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Phase II Study of Combination Chemotherapy with Etoposide and Ifosfamide in Patients with Heavily Pretreated Recurrent or Persistent Epithelial Ovarian Cancer

The aim of this trial was to investigate the efficacy and toxicity of combination chemotherapy with etoposide and ifosfamide (ETI) in the management of heavily pretreated recurrent or persistent epithelial ovarian cancer (EOC). Patients with recurrent or persistent EOC who had measurable disease and at least two prior chemotherapy participating in this phase II trial were to receive etoposide at a dose of 100 mg/m^2/day intravenously (IV) on days 1 to 3 in combination with ifosfamide 1 g/m^2/day IV on days 1 to 5, every 21 days. Thirty-seven patients were treated; about 78% had previously received more than two separate regimens. The response rate (RR) was 18.9% and median duration of response was 7 months (range, 1-15). Treatment free interval prior to ETI (TFI) has significant correlation with RR rate (P= 0.034). Patients (n=6) with TFI ≥6 months had 50% of RR, while patients (n=31) with TFI <6 months had 12.9%. Median survival was 9 months at a median follow-up of 9.2 months. Grade 3 or 4 toxicities included neutropenia in 20.1% of the 139 cycles of ETI, anemia in 7.2% and thrombocytopenia in 8.6%. The ETI produces relatively low toxicity and modest activity in heavily pretreated recurrent or persistent EOC. This is significant in patients with TFI ≥6 months.

Key Words : *Ovarian Neoplasms; Salvage Therapy; Etoposide; Ifosfamide*

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INTRODUCTION

Most women with epithelial ovarian cancer (EOC) treated with current, taxane-platinum-based combination chemotherapy regimens will respond to first-line chemotherapy (1). Nonetheless, complete clinical or pathological responses have not necessarily translated into long-term disease control or cure. Data from several first-line chemotherapy trials show that, even with the most advanced treatments, 60-70% of patients with advanced ovarian cancer will recur (2, 3).

The management of tumor recurrence remains a clinical challenge, since in the platinum-resistant population the chance of response to a secondary treatment is currently less than 20% (4). Several single chemotherapeutic agents have been used in this setting and have demonstrated modest activity such as topotecan (5, 6), gemcitabine (7, 8), liposomal doxorubicin (9), vinorelbine (10), oral etoposide (11, 12), and ifosfamide (13). 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. In refractory ovarian cancer, response rate (RR) with single agent etoposide have been reported to be less than 15% (14, 15).

Ifosfamide is a part of nitrogen mustard's alkylating agents. It has often been used as a single agent or in combination in EOC patients refractory or resistant to cisplatin (16). The RR, common to various studies, was between 12 and 25%, with a median of 20%. The progression-free survival (PFS) was between 4 and 6 months, and the overall survival (OS) between 7 and 11 months. Ifosfamide was active in patients refractory to cisplatin and also in patients already treated with cyclophosphamide, suggesting the absence of cross-resistance (17).

Very little information is available to combination chemotherapy as salvage treatment of EOC after more than two chemotherapy regimens. Etoposide and ifosfamide are one of the oldest drugs demonstrating clinical antitumor activity and relatively worldwide spread. In various animal tumors, etoposide has shown synergy with cyclophosphamide (18). Additionally, the combination of etoposide and ifosfamide (ETI) has also been demonstrated to be an effective regimen in solid neoplasms such as small cell lung cancer (14). In the field of EOC, several phase II studies were reported. Some indicated reasonable efficacy and another (19) showed dismal results which included only "true" platinum-resistant pati-

ents. However, there is no study on ETI in patients with heavily pretreated EOC patients.

Therefore, this phase II clinical study was designed to evaluate the efficacy and toxicity of 5-day regimen of ETI in patients with heavily pretreated EOC patients.

MATERIALS AND METHODS

Eligibility criteria for enrollment on this study included patients with histologically confirmed EOC treated with two or more prior chemotherapy regimens after primary cytoreductive surgery. Patients should have measurable disease on computerized tomography (CT) or magnetic resonance image (MRI) when first administration of ETI. Other eligibility criteria included no previous treatment with either ifosfamide or etoposide, normal end-organ function, WBC count of 3,000/μL or higher, platelet count of 100,000/μL or higher, granulocyte count of 1,500/μL or higher, a serum creatinine within institutional normal limits, hepatic enzymes (SGOT, SGPT and alkaline phosphatase) less than or equal to three 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 Karnofsky performance score greater than 60%. 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 hr in association with adequate hydration and mesna uroprotection. Etoposide was given at a dose of 100 mg/m^2/day IV on days 1 to 3 over 1 hr. Cycles were repeated every 3 weeks and at least two courses were given to all patients, while a minimum of four courses were given to responders. Delay of treatment was permitted if there was hematological toxicity greater than grade 3 during the previous cycle. A 25% dose reduction of ETI was required for grade 4 thrombocytopenia or grade 4 neutropenia with fever. 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 WHO standard criteria. The patients' response to treatment was assessed every two cycles by imaging techniques and every cycle by CA-125. The response is confirmed by last image after ETI according to RECIST criteria. 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 and resistant according to response showed at platinum-based first-line therapy. Treatment free interval prior to ETI (TFI) is the month(s) from the first day of last chemotherapy cycle to the first day of ETI chemotherapy.

Descriptive summary statistics were used to evaluate demographics and adverse events. Statistical analyses of frequency data were performed by means of the chi-square test. 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, U.S.A.) was used for statistical analysis.

RESULTS

Between March 2003 and July 2007, 43 patients enrolled in this study. Six patients were excluded from the response analysis but evaluable for toxicity because four patients revealed unmeasurable disease on image at first ETI and two received only one course. Therefore, thirty-seven patients received at least two courses of treatment and were evaluable for response and toxicity. The characteristics of the 37 patients are summarized in Table 1. The majority of the patients (81.1%) had serous type. Thirty patients (81.1%) had initial FIGO stage of III.

Of the 37 patients evaluable for response, seven (18.9%) patients showed a PR (Table 2) lasting median 7 months (range 1-15 months), another seven (18.9%) patients had SD and 23 (62.1%) progressed. There was no CR. Table 2 shows outcome according to clinical factors after ETI. Four

Table 1. Characteristics of patients (n=37)

Characteristics	No. of patients	%
Median age (yr), (range)	55 (34-74)	
Histology		
Serous	30	81.1
Clear	3	8.1
Endometrioid	2	5.4
Transitional	1	2.7
Undifferentiated	1	2.7
FIGO stage		
I	1	2.7
II	2	5.4
III	30	81.1
IV	4	10.8
First-line regimen		
Paclitaxel/cisplatin	23	62.2
Paclitaxel/carboplatin	8	21.6
Cyclophosphamide/cisplatin	4	10.8
Topotecan/cisplatin	1	2.7
Cyclophosphamide/adriamycin/cisplatin	1	2.7
No. of chemotherapy regimen prior to ETI		
2	8	21.6
3	15	40.5
4	5	13.5
5	5	13.5
6	1	2.7
7	2	5.4
8	1	2.7

ETI, etoposide and ifosfamide.

of 31 (12.9%) patients with TFI <6 months had response, while 3 of 6 patients (50%) with TFI ≥6 months had response. The RR of patients with TFI ≥6 months was about four times higher than that with TFI <6 months. As for initial platinum sensitivity, 30 (81%) patients were considered clinically sensitive to platinum compounds. Most responses (6/7) were observed in initial platinum-sensitive patients. However, there were no significant correlations between RR and platinum-sensitivity to first regimen (P=0.728), age (P=0.623), and total number of regimen prior to ETI (P=0.601). Only TFI had a significant correlation with RR (P=0.034).

With a median follow-up of 9.2 months, median OS for all 37 patients was 9 months (95% confidence interval: 7-11) (Fig. 1). Seven patients with a PR had no statistical significant (P=0.07) of survival gain (Fig. 2).

A total of 139 courses of ETI regimen were administered to the study population. Table 3 shows the toxicity profile. There was no treatment related death. The main hematological toxicity was grade 3-4 neutropenia in 28 of 139 cycles (20.1%). There were seven episodes of febrile neutropenia, but all episodes could be managed successfully with supportive care. A 25% dose reduction of both drugs was needed in four patients (10/139 courses; 7.2%) for a poor general condition. There was no severe bladder toxicity and other toxic effects were negligible.

Table 2. Outcome according to clinical factors after etoposide and ifosfamide chemotherapy

Parameters	No. of patients	OR, No (%)	P value*	OS, months Median (95% CI)	P value†
TFI prior to ETI					
≥6 months	6	3 (50.0)	0.034	10 (7-13)	0.351
<6 months	31	4 (12.9)		4 (2-6)	
Platinum sensitivity					
Sensitive	30	6 (20.0)	0.728	11 (1-21)	0.064
Resistant	7	1 (14.3)		6 (3-9)	
No. of chemotherapy regimen prior to ETI					
2	8	1 (12.5)	0.601	7 (2-30)	0.599
3-8	29	6 (20.7)		2 (7-10)	
Total	37	7 (18.9)		9 (7-11)	

*chi-square; †Log rank.
No., number; OR, objective response (CR or PR); OS, overall survival; CI, confidence interval; TFI, Treatment-free interval.

DISCUSSION

This is phase II trial that evaluated the efficacy and toxicity of ETI regimen for heavily pretreated patients with recurrent or persistent EOC. Five phase II studies about ETI regimen in EOC have been reported to date. We summarized the characteristics of these studies including our study (Table 4). Our study was different from the previous studies due to the number of prior chemotherapy regimens given before ETI. All of the trials used ETI as second- or third line of chemotherapy. Three of these phase II trials used IV etoposide (19-

Table 3. Toxicity of ETI regimen according to WHO criteria (n=139 cycles)

Toxicities	Proportion (%) of cycles affected grade				
	0	1	2	3	4
Neutropenia	53.2	10.1	15.1	12.9	7.2
Anemia	26.6	48.2	16.5	4.3	2.9
Thrombocytopenia	82.0	2.9	5.0	5.0	3.6
SGOT/SGPT	95.7	2.9	0	0	0
Nausea/Vomiting	46.7	50.4	2.9	0	0
BUN/Creatinine	95.7	2.9	0	0	0
	Number of patients affected grade				
	0	1	2	3	4
Alopecia	0	0	4	39	0
Peripheral neuropathy	8	33	2	0	0
Hematuria	43	0	0	0	0

ETI, etoposide and ifosfamide.

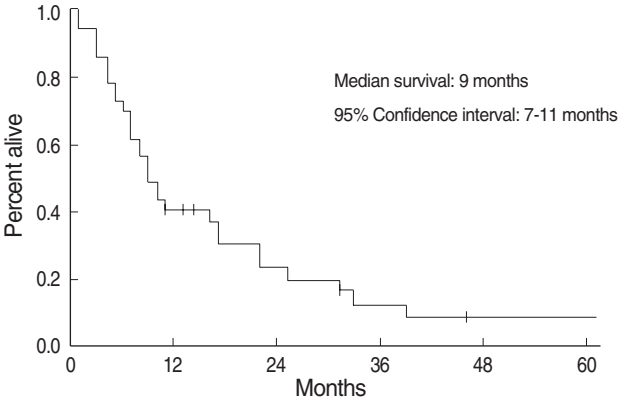

Fig. 1. Overall survival curve of 37 patients with a median follow-up of 9.2 months.

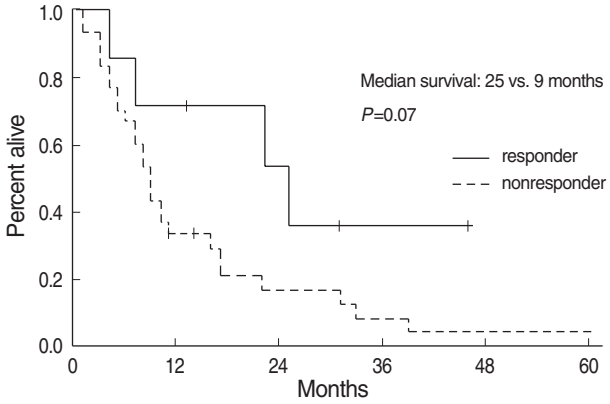

Fig. 2. Survival curves of 37 patients according to with or without response to ETI.

Table 4. Previous phase II trials of etoposide and ifosfamide for recurrent epithelial ovarian cancer

Parameters	This trial	Trope et al. (20)	Trope et al. (21)	Bruzzone et al. (19)	Aravantinos et al. (22)	Shaheen et al. (23)
No. of patients	37	29	103	12	35	14
Median age (yr)	55	53	56	N/A	65	59
No. of previous regimen	≥2	1-2	1-2 3 (in 3 patients)	1	1	1
Dosage						
Etoposide (mg/m^2)	100 IV, 3 d	100 IV, 3 d	100	80 IV, 3 d	100 PO, 10 d	37.5 PO, 14 d
Ifosfamide (g/m^2)	1.0 IV, 5 d	1.0 IV, 5 d	5.0	1.5 IV, 3 d	2.25 IV, 2 d	1.2 IV, 4 d
Cycle (week)	3	3	3	3	4	4
OR, % (CR+PR)	18.9 (0+7)	21.0 (1+5)	6.5 (0+6)	0 (0+0)	26 (4+5)	14 (0+2)
Median duration of response (months)	7	6	6	N/A	9	N/A
Median survival (months)	9	12	7	N/A	13	N/A

N/A, not applicable; PO, per oral; IV, intravenous; d, day.

21), while the other two used oral etoposide (22, 23). Bruzzone et al. (20) study resulted in no responses in 12 patients progressing or relapsing after primary cisplatin-containing combination, Trope et al. (21) obtained the following results; in 29 patients who received cisplatin as first-line and were deemed to be platinum-resistant, used ETI regimen same dose to ours, RR was 21%, the median time to disease progression was 6 months. They presumed the response to ETI was independent of prior response to first-line cisplatin-based chemotherapy, since there is no cross-resistance between ETI regimen and cisplatin. Our data (Table 2) showed similar outcomes. Therefore, there seems to be no cross-resistance between ETI and first-line cisplatin in heavily pretreated patients. Contrary to this pilot study, they reported ETI had dismal RR (6.5%) and ETI should be abandoned later (19). They explained the reason of dismal RR of ETI could be all patients in this large study had "true" platinum-resistant tumors. Additionally they introduced 1-day ETI regimen and compare with 5-day regimen, which was considered by the patients better tolerated because of the shorter hospital stay. Although administration dose was significantly higher in 1-day regimen due to less dose reduction, there was no difference in response between the two regimens. Another group obtained the following results; in 35 platinum resistant patients who used oral etoposide, RR was 26%, duration of response was 9 months and the median survival was 13 months (22).

Interestingly, the RR in the subgroup with TFI ≥6 months is high (50%; median duration 7 months) and statistically significant (P=0.034) compared to that of patients who had TFI <6 months though the number of patients was small. A trend appeared that the responders had survival gain (P= 0.07) (Fig. 2). Therefore, in the selected patients treated with multiple chemotherapeutic regimens with TFI ≥6 months, further study of ETI regimen is necessary.

In our patients, ETI regimen showed 18.9% RR. This was not higher than that of single recurrence regimen despite the combination chemotherapy. Some factors may be proposed to explain. First, our group of patients had particularly unfavorable clinical characteristics. In 78.3% of patients, the study regimen was given as fourth-line chemotherapy or more and the high proportion (84%) of the patients had TFI <6 months. Second, the compromised bone-marrow reserve of these heavily pretreated patients did not allow the administration of the regimen as scheduled. In 31 of 139 cycles (22.3%) there were delayed administrations for more than a week for hematological recoveries and in 10 cycles (7.2%), 25% dose reduction was needed. Last, a potential mechanism for the lack of additive or synergistic effect of adding ifosfamide to etoposide may stem from an observation that ifosfamide administration with or before other chemotherapeutic agents may actually antagonize these agents' activity, possibly by depleting cellular glutathione (24).

Apart from effectiveness, other variables may affect the decision to select a regimen in this heavily pretreated population. For example toxicity profile, quality of life, ease of administration, cost issues, and residual toxicity from prior therapy (25). Ifosfamide is the oldest group of drugs and produces less severe hematological toxicity (17). Together with etoposide, it produces an acceptable toxicity level with grade 3 or 4 neutropenia most common in 20.1% of the patients in this study (Table 3). Considering 29 of the 37 (78.3%) patients who were enrolled in the current study had already been treated with 3 or more regimens before ETI, delayed schedule of 22.3% of total 139 cycles and dose reduction of 7.2% were not more than expected. Therefore ETI combination chemotherapy could be administered in heavily pretreated patients with EOC.

According to NCCN guideline (26), patients who are considered platinum-sensitive have the greatest number of potential options for second-line therapy. Evidence suggests that combination chemotherapy may be superior to single-agent therapy in platinum-sensitive group (27). Options include carboplatin/paclitaxel (27), gemcitabine/carboplatin (28), or a recurrence regimen. In platinum-resistant patients, retreatment with a platinum compound or paclitaxel is not recommended. Options include treatment with a recurrence regimen that does not contain platinum (4) or supportive care. Several recurrence agents show similar effect as single regi-

men: topotecan, 20% (29); gemcitabine, 19% (7, 8); vinorelbine, 20% (30); liposomal doxorubicin, 26% (9); oral etoposide, 27% (11, 12); and ifosfamide, 12% (16). Most patients in this study were platinum-sensitive at first line chemotherapy, therefore, received combination chemotherapy that included topotecan, cyclophosphamide, cisplatin, carboplatin, paclitaxel, docetaxel, and belotecan as 2nd or 3rd-line. They did not receive gemcitabine or liposomal doxorubicin, because medical insurance in our country did not cover these chemotherapeutic agents.

In conclusion, ETI produces relatively low toxicity and modest activity in heavily pretreated recurrent or persistent EOC. In addition, this regimen should be further studied in the selected patients treated with multiple chemotherapeutic regimens and with TFI more than 6 months.

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