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Clinical Trials Summaries

Phase II Study of Intravenous Menogaril in Advanced Ovarian Carcinoma

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INTRODUCTION

COMPARATIVE preclinical data suggested that menogaril, a semisynthetic analogue of nogalamycin, had a better therapeutic index than doxorubicin, since menogaril was 5–10 times less active in murine tumours but 15 times less active in inducing cardiotoxicity in the chronic rabbit model [1].

When menogaril was given as a 2 h infusion every 4 weeks, leukopenia was the dose-limiting toxicity [2]; erythema and phlebitis, which were dose-dependent and occurred at the site of injection, were the other major manifestations of toxicity.

A single intermittent schedule for menogaril was chosen by the Early Clinical Trials Group for a programme of disease-orientated Phase II studies. The present report focuses on the results achieved in patients with advanced ovarian carcinoma.

MATERIALS AND METHODS

Only patients with a histological diagnosis of advanced epithelial ovarian cancer were considered eligible for this study. Eligibility criteria also included measurable or evaluable disease with documented progression within the last 2 months, and no prior treatment with anthracyclines or with more than two chemotherapeutic regimens.

Menogaril was administered i.v. every 4 weeks at doses of 160 mg/m^2 in poor-risk patients (WHO performance status 2; prior treatment with two or more myelosuppressive drugs) and 200 mg/m^2 in good-risk patients. The drug was supplied by Upjohn International, Inc., Brussels, Belgium, in vials of 50 mg of menogaril, 16.6 mg of lactic acid and 100 mg of mannitol. Each vial was reconstituted with 10 ml of sterile water for injections resulting in a concentration of 5 mg/ml. The total dose was subdivided into three parts, which were each diluted into 150–200 ml of 5% dextrose just before administration and infused over a period of about 30 min.

Drug administration was delayed by 1 week if full haematologic recovery had not taken place at the time of scheduled retreatment. The dosage was modified according to the lowest value of WBCs and platelets measured weekly during the previous course.

Responses and toxicity grades were defined according to WHO criteria [3]. Patients were classified as no change if the disease remained static for a period of at least 12 weeks.

RESULTS

Between July 1985 and October 1987, 28 patients were entered into this study. Six were subsequently defined as not eligible for the following reasons: more than two prior chemotherapeutic regimens (two patients); no documentation of progressive disease at the start of treatment (one patient); histological diagnosis not available (one patient); no prior treatment (one patient); treatment not given because of poor general conditions (one patient). Table 1 summarizes the characteristics of the remaining 22 eligible patients. All patients had been pretreated with cisplatin and/or platinum analogues. Alkylating agents had also been given in 19 cases. In 86% of the patients, the treatment-free

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Table 1. Characteristics of eligible patients

Characteristics	No. of patients	Percentage
Total	22	
Median age in years (range)	57 (43–74)	
WHO performance status		
0–1	18	82
2	4	18
FIGO stage		
III	13	59
IV	9	41
Largest tumour diameter		
≤5 cm	9	41
>5 cm	13	59
Previous treatment		
1 chemotherapy regimen	8	36
2 chemotherapy regimen	14 (2)	64

In parentheses, number of patients who also received radiotherapy.

interval between prior chemotherapy and menogaril was shorter than 6 months.

Twenty patients were evaluable for response and toxicity, one for toxicity only and one was not evaluable for any analysis because of a tumour-related death occurring during the first 4 weeks of treatment. One patient who had first responded to cisplatin and later to carboplatin, and had then shown a rapid tumour progression when carboplatin was reintroduced because of a new pelvic recurrence, achieved a partial response which was still continuing after 12 months. A total of 18 patients showed tumour progression which was documented after the first cycle in four cases. One patient with stable disease after two cycles discontinued the treatment because of severe local and cutaneous toxicity.

Among 10 patients treated at 160 mg/m^2, the median WBC nadir after the first cycle was $2.3 \times 10^3/\mu l$ (range $0.7–2.9 \times 10^3/\mu l$), occurring on day 14 (range 7–19) and recovering by day 29 (range 15–35). Among 11 patients treated at 200 mg/m^2, the median WBC and platelet nadir after the first cycle were $1.6 \times 10^3/\mu l$ (range $0.8–3.5 \times 10^3/\mu l$) and $85 \times 10^3/\mu l$ (range $68–113 \times 10^3/\mu l$) respectively. Mild to moderate nausea and vomiting on the day of treatment occurred in 67% of cases; other side-effects included alopecia (WHO grade 2 and 3) in 28% of patients, and mucositis (WHO grade 3 and 4) in 9%. Thirty-nine per cent of the patients presented a painful phlebitis, which was accompanied by an inflammatory erythema of the surrounding skin in all cases but one. One ineligible patient showed a possible drug-related generalized skin rash with erythema and pruritus, which appeared within 24 h of the third and last administration and resolved within 1 week. The highest cumulative dose given was 1650 mg/m^2; in that case there was no evidence of any impairment of cardiac function as evaluated by echocardiography.

DISCUSSION

The results of this study suggest that menogaril does not have any activity in epithelial cancer of the ovary resistant to cisplatin or platinum analogues. Similar negative results were achieved when drugs already known as active in ovarian carcinoma were given to patients who had failed a prior treatment with cisplatin [4]. It is therefore reasonable to assume that the potential activity of new selected agents might be discovered only by testing them as first therapy in those patients who are unlikely to benefit from standard treatments because of the unfavourable characteristics of their disease.

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