



Review article

Treatment of climacteric symptoms in survivors of gynaecological cancer



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ABSTRACT

Different treatments (surgery, radiotherapy, chemotherapy) for gynaecological cancers may cause ovarian failure or increase menopausal symptoms. There is a widespread reluctance among physicians to prescribe hormone replacement therapy (HRT) to the survivors of gynaecological cancer. This review analyses the use of HRT and of alternative therapies in such women. Squamous cervical cancer is not estrogen dependent and thus HRT is not contraindicated. While a cautious approach to hormone-dependent cancer is warranted, for women treated for non-hormone-related tumours alternative treatments for menopausal symptoms should be given due consideration, as any reluctance to prescribe HRT for them has neither a biological nor a clinical basis. In studies of HRT for survivors of endometrial and ovarian cancer, for instance, no evidence of increased risk was found, although no definitive conclusions can yet be formulated. The positive effect of HRT on quality of life seems to outweigh the unfounded suspicion of an increased risk of recurrence of non-hormone-related tumours. Effective non-hormonal alternatives for vasomotor symptoms are selective serotonin reuptake inhibitors and selective serotonin–norepinephrine reuptake inhibitors.

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1. Introduction

Due to advances in treatment, many women with gynaecological cancers survive long after their primary surgery, and thus the

long-term consequences of estrogen deprivation may affect their quality of life (QoL).

Hot flushes (HFs) are the most frequently reported menopausal symptoms, followed by insomnia, vaginal dryness and dyspareunia. Systemic hormone replacement therapy (HRT) is the most effective strategy in reducing menopausal symptoms in healthy women [1]. However, many physicians are reluctant to prescribe HRT to survivors of gynaecological cancers, regardless of exact tumor type and disease stage, because of the lack of international guidelines and the fear of medical litigation if a woman does go on to suffer a recurrence while taking HRT [2].

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This article reviews clinical studies on the use HRT as well as alternative therapies for menopausal symptoms in gynaecological cancer survivors.

2. Discussion

2.1. Endometrial cancer

Endometrial cancer (EC) is an estrogen-dependent disease with a favourable prognosis. Thus, relieving menopausal symptoms is important for maintaining a good QoL.

In a 13-year follow-up analysis of data from the Women's Health Initiative (WHI) [3], a reduced risk of EC in healthy women was observed with combined estrogen-progestogen HRT (HR=0.67, 95% CI 0.49–0.91). However, there was concern regarding HRT for women previously treated for EC because of the fear that, even after uterus removal, estrogens may stimulate the growth of occult foci of tumour cells.

The results of several small observational studies are reassuring. In the study by Creasman, 47 patients with stage I EC used conjugated estrogen by oral or vaginal routes for a median of 26 months. A lower recurrence rate (2.1% versus 14.9% of the placebo group) and significant longer disease-free survival (DFS) and overall survival (OS) were seen in the estrogen-treated group [4].

Lee [5] compared 44 stage I EC survivors using oral estrogens with or without combined progestogen with 99 controls. No recurrence was observed in the HRT group, while 8% of patients in the control group relapsed. However, selection bias was present since HRT was prescribed only to low-risk patients (stage IA, IB grade 1 or 2) while 37% of controls had high-risk disease (stage IC grade 3).

In the study by Chapman [6], 62 patients with stage I or stage II EC received HRT at a median time after surgery of 8 months and 61 similar patients did not receive HRT. No significant differences in the recurrence rate or in OS were observed between the two groups.

Suriano et al. [7] evaluated 75 women treated for stage I–III EC who received HRT and 75 matched controls. In the HRT group a lower recurrence rate (1%) was observed (14% in the control group); moreover, HRT users had a significantly longer DFS.

Ahyan et al. [8] compared 50 patients receiving combined HRT 4–8 weeks after surgery and 52 matched controls, all treated for stage I or stage II EC; no recurrence was observed in the HRT group, whereas, one control experience recurrence.

The only prospective randomized controlled trial (RCT) was from the Gynecologic Oncology Group (GOG) [9]. It involved 1236 women treated for EC randomized to estrogens alone or to placebo, but it was closed prematurely after publication of the WHI study [10]. The majority of the enrolled patients had well differentiated endometrioid EC; 91% had less than 50% myometrial invasion. No significant difference in recurrence rate was observed, being very low in both groups (2.1% in the 618HRT users versus 1.9% in the placebo group).

All these studies were included in a recent meta-analysis [11] that found no significant increased risk of recurrence in the 896 EC survivors employing HRT compared with the 1079 controls.

As regards the type of HRT, there was a protective effect of combined HRT (OR: 0.23; 95% CI: 0.08–0.66) on EC recurrence, whereas, there was no such effect for estrogen-only HRT (OR: 0.35; 95% CI: 0.06–2.10). However, in the studies where a progestin was added [5–7], with the exception of Ahyan et al. [8], only half of the HRT users received it. For this reason, it remains unclear whether the addition of progestins truly inhibits the stimulatory effect of estrogen on tumor cells.

The selection of healthier and younger women to begin HRT may explain the protective effect of HRT on recurrence in EC survivors seen in observational studies.

The minimum disease-free period before any HRT may be started is still controversial. Since most recurrent ECs occur within 2 years of the initial diagnosis, some authors suggest that HRT should not be started earlier than that [12]. However, in most studies patients received HRT sooner [4–7] and in the study by Ahyan et al. [8] HRT was started immediately after surgery.

The available guidelines are conflicting, which undermines their usefulness. For instance, the North America Menopause Society [1] states that HRT is not recommended in women with a history of EC and suggests that progestogen alone should be considered for the management of HFs, even if no long-term data are available. In contrast, the National Comprehensive Cancer Network (NCCN) Panel [13] states that estrogen-only HRT is a reasonable option for patients who are at low risk of tumour recurrence, but that the exact therapy should be individualised and discussed in detail with the patient.

In conclusion, no definitive conclusions can be drawn, since no long-term RCTs have been conducted. Patients should be counseled on an individual basis and given information on the limited evidence from the literature.

2.2. Uterine sarcomas

Among uterine sarcomas (carcinosarcomas, leiomyosarcomas, adenosarcomas, endometrial stromal sarcomas), only endometrial stromal sarcomas are considered to be estrogen dependent and HRT should be avoided [2].

2.3. Cancer of the cervix

The role of HRT on cervical cancer (CC) depends on the tumour histotype. Squamous CC is not considered to be estrogen responsive and HRT does not seem to have a role in human papilloma virus (HPV) replication. In the study by Ploch [14] on 120 women treated for stage I or stage II CC (80 women treated with HRT and 40 non-treated), HRT produced no change in either OS or DFS. Cervical adenocarcinomas account for 15% of all CCs and are dependent on estrogen stimulation in the same way as EC.

2.4. Ovarian cancer

Most ovarian epithelial cancers (OC) appear in menopausal women and disease prognosis is poor, with less than 30% of patients with stage II–IV tumours alive 5 years after diagnosis. Nonetheless, maintaining a good QoL is of course important.

Available data on HRT use in healthy women and OC risk are conflicting. The WHI trial did not find any increase in risk of OC for HRT users [10]. However, a meta-analysis of 52 studies [15] found an increased risk of OC in healthy HRT users.

Published studies on HRT use after OC treatment show no negative influence on disease prognosis and a great improvement in QoL [16–19].

Eeles et al. [16] compared 78 OC survivors using HRT with 295 controls and found no differences in OS and DFS between the two groups. In the only RCT [17], 130 OC survivors were randomly assigned to receive estrogen-only HRT or not 6–8 weeks after surgery. No statistically significant differences in DFS and OS were found between the two groups (32 recurrences in the HRT group versus 41 recurrences in the control group). In a study by Ursic-Vrscaj et al. [18], 24 OC survivors treated with HRT were compared with 48 non-users and no detrimental effect on outcome was observed in HRT users. The largest prospective study was published by Mascarenas et al. [19], who analysed the OS of 649

survivors of invasive OC and of 150 patients treated for borderline ovarian tumor (BOT) according to HRT use before and after diagnosis. In women with invasive OC, there was no overall difference in 5-year OS according to HRT use before diagnosis (HR 0.83, 95% CI 0.65–1.08) but a better OS was observed for patients who used HRT after diagnosis (HR 0.57, 95% CI 0.42–0.78). For BOT patients, no association was found between OS and HRT use before or after diagnosis. BOTs are known to have a low potential for malignancy and therefore carry a better prognosis than invasive OC.

Each OC histotype (high-grade serous, endometrioid, clear cell, mucinous and low-grade serous carcinomas) is a distinct disease, with different risk factors, hormone responsiveness and prognosis. In particular, endometrioid OC is estrogen sensitive and residual disease after treatment could be stimulated by HRT.

The overall consensus is that HRT should be considered in OC patients who exhibit troublesome menopausal symptoms [2].

2.4.1. Alternatives to hormone treatment

For HFs, the most effective treatments are selective serotonin reuptake inhibitors and selective serotonin–norepinephrine reuptake inhibitors [20]; most of the relevant studies have been performed on breast cancer survivors. Several recent studies in healthy women have suggested that vaginal laser treatment may be effective for dyspareunia and vaginal atrophy, but no RCTs are available. Bisphosphonates and the selective estrogen receptor modulator (SERM) raloxifene may be good alternatives for bone protection. Lifestyle modification such as diet and physical exercise can be considered for cardiovascular protection.

Research agenda

Consensus guidelines are needed. More RCTs on larger samples are needed to draw definitive conclusions.

Conflict of interest

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Authors contribution

All authors declare that have participated in this work and that have seen and approved the final version.

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