Climacteric Complaints after Breast Cancer – Is HRT an Option?

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Key Words

Breast cancer · Climacteric complaints · Hormone replacement therapy (HRT)

Summary

Systemic estrogen depletion is the mechanism of action of most endocrine treatment strategies, and a common side effect of most chemotherapy regimens that are currently used to treat invasive breast cancer. The ensuing immediate and profound decline in estrogen levels is, however, often associated with considerable climacteric complaints. While oral estrogen add-back therapy is effective in alleviating menopausal symptoms, it is feared that it might also promote tumor cell growth. This concern is largely based on circumstantial evidence from large trials in healthy women, in which hormone replacement therapy (HRT) resulted in a slight, albeit significant, increase in incident breast cancer. In breast cancer survivors, however, evidence from studies remains controversial. Despite these caveats, the severity of symptoms and the lack of effective alternatives still cause many women to opt for HRT. Nevertheless, HRT cannot generally be recommended as first-line therapy for climacteric complaints in women with a history of breast cancer. It may, however, be a valid option for selected women with climacteric symptoms refractory to previous non-hormonal treatments. In these cases, an individualized risk-benefit analysis is imperative before treatment initiation, and a treatment duration of less than 5 years with intermittent withdrawal attempts should be aimed for.

Schlüsselwörter

Brustkrebs · Wechseljahresbeschwerden · Hormonersatztherapie (HET)

Zusammenfassung

Die systemische Östrogendepletion ist der Wirkmechanismus der meisten endokrinen Therapiestrategien, die heute in der Behandlung des invasiven Mammakarzinoms eingesetzt werden. Der daraufhin einsetzende rasche und nachhaltige Abfall der Östrogenkonzentration ist häufig mit beträchtlichen klimakterischen Beschwerden verbunden. Obwohl eine exogene Östrogenzufuhr Wechseljahresbeschwerden effektiv behandelt, wird vermutet, dass dies gleichzeitig das Wachstum von möglicherweise vorhandenen Tumorzellen stimuliert. Diese Befürchtung basiert größtenteils auf indirekter Evidenz aus großen klinischen Studien an gesunden Frauen, bei denen die Hormonersatztherapie (HET) zu einer leichten, jedoch signifikanten Risikoerhöhung für die Entwicklung von Brustkrebs führte. Bei Frauen, die bereits einmal an Brustkrebs erkrankt waren, ist die Datenlage weiterhin umstritten. Trotz dieser Bedenken entscheiden sich viele Frauen aufgrund des Ausmaßes der Beschwerden sowie eines Mangels an Alternativen für eine HET. Dennoch kann gerade bei einer Brustkrebsanamnese die HET nicht generell zur Erstlinientherapie von Wechseljahresbeschwerden empfohlen werden. Sie ist jedoch eine valide Option für ausgewählte Patientinnen, die auf vorangegangene nicht-hormonelle Therapien nicht angesprochen haben. In diesen Fällen ist eine individuelle Risiko-Nutzenabschätzung imperativ, und eine Therapiedauer von 5 Jahren mit intermittierenden Auslassversuchen sollte angestrebt werden.

Introduction

While systemic treatment for early breast cancer has become very effective in preventing recurrence and in improving survival, it is still burdened by severe, in some cases almost unacceptable, side effects. Chemotherapy and endocrine treatment strategies can both lead to estrogen deprivation which results in severe and prolonged menopausal complaints [1]. These include hot flashes, vasomotor symptoms, palpitations, vaginal dryness, joint pain, depression, and a variety of other symptoms that can have profound effects on the quality of life of breast cancer survivors [2]. Estrogen-containing hormone replacement therapy (HRT) is effective in alleviating menopausal symptoms, but low-dose estrogens have been shown to promote tumor cell growth in vitro and in animal experiments [3]. It is therefore feared that HRT might exert a proliferative stimulus on remaining tumor cells, and ultimately result in increased recurrence rates. In addition, the concern of an increase in breast cancer risk in healthy postmenopausal HRT users has conventionally led to a general contraindication for HRT in women with a history of breast cancer.

Unfortunately, despite being widely used, many alternative, non-hormonal treatments have not been shown to be superior to placebo [4]. In addition, little is usually known regarding side effect profile and potential drug interactions with adjuvant endocrine therapy. While selective serotonin reuptake inhibitors (SSRIs) have shown some effects on menopausal symptoms, some may also inhibit the hepatic cytochrome P450 oxidase Cyp2D6, and are thus believed to have a profound negative effect on the metabolism of tamoxifen to its active metabolite endoxifen [5, 6]. It can thus not be excluded that, while patients experience symptom relief by taking SSRIs, they might at the same time jeopardize the therapeutic benefit of their antineoplastic endocrine therapy. The lack of safe and effective alternatives for the treatment of climacteric complaints in breast cancer survivors has led to a dissension between patients who experience severe impairment of their quality of life and who are thus more willing to accept potentially deleterious HRT treatment, and physicians who, because of potential medical and medico-legal implications, are considerably more restrictive [7]. In this publication, we will review epidemiological and trial-based evidence regarding breast safety in women who use HRT for the treatment of menopausal symptoms.

HRT and Breast Cancer Risk in Healthy Women

The Women's Health Initiative (WHI) Trial

Despite a wealth of observational evidence that had accumulated over the years, the risk/benefit ratio for hormone use in healthy postmenopausal women remained elusive until 2002, when the results of the Women's Health Initiative (WHI) led

to a premature stop and to subsequent publication of the WHI trial [8]. The objective of WHI had been to assess the major health risks and benefits of the most commonly used combined hormone preparation in the United States. In a randomized, controlled primary prevention trial in which 16,608 postmenopausal women with an intact uterus received either equine estrogens plus medroxyprogesterone acetate (MPA) or placebo. While the primary outcome parameters were coronary heart disease (CHD) and invasive breast cancer, a global index was used to balance overall risks and benefits. Besides the 2 primary outcome parameters, the global index also included the development of endometrial cancer, colorectal cancer, hip fracture, stroke, pulmonary embolism (PE), and death due to other causes. After a mean of 5.2 years, the trial was prematurely stopped because of a significant increase in invasive breast cancer and because of the emergence of an unfavorable risk/benefit ratio in the global index. While patients in the treatment arm had a 1.26-fold higher risk of developing breast cancer compared to the placebo arm, the risk of developing endometrial cancer was unchanged, and colon cancer was even more unlikely during hormone therapy with an estimated hazard ratio (HR) of 0.63. Estimated HRs for CHD, stroke, and PE were 1.29, 1.41, and 2.13, respectively. Overall, in comparison to placebo, hormone therapy in the WHI population resulted in 7 more CHDs, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while it saved 6 women from colorectal cancers and 5 women from hip fractures per 10,000 person years. The authors thus concluded that the overall health risks associated with a 5-year use of combined estrogen plus progestin preparations exceeds the benefits in healthy postmenopausal women, and this treatment should not be offered for primary prevention. While this statement is certainly true for the combination of conjugated equine estrogens in combination with synthetic MPA, the question still remains whether the unfavorable hazard ratio seen is a class effect rather than the response to stimulation by a particularly unphysiological combination.

A more recently published secondary analysis of the WHI study population, however, suggests that the effect of hormones on CHD may be modified by years since menopause, and by the presence of vasomotor symptoms. While CHD tended to be non-significantly reduced by hormone therapy in younger women and in women with less than 10 years since menopause, women aged ≥ 70 years and women who were 20 or more years into the menopause had the highest risk of developing CHD (HR 1.28; 95% confidence interval (CI) 1.03–1.58). By contrast, the risk of stroke remained elevated (HR 1.32; 95% CI 1.12–1.56), independent of age or time elapsed since menopause. The absence of excess absolute risk of CHD, and the observed trend towards a significantly reduced total mortality in women aged 50–59, offers some reassurance that HRT remains a reasonable strategy for the short-term treatment of menopausal symptoms. It does, however,

not imply that the long-term use of HRT is safe, and women who had experienced menopause more than 20 years ago have a particularly high risk of suffering from CHD [9].

The Million Women Study – Evidence from a Large Cohort Study

The Million Women Study was set up to investigate the effects of HRT on breast cancer incidence. Between 1996 and 2001, more than 1 million UK women aged 50–64 years were recruited into the study, and provided information about lifestyle and HRT use [10]. Approximately half of the women reported HRT use at one point during their life. After an average of 2.6 years of follow-up, 9,364 new invasive breast cancers were reported. Current HRT users were found to have a significantly elevated risk of developing breast cancer (adjusted relative risk (RR) 1.66; 95% CI 1.58–1.75), and to die from it (RR 1.22; 95% CI 1.00–1.48). Women who had used HRT in the past, were, however, not at an increased cancer risk (RR 1.01; CI 0.94–1.09). Within the group of current HRT users, those who were using estrogens had a somewhat smaller risk (RR 1.30; 95% CI 1.21–1.40) than those who used estrogen-progestagen combination formulations, and who thus experienced a doubling in the relative risk for incident breast cancer during the observational period (RR 2.00; 95% CI 1.88–2.12). The study did not suggest that either dose or mode of application (oral vs. transdermal vs. implant) had an effect on the relative risk of developing breast cancer. Length of exposure, however, was found to significantly increase the breast cancer risk with 5 additional tumors per 1,000 users of estrogen-only formulations, and 19 additional cancers per 1,000 users of estrogen-progestagen combinations in current users who had taken HRT for more than 10 years. Interestingly, lobular and tubular histological sub-forms were over-represented in these patients. The authors estimated that HRT use in women aged 50–64 was responsible for altogether 20,000 additional incident breast cancers during the investigated time period. Since these numbers are based on results obtained from an uncontrolled cohort group in which women self-reported HRT use during a relatively short study period, the results are subject to considerable bias, and should therefore be regarded with caution. The possibilities of misclassification, recollection bias, and the sequential use of multiple HRT regimens have been widely criticized. In addition, certain HRTs, such as tibolone, were preferentially prescribed to women with an elevated risk of developing breast cancer because of its presumed ‘breast safety’, thus potentially over-estimating its risk profile. Despite these caveats, the Million Women Study nevertheless provides strong evidence for a significant role of HRT in breast cancer development.

Recently, a large French cohort study (E3N) conducted in 98,995 women aged 40–65 who had taken HRT for a mean duration of 7 years, found that the chemical structure of the progestagen component of combination HRT has a major im-

pact on the relative risk of developing breast cancer. While women who received estrogen/progesterone combinations and estrogen/dydrogesterone combinations were not found to be at increased risk of developing breast cancer, those who used estrogen/MPA combinations were (RR 1.69; 95% CI 1.5–1.91). Interestingly, estrogen monotherapy was also associated with a slight increase in breast cancer incidence (RR 1.29; 95% CI 1.02–1.65), thus somewhat differing from the WHI estrogen alone arm. It should, however, be noted that women in the WHI trial tended to be older, and to have a higher body mass index [11].

HRT Use and Breast Cancer Incidence – Epidemiological Trends

Epidemiological data from the US has recently provided further evidence for a tumor-promoting role of HRT: By analyzing data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) registries, Ravdin et al. [12] found that the age-adjusted incidence rates of breast cancer in women fell considerably in 2003 and 2004 when compared to 2002. In a comparison of incidence rates of 2001 and 2004, the annual age-adjusted incidence dropped by 8.4% (95% CI 6.8–10.4). Interestingly, the decrease was evident only in women aged 50–69, and was more profound in estrogen receptor (ER)-positive tumors (14.7%; 95% CI 11.6–17.4) than in ER-negative tumors (1.7%; 95% CI -4.6–8.0). Reproductive factors, diet, medication intake pattern, and environmental exposures had not changed appreciably between 2001 and 2004, and the decrease in the rate of screening mammography by 3.2% that was apparent in 2003 when compared to 2000 is too small to have an effect. Furthermore, since breast cancers that are detected by mammography are more likely to be ER-positive, a drop in screening cannot possibly explain the relative decrease in ER-positive tumors that was observed [13]. The decrease in breast cancer incidence was, however, temporally related to the first report of WHI, and followed a time course that was similar to the subsequent decline in HRT use among postmenopausal women in the US. Discontinuation of HRT would be expected to result predominantly in a decline in ER-positive tumors, and the results from the Breast Cancer Prevention Trial indicated that estrogen deprivation results in a reduction of breast cancer incidence rates within months, thus suggesting a major role for HRT.

Using a state-wide cancer registry and data obtained from the California Health Interview Survey (CHIS), Robbins et al. [14] looked at estrogen-progestin hormone replacement therapy (EPHT) use and breast cancer incidence in almost 3 million female Californian residents aged 45–74. They examined trends in the age-adjusted incidence of invasive breast cancer, and compared these with trends in the use of EPHT, after grouping all California counties into 3 groups based on EPHT use in 2001, the year before WHI was published. The publica-

tion of WHI and the ensuing widespread media coverage resulted in a profound decrease of EPHT use in the subsequent 3 years. This decrease was strongest in the group of counties with high EPHT use, and was weakest in the group of counties with comparatively low EPHT use in 2001. Remarkably, during the same period, breast cancer incidence rates paralleled EPHT use in all 3 groups: In counties with the smallest EPHT reductions, breast cancer incidence declined by 8.8% ($p = 0.006$), in counties with intermediate EPHT reductions by 13.9% ($p < 0.001$), and in counties with the largest EPHT reductions by 22.6% ($p < 0.001$). CHIS data did not suggest changes in mammography pattern in Californian women during this time. Linear regression analysis results suggested that each 1% decrease in EPHT use prevalence was associated with a breast cancer incidence decrease of 3.1 cases per 100,000 women ($p < 0.001$).

Taken together, evidence from both prospectively designed trials and from large epidemiological studies now consistently show that combination hormone therapy increases the risk of developing breast cancer in healthy postmenopausal women. While estrogen therapy alone does not appear to increase breast cancer risk, its use in healthy, non-hysterectomized women is associated with an increase in endometrial cancers. Since hormone therapy in healthy women is now regarded as potentially unsafe, its use in women with a history of breast cancer is even more controversial because it is feared that it might potentially stimulate the growth of remaining breast cancer cells and promote the development of a second breast malignancy. It is therefore not surprising that only a few studies, mostly small and observational in design, have been conducted to study the safety of hormone therapy in women with a history of breast cancer.

Hormone Therapy in Women with a History of Breast Cancer

In a meta-analysis of 11 clinical trials investigating the safety and efficacy of HRT use in breast cancer survivors that was conducted in 2001, only 4 studies could be identified that had been designed with a control group. Together, these 4 trials monitored 214 HRT users over a mean follow-up of 30 months [15]. While in the HRT group 4.2 recurrences were observed per year, the 623 control patients experienced a similar relapse rate (5.4% per year; RR = 0.64, 95% CI 0.36–1.15). When the analysis was extended to all 11 studies, now comprising 669 HRT users, the combined relative risk compared to an estimated control group remained essentially unchanged (RR 0.82; 95% CI 0.58–1.15). The authors therefore suggested that HRT had no significant effect on breast cancer recurrence, although they cautioned that these findings were based on observational data and thus subject to a variety of biases.

With most individual observational studies on HRT use in breast cancer survivors being reassuring, 2 prospectively ran-

domized clinical trials were initiated in 1997 which were designed to investigate the effects of menopausal hormone therapy in women after they had been diagnosed with early-stage breast cancer: The relatively small HABITS (Hormonal replacement therapy After Breast cancer—Is it Safe?) trial with 434 randomized women, was stopped prematurely in December after a median follow-up of 2.1 years because the risk of recurrence was found to be significantly higher in women receiving HRT than in women who did not receive therapy (relative HR 3.3; 95% CI 1.5–7.4) [16]. The increased risk of developing a new breast cancer event in survivors who took HRT even persisted after an extended follow-up period [17].

The Stockholm trial, another prospectively designed open label trial that evaluated HRT in women with a history of breast cancer, however, found no evidence of an increased risk of recurrence in women treated with HRT compared to women who did not receive HRT (relative HR 0.82; 95% CI 0.35–1.9). Unfortunately, the trial, which had recruited 378 women and was terminated after a median follow-up of 4.1 years, was hampered by slow recruitment and poor compliance following population-wide awareness of the WHI results. The reason for the somewhat contradictory results are not entirely clear, but differing patient characteristics, a higher prevalence of tamoxifen co-medication, and the deliberate attempt to minimize the use of progestin in combination HRTs in the Stockholm trial population have been proposed as possible explanations [18].

Tibolone

Tibolone is a synthetic steroid with a distinct clinical profile that distinguishes it from both conventional HRT and selective ER modulators (SERMs). Because of its unique tissue-selective metabolism and its tissue-specific action, it has been classified as a selective tissue estrogenic activity regulator (STEAR) [19]. The efficacy of tibolone in reducing climacteric symptoms in healthy women has been confirmed in a number of trials [20, 21]. In addition, available clinical data suggest that it results in less breast tenderness than conventional HRT, and that it does not increase mammographic breast density [22].

A few small studies have even explored the feasibility of tibolone therapy in breast cancer patients: in a prospectively randomized, double-blind, placebo-controlled study in 70 postmenopausal women receiving tamoxifen for early breast cancer, tibolone was significantly more effective than placebo in reducing hot flashes. No breast cancer recurrences were reported during the 12 month therapy, however, the trial duration was too short to draw any conclusions regarding breast safety [23]. Results from the ADAGIO trial suggest that an add-back therapy using tibolone is also helpful in alleviating menopausal symptoms in premenopausal breast cancer patients who receive a combined gonadotropin-releasing hormone (GnRH) and aromatase inhibitor regimen [24]. More recently,

a 2-week application of tibolone in women with ER-positive early breast cancer in the preoperative setting has not been shown to be associated with a significant effect on tumor cell proliferation when compared to placebo [25]. These data, in combination with the favorable therapeutic profile of tibolone have resulted in its preferential prescription to women with a history of breast cancer who continue to complain about severe vasomotor symptoms after non-hormonal therapies have failed.

Although the results from small randomized pilot trials and from observational studies are promising, they are insufficient to conclude that tibolone is safe in breast cancer patients. In addition, results from the Million Women Study have recently indicated a somewhat worrying increase in the relative risk of developing breast cancer (RR 1.45; 95% CI 1.25–1.68) in women who at some point in their life had used tibolone. It should, however, be noted that the number of tibolone users in the cohort study was comparably small, and that until the publication of the report, tibolone had preferentially been prescribed to women with increased breast cancer risk, thus suggesting that the data might be somewhat biased [26].

The LIBERATE (Livial Intervention following Breast cancer: Efficacy, Recurrence And Tolerability Endpoints), a prospective, randomized, double-blind, multicenter trial has been designed to investigate safety and efficacy of 2.5 mg/day oral tibolone in women with vasomotor symptoms and a history of invasive breast cancer in the previous 5 years. The primary research objective was breast cancer recurrence, secondary objectives are effects on vasomotor symptoms as well as overall survival, bone mineral density, and health-related quality of life [27]. After successful recruitment starting in 2003, LIBERATE was halted in late 2007 because the primary endpoint, non-inferiority compared to placebo regarding the risk of breast cancer relapse, could not be reached [Kenemans P, personal communication].

Conclusions and Recommendations

The treatment of climacteric complaints poses a veritable dilemma for the treating physician: On the one hand, women

who experience bothersome, sometimes barely supportable episodes of profuse sweating that limit them in their professional, social, and sexual life, demand treatment modalities that have proven to be effective. On the other hand, there is now little doubt that estrogen-progestagen combinations increase the chances of developing incident, and in breast cancer survivors also recurrent breast cancer. It is exceedingly difficult to postulate guidelines for breast cancer survivors in the absence of convincing data, yet it is unlikely that following the premature halt of the LIBERATE trial, new evidence will come from prospective clinical trials anytime soon. Many physicians have nevertheless found the following suggestions helpful:

HRT offered to hysterectomized women should not contain a progestagenic component. From what we now know through circumstantial evidence from healthy women, estrogen monotherapy is only associated with a small increase in breast cancer risk, and has little to no effect on CHD [28]. In women with an intact uterus, it appears prudent to initiate HRT at the lowest possible effective dose. Approximately 1 month of HRT treatment is currently considered sufficient to determine the effectiveness in alleviating vasomotor symptoms. If ineffective, the dosage should be increased until the women experience symptom improvement. While the optimal duration of HRT remains unclear, both WHI and the HERS trial have identified a relative increase in breast cancer risk after only 2 years [29]. Since vasomotor symptoms usually resolve within an average of 4 years, it appears prudent to limit HRT use to a maximum of 5 years. Intermittent, gradual HRT withdrawal should be attempted to identify those women in whom symptoms have ceased, and who do therefore not require further treatment. Finally, the benefits and risks of HRT should be discussed in detail with each patient, and an written informed consent should be obtained before initiating therapy in order to ensure that women are fully aware of the potential health implications of their therapy. Further advice on symptomatic treatment of postmenopausal symptoms may also be drawn from the current AGO recommendations (www.ago-online.de).

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