Eur J Cancer Clin Oncol, Vol. 19, No. 4, pp. 461–465, 1983.
Printed in Great Britain.

0277-5379/83/040461-05$03.00/0

Moderate-dose Cyclophosphamide for Disseminated Ovarian Carcinoma: a Phase II Study

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Abstract—*Fifty-six evaluable patients with advanced ovarian carcinoma (FIGO III or IV), without prior cytotoxic chemotherapy, were studied to assess the activity of single-agent moderate-dose cyclophosphamide,* 40 mg/kg *to a maximum dose of* 3000 mg, *given intravenously as a bolus injection every* 3 weeks. *All patients were treated as outpatients. Moderate-dose cyclophosphamide resulted in* 36 (64%) *objective responses* (19 *CR*, 17 *PR*). *Nausea and severe vomiting occurred in all patients, but no patient needed hospitalization for this complication. Other side-effects observed were alopecia* (100%), *leukocytes* $\leqslant 2500/\mu l$ (18%), *chemical cystitis* (11%) *and sepsis* (4%). *The median duration of response was* 11 months, *and the estimated median survival by the life-table method for responders was* 16 months *and for non-responders* 4 months ($P < 0.001$). *Clinical trials previously performed by our group comparing cyclophosphamide alone, either vs* cis-*platinum, adriamycin and hexamethylmelamine or vs Hexa-CAF, showed a better remission rate with the use of moderate-dose cyclophosphamide alone. Therefore we suggest further investigation of this agent in a moderate dose in disseminated ovarian carcinoma.*

INTRODUCTION

DESPITE the recent reports [1–4] claiming superiority of combination cytotoxic chemotherapy over alkylating agents used alone, the management of advanced disease remains unsatisfactory. Buckner *et al.* [5], in 1974, showed a response rate of 89% (8/9 patients) using intermittent high-dose cyclophosphamide alone (120 mg/kg). Based on these data, Piver *et al.* [6] undertook another study also using high-dose cyclophosphamide alone (70–100 mg/kg), but obtained only 1 partial remission in 8 patients treated (12%). Young *et al.* [7] reported the results of a clinical trial using high-dose cyclophosphamide, 40 mg/kg i.v., followed in 12 hr by the same dose, obtaining 6 objective regressions in 10 patients (60%). The high toxicity of high-dose cyclophosphamide, much greater than the intermittent oral administration of melphalan, has discouraged its use. Recently, Twiggs and Morrow [8] failed to confirm the efficacy of high-dose cyclophosphamide (1000 mg/m^2), obtaining in 10 evaluable patients only 2 objective regressions (20%), but this alkylating agent was used in patients as a second-line treatment after the failure of a previous administration of melphalan.

Concurrently with these studies, we began a prospective phase II study in February 1973, at the Instituto Português de Oncologia de Francisco Gentil, Lisboa, using moderate-dose cyclophosphamide alone (40 mg/kg i.v. every 3 weeks) in patients with disseminated ovarian carcinoma without receiving prior cytotoxic chemotherapy, and the results are reported here.

MATERIALS AND METHODS

Sixty-one consecutive patients, referred to the Instituto Português de Oncologia de Francisco Gentil, Lisboa, Portugal with advanced ovarian carcinoma and, without previous cytotoxic chemotherapy, were entered in this study. All of them had ovarian tumors of epithelial origin, histologically shown to be either serous, mucinous or undifferentiated.

Five patients have been excluded from final evaluation as they were not treated according to

Accepted 15 September 1982.

the protocol. Three were unevaluable because of discontinued therapy and 2 were lost to follow-up. Patients were considered evaluable if they received at least one treatment cycle. The patients' characteristics are shown in Table 1. The staging used was that recommended by the International Federation of Gynecology and Obstetrics (FIGO). All patients had undergone a prior laparotomy (surgical staging).

Baseline studies included a hematologic and a biochemical survey, chest radiograph, barium enema, barium swallow, lymphangiography, an isotopic liver scan and, after 1976, an ultrasound scan of the abdomen and pelvis. Relevant radiographs were repeated at 3-monthly intervals, and the ultrasonograms and liver scans every 6 months. All patients were $\leqslant$75 yr, had normal hepatic and renal functions, a performance status equal or more than 20% according the Karnofsky's criteria, a minimum total white blood count of 4000 cells/mm^3 and a platelet count $\geqslant$100,000 cells/mm^3. The patients received cyclophosphamide alone 40 mg/kg i.v. on day 1 of a 3-weekly cycle. Hematologic and biochemical tests were repeated before each course of therapy. Cytotoxic chemotherapy was continued either until progression of disease after a response or evidence of failure to respond to therapy or refusal to go on with treatment.

Fifty-six evaluable patients untreated by previous cytotoxic chemotherapy were entered in this study. They received cyclophosphamide 40 mg/kg i.v. every 3 weeks.

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

Grade of toxicity	White blood count (per μl)	Platelet count (per μl)	Drug dosage (%)
0	$\geqslant$4000	$\geqslant$100.000	100
1	2500–3999	80.000–99.999	75
2	<2500	$\leqslant$ 79.999	0

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

Patients clinically disease-free after six months of treatment were restaged surgically by a second laparotomy. Biopsy specimens were taken from suspicious lesions. Not less than 2 weeks or more than 4 weeks after the second look operation, patients with or without residual disease were treated subsequently with the same regimen for 18 months more to complete 2 yr of treatment.

The treatment was evaluated by response rate, median duration of response, the 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 clinically evident tumor and resolution of all serous effusions. A *partial response* (PR) was defined as a decrease in the size of tumor masses equal to or more than 50%, without tumor growing elsewhere. In both cases, the response to therapy was determined by at least two observations not less than 1 month apart (clinical restaging) or at second-look operation (surgical restaging). *No change* (NC) means a decrease equal to or less than 50% or an increase equal to or more than 25% in the size of measurable lesions with no new evidence of tumor or worsening of symptoms. *Progressive disease* (PD) was when there was an increase in the size of some or all lesions and/or the appearance of new lesions.

The duration of response was determined from the start of cytotoxic chemotherapy until progression of the disease was documented.

Survival was dated from the onset of cytotoxic chemotherapy to death, or date of the last follow-up for the patients still alive (31 October 1981). The survival for the responders and non-responders has been analysed by the life-table method and the significance of differences between these two groups of patients by Students' t test.

RESULTS

The clinical characteristics of the patients are shown in Table 1, including age at diagnosis, time from diagnosis to the start of cytotoxic chemotherapy, FIGO stage, histology, histologic grade, type of preceding operation (biopsy only, excision of masses, total hysterectomy + salpingo-oophorectomy + omentectomy) previous radiotherapy, residual disease and performance status.

Antitumor effects

The results of treatment are shown in Table 2. Responses occurred in 36/56 (64%) patients, being complete in 19 (34%).

The median duration of remission was 11 months (range 3–82 months); 11 patients are still alive, 3 of whom have progressive disease.

The survival curve is shown in Fig. 1. The estimated median survival of responders was 16 months and for the non-responders 4 months, this difference being statistically significant ($P<0.001$). At the last follow-up 4 patients are still alive and in complete remission, lasting 82+, 32+, 25+ and 25+ months respectively.

Toxicity

The toxicity of treatment is shown in Table 3. The side-effects were predictable and reversible.

Table 1. *Clinical characteristics*

	No. of patients
No. of evaluable patients	56
Age at diagnosis (yr)	
Median	54
Range	30–74
Time from diagnosis to chemotherapy (months)	
Median	1
Range	1–28
FIGO Stage	
III	6
IV	50
Histology of tumor	
Serous	34
Mucinous	12
Undifferentiated	10
Histologic grade	
1	3
2	7
3	26
4	20
Type of operation	
Biopsy	15
Excision of masses	14
Total hysterectomy + bilateral salpingo-oophorectomy	15
Total hysterectomy + bilateral salpingo-oophorectomy + omentectomy	12
Previous radiotherapy	9
Residual disease	
⩾2 cm	49
<2 cm	7
Median performance status (range)	50 (20–90)

Table 2. *Objective response*

	No. of patients	
Total No. of patients	56	
Objective regression		
Complete response	19 (34%)	36 (64%)
Partial response	17 (30%)	
Median duration of remission (months)	11	
Median duration of survival (months)		
Responders	16*	
Non-responders	4*	

* $P < 0.001$.

Table 3. *Toxicity*

	No. of patients
Hematologic toxicity	
Leukocytes (per μl)	
⩾4000	38
2500–3999	10
1000–2499	8
<1000	–
Platelets (per μl)	
⩽100,000	–
Nausea and/or vomiting	56
Alopecia	56
Chemical cystitis	6
Sepsis	2

All patients experienced nausea and/or vomiting, which began 4–6 hr after the administration of the drug and lasted several hours, but not more than 24. Pretreatment and subsequent use of metoclopramide 10 mg i.m. 4 hr after the administration of cyclophosphamide and every 6 hr subsequently, lorazepan orally in the first 4 hr after the start of cytotoxic chemotherapy and/or diazepam 10 mg i.m. at the beginning of treatment and every 12 hr helped to minimize this severe side-effect. Alopecia developed in all patients. A chemical cystitis defined as a sterile hemorrhagic cystitis noted by gross hematuria was observed in 6 patients (11%). To avoid this side-effect patients were advised to drink 3 l. of water in the first 4 hr after the start of the cytotoxic chemotherapy and to maintain a high fluid intake as soon as the vomiting has stopped in order to maintain a large diuresis for at least 24 hr.

Two cases of septicemia occurred, but were treated successfully. Hematologic toxicity was mild and recovery was generally complete by day 20 of successive cycles of cyclophosphamide. Dose adjustments were performed in 10 patients, it being necessary in 8 to increase by one week the interval between the courses.

DISCUSSION

Recently, a large variety of schedules of combination cytotoxic chemotherapy have been reported for the treatment of ovarian carcinoma [1, 3, 9–15], with response rates varying from 36 to 90%. The variation can probably be explained by the differences in patient selection, prognostic factors and response criteria. The initial demonstration of superiority for a schedule of combination chemotherapy over a single alkylating agent was first reported by Young *et al.* [1]

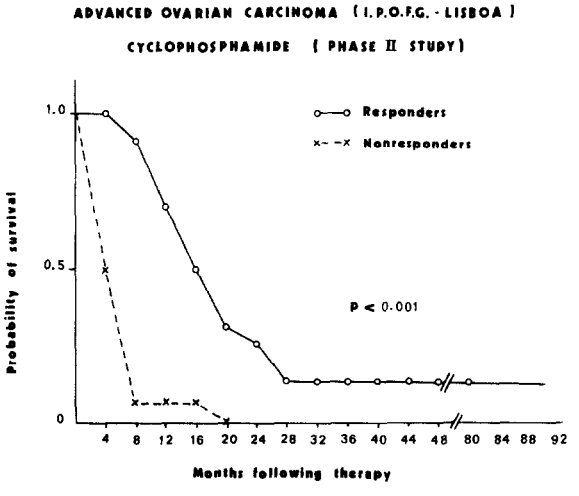

Fig. 1. *Overall survival of responders (median* 16 months) *and non-responders (median* 4 months) *(life—table method).*

and by Omura *et al.* [16], but these results so far lack confirmation [15, 17–19].

From our study, several points can be emphasized. With a response rate of 64%, the efficacy of moderate-dose cyclophosphamide in the treatment of advanced ovarian carcinoma has been demonstrated. This high response rate was achieved in spite of the fact that 49 of the 56 patients had larger residual disease (≥2 cm) prior to initiation of cytotoxic chemotherapy. Furthermore, the use of moderate-dose cyclophosphamide as a single agent is easier to manage and less toxic than Hexa-CAF [1, 19] or schedules that include *cis*-platinum [20], and is compatible with outpatient care. These results provide a standard against which to compare new regimens of treatment for advanced ovarian carcinoma.

Acknowledgement—The authors thank Dr. R. D. Rubens (Imperial Cancer Research Fund Breast Cancer Unit, Guy's Hospital, London) for criticism and suggestions.

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