ENDOCRINE DILEMMA

Managing menopausal symptoms after breast cancer

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Abstract

Managing the symptoms of menopause after a diagnosis of breast cancer offers some unique clinical challenges. For some women, vasomotor symptoms can be severe and debilitating, and hormone therapy is at least relatively contraindicated. Non-oestrogen therapies for hot flushes include SSRIs, clonidine, gabapentin and perhaps black cohosh extracts. Vulvovaginal atrophy can usually be alleviated by simple moisturizers, although some may need specialized physiotherapy such as vaginal dilators. In a small number, topical oestrogens may be the only treatment that works. The CO₂ laser may be a novel, non-oestrogen therapy to alleviate this unpleasant symptom. Bone loss can be accelerated in some patients on AIs or those who had early menopause induced by chemotherapy.

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Introduction

For many menopausal women, symptoms such as hot flushes, insomnia, mood swings and vaginal dryness are problematic. Hormone replacement therapy (HRT) and topical oestrogens are highly effective and safe when used for the short-term. However, for those with a personal history of breast cancer HRT, even topical oestrogens are considered at least relatively contra-indicated. Not only that, chemotherapy can induce premature menopause, provoking severe hot flushes. Many of the endocrine therapies used to treat ER+ breast cancer (tamoxifen and aromatase inhibitors (AIs)) can aggravate or induce hot flushes. Thus many breast cancer survivors will have poor quality of life and painful, unpleasant intercourse, if not treated.

Also, menopause *per se*, has long been associated with osteoporosis. Early menopause, induced by chemotherapy, and the AIs can accelerate this potentially devastating bone problem. Fortunately, there are many non-controversial options, such as the bisphosphonates, available to help these women (Table 1). The management of menopausal symptoms after a diagnosis of breast cancer is much more controversial and difficult.

Health professionals working with breast cancer survivors are very aware of the quality of life issues after breast cancer. Over the last two decades, there has been much research and many clinical trials aimed at finding effective non-oestrogen therapies to help such menopausal women.

Invited Author's profile

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Table 1 Treatment options for menopausal women with a personal history of breast cancer.

Symptom	Treatment option
Hot flushes	Remifemin SSRIs Clonidine Gabapentin (Moderate-dose progestin) (HRT)
Vulvo-vaginal dryness	Soap-free washes Moisturizers Lubricants (CO ₂ laser)
Osteoporosis	Bisphosphonates Denosumab Tamoxifen/Raloxifene

For this review, a literature search was performed using the search engine Primo at UNSW, using the following keywords: non-hormonal, meta-analysis, antidepressant, gabapentin, hot flush, hot flash, vaginal dryness, SSRI, SNRI, clonidine, progestin, medroxyprogesterone acetate and osteoporosis. Preference was given to more recent papers and reviews.

Managing hot flushes

For many breast cancer survivors, hot flushes are a major problem. Sweats and flushes are often worse at night and so disrupt sleep, often resulting in tiredness and mood swings. Simple measures such as staying cool, avoiding stress, hot drinks, and spicy food can help a little. Many women seek safe options from their medical practitioners to reduce these unpleasant hot sensations. Fortunately, several evidence-based, non-oestrogen options are available and recently, there have been several excellent reviews and meta-analyses published on this subject (1, 2, 3).

Of course, the endocrine therapies used to treat breast cancer such as the AIs and tamoxifen often induce hot flushes. In some patients, it may be difficult to know whether their flushes are due to menopause or their drug therapy. Sometimes, the only way to find out is to temporarily stop the drug therapy for 2–4 weeks. If most of the sweating disappears, then trying a different agent or reassessing the case may be indicated. Sometimes the patient may choose not to take the drug and accept a small increased risk of recurrence or new breast cancer, rather than putting up with severe flushes.

Black cohosh and other herbals

Many women would like to use a natural product to help their menopause symptoms. Amongst the many herbal

preparations offered as therapies for menopausal flushing, the two most common are phytoestrogens (soy or red clover based) and black cohosh. Nelson *et al.* (3) performed a meta-analysis of non-hormonal therapies for flushes, including red clover in their study. They showed that the effect of red clover extracts on hot flushes was not superior to placebo. Also, since these products are, at least theoretically oestrogenic, they should be considered relatively contraindicated in the breast cancer setting.

In contrast, black cohosh extracts are not oestrogenic and may in fact have some anti-oestrogenic properties on breast tissue (4, 5, 6). Einbond (4) exposed a number of human breast cancer cell lines to black cohosh extracts and showed inhibition of growth, particularly in those cell lines overexpressing HER2. Clinical trials in humans have shown that women taking black cohosh had no change in mammographic density or endometrial thickness over 6 months of usage (6). This would suggest a lack of oestrogenic effect on breast and uterine tissue by the extract. Furthermore, Obi *et al.* (5) performed a case controlled study of women using herbal extracts to manage menopausal symptoms. They found that usage of phytoestrogens or black cohosh extracts was associated with a decreased risk of breast cancer (OR 0.72, 95% CI 0.60–0.87).

Efficacy studies with black cohosh give mixed results (7). Part of the difficulty of performing meta-analyses in this area of research is heterogeneity, not just with the studies themselves but also with the different extracts. They are not all the same. Where and how the herb is grown, the extraction process and many other factors can influence the final composition of the herbal extract. Specifically, the German product, Remifemin, has at least four randomized trials (8, 9, 10, 11) showing efficacy. One trial (10) even showed equivalence with a low-dose oestradiol patch.

Concerns have been raised about occasional reports of hepatotoxicity associated with black cohosh usage. Teschke (12) has reviewed the cases and cast doubt on this association. Also, to date, no case of liver problems has been described in a patient using black cohosh for less than 6 months. In summary, a high quality black cohosh product like Remifemin would seem a reasonable starting point to help a patient who has been treated for breast cancer to try to reduce her hot flushes.

Antidepressants

The older tricyclic antidepressants commonly cause sweating and flushes as a side effect. SSRIs appear to be

different in this respect. In the last few years, there have been many trials examining the efficacy of SSRIs on hot flushes and several meta-analyses have been published (2, 3, 13). It seems to be a class effect; they are all helpful in low-dosage (e.g. citalopram 20 mg). Interestingly, in the high dosage used for severe depression (e.g. citalopram 60–80 mg), excess sweating is a common side effect. It is usual to commence therapy with a half-dosage for 2–4 days to minimize start up side effects such as headache and nausea. After that, the lowest effective dose for depression seems to help reduce hot flushes (e.g. citalopram 20 mg). They are generally very well tolerated.

Paroxetine should be avoided in those patients taking tamoxifen. This SSRI has been shown to interfere with the metabolism of tamoxifen (14). Over the long term, SSRIs may inhibit sexual responsiveness and orgasm. Interestingly, a placebo-controlled, randomized trial has shown that loss of orgasm associated with SSRIs can be restored with sildenafil 50–100 mg (15). Despite these problems, SSRIs are very useful in this setting. Depression and mood swings are common after a diagnosis of breast cancer as well as hot flushes. Thus the judicious use of a low-dose SSRI may markedly improve the quality of life after breast cancer.

Clonidine

The α -blocker, clonidine, in low-dosage has been shown in meta-analyses to be superior to placebo for hot flushes (3). The usual starting dose is half a tablet twice a day, increasing if needed to 1 twice a day. The half tablet twice a day dosage usually does not affect blood pressure, whereas the 1 twice daily dosage typically lowers blood pressure by around 5 mmHg. In these low doses, side effects are uncommon but may include dizziness (due to lowering blood pressure), dry mouth (anti-cholinergic effects) and in high dosage (not used for hot flushes), it may aggravate depression. Clonidine in these doses has been used as a migraine preventive agent too and the combination of hot flushes and migraine is common during the menopause transition. Thus for some patients, this agent may help two medical conditions.

Comparative trials of venlafaxine vs clonidine

There have been three trials published comparing the antidepressant venlafaxine with clonidine (16, 17, 18). Buijs performed a crossover study of venlafaxine 75 mg vs clonidine 50 μ g twice daily (one half of a 100 μ g tablet).

Both agents had a similar flush-reducing action (around 50% improvement) and more patients had side effects (and stopped medication) with venlafaxine than clonidine. Loibl (17) compared venlafaxine 37.5 mg twice daily with clonidine 75 μ g twice daily for 4 weeks. Venlafaxine was superior to clonidine for the relief of hot flushes. Boekhout (18) used a 2:2:1 design to compare venlafaxine 75 mg, clonidine 100 μ g and placebo for 12 weeks. Both active drugs were superior to placebo for hot flushes. Venlafaxine had a quicker effect than clonidine; clonidine was more effective than venlafaxine at 12 weeks and more subjects had side effects from venlafaxine (especially nausea and constipation).

Gabapentin

Gabapentin was initially developed as an anticonvulsant and was later found to have nerve-stabilizing effects making it useful for nerve pain (e.g. trigeminal neuralgia, shingles pain). It can be helpful for migraines, bipolar disorder and fibromyalgia (19, 20). There are numerous trials using gabapentin to relieve hot flushes. Three meta-analyses (2, 19, 20) have shown superiority over placebo. The usual dosage used was 900 mg daily in divided doses, although in a small number of studies much larger doses have been used.

Typically, treatment is commenced with 300 mg at night and then the dosage is increased every 4–7 days by 300 mg (in divided doses). Gabapentin is usually well tolerated. However, side effects may include dizziness, unsteadiness, fatigue and somnolence. In the setting of breast cancer, some patients develop nerve pain in surgical wounds and so gabapentin may help relieve pain as well as hot flushes. Gabapentin may also be an option for the migranous patient suffering concomitant hot flushes.

Moderate–high dose progestins

In the 1980s and 1990s, high dose progestin was one of the standard treatments for advanced breast cancer (21) and moderate to high dose progestins such as medroxyprogesterone acetate (MPA) and Megestrol were also used to relieve hot flushes (1, 22, 23). In contrast, the Women's Health Initiative study (WHI, (24)) showed that the combination of conjugated equine oestrogen 0.625 mg and MPA 2.5 mg daily was associated with an increased risk of breast cancer (eight extra breast cancers/10 000 women/year after 5 years). This apparent paradox can be explained in several ways.

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First, advanced breast cancer is likely to behave differently than very small breast cancer being stimulated by hormone therapy (HT). Second, the dose of progestin was markedly different. Sutherland *et al.* (25, 26) through a series of elegant experiments showed in the 1990s that low doses of progestins tended to stimulate the cell cycle of normal and malignant breast cells, in contrast to high-dose progestins which typically hurried the cell through one cell cycle and then arrested growth.

In current clinical practice, high-dose progestins are hardly ever used to treat breast cancer. As a treatment for hot flushes, high-dose progestins can cause fluid retention, glucocorticoid effects, mood swings and weight gain.

Hormone therapy

Today, the use of HT after breast cancer would seem an anathema. However, a few years ago, a number of clinical trials were performed to examine the safety of using HT after a diagnosis of breast cancer (23, 27, 28, 29).

The first was a retrospective observational study of 1122 women with a personal diagnosis of breast cancer, treated by five Sydney doctors between 1964 and 1999 (23). Two hundred and eighty six used HT after their diagnosis of breast cancer. Typically the patients were offered MPA 50–100 mg daily to relieve their hot flushes. If that did not relieve their hot flushes then oestrogen was added to the moderate dose progestin (138 took combined HT). Relative risks (RR) were determined using Cox regression analyses, adjusting to patient and tumour characteristics. One thousand one hundred and twenty two patients were followed up for an average of 6 years. The HT users had a reduced risk of recurrence (RR 0.62, 95% CI 0.43–0.87). This was a unique study that took into account the likely beneficial impact of a moderately high dose progestin in this setting.

There were two studies using ‘standard HT’ regimens of conjugated equine oestrogens and low-dose MPA, the Stockholm study (27) and the HABITS study (28). Both were terminated early. The Stockholm study was a randomized open label study with two parallel arms. Subjects had to be disease-free at time of entry and they were stratified according to tamoxifen usage, type of HT, and time since primary diagnosis. They were randomized to HT ($n=188$) or no HT ($n=190$). They recently reported on 10 year follow-up of this study group. There was no difference in new breast cancer events between the groups.

HABITS (28) was a randomized, non-placebo controlled non-inferiority trial. Cox models were used to

estimate RR of a breast cancer event. Four hundred and forty seven women were randomized and 442 were followed up for a median of 4 years. Thirty nine of the 221 women on HT and 17 of the control arm experienced a new breast cancer event (HR=2.4, 95% CI 1.3–4.2). After extended follow up, there was still a significantly increased risk of a new breast cancer event in the group who used standard HT.

Finally, LIBERATE was a randomized placebo controlled trial of tibolone 2.5 mg daily given to breast cancer patients having significant hot flushes ($n=3148$). After a median follow up of 3.1 years, there was a higher risk of recurrence in the treatment group compared to placebo (HR=1.40, 95% CI 1.14–1.70) and so the study was terminated early. The tibolone treated group had a significant improvement of their hot flushes and high bone density than the control group.

Managing vulvo-vaginal dryness

The vagina is the most sensitive tissue in the body to oestrogen. Menopause, natural or induced, commonly results in vulvo-vaginal atrophy with concomitant loss of rugal folds, thinning and drying of the vagina epithelium. This results in clinical problems such as painful intercourse, vulval ‘burning’ sensations, and recurrent urinary tract infections. The AIs typically aggravate these problems. Tamoxifen usage is often associated with an unpleasant yellow vaginal discharge. Oncologists are reticent to prescribe topical oestrogens for fear of systemic absorption and thus an increased risk of breast cancer recurrence (especially amongst patients on AIs).

Many women are embarrassed to talk about such intimate problems. Often when the clinician raises the issue with the patient, they are greatly relieved that something can be done about it. Many respond to simple measures such as the avoidance of soap, the use of soap-free washes and water-based moisturizers (e.g. Replens). Lubricants such as olive or coconut oil or Sylk are much more effective than water-based lubricants.

Women who have had the problem for many years may develop pain in their pelvic floor muscles which become myalgic. Physiotherapy aimed at relaxing these sore pelvic floor muscles can be very helpful. Sometimes vaginal dilator therapy and/or Botox infiltrated into the muscles (under general anesthetic) is needed. In such affected women, pelvic floor exercises should be avoided, as they aggravate the problem. A bike seat will also make the soreness much worse so bike riding should be avoided.

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There has been a cohort study of vaginal oestrogen usage after a diagnosis of breast cancer (31). One thousand four hundred and seventy two women with a personal diagnosis of breast cancer were recruited. Sixty-nine had used topical oestrogens after their diagnosis of breast cancer. Cox regression analysis was performed. Hormone usage was entered as a time-dependent covariate with disease-free intervals as the outcome. Subjects using topical oestrogens had a correct HR of 0.30 (95% CI 0.20–1.58). Although the numbers were small, these data were reassuring.

A novel recent development in this area is the use of a fractional, microablative CO₂ laser to treat vulvo-vaginal atrophy. In one uncontrolled prospective study (32), 77 postmenopausal women were treated with the CO₂ laser. Using the Female Sexual Function Index, marked and significant improvement in symptoms was seen over 12 weeks. At the moment, it is not known how long the effect lasts. The procedure itself is usually painless to perform.

Osteoporosis and breast cancer

Some breast cancer patients are at high risk of developing osteoporosis, either because of early menopause induced by chemotherapy and/or the use of AIs. Fortunately, the bisphosphonates and more recently, denosumab, have a strong track record as successful treatments for advanced breast cancer, particularly bone metastases (33, 34, 35). Typically the doses used in this situation are much higher than those used for osteoporosis. For example, in one recent randomized trial, denosumab 120 mg was compared with zoledronic acid 4 mg, given every 4 weeks as treatment for bone metastases. All took calcium and vitamin D. Denosumab was superior in delaying time to first skeletal-related event (SRE; HR 0.82, 95% CI 0.71–0.95). In general, adverse events (AEs) were similar in the two groups. Osteonecrosis of the jaw occurred infrequently (2% denosumab; 1.4% zoledronic acid).

Cheung *et al.* recently reviewed the relationship between breast cancer and osteoporosis (35). Most patients with ER+ breast cancer benefit from an endocrine treatment and for most menopausal patients, they will be offered an AI. These can accelerate bone loss and cause fractures. Interestingly, bisphosphonates used in the standard (low doses) used for osteoporosis treatment, not only prevented bone loss and fracture but seemed to be associated with improved disease-free survival and a decreased risk of death in postmenopausal women (35, 36, 37, 38). Tamoxifen and other SERMs (e.g. raloxifene) appear to decrease menopausal bone loss, in contrast to the AIs (35, 36). Of course, tamoxifen can cause other

side effects such as endometrial polyps and cancer as well as eye complications such as cataracts.

All women with a diagnosis of breast cancer should be offered the same prevention and monitoring of bone loss as other menopausal women. Supplements containing calcium and vitamin D are helpful. The combination of vitamin D deficiency and an AI can induce marked bone loss. Those with osteoporosis (low-T scores; fragility fractures; FRAX score consistent with high risk of fracture) especially those on AIs, should be offered standard doses of bisphosphonates or denosumab.

Conclusions

Over the last 40 years, there has been a steady improvement in survival rates after a diagnosis of breast cancer. Earlier diagnosis and better therapies have meant that many more women are surviving breast cancer. However, many have poor quality of life due to persistent severe hot flushes, insomnia and vulvovaginal dryness. Over the last fifteen years, or so there has been much research aimed at controlling menopausal symptoms (and side effects of endocrine therapies).

When planning therapy, consideration should be given to co-morbidities and other medical conditions. For example, the hypertensive patient with hot flushes might be offered clonidine and a first-line therapy. The migrainous flushing patient could be offered gabapentin or clonidine. Many would like to try a herbal therapy first and Remifemin should be considered. If mood swings, anxiety and/or depression are present as well as hot flushes, a low-dose SSRI is likely to be helpful.

It is important to ask menopausal women who have had breast cancer about genito-urinary health. Most women want to talk to a health profession about these problems. Most women suffering from vulvovaginal atrophy will respond to simple measures. Some will need referral to a pelvic floor physiotherapist or a gynaecologist. In a few cases, the only treatment that seems to work is a topical oestrogen. Obviously, the theoretical risks need to be discussed on an individual basis.

All menopausal breast cancer patients should be offered bone density screening. It seems clear that Tamoxifen has a positive bone effect, unlike the AIs which can accelerate bone loss. Fortunately, standard doses of bisphosphonates or denosumab are effective and safe in this setting.

In general, HRT and tibolone should be avoided in this setting. Trials using these therapies after a diagnosis of breast cancer suggest a higher risk of recurrence of cancer.

In a very small number of cases, a patient having severe intractable hot flushes who has failed to respond to all other treatments may choose to use HRT and accept the small increased risk of recurrence.

As the medical profession is curing more and more patients who have had breast cancer, it is hoped that we can also offer them safe and effective therapies to manage unpleasant menopausal symptoms.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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