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The safety of tibolone in epithelial ovarian cancer patients

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Abstract

Objectives: We evaluated whether tibolone had an adverse effect on the progression free survival and overall survival of epithelial ovarian cancer patients.
Methods: Forty-two tibolone users and 33 non-users who had been surgically managed for epithelial ovarian cancer at Gil Medical Center, Inchon, Korea, from January 1997 to December 2003 were reviewed retrospectively.
Results: There were no statistically significant differences in age, stage, histology, grade and surgical optimality between tibolone users and non-users. The progression free survival at 36 months was 60.0% among the users compared with 61.5% among the non-users ($p = 0.92$). There was also no significant difference in the overall survival between two groups ($p = 0.30$). For stage IIIc patients according to tibolone using, there were no significant differences in the progression free survival ($p = 0.86$) and overall survival ($p = 0.36$) between tibolone users and non-users.
Conclusions: There was no evidence that tibolone had detrimental effects on the progression free survival and overall survival of epithelial ovarian cancer patients. So, tibolone could be used in these patients.

Keywords: Tibolone; Ovarian cancer patients; Survival

1. Introduction

Ovarian cancer is the ninth most frequent cancer and the ninth most frequent cause of cancer death in Korean women [1]. Although the peak incidence of epithelial ovarian cancer is 56–60 years, many cases will occur in premenopausal and perimenopausal women [2]. It results in more death than any other gynecologic malignancies, because its symptoms are nonspecific until metastases have developed [3]. An analysis of the National Cancer Institutes' Surveillance, Epidemiology and End Results (SEER) database revealed that the survival for stage I was 93%, for stage II 70%, for stage III 37%, and for stage IV 25%. Compared with the interval 1983–1987, there was a statistically significant improvement in survival for stages I, III and IV disease [4].

The widely used staging system of International Federation of Gynecology and Obstetrics (FIGO, 1986) [5] can be determined with only exploratory

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laparotomy and thorough evaluation of all areas at risk. In surgically induced menopausal women, it would be wise to develop strategies for the management of menopausal symptoms because the improved survival of ovarian cancer survivors can result in the women calling for increased quality of life.

However, there are only a few studies that have investigated hormone therapy such as estrogen use in women with a history of ovarian cancer [6–8]. Also, the use of tibolone in these patients has not been yet reported as the authors know on.

So, we decided to conduct a retrospective analysis of women with epithelial ovarian cancer, who did or did not receive tibolone, to evaluate whether it had an adverse effect on the progression free survival and overall survival of these patients.

2. Materials and methods

2.1. Subjects

The records of 89 patients who underwent primary surgery for epithelial ovarian cancer at the department of Obstetrics and Gynecology, Gil Medical Center, Inchon, Korea, from January 1997 to December 2003 were reviewed. We reviewed the records including medical charts, electronic records and follow-up data. Stages were assigned according to the surgicopathologic system (FIGO, 1986).

Patients who had ever not taken estrogen derivatives or tibolone prior to treatment, or had the following conditions were included in the study: the patients underwent the usual preoperative workup including computed tomography, gastrofiberscopy and colonofiberscopy; the patients underwent the surgical procedures including peritoneal washing cytologic samples, hysterectomy, bilateral salpingo-oophorectomy, pelvic ± para-aortic lymphadenectomy, omentectomy, appendectomy and tumor debulking, followed by six cycles of cisplatin based chemotherapy based on the pathologic reports; the patients had no histologic evidence of borderline, non-epithelial and metastatic tumor of the ovary; the patients were less than 70 years of age.

All patients fulfilling the above criteria were divided into two groups based on tibolone using. The final analysis included 42 patients in tibolone users and 33 in non-users because five patients received estrogen derivatives as hormone replacement therapy, one patient in tibolone users and three patients in non-users were lost to follow-up, and one patient in tibolone users and four patients in non-users were beyond 70 years of age.

During the period, we recommended tibolone therapy if patients complained about postmenopausal symptoms. Before tibolone therapy, we specifically looked at presence or absence of breast cancer, cardiovascular diseases, diabetes, liver diseases, pulmonary embolus and thrombosis.

All patients receiving tibolone 2.5 mg daily started within 6 months after surgical management, and continued until progression would be diagnosed, or for a minimum of 24 months. Medication such as calcium supplement, antidepressant and antihypertensive drugs were permitted, but hormonal agents such as estrogens and progestogens were not permitted. All patients were followed every 3 months for first 2 years and 6 months thereafter. Physical examination and tumor markers such as CA-125, CEA or CA 19-9 were evaluated at every visit. Computed tomography was checked every 6–12 months or when clinically indicated. Mammogram was checked every 12 months. Second-line chemotherapy was done in all recurrent patients with platinum or other agents based on platinum sensitivity. Secondary cytoreduction was done, if indicated.

2.2. Statistical methods

The primary end point was disease progression and the secondary end point was cancer-related death. All of the end points were calculated from the completion of primary treatment. Frequency distributions were tested using the χ^2-test or linear by linear association. The Independent-Samples t-test was used for variables with a continuous distribution. All significant tests were two tailed, and differences were considered to be statistically significant when p was less than 0.05. The Kaplan–Meier method was employed to calculate the progression free survival and overall survival univariately against prognostic factors. The difference between survival distributions was determined by means of the log-rank test.

The influence of prognostic factors on outcome was assessed in multivariable analysis by the Cox proportional hazards model. In these analyses, only variables

with p-values of less than 0.20 were entered in the model and their relative risk were calculated. All end points were updated in December 2005.

3. Results

3.1. Patient characteristics

All of tibolone users complied with tibolone therapy and experienced relief of postmenopausal symptoms, although three patients complained about weight gain, and three patients bloating. Table 1 shows the characteristics of the two populations. The mean age was 49.0 years for the users and 51.5 years for the non-users; this difference was not statistically significant ($p = 0.26$). Out of the users, 10 (23.8%) were in surgical stage Ia, 4 (9.5%) in stage Ic, 3 (7.1%) in stage IIc, 1 (2.4%) in stage IIIa, and 24 (57.1%) in stage IIIc. Out of the non-users, 10 (30.3%) were in surgical stage Ia, 2 (6.1%) in stage Ic, 2 (6.1%) in stage IIa, 5 (15.2%) in stage IIc, 1 (3.0%) in stage IIIb, and 13 (39.4%) in stage IIIc. The distribution of patients for stage was similar in both the users and the non-users ($p = 0.28$). Serous tumors accounted for 25 (59.5%) of the users and 13 (39.4%) of the non-users, followed by mucinous (users: 8, 19.0% versus non-user: 13, 39.4%), clear cell (users: 5, 11.9% versus non-users: 3, 9.1%), endometrioid (users: 3, 7.1% versus non-users: 2, 6.1%), and others (users: 1, 2.4% versus non-users: 2, 6.1%); this difference was not statistically significant ($p = 0.29$). Grade 3 tumor accounted for 16 (38.1%) of the users and 12 (36.4%) of the non-users, followed by grade 1 (users: 12, 28.6% versus non-users: 12, 36.4%) and grade 2 (users: 14, 33.3% versus non-users: 9, 27.3%); this difference was not statistically significant ($p = 0.75$). The optimal debulking operation with largest residual lesion ≤ 1 cm were completed in 27 (64.3%) of the users and 25 (75.8%) of the non-users. There was no statistically significant difference in surgical optimality between tibolone users and non-users ($p = 0.29$).

Table 1
Patients characteristics

	Tibolone		
	Users ($n = 42$)	Non-users ($n = 33$)	p-value
Mean age (range)	49.0 (23–68)	51.5 (27–68)	0.26
Stage (%)			
Ia	10 (23.8)	10 (30.3)	0.28
Ib	0 (0.0)	0 (0.0)	
Ic	4 (9.5)	2 (6.1)	
IIa	0 (0.0)	2 (6.1)	
IIb	0 (0.0)	0 (0.0)	
IIc	3 (7.1)	5 (15.2)	
IIIa	1 (2.4)	0 (0.0)	
IIIb	0 (0.0)	1 (3.0)	
IIIc	24 (57.1)	13 (39.4)	
Histology (%)			
Serous	25 (59.5)	13 (39.4)	0.29
Mucinous	8 (19.0)	13 (39.4)	
Clear	5 (11.9)	3 (9.1)	
Endomerioid	3 (7.1)	2 (6.1)	
Others	1 (2.4)	2 (6.1)	
Grade (%)			
1	12 (28.6)	12 (36.4)	0.75
2	14 (33.3)	9 (27.3)	
3	16 (38.1)	12 (36.4)	
Optimality (%)			
Optimal	27 (64.3)	25 (75.8)	0.29
Suboptimal	15 (35.7)	8 (24.2)	

3.2. Survival rates

The median length of follow-up was 26 months (range: 14–75 months) in tibolone users and 24 months (range: 14–96 months) in non-users. A total of 16 cases (38.1%) in tibolone users and 12 (36.4%) in non-users had disease progression. The progression free survival at 36 months was 60.0% among the users compared with 61.5% among the non-users, and this difference was not significant (log-rank, $p = 0.92$) (Fig. 1). There was also no significant difference in the overall survival between tibolone users and non-users (log-rank, $p = 0.30$) (Fig. 2). In univariate analysis, stage and surgical optimality were found to be significant prognostic factors on the progression free survival and overall survival. However, there were no significant differences in subgroups according to histology, grade and tibolone using (Table 2).

Multivariate analysis of testing for the differences in progression free survival and overall survival among the subgroups of stage, histology, grade and surgical optimality was performed. The Cox-proportional hazards model showed that surgical optimality was the only independent prognostic factor for progression free survival (HR, 4.63; 95% CI, 1.56–13.76; $p = 0.006$)

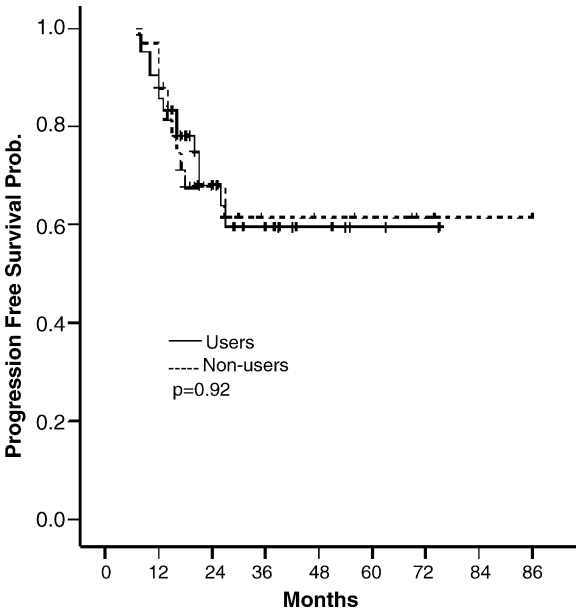

Fig. 1. Progression free survival according to tibolone using.

and overall survival (HR, 8.49; 95% CI, 1.89–38.16; $p = 0.005$).

For stage IIIc patients according to tibolone using, progression free survival and overall survival were calculated by the Kaplan–Meier method. Progression free survival did not differ significantly between tibolone users and non-users (log-rank, $p = 0.86$) (Fig. 3). There was also no significant difference in the overall survival between two groups (log-rank, $p = 0.36$) (Fig. 4).

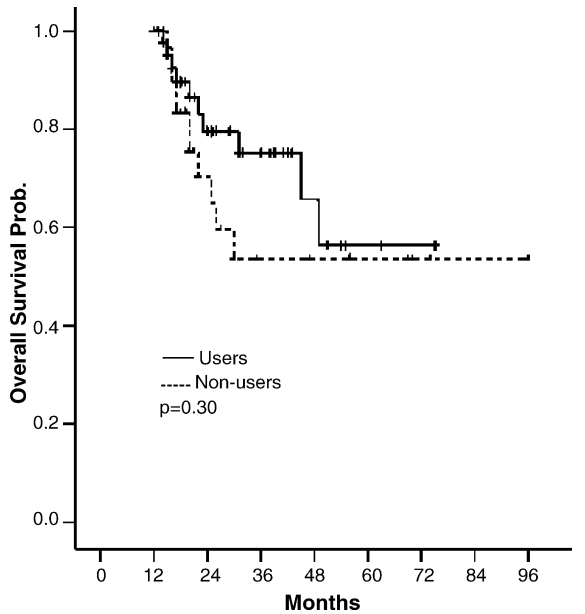

Fig. 2. Overall survival according to tibolone using.

Table 2
Prognostic factors on progression free survival and overall survival: univariate analysis

	Progression free survival (p-value)	Overall survival (p-value)
Stage[a]	0.01	0.01
Histology	0.19	0.09
Grade	0.17	0.11
Optimality	0.000	0.000
Tibolone using	0.96	0.54

[a] Stage; divided into stage I, stage II and stage III.

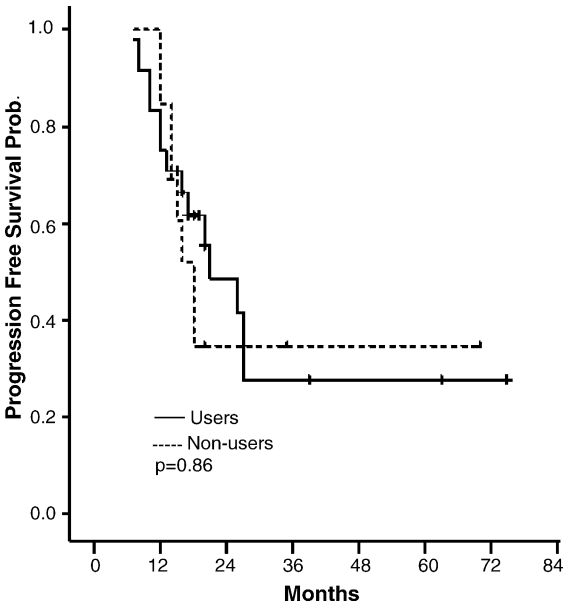

Fig. 3. Progression free survival according to tibolone using in stage IIIc patients.

4. Discussion

Although there have been endless debates whether estrogen replacement therapy (ERT) or hormonal replacement therapy (HRT) increases the risk of epithelial ovarian cancer [9–11], a few studies have not revealed that ERT had adverse effects on the ovar-

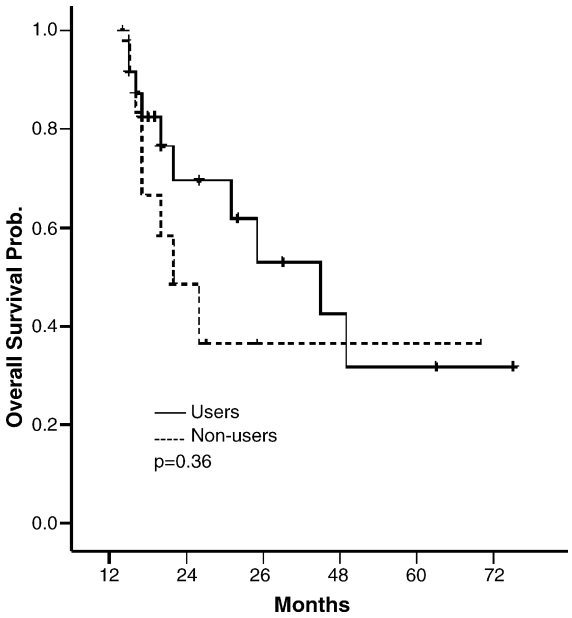

Fig. 4. Overall survival according to tibolone using in stage IIIc patients.

ian cancer survivors. Eeles et al. found no difference in overall and disease-free survival between women receiving HRT and those who did not in their retrospective analysis [6]. Guidozzi and Daponte performed the only randomized controlled trial in order to determine whether ERT had a negative influence on recurrence and survival in ovarian cancer survivors, and concluded that ERT did not have a negative influence on disease-free interval or overall survival [7]. However, many clinicians have been reluctant to give ovarian cancer survivors estrogen supplementation because of concerns that it would decrease the survival by increasing the risk of relapse of ovarian cancer.

Tibolone, a synthetic steroid whose metabolites have estrogenic, progestogenic, and angrogenic properties, is an alternative to conventional hormone therapy. Although the lack of approval from the Food and Drug Administration (FDA) has restricted its use in the United States, it is widely used in the rest of the world including Korea. A recent systemic review of randomized trials concluded that tibolone significantly reduces vasomotor symptoms and increase bone marrow density (BMD) in postmenopausal women [12]. The data also suggest potential beneficial effects on sexual function, hemostasis and lipid metabolism, but further clarification is required. No increase in the rate of mastalgia or mammographic density with tibolone treatment has been noted in small randomized trials [13,14]. Although the long-term effects of tibolone on reduction of fracture, cognitive function, breast cancer risk, and cardiovascular disease remains unclear, the authors commonly recommended tibolone for gynecologic cancer patients, if indicated.

While action of tibolone on breast cell both benign and malignant are well seen in several experiments which first started in early 1990s, no such effect is shown with tibolone on ovarian cancer cell as yet [15,16]. So, as mentioned earlier, this study was undertaken to evaluate whether tibolone had adverse effects on progression free survival and overall survival in ovarian cancer patients. There was no significant difference in age, stage, histology, grade and surgical optimality between tibolone users and non-users. And there was no statistically significant difference in progression free survival and overall survival between two groups.

This study has important limitations stemming from single institute' experience, its small sample size, lack of questionnaire on improvement of menopausal symptoms and a retrospective analysis. However, the type, dose and duration of HRT were consistent because we used only tibolone 2.5 mg daily as hormone replacement therapy, started within 6 months after surgical treatment, and continued until progression would be diagnosed, or for a minimum of 24 months.

The current study suggests that tibolone could be used in patients who underwent primary surgery for epithelial ovarian cancer and complained about postmenopausal symptoms.

Acknowledgement

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