JOURNAL OF HEALTHCARE SCIENCES
Volume 3 Issue 4 2022, Article ID: JOHS2023000640
http://dx.doi.org/10.52533/JOHS.2023.30401
e-ISSN: 1658-8967

Review

Use of Aromatase Inhibitors in the Treatment of Estrogen-Dependent Breast Cancer and its Impact on Bone Health

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Received: 15 April 2023, Accepted: 19 April 2023, Published: 30 April 2023

Abstract

With more than 1 in 10 new cancer diagnoses each year, breast cancer is the most common cancer in women and is responsible for being the second leading cause of cancer-related death among women worldwide. Among breast cancers, the majority diagnosed are estrogen-receptor-positive or estrogen-dependent breast cancers. Aromatase inhibitors are an effective form of targeted therapy for patients with estrogen-dependent breast cancer. The selective estrogen-receptor modulator tamoxifen is much less effective than the aromatase inhibitors anastrozole, letrozole, and exemestane in preventing recurrence in early breast cancer that is estrogen receptor positive. Selective estrogen-receptor modulators are expected to be replaced by aromatase inhibitors as the first-line adjunctive treatment for several patients. Third-generation aromatase inhibitors are quickly replacing tamoxifen as the endocrine medication of choice for post-menopausal women with breast cancer due to their superior efficacy in both adjuvant and metastatic settings. Aromatase inhibitor therapy for breast cancer patients undoubtedly provides benefits, particularly in terms of increased disease-free survival, but it may also have detrimental long-term effects on bone health. Lack of estrogen will invariably cause bone loss since any treatment that reduces estrogen could result in bone loss. The use of aromatase inhibitors is associated with an increased risk of fractures and accelerated rates of bone loss. The purpose of this research is to review the available information about the use of aromatase inhibitors in the treatment of estrogen-dependent breast cancer and their impact on bone health.

Keywords: *aromatase, inhibitor, estrogen-dependent, breast, cancer*

Introduction

Among women around the world, breast cancer represents the most prevalent malignant tumour accounting for up to 36% of oncological patients. In 2018, an estimated 2.089 million women were diagnosed with breast cancer. All across the world, the prevalence of breast cancer is rising, although industrialized nations have the highest prevalence and account for over half of the instances globally (1). Based on the identification of estrogen receptor expression by immunohistochemistry in approximately 1% of the tumour cells, more than 70% of all breast cancers are categorized as estrogen-receptor positive. It is documented that reproductive factors, such as early menarche, late menopause, and late pregnancies, affect ovarian hormone exposures, which in turn increase breast cancer risk. Progesterone signalling has been connected to breast cancer risk and tumor progression by exogenous hormone receptor agonist exposures in the context of hormonal contraception and hormone replacement therapy. Inhibition of estrogen receptor signalling is the cornerstone of estrogen-dependent breast cancer therapy and has significantly increased patient survival (2).

The main transcription factor driving oncogenesis in breast cancers with hormone response positivity is the estrogen receptor. Estrogen receptor alpha, which performs as a ligand-inducible transcription factor, is primarily responsible for mediating the biological effects of estrogens. About 30% of estrogen-dependent breast cancers do not respond to anti-estrogen therapy and have a poor prognosis. Around 40% and 20% of estrogen receptor-positive breast cancers are categorized as luminal A and B subtypes, respectively. Each subtype requires tailored management due to their distinctive risk factors, incidence, natural histories, and responsiveness to local and systemic medications (3). Aromatase inhibitors are an effective form of targeted therapy for patients with estrogen-dependent breast cancer as the enzyme aromatase catalyzes important phases in estrogen biosynthesis. Since aromatase inhibitors inhibit both the genomic and nongenomic functions of estrogen receptor, they are more efficient than selective estrogen receptor modulators. First-, second-, and third-generation aromatase inhibitors have all received Food and Drug Authority approval to date. The current recommended treatment for postmenopausal breast cancer employs the third-generation aromatase inhibitors, including Letrozole, Anastrozole, and Exemestane (4).

While improving the survival of breast cancer patients, aromatase inhibitors have a negative impact on bone health. Chemotherapy, ovarian suppression, and aromatase inhibitors are all widely employed methods of treating hormone receptor-positive breast cancer. Aromatase inhibitors prevent the formation of estrogen in peripheral tissues, and the three third-generation aromatase inhibitors exemestane, letrozole, and anastrozole lower circulating estrogen levels, which accelerate bone loss and raise fracture risk. Women with osteoporosis who are prescribed aromatase inhibitors experience more fractures (5). When compared to postmenopausal estrogen deprivation, estrogen depletion that happens after ovarian ablation or during aromatase inhibitor treatment is often sudden. Moreover, bone loss caused by treatment may occur at an accelerated rate. Breast cancer patients on aromatase inhibitor therapy incur a rate of bone loss approximated at 2.6% per year compared to untreated postmenopausal women (6, 7). The purpose of this research is to review the available information about the use of aromatase inhibitors in the treatment of estrogen-dependent breast cancer and their impact on bone health.

Methodology

This study is based on a comprehensive literature search conducted on March 30, 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about the use of aromatase inhibitors in

http://dx.doi.org/10.52533/JOHS.2023.30401

the treatment of estrogen-dependent breast cancer and its impact on bone health. There were no restrictions on the date, language, participant age, or type of publication.

Discussion

Studies have shown that estrogens play a part in both estrogen-positive and estrogen-negative breast cancer, with estrogens being a prominent driver of estrogen-dependent breast cancer. Breast epithelial cells, which are hormone-sensitive and express the estrogens, are located close to the adipose stromal cells that produce estrogen. They contribute significantly to the healthy growth of the breast epithelium by promoting ductal morphogenesis and proliferation. Yet, the pro-proliferative impact of these steroids may produce an accumulation of replication mistakes leading to mutations and the onset of breast cancer when exposed to high amounts of estrogens, such as in the context of obesity. Moreover, the increased energy demands of proliferating cells necessitate greater mitochondrial activity, which may increase reactive oxygen species as a consequence of cellular respiration. In several breast cancer cell lines, estradiol can directly induce the generation of intracellular reactive oxygen species from mitochondria (8). Aromatase inhibitors are the foundation of treatment for estrogen-dependent breast cancer. In postmenopausal women with endocrine-responsive breast cancer, adjuvant aromatase inhibitor therapy administered either alone for 5 years or sequentially after 2 to 5 years of adjuvant tamoxifen enhanced disease-free survival when compared to tamoxifen alone for 5 years. In comparison to tamoxifen, third generation aromatase inhibitors have a better safety profile with fewer thromboembolic and gynaecological side effects. However, randomized trial studies have demonstrated that, in contrast to tamoxifen, aromatase inhibitors cause more bone loss and fractures (5).

Evidence from literature

The aromatase inhibitors function by hindering the peripheral conversion of estrogen from androgen precursors, which effectively lowers tissue and circulating estrogen levels. The currently approved aromatase inhibitors for estrogen-dependent breast cancer are categorized into two distinct biochemical sub-types steroidal and non-steroidal. Exemestane, a steroidal aromatase inhibitor, is an androstenedione derivative, that acts by occupying the aromatase substrate-binding site in an irreversible manner, hence also being considered an aromatase inactivator. Exemestane is authorized as a second-line treatment for early estrogen-dependent breast cancer, following two to three years of tamoxifen use. Reversible binding occurs between nonsteroidal aromatase inhibitors like letrozole and anastrozole and the cytochrome P450 domain. The first-line adjuvant treatment for early estrogen-dependent breast cancer is anastrozole. Within three months of completing five years of tamoxifen course, letrozole is presently recommended as a second-line treatment for early estrogen-dependent breast cancer. However, aromatase inhibitors are not recommended for usage in premenopausal or perimenopausal women with breast cancer since they do not suppress estrogen synthesis in functional ovaries. The third-generation aromatase inhibitors are stronger than earlier pharmacological entities and all of them block aromatase activity by more than 98% (9). As a result of the obvious advantages in disease-free survival and decreased recurrence, aromatase inhibitors are now preferred over tamoxifen for the treatment of estrogen-dependent breast cancer in postmenopausal women. In comparison to tamoxifen, these inhibitors have a more favourable side effect profile; however, due to the nearly total depletion of estrogens, all aromatase inhibitors have negative long-term effects on bone, increasing the risk of fracture and elevating rates of bone loss (10).

Confavreux et al. revealed in their findings that, compared to an age-matched group of healthy postmenopausal women, osteopenic postmenopausal women receiving anastrozole for breast cancer experience an accelerated rate of bone loss at the spine and hip. Increased bone turnover markers and the reduction of endogenous 17-β estradiol production as measured by plasma 17- β estradiol are all associated with anastrozole-induced bone loss, which is especially prominent in early

http://dx.doi.org/10.52533/JOHS.2023.30401

postmenopausal patients. The authors further described that chemotherapy is one of the adjuvant treatments for early breast cancer that exacerbates aromatase inhibitor-induced bone loss. The induced menopause and the direct bone toxicity of the drugs used during courses are two potential ways in which it operates (11). Results of a randomized trial and an analysis of follow-up data for 100 months showed increased rates of fractures among patients receiving anastrozole in comparison to those receiving tamoxifen during active treatment [incidence rate ratio = 1.03 (0.81-1.31), p = 0.79], but it did not differ after treatment was completed [incidence rate ratio = 1.55 (1.31-1.83), p 0.001]. Hence, it appears that the elevation in fracture rates caused by anastrozole only occurs during active therapy and disappears once it is over (12).

Results of a study by Mincey et al. showed that in the aromatase inhibitor group, the prevalence of bone loss was 8.7% compared to 7.1% in the control group, yielding a higher relative risk of 1.3 (95% confidence interval [CI], 1.1-1.6; P = 0.01). With a relative risk of 1.4 (95% CI, 1.2-1.6, P = 0.001), the prevalence of bone fracture was also considerably higher in the inhibitor group compared to the controls (13.5% vs. 10.3%). After adjusting age and comorbidities, multivariate Cox proportional hazards regressions revealed that the risk of bone loss in the inhibitor group remained significantly higher than in the non-inhibitor group, with an increase in the risk of bone loss and fractures of 27% (95% CI, 4%-55%; P = 0.02) and 21% (95% CI, 3%-43%; P = 0.02), respectively (13). Similarly, results of a meta-analysis demonstrated that the fracture risk was observed to be 35% (95% CI 1.21-1.51) greater in the aromatase inhibitor group compared to the tamoxifen group. During the tamoxifen/aromatase inhibitor treatment period, the fracture risk associated with aromatase inhibitors increased by 33% (pooled relative risk 1.33; 95% CI 1.21-1.47) compared to the tamoxifen group, but there was no increase during the post-tamoxifen/aromatase inhibitor treatment phase (pooled relative risk 0.99; 95% CI 0.72-1.37). Women on aromatase inhibitors are at significantly greater risk of fracture, particularly during treatment (14).

Hadji et al. reported in their findings that bone mineral density at the spine decreased by 2.6% from baseline in exemestane-treated individuals at 6 months and by another 0.2% at 12 months. At 6 and 12 months, there were significant differences between tamoxifen and exemestane in the changes in bone mineral density (P = 0.0026 and P = 0.0008, respectively). At 6 and 12 months, exemestane and tamoxifen showed substantially different mean changes in bone mineral density from baseline at the total hip (P = 0.0009 and P = 0.04, respectively). The mean changes in bone mineral density from baseline at the femoral neck for tamoxifen and exemestane were comparable. At six months, exemestane increased bone loss; although after six to twelve months of treatment, bone loss stabilized (15). Within the first 12 to 24 months of treatment with an aromatase inhibitor, the rate of bone loss seems to be comparable between agents, despite the lack of evidence from direct comparator trials. Similar effects on bone and accelerated bone turnover are caused by all aromatase inhibitors, whether they are steroidal or non-steroidal. Awareness regarding the increased risk of fractures and bone loss associated with the use of aromatase inhibitors has increased in recent times (16).

The superiority of aromatic inhibitors to tamoxifen has been demonstrated in numerous randomized trials, with a notable improvement in disease-free, bone metastases-free, and overall survival. In contrast, studies comparing tamoxifen with anastrozole, letrozole, or exemestane have found that aromatic inhibitors increase the risk of fracture and induce a greater loss of bone mineral density. The majority of information on bone loss associated with adjuvant endocrine therapy, however, comes from a number of randomized studies where the loss of bone was noted as an adverse event or from sub-analyses carried out on the same trials to describe changes in bone mineral density and the risk of bone fractures. Moreover, tamoxifen and aromatase inhibitors have been examined in opposition to one another, increasing the latter's apparent adverse effects in terms of bone mineral density loss or

http://dx.doi.org/10.52533/JOHS.2023.30401

fractures (17). Rachner et al. described that in the adjuvant therapy regimen for postmenopausal women with estrogen-dependent breast cancer, aromatase inhibitors are entrenched as a hallmark. Despite the good long-term prognosis for many of these patients, unfavourable effects on bone are a side effect of aromatase inhibitor therapy that can cause significant bone loss and fragility fractures (18).

Despite the fact that aromatase inhibitor therapy for breast cancer patients clearly has its advantages, especially in the terms of improved disease-free survival, it can potentially have negative long-term effects on bone health. Loss of estrogen will inevitably result in bone loss. Any therapy that decreases estrogen has the possibility of causing bone loss, compromising bone integrity and increasing the patient's risk for fractures since estrogen has a negative regulatory influence on bone resorption. Due to age-related ovarian failure, a concomitant drop in estrogen levels, and potential disease-related bone loss, postmenopausal breast cancer patients already have an elevated risk of osteoporosis. A further risk factor can be potential bone loss spurred on by the medication (19). However, the benefits of aromatase inhibitor treatment for estrogen-dependent are far more beneficial and noteworthy than the risks associated with bone health, which can be efficiently managed through monitoring and the use of bisphosphonates, calcium, and vitamin D. Furthermore, clinical research comprising more randomized trials and comparative studies is required to extensively study the safety index of aromatase inhibitors at a larger-scale and aid in developing generalized preventive strategies for aromatase inhibitors treatment-related bone loss since the available studies in the literature are scarce and limited to past times.

Conclusion

Aromatase inhibitors are highly effective in the treatment of estrogen-dependent cancer, and their benefits outweigh the risks. However, the risks of compromised bone health associated with their long-term use can be successfully managed through fracture risk assessment, which should include clinical risk factors, biochemistry, measurements of bone mineral density, and risk factor-based monitoring. Additionally, calcium and vitamin D intake shall be promoted.

Disclosure

Conflict of interest

There is no conflict of interest

Funding

No funding

Ethical consideration

Non applicable

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection, and final writing of the manuscript.

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