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Short communication

Cisplatin, adriamycin and cyclophosphamide (PACe) combination chemotherapy in patients with ovarian carcinoma resistant to chlorambucil

Graham M. Mead, Christopher J. Williams, and J. Michael Whitehouse

C.R.C. Medical Oncology Unit, CF99, Southampton General Hospital, Southampton, Hampshire, SO9 4XY, England

Summary. Twenty patients with stage III or IV ovarian carcinoma refractory to chlorambucil were treated with IV cisplatin, adriamycin and cyclophosphamide. Two patients achieved CR and four PR, giving an overall response rate of 30%. All patients have since died at 0–18 (median 8) months. Use of this regimen was associated with marked toxicity, including three drug-related deaths. Second-line drug combinations should be regarded as experimental, and they should probably only be used in selected patients outside of clinical trials.

Introduction

A number of clinical trials are at present in progress to compare single-agent chemotherapy with drug combinations in the management of stage III or IV ovarian carcinoma. Second-line chemotherapy is commonly administered to patients who fail to achieve remission with alkylating agent treatment, and we present our experience of such therapy in 20 patients, the majority of whom were enrolled in a trial comparing chlorambucil with a cisplatin, adriamycin, and cyclophosphamide combination (PACe).

Materials and methods

Twenty patients with metastatic ovarian carcinoma primarily refractory to oral chlorambucil were treated IV with a three-drug combination (PACe) comprising cisplatin 80 mg m^{-2}, adriamycin 40 mg m^{-2}, and cyclophosphamide 1 G m^{-2} given on day 1 of a 28-day cycle. All patients had progressive disease whilst receiving chlorambucil and were not considered eligible for study in the absence of any of the following: evaluable disease, white cell count greater than 3.5×10^9/l, platelet count greater than 130×10^9/l, creatinine clearance greater than 50 ml/min.

Cisplatin administration was preceded by an infusion of 5% dextrose in ⅕ normal saline given IV until the urine output had exceeded 150 ml/h for at least 2 h. All three drugs were then given by bolus IV injection, and IV fluids were continued for a minimum of 16 h and until emesis stopped. Further cisplatin doses were adjusted according to renal function; a 50% dose was given if the creatinine clearance fell to 35–50 ml/min and the drug was omitted in the presence of more severe renal impairment.

Offprint requests to: G. M. Mead

Chlorambucil therapy (given prior to PACe) was administered at a dose of 10 mg PO for 14 days out of each 28.

Patients were examined prior to each treatment course, and appropriate investigations (CXR, ultrasound) were repeated to document disease response. We planned to treat all patients with five cycles of PACe in the absence of progressive disease. Second-or third-look laparotomy was not used to restage any patient. The following response criteria were used; CR was defined as total regression of all known disease sites; PR was defined as a $\geq 50\%$ reduction in measurable tumour mass, with complete regression of effusions where present; NR (no response) implied $< 50\%$ regression of evaluable disease; and PD (progressive disease) was recorded in the event of any increase in measurable tumour.

Survival was measured in months from the start of PACe treatment.

Results

Patient characteristics are summarised in Table 1. All patients were treated for symptomatic disease in the pelvis, abdomen or pleural cavity. Disease response and survival are reported in Table 2. Disease sites in responding pa-

Table 1. Patient characteristics

No.	20
Age range (median)	44–67 (53) years
Stage at presentation	
III	16
IV	4
Duration of chlorambucil medication: range (median)	1–24 (4) months

Table 2. Response to PACe and survival

Response to PACe	No.	Survival in months
CR	2	9, 12
PR	4	8, 14, 15, 18
NR/PD	11	1, 2, 3, 4, 4, 7, 8, 8 9, 9, 9
Toxic death	3	0, 0, 0

tients were as follows: CR, pleural effusion (one), ascites + pelvic mass (one); PR, abdominal mass (two), pelvic mass (two).

Patients were treated with one to five (median 3.0) cycles of PACe chemotherapy. In only four patients (2 CR, 2 PR), three of whom received five and one four treatment cycles, was therapy stopped for reasons other than progressive or unresponsive disease. In one of these patients seizures [4] and a cerebrovascular accident precluded further treatment after four cycles. Neither previous response to chlorambucil nor duration of chlorambucil therapy appeared to correlate with response to PACe chemotherapy.

PACe proved to be a toxic treatment. All patients experienced nausea and vomiting and most developed complete alopecia. In addition, seven required blood transfusions, five developed a platelet count $< 20 \times 10^9/l$, and seven developed a neutrophil count $< 500 \times 10^9/l$ during treatment, complicated by neutropenic fever in six patients and septic death in three. These three patients all developed profound pancytopenia following their first cycle of PACe chemotherapy, having previously received chlorambucil for 1, 4, and 14 months. No clear reason for their extreme sensitivity to this drug combination was apparent. Other complications included the development of mild peripheral neuropathy in one patient, seizures in one patient, and reduction of creatinine clearance to < 50 ml/min in three patients.

Discussion

PACe proved to be a toxic and relatively ineffective treatment regimen in this patient population. Our results are remarkably similar to those recently reported by Neijt et al. [5] using two comparable regimens in a similar patient population. This group were able to demonstrate that patients with late recurrence of disease (2 years after starting treatment) were more likely to benefit from such drug combination. It was recognised, however, that this might represent a characteristic of the disease rather than treatment efficacy. Other authors have published more encouraging results than our own [1–3, 6, 7] but none reported complete survival figures, as in this study.

We cannot recommend PACe chemotherapy for patients with ovarian carcinoma resistant to chlorambucil. Patients anxious to receive further treatment in this setting should be aware of possible toxicity as well as benefit. Those few patients developing late relapse of disease which proves resistant to chlorambucil may benefit from a drug combination, but we found no evidence in this study to support this hypothesis.

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