Impact of post-operative hormone replacement therapy on life quality and prognosis in patients with ovarian malignancy

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Abstract. The present study aimed to assess the impact of post-surgical hormone replacement therapy (HRT) on life quality and prognosis in women with ovarian malignancy. HRT (Premarin, Nilestriol and medroxyprogesterone) was administered following surgery in 31 patients with ovarian cancer. A total of 44 ovarian cancer patients of similar age, clinical stage and pathological features did not receive HRT following surgery. The expression of estrogen receptor (ER)-α, ERβ and progesterone receptor (PR) in cancer tissues was detected by immunohistochemical staining. Serum levels of calcitonin (CT) and transforming growth factor (TGF)-α were determined by radioimmunoassay and enzyme-linked immunosorbent assay, respectively. Data were analyzed using Kaplan-Meier survival curves, a log-rank test and a Cox scale risk model. Quality of life was assessed in the patient groups and in healthy post-menopausal women (control) based on a questionnaire developed by the European Organization of Research and Treatment of Cancer (EORTC-C30), as well as our own specific questionnaire. A log-rank test revealed no difference in survival between the patients with and without HRT ($p>0.05$), and a Cox model showed that HRT was not an independent prognostic factor. The accumulated survival rate did not differ significantly based on the expression of ERα, ERβ or PR in patients with or without HRT ($p>0.05$). The serum TGFα levels prior to and following surgery were not significantly different in either of the two patient groups ($p>0.05$). Serum CT levels were higher in patients without HRT at 1.5 years following surgery ($p<0.05$), but no significant difference was found in the serum CT levels of patients receiving HRT. The HRT and non-HRT groups differed significantly with regard to the body and emotional functional sub-scales of the EORTC-C30 ($p<0.05$) and the sex quality and autonomic nerve maladjustment categories of our specific questionnaire ($p<0.05$). Findings of this study showed that HRT administered following surgery exhibited no apparent negative effect on prognosis in patients with ovarian cancer, regardless of ERα, ERβ or PR expression in cancer tissues, and had no effect on serum transforming growth factor (TGF)-α levels. Post-surgical HRT aided in the stabilization of serum CT levels and improved the quality of life in these patients.

Introduction

Epithelial ovarian cancer (EOC) (1) is the most common type of ovarian cancer and the leading cause of gynecological cancer-related mortality (2). It typically develops as an insidious disease (1,3,4), with few distinct symptoms until the tumor has become large or disseminated (2). Thus, EOC is not usually diagnosed prior to reaching an advanced stage, when the five-year survival rate is poor (1). Currently, cytoreductive surgery combined with platinum-based chemotherapy is the standard treatment for patients with ovarian cancer (5). However, in patients of child-bearing age, cytoreductive surgery for a malignant ovarian tumor frequently results in the loss of ovarian function and menopausal symptoms. The symptoms of iatrogenic menopause are usually significantly more intense than those of natural menopause, due to the sudden onset of symptoms at a younger age and their effects on common physical and psychological problems of cancer therapy, including body image issues and sexual dysfunction (6). The oncologist may consider hormone replacement therapy (HRT) for these patients, but concerns regarding the safety of HRT following ovarian malignancy have rendered the advisability of its post-surgical use controversial.

Concerns center primarily on the potential stimulation of residual cancer by HRT and the induction of new hormone-dependent disease (7). Consistent with the female genital tract being a target organ of hormones, epidemiological investigations have suggested that malignancies of the

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genital tract may be associated with hormonal stimuli, and significantly higher risks for breast, endometrial and ovarian epithelium cancer have been observed in post-menopausal women ingesting long-term oral estrogen (8-11). *In vitro* experiments have yielded inconsistent results regarding the estrogen stimulation of cancer cell proliferation. Certain *in vitro* experiments have shown that estrogen is capable of stimulating the proliferation of malignant cells (12,13), whereas results of other studies showed tumor cell growth inhibition by estrogen (14), and yet other authors found no effect of estrogen on malignant cell growth (15,16). Furthermore, current scientific evidence does not show HRT to adversely affect outcome in patients following treatment for ovarian malignancy (6,16).

Since maintaining quality of life and minimizing the physical and psychological impacts of treatment side effects are crucial factors in cancer care, it is imperative to provide patients with unbiased information regarding whether their individual cancer status allows them to use HRT without any detrimental effects on their survival. However, currently there is no sufficient evidence from large-scale multicenter random prospective clinical trials to clearly indicate that HRT is safe and that the prognosis and tumor recurrence rate may not be affected by HRT. This study analyzed the effect of post-operative HRT on the prognosis and relevant clinical factors in patients with ovarian cancer.

Patients and methods

Patients. The medical cases included in this study comprised inpatients/outpatients with a pathologically confirmed diagnosis of ovarian cancer who were registered at the Department of Gynecological Oncology of the Cancer Hospital of Guangxi Medical University, China, between August 1999 and June 2003. The study was endorsed by the Ethics Committee of the Guangxi Medical University. The patients received an explanation of the aims of the study, provided signed informed consent and understood that they had the option of withdrawing from the study at any time without affecting their oncological or general medical treatment. The patients received cytoreductive surgery (total hysterectomy plus bilateral appendix resection), followed by 6-8 courses of platinum-based combination chemotherapy.

At 20 days following cytoreductive surgery, 90 patients were randomly divided into a HRT group and a non-HRT group (n=45 each), using the envelope method. A total of 15 patients were lost at follow-up or were non-compliant within 6 months. Of the remaining 75 patients, 31 patients, with an average age of 40.3 years (range 20-45), were in the HRT group. These patients included 21 cases of serous cystadenocarcinoma and 10 cases of mucinous cystadenocarcinoma, 11 of which were International Federation of Gynecology and Obstetrics (FIGO) stage Ib-II, and 20 of which were stage III. In the non-HRT group, the 44 patients, with an average age of 42.9 years (range 20-45), presented with 26 serous cystadenocarcinoma cases and 18 mucinous cystadenocarcinoma cases, 10 of which were FIGO stage Ib-II and 34 of which were stage III. No significant difference was found with regard to age, pathological type, differentiation level, clinical stage or treatment the between HRT and non-HRT groups.

The patients were regularly reviewed every 6 months by general examination, pelvic examination, CA125 assay, liver and kidney function tests, pelvic ultrasound scan and breast check. Follow-up lasted from 10 to 43 months (average 31.4 months).

Another 77 female individuals who were visiting the hospital for a routine health examination were selected as controls for the questionnaire study on quality of life. These individuals were all post-menopausal, 53-67 years of age, and had never been treated with HRT.

HRT. The 31 patients in the HRT group were randomly divided into two treatment groups of similar age, clinical stage and pathological type. One treatment group (n=14) received Premarin 0.625 mg/d + medroxyprogesterone 4 mg/d; the other (n=17) received nylestriol 2.5 mg/15 d + medroxyprogesterone 4 mg/d. HRT continued for 6-43 months (average 28.7), with no significant difference in the treatment period between the two groups (Chi-square test, $p>0.05$). To encourage compliance, certain oncologists, independent of this study, were assigned to guide the patients throughout the treatment period. Patients lost to follow-up and those who were non-compliant within 6 months were termed as withdrawn and were not included in the results and analysis.

Specimen collection and processing. The first blood sample (fasting) was obtained 1 week following the end of menses, in the morning prior to surgery. The second blood sample (fasting) was drawn 20 days following the operation. At that point, HRT was commenced. The third blood sample (fasting) was obtained 6 months or 1 year after HRT had begun. The serum was separated by centrifugation and stored at -20˚C until analyzed for serum calcitonin (CT) and transforming growth factor (TGF)-α.

Tissue samples obtained during surgery were paraffin-embedded and sectioned using a microtome. One slide was stained with hematoxylin and eosin for histopathological examination, and three additional slides were prepared for immunohistochemical staining of estrogen receptor (ER)-α, ERβ and progesterone receptor (PR), respectively.

Determination of CT and TGFα. Serum CT was determined using a CT RIA kit (Beijing Meidike Biotechnology, Beijing, China), and TGFα was determined using an ELISA kit (Promega, Madison, WI, USA), according to the respective manufacturers' instructions.

Detection of ERα, ERβ and PR expression. Immunohistochemical staining of tissue slides for the expression of ERα, ERβ and PR was performed using a streptavidin-peroxidase staining kit (Fuzhou Maixin Biotechnology Development, Fuzhou, China) according to the manufacturer's instructions. Anti-PR antibody was purchased from Fuzhou Maixin Biotechnology Development. Anti-ERα and -ERβ antibodies were provided by Professor Lihui Wei (People's Hospital, Beijing University, Beijing, China).

The immunohistochemical staining intensity of tumor and endothelial cells of the tissues was scored in a blinded manner by two experienced pathologists, using the following scale: 3, intracytoplasmic granules strongly stained brown;

Table I. Effect of hormone replacement therapy (HRT) on prognosis, according to pathology.

Pathology	Cases (n)	Average survival time (days)		Mid-survival time (days)		P-value
		HRT	Non-HRT	HRT	Non-HRT	
Type						
Serous	47	1134±34	1165±35	1097±62	1142±55	0.702
Mucous	28	1016±97	1031±73	986±152	994±67	0.678
Stage						
I-II	21	1108±59	1084±46	1048±66	996±88	0.988
III	54	1062±62	1018±54	998±71	1000±61	0.767

2, intracytoplasmic granules stained a medium brown; 1, intracytoplasmic granules weakly stained light brown; and 0, intracytoplasmic granules not stained distinctly compared with cytoplasm. The cells were counted under a high-power field, and the rate of positive cells was calculated as the number of positive cells divided by the total number of cells. The positive rates were assigned points as follows: <5%, 0 points; 6-25%, 1 point; 26-50%, 2 points; 51-75%, 3 points; and >75%, 4 points. The staining intensity score was multiplied by the positive rate points to yield the total score for each field. For each slide, five high-power fields were examined, and the average of the five total scores was taken as the final score. Slides with a final score of 0-2 were considered to be negative, and slides with a final score >2 were considered to be positive.

Assessment of quality of life. Patient quality of life was assessed using two questionnaires: the EORTC-C30, developed by the European Organization for Research and Treatment of Cancer (17), and the GMU-Gynae Index (18), a specific life quality questionnaire developed by the Department of Gynecology, Guangxi Medical University, China. The EORTC-C30 consists of five functional sub-categories (five body function categories, two role categories, two cognition categories, four emotion categories and two social function categories), three symptom subscales (fatigue, pain, nausea and vomiting, shortness of breath, insomnia, loss of appetite, constipation and diarrhea), and a scale of general health status. The GMU-Gynae Index assesses sexual life quality (sexual difficulties, emotional exchange between the couple, regression of sexual life and sexual desire), symptoms of lower urinary tract infection (urethral burning and frequent urination), autonomic dysfunction (itchy skin, dry skin and formication).

Following 6-12 months of HRT, the patients in the HRT and non-HRT groups were asked by their assigned oncologists to personally respond to the questions. Spouses were allowed to substitute only when the patient was incapacitated.

Statistical data analysis. Survival data were analyzed using Kaplan-Meier survival curves and the log-rank test. The Student's t-test was used to analyze averaged data, and the Chi-square test was used for ratio comparisons. All analyses were performed with SPSS.10 software (Statsoft, USA). P<0.05 was considered to be statistically significant.

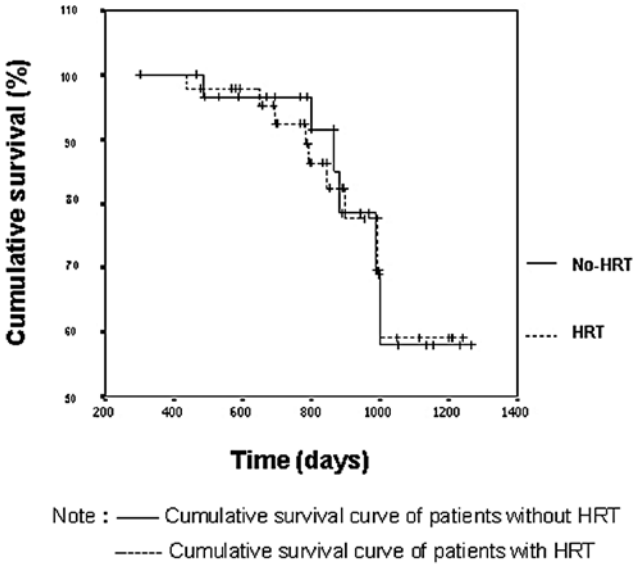

Figure 1. Kaplan-Meier plot of overall survival of ovarian cancer patients with and without hormone replacement therapy (HRT). A total of 31 patients with ovarian cancer were administered HRT following surgery (HRT), and 44 ovarian cancer patients did not receive HRT following surgery (Non-HRT). This figure shows that there is no statistically significant difference in patient survival between the two groups (log-rank test, p=0.9399). The average survival period was 1108±52 days in the HRT group and 1086±43 days in the non-HRT group.

Results

Effect of HRT on the prognosis of malignant ovarian cancer. The Kaplan-Meier curves showed that the cumulative survival was similar between the HRT and non-HRT groups. The average survival period was 1108±52 days in the HRT group and 1086±43 days in the non-HRT group (Fig. 1), with no statistically significant difference between the two groups (log-rank test, p=0.9399). No significant difference was found in clinical stage or pathological type between the two groups (log-rank test, p>0.05; Table I).

Factors with a possible effect on the prognosis of malignant ovarian tumors, including age, clinical stage, pathological type, greater omental metastasis, retroperitoneal lymph node metastasis, pleural effusion, ascites, HRT and postoperative residual lesion size, were analyzed according to a Cox model. At a level of a=0.05, only post-operative

Table II. Survival time in patients with and without hormone replacement therapy (HRT), according to the expression of estrogen receptor (ER)-α, ERβ and progesterone receptor (PR).

Expression	Cases (n)	Average survival time (days)		P-value
		HRT	Non-HRT	
ERα (+)	60	1008±75	944±122	0.559
ERα (-)	15	966±99	961±89	0.493
ERβ (+)	44	1040±70	1102±86	0.856
ERβ (-)	31	980±100	957±114	0.852
PR (+)	53	1220±42	1101±54	0.351
PR (-)	22	955±93	936±87	0.912

residual size was identified as an influential factor in the Cox model.

No breast disease or breast cancer was observed in either the HRT or non-HRT group at the end of follow-up.

Relationship between ERα, ERβ, and PR expression and survival during HRT. The log-rank analysis revealed no significant difference ($p>0.05$) in cumulative survival time among patients with different ERα, ERβ and PR expression status (Table II).

Effect of HRT on serum TGFα and serum CT levels. Although serum TGFα levels declined following surgery in the HRT and non-HRT groups ($p<0.05$), these levels did not differ significantly ($p>0.05$) between the two groups prior to surgery, following surgery, or 6-12 months following surgery (Table III).

As shown in Table IV, no significant difference was found in the serum CT levels between the HRT and non-HRT groups prior to or following surgery ($p>0.05$). At 6-12 months following surgery, the serum CT levels in the HRT group was higher than those in the non-HRT group ($p<0.05$). However, the serum CT levels in the HRT group did not differ among the three time periods ($p>0.05$).

Effect of HRT on quality of life. As shown in Table V, no significant differences were observed in the EORTC-C30 cognition, role and social function scores among the HRT, non-HRT and normal menopause groups ($p>0.05$), in contrast to the physical function and emotional function scores ($p<0.05$). The EORTC-C30 symptom sub-scale score differed significantly between the HRT and non-HRT groups ($p<0.05$), but not between the HRT and normal menopause groups ($p>0.05$). The urethral symptom score was not significantly different among the three groups ($p>0.05$). A difference was found between the HRT and non-HRT groups with respect to general health status ($p<0.05$). However, no difference was noted between the non-HRT and normal menopausal groups ($p>0.05$).

The GMU-Gynae index sexual behavior score of the HRT group was significantly different from that of the non-HRT group ($p<0.05$), but was not different from that of the normal menopause group ($p>0.05$). The GMU-Gynae index autonomic dysfunction score of the HRT group differed significantly from the scores of the non-HRT and normal menopause groups ($p<0.05$), with no difference between the scores of the two control groups ($p>0.05$).

Discussion

Patients with ovarian cancer who receive cytoreductive surgery suffer from post-menopausal symptoms due to the sudden reduction in estrogen levels and loss of ovarian function. In theory, HRT may improve this condition, but there remains controversy in the clinical arena. A number of *in vitro* experiments have suggested that estrogen is capable of stimulating the proliferation of ovarian cancer cells, and certain epidemiological studies have reported that HRT increases the risk of ovarian and breast cancer, creating concern about the effect of HRT on the prognosis of patients. Hopkins *et al* (6), after a systematic evaluation, concluded that HRT has no significant impact on recurrence, deterioration or mortality of ovarian cancer. These authors suggested that HRT improved the quality of life and should be useful for patients with menopausal syndrome.

As with other studies (19), we found no significant difference in the cumulative survival period between HRT and non-HRT groups ($p>0.05$), indicating that post-surgery HRT has no negative impact on tumor-free survival time, overall survival time or overall survival rate in patients with ovarian cancer.

Even after applying a Cox model risk analysis to account for other factors that may affect survival, HRT was not a significant factor in determining prognosis. Due to the limited number of cases in our study and the relatively short follow-up duration, more case observations with a longer follow-up period would be beneficial for confirming our findings.

Our previous *in vitro* study (20) has shown that exogenous estrogen stimulated the proliferation of ER-positive, but not ER-negative, tumor cells. The response of hormone receptors on cancer cells to exogenous estrogen may eventually cause a biological behavior change (21), but no concrete conclusion has been reached regarding receptor and cell responses to the clinical application of HRT. In the present study, the cumulative survival period did not differ significantly between HRT and non-HRT patients, regardless of the expression of ERα, ERβ or PR in the tumor tissues, indicating no direct correlation between ERα, ERβ or PR expression and HRT effects. This lack of correlation may be explained by the fact that the hormone concentrations used in HRT are within normal ranges, resulting in failure to inhibit or stimulate tumor cell proliferation in *in vitro* experiments.

Findings of our previous *in vitro* study (20) have shown that the estrogen stimulation of cancer cell proliferation may occur via a TGFα autocrine pathway in tumor cells. However, the present study failed to correlate HRT with any change in serum TGFα concentration or prognosis. This failure may be attributed to the fact that TGF is only a minor player in the highly complicated system of intracellular signal crosstalk *in vivo*. Alternatively, as the estrogen and progesterone levels used in HRT are within the normal concentration ranges, they may be insufficient to evoke the TGF pathway in the

Table III. Effect of hormone replacement therapy (HRT) on the serum transforming growth factor (TGF)-α levels.

Treatment group	Cases (n)	Serum TGFα (ng/ml)		
		Prior to surgery	Following surgery	6-12 months following surgery
HRT	31	30.0±22.6	12.7±7.3	12.6±9.8
Non-HRT	44	27.0±19.9	12.6±7.7	11.5±8.7[a]

[a]p<0.05.

Table IV. Changes in serum calcitonin (CT) levels according to hormone replacement therapy (HRT).

Treatment group	Cases (n)	Serum CT (μg/l)		
		Prior to surgery	Following surgery	6-12 months following surgery
HRT	31	93.43±14.38	91.91±10.52	90.09±18.46
Premarin	14	95.88±15.19	97.65±12.36	98.14±10.63
Nylestriol	17	92.40±16.57	93.18±10.01	91.60±14.77
Non-HRT	44	94.71±11.27	92.18±14.90	141.26±13.42

Table V. EORTC-C30 and GMU-Gynae index scores in the hormone replacement therapy (HRT), non-HRT and normal menopause groups.

Parameter	Normal menopause (n=77)	Ovarian malignancy	
		HRT (n=31)	Non-HRT (n=44)
Functional subscale			
Body function	1.03±0.39	1.84±1.50	12.69±10.20
Role function	1.30±0.92	3.23±1.81	13.54±3.91
Emotion function	9.94±7.03	1.45±0.82	12.90±11.61
Cognition function	2.81±0.82	3.03±0.84	4.93±1.61
Social function	1.24±0.22	2.42±1.95	4.44±2.03
Symptom subscale	2.59±2.02	6.82±2.61	21.82±10.85
General condition	28.21±9.64	27.51±11.3	13.84±6.42
Sexual behavior	0.95±0.56	1.05±0.74	10.10±3.21
Urinary symptoms	2.40±1.21	2.35±1.73	3.55±1.58
Autonomic dysfunction	1.82±4.87	1.77±1.08	13.09±4.30

few cancer cells remaining following adequate cytoreductive surgery and multi-course chemotherapy, as was the case in our study.

Bodurka-Bevers (22) reported that approximately 21% of patients with a malignant ovarian tumor suffered from depression and approximately 29% from anxiety. The ability of HRT to improve the quality of life for these patients remains controversial (23). In the present study, the EORTC and GMU-Gynae index results showed improved physical functions and emotional symptoms after HRT, and the general life quality in the HRT group was better than that in the non-HRT group. HRT also markedly improved sexual performance and automatic dysfunction, as in other reports. The primary concern about life quality for ovarian cancer patients was reported to be sexual dissatisfaction, followed by body state changes induced by surgery, chemotherapy and radiotherapy (24). By improving physical function, emotional symptoms, sexual quality and autonomic dysfunction, HRT may greatly enhance the quality of life for patients with ovarian cancer.

Epidemiological investigations (25,26) have shown that long-term oral estrogen may increase the risk for breast cancer. We did not confirm this in our study, perhaps due to the relatively short follow-up period and simultaneous progesterone usage.

The current literature (27,28) does not support the view that HRT facilitates the development and recurrence of ovarian cancer. Thus, ovarian malignancy after clinical management of cytoreduction and adequate chemotherapy is not a contra-indication for HRT. HRT may be a good option for patients with serious symptoms of menopause and osteoporosis. Nevertheless, the use of HRT still lacks the support of large-scale multi-center prospective double-blind randomized studies, particularly regarding its effect on tumor growth in patients with gross residual tumor. Therefore, care should be taken to limit the use of HRT as much as possible to patients with satisfactorily controlled ovarian malignancy. The suitable duration of HRT is currently under debate, with no definite conclusions based on large-scale studies. Consideration should be given to an individual's specific clinical circumstances as well as the severity of menopause symptoms. Due to the indefinite conclusions regarding its impact on ovarian cancer and its association with the long-term risk for breast cancer, HRT should be recommended only when the patient has been adequately informed as to whether their individual cancer status allows them to use HRT.

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References

1. Williams T, Toups KL, Saggese D, *et al*: Epithelial ovarian cancer: disease etiology, treatment, detection, and investigational gene, metabolite, and protein biomarkers. J Proteome Res 6: 2936-2962, 2007.
2. Jacobs IJ and Menon UM: Progress and challenges in screening for early detection of ovarian cancer. Cell Proteomics 3: 355-366, 2004.
3. Mok SC, Kwonga J, Welch WR, *et al*: Etiology and pathogenesis of epithelial ovarian cancer. Dis Markers 23: 367-376, 2007.
4. Lawrenson K and Gayther SA: Ovarian cancer: a clinical challenge that needs some basic answers. Plos Med 6: 126-129, 2009.
5. Deraco M, Baratti D, Laterza B, *et al*: Advanced cytoreduction as surgical standard of care and hyperthermic intraperitoneal chemotherapy as promising treatment in epithelial ovarian cancer. Eur J Surg Oncol 37: 4-9, 2011.
6. Hopkins ML, Fung MF, Le T, *et al*: Ovarian cancer patients and hormone replacement therapy: a systematic review. Gynecol Oncol 92: 827-832, 2004.
7. Singh P and Oehler MK: Hormone replacement after gynaecological cancer. Maturitas 65: 190-197, 2010.
8. Chikman B, Lavy R, Davidson T, Wassermann I, Sandbank J, Siegelmann-Danieli N and Halevy A: Factors affecting rise in the incidence of infiltrating lobular carcinoma of the breast. Med Assoc J 12: 697-700, 2010.
9. Braem MG, Onland-Moret NC, van den Brandt PA, *et al*: Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. Am J Epidemiol 172: 1181-1189, 2010.
10. Zhou B, Sun Q, Cong R, Gu H, Tang N, Yang L and Wang B: Hormone replacement therapy and ovarian cancer risk: a meta-analysis. Gynecol Oncol 108: 641-651, 2008.
11. Hinds L and Price J: Menopause, hormone replacement and gynaecological cancers. Menopause Int 16: 89-93, 2010.
12. Taube M, Hockenstrom T and Isakasson M: Low sex steroid environment affects survival and steroid secretion of ovarian tumor cell in primary cultures. Int J Oncol 20: 589-594, 2002.
13. Mabuchi S, Ohmichi M, Kimura A, *et al*: Estrogen inhibits paclitaxel-induced apoptosis via the phosphorylation of apoptosis signal-regulating kinase 1 in human ovarian cancer cell lines. Endocrinology 145: 49-58, 2004.
14. Seeger H and Mueck AO: The effect of estradiol metabolites and progestogens on the proliferation of human ovarian cancer cells. Panminerva Med 48: 13-17, 2006.
15. Zheng H, Kavanagh JJ and Hu W: Hormonal therapy in ovarian cancer. Int J Gynecol Cancer 17: 325-330, 2007.
16. Levgur M: Estrogen and combined hormone therapy for women after genital malignancies. J Reprod Med 49: 837-848, 2004.
17. Aaronson NF, Ahmedzai S, Bergman B, *et al*: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85: 365-376, 1993.
18. Zhong-Mian P, Li L, Xinqiu C, *et al*: Effect of HRT for the quality of life in patients with gynecologic malignancies of reproductive age. Guangxi Yikedaxue Xuebao 23: 921-923, 2006.
19. Eeles RA, Tan S, Wiltshaw E, *et al*: Hormone replacement therapy and survival after surgery for ovarian cancer. BMJ 302: 259-262, 1991.
20. Li L, Gao K, Zhang W, *et al*: Effects of estradiol and progesterone on ovarian cancer cell line. Zhonghua Zhongliu Zazhi 25: 553-554, 2003.
21. Landon SP, Crew AJ, Ritchie AA, *et al*: Growth inhibition of oestrogen receptor-positive human ovarian carcinoma by anti-oestrogens in vitro and in a xenograft model. Eur J Cancer 30A: 682-686, 1994.
22. Bodurka-Bevers D, Basen-Engquist K, Carmack CL, *et al*: Depression, anxiety, and quality of life in patients with epithelial ovarian cancer. Gynecol Oncol 78: 302-308, 2000.
23. Biglia N, Mariani L, Marenco D, *et al*: Hormonal replacement therapy after gynaecological cancer. Gynakol Geburtshilfliche Rundsch 46: 191-196, 2006.
24. Biglia N, Gadducci A, Ponzone R, *et al*: Hormone replacement therapy in cancer survivors. Maturitas 48: 333-346, 2004.
25. Wenzel LB, Huang HQ, Armstrong DK, *et al*: Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 25: 437-443, 2007.
26. Ponzone R, Biglia N, Jacomuzzi ME, *et al*: Vaginal oestrogen therapy after breast cancer: is it safe? Eur J Cancer 41: 2673-2681, 2005.
27. Bebar S and Ursic-Vrscaj M: Hormone replacement therapy after epithelial ovarian cancer treatment. Eur J Gynaecol Oncol 21: 192-196, 2000.
28. Ursic-Vrscaj M, Bebar S and Zakelj MP: Hormone replacement therapy after invasive ovarian serous cystadenocarcinoma treatment: the effect on survival. Menopause 8: 70-75, 2001.