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Effects of third-generation aromatase inhibitors on bone

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ABSTRACT

Low oestradiol levels in women are associated with decreased bone mineral density (BMD) and increased fracture risk. The third-generation aromatase inhibitors (AIs; anastrozole, letrozole, and exemestane) are used in the treatment of early and advanced breast cancer and act by substantially reducing oestrogen synthesis in postmenopausal women. However, due to their mechanism of action, there is concern regarding the long-term effects of these agents on bone, particularly when used in the adjuvant setting. In this paper, the currently available data on the effects of the third-generation AIs on markers of bone turnover, BMD, and fracture risk are reviewed, with the emphasis on results in the adjuvant treatment of early breast cancer. These data suggest that both the steroidal (exemestane) and non-steroidal (anastrozole and letrozole) AIs appear to affect bone turnover. Conclusions regarding any clinically relevant differences between these agents are difficult to make, and further data are awaited from long-term adjuvant use of these three agents in ongoing clinical studies. Postmenopausal women are at increased risk of osteoporosis and fracture, and the increasing use of AIs in the adjuvant treatment of postmenopausal breast cancer patients will require appropriate consideration of fracture risk, with the use of anti-osteoporotic therapies, if necessary.

1. Introduction

Oestrogens play a critical role in the development and growth of most breast cancers. Oestrogens stimulate normal breast epithelium and breast cancer cell proliferation,[1–3] with oestrogen deprivation—achieved by blocking or reducing endogenous levels of oestrogen—forming the basis of endocrine treatments for breast cancer. Until recently, the selective oestrogen receptor modulator tamoxifen had been the mainstay of early breast cancer treatment, although the partial oestrogen agonist activity of this agent has caused concern, as long-term treatment significantly increases the risk of endometrial cancer and thromboembolic events.[4] Oestrogens also play a critical role in maintaining normal bone mass,[5] therefore long-term oestrogen deprivation may be associated with the development of osteoporosis and increased susceptibility to fractures. The partial agonist effects of tamoxifen are associated with a protective effect on bone, which may be a benefit to postmenopausal women receiving adjuvant treatment with tamoxifen for breast cancer.[6,7] However, tamoxifen treatment is associated with a significant loss of bone mineral density (BMD) in premenopausal women.[8]

Due to their improved efficacy and tolerability profiles, it is likely that the third-generation aromatase inhibitors (AIs) will replace tamoxifen as the preferred treatment for postmenopausal patients with both early and advanced breast cancer. However, because AIs profoundly reduce the already low circulating oestrogen levels in postmenopausal women by a further 80–90%, these agents may also potentially have deleterious effects on bone. There are two types of AIs, steroidal (or 'irreversible', substrate-site binding type I) and non-steroidal (haem-binding, type II), known to be different with respect to enzyme binding site and their effect on the aromatase enzyme. Both the non-steroidal AIs, anastrozole and

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letrozole, and the steroidal AI exemestane, have been approved as second-line treatment for oestrogen receptor-positive metastatic breast cancer after first-line treatment with tamoxifen. Anastrozole and letrozole have been widely approved as first-line endocrine therapy for postmenopausal women with hormone receptor-positive metastatic breast cancer. Anastrozole is now also approved for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer, and letrozole as extended adjuvant therapy for women who have received 5 years of tamoxifen. The increasing use of these agents in the adjuvant treatment of early breast cancer, which usually entails treatment for >5 years, means that it is important to evaluate the long-term effects of these agents on bone health.

Bone, as living tissue, forms through a modelling process when mineralised tissue is deposited at specific sites. Subsequently, the skeleton undergoes continuous remodelling throughout life. Remodelling comprises a series of interactions between mesenchymal osteoblasts and haematopoietic osteoclasts. Mature osteoclasts resorb old bone whereas osteoblasts synthesise new bone, and bone mass is maintained when the volume of bone resorbed equals the amount of new bone formed.[9] Oestrogens are known to inhibit the activity of osteoclasts and have been linked, at least in high concentrations, to an increased number of osteoblasts and osteoblast-related collagen formation. In the normal bone microenvironment (Fig. 1A) pre-osteoblasts (pre-B cells) produce receptor activator of nuclear factor κβ ligand (RANKL), which binds to a receptor on osteoclasts increasing osteoclastogenesis and activating osteoclast precursors into mature osteoclasts, which then initiate bone resorption. The extent of osteoclastic resorption to some extent depends on the rate of apoptosis in osteoclasts. RANKL has been shown to be a potent negative regulator of osteoclast apoptosis[10,11] by providing survival signalling through several pathways. However, the underlying mechanism by which apoptosis is regulated by RANKL, in both osteoclast precursors and osteoclasts, remains largely unknown and requires further study. Osteoprotegerin (produced by osteoblasts in response to oestrogen) is present in the circulation and acts as a decoy receptor for RANKL, thus serving as an inhibitory factor to shutdown osteoclast function, helping to maintain the balance between bone resorption and formation.[12]

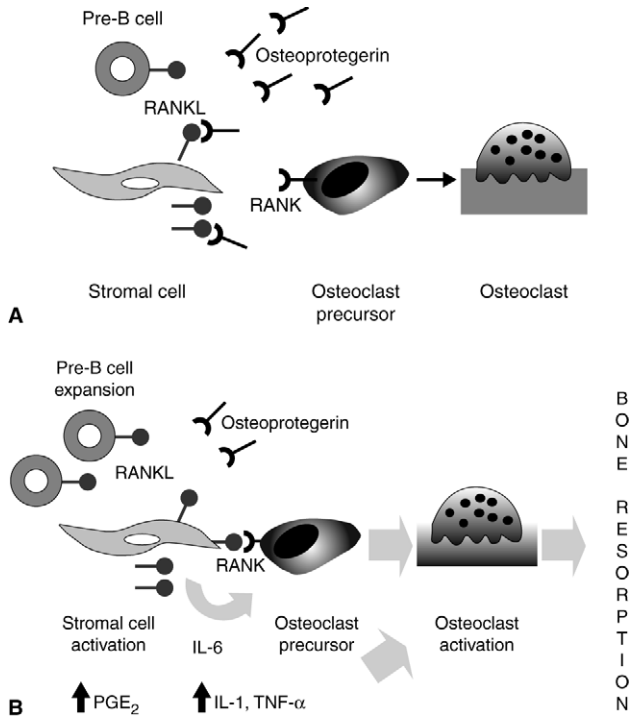

Fig. 1 – Cellular and cytokine activities in (A) the normal bone microenvironment and (B) the oestrogen-deprived microenvironment. RANK, receptor activator of nuclear factor-κβ; RANKL, RANK ligand; IL, interleukin; PGE_2, prostaglandin E2, TNFα, tumour necrosis factor α.

Oestrogen deprivation (Fig. 1B), such as that associated with AI treatment, leads to an expansion of pre-B cells, increased production of RANKL by stromal cells and increased activity of RANK, thus leading to increased levels of osteoclastic precursors and osteoclastogenesis. This, along with the reduction in circulating levels of osteoprotegerin, results in an increase in the number of mature osteoclasts and increased bone breakdown. This process is further augmented by interleukin-6 (IL-6) production, which occurs in response to oestrogen deprivation and may also occur as a consequence of the increased IL-1, prostaglandin E2 (PGE2), and tumour necrosis factor alpha (TNFα) levels observed in the presence of bone metastases in advanced breast cancer. Oestrogen deficiency may also have additional effects on bone by directly modulating the production, storage, or activity of bone growth factors (e.g., transforming growth factor-β [TGF-β]).[13] This reduces the ability of bone to respond to osteoclastic activity, and gives rise to an imbalance between bone resorption and formation thus exacerbating bone loss.

At menopause, oestrogen levels fall dramatically and the rate of bone turnover increases. As the regulatory effects of oestrogens on bone cells decline, bone resorption begins to exceed bone formation, leading to a net loss of bone and weaker bone micro-architecture.[7] This reduction in oestrogen level is associated with a reduction in BMD, and a 2- to 4-fold increase in the rate of bone loss is observed at menopause,[14] which in turn leads to an increased risk of bone fractures.[15] In fact, the risk of fractures has been shown to double for every 10% reduction in bone mass,[16] and almost one in every two women over 50 years of age will experience an osteoporosis-related fracture in their remaining lifetime.[17]

The World Health Organization (WHO) has defined osteoporosis as a BMD measurement 2.5 standard deviations (SD) or more below the young adult mean value (often expressed as a *T*-score $\leqslant -2.5$).[18] Osteoporosis commonly leads to fractures of the spine, wrist, or hip, which can cause disability or even fatality. Fractures of the hip are associated with the greatest morbidity, mortality and economic cost. Osteoporosis can significantly reduce the patient's quality of life and is proving to be a major contributor to healthcare costs.[15] Moreover, the yearly incidence of spine and hip fractures in women aged between 50 and 79 years increases with age[19,20] (Fig. 2).[21] Many other factors including family history, height, weight, general health, nutrition, and smoking also influence fracture risk.[22] As the incidence of breast cancer also increases following menopause, evaluation of the