Management of symptomatic side effects of anti-hormonal therapy in breast cancer survivors

HOT SPOT

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Breast cancer is a disease that will affect more than 22,000 women in 2009 (Canadian Cancer Society, 2009). That being said, women with early stage disease have a greater than 85% chance of long-term cure. As such, there is a need to pay increased attention to the symptomatic long-term side effects of breast cancer treatments. Some of the most prevalent long-term side effects of therapy are those related to menopausal symptoms. Women with breast cancer are more likely to suffer the effects of menopause for several reasons. These include, but are not limited to the following:

1. Average age of diagnosis is 62
2. Abrupt discontinuation of hormone replacement therapy at the time of diagnosis of breast cancer
3. Therapeutic hormonal manipulation with agents such as Tamoxifen and Aromatase inhibitors
4. Chemotherapy-induced ovarian failure in pre-menopausal women
5. Improved earlier detection of breast cancer resulting in more breast cancer survivors.

Estrogen deprivation causes many symptoms, but the most common are those related to vasomotor effects and urogenital atrophy. Due to the concerns about risk of recurrence or second breast malignancy of hormone replacement therapy, as raised by the HABITS (Brincat, Muscat Baron, & Ciantar, 2004) and Women's Health Initiative studies (Rossouw et al., 2002), systemic hormone replacement is not recommended in breast cancer survivors. Therefore, alternate strategies to minimize or ameliorate these symptoms are required. The remainder of this insert will address this issue.

Vasomotor symptoms

Also known as "hot flushes" or "hot flashes" are the most frequent menopausal symptoms, and are reported at a higher frequency than post-menopausal women without breast cancer (Carpenter et al., 1998). The symptoms are described as a sudden transient sensation of internal heat and redness of the face and upper body, often accompanied by sweating and dizziness, and may be followed by a chill. Objective findings include peripheral vasodilation, tachycardia and large skin conduction changes. Core body temperature is not elevated during the hot flush. Most women tolerate hot flushes and are able to remain active. However, others may find them distressing and some may even consider discontinuing breast cancer therapy. Advising patients as to the non-pharmacological strategies and the pharmacological options for dealing with hot flushes is important in order to ensure that women remain compliant with therapy.

Non-pharmacological strategies for dealing with hot flushes have been shown to improve severity of symptoms significantly. These strategies can also be combined with pharmacological therapy to improve outcome (Table One).

When considering introduction of pharmacological strategies for dealing with hot flushes, it is important for the clinician to consider that multiple placebo-controlled trials have shown a 25% decrease in symptoms with four weeks of placebo therapy alone. This must be considered, especially if the therapy used has only anecdotal evidence. Some of the more extensively studied agents include the SSRIs, Gabapentin, Clonidine, and hormonal agents. Hormone replacement therapy is the most effective pharmacological intervention for the treatment of hot flushes, but due to previous studies, which indicated that there may be an increased risk to breast cancer recurrence, these agents are, for the most part, avoided in breast cancer survivors. To date, the long-term effect of progesterone-only agents or alternate hormone agents such as tibilone are not known in breast cancer survivors. The most commonly studied non-hormonal agents are summarized in Table Two.

Urogenital atrophy

Postmenopausal women are at risk for developing urogenital atrophy, symptoms of which can include vaginal dryness resulting in dyspareunia, vaginal itching, frequency, urgency and recurrent urinary tract infections. This is due to a combination of physiologic aging and the effects of decreased estrogen levels on the urogenital tract. The reasons for symptoms of urogenital atrophy in breast cancer survivors are summarized in Table Three.

These symptoms are heightened by the further estrogen deprivation of the aromatase inhibitors, but, for the most part, the symptoms are under-reported by women. A recent survey study has shown that more than 63% of breast cancer survivors do experience these symptoms, as opposed to the reported

Table One: Non-pharmacological strategies for the treatment of hot flashes in breast cancer survivors

Approach	Description
Environmental	Cool ambient temperature, wear loosely woven cotton fabric, layering clothing so that pieces can be removed (Loprinzi et al., 2001)
Behavioural	Avoiding precipitants (spicy food, coffee, alcohol) (Loprinzi et al., 2001) Paced respiration during hot flash, biofeedback techniques such as progressive muscle relaxation training (Germaine & Freedman, 1984)
Physical	Regular aerobic exercise has been shown to decrease vasomotor symptoms (Ivarsson, Spetz, & Hammar, 1998)
Intervention	Acupuncture has been found to decrease number of hot flushes (Lee, Kim, Choi, & Ernst, 2009)

Table Two: Non-hormonal pharmacological agents to treat hot flushes in breast cancer survivors

Agent	Proposed mechanism	Efficacy
SSRIs (Venlafaxine)	Estrogen withdrawal is associated with decreased levels of serotonin and up-regulation of serotonin receptors in the hypothalamus, which may mediate heat loss. Venlafaxine has been the most extensively studied of this class	40%–60% decrease in number and severity of hot flushes vs. placebo (Loprinzi et al., 2000)
Gabapentin	GABA analogue, possibly due to up-regulation of binding site in hypothalamus due to estrogen withdrawal	20%–30% decrease in number and severity of hot flushes vs. placebo (Pandya et al., 2005)
Clonidine	Antihypertensive agent, centrally active adrenergic agonist that reduces vascular reactivity	20% decrease in number of hot flushes versus placebo (Loprinzi et al., 1994)

incidence of roughly 40% in studies of aromatase inhibitors (Chin et al., 2009).

Non-pharmacological strategies for the treatment of urogenital atrophy include topical vaginal moisturizers. These agents have been shown to substantially reduce vaginal dryness and dyspareunia in breast cancer survivors. In general, the water-soluble lubricants are usually found to be more effective. However, they do not relieve all vaginal symptoms and do not alter urinary symptoms. Some of the most effective non-hormonal agents include, but are not limited to the following:

- Replens
- K-Y Jelly
- Astroglide

Pharmacological treatment of urogenital atrophy has, for the most part, been in the form of hormone replacement therapy. While the systemic route of administration has been studied and demonstrated increase in breast cancer risk, the vaginal route has not. In addition, the vaginal route of administration may be more effective, as it allows delivery directly to the urogenital tissues and avoids the enterohepatic first-pass effect, providing a more rapid local response. To date, there have been no data to assess the risk of vaginal estrogen on breast cancer recurrence, but some data have been reported on the systemic absorption of estradiol, which may act as a surrogate marker for recurrence risk, but this is not yet known. The effects of vaginal estrogenic agents on serum estradiol levels are summarized in Table Four.

Table 3: Results of decreased estrogen on the urogenital tract

Changes resulting in vulvovaginal symptoms	Changes resulting in lower urinary tract symptoms
Vagina shortens and narrows Change in vaginal cytology from superficial cells to parabasal cells • loss of rogation • loss of elasticity • thinning of epithelium Decreased vascularity of vaginal epithelium Decreased vaginal secretions	Change in angle of the urethral meatus pubis form 90–180 degrees Decreased cellular glycogen levels causing decrease in amount of lactobacilli in vagina Increase in vaginal pH predisposes women to UTIs

The bottom line

- Menopausal symptoms are common in breast cancer survivors.
- Having an awareness of the symptoms and providing women with education and strategies to manage these symptoms may improve compliance with endocrine therapy in this population.

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Table 4: Efficacy and systemic absorption of estrogen in vaginal estrogen compounds

Agent	Efficacy (reported in non-breast cancer survivors)	Systemic absorption
Vaginal estrogen tablets (Vagifem)	80%–90% decrease in symptoms or urogenital atrophy	Non-breast cancer survivors have been shown to have rise in estradiol into pre-menopausal range (Notelovitz, Funk, Nanavati, & Mazzeo, 2002) Breast cancer survivors on AI therapy have been shown to have peak rise at week two of administration, but not to pre-menopausal range (Kendall, Dowsett, Folderd, & Smith, 2006)
Estradiol releasing vaginal ring (Estring)	80%–90% decrease in symptoms of urogenital atrophy	(Non-breast cancer survivors have been shown to have no change in levels of estradiol (Weisberg et al., 2005) Breast cancer survivors have been shown to have minimal rise in systemic levels

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