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A dose escalation study of carboplatin and ifosfamide in advanced ovarian cancer

Christopher J. Gallagher[1], Eve Wiltshaw[1], Robert E. Coleman[2], and Peter G. Harper[2]

The Gynaecological Oncology Unit, The Royal Marsden Hospital, Fulham Revad, London SW, England
[2] The Department of Medical Oncology, Guy's Hospital, London, England

Summary. A dose escalation study of carboplatin (CBDCA) and ifosfamide was carried out in 35 patients with advanced ovarian carcinoma to determine the toxicity and therapeutic effect of this combination. In all, 13 patients had recurrent ovarian carcinoma, 11 had abdominal carcinomatosis of probable ovarian origin and 9 had newly diagnosed stage III/IV ovarian cancer. Myelosuppression was the major dose-limiting toxicity. At a dose of 400 mg/m^2 CBDCA plus 5,000 mg/m^2 ifosfamide, 61% of courses were associated with grade 3 leukopenia and 27%, with grade 3 thrombocytopenia. The lowest leukocyte and platelet counts occurred at a median of 14 days after treatment and cytopenia persisted for a median of 8 days. Myelotoxicity was cumulative with successive courses at this dose level, whereas at a dose of 400 mg/m^2 CBDCA plus 4,000 mg/m^2 ifosfamide it was possible to deliver the planned six courses of treatment. No other untoward toxicities were observed. A clinical response was achieved in 16/33 patients (49%), with 10 complete remissions (CRs), of which 3 were pathologically confirmed at laparotomy. No significant dose-response relationship was demonstrated in this heterogeneous group of patients. The predicted median duration of response is 12 months. CBDCA plus ifosfamide is an active combination therapy for ovarian cancer that merits further comparison with CBDCA alone. The recommended doses for six courses are 400 mg/m^2 CBDCA plus 4,000 mg/m^2 ifosfamide.

Introduction

Carboplatin (CBDCA) is an active agent in recurrent ovarian carcinoma [3]. In a recent randomised comparison with the parent compound, cisplatin [11], treatment with CBDCA achieved a similar response and survival in patients with advanced ovarian carcinoma without the usual platinum dose-limiting renal or neurological toxicity [6]. The major dose-limiting toxicity of CBDCA has proved to be myelosuppression [3].

Alkylating agents are another active class of drugs for the treatment of ovarian carcinoma. Ifosfamide has recently been reevaluated and was found to have activity equivalent to that of cyclophosphamide [1], with less myelotoxicity and predominantly uroepithelial or neurological toxicity. The former can be prevented by the concomitant administration of mesna [2] and the latter by dose reduction in the presence of renal impairment or hypoalbuminaemia [9].

Combination chemotherapy with cisplatin has increased response rates in patients with ovarian cancer compared with those achieved by cisplatin alone, but improvements in survival await the introduction of more effective drugs [4]. A dose-escalation study with 33 patients was carried out to evaluate the toxicity and therapeutic effect of CBDCA and ifosfamide in combination, in the expectation that their differing toxicity profiles would allow the delivery of optimal therapeutic doses of both drugs.

Patients and methods

A total of 33 patients were treated between October 1984 and June 1986 in the Gynaecological Oncology Unit, The Royal Marsden Hospital, London, and the Department of Gynaecological Oncology, Guy's Hospital, London. In all, 22 patients had histologically confirmed advanced carcinoma of the ovaries that either had recurred after previous treatment (13 patients) or was newly diagnosed (9 patients). The remaining 11 cases were of only probable primary ovarian origin, due to a lack of distinguishing surgical or pathological features in 3 or a history of previous breast or colonic carcinoma in 8.

The diagnostic laparotomy included a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) in 20 patients but only a salpingo-oophorectomy or biopsy in 13. In 26 patients the maximal diameter of the residual disease at the time of treatment was greater than 5 cm. There was a predominance of adenocarcinomas among the histological subgroups due to the 11 patients with abdominal carcinomatosis of uncertain primary origin (Table 1). Seven patients had previously received cisplatin, three, alkylating agents, and three had recurrent disease after surgery alone.

CBDCA and ifosfamide were given by i.v. infusion once every 4 weeks for up to six courses in responding patients. Four dose levels were chosen, and it was intended that at least six consecutive patients should be entered at the lowest dose level before doses would be increased for the next six patients to a maximum of 400 mg/m^2 CBDCA plus 5,000 mg/m^2 ifosfamide. CBDCA was given as a 30-min infusion in 5% dextrose solution and ifosfamide, as a 24-h infusion accompanied by an equimolar amount of

Offprint requests to: Eve Wiltshaw

Table 1. Characteristics of patients treated with CBDCA and ifosfamide

Number	33
Diagnosis:	
Recurrent ovarian cancer	13
Ovarian and previous breast/bowel cancer	8
Ovarian uncertain primary	5
Ovarian stage III/IV	7
Histology:	
Serous	10
Mucinous	2
Adenocarcinoma	18
Other (endometrial, mesonephric)	3
Surgery:	
TAH + BSO	20
Biopsy or cytology only	8
BSO/USO	5
Residual disease:	
<5 cm	7
>5 cm	26
Previous treatment (13 patients):	
Alkylating agents	3
Cisplatin	7
Radiotherapy	0
Surgery only	3

mesna and a forced saline diuresis to maintain a urinary flow of at least 100 ml/h [2].

All patients were assessed for toxicity at each course of treatment with a full blood count, serum urea and creatinine and routine urinalysis. A ^{51}Cr-EDTA clearance test was carried out with every second course of treatment in 22 patients. All patients were clinically assessed for nausea, vomiting and neurological toxicity using WHO criteria [10]. Full blood counts were repeated at weekly intervals between treatments. Dose reduction to the previous dose level was permitted if the haematological toxicity was WHO grade 3 or higher.

A total of 31 patients were evaluable for response, which was clinically assessed at the completion of treatment by WHO criteria [10] as follows: complete remission (CR), with the resolution of all previously abnormal findings and a return to normal health, or partial remission (PR), with at least a 50% bidimensional reduction in the diameter of all measurable disease. Two patients were not evaluable for response; in retrospect, one had no assessable disease at the beginning of treatment, and the other stopped treatment after two courses following an allergic reaction to CBDCA. A second laparotomy was carried out in eight patients with previously untreated disease and incomplete primary surgery, that is, less than a TAH and BSO plus omentectomy. Durations of response and survival were calculated from the 1st day of treatment and life table analysis was carried out by the Kaplan and Meier technique [7].

Table 2. Treatment given to patients receiving CBDCA and ifosfamide

CBDCA (mg/m^2)	Ifosfamide (mg/m^2)	Patients	Total number of courses	Number at full dose
200	2,500	9	33	33
300	3,500	10	32	32
400	4,000	7	38	17
400	5,000	7	33	17
Totals		33	136	

Results

In all, 33 patients received a total of 136 courses of CBDCA plus ifosfamide at one of four dose levels, from 200 mg/m^2 CBDCA plus 2,500 mg/m^2 ifosfamide to 400 mg/m^2 CBDCA plus 5,000 mg/m^2 ifosfamide. Each of 17 patients completed at least five courses (Table 2).

Toxicity

A total of 19 patients were treated at doses of 200/2,500 mg/m^2 and 300/350 mg/m^2 CBDCA/ifosfamide, respectively. Interval blood counts from 42/65 courses of treatment revealed moderate myelosuppression, with no patient requiring dose reduction with repeated treatment (Table 3). At higher doses, myelosuppression became the major dose-limiting toxicity. Seven patients received 400/4,000 mg/m^2 CBDCA/ifosfamide for a total of 38 courses. Leukopenia of WHO grade >3 occurred in 13/23 (57%) courses, with thrombocytopenia of WHO grade >3 in 5/23 (22%) courses for which interval blood counts were recorded. Only three patients could complete six courses each without dose reduction (Table 3).

Another seven patients received 400/5,000 mg/m^2 CBDCA/ifosfamide for a total of 33 courses. Myelosuppression was more pronounced, with leukopenia of WHO grade >3 in 20/33 (61%) and thrombocytopenia of WHO grade >3 in 9/33 (27%) of the courses with interval blood counts, including six courses with platelet counts of $<25{,}000 \times 10^9$/l, requiring in-patient treatment (Table 3). Myelosuppression with repeated treatment was cumulative at this dose level such that a maximum of three courses, and frequently only one, could be delivered before dose reduction was required, often to the level of 300/3,500 mg/m^2 CBDCA/ifosfamide. The lowest leukocyte and platelet counts occurred at a median of 14 days (range, 10–16 days) following treatment, and the latter remained at $<100{,}000 \times 10^9$/l for a median of 8 days (range, 5–20 days). Haematological toxicity did not differ significantly between those who were newly diagnosed and those who had previously been treated.

Nausea and/or vomiting was transient and well controlled by standard anti-emetic medication. Alopecia was universal, but no patient developed renal or uroepithelial toxicity. CNS toxicity was observed in two patients who developed emotional lability and somnolence after the ifosfamide infusion. Both recovered spontaneously after 48 h and could tolerate subsequent treatment at a reduced dose of ifosfamide. There was no evidence of peripheral neuropathy or ototoxicity on clinical testing.

Response

A clinical remission was achieved in 16/33 patients (49%), with ten CRs and six PRs (Table 4). Second laparotomies in selected patients demonstrated a pathologically confirmed CR in 3/4 patients with clinical CRs. In addition, four patients with clinical PRs in whom initial surgery was incomplete underwent a second laparotomy during chemotherapy. The PR was confirmed in 4/4 and surgery was completed to include a TAH, BSO and omentectomy

Table 3. Haematological toxicity of CBDCA and ifosfamide according to drug dose at the start of therapy

	Dose of carboplatin + ifosfamide (mg/m²)			
	200 + 2,500	300 + 3,500	400 + 4,000	500 + 5,000
Leukopenia:				
Median WBC	3.1	3.2	1.9	1.5
Range (× 10⁹/l)	0.7–8.0	0.7–8.3	0.4–4.9	0.5–4.8
Number of courses with interval FBC	23	19	23	33
WHO grade 0	6	5	2	1
1	7	6	1	4
2	8	3	7	8
3	1	4	10	17
4	1	1	3	3
% > grade 3	9%	26%	57%	61%
Thrombocytopenia:				
Median platelets	226	233	82	171
Range (× 10⁹/l)	42–405	62–674	24–275	14–454
Number of courses with interval FBC	23	19	23	33
WHO grade 0	19	16	11	16
1	0	1	3	3
2	2	2	4	5
3	2	0	5	3
4	0	0	0	6
% > grade 3	9%	0%	22%	27%

before the patients received their final courses of chemotherapy.

There were more responses at the higher doses of 400 mg/m² CBDCA plus 4,000–5,000 mg/m² ifosfamide than at the lower doses [8/14 (57%) vs 8/19 (42%)], but this was not statistically significant (Table 4). Remissions were more frequent in previously untreated patients with proven ovarian carcinoma than in those with recurrent disease [7/9 (78%) vs 4/13 (31%); $P = 0.03$] or those with abdominal carcinomatosis [5/11 (46%); $P = 0.10$]. The four CRs in patients with recurrent ovarian cancer were all achieved in patients who had relapsed following a response to previous cisplatin treatment. After a median follow-up of 18 months, 9/16 patients remain free from relapse, for a predicted median duration of remission of 12 months and a median survival for the whole group of 16 months (Fig. 1).

Discussion

Our results proved that it is possible to give CBDCA and ifosfamide in combination to patients with ovarian carcinoma at close to the optimal therapeutic dose of each drug when it is used as a single agent. The major dose-limiting toxicity was myelosuppression, which was maximal at a median of 14 days after treatment but of brief duration (median, 8 days). Leukopenia and thrombocytopenia increased in frequency with increasing dose such that 61% of courses at 400 mg/m² CBDCA plus 5,000 mg/m² ifosfamide were associated with grade 3 leukopenia and 27%, with grade 3 thrombocytopenia. Cumulative myelosuppression was seen in all patients treated with 400 mg/m² CBDCA and 5,000 mg/m² ifosfamide, such that no more than three courses, and often only one, could be given before dose reduction was necessary (Fig. 2). This degree of myelosuppression is greater than that previously reported with CBDCA or ifosfamide given as single agents at the same dose [1, 3], suggesting an additive effect due to the combination. In addition, the nadir occurred 1 week earlier than that reported for CBDCA but was similar to that of ifosfamide as a single agent.

The lack of renal and neurological toxicity with CBDCA, along with the preservation of its therapeutic efficacy against ovarian cancer, has proved to be a major advantage in comparison with treatment using cisplatin [11]. It was therefore important that a combination of CBDCA with ifosfamide, a potentially nephrotoxic agent, not be associated with an increase in renal toxicity. Changes in ^{51}Cr-EDTA clearance have been shown to be a sensitive index of cisplatin-induced renal dysfunction [6];

Table 4. Response to treatment with CBDCA and ifosfamide in 33 cases

Dose	Patients	CR	PR	PD	NA	Response/Total
200/2.5	9 (2)	3 (1)	1 (0)	4 (0)	1 (1)	4/9
300/3.5	10 (2)	1 (0)	3 (2)	6 (0)	0 (0)	4/10
400/4	7 (1)	2 (0)	0 (0)	5 (1)	0 (0)	2/7
400/5	7 (4)	4 (2)	2 (2)	1 (0)	0 (0)	6/7
Totals	33	10	6	16	1	

Numbers in brackets represent patients with previously untreated ovarian cancer

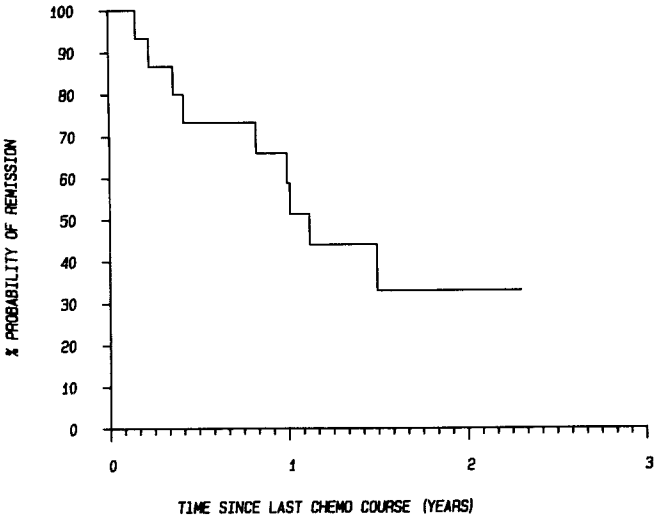

Fig. 1. Duration of remissions (complete and partial) in patients treated with CBDCA and ifosfamide

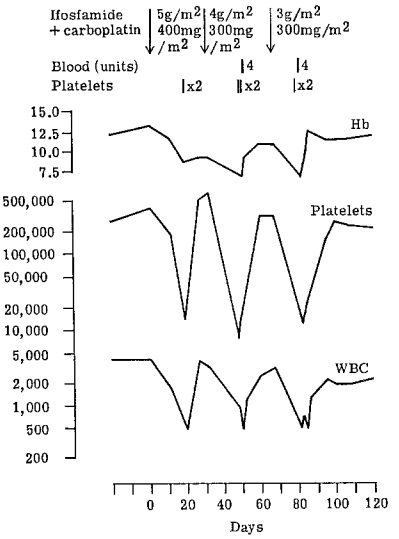

Fig. 2. A graph showing the effects of the combination on the peripheral blood count, with evidence of cumulative toxicity

this parameter was therefore prospectively followed in 22 of the patients. There was no evidence of nephrotoxicity from the combination, and uroepithelial toxicity due to ifosfamide was avoided by the use of mesna plus a saline diuresis. There was also no clinical evidence of peripheral neuropathy or ototoxicity, in keeping with previous experience with CBDCA [6]. CNS toxicity with somnolence similar to that attributable to single-agent ifosfamide occurred in 2/33 patients (6%), in keeping with previous experience [1]. However, the severe CNS toxicity previously seen in some patients with cervical and endometrial carcinomas did not occur [9].

The primary aim of this study being to determine the toxicity of CBDCA plus ifosfamide, it was gratifying to observe a high response rate in poor-prognosis patients with recurrent ovarian cancer or bulky and often inoperable residual disease. A clinical response was achieved in 49% of the patients for a median duration of 12 months after 5–6 courses of treatment, which is better than the results reported for single-agent CBDCA or ifosfamide in previously treated ovarian cancer [1, 5, 6]. However, the cases treated were a mixed group of untreated and previously treated patients, sometimes with abdominal carcinomatosis of uncertain origin, and no conclusions regarding improved efficacy can be drawn from this study. Certainly, the combination of 400 mg/m^2 CBDCA plus 4,000 mg/m^2 ifosfamide though not without toxicity – is reasonably safe and does produce remissions. There were no toxic deaths and the overall survival was reasonable (median, 21–25 months). Further investigation of this combination at a dose of 400 mg/m^2 CBDCA plus 4,000 mg/m^2 ifosfamide in previously untreated patients will be required in a randomised trial to assess this. Following previous experience with the addition of cyclophosphamide to cisplatin, which did not prolong survival, further follow-up will also be required before any increase in response rate can be equated with an overall improvement in the eradication and control of disseminated ovarian carcinoma [8].

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