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Review Article

Does estrogen play a role in response to adjuvant bone-targeted therapies?

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ABSTRACT

Bone remains the most common site of breast cancer recurrence. The results of population studies, preclinical research and clinical studies in patients with metastatic disease provided a rationale for testing bone-targeted agents in the adjuvant setting. Despite the initial optimism, results from eight prospectively designed, randomized control studies powered to assess the value of adjuvant bone-targeted therapy in early breast cancer are conflicting. Data have shown that, where benefit exists, it tends to be in women with a "low estrogen environment", either through menopause or suppression of ovarian function. In this manuscript, we review clinical data supporting the hypothesis that estrogen levels may play a part in explaining the response of patients to bone-targeted agents in the adjuvant setting. The results presented to date suggest that there may be data supporting a unifying role for estrogen in adjuvant trials. However, in the absence of any prospective randomized trials in which estrogen data has been systematically collected we cannot specifically answer this question. We await the results of the Oxford overview analysis of individual patient data with interest.

1. Introduction

In recent years there has been increasing interest in the role of bone-targeted agents, such as bisphosphonates (BP) and denosumab, as adjuvant therapies for breast cancer. The results of large randomized trials with BPs have been variable showing either; benefit [1–3], no benefit [4–7] or harm [8]. However, subgroup analyses have consistently shown that, where benefit exists, it is in women with a "low estrogen environment" either through menopause or suppression of ovarian function. In this manuscript, we review the link between estrogen and breast cancer risk and the hypothesis that estrogen levels may in part explain the response of patients to bone-targeted agents in the adjuvant setting.

2. Estrogen and breast cancer link

The pivotal role of cyclical estrogens in breast cancer risk is well recognized. This has been shown in epidemiological studies where risk is related to earlier age at menarche, later age at first birth and menopause, and parity [9,10]. Breastfeeding is protective and is theorized to be secondary to increased prolactin secretion and subsequent suppression of estrogen production [11–13]. Studies on hormone replacement therapy (HRT) have shown increased risk of breast cancer while receiving combined estrogen and progesterone hormone replacement [14,15] and, interestingly, a fall in risk on discontinuation [15–17]. Obesity has also been shown to increase breast cancer risk in postmenopausal women, which is likely due to adipose tissue facilitating the conversion of adrenally secreted dehydroepiandrosterone (DHEA) into estrogen, leading to elevated estrogen levels [18].

In addition, several studies note that higher serum levels of estrogen in postmenopausal women are associated with increased breast cancer risk [19–23]. A meta-analysis of nine prospective studies, with data on 2428 predominantly postmenopausal women, 663 with breast cancer, demonstrated a roughly twofold higher risk of breast cancer in women with higher serum estrogen (2nd–4th quartiles) compared to those with lower levels (1st quartile) [24].

3. Estrogen and bone

The importance of estrogen is maintaining bone health is well recognized [25,26]. The bone microenvironment is dynamic with

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on-going remodeling through the activity of both osteoclasts (bone resorption) and osteoblasts (bone formation). Osteoclastogenesis is tightly regulated by the receptor activator of nuclear factor kappa B ligand (RANKL), receptor activator of nuclear factor kappa B (RANK) and osteoprotegerin (OPG) system. RANKL is a protein synthesized by preosteoblast cells. When these proteins bind to their receptors (RANK) on osteoclast precursor cells, they stimulate osteoclast differentiation and activation, resulting in bone resorption [27,28]. Preosteoblast cells also express OPG, a soluble decoy receptor that binds to RANKL and blocks the interaction between RANKL and its receptor RANK, thereby inhibiting osteoclastogenesis [29,30]. OPG is also known to induce apoptosis in mature osteoclasts, further limiting bone resorption [31].

The amount of bone resorption is dependent on the balance between RANKL and OPG. Many cytokines and hormones are involved in regulation of the RANKL/RANK/OPG system, including sex steroids [27,30]. Estrogen is known to inhibit RANKL production [27,30], and stimulate the production of OPG [32,33]. Thus, estrogen deficient states result in increased RANKL production, which in turn overwhelms the OPG decoy receptors. This results in greater osteoclastogenesis and excessive bone resorption, which may eventually lead to reduced bone density. Throughout this process, growth factors are released into the bone microenvironment, which is hypothesized to result in tumor cell proliferation and survival [34,35]. Thus, in estrogen deficient states, increased release of growth factors driven by increased osteoclastic resorption activity may provide a favorable environment for tumor growth and progression. As such, bone-targeted therapies such as BPs that inhibit osteoclast activation, should in theory limit growth factor release and hence tumor cell proliferation.

4. Bisphosphonate use and breast cancer risk

BPs are commonly used in the management of postmenopausal osteoporosis. They consist of two phosphate groups, which give them a high affinity to bone. They attach to bone at exposed calcium hydroxyapatite binding sites, which are most accessible at sites of bone resorption. During bone turnover, BPs are released causing inhibition of osteoclast-mediated bone resorption [36,37]. In addition, BPs are known to decrease osteoclast development and recruitment as well as promote osteoclast apoptosis [38,39]. Through these mechanisms, BPs have shown to both increase bone mineral density (BMD) and decrease osteoporotic fractures [40–43].

Several studies also suggest that postmenopausal women on oral BPs for osteoporosis have a reduced risk of breast cancer incidence [44–46]. In theory, the reduction in osteoclast-resorption limits growth factor release into the bone microenvironment, which may limit cancer cells from proliferating and developing into malignant tumors. Furthermore, there are data which suggest BPs have direct anti-tumor effects [47,48].

A large study, the Woman's Health Initiative (WHI), included 154,768 women, 2816 of whom were taking oral BPs for osteoporosis at the time of enrollment. After 7.8 years of follow-up, multivariate analysis demonstrated a 32% risk reduction ($P<0.01$) in the incidence of invasive breast cancer and a 30% reduction ($P=0.02$) in the risk of estrogen receptor (ER) positive breast cancer in postmenopausal women on oral BPs compared to those not on BP therapy [44].

Rennert et al. observed similar results in their population-based, case-control study of 4039 postmenopausal women taking oral BPs, 1832 who were diagnosed with breast cancer [46]. A 28% relative risk reduction in the incidence of breast cancer was observed with the use of BPs for greater than one year. A significantly greater number of breast cancers were ER positive and were less frequently poorly differentiated tumors. Newcomb et al.'s population based, case-cohort study ($N=5911$) yielded comparable results [45]. Multivariate analysis demonstrated a significant reduction in the risk of breast cancer with BP use (OR 0.67; 95% CI 0.51–0.89). There was increased benefit with increasing duration of BP therapy. Interestingly, benefit was only observed in non-obese women (BMI < 30 kg/m^2).

5. Pre-clinical studies

In pre-clinical studies, BPs have shown anti-tumor effects directly through inhibition of tumor proliferation and induction of apoptosis, and indirectly, through their ability to inhibit tumor cell adhesion and invasion of the extra-cellular bone matrix, and their anti-angiogenic and immunomodulatory effects [48–51]. Pre-clinical animal studies have demonstrated a reduction in the development of new bone metastases with preventative and therapeutic dosing of BPs [52–58], as well as inhibition of the progression of existing bone metastases with therapeutic dosing [54,56,58].

6. Advance disease clinical trials

In patients with bone metastatic disease, studies have shown BPs to decrease the incidence of skeletal related events, delay the onset of these complications, and reduce bone pain [59–61]. There is also evidence that they may improve overall survival in subgroups of patients with advanced cancers [62].

7. Adjuvant bisphosphonate trials

These studies provided a rationale for testing bone-targeted agents in the adjuvant setting. Despite the initial optimism, results from eight large prospective randomized control studies powered to assess the value of adjuvant bone-targeted therapy in early breast cancer are conflicting (Table 1) [1–8,63]. These studies results are outlined below. However, subgroup analyses from these studies have shown that women with a “low estrogen environment,” either through menopause or suppression of ovarian function, tend to derive greater benefit from adjuvant BP treatment [64].

7.1. Powles study

Powles et al. were the first to show a survival benefit with the use of adjuvant BP in early breast cancer patients [1]. A total of 1069 women with stages I–III breast cancer were randomized to either two years of oral clodronate or placebo following surgery, radiotherapy and adjuvant chemotherapy. Results from this study showed that patients treated with two years of clodronate had a 41% reduction in the risk of developing bone metastases at five years ($P=0.043$). Additionally, there was a survival advantage in the clodronate arm with a 23% risk reduction in death with a median follow-up of 5.6 years ($P=0.048$). These benefits appear to be limited to postmenopausal patients or those with positive ER status. Results of subgroup analyses demonstrated a significant reduction in bone metastases at two-years ($P=0.017$) and a trend towards significance at five-years ($P=0.056$) in postmenopausal patients treated with two years of adjuvant clodronate therapy versus the premenopausal subgroup, which showed no benefit with clodronate on the risk of bone metastases either at two-years ($P=0.448$) or five-years ($P=0.334$).