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SPECIAL ARTICLE

Hormonal Replacement Therapy after Gynecologic Cancer Treatment

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ABSTRACT

Patients diagnosed with gynecologic cancers are principally managed by radiation, chemotherapy, and total hysterectomy with bilateral salpingo-oophorectomy. The resultant loss of ovarian function associated with gynecologic cancer treatments poses major health concerns as patients face the long-term effects of early menopause. The health implication entails vasomotor symptoms, osteoporosis, cognitive impairment, and increased cardiovascular risks, to name a few. Patients with gynecologic cancers are likely to require intervention, as loss of ovarian function due to cancer treatments tend to produce more severe symptoms than those from natural menopause. Hormonal replacement therapy (HRT) has shown to be an excellent option for treating menopausal symptoms. However, initiating HRT remains a challenge due to the expression of hormone receptors in most gynecologic cancers. This article aims to provide current evidence regarding HRT in managing menopause after gynecologic cancer treatment.

Keywords: hormonal replacement therapy, gynecologic cancer, menopause.

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Introduction

Worldwide, an estimated annual incidence of gynecologic malignancies is approximately more than 3.6 million[1]. Gynecologic malignancies are principally managed by radiation, chemotherapy, and total hysterectomy with bilateral salpingo-oophorectomy. The resultant precipitous loss of ovarian function especially in women less than 45 years of age causes more severe menopausal symptoms than the natural course. Vasomotor symptoms, psycho-cognitive effects, risk of osteoporosis, and cardiovascular disease are all heightened[2,3]. The management of menopausal symptoms after gynecologic cancer treatment depends on the patient's age, comorbidities, and tumor type and staging. The aim of this article is to provide current evidence regarding hormone replacement therapy (HRT) in managing menopause after gynecologic cancer treatment.

Epithelial ovarian cancer/fallopian tube/ primary peritoneal cancer

The five main histologic types of epithelial ovarian carcinoma are low-grade serous, high-grade serous, endometrioid, clear cell, and mucinous. The results of two randomized trials and two meta-analyses demonstrated that postoperative HRT has no deleterious effect on survival outcome in women with ovarian cancer. Guidozzi F et al[4] studied 130 women who had been diagnosed with epithelial ovarian cancer (EOC). They were randomized to continuous oral conjugated equine estrogen (ERT) or not (non-ERT). Follow-up 48 months revealed no significant difference in disease-free interval (DFI) and overall survival (OS) between the two groups. The ERT group and non-ERT group had median OS of 44 and 34 months, respectively. In another randomized study by Eeles RA et al[5], 150 premenopausal and postmenopausal women with EOC were randomly assigned to either no HRT or HRT group, and were provided various hormonal regimens according to physician preference. After a 5-year follow-up, this study showed that OS and relapsed-free survival were significantly improved in women who were receiving HRT. Based on the results of two meta-analyses[6,7], postoperative HRT used among women with ovarian cancer neither heighten tumor recurrence nor minimize OS. However, there are some limitations on how the results can be used. Small sample sizes in most studies limited available evidence to determine the use of HRT in the various histological subtypes of EOC. Additionally, there was also inconsistency in hormonal regimens among studies, which resulted in insufficient data for subgroup analysis for optimal HRT regimen.

The suitability of HRT may depend on the type of ovarian cancer. Estrogen receptor (ER) and progesterone receptor (PR) expressions vary with each type of EOC. The positivity of ER and PR are higher in low-grade serous carcinoma than that in high-grade serous carcinoma[8]. Consequently, the use of HRT in low-grade serous carcinoma is not recommended, especially in the advanced disease of this tumor type. Moreover, there is a paucity of evidence regarding high-grade serous carcinoma and HRT.(9) On the other hand, HRT does not seem to have an effect on survival for endometrioid ovarian cancer, which is an estrogen sensitive tumor. Therefore, HRT has been considered appropriate in early-stage disease. Nonetheless, HRT should be avoided in cases of advanced stage disease with residual disease after surgery[10]. Meanwhile, for all patients treated for clear cell and mucinous cancer, evidence showed that HRT can be implemented[3].

Ovarian germ cell tumors

Currently available data supports the use of HRT in patients with germ cell tumors if indicated[3].

Granulosa cell tumors

Since granulosa cells are estrogen dependent, a history of this type of ovarian cancer may be thought of as a contraindication for HRT. However, research has yet to show any negative effect[9].

Endometrial cancer

Endometrial cancer is found primarily among women with postmenopausal status, with only 25% of cases occurring in premenopausal women[11]. The

standard treatment begins with total hysterectomy with bilateral salpingo-oophorectomy and surgical staging. Subsequent adjuvant treatments are determined by the presence or absence of risk factors and risk of recurrence. Following surgical procedures, menopausal symptoms may be implicated.

The randomized controlled trial by Barakat et al[12] recruited 1,236 endometrial cancer patients who have undergone a total hysterectomy and bilateral salpingo-oophorectomy with or without subsequent adjuvant therapy. The patients were previously evaluated to include only those who had no other invasive malignancies in the last five years. Half of the patients were given ERT for three years, although the regimen and route were not specified. Meanwhile, the control group was given a placebo. After 35.7 months of follow-up, both ERT and control group had comparable progression free survival (PFS) and OS. In regards to exogenous estrogen replacement for relieving menopausal symptoms, the study concluded that endometrial cancer recurrence was low in patients with early stages of endometrial cancer. Nonetheless, the safety and recommendation of ERT for endometrial cancer patients remained inconclusive.

The Cochrane review attempted to assess the safety of HRT among patients previously treated for endometrial cancer by analyzing one randomized trial (Barakat et al) and five observational studies[13]. This review concluded that there was insufficient evidence to consider HRT after treatment of endometrial cancer. The benefit of treatment should be weighed against the risk of recurrence. However, the limited data suggest that HRT may be a reasonable option for women with low-grade and early-stage endometrial cancer. There was no data on higher stages of endometrial cancer.

Uterine Sarcoma

Uterine sarcoma accounts for about 3% of all uterine cancer cases. Histology of uterine sarcoma ranges from low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS), undifferentiated uterine sarcoma, and leiomyosarcoma (LMS), which is the most common subtype[14-15]. Uterine sarcoma may be hormone-dependent, as some are found to express ER and PR[16]. Therefore estrogen and progesterone receptor testing should be initiated to determine suitability for HRT for menopausal symptoms after cancer treatment. Regardless, non-hormonal treatment for menopausal symptoms should be considered for these patients[17].

Cervical Cancer

Squamous cell carcinoma constitutes up to 90% of cervical cancer histology, while adenocarcinoma makes up for the remaining 10-20%[18]. Chemotherapy, radiotherapy or surgery are the main treatment modalities for cervical cancer. These treatments may induce sudden-onset of premature menopause in women due to the removal of ovaries in surgical treatments or the destruction of oocytes from radiation toxicity[19]. Cervical cancers are hormonal-independent, thus contraindications for topical and systemic HRT have not been evident[3]. The choice of unopposed or opposed estrogen would be dependent on the patient's hysterectomy status. To prevent stimulation of the endometrium, opposed estrogen is provided for those who were treated with chemo-radiation with preservation of the uterus, while unopposed estrogen is provided for patients that underwent hysterectomy[3].

In the limited studies, no significant difference in oncologic outcome was observed amongst patients diagnosed with cervical squamous cell carcinoma who received HRT[20-22]. A prospective study by Ploch et al[20] examined 120 cervical cancer patients, 80 of whom received HRT in the form of opposed estrogen. Throughout five years of regular follow-up examination, no serious adverse effects of HRT were evident. The HRT and control group had 80 and 65 percent five-year survival, respectively, which was statistically insignificant. The difference in disease recurrence between the two groups was also statistically insignificant, where there were 20 and 32 percent recurrence in the HRT and control groups, respectively. Additionally, the HRT group was found to experience a milder degree and shorter duration of post-radiological complications.

There are differences in hormone receptor

expression between squamous cell carcinomas and adenocarcinomas. One study evaluated estrogen and progesterone receptor expression in patients with cervical adenocarcinoma and their oncologic outcomes. Estrogen and progesterone receptors were expressed in 39 and 33 percent, respectively. Throughout the 24 months period of follow-up, these receptor expressions did not influence the clinicopathological parameters, which included the clinical stage, age, histology, tumor size and grading, lymphovascular space invasion, lymph node status, and disease recurrence. The overall and disease-free survival of the patients were also not correlated[23]. Therefore, the estrogen and progesterone receptors are not recommended to yield the prognostic value of cervical adenocarcinoma. These results are in coherence with a systematic review of ten articles, which found no relationship between HRT and the incidence of cervical cancer[19]. Nonetheless, one study found HRT to have a positive association with cervical adenocarcinoma, although statistical significance was not reached[24]. Although there is a paucity of data, a majority of available studies suggested an absence of significant relationships between HRT and the risks of cervical cancer.

Conclusion

The management of menopausal symptoms after gynecological cancer treatment depends on their age, tumor type and stage, and thus should be individualized. Shared decision making is necessary for initiating HRT. High quality and randomized data examining the use of HRT are still lacking. Therefore more research is needed to provide stronger evidence to guide practice.

Potential conflicts of interest

The author declares no conflicts of interest.

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