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A phase II study of etoposide combined with ifosfamide as second-line therapy in cisplatin-resistant ovarian carcinomas*

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Summary. The response rate and survival obtained with the second-line chemotherapeutic regimen etoposide combined with ifosfamide were analyzed in a series of 32 patients progressing or relapsing after cisplatin-based front-line treatment. Etoposide (100 mg/m^2) was given i.v. for 3 days and 1.0 g/m^2 i.v. ifosfamide, for 5 days, with 200 mg/m^2 mesna being given i.v. at 0, 4, and 8 h after ifosfamide. The median age of the patients was 53.5 years (range, 26–72 years). In all, 32 patients were evaluable for toxicity and 29, for response; all patients had measurable lesions and all had previously received cisplatin-based chemotherapy. The overall objective response rate was 21%; the median duration of response was 6+ months (range, 2+–11 months), with that for stable disease being 5 months (range, 2–9+). The only patient who achieved a complete response is still alive after 13 months. The median survival for partial responders was 9+ months (range, 4+–13), and that for stable disease was 6+ months (range, 3+–14+). No major toxicity was observed, but myelosuppression caused dose reduction in 50% of the patients. Although the median follow-up time was short, this combination produced relatively low toxicity, with a 21% objective response rate in second-line chemotherapy after cisplatin failure, which means that this regimen is not cross-resistant to cisplatin.

Introduction

Cisplatin is the most active agent in ovarian cancer. Combined modality treatment of ovarian cancer with debulking surgery and cisplatin-containing chemotherapy produces a 50% clinical, complete response rate. However, this high response rate to front-line chemotherapy has not increased the long-term survival [6]. Second-line treatment of relapsing ovarian cancer after failure of alkylating agents gives a low response rate, around 20%, and a medium survival of <12 months [10]. Second-line treatment with cisplatin produces a higher response rate in alkylating agent-resistant ovarian cancer [2]. The low response rate and, above all, the short duration of response and survival of <12 months may reflect the lack of confidence of gynecologists in their ability to obtain a chemotherapeutic response in patients previously exposed to cisplatin. Very little information is available to salvage treatment of ovarian cancer after cisplatin.

Ifosfamide is an analogue of cyclophosphamide that has shown evidence of activity in ovarian cancer and lack of cross-resistance with cyclophosphamide in a number of tumors, including advanced ovarian cancer, with response rates ranging from 60% to 80% [1, 3]. Etoposide belongs to the plant alkaloids and has shown activity in ovarian cancer in both first- and second-line treatment after cisplatin failure [4, 5].

Since therapeutic possibilities are limited in ovarian cancer patients relapsing after cisplatin treatment, new approaches are urgently needed. We therefore tested ifosfamide with mesna uroprotection combined with etoposide in a phase II study, the aims of which were to determine the response rate, duration of response, and toxicity of this regimen.

Patients and methods

Between October 1987 and April 1989, 32 patients with histologically proven, recurrent ovarian cancer were selected. All patients had received first-line treatment with cisplatin given either alone or in cocmbination with cyclophosphamide or doxorubicin. Eligibility criteria included a leukocyte count of >3.0 × 10^9/l, a platelet count of >100 × 10^9/l, normal serum creatinine values, adequate heart and pulmonary function, Karnofsky performance index of >50, and a cytologically or histologically confirmed relapse of ovarian cancer. All 32 patients were evaluable for toxicity and 29, for response. All evaluable patients had lesions with a

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Table 1. Characteristics of 32 patients

Median age	53.5 (26–72) years
FIGO stage at primary diagnosis:	
I	2
II	5
III	22
IV	3
Histology:	
Serous	20
Mucinous	2
Endometroid	4
Clear-cell	5
Unclassified	1
Grading:	
Highly differentiated	8
Moderately differentiated	12
Poorly differentiated	11
Uncertain	1
Site of recurrences:	
Pelvis	6
Abdomen	7
Pelvis + abdomen	11
Pelvis + distant lymph nodes	4
Distant lymph nodes	4
Prior chemotherapeutic treatment:	
Cisplatin	18
Cisplatin-cyclophosphamide	8
Cisplatin-doxorubicin	6
Cycles of ifosfamide/etoposide (*n*):	
2–4	15
5–7	15
>8	2

Table 2. Dose modification schedule

WBC ($\times 10^9$/l)	Platelets ($\times 10^9$/l)	Ifosfamide (percentage of full dose)	Etopside	Mesna
3.0–3.9	75–99	100, days 1–4	75, days 1–3	100, days 1–4
2.0–2.9	50–74	100, days 1–3	50, days 1–3	100, days 1–3
<2.0	<50	Treatment postponed 1 week		

Table 3. Response data

Disease evaluation	Patients (*n*)		Median duration of response (months)	Median duration of survival (months)
Complete response	1	21%	8	13+
Partial response	5		6+ (range, 2+–11)	9+ (range, 4+–13)
Stable disease	21	72%	5 (range, 2–9+)	6+ (range, 3+–14)
Progressive disease	2			6,6
Nonevaluable	3			10+ (range, 6+–11+)
Totals	32			12+

Table 4. Toxicity observed in all patients

Toxicity	WHO grade: 0	1	2	3	4
Leukocytes	15	5	8	4	0
Platelets	25	4	3	0	0
Nausea/vomiting	7	13	6	5	1
Cystitis	31	0	1	0	0
Fever	31	0	1	0	0
Alopecia	0	0	0	32	0
Neurotoxicity	32	0	0	0	0
Renal toxicity	32	0	0	0	0

diameter of >5 cm. Three patients were excluded from the response analysis because of nonmeasurable disease. Detailed patient characteristics are shown in Table 1.

The treatment schedule consisted of 100 mg/m^2 etoposide given as an i.v. infusion in 1,000 ml 0.9% normal saline solution over 2 h, followed by 1,000 mg/m^2 ifosfamide given as a bolus dose, followed by 1,000 ml 5.5% glucose infused over 4 h; 200 mg/m^2 mesna was given 0, 4, and 8 h after each ifosfamide infusion. Ifosfamide was given from days 1 to 5, and etoposide was given from days 1 to 3; treatment was repeated every 3rd week (two courses were required for response and toxicity evaluation) and a minimum of five courses were given to responders. A dose-modification schedule is presented in Table 2. A total of 149 courses were given, with a median of 5 courses. Ten patients received more than six courses, and two patients completed more than nine.*

Response was documented by gynecological examination with the patients under anesthesia, by chest radiography, and by computerized tomographic (CT) scan. WHO criteria for toxicity as well as response were used [8]. The i.v. infusion of a moderate dose of metoclopramide was given to most patients over 5 days.

Results

Among the 29 evaluable patients, 1 complete clinical response and 5 partial clinical responses were seen, giving an overall response rate of 21%. The median time to disease progression was 6+ months, and the median duration of survival comprised 12+ months. Detailed response data are shown in Table 3. Responses seemed to be independent of prior response to first-line cisplatin-based chemotherapy. In all, 4 of 22 initial nonresponders and 2 of 7 initial responders improved on this two-drug combination, which indicates that there is no cross-resistance between this regimen and cisplatin.

Toxicity

Detailed toxicity data are shown in Table 4. Myelosuppression of grades 2 and 3 were seen in 12 patients. There was no thrombocytopenia more severe than grade 2. Myelosuppression caused the reduction of both the ifosfamide and the etoposide dose in 47% of the patients. All patients developed grade 3 alopecia. Encephalopathy and renal failure were not seen in this study. Septic fever was observed in one case, and only one patient had grade 2 cystitis. The Karnofsky index of four patients decreased by 20% during treatment; they refused further treatment after two courses.

Discussion

The response rate of 21% achieved in this study is moderate but may be acceptable in view of the extent of previous chemotherapy and of the fact that the responders achieved useful palliation with a tumor progression-free period of >6 months. The overall median survival was >12 months. The principal dose-limiting toxicity was myelosuppression, which necessitated dose reduction in almost 50% of the patients. The majority of those patients had received at least 6 courses of combination chemotherapy including cyclophosphamide or doxorubicin, and it is known that those two agents cause bone marrow toxicity. The present regimen does not seem to be cross-resistant to cisplatin.

Although this regimen produces low toxicity objectively, this study has shown that it is a heavy regimen, requiring 6 days' hospitalization. The response rate of 21% obtained in the present study is similar to that reported by Willemse et al. [7], who gave 5 g/m^2 ifosfamide as a 24-h continuous infusion with 5 g/m^2 mesna as uroprotection. We therefore think that the 5-day regimen should be abandoned. The combination of these two drugs at the doses we used does not give better response rates than either ifosfamide or etoposide alone in cisplatin-resistant ovarian cancer [4, 5, 7, 9].

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