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cis-Platinum, Adriamycin, and Hexamethylmelamine Versus Cyclophosphamide in Advanced Ovarian Carcinoma*

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Summary. *Fifty-three evaluable patients with disseminated ovarian carcinoma (FIGO III or IV) not treated with prior chemotherapy were randomized to receive either combination chemotherapy consisting of cis-platinum 40 mg/m² IV on day 1, adriamycin 40 mg/m² IV on day 1, and hexamethylmelamine 150 mg/m² PO on days 2–10 up to a maximum of 200 mg on a 4-weekly cycle, or moderate-dose cyclophosphamide alone 40 mg/kg given IV intermittently every 3 weeks. Entry was from 1. 11. 1978 until 30. 4. 1981 (last follow-up 31. 10. 1981). Pretreatment characteristics in both groups of patients, regarding median age at diagnosis, median time from diagnosis to chemotherapy, FIGO stage, histology, differentiation grade, type of surgery, residual disease, previous radiotherapy, and median performance status, were comparable. Objective responses were seen in 18 of 27 (66%) of patients receiving cyclophosphamide alone (range 5–32+ months) and in 10 of 26 (38%) of patients treated with the combination (range 3–30+ months), this difference being statistically significant (χ^2 = 4.228; $P < 0.05$). The median duration of objective response (11 vs 10 months) and the median survival (12 vs 11 months) were greater in the cyclophosphamide group, but these differences were not statistically significant.*

The toxicity of the combination was more severe. It is concluded that there is no therapeutic advantage for this combination schedule over the alkylating agent used alone.

Introduction

In the last 20 years, the most usual treatment of disseminated ovarian carcinoma has consisted in the use of single alkylating agents, mainly melphalan, until in 1978 Young et al. [13] reported a better overall response rate with a combination of cytotoxic drugs, Hexa-CAF (hexamethylmelamine, cyclophosphamide, methotrexate and 5-fluorouracil), demonstrating superiority of this combination (75%) over the single agent melphalan (54%). The usefulness of the Hexa-CAF regimen has been controversial and several reports have failed to confirm the original response rate [2, 3, 8]. It has not been shown that combination chemotherapy is superior to the use of moderate-dose cyclophosphamide alone (40 mg/kg). Since the introduction of *cis*-platinum many reports of randomized and nonrandomized clinical trials have appeared, showing response rates varying from 36% to 90% [1, 4, 6–10, 12, 14]. In an attempt to improve the cytotoxic chemotherapy of advanced ovarian carcinoma, several studies have been conducted at the Instituto Português de Oncologia de Francisco Gentil, in Lisbon. One of these prospective clinical trials, comparing moderate dose cyclophosphamide (40 mg/kg) with Hexa-CAF, did not demonstrate superiority of the combination over the alkylating agent alone.

The purpose of the present study was to compare the same schedule of moderate-dose cyclophosphamide alone with a combination comprising *cis*-platinum, adriamycin, and hexamethylmelamine.

Materials and Methods

Fifty-nine patients with disseminated ovarian carcinoma untreated by prior cytotoxic chemotherapy were entered in this trial, which began on 1 November 1978 and closed on 30 April 1981 (last follow-up 31. 10. 81). All of them had histologically proven serous, mucinous, or undifferentiated ovarian adenocarcinomas classifiable as stage III or IV according to the International Federation of Gynecology and Obstetrics (FIGO). Six patients were excluded from the final evaluation as they were not treated according to the protocol. Four were lost to follow-up and two were unevaluable because they discontinued therapy.

The patients were allocated randomly to receive either a single-agent or a combination regimen. Fifty-three evaluable patients were entered in this study. Twenty-seven were treated with cyclophosphamide alone 40 mg/kg IV on day 1 of a 3-weekly cycle. Twenty-six received a combination of *cis*-platinum 40 mg/m² IV on day 1, adriamycin 40 mg/m² IV on day 1, and hexamethylmelamine 150 mg/m² (maximum of 200 mg/day) on days 2–10, with 4-week intervals between courses (PAH). Chemotherapy was continued either until progression of disease after a response or failure to respond, or if a patient refused to go on with treatment.

The following dose modifications were adopted in the presence of bone marrow suppression:

Grade of toxicity	White blood count (per μl)	Platelet count (per μl)	Drug dosage (%)
0	≧ 4,000	≧ 100,000	100
1	2,500–3,999	80,000–99,999	75
2	< 2,500	≦ 79,999	0

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With grade 2 of toxicity the cyclophosphamide was omitted until at least grade 1 recovery, when therapy was resumed with 75% doses.

The maximum total dose of *cis*-platinum was 500 mg/m^2 [12]. To prevent nephrotoxicity, prehydration with dextrose saline at the rate of 1 l/h for 2 h was used, followed by 1 l of mannitol (37.5 g/l) containing the dose of *cis*-platinum. Finally, another liter of dextrose saline was given.

The maximum total dose of adriamycin was 450 mg/m^2 administered at the end of the second liter of dextrose saline.

A mild alteration of renal function or any signs of cardiac toxicity precluded the continuation of *cis*-platinum or adriamycin.

Before randomization baseline investigations were performed, including a full blood count, biochemical screen, chest radiography, ECG, barium enema, barium swallow, lymphangiography, isotopic liver scan, and abdominal and pelvic ultrasonograms. A full physical examination was carried out and repeated before each subsequent course of therapy. Hematologic and biochemical tests were repeated before each cycle. Radiographs were repeated at 3-monthly intervals and ultrasound scans at 6 months. Eligible patients were $\leqq$ 65 years, had normal cardiac and renal function, a performance status $\geqq$ 20% (Karnofsky), a minimum total white blood cell count of 4,000/mm^3, and a platelet count $\geqq$ 100,000 cells/mm^3.

After six cycles of therapy, the patients were restaged by physical examination, ultrasonography, and radiology (clinical restaging), and if appropriate, i.e., if no gross evidence of disease was detected by clinical and/or radiological examination, a second-look operation was performed (surgical restaging) when biopsy specimens were taken from lesions suspected of being malignant.

Between 2 and 4 weeks after the second-look operation, patients with or without residual disease resumed treatment according to the same regimen for more 18 months.

The two treatment regimens were evaluated with regard to overall response rate, median duration of response, median survival, and drug toxicity.

Objective regressions were assessed according to the following criteria of response:

A *complete response* (CR) was defined as total disappearance of all evidence of tumor and resolution of all serous effusions. A *partial response* (PR) was a decrease in the size of tumor masses by $\geq$ 50% with no tumor growing elsewhere. Response to therapy was determined by at least two observations not less than 1 month apart or at second-look operation. All patients not attaining CR or PR as defined (including patients with no change or progressive disease) were classed as nonresponders.

The *duration of response* was counted from the beginning of cytotoxic chemotherapy until the first signs of relapse.

Survival was calculated from the first cycle of chemotherapy to death, or date of the last follow-up for patients still alive (31 October 1981). The significance of differences between responders and nonresponders was calculated by the chi-square test and the log-rank method was used to analyze duration of remission and survival.

Results

Twenty-six (26) patients were randomized to receive the PAH regimen and 27, moderate-dose cyclophosphamide alone.

The clinical characteristics of each group are shown in Table 1. Essentially, both groups were comparable with regard to median age at diagnosis, time from diagnosis to start of cytotoxic chemotherapy, FIGO stage, histology, and histologic grade. The groups were also comparable in relation to prior surgery, previous radiotherapy, extent of disease remaining after surgery ($\geqq$ 2 cm or $<$ 2 cm), and performance status.

Antitumor Effects

The results of treatment are shown in Table 2. With the PAH protocol 10 patients (38%) achieved an objective regression, this being complete in five (19%), as against 18 patients (66%) who achieved objective regressions with the moderate-dose cyclophosphamide regimen, 12 of these (44%) achieving CR ($\chi^2 = 4.228$; $P < 0.05$).

Of five patients treated according to the PAH regimen who were in complete clinical response and underwent a second-look operation, three had no histologic evidence of residual tumor. Gross tumor was seen at operation in two patients, who relapsed clinically 8 months and 16 months after operation. The remaining five patients continue in remission 10+−30+ months after laparotomy.

Table 1. Clinical characteristics

	Number of patients	
	PAH	CYCLO
Number of evaluable patients	26	27
Age at diagnosis (years)		
Median	54	55
Range	32–65	34–65
Time from diagnosis to chemotherapy (months)		
Median	1	1
Range	1–27	1–28
FIGO stage		
III	22	24
IV	4	3
Histology of tumor		
Serous	16	18
Mucinous	5	6
Undifferentiated	5	3
Histologic grade		
1	2	1
2	5	4
3	10	12
4	9	10
Type of operation		
Biospy	4	7
Excision of masses	7	8
Total hysterectomy + bilateral salpingoophorectomy	9	7
Total hysterectomy + bilateral salpingoophorectomy + omentectomy	6	5
Previous radiotherapy	6	4
Residual disease		
$\geqslant$ 2 cm	21	23
$<$ 2 cm	5	4
Median performance status (range)	50 (20–90)	50 (20–90)

Table 2. Objective responses

	Number of patients	
	PAH (26)	CYCLO (27)
Objective regression		
Complete response	5 (19%)	12 (44%)
Partial response	5 (19%)	6 (22%)
	10 (38%)[a]	18 (66%)[a]
Median duration of remission (months)	10	11
Range	3–30*	3–32*
Median duration of survival (months)	11	12
Range	2–30*	3–36*

[a] $\chi^2 = 4.228$; * $P < 0.05$

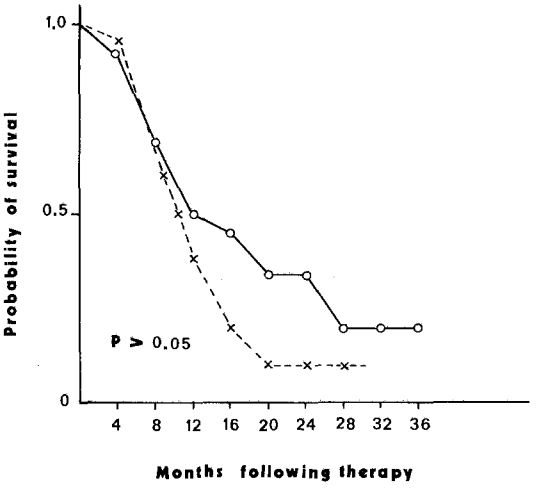

Fig. 1. Survival of the two treatment groups: PAH, 11 months; cyclophosphamide, 12 months (life-table method). (O———O) Cyclo; (× – – – ×) PAH

Table 3. Toxicity

	Number of patients	
	PAH	CYCLO
Hematologic toxicity		
Leukocytes (per μl)		
≧ 4,000	18	22
2,500–3,999	7	4
1,000–2,499	1	1
< 1,000	–	–
Platelets (per μl)		
≦ 100,000	–	–
Nausea and/or vomiting	26	27
Nephro-ototoxicity	–	–
Peripheral neuropathy	–	–
Alopecia	26	27
Chemical cystitis	–	–
Sepsis	2	1

Of the patients receiving the moderate dose cyclophosphamide regimen, nine underwent second-look operations and six of them had no evidence of disease. Gross tumor was observed at operation in three patients, who relapsed 7, 12, and 18 months later. The remaining patients continue in remission 8+–32+ months later.

No significant differences in duration of remission and survival were seen between the three different histological types (serous, mucinous, and undifferentiated adenocarcinomas). The number of patients is too small to discern whether prior radiotherapy affects the response rate.

The median duration of remission achieved in the PAH group was 10 months (range 3–30+ months), and it was 11 months (range 5–32+ months) with the moderate-dose cyclophosphamide alone, these differences not being statistically significant.

The survival life-table curve is shown in Fig. 1. The estimated median survival was 11 months for the combination schedule and 12 months for the single alkylating agent ($P > 0.05$).

Toxicity

The toxicity of the regimens, as shown in Table 3, was similar. The hematological toxicity observed was identical. Dose adjustments were made for seven patients to the PAH regimen, and in one the interval between the courses was increased by 1 week. In the case of the single alkylating agent adjustments were made for four patients, and again it was necessary in one case to increase the interval between the cycles by 1 week. All the patients suffered from nausea and vomiting, this side-effect being more extreme and disturbing in patients receiving the combination regimen, who always needed in-patient care. This symptom was also considerable in patients receiving moderate-dose cyclosphosphamide.

No cases of nephrotoxicity, ototoxicity, cardiac or neurologic toxicity or peripheral neuropathy were detected when both hexamethylmelamine and *cis*-platinum were given, but we did not exceed 500 mg *cis*-platinum/m^2 or 450 mg adriamycin/m^2. All patients developed alopecia. Six cases of chemical cystitis were detected with the single-agent protocol. To avoid this side-effect the patients were advised to drink 3 l of water in the first 4 h following cyclophosphamide administration. Two cases of septicemia occurred in the single-agent group and one in the PAH group, but these were treated successfully.

Discussion

The encouraging results obtained with the use of *cis*-platinum in previously treated patients with disseminated ovarian

carcinoma has influenced the chemotherapeutic approach to this disease. But the optimal dose for *cis*-platinum has not yet been determined, although data from the Royal Marsden Hospital, recorded in previously treated patients, suggest that response rates with doses of 30 mg/m^2 every 3 weeks are inferior to those obtained with 100 mg/m^2 every 4 weeks (28% versus 52%) [12].

To try to increase the effectiveness of *cis*-platinum, we have combined it with adriamycin and hexamethylmelamine, two compounds demonstrated to have significant activity in this disease when used singly or in combination [5, 11]. However, this study demonstrated an overall response rate of only 38% for the combination, compared with 66% obtained with moderate-dose cyclophosphamide alone. The smaller percentage of objective remissions obtained with the combination regimen can, however be explained by the lower doses used in this study compared with other equivalent schedules.

The relatively poor prognostic factors of both groups must be stressed. Forty-four (44) of the 53 patients (83%) had quite substantial residual disease ($\geqq$ 2 cm) prior to initiation of chemotherapy, 41 of 53 (77%) had a poor histologic grade and 10 had received previous radiotherapy.

cis-Platinum and adriamycin have to be discontinued after 10 or 11 courses of therapy, making it necessary to consider a maintenance regimen. Based on these data and on the relatively good response rate we have obtained with the moderate-dose cyclophosphamide alone, we intend to continue using this dose of cyclophosphamide alone as for maintenance until it is demonstrated unequivocally that a combination chemotherapy regimen is superior. In this trial, no therapeutic advantage was found for the combination over moderate-dose cyclophosphamide alone, which can be administered easily on an out-patient basis.

We are now starting a new prospective randomized clinical trial to compare moderate-dose cyclophosphamide alone against moderate-dose cyclophosphamide and *cis*-platinum for remission induction, followed by maintenance with cyclophosphamide alone at the same dose.

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