Black cohosh (Cimicifuga racemosa) in tamoxifen-treated breast cancer patients with climacteric complaints – a prospective observational study

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Abstract
Objectives. The antihormonal therapy of breast cancer patients with the antiestrogen tamoxifen often induces or aggravates menopausal complaints. As estrogen substitution is contraindicated, herbal alternatives, e.g. extracts of black cohosh are often used.

Design. A prospective observational study was carried out in 50 breast cancer patients with tamoxifen treatment. All patients had had surgery, most of them had undergone radiation therapy (87%) and approximately 50% had received chemotherapy. Every patient was treated with an isopropanolic extract of black cohosh (1–4 tablets, 2.5 mg) for 6 months. Patients recorded their complaints before therapy and after 1, 3, and 6 months of therapy using the menopause rating scale (MRS II).

Results. The reduction of the total MRS II score under black cohosh treatment from 17.6 to 13.6 was statistically significant. Hot flashes, sweating, sleep problems, and anxiety improved, whereas urogenital and musculoskeletal complaints did not change. In all, 22 patients reported adverse events, none of which were linked with the study medication; 90% reported the tolerability of the black cohosh extract as very good or good.

Conclusions. Black cohosh extract seems to be a reasonable treatment approach in tamoxifen treated breast cancer patients with predominantly psychovegetative symptoms.

Keywords: Black cohosh, Cimicifuga racemosa, climacteric complaints, hot flushes, breast cancer, tamoxifen, Menopause Rating Scale II

Introduction
Breast cancer is still the most frequent malignant disease in women. Anticancer therapy with cytostatics, GnRH-analogs, aromatase inhibitors, or antiestrogens frequently induce climacteric-like complaints or aggravate preexisting menopausal symptoms. Estrogen substitution against climacteric-like complaints is not recommended due to the assumed risk of hormone-induced tumor progression [1]. Therefore, breast cancer patients with climacteric complaints avidly search for alternatives. One of the treatment options are herbal drugs like extracts of the black cohosh rhizome (Cimicifuga racemosa). The medicinal use of black cohosh has been known for a long time, and numerous clinical studies have been performed, with controversial results, concerning its efficacy in climacteric complaints [2–10].

More recent preclinical data suggest that black cohosh has a tissue-selective estrogen receptor modulatory (SERM) activity which is accompanied by centrally acting dopaminergic, serotonergic, and GABAergic effects [11,12]. Although experimental and clinical data indicate the safety of black cohosh in patients with breast cancer [13–16], the data on the treatment of tamoxifen-associated climacteric complaints are inconclusive [17–20]. Therefore, our prospective observational study was conceived to provide data about the dosage, effectiveness, and tolerability of an isopropanolic extract of black cohosh in patients with breast cancer treated with tamoxifen and suffering from climacteric complaints.

Methods
This prospective observational study was performed at the Department for Oncological Rehabilitation and Aftercare at the Tumor Biology Center at Albert-Ludwigs-University Freiburg, according to Section 67, 6 AMG (German drug law) and adhering to recent recommendations [21] as well as to the Helsinki declaration. Only patients with breast cancer initially taking part in an inpatient rehabilitation program (physiotherapy as well as physical and psychological training measures) following primary cancer treatment were included.

On admission, these women were asked if they wanted to participate in the current study, if they had not used black cohosh preparations within the last 3 months, had not been treated with antihormonal drugs other than tamoxifen (e.g. GnRH-analogs or aromatase inhibitors) or concomitant chemo- or radiotherapy or participated in another clinical trial. Informed consent was obtained from all patients at the time of the first prescription of black cohosh extract, when the instructions for completing the MRS II questionnaires were also issued.
A total of 50 patients were recruited to study medication (Remifemin®, Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany) at a dosage of two tablets per day (patient characteristics, see Table I). Each tablet contains 0.018–0.026 ml liquid extract of black cohosh rhizome (d.e.r.: 0.78–1.14:1, corresponding to 20 mg herbal drug, excipient: isopropyl alcohol 40 vol %). After the first treatment phase of 4 weeks, the dosage of the study medication could be changed by patients.

The Menopause Rating Scale (MRS II) [22,23] was used as primary endpoint. MRS II is a questionnaire designed for the self-assessment of the profile and intensity of menopausal symptomatology and can be used for diagnostic purposes and for monitoring treatment effects. We used it to make baseline measurements as well as effectiveness measurements after 1, 3, and 6 months of treatment. It represents a validated tool that has been gauged with a representative sample of German females aged 45–60 years [22]. Women are asked to estimate the severity of 11 symptoms according to a five-level-scale: 0 = no, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe [23,24]. Three subscores can be defined within the groups of symptoms: (1) psychological complaints, (2) urogenital complaints, and (3) vegetative somatic complaints. The questionnaire is evaluated by adding up the intensity values for each item and thus obtaining an overall score as well as the three subscores. The results for symptom severity can then be classified according to Potthoff et al. [22]: 0–4 = none, 5–8 = mild, 9–15 = moderate, ≥16 = severe.

In addition to the first MRS II questionnaire, a baseline documentation of tumor history was provided by physicians at the first visit (t1). For all subsequent assessments, MRS II questionnaires were sent to patients by mail; only 12 inpatients completed their second questionnaire in the clinic. In addition, a questionnaire related to adverse events and co-medications as well as compliance, concomitant diseases and patients global assessments of effectiveness and tolerability was collected at t2–t4. All adverse events were documented according to standard procedures.

### Table I. Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Mean ± SD)</th>
</tr>
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<tbody>
<tr>
<td>Age (years, mean)</td>
<td>56 (43 – 77)</td>
</tr>
<tr>
<td>Time since first tumor diagnosis (mean ± SD, months)</td>
<td>8.6 (± 6.2)</td>
</tr>
<tr>
<td>Postmenopausal status (n)</td>
<td>35 (74%)</td>
</tr>
<tr>
<td>Estrogen therapy at the time of tumor diagnosis (n)</td>
<td>17 (36%)</td>
</tr>
<tr>
<td>Breast cancer (n)</td>
<td>44 (94%)</td>
</tr>
<tr>
<td>AJCC (stage I or II) (n)</td>
<td>42 (89%)</td>
</tr>
<tr>
<td>Radiating therapy (n)</td>
<td>41 (87%)</td>
</tr>
<tr>
<td>Chemotherapy (n)</td>
<td>24 (51%)</td>
</tr>
<tr>
<td>Tamoxifen (n)</td>
<td>47 (100%)</td>
</tr>
<tr>
<td>Breast surgery (n)</td>
<td>33 (70%)</td>
</tr>
<tr>
<td>Radiation therapy (n)</td>
<td>41 (87%)</td>
</tr>
<tr>
<td>Breast cancer (n)</td>
<td>44 (94%)</td>
</tr>
<tr>
<td>AJCC (stage I or II) (n)</td>
<td>24 (51%)</td>
</tr>
<tr>
<td>Tamoxifen (n)</td>
<td>47 (100%)</td>
</tr>
<tr>
<td>Comediations (n)</td>
<td>23 (49%)</td>
</tr>
<tr>
<td>Concomitant diseases (n)</td>
<td>29 (62%)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Dysfunctional thyroid gland</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Vitamins, minerals, herbal immunomodulators</td>
<td>9 (19%)</td>
</tr>
</tbody>
</table>

### Statistics

The software SPSS 11.5 was used for statistical evaluations. Missing data were imputed according to “last observation carried forward” (LOCF). The primary endpoint (MRS II) was analyzed using the two-tailed Wilcoxon-test for paired samples, separately comparing each evaluation, i.e. after 1, 3, and 6 months, with the baseline. To allow for repeat testing, a overall of 0.05 was divided by the number of visits (n = 3): i.e. \( x_3 = 0.05/3 = 0.0167 \).

All data were included in the final analysis, irrespective of whether patients had finished their treatment course. Patients’ overall perception of black cohosh extract effectiveness was analyzed descriptively. Safety was evaluated using all patients who took the study medication at least once (n = 50). Effectiveness was evaluated using all patients who reported on effectiveness at least once after baseline (n = 47).

### Results

During a recruitment phase of 18 months, 50 patients gave their informed consent for inclusion in the study (see Figure 1). At study entry hot flushes and sweating were the most prominent symptoms (mean assessment “severe”), followed by sleep problems and physical and mental exhaustion (mean assessment “moderate”). Psychological complaints (depressive mood, irritability, anxiety) were regarded as “mild” to “moderate.” In the overall MRS II score, 31 patients self-assessed their symptoms as “severe.” A mean MRS-II-overall score of 17.6 (± 6.1) was calculated, corresponding to a “severe” symptomatology (Table II).

In all patients, treatment commenced with the standard dosage of 40 mg black cohosh, but the dose could be adjusted according to patients’ requirements after 4 weeks (t2). Thus, 15 patients increased their dose to 80 mg, three to a total daily dose of 60 mg drug, whereas two reduced the dosage to 20 mg per day. Another four patients switched to a combination preparation of black cohosh extract and St. John’s wort extract. A total of 40 patients...
continued medication (40 mg (24), 80 mg (14), other (2)) for 3 months until t3, and 35 patients (40 mg (20), 80 mg (11), other (4)) for 6 months until t4. Finally, 30 patients wanted to continue medication after the end of the observation period (40 mg (11), 80 mg (12), other (7)).

During the observation period, the overall MRS II score decreased from 17.6 to 13.6 (Table II). All differences between baseline and month 1, 3, or 6 (or last observation) were statistically significant ($p < 0.001$). The subscores are summarized in Table II.

Symptoms that were initially most pronounced such as hot flushes, sweating, and sleep problems improved most during the observation (Figure 2). The differences in MRS II subscores “vegetative somatic complaints” and “psychic complaints” between study begin and month 1, 3, or 6 (or last observation) were also statistically significant ($p < 0.001$). However, no statistically significant differences were observed in the MRS II subscore “urogenital complaints” (Table II).

For the drug safety analysis, data from all 50 participants were consulted. The mean duration of exposition was $134 \pm 60$ days. In global self-assessment, 43 of 48 answering patients categorized the tolerability of black cohosh extract as “very good” or “good,” none as “bad.” In total, 36 adverse events (AE) were reported by 22 patients, four of whom discontinued therapy. One patient discontinued therapy due to nausea several days after study begin. The vast majority of AE can probably be attributed to the tamoxifen therapy: hot flushes, drowsiness, headaches, bone and joint aches [9] and endometrial polyps (an isolated case). According to physicians’ appraisal, none of the documented AE was causally related to black cohosh extract. Two severe AE led to patient hospitalization. One case required the removal of an endometrial polyp, which was linked to tamoxifen therapy, whereas the second patient underwent breast implantation. No tumor recurrence was reported during the observation period.

### Table II. MRS II and subscores

<table>
<thead>
<tr>
<th></th>
<th>t1 (n=50)</th>
<th>t2 (n=47)</th>
<th>t3 (n=40)</th>
<th>t4 (n=35)</th>
<th>Last observation (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRS II Score</td>
<td>17.6 (6.1)</td>
<td>14.0 (5.7)**</td>
<td>14.2 (5.1)**</td>
<td>13.8 (6.4)**</td>
<td>13.6 (6.5)**</td>
</tr>
<tr>
<td>Vegetative somatic symptoms</td>
<td>8.1 (2.6)</td>
<td>6.8 (2.6)*</td>
<td>6.4 (2.0)*</td>
<td>6.5 (2.7)*</td>
<td>6.4 (2.8)*</td>
</tr>
<tr>
<td>Psychic symptoms</td>
<td>6.6 (3.6)</td>
<td>4.6 (2.8)*</td>
<td>5.0 (3.0)*</td>
<td>4.5 (2.9)*</td>
<td>4.4 (3.1)*</td>
</tr>
<tr>
<td>Urogenital symptoms</td>
<td>3.0 (2.5)</td>
<td>2.7 (2.1)</td>
<td>2.8 (2.2)</td>
<td>2.8 (2.5)</td>
<td>2.8 (2.4)</td>
</tr>
</tbody>
</table>

Mean (SD); * $p < 0.01$; ** $p < 0.001$
Discussion

In this prospective observational study with 50 patients with breast cancer suffering from climacteric complaints under tamoxifen treatment, we observed a statistically significant improvement in the menopause rating scale II during intake of black cohosh extract over 6 months. Psycho-vegetative symptoms improved, especially hot flushes and sweating, but not somatic symptoms (e.g. vaginal dryness and muscle and joint pain).

Previous studies provided conflicting results. Pockaj et al. could not find any positive effect of black cohosh extract on Greene Climacteric Scale in a double-blinded cross-over RCT with 132 breast cancer survivors. However, patients received the medication for only 4 weeks, and then were crossed over without any washout period [19]. In a foregoing uncontrolled open-label pilot study with 23 women, partly patients with breast cancer, the authors had found a significant reduction in hot flashes (scores and frequency) [20]. In a further double-blinded randomized controlled trial with 85 breast cancer survivors, no statistically significant improvement in frequency and intensity of hot flashes was found for black cohosh extract versus placebo, but in a menopausal symptom questionnaire a significant reduction of sweating was described after 60 days of intake [17]. In a prospective randomized open-label trial with 136 breast cancer survivors, 46 patients were treated with tamoxifen alone, while the other 90 patients were randomized (2:1) for an additional black cohosh extract over 12 months. The frequency and intensity of hot flashes decreased statistically significantly compared to control [18].

The second study of Pockay et al. [19] and partly the study of Jacobson et al. [17] showed that the effect of black cohosh extract may be equal to placebo. However, these studies have had some limitations. The intake of herbal extracts is usually recommended for a longer time period as their whole effectiveness unfolds only after several weeks.

Only the last mentioned study with a medication period of 12 months considered this point and showed convincing improvements [18]. In our observational study orientated on daily practice, patients took the black cohosh extract for 6 months. They had the opportunity to change the dosage according to their self-assessment, e.g. to increase dosage when dissatisfied with treatment effect or to reduce it if side effects occur. Thus, in contrast to RCTs with fixed doses, an individualized treatment is possible and may improve the outcome.

Unquestionably this study has some relevant shortcomings. Without a placebo control we cannot distinguish treatment effects from placebo. Furthermore, during the initial treatment phase, patients had an intensive inpatient rehabilitation care program. This may have contributed to the overall benefit. Nevertheless, the persistence of benefit for additional 5 months argues for a sustaining effect of the black cohosh extract.

With regard to drug tolerability, results from earlier trials correspond well. Of our patients, 90% reported “very good/good” tolerability; only one adverse event (nausea) was possibly related to the study medication. Briese et al. [25] described in their postmarketing surveillance study that physicians classified drug tolerability in 92% of the 3027 patients as “very good/good.” Osmers et al. [26] and Liske et al. [27] reported no serious side effects in their randomized clinical trials. Walji et al. [13] judged the use of black cohosh extract in breast cancer patients to be safe.

The effectiveness of black cohosh extract in treating climacteric complaints in patients with breast cancer remains inconclusive. However, in view of the results of our study together with the findings of other trials described here, we see a possible therapeutic option in this herbal drug which may help in some cases to reduce the side effect symptomatology of antihormonal treatment and thus may support patient adherence, which is very often at risk [28–30].

Figure 2. Menopause Rating Scale (MRS) II (Mean +/- SD).

Symptom scores under treatment with black cohosh extract
t1 = day 1; t2 = day 28 ± 7; t3 = day 90 ±14; t4 = day 180 ±28
Acknowledgements

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References