Benefit–risk profile of black cohosh (isopropanolic Cimicifuga racemosa extract) with and without St John’s wort in breast cancer patients

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\textbf{ABSTRACT}

Endocrine therapy in breast cancer survivors can cause severe ‘climacteric’ symptoms, which may compromise therapy adherence. To determine whether such symptoms can be treated with herbal medication containing black cohosh in the form of isopropanolic \textit{Cimicifuga racemosa} extract (iCR) alone or in fixed combination with St John’s wort (\textit{Hypericum perforatum} [HP]) (iCR + HP), a systematic literature search was conducted. Results were viewed in relation to experimental data and metabolism of endocrine therapies. Most breast cancer survivors receiving endocrine therapy experienced reductions in climacteric symptoms under iCR/HP. Tamoxifen’s interference potential may be countered by using higher iCR doses or iCR + HP. No estrogen-like effects at the breast or on hormones were seen. After breast cancer, even if receiving tamoxifen, patients using iCR/HP had significantly decreased recurrence-free survival rates compared to non-users. These results are substantiated by experimental data demonstrating antiproliferative and anti-invasive effects of iCR in breast cancer cells and enhancement of the antineoplastic effects of tamoxifen. There are no known clinical interactions for iCR and HP with endocrine therapies. The HP extract used in iCR + HP did not exhibit any clinically relevant interaction potential. In conclusion, with its positive benefit-risk profile, iCR/HP may offer a safe non-hormonal therapeutic option for breast cancer survivors receiving endocrine therapy.

\textbf{Introduction}

Breast cancer patients receiving endocrine therapy (e.g. tamoxifen) often suffer from adverse reactions like hot flushes, sleep problems, depressive symptoms, irritability, and mood swings. With increasing severity, these complaints can force patients to discontinue their antihormonal therapy.\textsuperscript{2,3} Hormone therapy (HT) is generally not recommended for breast cancer survivors.\textsuperscript{4} Consequently, non-hormonal treatment options are highly appreciated.

Among these options, herbal medicinal products with \textit{Cimicifuga racemosa} (CR; \textit{Actaea racemosa} or black cohosh) are widely used and are also recommended by the European Medicines Agency (EMA) for the treatment of climacteric complaints.\textsuperscript{5} Oxford Level 1 evidence for ameliorating natural neurovegetative and psychic menopausal symptoms is available for the special isopropanolic \textit{C. racemosa} extract (iCR), used as standard-dose monotherapy or higher dosed in a fixed combination with St John’s wort (\textit{Hypericum perforatum} [HP]) (iCR + HP).\textsuperscript{6,7} In randomized controlled trials (RCTs), iCR and iCR + HP significantly improved climacteric symptoms compared to placebo.\textsuperscript{8–12} RCTs showed the comparable efficacy of iCR to low-dose transdermal hormone therapy or tibolone.\textsuperscript{13,14} In patients with more intense symptoms and/or pronounced psychic components, iCR + HP was superior to iCR monotherapy.\textsuperscript{15}

In clinical practice, it is often asked whether breast cancer patients suffering from side effects of endocrine therapy can be treated with iCR or iCR + HP: what about safety at the breast and interactions commonly attributed to HP? Answers to this question could have consequences for the treatment schedule of thousands of patients as breast cancer has become the most common cancer in women worldwide, comprising 16% of all female cancers and 22.9% of female invasive cancers.\textsuperscript{16,17} Like in western countries, the breast cancer incidence is increasing in Asia.\textsuperscript{18} In China, breast cancer constitutes 12.2% of all newly diagnosed breast cancers in the world, accounting for 9.6% of the global breast cancer deaths. In 2015, of the 4.292 million newly diagnosed cancer cases in China, 268,600 were breast cancer, accounting for 15% of new female cancers.\textsuperscript{19} The incidence rate among those aged 45–59 years was 23%.\textsuperscript{19}

This review intends to offer orientation for health care providers by giving an overview of the experimental and clinical data on iCR/ICR + HP safety at the breast, its use in
breast cancer patients, and putative interactions with endocrine treatment.

Methods

MEDLINE, EMBASE, EMBASE Alert, BIOSIS, and PubMed were searched for clinical studies with iCR/iCR + HP (Remifemin/Remifemin plus) and iCR + HP’s specific HP component. All clinical data regarding safety at the breast, efficacy and safety in breast cancer patients, and interactions published from 1997 (when the EU Guideline on Good Clinical Practice E6 came into effect) until April 2018 were included. The search was complemented by a manual search in the authors’ libraries.

Inclusion criteria were the medical use of iCR/iCR + HP or iCR + HP’s specific HP component, their efficacy and safety in breast cancer patients, influences on the breast, and safety with regard to interactions. Patient-relevant endpoints were the reduction of climatric complaints (e.g. frequency and severity of hot flushes, climatic symptom scales), recurrence-free survival, findings with possible impact on breast cancer, and frequency and severity of adverse events (AEs) including interactions.

Additionally, a narrative overview is given on experimental data in breast tissue, breast cancer cells (BCCs), and animal models. Potential clinical interactions of HP and iCR/iCR + HP, which are officially recorded in monographs or standard summaries of product characteristics, are viewed in relation to metabolism pathways of endocrine therapies.

Results

Clinical studies with iCR/iCR + HP in breast cancer patients

The searches revealed six studies in which breast cancer patients were treated with iCR or iCR + HP20–24,26. In a double-blind RCT, 85 breast cancer patients, who were mainly medicated with tamoxifen (dosage not reported), received iCR (n = 42 with n = 29 tamoxifen users; 1 tablet twice daily [b.i.d.]) or placebo (n = 43 with n = 30 tamoxifen users) for 2 months. A comparable decrease in number (−27%) and intensity of hot flushes was reported without significant group differences. However, iCR-treated patients experienced significantly less sweating compared to the placebo group (p = 0.04). Gonadotropin levels did not change significantly under treatment. AEs were mainly minor and related to tamoxifen. A few serious AEs occurred; they were not related to iCR.

Fifty breast cancer patients receiving 10–40 mg tamoxifen after primary therapy (100% surgery, 87% radiation, 50% chemotherapy) were treated with iCR for 6 months21,25. Treatment started with 1 tablet b.i.d. and could be adjusted according to patients’ requirements after 4 weeks, resulting in dosages of 1–4 tablets iCR/day or a switch to iCR + HP. The total Menopause Rating Scale II decreased significantly from severe (17.6) to moderate (13.6), with the best improvements in hot flushes, sweating, sleep problems, and anxiety. The responder rate, defined as satisfying/good/very good efficacy by patients’ self-assessment, was 70.2% at last observation. Sixty percent of the patients wanted to continue iCR medication after study termination. Twenty-two patients reported AEs, which were not linked to iCR/iCR + HP. Ninety percent judged the tolerability as good or very good, none as bad. No recurrences occurred during the observation period.

Patients with (n = 13, n = 6 using tamoxifen or raloxifene) and without (n = 8) breast cancer, who suffered severely from an average of 8.3 hot flushes/day, were treated with iCR (1 tablet b.i.d.) in a pilot study22. They experienced significant reductions in daily hot flush frequency (−50%), weekly hot flush score (−56%), hot flush severity (−22%), and sweating (−80%) after 4 weeks. Fifty-two percent of the patients reported a 50% or greater decrease in hot flush frequency. Large improvements were also noted for sleeping problems and fatigue.

Another open, uncontrolled study in 23 Asian patients with gynecological cancers, including two breast cancer cases, reported significant reduction of the Kupperman Menopause Index, hot flushes, sweating, and depressive moods after 3 months of iCR treatment (1 tablet b.i.d.). Estradiol and gonadotropin values remained uninfluenced.

A study in 15 Asian breast cancer patients after surgery and chemotherapy (12 receiving endocrine therapy) found significant improvements in the Kupperman Menopause Index, hot flushes, sweating, Traditional Chinese Medicine syndrome scores, and quality of life after 4 weeks of iCR use (1 tablet b.i.d.). All patients reported good or very good tolerability.

A pharmacoepidemiological cohort study based on the IMS Disease Analyser Medipus database included 18,861 breast cancer survivors, of whom 1102 were treated with iCR or iCR + HP24. The mean overall observation time was 3.6 years (6 months to >9 years). Compared to non-iCR users, patients taking iCR or iCR + HP had a lower recurrence rate. This was also the case for patients receiving tamoxifen, regardless of whether they had used iCR monotherapy or iCR + HP24,27. Patients treated with iCR/iCR + HP had an average 4.5-year increase of recurrence-free survival.

Clinical data relevant for breast safety

Mammographic breast density (visually assessed) and proliferation of breast epithelial cells (fine-needle aspiration biopsies) did not increase after 6 months of treatment with iCR (n = 74)28. Digitized assessment of the mammograms confirmed these findings29. Breast ultrasound did not reveal changes after 6 months of iCR treatment (n = 54)11,30. Three to 6-month treatment with iCR (1–3 tablets b.i.d.) did not significantly change estradiol, follicle stimulating hormone, luteinizing hormone, prolactin, sex hormone-binding globulin, or testosterone levels (n = 523)10,11,13,20,23,30–36. Ultrasound did not reveal any increase in endometrial thickness after 3 to 6-month iCR use (n = 451)10,11,13,14,28,30,32,34,35. Two case–control studies found that taking iCR/iCR + HP was associated with a reduced risk for breast cancer37,38. The larger study (6646 controls) with 320 iCR/iCR + HP users; 3257 breast cancer cases
with 112 iCR/iCR + HP users) demonstrated that lifestyle factors, tumor histology, and receptor status did not influence the results. Treatment duration was positively associated with risk reduction.

**Experimental data in breast cancer cells, animal models of breast cancer, and human breast tissue**

No increase of proliferation in estrogen receptor-positive MCF-7 BCC occurred under iCR. Instead, iCR dose-dependently inhibited MCF-7 BCC proliferation and enhanced the antineoplastic effects of tamoxifen. iCR suppressed tumor cell invasion in estrogen receptor-negative and highly invasive MDA-MB 231 BCC. Antiproliferative effects of iCR on MCF-7 and MDA-MB 231 BCC were caused by activation of caspases and induction of apoptosis.

The well-established dimethylbenz(a)-anthracene-induced estrogen receptor-positive mammary tumor model in Sprague Dawley rats was used in most in-vivo studies. In contrast to mestranol-treated rats, no stimulation of tumor growth was found in animals treated with iCR in doses up to 100-fold the human therapeutic dose. No significant differences to vehicle control were observed, but a trend toward reduced tumor growth was seen. Prolactin, follicle stimulating hormone, luteinizing hormone, organ weight, and endometrial proliferation remained unaffected by iCR. Compared to vehicle control, iCR treatment, starting from prepubertal age, resulted in marked retardation of tumor growth and a significantly prolonged life span. Combination of iCR with tamoxifen increased the incidence of tumor-free rats from 20 to 50% with a pronounced retardation of neoplastic growth. Necropsy found the individual tumor burden to be reduced by 50%. Concomitant iCR application neither affected serum estradiol nor the antineoplastic effects of the aromatase inhibitor (AI) formestane. One study used a transgenic MMTV-neu mouse model, in which breast cancer is promoted by mouse mammary tumor virus (MMTV). Mice bear the rat oncogene neu, the rodent homolog of human epidermal growth factor receptor 2 (HER2); thus, this artificial model generates spontaneous, highly progressive breast cancer with rapidly developing lung metastases. No differences were detected in the incidence and onset of breast cancer between iCR and control. Incidence of lung metastases was increased; however, neu transgene was not upregulated in the treatment group. Estrus cycling and hormone levels were not modified. No uterotrophic activity occurred.

In benign breast tissue from premenopausal and postmenopausal women, iCR dose-dependently inhibited steroid sulfatase activity and reduced local estrone and estradiol production.

**Clinical data on interactions of iCR, iCR + HP, or the HP component**

Since 1997, 27 clinical studies, including 12,318 patients treated with iCR/iCR + HP, have monitored AEs and allowed co-medication. Apart from case-control studies, two further studies, including 128 patients taking iCR, were excluded due to missing AE reporting in the corresponding publications. None of the clinical studies with iCR/iCR + HP revealed any AEs in terms of adverse interactions.

Two double-blind RCTs versus placebo were conducted with 28 healthy volunteers to examine the pharmacokinetic interaction potential of the HP extract used to produce iCR + HP. The daily HP dose equaled the HP intake of the maximum recommended iCR + HP dosage (2 tablets b.i.d.) and corresponded to 1.0 mg total hypericin and 3.5 mg hyperforin. The substrates used in study A were single doses of alprazolam (1 mg, for cytochrome P450 3A4) and caffeine (100 mg, for CYP1A2) on days 1 and 11. In study B, single doses of tolbutamide (500 mg, for CYP2C9) on days 1 and 11 and multiple doses of digoxin (0.75 mg on days 2 and 1, 0.25 mg on days 2–11, for p-glycoprotein) were used. No statistically significant differences between HP and placebo were found for the area under the curve (AUC0–24) for alprazolam, caffeine (AUC0–12), paraxanthine, tolbutamide, 4-hydroxytolbutamide, and digoxin. HP-induced AUC change was less than 12% of the initial median AUC and, thus, clinically irrelevant.

**Discussion**

**Efficacy of iCR/iCR + HP in breast cancer**

In natural climacteric complaints, efficacy data gained with iCR/iCR + HP are consistently positive (Oxford Level 1 evidence), yet the efficacy data we analyzed for breast cancer patients with tamoxifen-induced symptoms are mixed. In practice-oriented, uncontrolled studies, iCR ameliorated neurovegetative and psychic symptoms caused by antihormonal treatment. In the pilot study, reduction of sweating (~80%) was also greater than for hot flushes (~50%). A relevant shortcoming of these two studies is their short duration, which does not meet the EMA’s and Food and Drug Administration’s requirements of at least 12 weeks of treatment. CR exhibits the first effects after 2–4 weeks but efficacy increases with longer treatment duration and should not be definitively assessed before 12 weeks. In the longer observational study (24 weeks), the reduction of tamoxifen-induced neurovegetative and psychic complaints by iCR was significant and clinically relevant after 3 and 6 months. An increase in iCR dose or a switch to iCR + HP was allowed, which may have contributed to better treatment effects. In natural climacteric complaints, iCR + HP, with a higher iCR dose, demonstrated superior efficacy compared to standard-dose iCR. Practical experience suggests that patients with tamoxifen-induced complaints benefit from higher CR doses than the standard dose used for natural menopausal symptoms. A responder rate of 70% shows that most, although not all, patients with tamoxifen-induced complaints benefit from iCR. This is consistent with hot flush reductions observed in an open, controlled, 1-year study. Over several years, comprehensive everyday experience has been gained by two of...
the authors at the Beijing Obstetrics and Gynecology Hospital, Capital Medical University, its Menopause Clinic, and its Centre for Ovarian Tissue Retransplantation. These institutions, the first official ones of their kind in China, are highly frequented by breast cancer patients needing treatment for severe climacteric complaints. The Gynecological Endocrinology Department treats approximately 100,000 patients every year (96,908 in 2016); the approximately 1% of patients diagnosed with hormone-dependent breast cancer receive a standard dose of iCR for 6–48 months. Recently, within this department the first official International Fertility Protections Center using Ovarian Tissue Cryopreservation in China has been established, a method increasingly used for breast cancer patients. So the need to treat climacteric symptoms of these patients is strongly increasing, and because hormone therapy mostly is contraindicated, often black cohosh (iCR) is now used. Efficacy and tolerability of this treatment is judged in this department as good. For iCR, good efficacy on iatrogenic climacteric symptoms has also been demonstrated after endometrial cancer surgery, in hysterectomized premenopausal women, or in endometriosis patients with goserelin-induced complaints.30,35,66.

Safety of iCR/iCR + HP after breast cancer – experimental data

In vitro, iCR inhibited MCF-7 BCC proliferation and enhanced the anti-estrogenic effects of tamoxifen39–45. In vivo, iCR did not stimulate but, rather, retarded tumor growth and increased the life span47,48. Concomitant iCR treatment enhanced tamoxifen efficacy and had no influence on the effects of the AI formestane49,50. In the MMTV-neu mouse model, iCR did not promote tumor growth. However, an increase in lung metastases was seen that could not be explained by neu upregulation and has never been reproduced51. Relevance of this artificial model (with its viral promoter and development of lung metastases prior to primary tumors) and treatment conditions (almost lifelong therapy with dosages far above the human therapeutic dose) for human HER2-positive breast cancer is doubtful. CR actually inhibited the growth of HER2-overexpressing human MDA-MB435 cells, and the CR ingredient actein induced apoptosis in MCF-7 cells transfected for HER267.

The anti-invasive effects of iCR in MDA-MB 231 BCC demonstrate that iCR inhibits at least the first step of the metastasis cascade.46 Long-term iCR treatment led to a higher rate of carcinoma-free animals and did not affect metastasis in the DA/Han rat endometrial carcinomas.66. In the RUCA-I rat endometrial carcinoma model, a slight decrease in lung metastases was seen under iCR treatment69. Embryonic stem cell-expressed RAS was identified as a potent oncogenic driver in the HER2-positive MMTV model, acting via hyperactivation of the phosphatidylinositol-3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, which stimulates tumor cell proliferation and metastasis and induces therapy resistance70,71. Recently, actein was identified as an effective inhibitor of the PI3K/AKT/mTOR pathway, showed anti-angiogenic effects in vitro, and decreased breast tumor size and metastasis in vivo.72,73. CR activated AMP-activated protein kinase, which is known to inhibit mTOR74. Tamoxifen upregulates HER2 expression in the dimethylbenz(a)-anthracene tumor model, leading to tamoxifen resistance. The increase of tumor-free animals and the retardation of tumor growth, observed when iCR was combined with tamoxifen, may indicate a potential of iCR to counter therapy resistances49,75.

Regarding the effect of iCR in benign breast tissue, the inhibition of steroid sulfatase may suggest a reduced primary risk of breast cancer using iCR: the decrease of local estrone and estradiol production lowers the rapid proliferation potential that could lead to replication mistakes generating breast cancer cells. In addition, direct anti-estrogenic effects of iCR were detected in reporter gene assays39.

Safety of iCR/iCR + HP after breast cancer – clinical data

Breast cancer patients tolerated iCR treatment well; this was also reported for naturally climacteric women in whom AE frequency and intensity were comparable to placebo.6,7,20–23,26. It was previously believed that CR, due to its putative ingredient formononietin, may exert estrogenic effects. However, iCR does not contain formononetin and did not exhibit ER activity76,77. Consistent clinical data show that iCR does not influence hormone levels, breast density, breast cell proliferation, or endometrial thickness.10,11,13,14,20,23,28–31,33–35.

The association of iCR/iCR + HP intake with a reduced risk to develop breast cancer was independent from tumor receptor status, with 20.3% HER2-positive patients.37 Breast cancer survivors treated with iCR/iCR + HP benefited from an additional 4.5 years of recurrence-free survival compared to iCR non-users.24. A re-evaluation of the study data also demonstrated a decreased rate of distant (e.g. lung) metastases in iCR/iCR + HP users compared to non-users.78. The clinical data are promising and justify further prospective, controlled trials focusing on the potential protective effects of iCR on breast cancer initiation and progression.

HP interactions and relevance for breast cancer patients receiving endocrine therapy

In contrast to CR, for which no interactions are known, HP is noted for various interactions, which are listed in the HP monograph of the Herbal Medicinal Products Committee of the EMA.79 However, interactions with tamoxifen or AIs do not belong to these known HP interactions and no such clinical data have been described79,80.

HP interactions, which arise mainly via induction of CYP3A4 and p-glycoprotein, are especially known for high-dose preparations and extracts rich in hyperforin31,82. Hyperforin, an agonist at the pregnane X receptor, upregulates genes for the metabolism of xenobiotics83. Therefore, HP’s compatibility with concomitant medication depends on the dosage and hyperforin content. The hyperforin content of German HP herbal medicinal products varies greatly84. While high-dose hyperforin extracts induced CYP3A, no clinically relevant influence on CYP3A or p-glycoprotein was found for HP preparations low in hyperforin85–87. This is in
line with the lack of clinically relevant interactions of the HP extract used to produce iCR + HP. Due to synergistic effects with CR, iCR + HP does not need a high HP dose; thus, the extract does not contain much hyperforin.

**Tamoxifen**
Concomitant medication with CYP2D6 inhibitors (e.g., paroxetine, fluoxetine) should be avoided in patients using tamoxifen since it leads to reductions of endoxifen levels. Tamoxifen is metabolized into its active metabolite endoxifen mainly via CYP2D6 and CYP3A4. Therefore, inhibition of CYP2D6 (and, as the case may be, inhibition of CYP3A4) reduces the generation of endoxifen and possibly the efficacy of tamoxifen. The pharmacokinetics of tamoxifen is complex, involving additional CYP isoenzymes and the inactivation of tamoxifen and its active metabolites via phase II reactions. Tamoxifen’s metabolism and the impact of endoxifen levels on tamoxifen’s efficacy are controversially discussed. A recently published prospective multicenter study showed that the objective response rate (using RECIST criteria 1.0), clinical benefit, progression-free survival, and tolerability were not associated with endoxifen levels.

HP does not influence CYP2D6 but induces CYP3A4. Theoretically, a CYP3A4 induction could – via increased metabolism of tamoxifen into its active metabolite endoxifen – even lead to an enhancement of tamoxifen efficacy. A reduction of tamoxifen plasma levels of unclear clinical relevance has been described during the application of strong CYP3A4 inducers like rifampicin. Such a reduction may suggest increased metabolism into the active metabolite endoxifen. Because rifampicin’s induction effect on CYP3A4 substrates is 25 times that of HP and rifampicin also induces tamoxifen glucuronidation, it is arguable whether HP would have rifampicin-like effects on tamoxifen plasma levels.

In contrast to CYP2D6 inhibitors, it is not deemed necessary to abstain from the application of CYP3A4 inducers during tamoxifen therapy. This seems appropriate for iCR + HP regarding the reduced recurrence risk in tamoxifen-treated patients, which was not only apparent in patients using iCR monotherapy but also in patients using iCR + HP. If the HP component in iCR + HP had attenuated tamoxifen’s efficacy, a decrease but not actual prolongation of recurrence-free survival could have been expected.

**Aromatase inhibitors**
Anastrozole metabolites (triazole, hydroxyanastrozole, hydroxyanastrozole glucuronide, and anastrozole glucuronide) result from N-dealkylation, hydroxylation, and glucuronidation processes. The main metabolite, triazole, is inactive. Enzymes involved in anastrozole metabolism have not been completely identified. In vitro, the formation of hydroxyanastrozole was mainly catalyzed by CYP3A4/5 and, to a lesser extent, by CYP2C8, CYP2D6, and
CYP2B6 (Figure 2). CYP3A4 inducers could possibly increase the production of one of the metabolites (hydroxynastrozole), but it should be taken into account that anastrozole itself inhibits CYP3A4. No influence of potent CYP inducers on anastrozole metabolism is known, and safety data analyses from clinical studies did not show significant interactions with commonly prescribed drugs.

Letrozole elimination resulting from metabolic clearance ($\text{Cl}_{\text{m}} = 2.1 \text{ l/h}$) is rather slow compared to liver perfusion (ca. 90 l/h). In vitro, CYP2A6 and CYP3A4 were active in transforming letrozole to its main, inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile), which is further glucuronidized (Figure 2). In vivo, only CYP2A6 genotypes showed significant associations with plasma letrozole concentrations, suggesting that CYP2A6 is the principal clearance mechanism. Therefore, significant interactions of HP with letrozole are not to be expected.

Exemestane is metabolized via oxidation into inactive 6-hydroxymethyl exemestane (MI), primarily by CYP3A4 and CYP2B6, and reduced by aldoketoreductases, CYP4A11, and CYP1A2 to 17-hydroxymethylexemestane (MII), primarily by CYP3A4 and CYP2B6 (Figure 2). The potent CYP3A4 inducer rifampicin led to an AUC reduction of exemestane. To date, the clinical relevance has not been clarified, and it cannot be excluded that CYP3A4 inducers like HP could reduce exemestane's efficacy. Exemestane plasma concentrations depend on various other factors (liver and kidney function, ethnicity, body mass index, previous chemotherapy, genetic CYP polymorphisms). The German summary of product characteristics does not deem dosage adjustments necessary, the US prescribing information recommends exemestane updosing for patients using strong CYP3A4 inducers like rifampicin or phenytoin. However, for HP no clinical interactions with exemestane are reported and for the HP in iCR + HP no clinically relevant interactions could be detected. Therefore, such updosing in patients on iCR + HP therapy may increase exemestane's side effects due to overdosing. When uncertain or in patients prone to lower exemestane levels (e.g. black ethnicity, high body mass index, prior chemotherapy), monitoring estradiol values may be helpful to determine the necessity of updosing exemestane.

**Conclusion and practical consequences**

Most breast cancer patients experience beneficial effects of iCR on tamoxifen-induced neurovegetative and psychic complaints. Still, RCTs with sufficient treatment duration should be conducted in breast cancer patients to confirm these results. Considering the consistently convincing effects of iCR for natural climacteric complaints, tamoxifen seems to affect treatment efficacy; this may be countered by applying higher iCR doses or iCR + HP, respectively. Clinical and experimental data have consistently demonstrated that iCR lacks estrogen-like effects at the breast or uterus. Therefore, the use of iCR in breast cancer patients can be regarded as safe. Epidemiological data and increasing knowledge on CR's mechanisms of action suggest protective effects of iCR in terms of prolonged recurrence-free survival, warranting future prospective trials. No interactions with endocrine therapy are known for iCR or have been reported for HP. The HP extract used in iCR + HP did not exhibit clinically relevant interactions. Therefore, iCR/iCR + HP can also be used in breast cancer survivors receiving endocrine therapy. The overall benefit-risk profile of iCR/iCR + HP for breast cancer patients is positive, and treatment adherence of patients suffering from side effects of antihormonal treatment could be increased by offering iCR/iCR + HP.

**Conflict of interest** A. O. Mueck, X. Ruan, and A.-M. Beer report no conflict of interest. B. Naser and S. Pickartz are employees of Schaper & Brümmern, the manufacturer of iCR/iCR + HP. The authors alone are responsible for the content and writing of this article.

**Source of funding** Nil.

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