Published in final edited form as:
Nat Rev Endocrinol. 2015 March ; 11(3): 138–139. doi:10.1038/nrendo.2014.220.

Will breast cancer chemoprevention stand on 'solid bone'?

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Abstract

Aromatase inhibitors are the most effective agents for preventing breast cancer; however, their use is associated with bone loss and an increased risk of fractures. Sestak and colleagues show that administration of an oral bisphosphonate prevents aromatase-inhibitor-induced bone loss in postmenopausal women with osteopenia or osteoporosis who are at high risk of breast cancer.

Estrogens are crucial factors in the development and progression of breast cancer in women throughout life. The enzymatic activity of aromatase in peripheral tissues converts androgens to estrogen and serves as the main source of estrogens in post-menopausal women. Targeting aromatase is, therefore, an attractive strategy for the prevention and treatment of breast cancer. Indeed, inhibition of aromatase has been shown to effectively prevent breast cancer in postmenopausal women.[1,2] However, the resulting decrease in levels of estrogen, which considerably impedes tumour growth, also results in notable decreases in bone mass and strength; thus, patients receiving therapy with aromatase inhibitors have an increased risk of fracture. The bone substudy of the IBIS-II study, reported by Sestak and colleagues,[3] was designed to specifically assess the effects on bone of the aromatase inhibitor anastrozole in the absence of tamoxifen (the comparator that confounded assessment of the changes in BMD in previous studies) and to evaluate the preventive effects of the bisphosphonate risedronate on anastrozole-induced bone loss.[3]

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Competing interests
The authors declare no competing interests.

The IBIS-II study included 3,864 healthy postmenopausal women who were at increased risk of breast cancer. These women were randomly assigned to receive either an aromatase inhibitor (oral anastrozole; 1 mg per day) or matched placebo. The bone substudy included 1,410 of these women, who were stratified on the basis of baseline BMD T-scores at the spine or femoral neck. Women in stratum I (those with normal BMD) were monitored only; women in stratum II (those with osteopenia) were randomly assigned to receive oral risedronate (35 mg per week) or matched placebo; and women in stratum III (those with osteoporosis) all received oral risedronate (35 mg per week). The primary end point was the effect of risedronate versus placebo on BMD (at the hip and spine) at 3 years in stratum II women who were randomly assigned to receive anastrozole or placebo. The secondary end point was the effect of anastrozole on BMD in women who did not receive risedronate (strata I and II) and in women with osteoporosis who were treated with risedronate (stratum III).

Bisphosphonates are potent, long-acting antiresorptive agents that are approved for the treatment of bone loss and the prevention of fractures in postmenopausal women with osteoporosis, as well as for the reduction of skeletal morbidity in patients with cancer. In the IBIS-II bone substudy,[3] risedronate treatment for 3 years significantly decreased bone loss at the hip and spine in all patient treatment strata. These effects were mediated, as expected, by decreased osteoclastic-bone resorption, which was measured by changes in levels of urinary N-terminal telopeptide (NTx)—a biomarker of bone resorption whose production is markedly suppressed by bisphosphonate treatment. Although bone loss was ameliorated by risedronate treatment, the study was not powered to ascertain if there was a corresponding decrease in the incidence of fractures in patients. Furthermore, the study was analysed on a per-protocol basis, which means that the 36% of patients who withdrew from the study were not included in the final analysis. For efficacy studies, this type of analysis is acceptable; however, proving effectiveness at the population level requires a specifically designed study using intent-to-treat analysis to demonstrate that improvements in bone density translate to a decreased fracture rate despite noncompliance and patient withdrawal. Obtaining these critically important data will require larger patient cohorts and increased duration of follow-up. In the clinical setting of patients at high risk of breast cancer, oral risedronate was well tolerated among the analysed patients and although many adverse events were reported, the incidence of these events did not differ between treatment allocations in the various strata. However, in the group receiving anastrozole and risedronate, twice as many patients withdrew from the study as in the matched-placebo group in stratum II. This result was probably due to adverse effects, which suggests that per-protocol analysis might not be appropriate for the comparison and reporting of therapy toxicity.[4]

Although the finding that risedronate therapy effectively blocks anastrozole-induced bone loss in women with osteopenia or osteoporosis is perhaps not surprising, the data do illustrate the use of oral antiresorptive agents in the setting of breast cancer prevention in postmenopausal women at high risk of the disease. The current American Society of Clinical Oncology (ASCO) clinical guidelines[5] recommend that antiresorptive treatment should be considered for women who are being treated for breast cancer. It is important to recognize that despite the robust antiresorptive and bone-protective effects of bone-modifying agents such as risedronate, these therapies do not prevent the development of bone metastasis in

patients with breast cancer who do not have existing bone metastasis; to date, no overall survival benefits have been reported for antiresorptive treatments. The weight of clinical evidence suggests that alternative mechanisms control breast cancer progression and patient survival, which are independent of the extent of bone resorption and/or involve cellular targets in bone that are not affected by current antiresorptive therapies.

Despite several positive randomized breast cancer chemoprevention trials, the strategy of primary chemoprevention has not yet been widely adopted in healthy women. The role of primary chemoprevention has been called into question by a lack of evidence showing that it decreases mortality from the disease and by the numerous adverse effects of the drugs. Considering the modest adoption rate of breast cancer chemoprevention, we should consider whether the addition of another agent with its own set of adverse effects could make the whole strategy even more difficult to implement in a large population.[6]

As intravenous bisphosphonate therapy is a common treatment to control bone loss induced by anastrozole in the preventative setting, the study by Sestak and colleagues,[3] which shows robust efficacy of an oral agent, provides oncologists with another important cost-effective tool that has the potential to change current clinical practice. The data provide a rationale to consider oral risedronate treatment and careful BMD monitoring in patients receiving anastrozole and other aromatase inhibitors in the primary prevention setting. However, if primary prevention does not gain more momentum, this drug might find application in secondary prevention and adjuvant settings in which the use of aromatase inhibitors is widespread.

Acknowledgments

L.J.S. acknowledges research support from the NIH (R01 CA166060).

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