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General and Supportive Care

Management of hot flashes in women with breast cancer receiving ovarian function suppression

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ABSTRACT

Most breast cancers express estrogen and/or progesterone receptors, allowing the opportunity to use anti-estrogen therapies, which have demonstrated substantial efficacy in both the metastatic and adjuvant settings. Young premenopausal women with early-stage high-risk or with metastatic hormone-receptor positive breast cancer may benefit from ovarian function suppression in addition to anti-estrogen medications. While these endocrine manipulations have successfully improved breast cancer outcomes, they may lead to a significant proportion of women experiencing vasomotor symptoms. While not life-threatening, vasomotor symptoms adversely impact quality of life and can result in early treatment discontinuation. For these reasons, supportive management of this treatment-related toxicity is crucial, and clinicians caring for breast cancer patients and survivors should be familiar with the options available and the data behind them. This manuscript will review the pathophysiology, clinical manifestations, quality of life implications and non-estrogenic management options of vasomotor symptoms for women with breast cancer undergoing estrogen depletion.

Introduction

Breast cancer remains the most frequently diagnosed cancer and the second leading cause of cancer death among American women. In 2016, an estimated 249,260 patients will be diagnosed with breast cancer, and 40,890 will die from the disease in the United States [1]. The vast majority of breast cancers are positive for the estrogen and/or progesterone receptors, allowing the opportunity to use antiestrogen therapies in their treatment, which have demonstrated substantial efficacy in both the metastatic and adjuvant settings [2]. In the adjuvant setting, endocrine therapy is typically administered for at least 5 years, with contemporary data suggesting that a subset of women may benefit from extension of endocrine therapy to up to 10 years [3,4]. Additionally, aggressive estrogen depletion with ovarian function suppression [OFS, via oophorectomy or gonadotropin-releasing hormone (GnRH) analogs] along with either tamoxifen or aromatase inhibitors in young premenopausal women with early-stage high risk breast cancer has recently proven to further improve outcomes [5,6]. In premenopausal women with metastatic disease, OFS is also commonly added to anti-estrogen medications and has been part of the strategy in modern endocrine therapy clinical trials [7]. While these endocrine manipulations have successfully decreased recurrence and mortality from breast cancer, tolerability remains an important challenge. Furthermore, administration of chemotherapy in patients with either hormone receptor positive or negative breast cancer can lead to cessation of ovarian function, causing symptomatology that can be similar to that experienced by women receiving anti-estrogen therapy.

A significant proportion of women receiving endocrine therapy or with chemotherapy-induced ovarian failure experience vasomotor symptoms (VMS). While not life-threatening, VMS adversely impact quality of life and can result in early treatment discontinuation [8], which in turn might adversely affect cancer outcomes in women unable to tolerate aggressive estrogen depletion. In the SOFT and TEXT trials, while almost 80% of women treated with tamoxifen alone developed VMS, the addition of OFS increased the rate of hot flashes to 93% in the tamoxifen-OFS group and 92% in the exemestane-OFS group [9,10]. Other side effects of estrogen deprivation, like sweating, decreased libido, vaginal dryness, insomnia and depression, were also more frequent when OFS was added.

The current manuscript will review the pathophysiology, clinical manifestations, quality of life implications and non-estrogenic management options of VMS for women with breast cancer undergoing estrogen depletion.

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Table 1
Summary of drugs with good evidence of efficacy against hot flashes.

Agent	Recommended dose	Major side effects/cautions/comments	Major trials
Antidepressant drugs			
Venlafaxine	37.5 mg daily × 1 week, then increase to 75 mg daily	Dry mouth, insomnia, decreased appetite, constipation	Loprinzi et al. [33] Evans et al. [37] Boekhout et al. [36]Bordeleau et al. [51]
Desvenlafaxine	50 mg daily × 3 days, then increase to target dose of 100 mg daily	Nausea, insomnia, dry mouth	Speroff et al. [38] Archer et al. [39]
Citalopram	10 mg daily	No difference compared to placebo; Potential preferred antidepressant to use first, based on good tolerance and cost	Barton et al. [43]
Escitalopram	10–20 mg daily	No difference compared to placebo	Freeman et al. [44]
Paroxetine	10 mg daily, if ineffective consider increasing to 20 mg daily	Nausea, headache, insomnia.Potent CYP2D6 inhibitor (Caution with concomitant tamoxifen use)	Stearns et al. [40] Stearns et al. [61]
Sertraline	50 mg daily	Nausea, fatigue, dry mouth, dizziness, diarrhea, anxiety/nervousness; Does not appear to work as well as most other noted antidepressants; Potent CYP2D6 inhibitor (Caution with concomitant tamoxifen use)	Gordon et al. [42] Kimmick et al. [45] Grady et al. [46]
Fluoxetine	20 mg daily	Nausea, fatigue insomnia, nervousness, constipation; Does not appear to work as well as most other noted antidepressants; Potent CYP2D6 inhibitor (Caution with concomitant tamoxifen use)	Loprinzi [34] Suvanto-Luukkonen et al. [41]
Gabapentinoids			
Gabapentin	900 mg daily	Somnolence, dizziness, rash, peripheral edema.	Guttuso et al. [47] Pandya et al. [48] Reddy et al. [49] Bordeleau et al. [51]
Pregabalin	75 mg twice daily (target)	Insomnia, dizziness, weight gain. Cognitive dysfunction with higher doses (150 mg daily)	Loprinzi et al. [52]
Progesterone analogs			
Megestrol acetate	40 mg daily	Some theoretical concerns about potential increased risk of breast cancer	Loprinzi et al. [67] Bertelli et al. [69]
Medroxyprogesterone	500 mg IM ever 2 weeks × 3 doses	Some theoretical concerns about potential increased risk of breast cancer	Loprinzi et al. [68] Bertelli et al. [69]
Miscellaneous			
Oxybutynin	15 mg/daily	Dry mouth, dyspepsia, diarrhea; Lower doses being evaluated in a clinical trial	Simon et al. [71]
Clonidine	0.1 mg daily (or equivalent transdermal dose)	Dry mouth, constipation, pruritus, drowsiness, insomnia, dizziness; not commonly used due to toxicity and other better options availability	Goldberg et al. [63] Pandya [64]
Zolpidem (as an adjunct to an antidepressant to decrease nighttime awakenings)	10 mg daily	Nausea, headache, fatigue, dry mouth	Joffe et al. [62]

Pathophysiology

Hot flashes represent thermoregulatory dysfunction at the level of the hypothalamus and are precipitated by a drop in estrogen levels [11]. In the postmenopausal state, there is recalibration in the core body temperature set-point, such that standard physiologic mechanisms to dissipate heat are initiated at lower body temperatures than is the case for premenopausal women [12]. This results in the characteristic features of hot flashes, such as sensation of warmth, flushing, and perspiration. As heat is lost and body temperature drops, corrective physiologic responses, such as shivering, are experienced.

The specific mechanism of how decreased estrogen levels contribute to hot flashes is not known, but the phenomenon of estrogen withdrawal appears to be instrumental to this process [13]. This is supported by the observation that oophorectomy precipitates rapid onset of hot flashes in premenopausal women, whereas gonadal dysgenesis (which represents a chronic state of low estrogen levels) does not [14]. Similarly, when women with gonadal dysgenesis abruptly discontinue exogenous estrogen therapy, they experience hot flashes [13].

The neuro-regulatory source of hot flashes appears to be centered in the hypothalamus [15]. Perspiration and vasodilation are initiated in the preoptic area of the hypothalamus and serve as heat loss mechanisms to regulate core body temperature [13]. It has been shown that changes in core body temperature tend to occur about 15 min before the majority of hot flashes [16], and that postmenopausal women seem to have a particularly sensitive homeostatic physiology that results in triggering of compensatory heat loss mechanisms even with subtle core temperature changes [17].

At the molecular level, multiple neurotransmitters have been implicated along complex neuro-hormonal pathways in the development of hot flashes, but norepinephrine is thought to be the most important neurotransmitter in lowering the thermoregulatory set point [17,18]. Norepinephrine release in the thermoregulatory nucleus is inhibited by endorphins and catecholestrogen, which is a by-product of estrogen metabolism [13,18]. Serotonin