Bone health in the treatment of postmenopausal women with aromatase inhibitors and premenopausal women treated with ovarian suppression and aromatase inhibitors: a hands-on guide

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Abstract
In postmenopausal women, and premenopausal women treated concomitantly with ovarian suppression, aromatase inhibitors are a standard of care in the adjuvant treatment of hormone sensitive breast cancer. Dosed daily for up to 10 years, these drugs are not without significant toxicity. Given such protracted duration of treatment and that the majority of women treated in this setting have very favourable disease free and overall survival from their early stage breast cancer, long-term toxicity is a particular concern. The most concerning long-term toxicity is the deleterious effect of aromatase inhibitors on bone density. Accelerated bone loss due to aromatase inhibitors confers increased fracture risk and thereby significant morbidity. Therefore it is important to investigate and monitor bone health prior to commencement of and during aromatase inhibitor treatment, and ensure appropriate measures to optimize bone health are instituted. Recommendations from the summary of the literature to date, relevant to the Australian setting are outlined in this paper.

Approximately 70% of early breast cancers are hormone sensitive (in that they express either or both oestrogen and progesterone receptors) and adjuvant endocrine therapies, with or without chemotherapy, reduce the risk of cancer recurrence, improve survival and are therefore regarded as standard treatment. Evidence to date has demonstrated that to derive maximal adjuvant benefit, at least five years of daily dosing of endocrine therapy is required. While tamoxifen is active in both pre and postmenopausal women, aromatase inhibitors are only active in postmenopausal women.

When compared with tamoxifen, adjuvant treatment with aromatase inhibitors leads to improved breast cancer specific disease free survival and overall survival and differences in toxicity profiles. Accelerated loss of bone mineral density is a well-recognised toxicity of the aromatase inhibitors, whereas tamoxifen does not detrimentally affect bone mineral density in postmenopausal women. However tamoxifen confers a small but established increased risk of endometrial cancer and venous thromboembolism and therefore aromatase inhibitors are often used instead. Bone health thus becomes not only an immediate, but also a long-term issue, as the five year survival for all women with early breast cancer is now 90%, and a majority of these women will survive for decades beyond their initial diagnosis.

Aromatase Inhibitors and bone loss
Large trials testing aromatase inhibitor treatment have examined bone outcomes. While women with normal bone density (T-score > -1.5) did not develop osteoporosis (T-score < -2.5) after five years of treatment, there was an increase in fractures in the cohorts as a whole. Women commenced on an adjuvant aromatase inhibitor may develop significant bone loss (>10%) over the initial 12 months with further development of osteopenia or osteoporosis during the years of their adjuvant treatment.
Such an increased fracture risk may require additional treatment or a change to tamoxifen depending on clinical appropriateness. While early studies did not suggest that such effects on bone from aromatase inhibitors were a significant problem, subsequent reports that have been more focused on bone-related outcomes and suggest otherwise. Gnant and colleagues published the results of their randomised trial in 2015, examining the use of the RANK-ligand inhibitor, denosumab, to combat bone mineral density-related adverse events. In this study, the fracture rate in patients in the placebo arm was alarmingly high. These new data further support the utility of adjuvant antiresorptive agents in the prevention of bone loss, and serve to augment their importance in this role more so than once thought. In fact, there is emerging evidence and some recent published data suggesting that antiresorptive agents may improve disease free survival in addition to preventing bone loss. It is quite reassuring, however, that once aromatase inhibitor treatment is completed, the accelerated bone demineralisation and increased fracture risk does not progress nor continue.

Thus in these generally fit women in whom we induce pharmacologic acceleration of bone demineralisation due to their adjuvant breast cancer treatment, it is important to identify those who require additional treatment to preserve bone mass.

General measures to minimise bone loss

Weight bearing exercise and smoking cessation
Both of these lifestyle measures are important in maintaining both health.

Ensuring adequate calcium intake
All women treated with adjuvant aromatase inhibitor should ingest 1g (equivalent to 4 serves of dairy) per day of calcium in dietary intake. Should dietary intake fall short of this, supplemental calcium is recommended at 600mg depending on dietary intake. Previous concerns regarding the potential for calcium supplementation to increase coronary artery calcification have been largely allayed with reference to postmenopausal women.

Ensuring adequate vitamin D levels
Vitamin D levels fluctuate, largely depending on season, sun-exposure and individual genetics. Vitamin D insufficiency has been found in a significant proportion of women commencing aromatase inhibitors. Australian guidelines define levels of 50 nmol/L and above at the end of winter as acceptable though low normal, and levels of 75 nmol/L and above as normal. All patients should have their vitamin D levels checked at baseline, prior to commencing adjuvant aromatase inhibitor endocrine therapy. In the case of subnormal vitamin D levels, replacement is recommended as specified in the Australian vitamin D position statement paper.

Assessment of bone mineral density

Recent evidence confirms that improving bone mineral density (BMD) with anti-resorptive agents can reduce fracture risk, so it is prudent to check baseline BMD with a dual energy x-ray absorptiometry (DEXA) scan at the time of commencement of an aromatase inhibitor in all patients. If T-score of either femoral neck or lumbar spine is > -1.5 then the DEXA should be repeated in a year's time, as the most precipitous reduction in BMD is expected to occur in the first year. A 10% or more loss of BMD suggests there may be additional processes other than aromatase inhibitor toxicity accounting for loss of BMD. Therefore, should there be 10% of BMD loss or more compared with the baseline DEXA and T-score < -1.5, a referral to an endocrinologist for further investigation should be made.

If at any stage the T score is < -1.5, then treatment should be considered. For T scores -1.5 to -2.5 (osteopenic), a lateral thoracic plain x-ray should be performed, as there is a reported high incidence of pre-existent vertebral fractures in such women commencing aromatase inhibitor. In these patients, should there be evidence of vertebral fractures (or >20% loss of anterior compared with posterior vertebral height) this will qualify for Pharmaceutical Benefits Scheme supported bisphosphonate therapy or rank-ligand inhibitor. A DEXA scan should then be repeated every two years.
For those with T score < -2.5 (osteoporotic), those who are also over 70 years of age qualify for denosumab, as do those under 70 but with a history of fracture or evidence of vertebral body fracture on x-ray. For those who do not qualify, oral bisphosphonates may now be prescribed off Pharmaceutical Benefits Scheme quite inexpensively.

Bone-active agents

Bisphosphonates
The role of bisphosphonates is clear in the treatment of osteoporosis in the presence of minimal trauma fracture or in the elderly, and is reimbursed by the PBS. In the treatment of aromatase inhibitor accelerated bone density loss however, there is a clear role also, though the indication without advanced age or fracture is not reimbursable.

In a recently reported clinical study, patients have volunteered that oral bisphosphonate regimens are not only equivalent in efficacy to intravenous administration, but preferred over intravenous regimens.30 These drugs however are not without toxicity. Given in the oral form, upper gastrointestinal side effects include dyspepsia, gastro-oesophageal reflux and peptic ulceration, and both intravenous and oral preparations can very rarely induce the potentially serious complication of osteonecrosis of the jaw.11,31 There may be a role for use of oral bisphosphonate on private prescription to prevent further bone loss in the absence of minimal trauma fracture, as the cost is similar to PBS subsidised risedronate and alendronate.

Baseline calcium levels also need to be monitored pre-treatment with bisphosphonates, with hypocalcaemia being an occasional but potentially serious toxicity of these drugs in clinic. Additionally, renal function needs to be monitored.32 Despite this, though effective in maintaining BMD, it seems there is still a persistent fracture risk with this treatment.33-35

RANK-ligand inhibitors
Denosumab, a rank-ligand inhibitor, is an effective alternative to the bisphosphonate, zoledronic acid in the treatment of osteoporosis. This is a well-tolerated drug given as a six monthly subcutaneous injection, and has been shown to be effective in the management of aromatase inhibitor induced bone loss.18,36 Although osteonecrosis of the jaw can occur with RANK ligand inhibitors, it may occur less frequently than that which is seen with bisphosphonates and reassuringly in a recently reported large trial, no cases were reported with denosumab.18 Hypocalcaemia occurs more frequently with rank-ligand inhibitors than with bisphosphonates and vitamin D should be >50nmol/L before administration of RANK ligand inhibitors. Renal failure is not a limiting factor with this drug.

Conclusion
It is clear that the management of bone health in postmenopausal women treated with adjuvant aromatase inhibitor endocrine therapy is multifaceted, requires coordination and close follow-up to ensure optimal well-being with improved survival rates. With the aforementioned strategies outlined, bone health can be optimised and the deleterious impact of aromatase inhibitors on bone can be countered if appropriately managed. Ultimately, the steps described here can be utilised within a multidisciplinary context and should assist in the processes to ensure optimal bone health in our patients.

References


