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Retrospective study of combination chemotherapy with etoposide and ifosfamide in patients with heavily pretreated recurrent or persistent epithelial ovarian cancer

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Objective
This retrospective study is to evaluate the efficacy and toxicity of combination chemotherapy with etoposide and ifosfamide (ETI) in the management of pretreated recurrent or persistent epithelial ovarian cancer (EOC).

Methods
Patients with recurrent or persistent EOC who had measurable disease and at least one chemotherapy regimen were to receive etoposide at a dose of 100 mg/m^2/day intravenous (IV) on days 1 to 3 in combination with ifosfamide 1 g/m^2/day IV on days 1 to 5, every 21 days.

Results
From August 2008 to August 2016, 66 patients were treated with ETI regimen. Most patients were heavily pretreated prior to ETI: 53 (80.3%) patients had received 3 or more chemotherapy regimens. The response rate (RR) of ETI chemotherapy was 18.2% and median duration of response was 6.8 months (range, 0–30). Median survival of all patients was 5 months at a median follow up of 7.2 months. Platinum-free interval (PFI) more than 6 months prior to ETI has statistically significant correlation with overall survival (OS; 9.2 vs. 5.6 months; P=0.029) and RR (34.5% vs. 5.4%; P<0.010). However, treatment free interval before ETI, number of prior chemotherapy regimen, and optimality of primary surgery did not show significant difference for RR or OS. Grade 3 or 4 hematologic toxicities were observed in 7 cases (3%) of the 232 cycles of ETI.

Conclusion
The ETI combination regimen shows comparatively low toxicity and modest activity in heavily pretreated recurrent or persistent EOC patients with more than 6 months of PFI after last platinum treatment.

Keywords: Ovarian cancer; Recurrence; Platinum-free interval

Introduction

Ovarian cancer is a leading cause of death from gynecologic cancers worldwide [1]. The standard treatment is optimal debulking surgery followed by taxane-platinum-based combination chemotherapy regimens for first-line chemotherapy. Despite a high initial response rate (RR) to 1st line chemotherapy, 60–70% patients eventually relapsed [2]. In platinum sensitive recurrence (recurrence more than 6 months after

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last treatment), platinum based combination chemotherapy can be given with more than 60% of response. However, the management of tumor recurrence remains a clinical challenge, since in the platinum-resistant (recurrence less than 6 months) population the chance of response to a secondary treatment is currently less than 20% [3]. Several single chemotherapeutic agents have been used in this setting and have demonstrated modest activity such as topotecan [4,5], gemcitabine [6,7], liposomal doxorubicin [8], oral etoposide [9], and ifosfamide [10]. It cannot be overemphasized the importance of clinical trials to identify agents active in this group of resistant patients.

Etoposide is a semisynthetic glucosidic derivative of podophyllotoxin. The inhibition of DNA topoisomerase II is known to be a major mechanism of action. Ifosfamide is a part of nitrogen mustard's alkylating agents. Very little information is available to combination chemotherapy with etoposide and ifosfamide (ETI) as salvage treatment of epithelial ovarian cancer (EOC) after more than 2 chemotherapy regimens. In various animal tumors, etoposide has shown synergy with cyclophosphamide [11]. Additionally, the combination of ETI has also been demonstrated to be an effective regimen in solid neoplasms such as small cell lung cancer [12]. In EOC, a few phase II studies have been reported. Some indicated reasonable efficacy and another [13] showed dismal results which included only "true" platinum-resistant patients. We also have previously reported the results of phase II study of the combination chemotherapy with ETI in particular in patients with heavily pretreated recurrent EOC [14]. The RR was 18.9%, median duration of response 7 months (range 1–15 months), and 9 months of median survival in the study. It was estimated good treatment option in such patients with modest activity and tolerable toxicity, so the regimen has been incorporated in clinical practice of our institution since 2008. Here we evaluated the efficacy and toxicity of the combination chemotherapy with ETI in real world clinical practice and compared them with those of previous phase II clinical trial setting.

Materials and methods

We used electric medical record data base for EOC treated by ETI at Samsung Medical Center from August 1, 2008 to August 31, 2016. Eligible patients should have measurable disease on computed tomography (CT) or magnetic resonance image (MRI) before administration of ETI. Other eligibility criteria included no previous treatment with either ifosfamide or etoposide, normal end-organ function, white blood count of 3,000/μL or higher, platelet count of 100,000/μL or higher, granulocyte count of 1,000/μL or higher, a serum creatinine within institutional normal limits, hepatic enzymes (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and alkaline phosphatase) less than or equal to 2.5 times the upper level of institutional norm and bilirubin less than or equal to 1.5 times the upper level of institutional norm, and a Eastern Cooperative Oncology Group performance score 0–2. Informed consent was obtained according to the guidelines of our hospital Institutional Review Boards. Patients received ifosfamide 1 g/m^2/day on days 1 to 5 as an intravenous (IV) infusion in 500 mL 5% dextrose solution over 1 hour in association with adequate hydration and mesna uroprotection [15]. Etoposide was given at a dose of 100 mg/m^2/day IV on days 1 to 3 over 1 hour. Cycles were repeated every 3 weeks, while a minimum of 4 courses were given to responders. Delay of treatment was permitted if there was hematological toxicity greater than grade 3 during the previous cycle. Toxicity evaluations were conducted just before next treatment cycle by performing a complete blood count, urinalysis, renal and liver function tests, and a performance status evaluation. Toxicity was defined according to World Health Organization standard criteria. The patients' response to treatment was assessed every 2 or 3 cycles by imaging techniques (CT and/or MRI) and every cycle by cancer antigen 125. The response is confirmed by image analysis according to Response Evaluation Criteria In Solid Tumors criteria [16]. The response duration was defined from the time of partial response (PR) or complete response (CR) to the appearance of progressive disease. Survival was measured from the time of the initiation of ETI therapy to the time of death or to the date of the last contact. We drew a line between sensitive to platinum (recurrence more than 6 months) and resistant (recurrence less than 6 months) according to response showed at platinum-based previous therapy. Treatment-free interval (TFI) prior to ETI is the month(s) from the first day of last chemotherapy cycle to the first day of ETI chemotherapy. Platinum-free interval (PFI) is treatment free interval from first day of last platinum chemotherapy regardless of any lines to first day of ETI. Descriptive summary statistics were used to evaluate demographics and adverse events. Statistical analyses of frequency data were performed by means of the χ^2 test.

Table 1. Characteristics of patients (n=66)

Characteristics	No. of patients (%)
Median age	53
Histology	
Serous	56 (84.9)
Clear cell	3 (4.5)
Mucinous	1 (1.5)
Endometrioid	0 (0.0)
Others	6 (9.1)
FIGO stage	
I	1 (1.5)
II	2 (3.1)
III	60 (90.9)
IV	3 (4.5)
First-line regimen	
Paclitaxel/carboplatin	64 (96.8)
Docetaxel/carboplatin	1 (1.6)
Irinotecan/cisplatin	1 (1.6)
No. of chemotherapy regimen prior to ETI	
1	4 (6.2)
2	9 (13.6)
3	25 (37.8)
4	23 (34.8)
5	5 (7.6)

FIGO, International Federation of Gynecology and Obstetrics; ETI, etoposide and ifosfamide.

Overall survival (OS) and response duration were measured with the Kaplan-Meier method. *P*-value of less than 0.05 was considered as significant. The SPSS 11.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Between August 2008 and August 2016, a total of 66 patients were eligible. The characteristics of the 66 patients are summarized in Table 1. The majority of the patients (84.9%) had high-grade serous type. Sixty patients (90.9%) had initial International Federation of Gynecology and Obstetrics stage III. Median OS for all 66 patients was 5 months (95% confidence interval, 4–8 months; Fig. 1).

Sixty-six patients were evaluable for response by radiologic image. The RR was 18.1% and median duration of response

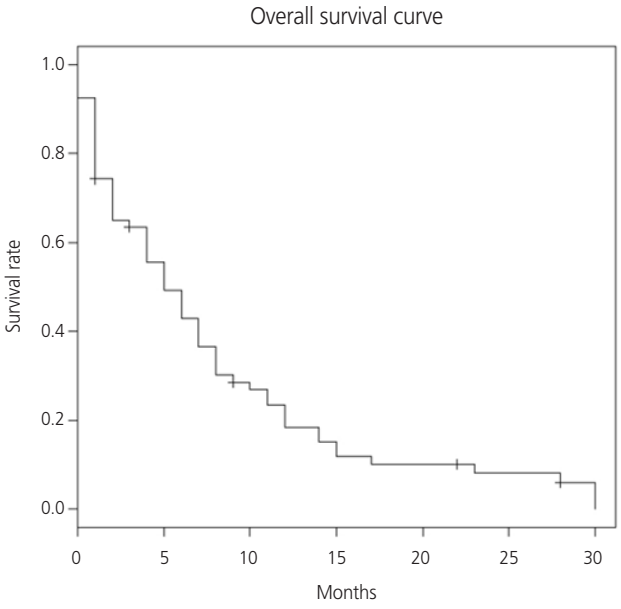

Fig. 1. Overall survival of patients who received etoposide and ifosfamide.

was 6.8 months (range, 0–30). There were 3 patients (4.5%) with CR; 9 patients (13.6%) showed a PR, 2 (3.0%) showed stable disease and 51 (77.2%) progressed. Three patients who showed CR. Table 2 shows outcome according to clinical factors after ETI. The RR of patients with TFI ≥6 months was about 2 times higher than that with TFI <6 months without statistical significance: 42.8% (3/7) with TFI ≥6 months and 15.2% (9/59) with TFI <6 months respectively (*P*=0.073). Median survival also was not significantly different by TFI (7.6 months with TFI and >6 and 7.2 months with TFI <6 months, respectively, *P*=0.952). Number of prior chemotherapy regimen, optimality of primary surgery also did not show difference for RR or OS. Interestingly, only PFI prior to ETI chemotherapy exhibited statistically different RR and OS to ETI chemotherapy. Prior to ETI chemotherapy, 29 (43.9%) patients showed PFI more than 6 months (Table 2). Ten (34.5%) of these 29 patients responded to ETI chemotherapy. In contrast, 2 (5.4%) of 37 patients who showed less than 6 months of PFI responded to ETI chemotherapy (*P*<0.01). In addition, there were statistically significant correlations between OS and PFI >6 months before ETI chemotherapy (9.2 vs. 5.6 months; *P*=0.029, Table 2 and Fig. 2).

A total of 232 courses of ETI regimen were administered to the patients. Table 3 shows the toxicity profile. There was no treatment related death. The grade 3–4 hematological toxicity

Table 2. Outcome according to clinical factors

Clinical factors	No. of patients	RR, No. (%)	*P*-value	Mean OS (mon)	*P*-value
TFI before ETI					
TFI <6	59	9 (15.2)	0.07	7.2	0.95
TFI >6	7	3 (42.8)		7.6	
Optimality of primary surgery					
Optimal	41	7 (17.1)	0.76	7.8	0.47
Suboptimal	25	5 (20.0)		6.5	
Platinum free interval					
<6	37	2 (5.4)	<0.01	5.6	0.03
≥6	29	10 (34.5)		9.2	
Prior chemotherapy regimen					
<4	38	4 (10.5)	0.06	7.4	0.92
≥4	28	8 (28.5)		7.0	

RR, response rate; OS, overall survival; TFI, treatment-free interval; ETI, etoposide and ifosfamide.

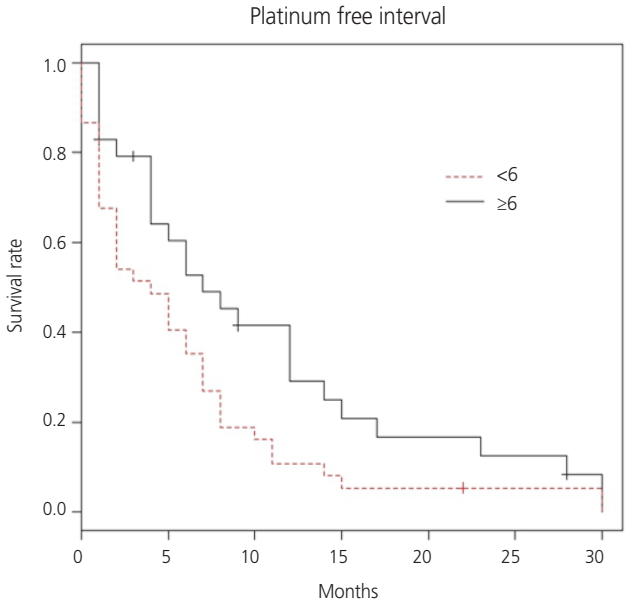

Fig. 2. Overall survival in the subdivided groups of patients by platinum-free interval.

was observed in 7 of 232 cycles (3.0%). There were 4 grade 3–4 gastrointestinal toxicity (severe vomiting) and 2 grade 3–4 renal toxicity. Other toxicities were negligible.

Discussion

This is a single institutional retrospective study in real world clinical practice setting that evaluated the efficacy and toxicity of ETI regimen for heavily pretreated patients with recurrent or persistent EOC. We have previously published the results of ETI chemotherapy in these patients in phase II clinical trial [14]. The RR of 18.9% and 9 months of median survival were regarded as modest activity and it can be a good treatment option in these patients together with tolerable toxicity. So, the regimen has been incorporated in clinical practice of our institution since 2008, out of clinical trial setting. It might be worth to evaluate the efficacy and toxicity of the regimen in real world clinical practice and compare them with those of previous phase II clinical trial since these 2 conditions have different settings: clinical trials are performed with more strict inclusion criteria, less flexibility of each physician's discretion for treatment, and more careful monitoring of patients etc. than real world clinical practice. So, it is possible that different results were observed in real world clinical practice compare to clinical trial and the new treatment could not be incorporated into real world clinical practice sometimes. For example, randomized clinical trials of intraperitoneal chemotherapy demonstrated that it was superior to IV chemotherapy in OS of ovarian cancer patients, but it has not been widely accepted in real world clinical practice due to problem of toxicity management [17]. Therefore, we performed a retrospective analysis of ETI chemotherapy after incorporation of the regimen into real world clinical practice.

In regard to outcome of ETI chemotherapy, RR was 18.2% in this study similar to 18.9% in previous clinical trial [14], but CR was observed in 3 patients in the current study compare

Table 3. Toxicity of etoposide and ifosfamide regimen according to World Health Organization criteria

Toxicities	Grade (% of cycles affected)				
	0	1	2	3	4
Hematologic toxicities	186 (80.2)	23 (9.9)	16 (6.9)	7 (3.0)	0 (0.0)
Neutropenia	227 (98.0)	0 (0.0)	2 (0.8)	3 (1.2)	0 (0.0)
Anemia	197 (84.9)	20 (8.6)	13 (5.6)	2 (0.8)	0 (0.0)
Thrombocytopenia	226 (97.6)	3 (1.2)	1 (0.4)	2 (0.8)	0 (0.0)
AST/ALT	232 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea/vomiting	220 (94.9)	1 (0.4)	7 (2.9)	1 (0.4)	3 (1.4)
BUN/Cr	227 (97.8)	3 (1.4)	0 (0.0)	1 (0.4)	1 (0.4)

Values are presented as number (%).
AST, aspartate transaminase; ALT, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine.

Table 4. The characteristics of the patients who showed complete response after etoposide and ifosfamide

Histology	No. of prior chemotherapy regimen	FIGO stage	Initial platinum sensitivity	Optimality of primary surgery	TFI before ETI (mon)	Platinum free interval before ETI (mon)	Previous line treatment	ETI cycles	OS (mon)
Transitional	4	IIIc	Yes	Suboptimal	0	14	PC → PC→ ToC → D	6	30
Serous	3	IIIc	No	Optimal	0	16	PC → Topotecan → D	6	28[a]
Serous	5	IV	No	Optimal	5	15	PC → PC → ToC → DC → PLD	6	3[a]

ETI, etoposide and ifosfamide; FIGO, International Federation of Gynecology and Obstetrics; TFI, treatment-free interval; OS, overall survival; PC, paclitaxel/carboplatin; ToC, topotecan/carboplatin; D, docetaxel; DC, docetaxel/carboplatin; PLD, pegylated liposomal doxorubicin.
[a]Alive.

to no CR in previous one. Duration of response was similar (7.0 vs. 6.8 months), but OS was worse in this study (5.0 months) than previous one (9.0 months). Toxicity profile was also similar in this study (Table 3).

No prognostic parameter affecting OS was demonstrated in previous study. In previous our study [14], there was a trend for correlation with OS and platinum sensitivity in first-line chemotherapy without statistical significance (median survival, 11 vs. 6 months; P=0.064). Also in this study, we did not observe correlation between OS and initial platinum sensitivity (11.5 vs. 6.4 months; P=0.154, data not shown). Interestingly, however, we found PFI more than 6 months (from last dose of platinum to start of ETI chemotherapy regardless of non-platinum regimen used during the period) exhibited survival advantage (9.2 vs. 5.6 months; P=0.029) as well as higher RR (34.5% vs. 5.4%; P<0.01) in this study. Notably, all 3 patients who showed CR had long PFI (14, 15, and 16 months) and they exhibited favorable survival. One patient died 30 months after ETI chemotherapy and 2 patients are alive until last follow up (28 and 3 months) (Table 4).

The PFI is well known the most important predictive factor of a response to subsequent lines of chemotherapy and the most important prognostic factor for progression-free and OS in patients with recurrent EOC [18]. In this study, we also demonstrated PFI was strong predictor for survival advantage as well as good response to ETI chemotherapy (Table 2). The molecular mechanism for better outcome of long PFI has been extensively investigated. Among the studies, germline BRCA mutation was most frequently reported to be associated with platinum sensitivity and better survival [19]. In the current study, we could not confirm such a correlation since we unfortunately did not perform mutational study for *BRCA* gene in most of our patients. In addition, it has been also reported that prolonged PFI by itself could make re-sensitize platinum treatment in several reports [20-22]. Although mode of action mechanism may be different, prolonged PFI could sensitize ETI chemotherapy. Therefore, ETI regimen could be administered in patients with EOC pretreated 3 or more platinum chemotherapy showing progression more than 6 months after last dose of platinum chemotherapy (or regardless of

non-platinum regimen during this interval). In this condition, we can expect 34.5% RR and 9.2 months of median survival.

Several reports including ours have been published on ETI regimen in recurrent EOC [13,23-26]. It has been reviewed by Kang et al. [14] Most of them used IV etoposide and ifosfmaide, but 2 investigators used oral etoposide and IV ifosfamide. RR was 0–26%. Median duration of response was 6–9 months. Median survival was 7–13 months. The indications were different in each study so we could not compare the results directly, but efficacies and toxicities seem to be similar. In the current study, we demonstrated that the patients who had long PFI showed relatively good response (10 of 29, 34.5%) and long OS (9.2 months) to ETI chemotherapy.

Aside from response, other factors may affect the decision to select a regimen in these heavily pretreated patients. For example toxicity profile, quality of life, ease of administration, cost issues, and residual toxicity from prior therapy [27]. In platinum-resistant patients, retreatment with a platinum compound is not recommended. Options include treatment with a recurrence regimen that does not contain platinum or supportive-palliative care. Several recurrence agents show similar effect as single regimen: topotecan, 20% [4]; gemcitabine, 19% [7]; vinorelbine, 20% [28]; liposomal doxorubicin, 26% [8]; oral etoposide, 27% [9]; and ifosfamide, 12% [10]. Ifosfamide is the classical group of alkylating chemotherapeutic agent, that produces renal toxicity [15], but toxicity could be overcome using mesna for uroprotection and massive hydration. Together with etoposide, it produces an acceptable toxicity level with grade 3 or 4 neutropenia most common in 3% of the patients in this study (Table 3). One patient showed acute renal failure after ETI 2 cycles, but recovered without any sequelae after supportive care and completed 6 cycles until disease progression. Considering 53 of the 66 (80.3%) patients who were treated in this study had already been administered with 3 or more regimens before ETI, the toxicity was tolerable and efficacy including RR and OS of this study were modest. Therefore, ETI combination chemotherapy could be considered a good option for non-platinum combination chemotherapy in heavily pretreated patients with EOC.

In conclusion, real world clinical practice data also showed that ETI produced relatively low toxicity and modest activity in heavily pretreated recurrent or persistent EOC. In particular, this non-platinum combination regimen would be helpful to the selected patients treated with multiple chemotherapeutic regimens and with more than 6 months of PFI.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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