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Title: Adjuvant endocrine therapy in women with oestrogen-receptor-positive breast cancer: How should the skeletal and vascular side effects be assessed and managed?

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Summary

Adjuvant endocrine therapy provides oncological benefits in women with early oestrogen receptor positive breast cancer, but has adverse effects consequent to induced oestradiol deficiency. Bone loss is accelerated, predisposing to increased fracture risk. Metabolic effects include changes in lipid metabolism and body composition although effects on cardiovascular risk are still unclear. Women commencing endocrine therapy should be proactively counselled about and monitored for these and other therapy-related complications including arthralgia and vasomotor symptoms. We provide strategies for prevention and management of these adverse effects, based, where available, on randomised controlled trial evidence specific to breast cancer survivors receiving endocrine treatment.

Introduction

Due to earlier detection and advances in adjuvant systemic treatment, most women with a diagnosis of early oestrogen receptor (ER)-positive breast cancer now have a good prognosis with 10-year survival greater than 90%. Survivorship issues such as unfavourable breast cancer treatment effects are of paramount importance.

Adjuvant endocrine therapy, either with selective oestrogen receptor modulators (SERM) or aromatase inhibitors (AI), is generally given for 5-10 years. SERMs act as ER antagonists in the breast, but have partial agonistic activity in tissues such as bone and endometrium. AIs block the conversion of androgens to oestradiol. In postmenopausal women, this results in near complete (>98%) deprivation of circulating oestradiol. As AIs inhibit the oestradiol-mediated negative feedback on gonadotropin production, they cannot be used in premenopausal women unless ovarian function is suppressed, typically by pharmacological or surgical means.

In postmenopausal women, AIs are preferred because of modest improvements in breast cancer outcomes, including lower 10-year breast cancer mortality compared to tamoxifen (12.1% vs. 14.2%; relative risk (RR) 0.85; 95% confidence interval (CI) 0.75-0.96, $p<0.01$)[1]. In premenopausal women, tamoxifen has traditionally been first line treatment, although a combined analysis of two large randomised controlled trials (RCT), TEXT and SOFT, reported improved 5-year disease-free survival with ovarian suppression (OS) plus the AI exemestane compared to OS plus tamoxifen (91.1% *vs.* 87.3%, hazard ratio (HR) 0.72; 95%

CI, 0.60-0.85; p<0.001)[2]. While endocrine treatment in premenopausal women is evolving, the use of OS plus AI is becoming more frequent, especially in younger (< 35-40 year old) women with high-risk breast cancer[3].

The adverse effects of endocrine therapy may have a significant negative impact on quality of life, treatment compliance, and on short and long-term health consequences. Contemporary management involves expertise outside the traditional oncological specialties including endocrinologists, exercise physiotherapists, sexual health therapists and psychologists. This review focuses on the skeletal and vascular effects of endocrine therapy.

Bone loss and fractures

Tamoxifen has differential effects on bone mineral density (BMD) depending on ovarian oestradiol production. In postmenopausal women, tamoxifen modestly increased BMD (+1.2% at the lumbar spine at 2 years vs. -2.0% with placebo)[4]. In women who continue to menstruate after chemotherapy, tamoxifen reduced lumbar spine BMD by 4.6% at 3 years of follow-up[5].

In postmenopausal women, AIs are associated with increased bone remodelling, a 2-3-fold accelerated BMD decline, and increased fracture rates. In one study, hip BMD declined by 7.24% after 5 years of AI treatment, and the magnitude of bone loss was greatest within the first 2 years[6]. In a meta-analysis of 7 RCTs enrolling 30,023 patients[7] AI use was associated with a 47% increased fracture risk compared with tamoxifen (odds ratio 1.47; 95% CI 1.34-1.61; p<0.001). The absolute difference between the two groups was 2.2%, with a number needed to harm to cause one fracture of 46. Fracture rates were not uniformly collected and varied from 0.9% to 11.0% in these RCTs[7]. Fractures were not adjudicated as primary endpoints and the true risk is likely underestimated; indeed in a recent RCT where bone health was the primary focus, 10% of patients will have a new clinical fracture within 3 years of AI treatment[8].

The largest magnitude of bone loss, 7-9% in the first 12 months, occurs in premenopausal women with chemotherapy-induced menopause or treatment with OS plus AI (Figure 1, adapted from Gralow JR et al)[9]. Alkylating chemotherapy and age >40 years are associated with the highest risk of ovarian failure. In TEXT/ SOFT, the use of OS and AI was associated with twice the prevalence of osteoporosis compared to OS and tamoxifen use (13.2% vs. 6.4% at 68 months)[2].

In RCTs of postmenopausal women, bisphosphonates consistently prevent endocrine therapy-induced bone loss, but fracture outcome data are lacking. By contrast, the ABCSG-18 trial reported a 50% reduction in clinical fracture rates with denosumab (60 mg given 6-monthly for 3 years) compared to placebo (HR 0.50; 95% CI 0.39-0.65; p<0.0001) in postmenopausal women receiving AI treatment[8]. Although fracture numbers were small (overall n=268), the 55% of patients with normal baseline lumbar spine T score (≥1.0) had similar benefit (HR 0.44; 95% CI 0.31-0.64;p<0.0001) compared to patients with a T score of < 1.0 (HR 0.57; 95% CI 0.40-0.82;p<0.0001)[8]. A recent meta-analysis reported that bisphosphonates reduced the risk of breast cancer recurrence (RR 0.86; 95% CI 0.78–0.94; p=0·002), and mortality (0.82, 0.73–0.93; p=0·002)[10]. In premenopausal women receiving AI and OS, bone loss (mean loss 11% at the lumbar spine three years in the absence of antiresportive treatment) was completely prevented by 6-monthly administration of zoledronic acid[11].

Assessment and management of bone health

Prior to commencement of adjuvant endocrine therapy, all women should have a baseline assessment of fracture risk (Figure 2) which includes ascertainment of clinical risk factors, basic laboratory testing (electrolytes, calcium, alkaline phosphatase and vitamin D), BMD, and if reduced bone mass is present, individualised assessment to identify secondary causes of osteoporosis. In women with osteopenia, plain radiographs of the thoracolumbar spine should be considered to exclude subclinical vertebral fractures. The World Health Organisation Fracture Risk Assessment Tool (FRAX) does not take AI treatment or chemotherapy into consideration. Therefore, FRAX may substantially underestimate fracture risk in women receiving these treatments. The utility of bone remodelling markers or bone imaging other than DXA requires further evaluation. DXA should be repeated 12 months after commencement of endocrine therapy, with subsequent individualised monitoring frequency.

General measures to prevent bone loss should be implemented in all women starting endocrine therapy including ensuring calcium and vitamin D sufficiency (Figure 2). Medications with adverse effects on BMD should be avoided.

In line with general recommendations of the National Osteoporosis Foundation[12], women ≥ 70 years with a BMD T-score ≤ -2.5 or with a minimal trauma fracture should commence antiresorptive therapy unless contraindicated. There is limited evidence specific to women

receiving endocrine therapy to guide recommendations outside these criteria, especially in premenopausal women. Although recommendations differ slightly between guidelines[9, 13-15], antiresorptive therapy should be initiated in AI-treated women not fulfilling NOF criteria if the BMD T-score is <-2.0 or ≥ 2 fracture risk factors are present, and be considered where there is a >5-10% decrease in BMD in 1 year[14].

The duration of antiresorptive treatment should be individualised based on absolute fracture risk. Bone loss in most untreated women is most marked in the 12-24 months post AI initiation, and limited data suggest partial BMD recovery after cessation of endocrine treatment.

Premenopausal women commonly have normal baseline BMD with low short-term fracture risk, yet lose bone more rapidly than older postmenopausal women. Decisions regarding antiresorptive treatment should be carefully discussed with the patient. Bisphosphonates can persist in the bone matrix for years after therapy is discontinued, potentially resulting in fetal exposure during pregnancy.

Aromatase Inhibitor-Induced Arthralgia

Musculoskeletal symptoms (arthralgia, carpal tunnel syndrome, musculoskeletal pain) occurred in 43% of AI- compared to 28% in tamoxifen-treated women in one large study[16]. They lead to AI discontinuation in up to 20% of patients. Although the underlying aetiology is unclear, risk factors include obesity, ER-positive breast cancer and prior chemotherapy[17]. In one third of women who continue therapy, symptoms improve within 6 months[17]. In the majority, switching from one AI to another does not help arthralgia.

In a 12 month RCT among 121 women receiving an AI and reporting arthralgia, exercise (150 minutes per week of aerobic exercise and supervised strength training twice per week) reduced worst joint pain scores by 29% versus a 3% increase with usual care, and decreased overall pain severity and interference[18]. Although some RCTs reported benefits from acupuncture, this was not confirmed in a recent meta-analysis[19]. Symptomatic treatment includes analgesia including nonsteroidal antiinflammatory drugs, and potentially duloxetine[20], currently being evaluated in a phase III RCT (NCT01598298). In patients in whom arthralgias compromise their quality of life significantly, a discussion should be made

about switching over to tamoxifen. The clinician and patient need to weigh this up against the small increase in recurrence rates of tamoxifen compared to AIs.

Metabolic and Cardiovascular Effects

The menopausal state is associated with increased cardiovascular risk partially attributed to the negative effects of oestradiol deficiency on lipid metabolism and visceral fat accumulation with resultant insulin resistance. According to the timing hypothesis, early oestradiol deprivation may have adverse cardiovascular effects[21]. This could be particularly detrimental to young premenopausal women in whom treatment with OS plus AI leads to oestradiol levels lower than menopausal levels. However, little is known about the long-term metabolic and cardiovascular effects in these women.

In postmenopausal women, a meta-analysis[7] of large efficacy RCTs of adjuvant endocrine therapy demonstrated an increased cumulative risk of cardiovascular disease (CVD) with the use of AIs compared to tamoxifen (OR=1.26; 95% CI 1.10-1.43; p<0.001; number needed to harm = 132). In contrast, in a recent retrospective cohort study[22] of 13,273 postmenopausal women without prior CVD, AI users had a similar risk of cardiac ischaemia (HR 0.97; 95% CI 0.78-1.22) or stroke (HR 0.97; 95% CI 0.70-1.33) compared to tamoxifen users [22]. The differential CVD risk of AI compared to tamoxifen may be related to effects on lipid metabolism. Tamoxifen modestly decreases LDL-cholesterol and increases HDL[23], whereas opposite changes have been reported for AIs[24] although not all studies concur. Conversely, small studies suggest that AI use, compared to tamoxifen is associated with modest changes in body composition expected to be metabolically favourable, although data are far from definitive[25,26].

In the absence of specific evidence, CVD assessment, management, and risk factor control should follow to guidelines established in patients without breast cancer[27], noting that CVD events are a common cause of mortality in older breast cancer survivors. Lifestyle measures including maintaining a healthy weight, regular physical activity and smoking cessation should be recommended routinely; these measures also reduce adverse breast cancer-associated oncological outcomes [28].

Vasomotor Effects

Vasomotor symptoms occur in the majority of breast cancer survivors, especially with tamoxifen. Although frequency and severity may decrease over time, they can negatively

impact treatment compliance, sleep, mood and quality of life. Extrapolating from evidence in post-menopausal women without breast cancer, an initial trial of lifestyle modifications is a rational approach. Weight loss, not exercise, has been associated with benefit in overweight/obese women[28]. There is no consistent evidence for efficacy of complementary and alternative therapies.

For moderate to severe hot flushes, selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, and gabapentin appear to be the most successful non-hormonal pharmacotherapies, although there is marked variability in treatment response and a significant placebo effect (up to 50% in some trials)[29]. Clonidine has also a 20-30% reduction compared to placebo, but is not commonly used due to significant side effects of mouth dryness, drowsiness and constipation[30]. In women being treated with tamoxifen, potent inhibitors of cytochrome P450 2D6 such as fluoxetine and paroxetine should be avoided due to potential inhibition of tamoxifen bioactivation. In severe cases adjuvant endocrine therapy might need to be ceased. Hormonal treatments such as oestradiol[31] or tibolone[32] have been shown to increase the risk of breast cancer recurrence in some RCTs of breast cancer survivors and we do not recommend their use. While there is no question that hormonal treatments are absolutely contraindicated in women on AI, some authorities would consider hormone therapy in breast cancer survivors on tamoxifen for quality of life if other measures have failed to provide adequate symptomatic relief, although this remains controversial (for review see[33]). It is our practice to avoid systemic oestrogens in our patients with a history of breast cancer.

Conclusions

Prior to commencement of adjuvant endocrine therapy all patients should be counselled about associated side effects, and these should be considered in the decision making process, especially in women at high risk for cardiovascular events or fractures. Treating clinicians should be assiduous in ascertaining treatment-related adverse effects and pursue interventions known to mitigate these effects and enhance treatment adherence. Management is best done using an individualised, multidisciplinary approach. Future clinical trials are needed to better delineate the long-term sequelae of adjuvant endocrine therapy, in particular cardiovascular and fracture risks, and to determine the efficacy of interventions designed to minimise or prevent these risks.

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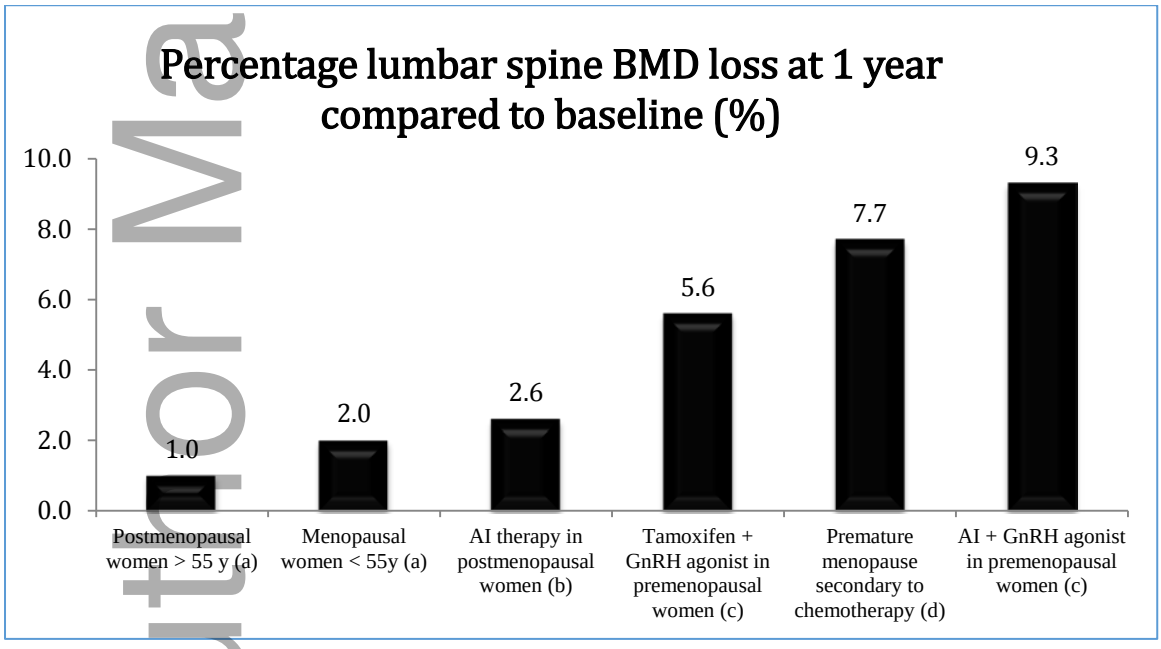
Figure 1 Rates of bone loss with normal aging and cancer therapies – Lumbar spine BMD loss (%) at 1 year.



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416 **Figure 2 Monitoring and management of bone health in women with breast cancer**

BASELINE ASSESSMENT

Clinical risk factors for osteoporosis: age >65 years, previous minimal trauma fracture after age 50, parental history of hip fracture, low body mass index (<20kg/m^2), current or previous cigarette smoking, consumption of >3 units of alcohol per day, glucocorticoid use for more than six months, and relevant co-existing medical conditions such as rheumatoid arthritis

Clinical risk factors for osteoporosis specific to breast cancer: high prevalence of vitamin D deficiency (up to 88%), decreased physical activity, increased risk of falls secondary to treatment-induced neuropathy, chemotherapy induced ovarian failure, AI therapy, OS plus AI or tamoxifen in premenopausal women, and use of glucocorticoids with chemotherapy regimens

Falls risk

Laboratory testing to exclude secondary causes of osteoporosis: serum calcium, parathyroid hormone, 25-hydroxy vitamin D, creatinine clearance, liver function, coeliac serology and thyroid stimulating hormone

Hip and spine BMD measurement by dual energy X-ray absorptiometry

Thoracolumbar spine X-rays in women with osteopenia or osteoporosis (BMD T-score <-1.0 and ≤ -2.5 respectively)

MANAGEMENT

Non-pharmacological

- Regular moderate physical activity (weight-bearing exercises and resistance training)
- Smoking cessation,
- Limitation of alcohol to <3 standard drinks per day
- Calcium intake of 1000-1300mg, preferably dietary
- 25-hydroxy vitamin D supplementation to achieve and maintain levels >75nmol/L

Pharmacological

Antiresorptive therapy in women with:

- Clinical or radiological minimal trauma fracture
- Baseline BMD T-score of <-2.0
- Annual BMD loss of 5-10%
- 10-year absolute risk of a major osteoporotic fracture of >20%, or of a hip fracture of >3%

417

418 AI, aromatase inhibitor; OS, ovarian suppression; BMD, bone mineral density