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Management of Hot Flushes in Breast Cancer Patients

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In breast cancer patients, menopausal symptoms such as hot flushes can be a bothersome problem, with a significant impact on quality of life. Hormone replacement therapy, the mainstay for treatment of these symptoms in healthy women, is traditionally contraindicated. There are, however, several other strategies for the management of flushes in breast cancer patients and these are reviewed in this article.

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Recently, two meta-analyses of adjuvant treatment for patients with resectable breast cancer have been published (1, 2). Adjuvant systemic therapy will be offered to those patients with a high risk of recurrence of cancer, based on several characteristics of the primary tumour and the presence of lymph node metastases. Adjuvant treatment includes polychemotherapy, anti-oestrogen therapy or a combination of both. Until now, the most commonly used anti-oestrogen drug is tamoxifen. However, in recent years, other hormonal agents have also been studied for their efficacy in adjuvant treatment of breast cancer; e.g. aromatase inhibitors either as first-line therapy or in sequence with tamoxifen, or luteinizing hormone-releasing hormone (LHRH) agonists alone or in combination with tamoxifen.

In premenopausal women, adjuvant chemotherapy often leads to chemical castration and induction of premature menopause. The frequency of chemotherapy-related amenorrhoea varies with age, the cytotoxic agents used and the cumulative dose. For regimens based on cyclophosphamide, methotrexate and fluorouracil, the incidence of chemotherapy-related amenorrhoea is 68%, with a range of 20%–100% (3). This menopause often induces inconvenient symptoms such as flushes, night sweats, vaginal dryness and dyspareunia. The prevalence of hot flushes in these postmenopausal women after adjuvant treatment for breast cancer is about 65%, and about one-third of patients reported these flushes as extremely severe (4, 5). During treatment, these figures are only slightly better; 40% of patients experience flushing and one-quarter graded them as severe (6). In addition, a well-known side effect of treatment with tamoxifen is flushing which occurs in almost half of the persons treated (7, 8). The reported incidence of flushes caused by tamoxifen decreases with age, but patients experiencing side effects are more likely to terminate this adjuvant treatment (9). Aromatase inhibitors also induce flushes in a substantial number of patients, whereas the effect of LHRH agonist can be regarded as medical castration inducing profound menopausal symptoms (10, 11). Flushes have a significant impact on the quality of life of breast cancer patients, and therefore symptom management merits more attention (5, 6, 12, 13).

In otherwise healthy postmenopausal women with flushes, hormone replacement therapy is the cornerstone of treatment. In breast cancer patients, hormonal therapy is traditionally contraindicated, because of concern about growth-promoting effects on residual tumour cells. However, this practice is increasingly under debate, because especially in young breast cancer survivors with excellent prognoses, prolonged oestrogen deficiency may induce cardiovascular and skeletal morbidity. In a non-randomized prospective cohort observation, oestrogen replacement therapy did not increase breast cancer events in patients previously treated for localized breast cancer (14, 15). Not long ago, the existing data with respect to hormone replacement in breast cancer patients, all derived from non-randomized studies, were reviewed, and hormone replacement therapy did not seem to increase the risk of breast cancer recurrence (16). Moreover, in a recent case-control study, a lower risk of recurrence and mortality was

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observed in women taking hormone replacement therapy after a diagnosis of breast cancer than in those who did not (17). However, before changing the current standard, results of prospective randomized trials such as the HABITS-study in Sweden (18) evaluating the hazards and benefits of hormone replacement in breast cancer survivors are needed.

Several other strategies for the management of flushes in breast cancer patients have been used and will be the issue of this review. To find these respective strategies, we performed a medline search from 1966 through 2001 using the Medical Subject Heading terms 'breast cancer', 'menopausal symptoms', 'flush' or 'flash' and 'tamoxifen'. From this search we selected randomized phase III trials for this overview, and if these were not available for a certain class of drugs, phase II studies were acceptable as well.

PATHOPHYSIOLOGY

There is still controversy about whether transition to menopause in healthy women is initiated by ovarian exhaustion of follicles or by changes in the hypothalamus, but probably both ovary and brain contribute to this transition (19). One of the first hormonal signs of menopause is an elevated follicular stimulating hormone (FSH) serum level, which precedes the elevated serum levels of luteinizing hormone (LH). This increase in FSH might be the result of a diminished follicular development with lowered oestrogen and inhibin levels, but could also be the result of a decreased frequency of gonadotropin-releasing hormone (GnRH) pulses or a reduced concentration of GnRH. GnRH secretion is regulated by several neurotransmitters and neuropeptides, which can alter with age. In healthy women, the transitional period can last several years with gradual changes in hormone levels, allowing women to adjust to the oestrogen-deficient state. In contrast, in breast cancer patients treated with chemotherapy, the menopause occurs abruptly, and symptoms such as flushes can be profound.

The onset of a flush is abrupt, and usually starts with a feeling of heat in the upper body that generally is associated with a visible reddening of the face. The heat sensation rapidly disseminates and is often accompanied by palpitations, feelings of anxiety, and diffuse sweating. This sweating is the result of a drop in skin resistance, with an increase in skin conductance, increased blood flow in the skin and elevation in finger temperature. Flushes are frequently followed by chills, especially when the core temperature drops. Flushes may occur occasionally or as often as hourly throughout the day and night, and can alter daily activities and decrease quality of life and quality of sleep (20). The pathophysiology of flushes is not entirely elucidated. Casper and Yen have hypothesized that physiologic plasma levels of oestrogen and progesterone maintain endogenous opioid peptide concentrations in the hypothalamus and brain stem. At menopause, declining oestrogen levels result in a decrease in the endogenous opioid peptide activity that releases noradrenergic activity from its usual tonic inhibition. This noradrenergic hyperactivity leads to activation of medial preoptic heat loss mechanisms resulting in hot flushes, which are coincident with elevated gonadotropin-releasing hormone levels (21). In some studies aimed at reduction of flushes, LH serum levels were determined and related with efficacy of treatment. For example, in a study using methyldopa, a decrease in frequency of LH peaks was observed (22), whereas in a study with veralipride, a decrease in mean plasma LH level without changes in frequency or amplitude of LH pulses was observed (23).

Based on this pathophysiology, treatment strategies for alleviating flushes can be categorized in hormonal agents, α-adrenergic agonists, selective serotonin re-uptake inhibitors, a rest group of drugs as well as behavioral treatment.

An obstacle to evaluation and comparison of approaches aimed at reduction of flushes is the lack of a standard scoring system. Moreover, clear definitions of flushing are missing (24). Many studies assess the frequency and severity of flushing. Counting the number of flushes can be regarded as quite reliable, at least when assessed prospectively, for example by using a dairy. One might argue whether retrospective self-reports ('how many flushes did you experience last week') are valid. The grading of severity is even more difficult to assess. As a clear commonly accepted definition is lacking, most studies have their own definition for grading severity (e.g. mild—moderate–severe). As intraindividual variability of the grading of severity might have been worse, the interindividual variability could be enormous.

In some earlier studies more objective physiological markers such as the skin or finger temperature (22, 25–27), core temperature (28), skin resistance (26, 27), or sternal skin conductance (29) have been used. Even combinations of several objective assessments are reported for assessment of flushing. Swartzman et al. developed the 'physiological flush profile', which is composed of several physiological changes in circulation and skin conductance, such as heart rate, palmar and dorsal skin temperature, finger pulse volume, palmar and sternal skin conductance (30). When this physiological flush profile was directly compared with sternal skin conductance, the increase in sternal skin conductance appeared much more specific, although less sensitive (64% vs. 89%) for detecting subjectively reported flushes (31). The frequency and/or amplitude of LH pulses, which previously appeared to be associated with flushes, was determined in some studies (22, 25, 32). In more recent studies, assessments of quality of life have been implemented (33–35). As symptoms are subjective, methods using self-reports and quality of life

assessments prevail as of principal importance and of strongest clinical relevance in studies focusing on relief of flushing. Another issue in this respect that merits attention is the fact that almost all studies including a placebo group show a reduction in flushes in the placebo group of about 25–30%.

HORMONAL AGENTS

The most frequently used hormonal agent for prevention of flushes in breast cancer patients is megestrol acetate, while less frequently prescribed drugs are other progestational agents such as medroxyprogesterone acetate and tibolone.

In a randomized crossover trial, Loprinzi et al. showed that megestrol acetate is effective in reducing the frequency of hot flushes (36). This study included 97 women with a history of breast cancer and 79 of these patients used tamoxifen. Flushes occurred at least seven times a week and were sufficiently severe for patients to request treatment. After a one-week pretreatment observation period, patients were randomized in a double-blind fashion to receive megestrol acetate (20 mg twice daily) for 4 weeks, followed by 4 weeks on placebo, or vise versa. After the ninth week, the code was broken and patients were allowed to continue megestrole acetate if they wished. Megestrol acetate decreased the number of flushes by 74% compared with baseline, whereas the severity of flushes was reduced by 83% compared with baseline. For the placebo, these figures were 27% and 27%, respectively. It required 2–3 weeks to achieve this effect, but it could persist for weeks after discontinuation. After 3 years, 31% of women were still using megestrol acetate (37). Surprisingly, 76% of the patients used lower doses than in the original protocol. Some patients were using doses as low as 20 mg every 2–3 days, while maintaining control of flushes. Side effects reported as a result of megestrol acetate in these doses included appetite stimulation, weight gain, abnormal vaginal bleeding and carpal tunnel syndrome symptoms. Generally, this treatment is well tolerated. In conclusion, megestrol acetate is effective in reducing the number and severity of flushes. The starting dose is 20 mg twice daily, which can be reduced—striving for the lowest dose that can effectively control flushing. It is recommended that a selected dose be maintained for 3 or 4 weeks before changing the dose as it may take that amount of time to reach a new equilibrium.

Medroxyprogesterone acetate appeared also useful in reducing vasomotor symptoms, either administered as a monthly intramuscular injection (150 mg depomedroxyprogesterone acetate) as well as orally (20 mg daily) ((25, 38)).

Tibolone is a progestational agent with weak oestrogen- and androgen activity. In a double-blind randomized trial in 437 postmenopausal women, tibolone (2.5 mg daily) seemed to be as effective as combined hormone replacement therapy (17β-oestradiol 2 mg and norethisterone acetate 1 mg) in reducing hot flushes, sweating episodes and vaginal dryness (39). Vaginal bleeding periods, often disliked by women, occurred less frequently in the tibolone-treated patients. In both treatment arms, one case of breast cancer occurred, which retrospectively in the patient taking tibolone appeared to be already present on the baseline mammography. It is, however, questionable whether tibolone should be recommended to breast cancer patients because of the partial oestrogen activity. Moreover, one might argue about whether progestins are safe in the treatment of flushes in breast cancer patients, considering their possible effects on tumour growth, which might be comparable to those of oestrogens.

α-ADRENERGIC AGONISTS

In two double-blind, cross-over, placebo-controlled studies the efficacy of methyldopa on flushes was reported (22, 40). Methyldopa, in a daily dose varying between 250 mg and 1000 mg was more effective in reducing vasomotor symptoms as well as in LH-peaks compared with placebo, but concurrently induced substantial side effects such as fatigue, nausea and dry mouth. Therefore, methyldopa is not an attractive option in the treatment of flushing.

The anti-dopaminergic drug veralipride, given in a daily dose of 100 mg orally, eliminated flushes in the majority of patients in two studies (23, 41). This drug also caused side effects, which did not appear exactly similar in both studies, probably resulting from the different dosing schedules. As a result of treatment-related hyperprolactinemia, David et al. (41) reported a reversible galactorrhoea in 14 out of 50 patients (28%) and breast tension in 8 others (16%), whereas Melis et al. (23) reported mastodynia and mammary tension only in 15% of patients. The effects of veralipride on plasma oestrogen levels were also inconsistent. David et al. reported a rise in oestradiol levels from normal menopausal levels to values found in the first days of the follicular phase of the menstrual cycle as a result of an increase in dihydroepiandrosterone levels. Such a rise might not be desirable in breast cancer patients. Melis et al. did not observe significant changes in oestrogen levels. No data on treatment of flushes in breast cancer patients with veralipride are available, and therefore veralipride should not be advised in this category of patients.

Clonidine is a centrally active α-agonist that reduces vascular reactivity and is primarily used for the treatment of hypertension. In lower dosages, clonidine appeared effective in the reduction of flushes caused by normal menopause or by surgical castration, either when administered orally or transdermally (27, 32). Transdermal clonidine also has been studied in tamoxifen-induced flushes in breast cancer patients (42). In a double-blind,

randomized, cross-over trial, clonidine patches (in a dose equivalent to an oral daily dose of 0.1 mg) significantly reduced the frequency and severity of flushes. However, this effect was clinically modest, at the expense of substantial drug-related toxicities such as constipation, drowsiness and dry mouth. Remarkably, a recent study of oral clonidine in an equal dose (0.1 mg daily) in 194 postmenoposausal women with breast cancer using adjuvant tamoxifen showed better results (34). After 8 weeks, the mean decrease in flushes was greater in the clonidine group than in the placebo group. Efficacy was already observed after 4 weeks and maintained during 8 weeks of treatment but long-term effects were not evaluated. Moreover, the quality of life scores in the clonidine group improved during treatment compared with a slight decrease in the placebo group, although the median score in both groups was similar. The only different side effect between clonidine and placebo was more sleep disturbances in the clonidine-treated patients. No effect on blood pressure was reported. Therefore, oral clonidine could be a treatment option in alleviating flushes in breast cancer patients.

SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

Selective serotonin re-uptake inhibitors inhibit neuronal serotonin re-uptake, which may alter dopaminergic pathways and therefore may be effective in reducing flushing.

Venlafaxine hydrochloride is an antidepressant that inhibits neuronal serotonin and norepinephrine re-uptake. Based on anecdotal experience that low-dose venlafaxine was effective in reducing flushes, a pilot trial was performed in 28 breast cancer patients with bothersome flushes (43). Venlafaxine in a dose of 12.5 mg twice daily appeared effective in alleviating hot flushes. This efficacy was confirmed in a double-blind randomized trial (33). This study included 229 patients with a history of breast cancer or who were concerned about taking oestrogen for fear of breast cancer. The patients had to experience bothersome flushes that were severe enough for them to seek therapeutic intervention. Sixty-nine percent of patients used tamoxifen. Patients were randomized to one out of four treatments: placebo (for 28 days), venlafaxine 37.5 mg (for 28 days), venlafaxine 75 mg (37.5 mg for 7 days, 75 mg for 21 days) or venlafaxine 150 mg (37.5 mg for 7 days, 75 mg for 7 days, 150 mg for 14 days). After 4 weeks, the reduction in flushes compared with baseline was 27% in the placebo group, 37% in the 37.5 mg group and 61% in both the 75 mg group and the 150 mg group. In addition, quality of life scores improved in the venlafaxine-treated patients. Side effects included mouth dryness, decreased appetite, nausea and constipation, and were more frequently observed in the group taking 150 mg. Therefore treatment should start with 37.5 mg venlafaxine daily and then should be increased to 75 mg if necessary. Provisional data indicate a similar efficacy of other serotonin re-uptake inhibitors. In a pilot study, paroxetine hydrochloride (10–20 mg daily) in breast cancer patients showed a comparable reduction in flushes as well as improvement in depression, sleep, anxiety and quality of life measures (35). Serotonin re-uptake inhibitors are effective and relatively safe drugs for amelioration of flushes in breast cancer patients, although optimal dose and duration of therapy have not been defined exactly.

OTHER REMAINING AGENTS

Several other drugs have been studied for their role in the management of flushes, but did not result in a commonly accepted strategy. In a small study, propranolol reduced flushes (44). The same applies to bellergal retard (45). Naloxone, which interferes with endogenous opioid peptide activity, did not influence flushes (26). In a placebo-controlled, cross-over trial including 120 breast cancer patients, vitamin E 800 I.U. per day significantly reduced the frequency of flushes (46). However, the clinical benefit was marginal as this reduction in flushing represented only one less flushing incidence per day. Although the authors were not enthusiastic, they suggested that vitamin E can be used because it is non-toxic, inexpensive, widely available and it might allow the patients to obtain the well-described placebo effect (and perhaps a little more). Black cohosh, a herbal remedy for menopausal symptoms, did not show any benefit over placebo in a randomized trial in breast cancer patients (47). Phytoestrogens are a group of non-steroidal plant compounds that can behave as oestrogens as well as anti-oestrogens depending on many factors such as circulating levels of endogenous sex-hormones, their own concentration, the number and type of oestrogen receptors, gender and menopausal status (48–50). Phyto-oestrogens are found in a variety of plants, including fruits and vegetables, with leguminous plants, flax and soy as the richest sources. Phyto-oestrogens recently received a considerable amount of attention in health- and women's magazines as well as in the medical literature for their beneficial effects in cardiovascular diseases, osteoporosis, cancer and menopausal symptoms. Generally, these benefits of the 'natural alternative' do not prevail over those achieved by conventional hormone replacement therapy. In a double-blind, randomized trial comparing phyto-oestrogens with placebo in breast cancer survivors, no reduction in flushes was observed (51). In addition, one has to consider the potential risks of phyto-oestrogens in breast cancer patients, whether they use tamoxifen or not (50).

ALTERNATIVE STRATEGIES

To relieve the sensations of heat, women sometimes stand in front of an air-conditioner or an open refrigerator and they often wear light, loose clothing (20).

In several small studies, behavioural therapies were shown to be beneficial in flushing control. Paced respiration training resulting in a slower respiration rate with an increased tidal volume showed a reduction in flush frequency (52). A multiple component treatment including four behavioural therapy techniques (relaxation, self-suggestion of cool thoughts and images, marital contingency contracting and temperature biofeedback training) reduced the number of flushes, and this treatment gain was still maintained at 6 months' follow-up (53). A single coping technique of applied relaxation, trained in 11 sessions, also proved to be useful in decreasing the number of flushes. This reduction in flushes did not appear to be unequivocally related to changes in mood scores (54).

Hunter and Liao studied the differences between patients with flushes who wished to have treatment for flushes and those who did not, and examined the psychological differences between women who chose hormonal versus psychological treatment (55). The study included 61 women who were recruited from five general practices. Seventy-five percent of women wanted treatment, and about 40% of these women preferred hormone replacement therapy and 60% cognitive relaxation therapy. There were no socio-demographic differences nor differences in flush frequency between those who desired treatment and those who did not, but those seeking treatment regarded their flushes as being more problematic. The women seeking treatment were more anxious, less able to cope with stress, had a lower internal locus of control scores and had lower self-esteem than those who did not want treatment. Few differences emerged between the two treatment groups.

These studies focusing on behavioural treatment were not designed for breast cancer patients, but in this group behavioural therapy probably induces similar efficacy. Recently, in a randomized controlled trial in breast cancer survivors experiencing severe menopausal symptoms, a comprehensive menopausal assessment and an intervention program improved the symptoms (56). The intervention program included an individualized plan of education, counseling, pharmacological and/or behavioural interventions, psychosocial support, referrals and follow-up tailored to each woman's individual preferences.

CONCLUSIONS

Menopausal symptoms such as hot flushes occur frequently in healthy postmenopausal women. In young breast cancer patients these flushes are for several reasons at least as bothersome. The adjuvant cytotoxic therapy often induces an abrupt and premature menopause, with related symptoms. In addition, one of the most prominent side effects of adjuvant treatment with hormonal therapy is flushing. And last, but not least, hormone replacement therapy, the mainstay of treatment for menopausal complaints, is not advocated because of possible tumour growth-promoting effects, until the results of randomized trials evaluating the efficacy and safety of hormone replacement therapy in breast cancer patients have become available. In an attempt to relieve these flushing episodes, several drugs have been studied to evaluate their efficacy on this symptom. Based on the literature, oral clonidine and serotonin re-uptake inhibitors such as venlafaxine and paroxetine appeared effective and showed an acceptable toxicity profile. Therefore these drugs, probably combined with an intervention or educational program, should be considered in the treatment of breast cancer patients suffering from hot flushes.

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