AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Breast Cancer and Menopause

Key Points

- Menopause/menopausal symptoms in women with breast cancer have a significant negative impact on quality of life, with both short- and long-term health consequences.
- Management of menopause in women with breast cancer is directed at relieving troublesome symptoms and minimising risks of cardiovascular disease, osteoporosis and breast cancer recurrence.
- Menopausal hormone therapy after breast cancer is not usually recommended, regardless of the hormone receptor status of the tumour.
- A variety of non-hormonal therapies for vasomotor symptoms have been investigated.
- The safety of botanicals and phytoestrogens in breast cancer survivors is unclear.

Introduction

Menopause/menopausal symptoms in women with breast cancer (BC) have a significant negative impact on quality of life, with both short- and long-term health consequences, and can affect BC treatment adherence. Menopause/menopausal symptoms in women with BC may be associated with (1) natural menopause occurring concurrently with a BC diagnosis, (2) recurrence of menopausal symptoms following cessation of menopausal hormone therapy (MHT) upon breast cancer diagnosis, (3) risk-reducing bilateral oophorectomy, chemotherapy or ovarian suppression secondary to gonadotropin releasing hormone (GnRH) analogues in premenopausal women, and/or (4) endocrine adjuvant therapy with tamoxifen or aromatase inhibitors[1].

Women with breast cancer, especially younger women, experience more severe menopausal symptoms than women without breast cancer[2] . The spectrum of symptoms is similar to usual age menopause (See AMS information sheet *What is menopause?*) and a study of 843 Australian women indicated that most women aged 50-69 years had persisting vasomotor, psychosocial, physical and sexual symptoms at 6 years post BC diagnosis despite having ceased adjuvant endocrine therapy[3].

Women with BC may be at increased risk of cardiovascular disease (CVD). A systematic review assessing CVD mortality in women with BC reported that 9.4-10.4% died of CVD compared to 7.4-7.5% women without BC[4]. Multiple factors may influence CVD risk including the indirect/ direct effects of therapies including chemotherapy, radiotherapy,

adjuvant endocrine therapies, lifestyle changes and weight gain accompanying BC diagnosis. The ten-year predicted CVD risk was greater than or equal to BC risk recurrence in a study of 415 women with BC, mean age 60 years[5]. Osteoporosis and fracture risk is also increased in women with BC, the greatest bone loss observed in younger women treated with GnRH analogue + aromatase inhibitor[6]. Adjuvant endocrine therapy, vitamin D deficiency and increased falls risk secondary to chemotherapy-induced neuropathy are some of the factors which contribute to osteoporosis risk[6]. Oestrogen depletion due to aromatase inhibitors is associated with accelerated bone loss which predisposes to increased fracture risk. In contrast, tamoxifen in postmenopausal women acts as an oestrogen on bone and retards bone resorption and reduces fracture risk.

Management of menopause in women with breast cancer is directed at relieving troublesome symptoms and minimising risks of cardiovascular disease, osteoporosis and breast cancer recurrence.

Diagnosis of menopause

The diagnosis of menopause is obvious after bilateral oophorectomy or where menopause occurred prior to BC diagnosis. However, in premenopausal women the diagnosis of menopause following BC chemotherapy can be difficult especially with concurrent tamoxifen therapy. FSH levels can be difficult to interpret in the women receiving tamoxifen, since, in contrast to its action in premenopausal women, tamoxifen partially suppresses gonadotrophins in the postmenopausal woman[7]. A model combining anti-mullerian hormone levels with age has been proposed to assist with the prediction of amenorrhoea post-chemotherapy[8]; however, validation in the real world setting is lacking.

Management of Menopause

1. Vasomotor symptoms

Although oestrogen containing MHT is the most effective therapy for vasomotor symptoms, there is conflicting evidence regarding safety of MHT after BC and it is not recommended, regardless of the hormone receptor status of the tumour. Clinical trials of MHT in women with early BC indicated that BC recurrence was increased after 2 years average follow-up in the HABITS study[9] (Relative hazard [RH] = 3.3, 95% confidence interval [CI] = 1.5 to 7.4) but not after 4 years of follow-up in the Stockholm study[10] (RH = 0.82, 95% CI = 0.35 to 1.9). These differences may relate to differences in progestogen exposure (continuous in HABIT and sequentially every 1-3 months in Stockholm), less tamoxifen use and higher rate of node positive patients in the HABITS trial[10]. Results from the LIBERATE trial indicated an increased risk of BC recurrence with tibolone therapy BC survivors (overall RR 1.40 95%CI 1.14-1.70)[11] regardless of whether the tumour was oestrogen and/or progesterone receptor positive. Although, the recurrence risk may be less in women with oestrogen receptor negative cancer[11]. Historically, high dose progestogen therapy was used as adjuvant therapy. As MHT is not generally recommended, a variety of non-hormonal therapies for vasomotor symptoms have been investigated (see AMS information sheets *Nonhormonal*

treatments for menopausal symptoms and *Complementary and herbal therapies for hot flushes*). Findings from a recent comparative analysis[12] are shown in Figure 1, indicating that the non-hormonal SSRIs/ SNRIs and neuroleptic agents (including gabapentin and pregabalin) had the greatest efficacy; whereas botanicals, magnesium and Vitamin E were comparable to placebo. These findings are consistent with recommendations of the North American Menopause Society (NAMS) position statement which also recommended cognitive behavioural therapy and hypnosis as treatment options (http://www.menopause.org/docs/default-source/professional/2015-nonhormonal-therapy-position-statement.pdf). The safety of botanicals and phytoestrogens in BC survivors is unclear. Compounded bioidentical hormone preparations may contain oestrogens and progestogens and their safety in BC is unknown.

2. Urogenital symptoms

Up to 75% of women with BC report at least one urogenital symptom if asked; however, many women do not raise this issue. Urogenital symptoms were considered to have the highest prevalence of "unmet need"[13]. Chemotherapy, aromatase inhibitor treatment and smoking are risk factors for urogenital symptoms. Vaginal oestrogens are the most effective treatment for urogenital symptoms; however, the use of these agents by women with BC, especially those taking aromatase inhibitors, is controversial. Recommendations from NAMS (https://www.menopause.org/docs/default-source/professional/management_of_genitourinary_syndrome_of_menopause.pdf) and the American College of Obstetricians and Gynaecologists (https://www.acog.org/-/media/Committee-Opinions/Committee-on-Gynecologic-Practice/co659.pdf?dmc=1&ts=20190527T0539259779) regarding management are:

(a) comprehensive assessment including history and physical examination
(b) counselling with validation and explanation of symptoms
(c) Non-hormonal moisturisers and lubricants, pelvic floor physiotherapy and dilator therapy are first line agents
(d) Long term safety and efficacy data are lacking for laser therapy (See AMS fact sheet *Vaginal laser therapy*)
(e) For women taking adjuvant endocrine therapy who have an inadequate response with non-hormonal agents, discussion with the women, her oncologist and an individualised risk assessment is required for consideration regarding use of vaginal oestrogen. The use of intravaginal oestrogens with tamoxifen is of less concern compared to that in women taking aromatase inhibitors.

The safety of ospemifene, intravaginal DHEA and intravaginal testosterone is unknown in women with BC.

3. Lifestyle

Weight gain of 2.3-5kg occurs following BC diagnosis/ treatment and is multifactorial[14]. Excess weight is associated with increased BC recurrence. In overweight women,

weight loss may assist with control of vasomotor symptoms and reduce CVD risk (see AMS information sheet *Weight management and healthy ageing*).

4. Bone health

Assessment of fracture risk is important for all women diagnosed with BC due to the negative impact of cancer therapies on bone health. A position statement[6] , co-authored by the Australasian Menopause Society, recommends a comprehensive assessment of bone health including history to identify additional risk factors and investigations including biochemistry (serum electrolytes, liver function, 25OH Vitamin D, TSH, calcium, magnesium and phosphate), bone densitometry (DXA) and plain thoracolumbar Xrays (or VFA as part of DXA). Management should be directed at optimising dietary calcium intake (1000-1200mg/day), weight bearing exercise and vitamin D. Anti-resorptive therapy may be required in the setting of (i) prevalent or incident fragility fracture (ii) T score < -2.0 or significant bone loss.

5. Contraception

Pregnancy should be avoided during active treatment for BC. Systemic hormonal contraception (including oral, vaginal rings, subdermal or intrauterine) is not recommended[15]. The copper T IUD is recommended as a safe and effective form of contraception for women with BC. IUDs are 99.2% effective and provide contraception for 10 years[15]. Barrier and natural methods can be used although are less effective.

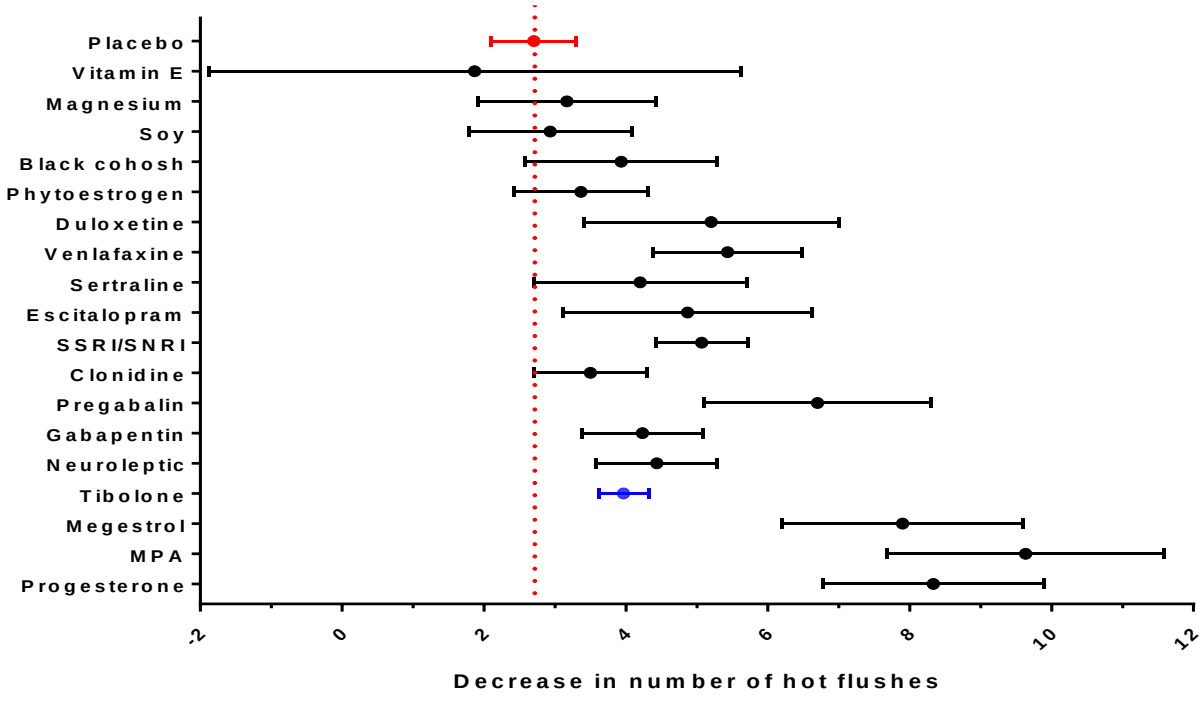

Figure 1: Calculated comparative efficacy (with 95% confidence interval) in reduction of hot flush frequency. Red dotted line indicates calculated placebo value and blue point indicates tibolone. Data derived from[12].

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