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High-dose cyclophosphamide followed by cisplatinum in the treatment of ovarian cancer

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Summary. Twenty patients with previously untreated ovarian cancer received intensive chemotherapy after initial surgery. Treatment comprised two courses of cyclophosphamide at 7 g/m^2 with mesna, re-evaluation with second-look laparotomy where appropriate, followed by five courses of cisplatin at 100 mg/m^2. Three patients achieved pathologically documented complete remission (PDCR) with high-dose cyclophosphamide, and eight patients achieved partial remission. Fifteen patients went on to receive cisplatin. Nine of these patients had no assessable disease; of six patients who were assessed for response two achieved PDCR and three achieved partial remission. The overall response rate to the sequential regimen was 14/20 (70%). High-dose cyclophosphamide was associated with marked haematological toxicity, which was cumulative and fatal in two patients. The median duration of first remission was 14 months, and the median duration of survival was 20 months. It is concluded that sequential treatment with high-dose cyclophosphamide and cisplatin appears to be no more effective than conventional treatment in advanced ovarian cancer, judging by the PDCR rate and median survival achieved.

Introduction

A small proportion of patients with advanced ovarian cancer treated with alkylating agents at conventional dosage levels achieve long-term survival [15]. Evidence of a dose-response effect for alkylating agents [2, 7, 10], suggests that the use of higher doses than normal may be reflected in a greater therapeutic benefit.

A number of studies have examined the use of high-dose cyclophosphamide in solid tumours. Although most have been directed at the treatment of small cell lung cancer, some investigators have treated patients with ovarian cancer with high-dose cyclophosphamide. A limited evaluation of high-dose cyclophosphamide performed by Young et al. [18] failed to demonstrate a survival benefit compared with conventional-dose melphalan. However, the dose of cyclophosphamide used in this study (80 mg/kg) was considerably lower than that used in more recent protocols [11], and may have been insufficient to reveal any benefit from high-dose therapy. Buckner et al. [3] investigated the activity of repeated courses of cyclophosphamide at 120 mg/kg in nine patients with stage III ovarian cancer who had received no prior chemotherapy. A high clinical response rate was observed but only two patients achieved pathologically documented complete remission PDCR), one of whom relapsed after 9 months despite consolidation therapy with abdominopelvic radiotherapy. Major toxic effects included total alopoecia, nausea and vomiting and septicaemia during episodes of neutropenia.

Early intensification may reduce the chance of development of specific or multiagent resistance [3] and hence improve response rates and long-term survival. We nave therefore examined a sequential regimen of two courses of high-dose cyclophosphamide followed by cisplatin in advanced ovarian carcinoma. Our objectives were to assess the efficacy of remission induction with high-dose cyclophosphamide, to examine the role of cisplatin as consolidation treatment, and to determine the overall activity of the sequential regimen as judged by survival duration.

Patients and methods

Patients. The study was a joint project conducted by the I.C.R.F. Department of Medical Oncology, St. Bartholomew's and Homerton Hospitals, and the Department of Medicine, Royal Marsden Hospital, London.

Twenty patients with stage III or IV epithelial ovarian cancer were included in the study after initial surgery had been completed and informed consent obtained. Patients who were considered fit enough to undergo high-dose therapy were selected from the population of patients with ovarian cancer who were referred for chemotherapy. All were aged less than 66 years, and no patient had received prior chemotherapy. Patients with pre-existing cardiac problems were excluded, in view of the reported cardiotoxicity of high-dose cyclophosphamide [8, 9, 12]. Postoperatively, 9 of the 20 patients had residual disease exceeding 2 cm in diameter. In 3 of these, biopsy-only procedures had been performed. In six, residual bulky disease was left postoperatively despite maximum surgical effort. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and other necessary debulking procedures, including bowel resection where required, had been performed in 11/20 patients with postoperative disease measuring less than 2 cm in diameter.

Table 1 details the patient characteristics.

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Table 1. Patient characteristics

Patient no.	Age (years)	Stage	Residual	Grade	Histology	Courses HD cyclophosphamide	2nd-look findings	Response to HD cyclophosphamide	Courses cisplatin	% Dose	Status after cisplatin	Current status	Response duration	Survival (months)	Comments
1	54	III	S	W	M	3	Micro	PR	3	100	CCR	Relapse	17	37+	
2	51	IVp	B	P	S	3	ND	Prog., died	–	–	–	Dead	0	5	Died from complications of treatment
3	42	III	S	M	S	2	Micro	PR	4	100	CCR	CCR	18+	22+	
4	47	III	B	P	S	2	Macro 4×4 cm	PR	4	100	PR	Relapse	13	24+	3rd-look laparotomy after cisplatin confirmed PR
5	45	IVp	S	P	S	2	Micro	PR	3	83	CCR	Relapse, dead	8	19	
6	36	IVp	S	P	S	2	Micro	PR	1	100	CCR	Relapse, dead	21	26	Declined further treatment after 1st course of cisplatin
7	45	IVn	B	P	S	2	Small macro	PR	3	75	CCR	Relapse, dead	7	14	
8	24	IVp	B	P	M	2	ND clin.PR	PR	2	100	Prog	Dead	3	10	
9	43	III	B	P	S	2	ND clin.PR	PR	5	85	PR	Relapse, dead	14	21	
10	53	III	S	M	S	2	Clear	PDCR	4	100	CCR	CCR	23+	27+	
11	51	III	B	P	S	2	Clear	PDCR	4	90	CCR	CCR	22+	24+	
12	48	III	B	P	M	2	Clear	PDCR	5	100	CCR	CCR	32+	36+	
13	52	IVp	B	P	S	2	ND, prog.	Prog.	–	–	–	Dead	0	8	Received JM8 after HD cyclophosphamide
14	31	III	S	M	M	2	ND, prog.	Prog.	5	70	PR	Relapse, dead	3	13	2nd look after cisplatin confirmed PR
15	47	III	B	P	U	2	ND, not clin. assess.	UN-assess.	5	100	PDCR	CCR	8+	18+	2nd look after cisplatin confirmed PDCR
16	66	III	S	P	S	2	ND, died	Un-assess.	–	–	–	Dead	Un-assess.	6	Died from complications
17	57	IVp	S	M	S	2	ND, not clin. assess.	Un-assess.	–	–	–	Relapse, dead	Un-assess.	20	Severe opportunist infections after HD Cyclo phosphamide precluded 2nd look
18	52	IVp	S	M	S	1	ND, not clin. assess.	Un-assess.	–	–	–	Relapse, dead	0	5	Received chlorambucil after HD cyclophosphamide
19	37	III	S	P	E	1	ND, not clin. assess.	Un-assess.	5	85	PDCR	Relapse, dead	10	17	2nd look after cisplatin confirmed PDCR
20	25	III	S	U	S	1	ND, not clin. assess.	Un-assess.	5	100	CCR	CCR	Un-assess.	52+	

Stage: Pl, lymph node (extra-abdominal); P, pleural effusion. Residual: S, small; B, bulk (< 2 cm). Grade: W, well differentiated; M, moderately differentiated; P, poorly differentiated; U, unkown. Histology: S, serous; M, mucinous; E, endometroid; U, undifferentiated. Response: CCR, clinical CR; PDCR, pathological CR; PR, partial remission
ND, not done

Treatment schedule. The initial phase of treatment comprised two courses of high-dose cyclophosphamide at 7 g/m^2, the first of which was administered as soon as was practicable after initial debulking surgery. Response to two courses of high-dose cyclophosphamide was assessed as accurately as possible, employing second-look laparotomy where necessary, since the major aim of the study was to determine the activity of this treatment. Subsequently patients proceeded to treatment with cisplatin at 100 mg/m^2 for a planned five courses, the frequency of treatment

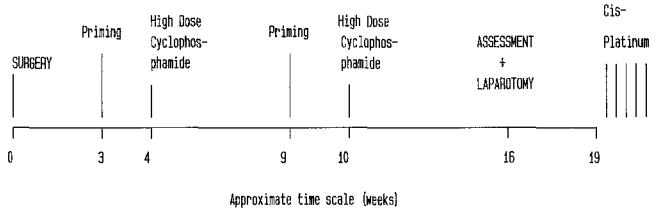

Fig. 1. Treatment plan

dictated by bone marrow recovery. The treatment schedule is summarised in Fig. 1.

High-dose cyclophosphamide was preceded in each case by a priming dose of cyclophosphamide (500 mg i.v.) given 7 days before treatment, in an attempt to reduce bone marrow toxicity [6].

On the day of treatment, following pre-hydration, cyclophosphamide 7 g/m^2 was given in five divided doses. This schedule was used because of evidence suggesting that the toxicity of cyclophosphamide is reduced when it is given in divided doses [4]. Each dose of 1.4 g/m^2 was given in 250 ml normal saline over 30 min and was followed by 500 ml 5% dextrose over 2.5 h. Treatment therefore extended over 12.5 h. Mesna 7 g/m^2, given in 11 divided doses at 3-h intervals from the commencement of treatment, failed to completely abolish urothelial toxicity, and therefore 13/20 patients received mesna 10.5 g/m^2 in the same schedule. After treatment the administration of i.v. fluids was continued to maintain an adequate urine output until the patient was able to take oral fluids adequately. All patients received i.v. lorazepam and prochlorperazine as antiemetics.

Response criteria. Responses were defined according to WHO criteria [17]. Response was assessed wherever appropriate by performing second-look laparotomy after full clinical and radiological studies. At laparotomy multiple biopsies were taken from areas of obvious disease, from sites of previous disease, and from any suspicious or high-risk areas (diaphragm, uterosacral ligaments, vaginal vault). All second-look laparotomies were performed by the same surgeon (JHS).

Survival was calculated from the date of diagnosis. Response duration was calculated from the time response was first documented until relapse.

Results

High-dose cyclophosphamide alone

Among the 20 patients there were 17 who completed two courses of high-dose cyclophosphamide and 3 who were unable to have more than one course because of excessive toxicity. In all, 14/20 patients were evaluable for response to high-dose cyclophosphamide: 9 patients with no clinically or radiologically assessable disease underwent second-look laparotomy, and 5 patients had disease which was detectable and measurable by clinical and radiological means.

Pathologically documented complete remission (PDCR) was achieved by 3 patients, and 8 patients, including 1 who received three courses of treatment prior to response assessment achieved partial remission. The overall response to high-dose cyclophosphamide was thus 11/20 (55%), or 11/14 (79%) of those evaluable for response.

There were 6/20 patients who were not evaluable for response to high-dose cyclophosphamide. None of these patients had clinically assessable disease, and none underwent a second laparotomy.

High-dose cyclophosphamide and cisplatin

Of the 20 patients, 15 proceeded to treatment with cisplatin after high-dose cyclophosphamide, these being the 11 responders plus 1 with progressive disease and 3 who had not been evaluable for response. Only 2 of the 15 patients were able to complete the intended five courses of cisplatinum at 100 mg/m^2, the remainder requiring dose reduction or early cessation of treatment because of haematological toxicity. There were 5 patients who did not receive cisplatin: this was due to excessive toxicity following high-dose cyclophosphamide in 4 and to protocol violation in 1 patient.

Six patients were assessed for response after cisplatin (5 by laparotomy and 1 clinically), while the remaining 9 had no clinically assessable disease and did not have further surgery. Complete remission was pathologically documented in 2 patients, though because these patients had not been assessed after high-dose cyclophosphamide the contribution of each drug to the remission is unknown. Partial remission was achieved in 3. All 9 non-evaluable patients, including 3 in PDCR after high-dose cyclophosphamide, remained clinically free of disease after cisplatin. The overall PDCR rate after high-dose cyclophosphamide and cisplatin was thus 5/20 (25%), or 5/15 (33%) of those receiving both drugs. The total response rate was 14/20 (70%).

Of the 14 responders to the sequential treatment, 4 patients in PDCR and 2 in clinical CR remain relapse-free at 18–52 months from the initiation of treatment. Relapse has occurred in the other 9 patients, up to 37 months from commencing treatment. The median duration of remission is 14 months.

There have been 12 deaths, 11 patients dying with progressive disease and 1 as a result of treatment with high-dose cyclophosphamide. The median survival is 20 months, with a median follow-up of 27 months. For pa-

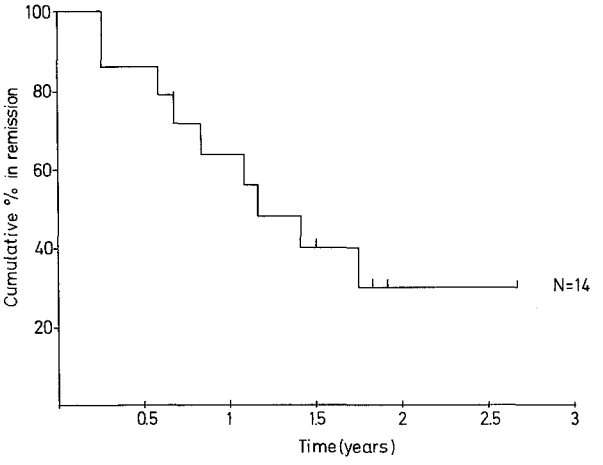

Fig. 2. Remission duration in ovarian cancer patients treated with sequential high-dose cyclophosphamide and cisplatin

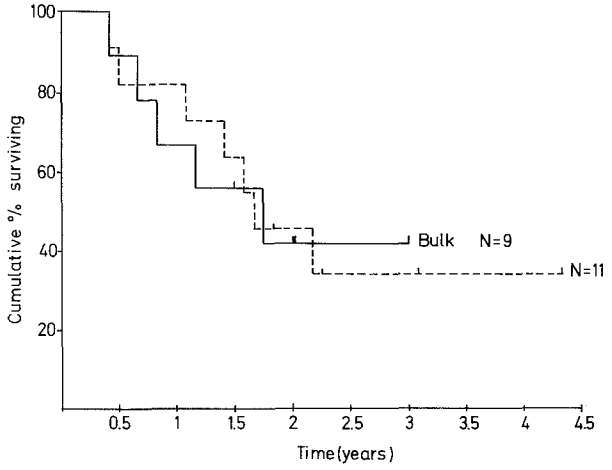

Fig. 3. Survival in ovarian cancer patients treated with sequential high-dose cyclophosphamide and cisplatin: bulky disease us small residual disease. p = N. S.

tients with bulky residual disease median survival was 14 months, while for those with small residual disease median survival was 20 months.

The results discussed above are summarised in Table 1, and shown in Figs. 2, 3 and 4.

Toxicity

General

All patients experienced severe nausea and vomiting (WHO grade III) after high-dose cyclophosphamide treatment, which lasted for up to 1 week in some cases. Mesna at a dose of 10.5 g/m^2 was tolerated without adverse effects. The majority of patients developed an erythematous skin rash in the necklace area, which began approximately 5 days after treatment. This subsequently became purpuric and faded over a period of weeks. Total reversible alopoecia developed in all patients treated. No other cutaneous side effects were observed.

Serum amylase levels were measured in five patients during seven cycles of high-dose cyclophosphamide. Elevated amylase levels, up to 1150 IU/l (normal range up to

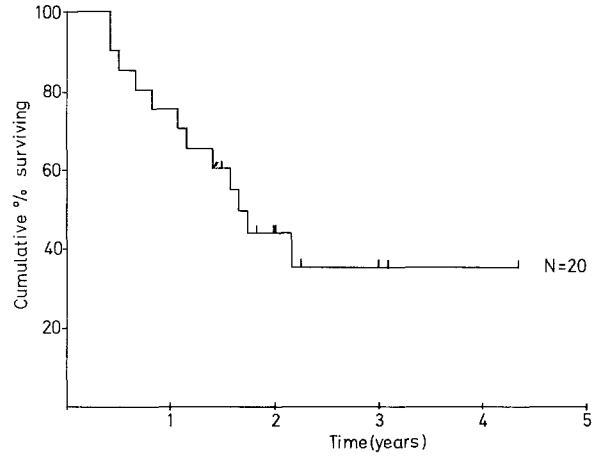

Fig. 4. Survival in ovarian cancer patients treated with sequential high-dose cyclophosphamide and cisplatin

Table 2. Haematological toxicity

Course	Patients	Days with neutrophils less than 1×10^9/l: Mean (range)	Days with platelets less than 100×10^9/l: Mean (range)
1	20	12.2 (8–16)	8.0 (0–13)
2	17	19.6 (8–115)	25.8 (3–116)
3	2	20 14–26	59.5 19–100

400 IU/l) were observed during four cycles (in 3 patients), occurring within the first 72 h after treatment and subsiding within 5 days.

Detailed assessment of possible cardiotoxicity was performed in 13 patients treated at Homerton Hospital. Patients were studied with echocardiography and nuclear angiography before each course of treatment with high-dose cyclophosphamide. Continuous ECG monitoring, cardiac enzymes, and daily ECG were performed following treatment. Minor elevations of cardiac enzymes were commonly seen. One patient experienced significant transient cardiac conduction abnormalities following treatment. Full details of this study will be reported at a later date.

Toxicity

Haematological

Severe haematological toxicity occurred in all patients and was cumulative, patients experiencing a longer-lasting nadir with each successive course of high-dose cyclophosphamide. Neutropenia (less than 1×10^9/l) occurred during every course of treatment, and thrombocytopenia (less than 100×10^9/l) occurred in 38 of 39 courses. Details of haematological toxicity are shown in Table 2.

Two patients treated with two courses of high-dose cyclophosphamide experienced particularly severe marrow toxicity. In one (aged 66 years) the marrow failed to recover after the second course, and she died 121 days after treatment. In the second, thrombocytopenia persisted for more than 100 days, and the clinical course was complicated by recurrent opportunistic infections which precluded further chemotherapy.

Discussion

The failure of combination chemotherapy to consistently improve survival of patients with ovarian cancer over that achieved with single-agent therapy [1, 14, 16] led us to explore whether more intensive single-agent therapy could achieve this end. However, despite the theoretical advantages, this study of high-dose treatment with cyclophosphamide has failed to demonstrate a higher PDCR rate than that achieved with conventional-dose treatment [16]. The low rate of PDCR (3/14; 21%) is particularly marked in view of the relative preponderance in this study of patients who were optimally debulked prior to chemotherapy.

Subsequent treatment with cisplatin at a time when most patients had small macroscopic or microscopic disease also proved relatively unsuccessful, with only 1/9 pa-

tients known to have residual disease entering a prolonged remission after cisplatin. The dosage delays necessitated by prior high-dose cyclophosphamide treatment may have compromised the efficacy of this part of the regimen.

Severe haematological toxicity occurred following high-dose cyclophosphamide, and this was fatal in two patients. All patients required prolonged hospitalisation for management of neutropenia and thrombocytopenia after treatment with high-dose cyclophosphamide, and further admissions were often required during the profound nadir occurring after cisplatin treatment.

In addition to haematological toxicity, other, less well-recognised side effects of high-dose cyclophosphamide emerged. Hyperamylasaemia was noted and warrants further investigation. There are two possible causes for this phenomenon. First, cyclophosphamide may directly cause pancreatic damage (though none of these patients had symptoms of pancreatitis). Alternatively, hyperamylasaemia may be a manifestation of tumour lysis. It is well known that serous ovarian neoplasms may be associated with hyperamylasaemia, and amylase has been proposed as a marker for this disease [13]. It is possible that cell lysis following high-dose cyclophosphamide is sufficiently rapid to cause detectable release of amylase. Further studies are required to determine the amylase isoenzyme (pancreatic or ovarian) released after high-dose cyclophosphamide treatment.

The disadvantages inherent in high-dose chemotherapy mean that substantial benefits should exist before such treatment is adopted in place of conventional dose therapy. In this small study PDCRs were achieved as frequently as would be expected with conventional treatment. The median survival is no longer than that achieved with other, less toxic regimens. It is therefore concluded that the toxicity encountered during sequential administration of high-dose cyclophosphamide and cisplatin makes this regimen unsuitable for use in the general population of ovarian cancer patients and that further use of this regimen is unwarranted.

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