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Pilot Evaluation of Black Cohosh for the Treatment of Hot Flashes in Women

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ABSTRACT

Background. Hot flashes cause significant morbidity in postmenopausal women, including women with breast cancer. We undertook a pilot study to estimate the effectiveness of black cohosh to reduce hot flashes. *Methods.* Women who reported significant hot flashes ($\geq$14 per week) were enrolled. Black cohosh was given in the form of the commercial product Remifemin. The first week was a no-treatment baseline period, and therapy was given for the subsequent 4 weeks. Hot flash data were collected by daily questionnaires during baseline and treatment weeks. Adverse effects were recorded. *Results.* Twenty-one women completed the study. Their mean age was 56 years (range, 38–80). Thirteen patients had a history of breast cancer. Six patients were taking tamoxifen or raloxifene. Patients reported an average of 8.3 hot

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flashes per day during the baseline week. The reduction in mean daily hot flash frequency was 50% (95% CI, 34%–65%), while weekly hot flash scores were reduced 56% (95% CI, 40%–71%) at completion of the study. Overall, patients reported less trouble with sleeping, less fatigue, and less abnormal sweating. No patients stopped therapy because of adverse effects. *Conclusions.* Black cohosh appeared to reduce hot flashes and had a low toxicity. The efficacy found in this trial seems to be more than would be expected by a placebo effect (20%–30% hot flash reduction in previous trials). These results suggest that further evaluation of this black cohosh preparation with a phase III randomized trial is indicated.

Key Words: Alternative medicine; Breast cancer; Hot flashes; Medicine, herbal; Menopause.

INTRODUCTION

Hot flashes can be a significant clinical problem in women experiencing diminished ovarian function as a result of menopause or breast cancer therapy, including chemotherapy or antiestrogens such as tamoxifen citrate. Estrogen has been the mainstay of therapy for most women with hot flashes. Because of the link between estrogen use and the possible development of breast cancer however, the use of estrogens in survivors of breast cancer has long been considered contraindicated.[1] In addition to patients with breast cancer, an increasing number of women who are at high risk for the development of breast cancer or fear the diagnosis of breast cancer, similarly do not want to use estrogens.

Hot flashes produce several symptoms that cause women to seek treatment. Patients describe sweating requiring a change of clothing and bedding, noticeable flushing, disruption of sleep, anxiety, and general decrease in quality of life.[2] Many nonhormonal therapies, such as clonidine, methyldopa, and belladonna alkaloids, have been studied for the treatment of menopausal symptoms, but success with these agents has been limited.[3–5] A placebo-controlled crossover randomized trial with megestrol acetate demonstrated an 80% reduction in hot flashes; this result appears to be similar to the effect of estrogen on hot flashes.[6] Subsequently, anecdotal reports suggested that the new antidepressants, including the new selective serotonin reuptake inhibitors (SSRIs), may relieve hot flashes. Subsequent placebo-controlled randomized studies demonstrated approximately a 50–60% reduction of hot flashes with venlafaxine (Effexor)[7,8] and with fluoxetine (Prozac).[9] In addition, paroxetine (Paxil) appeared to have similar efficacy in a pilot trial.[10]

The use of alternative and complementary medicine therapy has skyrocketed in recent years, with the estimated amount of money spent on these alternative therapies being $21.2 billion.[11] Up to 67% of people have used at least one such therapy in their lifetimes, and the use of this therapy increases with age.[12] The use of complementary therapies seems to be more common among patients with cancer, especially those with breast cancer (84% utilization).[13] Many consumers perceive that alternative and complementary medicine therapies offer a more ''natural'' and less toxic alternative than ''synthetic'' drugs. However, because data are limited, verification of these claims is difficult. Thus, it is important for the medical community to investigate these agents and provide sound information to patients so they can make informed decisions.

Epidemiologic data from Japan suggest that soy products may reduce the severity of hot flash symptoms,[14] but a double-blind, placebo-controlled randomized crossover study concluded that soy products had the same ''efficacy'' as a placebo.[25] Vitamin E, evaluated with the same randomized study method, demonstrated a mild reduction of hot flashes (39%) compared with placebo (21%).[15]

Black cohosh, *Cimicifuga racemosa*, is an herbal remedy that has been used to treat menopausal symptoms. A member of the buttercup family, it is a plant native to North America. American Indians used the herb to treat women's diseases and rheumatism.[16] Prospective trials with black cohosh, conducted in Europe, reported an improvement in menopausal symptoms.[17–19] Three small, German, double-blind, placebo-controlled trials reported a significant improvement of menopausal symptoms in women receiving black cohosh.[17–19] One recent randomized, placebo-controlled trial did not reveal any improvement with black cohosh administration but did note a decrease in sweating.[20]

The mechanisms of action of black cohosh have not been elucidated. An overview of the estrogen- and progesterone-stimulating activity of many foods showed

that an ethanol extract of black cohosh did not stimulate growth of estrogen- and progesterone-positive breast cancer cells in vitro.[16,21] Administration of black cohosh has not caused changes in hormonal or vaginal cytologic variables.[17–19] It does not change serum follicle-stimulating hormone or luteinizing hormone levels.[20]

Thus, the preliminary data on black cohosh suggest that this herb has potential clinical benefit, without any evidence of hormonal stimulation, in women who have hot flashes. This current pilot trial was developed prior to knowing about a randomized trial conducted elsewhere[20] to investigate the use of black cohosh in the treatment of hot flashes. We planned to use the results of this pilot trial to determine whether a larger randomized trial should be performed.

MATERIALS AND METHODS

All participants considered for this study were women older than 18 years. Eligible women 1) had a history of breast cancer but were currently without evidence of cancer, 2) were considered to be at high risk for the development of breast cancer, or 3) did not want to take estrogen. The patients had bothersome hot flashes that occurred at least 14 times per week and had begun at least 1 month before the start of the study. The patients' life expectancies were more than 6 months and they had an Eastern Cooperative Oncology Group performance status of 1 or better. The patients had not received antineoplastic chemotherapy, androgens, estrogens, progestational agents, clonidine, or Bellergal-S (ergotamine, belladonna alkaloids, and phenobarbital) within the preceding 4 weeks. The patients had not used antidepressants within the preceding year. The patients were not receiving, and did not plan to receive, other agents to treat hot flashes during the 5-week study. If a patient was receiving tamoxifen or raloxifene, therapy with these drugs had to have been started at least 1 month before the study and the patient had to have plans to continue this therapy during the entire trial.

A commercial preparation of a standardized extract of *Cimicifugaracemosa*, Remifemin, which has been in use in Germany for menopause management since the mid 1950s, was chosen as the preparation of black cohosh for the study.[20] Remifemin has been approved by the Complete German Commission E Monographs for treatment of premenstrual discomfort, dysmenorrhea, and climacteric neurovegetative ailments. There are no known contraindications and no known drug interactions. The main reported side effect is occasional gastric discomfort.[22] Testing of Remifemin with the *Salmonella*-microsome test (Ames test) has shown no evidence of mutagenic activity.[17–19]

After meeting the study requirements, patients gave informed consent and were registered in the study. They agreed to fill out a daily diary that has been used in several other studies of hot flashes.[6,8,14,15,23] The patients filled out the daily diary for 1 week before beginning black cohosh therapy, a period that served as a baseline control. After this 1-week period, patients began taking Remifemin, 1 tablet orally twice a day. Patients continued to complete the daily diary during the subsequent 4 weeks. A study nurse contacted the patients during the second and fifth weeks to monitor compliance and address any problems.

The estrogenic activity of black cohosh was assessed in a growth-based assay with the *Saccharomyces cerevisiae* strain PL3 (*ura3*-Δ1, *his3*-Δ200, *leu2*-Δ1,*trp1*::*3ERE-URA3*) construct with the human α-receptor (a gift of R. Losson, M.D.). The human β-estrogen receptor (a gift from T. Watanabe, M.D.) was cloned into a yeast expression vector in the laboratory and then introduced into the *Saccharomyces cerevisiae* strain PL3 (β-receptor) as previously described.[24] The PL3 carries a *URA3* gene that is under control of the estrogen-response element. Transcription of *URA3*, which is required for the growth of the cells in medium lacking uracil, is dependent on the activation of the human estrogen receptor by a ligand. Cells were seeded in 96-well plates in 190 μL of medium lacking uracil. Serial dilutions of 10 μL of β-estradiol or black cohosh were added to the cultures, and growth was observed for 4 days.

Statistical Methods

This pilot study was handled in a descriptive manner. The primary question was to determine whether any reduction in hot flash activity occurred beyond what was expected from placebo (20%–30%).[8,15,23,25] Basic summary statistics were supplemented by confidence intervals and graphical representations.

Efficacy measures included the average number of daily hot flashes per week, the average hot flash score (the number of mild hot flashes plus twice the number of moderate hot flashes plus three times the number of severe hot flashes plus four times the number of very severe hot flashes) per week, and the proportion of patients who reported a substantial reduction ($\geq$50%)

of their hot flash scores. Simple incidence data were used to evaluate toxicity data.

RESULTS

A total of 23 consecutive patients entered the trial from October 2000 to March 2001. Two patients dropped out prior to starting any of the study medication. The characteristics of the 21 evaluable patients are listed in Table 1.

The mean number of hot flashes experienced by the patients at baseline was 8.3 per day (range, 3.7–18.9). After 1 week of black cohosh administration, the mean number of hot flashes decreased to 6.6 per day (range, 0.6–19.9). At completion of the 5-week study, the mean number of hot flashes decreased to 4.2 per day (range, 0–18.1). During the fifth week, there was a 50% reduction of mean daily hot flash frequency (95% CI, 34%–65%), a 56% reduction in weekly hot flash score (95% CI, 40%–71%), and a 22% decrease in mean hot flash severity (95% CI [confidence interval], 8%–37%) when compared to the baseline week. At conclusion of the study, 11 patients (52%) reported a 50% or more decrease in hot flash frequency.

To examine further the efficacy of black cohosh, we evaluated the combination of hot flash frequency and severity by using the hot flash score (frequency times average severity). Changes in the hot flash score over the 4-week course of treatment are shown in Fig. 1. The hot flash score decreased in all but five patients during the first week of treatment. The greatest clinical effect appeared to occur after the first week of therapy, but gradual improvement in symptoms continued during the course of treatment. Individual patient changes in hot flash scores over the study period are illustrated in Fig. 2.

To better evaluate the potential efficacy of black cohosh, we compared our pilot data with those of other

Table 1. Characteristics of 21 patients treated with black cohosh.

Variable	%
Age, yr	
18–49	33
≥50	67
Reason for entry in study	
Breast cancer or DCIS*	62
High risk for breast cancer development	9
Did not want estrogen therapy	29
Tamoxifen or raloxifen use	
Yes	29
No	71
Duration of hot flashes, mo	
<9	43
≥9	57
Average frequency of hot flashes, per day	
4–9	76
≥10	24

*Ductal carcinoma in situ.

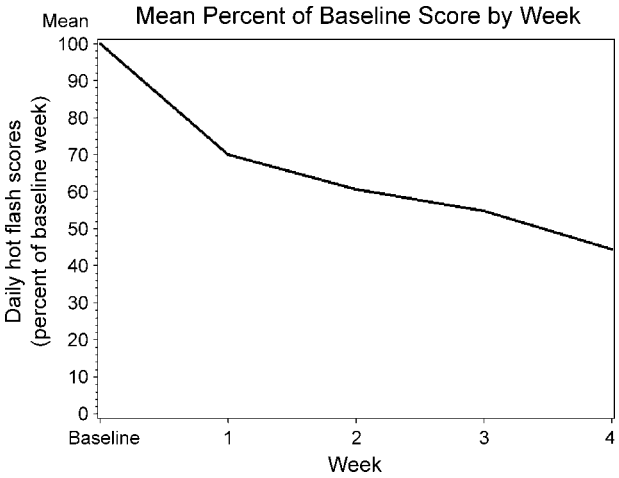

Figure 1. Hot flash scores for 21 patients treated with black cohosh.

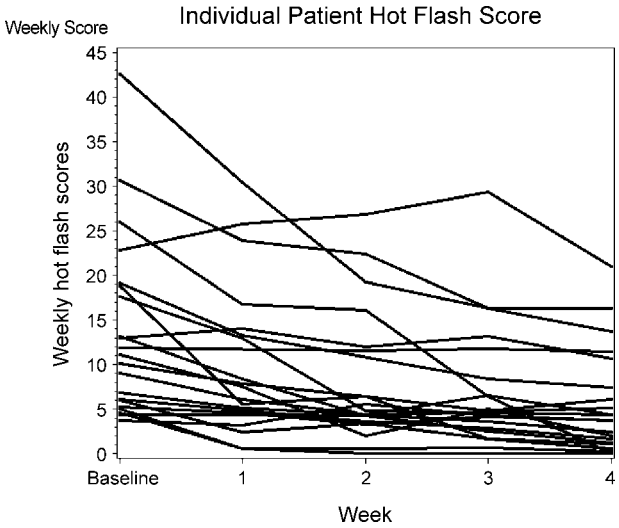

Figure 2. Hot flash score changes in individual patients.

Table 2. Percent of baseline hot flash scores during the fourth week of therapy for patients providing data.

	N	0–24%	25%–49%	50%–74%	75%–100%	>100%
Gabapentin (400 mg/d) (31)	16	44%	38%	13%	6%	0%
Venlafaxine (25 mg/d) (7)	25	35%	23%	12%	19%	12%
Black cohosh	21	33%	33%	10%	19%	5%

pilot trials we have conducted in a similar manner (Table 2).

During the study, the patients were asked to report the occurrence of any of the following symptoms: appetite loss, weight loss, sleepiness, anxiety, restlessness, tiredness (fatigue), trouble sleeping, nervousness, mood changes, and constipation. These data were collected to evaluate toxicity. All symptoms were reported with lower frequency after 4 weeks of treatment with black cohosh. The greatest reductions were seen in sleeping difficulties, fatigue, and abnormal sweating after starting black cohosh. The frequency of abnormal sweating decreased from 65% in the baseline week to 13% at the conclusion of the study (Table 3). One patient reported joint pain; the pain was worst in her hands and was accompanied by erythema. During hot flashes, her hands would become red and painful and they throbbed. This adverse reaction was witnessed during a physical examination. After the black cohosh therapy was discontinued, these symptoms resolved.

Because many people believe that black cohosh is a phytoestrogen, we tested the estrogenic activity of the herb and estradiol with transcriptional-activation assays in yeast (estrogen-dependent *S. cerevisiae* strain PL3). Interestingly, estradiol supported growth on the yeast at a minimal concentration of 20 μM in both constructs. Growth was not supported by black cohosh in α- or β-estrogen-receptor constructs.

Table 3. Symptom frequency in 21 patients treated with black cohosh.

	Patients with symptom	
Symptom	Baseline week	Fourth week of therapy
Mood change	31%	7%
Tiredness (fatigue)	47%	13%
Dry mouth	18%	8%
Abnormal sweating	65%	13%
Trouble sleeping	65%	20%
Nervousness	6%	7%
Constipation	6%	0%
Restlessness	25%	6%

DISCUSSION

In 1989, the North Central Cancer Treatment Group began developing clinical trials to evaluate various therapeutic agents for the treatment of hot flashes in breast cancer survivors, women with a fear of estrogen use because of the possible development of breast cancer, and men with prostatic cancer who were receiving androgen-deprivation therapy. A total of more than 1,000 patients with hot flashes have been evaluated during a 10-year period. This research has led to the development of instrumentation and analytical methods to assess the efficacy of treatment to reduce hot flash symptoms.[23] This work suggests that a reduction of hot flash activity of at least 45% in a pilot trial suggests that it is reasonable to pursue further testing of a particular agent in a larger phase randomized trial. The current pilot trial fulfills this criterion, in that the reduction of hot flash activity with black cohosh therapy was 56%.

Currently, the known information regarding the use of black cohosh is limited to several older European trials[15–19,26] and one recent placebo-controlled randomized trial conducted in the United States.[20] The European trials were composed of both prospective and placebo-controlled randomized trials. Hot flash symptoms were reportedly improved in the majority of women after a 4-week course of therapy, and the symptoms continued to improve over 12 weeks. A recently completed placebo-controlled trial, however, was unable to confirm the activity of the prior European trials. This American trial, however, did find a significant decrease in sweating among women taking the black cohosh, a finding that was also prominently observed in our pilot study. Because excessive sweating is a common and often debilitating symptom that accompanies hot flashes, an improvement in this clinical manifestation of menopause would be a welcome relief to many women.

Based in part on these pilot data, the National Carrier Institute has approved a placebo-controlled randomized trial to more thoroughly evaluate the utility of black cohosh for alleviating hot flashes in women. One might ask whether this is reasonable, given the availability of other agents that are known to alleviate hot flashes, such as estrogen, progesterone, and newer antidepressants. The answer is yes, since many women prefer not to take hormones or antidepressants. In fact, many women appear to be more comfortable taking something considered to be a ''natural herbal preparation'' as opposed to a more classic pharmaceutical agent.

Although we do not currently feel comfortable claiming that black cohosh clearly is better than a placebo for alleviating hot flashes, it is reasonable to explore whether there is a potential mechanism of action that might explain how it might work against hot flashes. This herb was previously thought to be a phytoestrogen. Data supporting this contention, however, have been inconclusive. The isoflavone formononetin, which exhibits a weak estrogen-like effect, was isolated from black cohosh in 1991.[27] Nonetheless, more recent studies have demonstrated that commercially available black cohosh does not contain the isoflavones formononetin, kaempferol, or genistein.[17] Thus, the earlier reported findings may have been due to a contaminant.[17] Black cohosh has not exhibited any estrogen-receptor binding activity or mitogenic effect on estrogen-receptor–positive breast cancer cell lines in vitro.[16,21,28] The laboratory study in this present report also does not demonstrate any activity on the estrogen receptor in vitro. There have been conflicting reports about the effect of black cohosh on luteinizing hormone and follicle-stimulating hormone. Earlier studies observed suppression of luteinizing hormone but no effect on follicle-stimulating hormone or prolactin in serum levels of postmenopausal women and ovariectomized rats,[29] but the recently reported randomized trial did not show a change in luteinizing hormone or follicle-stimulating hormone in serum blood levels among women with hot flashes.[20] Interestingly, evaluation of the Chinese herb shengma, which contains *Cimicifuga rhizome*, has been shown to attach to serotonin receptors ($5\text{-}HT_{1A}$) by in vitro binding assays and animal studies.[17,30] Thus, it is plausible that this herb might work in a similar manner to the antidepressants[8–10] by some central nervous system modulation.

In summary, this pilot study supports the hypothesis that black cohosh decreases hot flashes in women with breast cancer, premalignant breast diseases, and/or an antipathy to estrogen therapy. Further evaluation by a randomized trial is warranted.

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