Hormone replacement therapy after epithelial ovarian cancer treatment

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Summary

Purpose: Our report deals with the presumed influence of hormone replacement therapy (HRT) on the recurrence of epithelial ovarian cancer.

Materials and Methods: Our study group consisted of 31 patients who had been treated for invasive epithelial carcinoma of the ovaries. In all the patients the primary treatment was surgery. The mean duration of follow-up was 55 months. All the patients received HRT with non-conjugated estrogens. The data were analyzed using analytical descriptive epidemiological methods.

Results: The mean duration of HRT was 25 months, starting on average 18 months after completed therapy for ovarian cancer. Progression of the disease was established in 3 patients with advanced disease, 2 patients with moderately- and poorly-differentiated serous adenocarcinoma respectively, and in one patient with well-differentiated endometrioid adenocarcinoma. The progression of ovarian cancer occurred 1, 2 and 10 months after the beginning of HRT. Two patients died due to progressive disease, while one patient is still alive with evidence of the disease. Eleven months after the beginning of HRT, one patient without evidence of ovarian cancer progression presented with a new primary cancer – carcinoma of the breast.

Conclusions: According to the results of our review study, HRT does not seem to have a noteworthy effect on the progression of epithelial carcinoma of the ovary. However, only further – carefully designed – prospective studies could provide more conclusive results.

Key words: Ovarian carcinoma; Hormone replacement therapy; Recurrence.

Introduction

Ovarian cancer is a disease which is generally detected at an advanced stage in elderly women. Nevertheless, it may also occur in younger premenopausal women. In these, surgery and chemotherapy result in a premature onset of menopause. The patient's distress due to the primary disease and the associated fear of recurrence is further aggravated by severe and acute menopausal problems. In such patients hormone replacement therapy (HRT) can be of great benefit, as it can prevent or alleviate the current menopausal symptoms, while in the long run it reduces the patient's risks of osteoporosis and cardiovascular disease [1]. Due to controversy surrounding the hypothesis that ovarian carcinomas – in particular endometrioid ovarian adenocarcinoma – are hormone dependent, the question of the possible influence of HRT on the progression and recurrence of ovarian carcinoma needs to be resolved. However, the lack of reliable data renders any definite conclusions impossible. The present (intermediate) report of our review study is published with the aim to help resolve this problem.

Materials and Methods

We collected the data on a total of 31 patients with HRT who had been treated and followed-up for invasive epithelial carcinoma of the ovary at the Institute of Oncology in Ljubljana. Mean follow-up of the patients after confirmed ovarian cancer was 55 months (range 2 - 161 mos).

Patients with a simultaneously or previously established second primary carcinoma were not included, and neither were the patients receiving HRT in the form of stickers or local estrogen-based HRT treatment. All the patients received non-conjugated estrogens, either alone or in combination with progestogens, in the form of tablets or injections.

The description of the patient group and some of their epidemiological characteristics were accomplished by means of descriptive epidemiological methods.

Results

At the time of diagnosis, the mean age of patients was 42 years, the youngest being 26 and the oldest 52 years old. The largest number of patients, i.e. 19 (61%) had stage I disease by FIGO; only 3 (10%) patients had stage II and 9 (29%) stage III disease (Table 1).

The most frequent pathohistological types were serous adenocarcinoma – in 15 patients (48%), and endometrioid adenocarcinoma – in 11 patients (36%). There were also 2 mucinous, 2 clear cell adenocarcinomas and one non-differentiated carcinoma detected. Well-differentiated carcinomas seen in 16 patients (52%) were prevailing, while moderately-differentiated were found in 8 (26%), and poorly-differentiated in 7 cases (22%) (Table 1).

All the patients were primarily treated by surgery. In 4 (13%) patients, this consisted of abdominal hysterectomy with bilateral adnexectomy (TELA), while 21 (68%) underwent TELA and omentectomy, and 6 (19%) TELA, omentectomy and lymphadenectomy. None of the

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patients with lymphadenectomy had evidence of metastases in the resected lymph nodes. Mean tumor diameter was 102 mm (range 30 - 200 mm).

In 23 (74%) patients after surgery there was no evidence of residual disease in the abdominal cavity, in 5 (16%) the residual tumor measured up to 2 cm while in 3 patients (10%) it exceeded 2 cm (Table 1). In 6 (19%) patients surgery was the only method of treatment; 22 (71%) patients received adjuvant chemotherapy and 3 (10%) a combination of chemotherapy and irradiation.

The mean age of patients at the beginning of HRT was 44 years (range 29 - 52 yrs). The mean time interval from the completed ovarian carcinoma treatment to the onset of HRT was 18 months (range 0 - 115 mos), and from the last menstrual cycle to HRT 23 months (range 1 - 125 mos). Only three patients presented with a natural onset of menopause before the diagnosis of ovarian carcinoma; in all others menopause was induced artificially as a result of treatment.

The majority of patients – 20 (65%) received only estrogen-containing HRT, while combined estrogen-progesterone medications were used in 11 (35%) patients. It should be pointed out that all the patients received only preparations with non-conjugated estrogens. In 23 (74%) patients HRT was continuous, and in 8 (26%) it was intermittent.

The mean duration of HRT was 25 months (range 1 - 129 mos) (Table 1). HRT was discontinued in 11 (32%) patients, in 7 of these at the patient's own initiative; only one of those patients complained of an uncontrollable increase in her body weight, while others did not state any particular reason for discontinuation. In 4 patients HRT had to be discontinued for medical reasons: in 2 due to recurrence and in one due to the occurrence of a new primary carcinoma. The fourth, a younger patient, presented with thrombosis of a vein in her leg soon after the onset of HRT; of course, HRT had to be discontinued immediately, and the already present osteoporosis was treated with non-steroid preparations.

The mean duration of follow-up was 55 months (2 - 161 mos). Twenty-four patients (83%) are still using HRT. Seven patients had positive familial history for breast and gynecological cancer: mothers of these patients had breast cancer in two cases, endometrial carcinoma in two and ovarian carcinoma in three cases.

Three patients presented with a progression or recurrence of the disease (3/31, 10%), (Table 1). At the onset of therapy, their disease was classified as stage IIC, IIIB and IIIC, respectively. The first patient had a well-differentiated endometrioid adenocarcinoma, the second one a poorly-differentiated serous adenocarcinoma and the third one a moderately-differentiated serous adenocarcinoma. The mean follow-up of these patients was 30 months (range 12 - 51 mos). The disease recurred 1, 30 and 5 months after completed therapy for ovarian carcinoma, and 1, 2 and 10 months after the beginning of HRT. While the first patient received a continued estrogen-based HRT, the remaining two were maintained on an intermittent combined estrogen-progesterone treatment regimen. The first two patients have died, whereas the third one is still alive with evidence of progressing disease. Due to severe menopausal difficulties, she is still receiving HRT, despite of the recurrence (Table 2).

A new primary cancer, i.e. carcinoma of the breast, occurred in one patient (1/31, 3.2%). At the onset of therapy for the first cancer (poorly-differentiated serous adenocarcinoma of the ovaries) the patient was 45 years old. Severe and persistent menopausal symptoms required that this patient had HRT introduced 18 months after completing therapy for her primary disease. She was receiving continuously a non-conjugated estrogen-containing drug. After 11 months of HRT, breast cancer was detected; the disease was assessed as T2N1M0. Histological examination revealed a poorly-differentiated invasive ductal carcinoma with metastatic involvement in the axillary lymph nodes. Estrogen and progesterone receptors were negative and the tumor was considered hormone-independent. The patient was treated by surgery and adjuvant chemotherapy. HRT was discontinued immediately upon the verification of breast carcinoma. Twenty-one months have passed since then, and the patient is still alive with hepatic metastases that were established 6 months ago. No ovarian cancer recurrence has been found.

Discussion

Published information on the use of HRT in ovarian cancer patients is scarce. Neither are there any reliable data that would support the hypothesis that HRT acts as an initiator nor promoter in the etiology of ovarian carcinoma.

Some authors still believe ovarian carcinoma to be a hormone dependent tumor and therefore refuse to prescribe HRT to patients with these tumors [2]. Presumptions which associate the use of hormones, particularly of estrogen, with ovarian cancer are rare, and are based on some of the following findings:

1. It has been found that the cells of ovarian carcinoma contain estrogen, progesterone and androgen receptors [3, 4]. According to the data available so far, these receptors are not functional, except perhaps in well-differentiated endometrioid carcinomas [5, 6]. Advanced and recurrent epithelial ovarian carcinomas rarely respond to a progesterone-based therapy [5, 7].

2. Some cases of ovarian carcinoma occur within the setting of familial breast-ovarian cancer syndrome. Studies have shown that 76% - 95% of families with this syndrome are associated with mutations of BRCA1 and BRCA2 genes [8].

3. Some epidemiological studies have shown an increased risk of ovarian carcinoma in women receiving HRT. Estrogen replacement therapy (ERT) should increase the risk by promotion of proliferation and transformation of ovarian cells [9]. According to a second theory, ERT should reduce the risk of ovarian carcinoma occurrence by decreasing gonadotrophin concentrations in the blood [10, 11]. This theory is based on the gonadotrophin hypothesis,

Table 1. — *Distribution of studied patients by age, stage, subgroup, tumor differentiation grade, pathohistological diagnosis, residual tumor after surgery, months of HRT, recurrence, and second primary cancer.*

Epidemiological characteristics	No. of patients n=31	Percentage (%)
Age (years)		
Up to 39	9	29%
40 - 49	18	58%
50 and more	4	13%
Stage		
I	19	61%
II	3	10%
III	9	29%
Subgroup		
A	9	29%
B	7	23%
C	15	48%
Differentiation		
G1	16	52%
G2	8	26%
G3	7	22%
Histology		
Serous	15	48%
Mucinous	2	7%
Endometrioid	11	36%
Other	3	9%
Residual disease after surgery		
None	23	74%
Up to 2 cm	5	16%
More than 2 cm	3	10%
HRT (months)		
Up to 6	7	23%
Up to 24	13	41%
Up to 60	9	29%
More than 60	2	7%
Recurrence		
Yes	3	10%
No	28	90%
New primary cancer		
Yes	1	3%
No	30	97%

Table 2. — *Distribution of patients with HRT and recurrence of epithelial ovarian carcinoma by age, pathohistological diagnosis, stage, differentiation degree, residual tumor after surgery, months of HRT, follow-up and stage on check-out.*

Patients	Age (yrs)	Histology	Stage	Diff.	Res.to after surg.	HRT to recur.	Follow-up (mos)	Patients's condition
A	46	ENDOM.	2C	G1	>2 cm	1	12	Died due to disease
B	51	SER	3B	G3	1 cm	2	51	Died due to disease
C	48	SER	3C	G2	Microsc. disease	10	27	Alive with disease

according to which the exposure of ovarian epithelium to permanently high doses of gonadotrophin stimulates the transformation of ovarian cells into cancer cells [9].

There are 16 reports available in the literature which deal with the occurrence of ovarian carcinoma and HRT after menopause.

Twelve studies failed to show any significant correlation between HRT and ovarian cancer occurrence, the relative risk (RR) being 1.1 (95% confidence intervals 0.6-2) [12]. One of the studies included women who received diethylstilbestrol [13]. The results of another study showed that the increased risk can be seen only in the occurrence of endometrioid carcinomas [14], which might be attributed to a greater precaution in prescribing HRT also to patients treated for endometrioid ovarian carcinoma.

Only two studies have shown an increased risk for the occurrence of ovarian carcinoma associated with the use of HRT in menopause. The first one was a case-control study with RR 1.6 (CI 1.2 - 2.4), although there was no significant correlation with HRT [15]. The second was a prospective cohort study following 240,273 women on long-term ERT; 436 death cases were reported due to ovarian carcinoma and RR 1.15 (CI 0.94 - 1.42), RR increasing with the time of ERT (RR 1.40, CI 0.91 - 2.77). A possible correlation between ERT and histological type of ovarian carcinoma was not studied [16].

4. Experimental supplementation of steroid hormones to laboratory animals should presumably cause the occurrence of non-epithelial ovarian tumors [7].

Is it therefore justifiable that HRT to given to patients that have been treated for epithelial ovarian carcinoma? Generally, this treatment is chosen after a non-steroid therapy in order to alleviate severe menopausal symptoms occurring as a result of naturally or artificially (surgically) induced menopause, which considerably decrease the quality of the patient's life. It should not be ignored, however, that HRT may entail a potential danger of hormone substitution-related reactivation of malignant disease. This concern stems from the fact that the presence of estrogen receptors was confirmed in approximately half of the ovarian carcinoma tissue samples studied [18]. There is no reliable laboratory evidence to support the theory that estrogens have the potential of reactivating the dormant cells of epithelial ovarian carcinoma.

In reviewing the British medical literature, we found but one report on HRT after ovarian cancer treatment. This was a retrospective study published by Eeles *et al.* [19]. A group of 78 patients receiving HRT after treatment for ovarian carcinoma was compared with a group of 295 patients that were not receiving HRT. The author did not establish any significant difference in the distribution of stages in either group. A statistically significant difference was noted in the number of well-differentiated tumors, i.e. 20/78 (25.6%) in group 1 vs. 42/295 (14.2%) in group 2. The age in group 1 was statistically significantly lower than in group 2. Mean duration of hormone treatment was 28 months (<1 to >200). In 32/78 patients the prescribed hormone preparations contained conjugated estrogens alone (0.625 mg), while 38 patients were receiving a combination of estrogens and progestogens, 6 progestogens alone, and 2 patients testosterone preparations. The mortality rate in the group with HRT was 17/78 patients vs. 145/295 patients in the control group. It is believed that HRT should not adversely affect the

patients with ovarian carcinoma since the group with HRT survived statistically significantly better than the group without HRT. Also, the quality of life in the former group of patients was much better. The author believes that either estrogen or combined estrogen-progesterone therapy have similar effects, however, in hysterectomized patients HRT with estrogens alone should be recommended, the only exception being patients with endometrioid adenocarcinoma of the ovaries where a combined estrogen-progesterone therapy would be more appropriate [19].

Although the results of Eeles' study are very important, perhaps they do not reflect the real situation owing to the incomparable criteria for the distribution of patients into groups with/without HRT. Namely, the patients with HRT were younger, with earlier stages of the disease and well-differentiated tumors. These differences between both groups might mask possible adverse effects of HRT [18, 20]. Nevertheless, the critics agree with the author who believes that the question on how HRT influences the course of disease and treatment in ovarian cancer can only be resolved by randomized studies.

In our review study, ovarian cancer recurred in 3 patients with the epithelial type of the disease (3/31, 10%), in 2 patients with serous adenocarcinoma (2/15, 13%) and in one patient with endometrioid adenocarcinoma of the ovaries (1/11, 9%). Each of those three patients presented with a number of unfavorable prognostic factors, such as a higher stage of the disease, worse tumor differentiation and residual disease after surgery, which all contribute to a greater probability of progression or recurrence as compared to patients with favorable prognostic factors [21]. Therefore, the evaluation of a possible influence of HRT on faster progression and recurrence is all the more difficult and unreliable.

Progression of endometrioid ovarian carcinoma, which is believed to be more risky for HRT, was established in one patient only. Therefore it would be difficult to draw any conclusion on a clearly adverse effect of HRT on the progression of endometrioid ovarian cancer. It is perhaps noteworthy that progression of the disease occurred in a patient with continuous ERT, after therapy for well-differentiated endometrioid adenocarcinoma of the ovaries. Some authors believe that the very patients with well-differentiated endometrioid adenocarcinoma of the ovaries, receiving ERT without added progesterone, are at a greater risk of progression than others. It is true however, that our patient with progression of endometrioid ovarian carcinoma had a more advanced disease at the time of diagnosis; her residual tumor after surgery exceeded 2 cm, and the progression already occurred a month after the treatment for primary disease. Considering the given circumstances, the influence of one-month continuous HRT on the progression cannot be reliably assessed.

A second primary carcinoma was established in one patient only (1/31, 3%). This was a poorly-differentiated invasive ductal carcinoma of the breast, stage T2N1M0, established in a patient after treatment for poorly-differentiated serous adenocarcinoma of the ovary. Breast cancer was detected during HRT, precisely 11 months from its beginning. Estrogen and progesterone receptors were negative. Since the breast carcinoma was hormone independent, we presume that a couple of months of continuous ERT could not have had a major influence on the occurrence of this cancer. In this case, however, familial anamnesis seems interesting and noteworthy. Since the mother of our patient also had a history of breast cancer, it is quite possible that the patient belongs to the group of women with familial ovarian-breast cancer syndrome. Unfortunately, there is no information available on any genetic tests performed.

Conclusions

Our report represents a review of certain epidemiological data pertinent to a group of patients who had been receiving HRT after a previous treatment for *invasive* epithelial ovarian carcinoma. The small number of patients and our study approach render a more precise evaluation of the data impossible. However, we can presume with certainty that the use of HRT in patients after epithelial ovarian carcinoma treatment contributed to a better quality of the patient's life. Based on the published information, it cannot be concluded that HRT would adversely affect the course of disease in patients that have been treated for epithelial ovarian carcinomas. Nevertheless, some authors believe that certain caution is required in patients with well-differentiated endometrioid carcinomas due to a possible hormone dependence of these tumors. Further, carefully designed prospective studies will be warranted to finally resolve the question of the role of HRT in the etiology, progress and recurrence of epithelial ovarian carcinoma.

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