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Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer

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Abstract

Objectives: To examine the effect of *Cimicifuga racemosa* (CR BNO 1055) on hot flushes caused by tamoxifen adjuvant therapy in young premenopausal breast cancer survivors. This treatment presents an off-label use of CR BNO 1055. *Methods:* Between May 1999 and December 2001, we accrued 136 breast cancer survivors aged 35–52 years. After treatment with segmental or total mastectomy, radiation therapy and adjuvant chemotherapy, participants were in open-label randomly assigned (1–2) to receive tamoxifen 20 mg per day orally (usual-care group; $n = 46$) or tamoxifen (same dose and posology) plus CR BNO 1055 (Menofem®/Klimadynon®, corresponding to 20 mg of herbal drug; intervention group $n = 90$). Duration of treatment was 5 years for tamoxifen, according to international standards for adjuvant therapies, and 12 months for CR BNO 1055. Follow-up included clinical assessment every 2 months; the primary endpoint was to record the number and intensity of hot flushes. *Results:* Comparing patients assigned to usual-care group with those assigned to intervention group, the number and severity of hot flushes were reduced after intervention. Almost half of the patients of the intervention group were free of hot flushes, while severe hot flushes were reported by 24.4% of patients of intervention group and 73.9% of the usual-care group ($P < 0.01$). *Conclusions:* Hot flushes were the most frequent adverse reaction to tamoxifen adjuvant therapy in breast cancer survivors. The combined administration of tamoxifen plus CR BNO 1055 for a period of 12 months allowed satisfactory reduction in the number and severity of hot flushes.

Keywords: *Cimicifuga racemosa*; Tamoxifen; Hot flushes; Breast cancer survivors

1. Introduction

1.1. Background

Aging ovaries stop secreting estradiol when menopause occurs; by then, estrone (less active estrogen) replaces estradiol. The lack of physiological feedback of estradiol production increases

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serum levels of both, follicle stimulating hormone (FSH) and luteinizing hormone (LH). During this time period, the quality of life is reduced in most women due to vasomotor episodes [1].

Frequent hot flushes are associated with psychosomatic complaints such as tenseness, tiredness, irritability, headache, muscle and joint pains and depression. Vasomotor complaints vary widely in both, severity and duration. Severe vasomotor complaints in menstruating women cause larger decrease in wellbeing than in non-menstruating women. As a consequence of decreased levels of estrogen, bone turnover increases and bone resorption prevails over bone formation [2]. Menopause is also linked to cardiovascular health and to reduction in cognitive function [3,4].

Of primary importance in the treatment of postmenopausal women are the prevention of bone loss and the amelioration of vasomotor systems, which have established benefits of replacement therapy. Since 1980, hormone replacement therapy (HRT) that includes both an estrogen and a progestin has been seen as a specific treatment for symptoms in the short-term and preventive therapy in the long-term.

Recent data from a randomized, blinded and controlled clinical trial indicate that HRT for up to more than 5 years is not beneficial overall and that there is early harm for stroke and venous thromboembolism, and increasing harm for breast cancer with increasing duration of treatment [5]. Moreover, the comparison of HRT with placebo in older women with coronary disease reveals increased rates of venous thromboembolism and biliary tract surgery without favorable trends in overall rate of cardiovascular disease [6]. These contradictory evidences indicate that HRT should be applied when beneficial clinical outcomes outweigh harmful ones.

As would be expected, the issues of HRT become even more complicated when its use is considered for women with a known history a breast cancer. This population of postmenopausal breast cancer survivors is rising. In addition, the increasing use of adjuvant chemotherapy for patients whose axillary lymph nodes are negative or positive for disease results in an additional population of younger patients who are rendered prematurely menopausal [7]. It has been demonstrated that ovarian ablation may be associated with a 15–25% reduction in rates of breast cancer recurrence and of mortality [8]. This has led to speculation that the ovarian failure induced by chemotherapy may contribute to the survival benefit derived from adjuvant therapy. The evidence that estrogens have an adverse effect on breast cancer risk is based on the in vitro effects of estrogens on breast cancer cell lines and the recent epidemiological data suggesting that long-term use of HRT may increase the risk of developing breast cancer [5].

Due to the uncertainty of this situation, most clinicians chose to use alternative therapeutic routes; moreover, women with a previous diagnosis of breast cancer are averse to accept much increased risk of recurrence in order to take HRT [9].

1.2. The selective estrogen receptors modulators alternative

The selective estrogen receptors modulators (SERMs) are a new class of pharmacological agents now available to women who cannot tolerate or are unwilling to use conventional HRT. SERMs were formerly referred to as anti-estrogens, a description that is now known to be inappropriate. The term SERM has been coined to describe compounds that, in contrast to pure estrogen agonists or antagonists, have a mixed and selective pattern of estrogen agonist–antagonist activity, which largely depends on the tissue targeted [10].

The pharmacological goal of these drugs is to produce estrogenic actions in those tissues, where these actions are beneficial (bone, brain, liver) and to have either no activity or antagonistic activity in tissues such as breast and endometrium, where estrogenic actions (cellular proliferation) might be deleterious. The most actively studied SERMs commonly are tamoxifen and raloxifen. Tamoxifen is currently approved as an adjuvant for the treatment of breast cancer (node-negative or node-positive) in women after total or segmental mastectomy and breast irradiation, in the treatment of women with advanced or metastatic breast cancer, and as a preventive agent for women at high risk for breast cancer. The NSABP P-1 trial has shown that 20 mg per day of tamoxifen reduced the risk of invasive breast cancer by 49% (69 months of follow-up). The decreased risk occurred in women of all age groups with ER-positive breast cancer; it had no effect on ER-negative tumors. However, women aged 50 or older, receiving tamoxifen, had more than a twofold increased risk of early stage endometrial cancer; women younger than 50 had no increased incidence of adverse events, including endometrial cancer [11]. Moreover, NSABP P-1 study shows that the use of tamoxifen is associated with an increase in specific vasomotor and gynecological symptoms [12].

1.3. Combination tamoxifen–CR BNO 1055

Hot flushes are a well-known side effect which occur in pre- and postmenopausal breast cancer patients treated with tamoxifen. Severe hot flushes are more frequent in menstruating women with a greater impact on quality of life; the majority of them cannot use conventional HRT for the control of the menopausal symptoms. Medications other than estrogens have to be used to control such symptoms among breast cancer survivors.

Preparations with extracts of *Cimicifuga racemosa* were originally used for menstrual and climacteric conditions. In recent years, *C. racemosa* has increasingly been recommended for use in the treatment of the physical and psychological symptoms of menopause [13,14]. The exact mechanism by which these preparations elicit their effects on menopausal symptoms has not been elucidated. While some have proposed that its effectiveness is mediated by an inhibitory effect on the hypothalamus or an effect on neurotransmitters [15], others have suggested that it has a direct estrogenic effect with the hypothesis that *C. racemosa* contains phytoestrogens, estrogen-like compounds found in plants [16]. To date, no known phytoestrogens have been identified in *C. racemosa*. An estrogenic activity is supported by some preclinical and clinical trials and not by others. The results of preclinical research appear to indicate that CR BNO 1055 contains phyto-SERMs (Jarry et al., Seidlovà-Wuttke et al. and Wuttke et al., this volume).

Of theoretical importance in this controversy is the safety of *C. racemosa* in women with estrogen-sensitive conditions such as breast cancer. On this respect, the manufacturer of CR BNO 1055 states that the preparation should not be given to patients who have or have had a history of estrogen-dependent tumors. We conducted an open randomized clinical trial to assess the efficacy and side effects of CR BNO 1055 in controlling hot flushes among breast cancer survivors under tamoxifen adjuvant therapy. This is an off-label use of the preparation. The combination therapy tamoxifen–CR BNO 1055 invites for theoretical speculations: it is known that CR BNO 1055 does not bind to ERα or ERβ-recombined proteins. It does bind, however, to cytosolic estrogen-binding proteins of human and porcine origin. Therefore, the possibility exists that other, possibly not yet identified, ERs exist (Jarry et al., this volume).

2. Methods

2.1. The clinical practice

At the Mastology Unit of the Centro Clinico de Maternidad "Leopoldo Aguerrevere", we have treated with tamoxifen (20 mg per day) 1600 breast cancer survivors women of all types, irrespective of age, menopausal, nodal and ER status (Table 1). Tamoxifen duration therapy for

Table 1
To whom we offer tamoxifen

Women aged 35–50 with a 5-year gail risk 1.7%
Women > 50
Without a uterus
With a uterus
Women with a history of
ER-positive ductal carcinoma
ER-positive lobular carcinoma
In situ or infiltrating carcinoma
ER-negative tumor

Data on file at Centro Clínico de Maternidad "L. Aguerrevere".

our patients is usually programmed for a 5-year period. The improvements in recurrence-free survival and in overall survival have been between the ranges reported by the published literature. However, into the total treated group, we have found only one case of endometrial cancer, well differentiated and of small size (Table 2).

Tamoxifen has been extremely well tolerated by our patients, and withdrawal has been fewer than 5%. The most common adverse effects of tamoxifen have been vasomotor symptoms, being more common in women before menopause than afterwards: 25% of postmenopausal patients reported hot flushes, while in premenopausal women hot flushes were higher up to 74%, mostly severe. Many of these women had recently stopped HRT, at the time of the diagnosis of breast cancer. In order to improve the quality of life of patients treated with tamoxifen, in separate experiences, we tried to control vasomotor symptoms by the use of clonidine, high dose of vitamin E or progesterone, but with very unsatisfactory results. On the contrary, very promising results were obtained when tamoxifen was administered together with CR BNO 1055 while this treatment option represents an off-label use of Menofem®.

2.2. Study participants

The study was approved by the institutional ethics review committee. Study recruitment started on May 1999 and was finished on December 2001.

Table 2
Adverse effects of tamoxifen

Menopausal symptoms
Hot flushes
Psychosomatic complaints
Irregular menses
Ocular toxicity
Gynecologic complications
Vaginal discharge
Endometrial hyperplasia and polyps
Ovarian cysts
Endometrial cancer (low grade)

Data on file at Centro Clínico de Maternidad "L. Aguerrevere".

Study participants were women over age 35, who attended the Mastology Unit of the "Centro Clínico de Maternidad Leopoldo Aguerrevere" for breast control. The main reason for eligibility was the premenopausal status with regular menstruation and normal duration of cycle, and breast cancer diagnosis with ER-positive tumor. The most common reason for exclusion was refusal to consider a study treatment for relief of symptoms, a history of other cancers and serious chronic medical conditions. Informed consent was obtained from all participants. We planned to enroll 150 patients in 18 months.

2.3. Procedures

Physical and gynecological examination including Pap smear were performed, together with intravaginal ultrasound, which was repeated 6 months later and successively every year, in order to measure the endometrium thickness; in cases the endometrial thickness was greater than 10 mm, biopsy was done. Patients under therapy were evaluated every 2 months.

Tumor stages T1, T2 and T3 (according to the TNM classification of the IUAC) were diagnosed and treated: T1 and T2 (tumor up to 3 cm) received lumpectomy, followed by radiation therapy and, when node was positive, adjuvant chemotherapy. Clinically and surgically, 65% of patients were node-negative, while 20% had 1–3 positive nodes and 15% had 4 or more positive nodes. Women with tumor T2 > 4 cm or T3 (5–10 cm) were treated with chemotherapy, pre- and postmastectomy and radiation therapy after surgery.

2.4. Study design

In order to assess the effect of CR BNO 1055 on the frequency and intensity of hot flushes, the study design was two-armed, randomized and open. Patients were instructed not to initiate new therapies for hot flushes, while participating in the study.

Tamoxifen was supplied by the insurance system of the patients, while CR BNO 1055 was supplied by the manufacturer. Tamoxifen was indicated as a single dose of 20 mg once daily for a period of 5 years. Each study participant's supply of CR BNO 1055 (Menofem®/Klimadynon® film-coated tablets, one tablet corresponds to 20 mg herbal drug) consisted of 120 tablets encased in aluminum double sheets in four boxes. Participants were instructed to take one tablet twice daily with meals for a period of 60 days. Control visits were scheduled every 2 months and supply of CR BNO 1055 was replaced. Patients were also asked to record number of hot flushes and the intensity of each. Hot flushes were considered severe when five or more sudden episodes of heat are experienced during the day, accompanied by sweating, sleep disturbances, feeling of irritation and anxiety. A few episodes of heat with discrete sweating were classified as moderate hot flushes. Study participants completed a menopausal symptom questionnaire before starting, at each control visit and at the completion of the study (12 months). The patients were asked to report adverse events to the consulting investigator.

Patients randomized to the usual-care group were treated from the beginning with tamoxifen alone, while those patients randomized to the intervention group started the treatment 15 days before tamoxifen with CR BNO 1055.

Statistical analysis was performed according to usual methods in order to detect a difference between groups.

3. Results

Of the 150 patients, who were initially enrolled and completed the menopausal symptoms index, 14 decided not to participate in the rest of the study, although they maintained the tamoxifen adjuvant therapy. The participants into the study were 136, of whom 90 were treated with the combination therapy tamoxifen–CR BNO 1055, while 46 were randomly assigned to the usual-care group. The medical and demographic characteristics of the study participants are comparable between the two groups (Table 3). To 10% of them, a total hysterectomy with retention of the adnexa had been performed. All those patients who remained in the study (136) completed hot flushes diaries at baseline, at every control visit and at the end of the study. Among the 46 study participants included into the usual-care group, 73.9% suffered from severe hot flushes and 26.1% from moderate symptoms. Patients included in this group were maintained into the study during 6 months without any therapy for hot flushes. Afterwards, many of the women, randomized to usual-care group, took open-label therapy for hot flushes prescribed by their personal physicians. In the course of the study, the bimonthly reported numbers of hot flushes in the usual-care group showed some decrease from baseline. However, the difference between values at baseline and at 6 months of initiating tamoxifen adjuvant therapy was not significant, either for severe or for moderate hot flushes (5–9% decline; $P = 0.71$; stratified Wilcoxon test from baseline to completion difference). Among the 90 study participants included in the intervention group, at the end of the study, 46.7% were free of hot flushes, while only 24.4% still suffered from severe symptoms

Table 3
Medical and demographic characteristics of 136 female breast cancer survivors

Characteristic	Usual-care group ($n = 46$)	Intervention group ($n = 90$)
Age	47 (36–51)	46 (35–52)
Ethnicity		
Hispanic	30 (65%)	52 (57%)
White	16 (35%)	38 (43%)
Type of surgery		
Lumpectomy	28 (60%)	59 (65%)
Mastectomy	18 (40%)	31 (35%)
Cancer treatment		
Tamoxifen	46 (100%)	90 (100%)
Prior radiation therapy	27 (60%)	65 (72%)
Prior chemotherapy	20 (45%)	42 (47%)
Node		
Negative	29 (62%)	59 (65%)
Positive	17 (38%)	31 (35%)
Medical conditions		
Arthritis	12 (25%)	25 (28%)
Hypertension	6 (12%)	14 (15%)
Other	8 (17%)	12 (13%)

Table 4
Hot flushes reduction by CR BNO 1055

Hot flushes	Usual-care group[a] ($n = 46$)	Intervention group[b] ($n = 90$)
Severe	34 (73.9%)	22 (24.4%)
Moderate	12 (26.1%)	26 (28.9%)
None	–	42 (46.7%)

[a] Tamoxifen adjuvant therapy.
[b] Combined therapy: tamoxifen+CR BNO 1055.

(Table 4). The patterns were significantly different between the two groups on testing the differences between proportions with Fisher's exact test ($P < 0.01$).

Eleven minor adverse events occurred: seven in the usual-care group and four in the intervention group. No serious events were reported.

4. Discussion

The SERM tamoxifen is the first-line therapy for the hormonal treatment of breast cancer, both for adjuvant treatment and as a preventive therapy for women at high risk for breast cancer. The most frequent adverse reaction to tamoxifen includes hot flushes. Most women who undergo spontaneous menopause may not seek treatment for hot flushes. However, when these symptoms are severe, they may have a significant adverse effect on the quality of life. Since the number of breast cancer survivors is expected to increase, this clinical problem will become more common. It is not possible to tell these women that there is nothing to be done. It is our obligation to address their symptoms and concern through the use of alternative strategy.

Alternative menopause therapies have to be sought for those patients who have contraindications to HRT or who reject a hormonal-based regime: this is the case of breast cancer survivor women. Surgically or pharmacologically induced hormonal deficiency causes severe vasomotor episodes, which adversely affect the quality of life of many women to a greater or lesser extent.

Extracts of the rhizome of *C. racemosa* have been traditionally used in the treatment of menopausal symptoms with promising results.

In our intervention group, the previous administration of CR BNO 1055 significantly reduced the vasomotor episodes induced by tamoxifen, and eventually by chemotherapy in breast cancer survivors women. Uncontrolled, comparative study with clonidine, high dose of vitamin E or progesterone failed to reach a satisfactory control of the severe hot flushes experienced by premenopausal breast cancer survivors treated with tamoxifen. In a recent randomized, double-masked and placebo-controlled study, the effect of *C. racemosa* on the frequency and intensity of hot flushes was investigated in patients with history of breast cancer. The study was stratified on tamoxifen/no tamoxifen use; for eligibility, women had to have completed primary therapy, including chemotherapy and radiations therapy. Both the treatment and placebo groups, whether using tamoxifen or not, reported a reduction in the intensity of hot flushes, but the difference between the treatment/no tamoxifen group and the other group was not statistically significant [17]. A limitation of this study is that participation lasted only 2 months. When used for a longer period of time, *C. racemosa* may show increased efficacy relative to placebo. In accordance with this statement, we have demonstrated that combination therapy tamoxifen–CR BNO 1055, administered for a longer period of time, represents a very important therapeutic tool for the reduction of hot flushes and an improvement of the quality of life in this group of patients. A similar combined therapy may be used when tamoxifen is administered as a preventive agent for women at high risk for breast cancer.

Phytoestrogens are a popular method of treating hot flushes for many women, and breast cancer survivors are among this group. These agents have enormous appeal because they are "natural" and because they are claimed to be safe.

If women choose to use phytoestrogens, physicians should recommend that they should use only products that detail all their ingredients and contain standardized extracts, like in the case of CR BNO 1055, which we used in the present study.

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