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Carboplatin and ifosfamide in ovarian cancer phase II and III trials*

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Summary. Over the past few years controversy has continued as to whether alkylating agents such as cyclophosphamide or chlorambucil are as effective as cisplatin in advanced ovarian cancer. Arguments have also been put forward against the use of combination chemotherapy, which is clearly more toxic than single-agent treatment and is probably no more effective than a single-agent platinum compound except in terms of producing a higher response rate. Certainly survival is not improved.

Introduction

Both carboplatin [2, 3] and ifosfamide [1] have been shown to have activity in late-stage ovarian cancer and in recurrent disease. Both are less toxic than their parent compounds cisplatin and cyclophosphamide at equivalent therapeutic doses. Carboplatin produces little renal or neurological toxicity and ifosfamide can be given without urothelial damage if adequate amounts of mesna are given concomitantly.

It was intended that a randomised study be conducted using single-agent carboplatin vs single-agent ifosfamide, followed by carboplatin vs a combination of these two drugs. The purpose of such a three-armed study was to show whether three courses of the single or combined drugs were different in their immediate therapeutic effects (response rates) and whether any differences were reflected in overall survival or survival of responding patients.

Patients and methods

Pilot study. It was known what the maximum tolerated dose of these agents would be in combination; thus, a pilot study was done in 33 cases of abdominal carcinomatosis. The dose of each drug was escalated after six consecutive patients had been treated for a maximum of six courses at 28-day intervals (Table 1). Carboplatin was given by i.v. infusion over 30 min in 5% dextrose on the basis of doses of 200–400 mg/m^2. Ifosfamide was given as a 24-h infusion in normal saline together with an equimolar amount of mesna and forced diuresis to maintain a urinary flow of at least 100 ml/h. Doses ranged from 2,500–5,000 mg/m^2.

Toxicity was assessed before each new treatment, when blood count and chemical analyses were also done. A ^{51}Cr-EDTA clearance analysis was carried out every second treatment and dose reductions could be made if myelosuppression reached WHO grade 3 or more. Of the 33 patients treated, 13 had recurrent ovarian cancer, 15 had previously untreated ovarian cancer, and 5 had abdominal carcinomatosis of uncertain origin.

Randomised study. The study design (Fig. 1) compares six courses of carboplatin (400 mg/m^2) at monthly intervals (arm 1) with three courses of ifosfamide (5,000 mg/m^2 at 21-day intervals followed by three courses of carboplatin (400 mg/m^2) (arm 2) at monthly intervals. Only previously untreated patients with stage III epithelial ovarian cancer were randomised.

Patients were entered from the Royal Marsden, Guy's, St. Bartholomew's and St. George's Hospitals; a total of 124 patients were entered and 113 were fully evaluable for response. Patient characteristics were similar within the two arms, and the major ones are shown in Table 2.

Following staging laparotomy, all patients were investigated by ultrasound of the pelvis and liver, computerised tomographic (CT) scan of the abdomen and pelvis, chest X-ray and blood count was well as biochemistry. A ^{31}Cr-EDTA clearance analysis was carried out in all cases. After three courses, a full clinical, radiological and ultrasound

Table 1. Dose schedule for patients receiving carboplatin combined with ifosfamide

Carboplatin (mg/m^2)	Ifosfamide (mg/m^2)	Patients (N)	Total courses (N)
200	2,500	9	33
300	3,500	10	32
400	4,000	7	38
400	5,000	7	33

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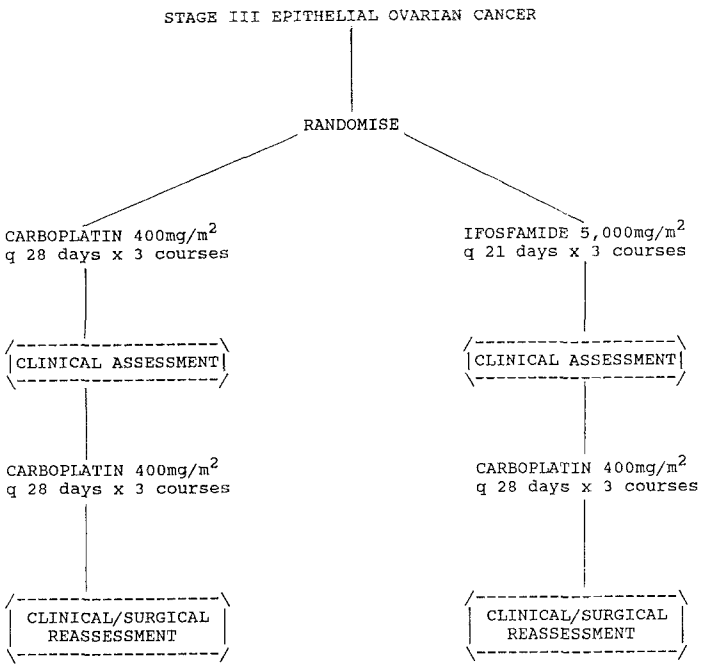

Fig. 1. A randomised trial of carboplatin vs ifosfamide followed by carboplatin

Table 2. Patient characteristics[a]

Characteristic	Arm 1 Number (%)	Arm 2 Number (%)
Patients (*n*)	63	61
Performance status:		
0–1	43 (68)	41 (67)
2	7 (11)	6 (10)
Unknown	13 (21)	14 (23)
Complete surgery[b]	37 (59)	33 (54)
Pathology:		
Serous	34 (54)	32 (52)
Other	12 (20)	18 (30)
Not specified	17 (27)	11 (18)
Grade – poorly differentiated	31 (50)	28 (46)
Residual disease:		
0	3 (5)	4 (7)
<2 cm	17 (27)	23 (28)
⩾2 cm	16 (25)	10 (16)
Unknown	5 (8)	5 (8)

[a] Carboplatin (arm 1) vs ifosfamide followed by carboplatin (arm 2) in stage III ovarian cancer
[b] Total abdominal hysterectomy + bilateral salpingo-oophorectomy ± omentectomy

Table 3. Responses after six courses of treatment

	Arm 1: JM8 × 6	Arm 2: IFO × 3, JM8 × 3
Number (%)		
NA	4 (7)	5 (9)
CR	20 (34)	13 (24)
PR	19 (32)	19 (34)
NC + PD	15 (26)	18 (32)
CR + PR		
Evaluable	72%	64%

IFO, ifosfamide; JM8, carboplatin; NA, not assessable

reassessment was made, which was repeated after six courses of treatment. At six months, most patients without progressive disease underwent a second-look laparotomy, with removal of residual tumours, uterus, ovary or omentum if disease was found. If no further surgical excision was considered to be useful, a laparoscopy was done

Results

Pilot study

Myelosuppresion was the major dose-limiting toxicity. At doses of 400 mg/m^2 carboplatin and 4,000 mg/m^2 ifosfamide, leukopenia of grade >3 occurred in 13/23 (57%) courses, with thrombocytopenia of grade >3 in 5/23 (22%) courses, for which interval blood counts were recorded. Only three of seven patients receiving these doses could complete six courses without dose reductions. When 5,000 mg/m^2 ifosfamide was given, toxicity of grade >3 was seen somewhat more often and platelet transfusions were sometimes required. Dose reductions were frequent; no patient completed more than three courses at these dose levels because of cumulative myelotoxicity. Other toxicities seen included alopecia in all patients and some emotional lability and somnolence in two patients, but there was no renal or uroepithelial toxicity.

The response rate in these patients was 49% (16/33), with ten clinically complete responses (CRs) and six partial responses (PRs). However, the mixture of cases treated did not enable a prediction to be made for the response rate in untreated, unequivocal ovarian cancer. Nevertheless, the study did result in a recommendation that the maximally safe dose of this combination be 400 mg/m^2 carboplatin plus 4,000 mg/m^2 ifosfamide [4].

By the time this study was complete, it became evident that a three-armed study as initially intended would not be possible in untreated ovarian cancer; thus, the randomised study was confined to asking the following questions:
1. Is ifosfamide as good as carboplatin in producing remissions after three courses of treatment?
2. If ifosfamide is used before carboplatin, is the overall response improved and is survival affected?

Randomised study

When treatment began, 13 (22%) patients in the carboplatin arm and 17 (31%) in the ifosfamide arm had no assessable or measurable disease. Of the remaining 45 patients given carboplatin, a CR was evident in 7 (12%) and a PR, in 22 (38%) after three treatments. In the ifosfamide arm, however, only 1 CR (2%) and 9 PRs (16%) were observed after 3 courses in 38 patients. Overall responses were 64% and 26%, respectively, in evaluable cases; the difference was significant ($P = 0.001$). After six courses of treatment, the difference in clinical response rate was less obvious and more patients were assessable, since second surgery was done at this stage.

Table 3 shows the responding cases in the two arms. The overall responses in evaluable cases was 72% for six courses of carboplatin and 64% for three courses of ifos-

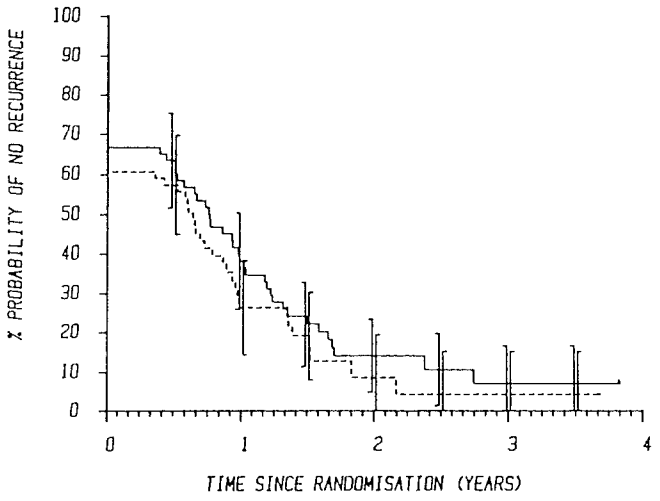

Fig. 2. Time to recurrence in 80 cases either responding to chemotherapy or with no assessable disease at the start of treatment. ——— Arm 1: JM8 × 6 ($n = 43$); – – – Arm 2: IFO × 3, JM8 × 3 ($n = 37$)

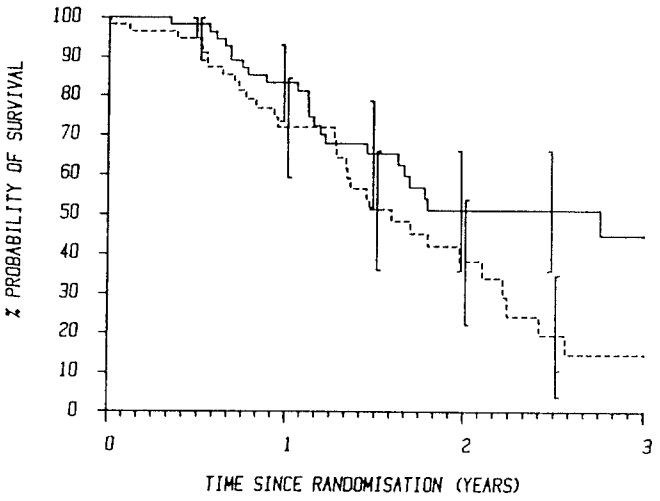

Fig. 3. Overall survival of all patients related to initial treatment. ——— Arm 1: JM8 × 6 ($n = 63$); – – – Arm 2: IFO × 3, JM8 × 3 ($n = 61$)

famide followed by three courses of carboplatin. After six cycles of carboplatin, 14 patients underwent a laparoscopy and 7 had a laparotomy, whereas in arm 2, 7 had a laparoscopy and 20, a laparotomy.

Survival

Analysis of survival to date has been limited to the overall survival of the two treatment arms and survival to recurrence. For patients who were not assessable at the start of therapy, together with those responding to treatment, there was no difference in time to recurrence between the two treatment arms (Fig. 2). However, overall survival favoured treatment with six courses of carboplatin rather than that starting with ifosfamide and continuing with carboplatin (Fig. 3); the difference was significant ($P < 0.05$).

Discussion and conclusions

Full discussion of these studies await a multivariate analysis of the data. What can be said now is that ifosfamide can be given safely in combination with carboplatin so long as doses are related to renal clearance of carboplatin. There was a credible response rate to combined therapy, but, as with much combination therapy in ovarian carcinoma, the benefits of combination over single-agent drugs remains obscure.

The phase III study clearly shows that after three courses of therapy, carboplatin produces more responses in patients with measurable disease than does ifosfamide. It is therefore very interesting that survival of "responding patients" was not higher in the carboplatin arm. This result may be due to the fact that when responders to carboplatin in arm 2 (three courses) did not achieve a CR, more carboplatin was usually given, up to a total of six courses. On the other hand, if a CR had not been achieved by the end of six courses of carboplatin (arm 1), no further drug was given. Although such a policy tended towards a less "clean" study, it was felt that to do otherwise would be unethical.

However, despite the use of extra carboplatin in arm 2, overall survival definitely seemed to be better in arm 1. This result was unexpected and remains thus far unexplained. It may be due to the fact that effective therapy was started later in arm 2 than in arm 1 and would not appear to be related to any lack of balance in initial prognostic features, since these were well matched. Over the first three courses, 5/58 patients on carboplatin showed progressive disease, whereas in the ifosfamide arm over the same period 11/55 progressed. Following carboplatin therapy in the 11 cases that progressed on ifosfamide, there were two CRs and three PRs, whereas in three patients disease continued to advance.

Other investigators have reported much better response rates for ifosfamide as a single agent in recurrent and primary ovarian cancer, but at the present time our evidence suggests that this drug is not a useful first-line agent. Further work on such a trial is being actively pursued.

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