: Estrogen/Progesterone Receptor; ATAC: Arimidex Tamoxifen Alone or in Combination; BMD: Bone Mineral Density; ASCO: American Society of Clinical Oncology; USPSTF: US Preventive Services Task Force; WHO: World Health Organization; NOF: National Osteoporosis Foundation

Introduction

AIs significantly suppress plasma estrogen levels in postmenopausal women. Unlike Tamoxifen, AIs do not have partial agonist activity. The partial agonist activity by Tamoxifen may be beneficial since it may help prevent bone demineralization in postmenopausal women but is also detrimental because of increased risk of uterine cancer and thromboembolism [1-4].The third generation AIs was found to be more potent than first generation AIs (Aminoglutethimide) and are better tolerated [5]. The increased potency of the third generation inhibitors is associated with better clinical efficacy than that offered by aminoglutethimide or second generation inhibitor fadrozole. The mean degree of estrogen inhibition with third generation AIs is greater than 97% as compared to 90% for first generation AI [6-8]. Hence, the third generations AIs are a standard of care for preventing recurrence and treating metastatic breast cancer in postmenopausal women [9]. AIs appear to be very well tolerated with remarkably low incidence of short term adverse events. Common side effects are hot flashes, vaginal dryness, musculoskeletal pain and sometimes headache. The risk of long term skeletal side effects including osteoporosis may increase with the prolonged use of AIs. Short term use of AIs has been shown to be associated with an increase in bone resorption markers in plasma and urine [10,11] and adjuvant therapy with anastrozole appears to be associated with a higher incidence of fractures than adjuvant Tamoxifen therapy in earlier comparative studies [12]. In the Arimidex Tamoxifen alone or in combination (ATAC) trial, lumbar spine and total hip bone mineral density (BMD) continued to decline over 5 years of anastrozole therapy [12]. The bone loss observed during the AI therapy is consistent with the rapid bone loss observed after abrupt estrogen removal in post-menopausal women who discontinued hormone replacement therapy because of breast cancer [13]. Together, the evidence indicates that the rate at which estrogen is removed may play a role in bone loss. Through the rapid and prolonged bone loss and decreased BMD associated with AI therapy, there is increased risk of fracture that may result in decreased quality of life Table 1.

Generation	TYPE 1: Steroidal inhibitor	TYPE 2: Non-steroidal inhibitor
FIRST	None	Aminoglutethimide
SECOND	Formestane	Fadrozole Rogletimide
THIRD	Exemestane	Anastrozole Letrazole Vorozole

Table 1: Aromatase inhibitors.

Short and Long- Term Risks and Benefits

AIs are very well tolerated and have very few serious short term side effects. One of the most common one is musculoskeletal pain. Generally, the pain presents with symmetrical joint pains, most commonly affecting the wrists, hands, and knees [14]. Carpel tunnel and trigger finger may be common complaints as well. Other symptoms may include morning stiffness, myalgia, and decreased grip strength. The median time to onset of symptoms is 1.6 months, though it can range from a couple of weeks to more than 10months. Symptoms tend to peak at 6 months [15]. Other common symptoms are listed in Table 2.

Estrogen indirectly regulates the activity of bone resorption by osteoclasts, and reducing estrogen levels increases bone resorption. An earlier study consisting of 10,000 healthy women age 65 or older, reported higher risk of fracture for both hip and spine with reduced estrogen levels. Especially women who had undetectable estrogen levels (<5 pg/mL) were found to have the greatest fracture risk. On the other hand, low but detectable estrogen levels (> 5pg/mL) reduced the fracture risk by 60% [16,17]. AIs have demonstrated better disease free survival than Tamoxifen with favorable side effects profile but they

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Received July 30, 2015; **Accepted** August 26, 2015; **Published** September 02, 2015

Citation: Razaq W, Tanaka T, Razaq MA (2015) Aromatase Inhibitors and Osteoporosis - Risk, Prevention and Treatment Review. J Osteopor Phys Act 3: 155. doi:10.4172/2329-9509.1000155

Adverse effects	Anastrozole (n=3092)
Hot flashes	34.3%
Nausea/Vomiting	10.5%
Fatigue	15.6%
Mood swings	15.5%
Musculoskeletal disorder	27.8%
Vaginal bleeding	4.5%
Fracture	5.9%
Ischemic cardiovascular event	2.5%
Deep venous thromboembolic event	1.0%
Endometrail cancer	0.1%

Table 2: Common side effects of aromatase inhibitors (Incidence in ATAC trial) [12].

rapidly suppress about 99% of estrogen within few weeks. As a result, there is an associated increase in bone loss. The rate of bone loss initially is rapid but with prolonged use of AIs, the severity increases throughout the duration of treatment [17,18]. A cohort study of women with breast cancer reported a 27% and 21% increase in risk of bone loss and clinical fracture respectively, after controlling for age, comorbidities, income, geographic region and health plan type. Older age was also reported to be an independent risk factor for bone loss and bone fracture [19].

Other significant evidence to quantify the effects of AIs on the bones comes from clinical trials primarily designed to compare AIs with tamoxifen or placebo. The first study, a double blind placebo controlled trial of postmenopausal women treated for early stage breast cancer after completing 5 years of tamoxifen therapy, reported 8.1% women receiving letrozole therapy developed osteoporosis compared with 6% women in placebo arm (p=0.003). Also, 5.3% women in letrozole arm experienced fracture as compared to 4.6% in placebo arm (p=0.25) [20]. In the second study, a double blind, randomized trial where tamoxifen was switched to exemestane after 2-3 years to complete 5 years of hormonal therapy vs. 5 years of tamoxifen. 7.4% women in exemestane arm developed osteoporosis as compared to 5.7% in tamoxifen arm (p=0.05). Also 3.1% women in exemestane arm developed bone fracture compared to 2.3% women in tamoxifen arm [21].

Several other studies have also shown the significant association between AIs and bone loss. The natural bone loss in postmenopausal breast cancer women is complicated by further reduction in circulating estrogen levels as a result of AIs, putting these women at increased risk of bone loss and subsequent fractures.

AI- Associated Bone Loss and Postmenopausal Osteoporosis

Current bone mineral density (BMD) in a woman is determined by the peak bone mass achieved at maturity and the subsequent bone loss over time [22]. Postmenopausal osteoporosis is defined as a systemic disease of the skeleton with decreased BMD and architectural deterioration leading to increased susceptibility to fracture [22]. During menopause, the natural reduction in ovarian estrogen is associated with rapid bone loss during the first 4-8 years, when the rate of bone resorption surpasses that of formation and 3% bone mass may be lost each year [23]. Then the rate slows down to 1% per year as estrogen production switches to non-ovarian tissues. These residual estrogen levels are thought to slow bone loss and prevent fracture, because as mentioned earlier women with undetectable estrogen levels were at higher risk of fractures.

Normal BMD is defined as T-score>-1, whereas a T-score between -1 and -2.5 is considered to be osteopenic and T-score<-2.5 is considered osteoporotic [24].Women with osteoporosis are generally thought to have increased incidence of fractures but about 82% of fractures are reported in women (mean age 65 years) with T-score>-2.5 [25]. This suggests that fracture cannot be predicted based on BMD alone and therapeutic intervention may be needed for some women with T-score>-2.5.

Compared with annual 1% bone loss in healthy post-menopausal women, patients with breast cancer receiving AIs, experience an average of 2% bone loss per year [26]. Results from the ATAC trial after a median follow up of 100 months indicate that AIs had a significantly higher fracture incidence (2.93% for anastrozole vs. 1.9% for tamoxifen) but this pronounced difference in annual fracture rate does not appear to persist beyond 5 year treatment period (1.56% vs. 1.51% at 100 months) [27]. Even if annual bone loss returns to the postmenopausal rate after cessation of therapy, women with AI therapy will still have lost significant BMD during cancer treatment compared with their healthy counterparts.

Fractures are the most dangerous aspect of osteoporosis. Debilitating acute and chronic pain in the osteoporotic patients is often attributed to fractures from osteoporosis and can lead to further disability and early mortality. The most common osteoporotic fractures are of the wrist, spine, shoulder and hip. The symptoms of a vertebral collapse are sudden back pain, often with radicular pain and rarely with spinal cord compression or cauda equina syndrome. Multiple vertebral fractures lead to a stooped posture, loss of height, and chronic pain with resultant reduction in mobility. Fractures of the long bones acutely impair mobility and may require surgery. Hip fracture, in particular, usually requires prompt surgery, as serious risks are associated with it, such as deep vein thrombosis and pulmonary embolism, and increased mortality.

Current Guidelines for Breast Cancer Patients with Increased Fracture Risk

The American Society of Clinical Oncology (ASCO), US Preventive Services Task Force (USPSTF), World Health Organization (WHO) and National Osteoporosis Foundation (NOF) guidelines rely on BMD to recommend therapy. In general, they recommend bisphosphonate therapy when T-score have dropped into or near the osteoporotic range [25,28-30]

ASCO guidelines are specific for breast cancer women and recommend lifestyle change plus Calcium (1200 mg/day) and vita min D (400-600 IU/day) for women with T-scores>-1; osteopenic women may be considered for bisphosphonate therapy plus supplements based on additional risk factors for fractures [28]. Currently, ASCO guidelines only recommend bisphosphonate therapy for women with osteoporosis (T-score ≤ 2.5). Guidelines from other societies and expert groups are as follows:

A United Kingdom expert group [31]

Recommends bisphosphonate therapy for older women (>75 years) who have one or more risk factors for osteoporotic fracture, regardless of BMD. In addition, they recommend bisphosphonates for postmenopausal women <75 years of age with T-scores<-2.0 or if bone loss in women with preexisting osteopenia (T-score between -1.0 and -2.0) occurs at a rate ≥ 4 % per year. Due to the rapid bone loss that occurs in premenopausal women receiving ovarian suppression with a GnRH agonist and AI, they recommend bisphosphonates for such women if the T-score is ≤ -1.0.

The Belgian bone club (BBC) [32]

Recommends bisphosphonates for patients with a T-score<-2.5 or history of fragility fracture. In addition, they recommend treatment for patients with T-scores between -1.0 and -2.5 in the presence of risk factors (other than AIs). In patients not prescribed bisphosphonates, regular measurement of BMD is necessary. Bisphosphonates should be initiated if significant bone loss occurs.

The WHO Fracture Assessment Tool or FRAX is designed to estimate 10-year risk of hip and major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture) in individuals between ages 40 and 90 years, using easily obtainable clinical risk factors and femoral neck BMD. Although FRAX may underestimate bone loss attributed to AIs or other cancer treatments, the **National Comprehensive Cancer Network (NCCN)** incorporates FRAX into its guidelines. NCCN recommends treatment when the FRAX 10-year fracture risk is >20 percent for major fracture or >3 percent for hip fracture, or when the T-score is <-2.0 (<-1.5 if there has been significant loss of BMD as a result of cancer therapy) [33].

Early vs. Late Intervention

Several trials have demonstrated accelerated bone loss and increased fracture risk with AI therapy. When stratified by baseline BMD, around 50% patients with normal BMD became osteopenic during treatment, but none developed osteoporosis [34]. Among patients who were osteopenic at baseline, only 5% became osteoporotic. The fracture rate was higher in this study than predicted based on the number of patients with osteoporosis, pointing to the fact that other risk factors in addition to BMD may be involved. Analysis in healthy women support this idea because as mentioned earlier the fracture risk is higher in osteoporotic women but the majority fractures (>80 %) occur in osteopenic women [25].

Literature review shows possible benefit of earlier use of bisphosphonates in breast cancer patients on AIs. ARIBON study subset analysis of 50 patients suggested that women receiving anastrozole may benefit from monthly ibandronate to prevent AI related bone loss. At 2 years, patients on ibandronate experienced 2.98% and 0.6% in lumbar spine and hip BMD respectively and those receiving placebo had -3.22 % and -3.9 % bone losses respectively. No data with normal BMD patients is available as they did not receive ibandronate [35]. The Study of Anastrozole with the Bisphosphonate RisedronatE (SABRE) with 154 women also showed significant increase in the lumbar spine and hip BMD in the residronate arm [36].

Studies with Intravenous bisphosphonates have also shown the same but has higher compliance rate. The Z-FAST (Zometa/Femara Adjuvant Synergy Trials), ZO-FAST and E-ZO-FAST were designed to establish if 4mg zoledronic acid administered every 6 monthly concomitantly with AI therapy (upfront) would provide clinical benefit over zoledronic acid administered at the first sign of bone loss (T-score<-2or fracture) [37,38]. Results from Z FAST trial (n=602) in the first 12 months showed that upfront zoledronic acid treatment increased lumbar spine and total hip BMD by 1.9% and 1.3%, respectively, whereas delaying treatment resulted in a BMD loss of -2.4% and -1.98%, respectively [39]. The bone turnover markers N-telopeptide of type I collagen (NTX) also showed improvement in the bisphosphonate arm. Similar results were reported from ZO-FAST and E-ZO-FAST trials. Taken together, zoledronic acid administered every 6 monthly is well tolerated, safe and helped in preventing bone loss associated with AI therapy. Austrian Breast and Colorectal Cancer study Cancer Study Group (ABCSG) -12 trials in premenopausal women receiving goserelin followed by Tamoxifen or anastrozole also indicates that zoledronic acid prevents bone loss and maintained stable BMD in patients on hormonal therapy. A 60 month update of the study showed that the patients in hormonal therapy alone arm partially regained BMD 2 years after completion of therapy but still their BMD remained significantly below baseline (p=0.0005). On the other hand, patients on hormonal therapy with 3 years of zoledronic acid had significantly increased BMD at the end of the same 2 year post-treatment period (p=0.02) [40]. In summary, these trials clearly show the clinical benefit of upfront bisphosphonates to the hormonal therapy regimens for both pre and post-menopausal women.

Conclusions

It is evident now that patients with breast cancer especially on AI therapy are at higher risk for accelerated bone loss and the related fractures will impact on their independence, quality of life and associated cost of treatment. As bisphosphonates become more popular during the AI therapy, treatment recommendations and comprehensive fracture risk assessments are needed. Future guidelines should assess the fracture risk factors that may already be present in patients starting AI therapy e.g., age>65, BMI<20 kg/m^2, family history of osteoporosis, other cancer treatments, low trauma fractures after age 50 and BMD [41]. This all-inclusive assessment will enable physicians to identify patients with higher risk for fractures and will be able to direct treatment according to their needs.

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