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REVIEW

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Vasomotor symptoms and management of women undergoing treatment for breast cancer: literature review with focus on the therapeutic potential of cytoplasmic pollen extract

Stefano Lello[a], Ida Paris[a], Angelo Cagnacci[b], Donata Sartori[c], Salvatore Caruso[d] and Aldo Iop[e]

[a]Department of Woman and Child Health, Policlinico A. Gemelli Foundation-IRCCS, Rome, Italy; [b]Department of Obstetrics and Gynecology, San Martino Hospital, Genoa, Italy; [c]Oncology Unit, AULSS 3, Mirano, Italy; [d]Obstetrics and Gynecology Unit, Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy; [e]University Local Health Authority Giuliano Isontina ASUGI, Trieste,Italy

ABSTRACT

Objective: Effective management of vasomotor symptoms (VMS) in patients undergoing treatment for breast cancer (BC) represents a critical but frequent unmet need. This review summarizes the epidemiology, pathophysiology, and clinical features of VMS in patients with BC and provides a synopsis of the complementary and alternative medicine (CAM) approaches in relieving VMS with a focus on purified cytoplasm of pollen (PCP).

Methods: The literature on VMS epidemiology, pathophysiology, clinical burden, and CAM treatment in healthy women and patients with BC was reviewed.

Results: VMS are common in patients with BC undergoing hormonal treatment and negatively impact quality of life, leading to treatment discontinuation in up to 25% of patients with detrimental impact on risk of BC recurrence and overall survival. CAM approaches to treat VMS in patients with BC include vitamin E, phytoestrogens, and black cohosh, even if there is a lack of solid evidence to guide clinicians in the choice of treatment. PCP, obtained according to standards of good manufacturing practice, has a definite pharmacological mechanism of action, is devoid of estrogen activity, and has shown clinical efficacy on menopause-associated symptoms with a favorable safety profile and high compliance. As such, it appears to represent a valid management option to improve quality of life in patients with pre- and postmenopausal BC.

Conclusions: Physicians should actively investigate the presence and impact of VMS in patients receiving therapy for BC. Additional and appropriately sized randomized clinical trials are needed to provide clear evidence on how to best meet the needs of patients with BC suffering from menopause-associated symptoms.

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Introduction

The survival rate of patients with breast cancer (BC) has significantly increased due to earlier diagnosis and advances in adjuvant therapies with 5-year relative survival of about 90% [1]. Treatments for BC, including endocrine therapy with or without ovarian function suppression and chemotherapy, suppress endogenous estrogen levels by different mechanisms to induce pharmacological menopause with symptoms that adversely affect women's quality of life (QoL) [2]. Vasomotor symptoms (VMS) are common. However, despite the high discomfort they bring about, these adverse events are not always reported by patients, intercepted by physicians, appropriately assessed, and subsequently treated. Pharmacological and non-pharmacological options are available to treat VMS in patients with BC, although there are limited robust data to guide clinicians in the selection of therapies. Effective management of VMS in patients with BC is therefore a critical but frequent unmet need.

Purified cytoplasm of pollen (PCP) is a non-hormonal nutraceutical with inhibitory action on serotonin reuptake [3], whose efficacy and safety in treating postmenopause VMS has been assessed in several studies [4,5]. The aims of this review are: (1) to review the epidemiology, pathophysiology, and clinical features of VMS in patients with BC as well as the state of the art of complementary and alternative medicine (CAM) approaches in relieving these symptoms; (2) to review the effectiveness of PCP based on available literature and the authors' clinical experience.

Methods

The literature on VMS epidemiology, pathophysiology, clinical burden, and CAM treatment in healthy women and patients with BC was reviewed. Literature was identified through a search on PubMed and selection of all references held to be relevant by the authors.

Results

VMS in women treated for BC

Epidemiology

Evidence on the prevalence and frequency of VMS in BC survivors is scarce and there are even less data on their impact on

CONTACT Stefano Lello lello.stefano@gmail.com Department of Woman and Child Health, Policlinico A. Gemelli Foundation-IRCCS, Rome, Italy.

QoL. VMS, including hot flashes (HFs) and night sweats, are the most common symptoms of physiological menopause [6]. In patients with BC, VMS have greater prevalence and frequency and are more severe than in age-matched women without BC [7,8]. Up to 95% of pre-menopausal women and over 30% of postmenopausal women will experience VMS as a result of treatments for BC, and especially aromatase inhibitors, tamoxifen, or other menopause-inducing therapies [9,10]. In a study in patients with BC undergoing endocrine therapy, HFs were reported by 70% of women [11]. Up to 50% BC survivors were reported to experience HFs at daily and or weekly intervals [12]. Related sleep disturbances are present in 18.6 to 56.6% of patients with BC [13,14]. VMS are usually more severe in younger survivors because of the premature ovarian failure induced by BC treatments and can have significant impact on QoL [15]. In addition, in postmenopausal women who already suffer from VMS, endocrine therapy for BC can exacerbate symptoms [16].

Pathophysiology

VMS, and in particular HFs, are early signs of menopause that tend to increase during the menopausal transition, peak in the first 2 years of menopause, and then decline over time [17]. VMS are a form of temperature dysfunction that is related to changes in ovarian hormones. Disruption of this tightly controlled temperature circuit results in exaggerated heat-loss responses presenting as VMS, with peripheral vasodilation and elevated skin blood flow and temperature [18]. Decreased estrogen levels play a major role in VMS. However, it is recognized that estrogen withdrawal is necessary but not sufficient to explain the occurrence of VMS, whose precise etiology and mechanism are not yet completely clarified [19]. HFs occur in conditions of negative fluctuation (spontaneous menopause) or an abrupt drop (surgical menopause) in estrogen levels. The correlation is more significant with abrupt estrogen decreases than with chronically low levels [20].

Women who experience HFs were shown to have a restricted thermoregulatory zone, which makes the crossing of the upper threshold more likely with subsequent development of peripheral dilation and sweats as heat dissipation responses [21]. Furthermore, with the decline of estrogen levels in menopause, norepinephrine levels increase, and experimental data have shown that increased brain norepinephrine further narrows the width of the thermoneutral zone [22]. Overall, the regulation of internal body temperature involves neuroendocrine pathways with complex interactions between noradrenaline, estrogen, testosterone, and serotonin [23]. Several clinical studies have found that compounds that increase serotonin availability can improve HFs [24–26].

Symptoms other than VMS are reported by menopausal women. The genitourinary syndrome of menopause (GSM) is the new term for vulvovaginal atrophy and encompasses urinary, genital, or sexual dysfunction related to a hypoestrogenic state. GSM, typically related to postmenopausal estrogen loss, can also be induced by BC therapies such as chemotherapy, radiation therapy, and endocrine therapy [27]. Common symptoms of GMS are vaginal dryness, dyspareunia, vulvovaginal irritation, and pruritus. Other aspects of sexual dysfunction include decrease of libido, arousal level, and sexual satisfaction [28]. Moreover, a low level of estrogens can lower vaginal pH, favoring the development of genitourinary infections.

Predictors

Identification of factors that can predict VMS occurrence following BC therapy may be helpful in appropriately addressing these symptoms in women who are at higher risk of developing them. However, little is known about the characteristics that may affect the risk of VMS during and after treatment for BC, other than treatment with tamoxifen or aromatase inhibitors. Age and duration of treatment have long been identified as the strongest predictors [29]. More recently, the Life and Longevity after Cancer Study (LILAC) in 3,595 women identified prior chemotherapy and adjuvant hormone therapy as strong predictors of VMS [30]. Other factors associated with an increased risk of VMS are postmenopausal hormone therapy use, previous occurrence of VMS during menopausal transition, bilateral oophorectomy, and baseline antidepressant use. Another very recent analysis of the cohort of midlife women enrolled in the Study of Women's Health Across the Nation (SWAN) study found no differences in risk factors for VMS between women with incident BC and cancer-free controls [7].

Clinical features

HFs can be described as subjective sensations of heat associated with objective signs of cutaneous vasodilation and subsequent drop in core temperature and may be accompanied by sweating, especially at night, as well as palpitations, anxiety, irritability, and even panic [31]. Night sweats and sleep disturbances, mostly considered secondary to HF, are among the most troublesome symptoms reported by women with BC [32]. In addition, over half of women with BC would consider a treatment to be effective if it reduced nighttime awakenings [32].

Women who were premenopausal at diagnosis of BC generally report more severe VMS following BC treatment compared to postmenopausal patients [33]. Overall, significantly reduced physical health-related QoL has been observed at the end of adjuvant endocrine therapy compared with a normal population, which is substantially worse in patients treated with aromatase inhibitors. While significant improvement was observed in the subsequent 12 months in the tamoxifen group, in patients treated with aromatase inhibitors, at the end of treatment, there was a plateau in recovery [16].

Musculoskeletal problems have been reported in BC patients undergoing endocrine therapy, especially with aromatase inhibitors, including arthralgia, accelerated bone loss, and an increased incidence of osteoporotic fractures [16].

Management of VMS in patients with BC

According to the "North American Menopause Society" (NAMS), in women hormonal replacement therapy should be individualized using the best available evidence to maximize benefits and minimize risks. In general, in those younger than 60 years or within 10 years of menopause onset and no contraindications, the benefit–risk ratio is generally favorable while for those who initiate hormone therapy more than 10 years from menopause onset or who are aged older than 60 years the benefit–risk ratio is less favorable [34]. Although a number of pharmacological approaches may be used to treat VMS, including hormone replacement therapy [35–37], selective serotonin reuptake inhibitors (SSRIs)[38], selective serotonin-norepinephrine reuptake inhibitors (SNRIs) [38], gabapentin [39,40], and clonidine [41], albeit with some controversy and not recognized in many settings, herein focus is placed on CAM and PCP.

Complementary and alternative medicine

Many patients with BC prefer to manage their VMS with non-hormonal and non-psychotropic medications and seek CAM approaches. CAM includes different types of approaches including: (i) mind–body practices, such as hypnosis, cognitive behavioral therapy, relaxation, yoga, sofrology, biofeedback, and meditation; (ii) natural products, (iii) acupuncture. There is some evidence that mind–body interventions can reduce the stress and discomfort associated with VMS, with very few side effects, and may thus be worth considering [42]. Herein, however, focus is placed on natural products.

Vitamin E. Vitamin E is a fat-soluble vitamin with antioxidant properties. In a trial investigating the effect of vitamin E on VMS reduction in healthy menopausal women, participants reported a non-clinically meaningful decrease of 1–2 daily HFs [43]. In two randomized trials in patients with BC with menopausal symptoms comparing vitamin E with placebo [44] and gabapentin [39], no clinically meaningful benefit on VMS was observed.

Phytoestrogens. Phytoestrogens are plant-derived, naturally occurring compounds that are capable of binding to and activating estrogen receptors. They include isoflavones (derived from soy and red clover), lignans (from flexseed), and hops (*Humulus lupulus*). Phytoestrogens may have both estrogenic and antiestrogenic effects in humans [45]. A systematic review of 43 randomized controlled trials on 4364 healthy peri- and postmenopausal women did not support the use of phytoestrogens to relieve VMS symptoms [46]. In BC survivors, the estrogenic properties of these compounds suggest that they may stimulate cancer recurrence and worsen prognosis [47]. As such, they should be considered as contraindicated in women with BC for relief of VMS symptoms.

Black cohosh. Black cohosh is a perennial medicinal plant native to North America that is indicated for menopause-related neurovegetative and emotional symptoms. Several mechanisms have been suggested, including estrogen receptor modulation, partial agonism of serotonin, with antioxidant and anti-inflammatory properties [48]. A Cochrane review of 16 randomized clinical trials on over 2000 healthy menopausal women with VMS concluded that there is no sufficient evidence to support the use of black cohosh in controlling menopausal symptoms [49]. However, black cohosh appears to have a good safety profile in BC survivors [50].

Cytoplasmic extract of pollen for management of VMS in patients with BC

Production of purified cytoplasm of pollen

PCP is a non-hormonal nutraceutical containing two major active ingredients, a pure pollen extract (GC Fem) and a combined pollen and pistil extract (PI 82). PI 82 is an extract of pollen from *Secale cereale, Dactylis glomerata*, and *Pinus silvestris* and a pollen-pistil extract from *Zea mays*. GC FEM is an extract of pollen from *S. cereale, Z. mays,* and *P. silvestris*. The plants of origin are cultivated and harvested separately by plant type using a standardized method in accordance with the recommendations of the European Medicines Agency. The extraction procedure, performed according to Good Manufacturing Practice, removes the cytoplasmic pollen extract from its shell, which is highly allergenic, enabling the retention of the active pollen components. The exclusion of the shell also makes the active compounds highly bioavailable. The final pollen cytoplasm extract is highly purified and removes at least 180 nutrients and pollen allergens. The production procedures are standardized to ensure that different batches of PCP are reproducible.

Composition of PCP

PCP contains three active agents with antioxidant enzymes and natural non-steroidal anti-inflammatory agents: purified pollen extract (GC Fem), a mixture of cytoplasmic pollen, and pistil extracts (PI 82), and vitamin E.

Mechanism of action

Inhibition of serotonin reuptake seems to be responsible for at least part of activity of PCP, since animal studies have demonstrated a dose-dependent inhibitory effect on the reuptake of [^{3}H]-serotonin into rat cortical synaptosomes [3]. It has been hypothesized that PCP may have an amplifying effect on other neurotransmitter pathways that control thermoregulation, sleep, and mood [3].

The decrease in estrogens during menopause has been shown to increase the levels of oxidative stress in the body [51]. Part of the mechanism of action of PCP may also be explained by the high antioxidant action of the enzyme superoxide dismutase contained in pollen and pistil extracts [52].

Clinical studies

The first important clinical study was a randomized trial comparing the effect of two daily tablets of PCP (320 mg of purified pollen extract and 10 mg of vitamin E per tablet) and placebo for 3 months on menopausal symptoms, measured by the 16-symptom Menopausal Rating Scale (MRS) in addition to the patients' daily diary [4]. The study involved 64 menopausal women, 54 of whom completed the trial. The effect of PCP on HFs was significant after 2 months and even more evident at 3 months. The overall trend in 15 other QoL parameters was also in favor of PCP. No safety concerns emerged.

An open-label multicenter study carried out in France involving 417 menopausal women evaluated the efficacy of PCP using visual analogue scales for HFs, sweats, irritability, fatigue, quality of sleep, and QoL [53]. At the 3-month end-of-study visit, HFs, night sweats, irritability, and fatigue were reduced, while quality of sleep and QoL had improved.

A randomized controlled study compared three small groups of menopausal women treated with placebo, PCP, or a combination of E2 and drospirenone (E2 + DRSP) [54]. Neurovegetative symptoms, including HFs, sweating, asthenia, palpitations, insomnia, headache, and moodiness, were assessed with the Kupperman Index (KI) at baseline and after 3 and 6 months of treatment. With similar baseline values, a considerable reduction in the KI was obtained in the two active treatment groups at the 3- and 6-month evaluations, while the placebo group remained stable.

A prospective, open, observational, multicenter study in 104 menopausal women assessed the effectiveness of PCP over 3 months on menopausal symptoms by the Menopausal Rating Scale (MRS) [5]. After 3 months of treatment, HFs, sleep disturbance, depressive mood, irritability, and fatigue were reduced by about half.

A 6-month prospective observational study in healthy menopausal women with VMS symptoms compared PCP (2 tablets/day, each containing 320 mg of purified pollen extract and 10 mg of vitamin E; $N = 57$) with soy isoflavones containing 30 mg of genistein and 30 mg of daidzein (one 60 mg tablet/day; $N = 60$) and no treatment ($N = 47$) [55]. The active treatment groups showed significant improvement in HFs after 3 and 6 months. At 6 months, the PCP group showed greater decrease in the number of daily HFs compared with the isoflavone group. Improvement in global sleep quality was also greater in the PCP group at both 3 and 6 months.

A multicenter prospective observational study conducted in 108 Italian symptomatic peri- and postmenopausal women investigated the effects of PCP on HFs and other menopausal symptoms including the Greene Climacteric Scale (GCS) [56]. After 3 months, significant improvement was observed in HFs and night sweats and in almost all GCS items, including nervousness, irritability, and depressed mood.

PCP in patients with breast cancer

When managing patients with BC for treatment-induced menopausal symptoms, the main consideration is to avoid tumor relapse during or after hormonal therapy, avoiding substances with estrogenic activity. Preclinical studies have demonstrated that the pollen extract in PCP does not have any estrogenic effects. High-performance liquid chromatography analyses of phytoestrogens showed low, subeffective concentrations of daidzein and genistein, whereas formononetin and biochanin A were not detected [57]. The estrogenic activity of PCP was also examined in a bioassay using immature female rats, showing that up to a high dose of 500 mg/kg/day it did not induce uterine growth [57].

Experimental data showed that estrogens can stimulate a proliferative effect on BC cells via the progesterone receptor membrane component (PGRMC1) in addition to intracellular receptors. In an *in vitro* study, PCP at different concentrations and in combination with estradiol or mixed growth factors did not stimulate proliferation of MCF-7 cells – a human BC cell line that endogenously expresses estrogen receptors – whether or not transfected with PGRMC1 [58].

A case series was recently published that included women with BC (12 with HR+, 8 with luminal A, and 4 with luminal B cancer) with a median age of 47 years who received PCP for 3 months [59]. Menopausal symptoms were evaluated with the MRS. After 3 months, all women had improvement in HFs, cardiac symptoms, irritability, and anxiety. No side effects were reported, and compliance was very high.

Conclusions

VMS and especially HFs are extremely common in patients with BC receiving hormonal treatment and negatively impact QoL in both pre- and postmenopausal women, leading to treatment discontinuation in up to 25% of patients, with detrimental impact on the risk of BC recurrence and overall survival. Despite their frequency and impact on patients, VMS are not always adequately recognized, reported, evaluated, and consequently treated. There is thus the need to actively investigate the presence and impact of VMS in patients receiving BC therapy and discuss the most appropriate management strategy with the patient.

Pharmacological and CAM options for VMS are available, although there is a lack of solid evidence to guide clinicians in the choice of treatment. Furthermore, clinical results are often unsatisfactory and effective management of VMS in patients with BC still represents a frequent unmet need. PCP, obtained by GMP standards, has a defined pharmacological mechanism of action and is devoid of estrogen activity. In our opinion, PCP represents a valid option to improve QoL in pre- and postmenopausal patients with BC. It has shown clinical efficacy on menopause associated symptoms and is not associated with any adverse effects. Additional randomized clinical trials with patient-focused outcomes are needed to adequately meet the needs of patients with BC suffering from symptoms associated with menopause.

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Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Ida Paris received honoraria for public speaking from Novartis, Lilly, Pfizer, Gilead, Genetic, Astra Zeneca, MDS; Consultant for Seagen. Angelo Cagnacci was a speaker at scientific meetings for Shionogi. All the other authors declare no conflict of interest.

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ORCID

Stefano Lello http://orcid.org/0000-0002-1616-9105
Ida Paris http://orcid.org/0000-0002-7445-3366
Angelo Cagnacci http://orcid.org/0000-0003-2714-623X
Salvatore Caruso http://orcid.org/0000-0002-1387-0932

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