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Ifosfamide given as a 24-h infusion with mesna in patients with recurrent ovarian cancer: preliminary results*

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Summary. The continuous 24-h infusion of ifosfamide (IFX) with mesna was studied in 44 patients with therapy-resistant or relapsing ovarian cancer. All patients had stage III disease and had been pretreated with at least one combination comprising an alkylating agent and a cisplatin analogue (22, with one combination; 16, with two; and 6, with three or more). The median number of IFX cycles received was two. Of 40 evaluable patients, 2 achieved a complete response, 5 showed a partial response and 6 had stable disease. A total of 27 patients had tumor progression after one or two treatment cycles. All seven responders had responded to previous treatment for a median duration of 5 months (range, 5–41 months). No patient who progressed during alkylating-agent treatment responded to IFX given subsequently. The median progression-free period was 6 months (range, 4–12 months), and the median overall survival was only 6 months, indicating the advanced stage of disease in these patients. The median overall survival in progressive patients was 5 months (range 2–13+ months) and that in the remaining group was 13 months (ranges 3+–24 months) ($P < 0.05$). This treatment was moderately well tolerated. Grade 3 nausea and vomiting occurred in 27% of cycles and grade 3–4 leukopenia was observed in 47%, but thrombocytopenia was hardly ever found. In eight patients there was a deterioration of renal function. Among a total of 131 cycles, the dose was reduced for only 9 due to myelotoxicity and for 3 due to nephrotoxicity. IFX seems to be active only in patients who have relapsed after responding to previous cytotoxic treatment.

Introduction

Ovarian cancer (OC) is usually sensitive to a number of cytotoxic drugs, especially alkylating agents and cisplatin. In patients with advanced ovarian cancer treated with a combination of both drugs, complete remissions may be reached in about 40% of patients after adequate debulking. Tumors either resistant to this combination or relapsing after a partial remission are often difficult to treat, as they respond poorly to other cytostatic drugs [1]. Recently, responses have been reported in patients with ovarian carcinoma resistant to alkylating agents after treatment with high-dose ifosfamide (IFX) given over 24 h together with the detoxifying agent mesna [10]. In the past, responses have been reported after 5-day IFX treatment in patients with ovarian cancer who had previously been treated with cyclophosphamide [3, 5, 14]. In this study the efficacy of IFX given at 5 g/m^2 over 24 h was evaluated in patients with therapy-resistant ovarian cancer.

Patients and methods

IFX was given over a 24-h period every 4 weeks at a dose of 5 g/m^2. 2.5 g/m^2 mesna was dissolved in the infusion fluid and given concomitantly, followed by the infusion of an additional 2.5 g/m^2 mesna over the next 12 h.

Evaluation of the effectivity of IFX was done every two cycles on the basis of tumor measurements. Patients went off study when the tumor showed progression or when toxicity became prohibitive. Toxicity was graded according to WHO criteria. Of the 44 eligible patients, 4 could not be evaluated (Table 1). All patients had received prior treatment with cisplatin and an alkylating agent. The number of previous combinations, performance status and number of cycles of IFX given are shown in Table 1.

Results

Of the 40 evaluable patients, 2 achieved a complete remission, 5 showed a partial response, 6 had stable disease and 27 showed disease progression, resulting in an overall response rate of 18% (Table 2). All of the 7 responders had

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Table 1. Patient characteristics

Entered	45 patients		
Ineligible	1 patients (renal function)		
Non-evaluable	4 patients:		
	1 mesna allergy		
	1 ileus		
	1 sepsis		
	1 refused treatment		
Evaluable	40 patients		
Prior chemotherapy:			
	Combinations (n):	Patients (n):	
	1	22	
	2	16	
	3	6	
Performance status:			
	WHO grade		
	0	20	
	1	14	
	2	10	
Treatment received by 44 patients:			
	IFX cycles (n):	Patients (n)	Cycles (n):
	1	10	10
	2	13	26
	3	7	21
	4/5	6	25
	≥ 6	8	51
	Total	44	133

Table 2. Treatment results

Response:	Number (%):	
Complete remission	2 (5)	
Partial remission	5 (12.5)	
Stable disease	6 (15)	
Progression	27 (67.5)	
Progression-free period (months):		
	Median	6
	Range	4–12
Overall survival (months):		
	Median	6
	Range	2–24
Survival of patients with response/stable disease (n = 13):		
	Median	13
	Range	3+–24
Survival of patients with progression (n = 27):		
	Median	5*
	Range	2–13+

* P <0.05 vs non-progressive patients

Table 3. Toxicity observed in 133 cycles of IFX

WHO grade	Leukopenia	Nausea/vomiting	Thrombocytopenia (cycles)	Diarrhoea (cycles)	Nephrotoxicity
1	16%	2%	1	1	3 patients
2	37%	69%	1	4	3 patients
3	38%	27%	1	2	1 patient
4	9%	2%	–	–	1 patient
Total	100%	100%	3	7	8 (18%)

shown a response to previous cytostatic treatment for a duration of 5–41 months (median, 8 months). No patient who progressed during treatment with an alkylating agent responded to subsequent treatment with IFX. The median progression-free period was 6 months (range, 4–12 months), and median overall survival was 6 months (range, 2–24 months). The median overall survival was 5 months in progressive patients (range, 2–13+) vs 13 months in the remaining group (3+–24) (P <0.05) (Table 2).

Toxicity

A total of 133 cycles were given, and the IFX dose was reduced in only 9 cycles due to leukopenia in 4 patients (Table 3). Myelotoxicity was generally tolerable (Table 3), reaching grade 3–4 leukopenia in 47% of cycles, whereas thrombocytopenia was hardly seen. Only three patients with grade 4 leukopenia also developed thrombocytopenia (platelet nadirs of 38,000, 54,000, and 74,000/mm^3). Renal toxicity was observed in eight patients, requiring dose reduction due to impaired renal function for three cycles in two patients (Table 3) and termination of therapy in two others, one of whom succumbed to renal failure with tumor relapse. We did not encounter any case of encephalopathy, despite the IFX dose given in this study. Grade 3 nausea and vomiting was seen in 27% of all cycles but was not prohibitive.

Discussion

This study was undertaken to determine the efficacy of IFX given as a continuous 24-h infusion in tumors resistant to or relapsing after prior chemotherapy. IFX appears to be active only in patients who have relapsed after achieving a remission during previous cytostatic treatment, i.e. in patients having chemosensitive tumors. IFX seems to be ineffective in tumors resistant to alkylating agents. These findings are in accordance with those of several other authors [6, 9], but some investigators have reported impressive response rates obtained with IFX given as second-line treatment (Table 4). We have no simple explanation for this discrepancy, as the only variable appears to be the administration of mesna.

Toxicity

In this extensively pretreated group of patients, IFX was not free of toxicity. One patient died of *Clostridium* sepsis and one developed severe renal insufficiency. All patients had previously received cisplatin, and a number of them had a pre-existing compromised renal function that sensitized them for this kind of toxicity [4, 12]. Most patients who developed renal toxicity had received four or more cycles of IFX. Mesna is very effective in preventing the urothelial toxicity of IFX. It is dubious, however, whether it prevents the tubular toxicity of IFX, which is more often found after higher IFX doses.

Table 4. IFX in pretreated patients with relapsed ovarian cancer

IFX dose	Mesna (% of IFX dose)	Patients evaluable (*n*)	CR	PR	%	Side effects	Reference
60 mg/kg, days 1–5 in most patients	–	16	5	8	81	Cystitis, 30% Renal, 4% Cerebral, 18%	[5]
0.6 g/m² days 1–5 and 8–12	–	12	4[a]		33	Urinary cylinders, 38%	[3]
80–180 mg/kg, days 1–3	–	26	2		F	Cystitis, 27% Renal, 13% Cerebral, 12%	[7]
40 mg/kg, days 1–5	–	25	3	9	48	Cystitis, 24%	[14]
50 mg/kg, days 1–5	60	5	–	0	–	Microscopic hematuria, 2%	[15]
5 g/m² over 24 h	20+100+50	15		1	6	Grade 2 leukopenia, 10 patients Grade 3 leukopenia, 5 patients Cystitis, 2 patients	[6]
1.5 g/m², days 1–5; later 1.2 g/m²	75	37	3	5	22	2 died of renal failure, no cystitis Grade 3–4 leukopenia, 61%	[10]
5 g/m² over 24 h	100	40	2	5	17.5	2 renal failures Grade 3–4 leukopenia, 47%	Present study
Totals		176	17	30	27		

[a] All 4 pts were resistant to chlorambucil

Table 5. IFX as first treatment in advanced ovarian cancer

IFX dose	Mesna (% of IFX dose)	Patients (*n*)	CR	PR	%	Reference
60 mg/kg, days 1–5	–	61	28	20	79	[5]
50–60 mg/kg, days 1–5	–	73	30	27	78	[8]
130–170 mg/kg over 2–3 days	–	49	2	31[a]	64	[11]
1.5 g days 1–5	–	20	5	8	65	[2]
50 mg/kg, days 1–5	60	15	2	3	33	[15]
Totals		218	67	89	71	

[a] Only the percentage was reported

Leukopenia was not marked in this study, with only 9% of the cycles producing grade 4 toxicity. Only three patients with grade 4 leukopenia developed thrombocytopenia. The gastrointestinal toxicity of IFX given in this way was trying but not prohibitive; anticipatory nausea and vomiting may have played a part in many patients after cisplatin treatment. Diarrhoea was not a problem. Alopecia was pronounced in most patients receiving more than two cycles of treatment. No patients developed symptoms of encephalopathy.

Conclusion

Despite the dose used in this study, IFX given over a period of 24 h was not effective in patients whose disease either had progressed during prior chemotherapy or proved to be resistant to cyclophosphamide. IFX may induce responses in patients who relapse after having responded to first-line treatment, but such second remissions are usually of limited duration. Myelotoxicity is not a major problem, but renal function should be carefully monitored in patients with compromised renal function after prior exposure to cisplatin.

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