Original Article

Efficacy of Postoperative Hormone Replacement Therapy on Prognosis of Patients with Serous Ovarian Carcinoma

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Abstract

Background: Ovarian cancer is the most common cause of gynecological cancer-associated death. Iatrogenic menopause might adversely affect the quality of life and health outcomes in young female cancer survivors. We evaluated whether postoperative hormone replacement therapy (HRT) had a negative influence on the progression-free survival (PFS) of patients with papillary serous ovarian cancer (SOC).

Methods: We retrospectively reviewed the medical records of patients with papillary SOC, treated from January 1980 to December 2009, who suffered from menopause with or without HRT. Clinical characteristics of patients were compared between the two groups (HRT and non-HRT). Blood samples were collected from all the participants to detect serum cancer antigen (CA) 125. Hazard ratios with 95% confidential intervals for each variable were calculated by univariable and multivariable conditional Logistic regression analyses.

Results: Among 112 identified patients, 31 were HRT users and 81 were not. The two groups did not significantly differ in median age at diagnosis ($t = 0.652$, $P = 0.513$), International Federation of Gynecology and Obstetrics (FIGO) stage ($\chi^2 = 0.565$, $P = 0.754$), differentiation ($\chi^2 = 1.728$, $P = 0.422$), resection status ($\chi^2 = 0.070$, $P = 0.791$), relapse ($\chi^2 = 0.109$, $P = 0.741$), chemotherapy course ($t = -1.079$, $P = 0.282$), follow-up interval ($t = 0.878$, $P = 0.382$), or PFS ($t = 0.580$, $P = 0.562$). Median Kupperman score at the onset of HRT was 30.81 and 12.19 after the therapy ($t = 3.302$, $P = 0.001$). According to the analysis, the strongest independent variables in predicting PFS were FIGO stage and disease that was not optimally debulked.

Conclusions: Postoperative HRT is not a prognostic factor for PFS of patients with papillary SOC. However, multicenter studies are needed to verify and extend our findings.

Key words: Hormone Replacement Therapy; Prognosis; Progression-free Survival; Serous Papillary Ovarian Cancer

Introduction

Ovarian cancer (OC) is the most common cause of gynecological cancer-associated death.[1] Among OCs, 85%–90% are epithelial ovarian cancer (EOC) types[2] and serous OC (SOC) accounts for 70% of all epithelial cancer.[3] The mean age at diagnosis for EOC is 51 years, <20% of epithelial cancers are diagnosed before the onset of menopause.[4]

The established standard strategy for treatment of advanced OC, up until recently, has been debulking surgery for platinum/taxane-based chemotherapy followed by surveillance for potential recurrence.[5] A series of relevant clinical symptoms will appear due to deficiency of estrogens after the surgery, such as perimenopausal syndrome, tidal fever, night sweating, and labile mood.[6] Symptoms of iatrogenic menopause are usually considerably more severe than those of natural menopause because of their sudden onset at a younger age[7] and might adversely affect the quality of life and health outcomes in young female cancer survivors. With the improvement of prognosis for OC patients, this problem has become more serious.

The most effective treatment for menopausal symptoms is hormone replacement therapy (HRT). HRT is highly effective in improving menopausal symptoms such as hot flushes, night sweats, dyspareunia, impaired sexual

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function and insomnia, and reduces the risk of fractures from osteoporosis.[8,9] However, no consensus about the use of HRT in the case of OC patients exists, hormone therapy (HT), regardless of type or regimen, is associated with an increased risk of SOC in postmenopausal women.[10] HRT has often been withheld from women with gynecologic cancer. The main concerns are the potentially increased risk of relapse and the development of new hormone-dependent primary disease.[6]

Up to now, as some retrospective studies could have been biased by selective participation or recall,[11] uncertainty remains about the use of HRT for patients with surgically induced menopause. Rare study examined premenopausal patients with SOC as its sole research object. Therefore, the aim of the present study is to evaluate the influence of HRT on the prognosis of the enrolled patients and investigate the feasibility of HRT for premenopausal women with SOC after cytoreductive surgery.

Methods

Participants

The present study was a retrospective descriptive review of data from patients who underwent cytoreductive surgery for OC at the Department of Obstetrics and Gynecology of Shanghai First Maternity and Infant Hospital from January 1, 1980 to December 31, 2009. The 2014 International Federation of Gynecology and Obstetrics (FIGO) classification and staging system[12] for OC histology and stage was applied to each case. All histopathologic evaluations were performed by experienced pathologists from the hospital's Pathology Department. Platinum-based chemotherapy regimens were adopted after the surgery. The study procedure was approved by the ethics committee of the hospital, and written consent was obtained from the patients during outpatient follow-up. For the dead patients, we received written informed consent from their family members. All results would be used only for research purposes.

Study design

Six inclusion criteria were defined: (a) at the time of surgery, subjects were premenopausal; (b) 20–50 years of age; (c) without severe internal complications or HRT contraindications; (d) diagnosed with papillary SOC; (e) without previous HRT history, including estrogen via vaginal creams or patches, oral contraceptives, or HT; and (f) were followed up after surgery for at least 1 year. Of 132 women who met the first five criteria, we enrolled 112 who had been followed up for more than 1 year; of these 112 patients, 31 had accepted HRT after primary surgical treatment (HRT group) and 81 did not receive HRT (control group). Clinical data for the 112 patients were reviewed retrospectively.

Data and follow-up

Study data were collected from the patients' medical files, including age at diagnosis, gravidity, parity, stage, differentiation, resection status, relapse, postoperative chemotherapy, follow-up interval, onset and duration of HRT, Kupperman score, and progression-free interval. All of the patients underwent thorough follow-ups, with pelvic examinations and ultrasonography or periodic computerized tomography of the abdominopelvic cavity to detect any tumor recurrence at each follow-up visit. The concentration of cancer antigen (CA) 125 was measured. Follow-up data regarding progression-free survival (PFS) and overall survival (OS) were obtained from outpatient medical records and telephone inquiries. PFS was defined as the interval between treatment initiation to disease progression or to the date of last follow-up. OS was defined as the time interval between the date the disease was histologically diagnosed and death. All follow-up data were updated until June 30, 2014. PFS was analyzed using the *Cox* proportional hazards model.

We also used the Kupperman index[13] to assess surgically induced menopause of patients in the HRT group. Their medical files were reviewed and their pretreatment and posttreatment clinicopathological characteristics were compared.

Statistical analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. Descriptive statistics were used to describe patient characteristics. Groups were compared by Fisher's exact test for categorical variables and Student's *t*-test for continuous data. Survival data were analyzed by the Kaplan-Meier method. Multivariate analysis used a *Cox* proportionate hazards model. Because the number of variables that reflected baseline cohort characteristics was large compared with the number of endpoints, a univariate analysis was conducted to screen for variables; $P \leq 0.1$ was required for inclusion in the multivariate analysis.[14] $P \leq 0.05$ (two-sided) was considered significant.

Results

Patients' baseline characteristics

Patients' average age at diagnosis in HRT group was 33.5 years (range: 21–50 years); control group: 31.2 years (range: 22–50 years), and did not significantly differ [Table 1].

Gravidity, parity, differentiation, FIGO stage, resection status, postoperative adjuvant therapy, recurrence, and follow-up interval and death were also similar between the two groups [Table 1]. Each group had one patient with FIGO Stage Ia disease who received no chemotherapy; the rest received chemotherapy based on 3–6 regular courses of paclitaxel.

Six of the HRT patients and 18 of the control patients suffered recurrence, and five of the HRT patients and 14 of the control patients died [Tables 1 and 2]. The two groups did not significantly differ for any of the characteristics studied.

Hormone replacement therapy

Because these patients were deficient in estrogen, the HRT group mainly received estrogen supplements. Among the patients, 18 took estrogen only and 13 took either estrogen with tibolone or tibolone only. Those who took estrogen usually took conjugated estrogen at dosages of 0.3 or 0.625 mg, once a day or every 2 days or twice weekly. Tibolone has a weak androgen-like action and might improve some clinical symptoms; it was taken in dosages of 1.25 or 2.5 mg, once a day or once every 2 days. When estrogen and tibolone were taken together, the respective doses were usually 0.3 and 1.25 mg, once a day or once every 2 days or twice weekly [Table 3].

Patients started HRT on average at 7 months (range: 2–19 months) after completing chemotherapy. One patient with Stage Ia OC started HRT 2 months after her surgery without chemotherapy; the other 30 patients started HRT after completing chemotherapy. Eight patients discontinued HRT, six because of recurrence, and two because of breast hyperplasia. Clinical characteristics of patients treated by the two HRT regimens were similar [Table 4]. Their symptoms improved after 2–3 months of HRT. The median HRT duration was 20 months, but 12 patients used it for more than 2 years.

Clinical symptoms were ameliorated after 1–2 months HRT. Patients' median Kupperman scores significantly changed during HRT, at 30.81 when starting HRT, and 12.19 at the end ($t = 3.302$, $P = 0.001$). Hot flushes, insomnia, and nervousness are obviously improved.

In addition, median postsurgery PFS in HRT group was: 58.8 months (range: 16–89 months); and control group: 47.3 months (range: 16–89 months), which were not

Table 1: Clinical characteristics of patients treated with HRT or not

Characteristics	HRT group ($n = 31$)	Control group ($n = 81$)	t/χ^2	P
Age (years)	33.5 (21–50)	31.2 (22–50)	0.652*	0.513
Gravidity	2.0	2.1	−0.145	0.885
Parity	0.85	0.93	−0.439	0.622
Stage				
I	23	58	0.565	0.754
II	3	12		
III	5	11		
Differentiation				
Well	24	53	1.728	0.422
Moderate	4	19		
Poor	3	9		
Resection status				
Optimally debulked	27	72	0.070	0.791
Not optimally debulked	4	9		
Chemotherapy course (months)	5.3	6.1	−1.079	0.282
Relapse	6	18	0.109	0.741
Follow-up interval (months)	59.0 ± 37.9	50.5 ± 18.7	0.878*	0.382
Progression-free interval (months)	58.8 (16–89)	47.3 (16–89)	0.580*	0.562
Death	5	14	0.021	0.884

Values are given as median, mean ± SD, or number unless indicated otherwise. *t value. SD: Standard deviation; HRT: Hormone replacement therapy.

Table 2: Clinical characteristics of patients with relapse of the disease

Variables	HRT group with relapse ($n = 6$)	Control group with relapse ($n = 18$)	t/χ^2	P
Age (years)	37.2 (32–48)	38.1 (30–49)	−1.235*	0.726
Stage				
I	0	0	1.000	0.317
II	1	7		
III	5	11		
Differentiation				
Well	0	0	0.056	0.813
Moderate	3	10		
Poor	3	8		
Resection status				
Optimally debulked	2	9	0.503	0.478
Not optimally debulked	4	9		
Recurrence time (months)	40.2 ± 13.9	33.6 ± 17.2	1.582*	0.632

Values are given as median (range), mean ± SD, or number. *t value. SD: Standard deviation; HRT: Hormone replacement therapy.

Table 3: Specific application and dosage of HRT

Groups	Case (n)	Dose (mg)	Usage
Estrogen (premarin)	18	0.3 or 0.625	qd, qod, or twice weekly
Tibolone (lavial)	9	1.25 or 2.5	qd or qod
Estrogen + tibolone	4	0.3 + 1.25*	qd, qod, or twice weekly

*Dose of premarin is 0.3 mg and dose of lavial is 1.25 mg unless indicated otherwise. HRT: Hormone replacement therapy. qd: Once a day; qod: Once every 2 days

Table 4: Characteristics of patients treated with different HRTs

Characteristics	Estrogen ($n = 18$)	Estrogen + tibolone or tibolone alone ($n = 13$)	χ^2	P
Stage				
I	13	10	0.121	0.941
II	2	1		
III	3	2		
Differentiation				
Well	14	10	0.199	0.905
Moderate	2	2		
Poor	2	1		
Resection status				
Optimally debulked	15	12	0.541	0.462
Not optimally debulked	3	1		

Values are given as number. HRT: Hormone replacement therapy.

significantly different [t = 0.580, P = 0.562, Table 1]. Five-year OS rates in HRT group were: 84%; and control group: 78% (χ^2 = 0.510, P = 0.475).

Cox analysis

Our univariate analysis of commonly known prognostic factors significantly associated FIGO stage with PFS [Tables 5 and 6]. The univariate analysis also showed the HRT group and control group did not significantly differ in relapse rates (hazard ratio [*HR*] in HRT group: 0.290; 95% confidence interval [*CI*]: 0.31–2.47), Kaplan–Meier analysis showed the prognosis of HRT patients who received estrogen only was not significantly different from those who received combined estrogen-tibolone or tibolone only [Table 4].

Cox regression multivariate analyses were performed for FIGO stage, differentiation, and resection status, with PFS as the endpoint. The strongest independent predictor of longer PFS was FIGO stage and resection status. Higher FIGO stage (*HR* = 1.831) and suboptimal debulking (*HR* = 1.375) increased the risk of relapse [Table 6].

Table 5: Simple survival analysis for progression-free survival

Characteristics	Replase (n = 24)	Without replase (n = 88)	χ^2	P
Stage				
I	0	81	89.826	0.001
II	8	7		
III	16	0		
Differentiation				
Well	0	77	72.985	0.001
Moderate	13	10		
Poor	11	1		
Resection status				
Optimally debulked	11	88	48.776	0.000
Not optimally debulked	13	0		
Chemotherapy				
Yes	24	86	0.555	0.456
No	0	2		
HRT				
Yes	6	25	0.109	0.741
No	18	63		

Values are given as number. HRT: Hormone replacement therapy.

Table 6: Univariate and multivariate survival analyses evaluating the factors influencing recurrence

Variables	Univariate analysis	Multivariate analysis		
		P	*HR*	95% *CI*
Age	0.813	–	–	–
Gravidity	0.492	–	–	–
Parity	0.780	–	–	–
Stage	0.001	0.004	1.831	1.232–2.419
Differentiation	0.001	0.437	1.312	0.882–4.790
Resection status	0.000	0.046	1.375	0.962–2.889
Chemotherapy course	0.456	–	–	–
HRT	0.290	–	–	–

HR: Hazard ratio. *CI*: Confidence interval; HRT: Hormone replacement therapy; –: No data.

Discussion

New convincing data have shown estradiol concentrations in ovarian tissues to be more than 100-fold higher than that in serum and higher still in the ovulatory follicular fluid.[15] Thus, ovarian surface epithelium and its cystic derivatives are likely to be exposed to high levels of these steroids. Estrogens favor neoplastic transformation of the ovarian surface epithelium;[16] 86% of ovarian tumor specimens are positive for estrogen receptor.[17]

Recent studies have shown that estrogen replacement therapy might increase the risk of OC. In a meta-analysis of 52 epidemiological studies that included 12,110 postmenopausal women, 55% (6601) of those who had used HRT, developed OC. Women who used HRT for at least 5 years from around age 50 years had about one extra OC per 1000 users, which (assuming typical prognosis) would cause about one extra OC death per 1700 users; this risk increased only for the two most common types, serous (relative risk [*RR*]: 1.53, 95% *CI*: 1.40–1.66; $P < 0.0001$) and endometrioid (*RR*: 1.42, 95% *CI*: 1.20–1.67; $P < 0.0001$).[11]

A prospective study of 82,905 women who received HRT, including 389 with OC, found both current and past users of HRT for at least 5 years had significantly higher risks of OC (current-*RR*: 1.41, 95% *CI*: 1.07–1.86; past-*RR*: 1.52, 95% *CI*: 1.01–2.27). Results were similar for serous tumors (*RR* for 5-year increment of unopposed estrogen use: 1.23, 95% *CI*: 1.07–1.40).[18] A meta-analysis showed similar results: HRT was associated with an increased SOC risk (pooled *HR*/*RR*: 1.46, 95% *CI*: 1.28–1.67).[10]

Patients with surgically induced menopause suffered from intense symptoms such as hot flushes, night sweats, and insomnia[6] and experienced higher risk of atherosclerosis and osteoporosis.[19] Although HRT is considered an effective therapy, no consensus exists on its use for OC patients. Over two-third of women with surgically induced menopause were not on HT, many of whom were still having daily hot flushes.[20]

Despite opposing reports on HRT use, various retrospective and prospective studies have provided proof of its safety, particularly after surgery in EOC patients. Use of HRT was likely to have improved the quality of life through relief of menopausal symptoms.

According to Guidozzi and Daponte, the difference between PFS (P = 0.785) and OS (P = 0.354) for patients who received HRT after debulking surgery or not was not statistically significant.[21] Another study of 24 women with ovarian serous cystadenocarcinoma who started HRT at 21 months (mean value) after surgery, for a median duration of 24 months found their risk for death did not increase

(*RR*: 0.9, 95% *CI*: 0.24–5.08).[22] Moreover, Hinds and Price[23] pointed out that little evidence exists for an obvious effect of estrogen replacement therapy on early-stage EOC.

In 2006, a small-sample study confirmed that OC patients who received HRT therapy had an improved survival rate (*HR* = 0.57; 95% *CI*: 0.42–0.78) and HRT had a protective effect on SOC patients.[24] A later study (an intention-to-treat analysis; *n* = 150) found that OS and PFS were significantly better in the HRT group.[25] In the study, 77% of patients were postmenopausal and 63% had FIGO disease Stage III–IV; 53 (71%) of the HRT patients and 68 (91%) of the control patients died.[25]

Premenopausal women with excised bilateral ovaries might develop menopausal syndrome 2 weeks after the surgery, which will peak in about 2 months and last for 2 years.[26] Adverse effects of HRT therapy are often underemphasized. Recent studies indicated that use of conjugated equine estrogens and synthetic progestin medroxyprogesterone increased the risk of breast cancer (*RR*: 1.26, 95% *CI*: 1.00–1.59)[27] and estrogen without progesterone antagonist increased risks for phlebothrombosis, shock, paralysis, pulmonary embolism, and cardiovascular disease.[28] In our study, two patients discontinued HRT because of breast hyperplasia.

Low-dose, single-agent regimens might decrease adverse effects of HRT. The NCCN guideline on HRT therapy[29] points out that selective estrogen receptor modulators help to maintain benefits for skeleton and lipometabolism without irritating the breasts but cannot alleviate symptoms of vasoconstrictive instability, such as tidal fever. Selective estrogen receptor modulators, including tamoxifen, raloxifene, and toremifene, might be attractive selections for HRT therapy.

Therefore, as maintaining the quality of life and minimizing the physical and psychological adverse effects of treatment are critical aspects of cancer management, patients must receive unbiased information about their individual cancers; in most cases, they can use HRT without any detrimental effect on their survival.

This study found that survival of patients with SOC correlates inversely with disease stage and resection status and was not significantly associated with the type of treatment. However, this study was a single-center, retrospective investigation, which might affect its homogeneity. Multicenter, randomized prospective studies are needed to verify and add insight to our findings.

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Conflicts of interest

There are no conflicts of interest.

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