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Phase II study of combination 4'-epidoxorubicin and mitomycin C in recurrent epithelial ovarian cancer

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Summary. Thirty-three evaluable patients who had epithelial ovarian cancer that had not responded to treatment were entered into a phase II study of combination epirubicin and mitomycin C. Epirubicin (65 mg/m^2) and mitomycin C (4 mg/m^2) were administered separately, each as an i.v. bolus every 4 weeks. Ten patients (30%) had a complete or partial responses. The median duration of response was 20 weeks (range, 9–53). The regimen was well tolerated. Myelotoxicity occurred in four patients requiring hospitalization for septicaemia. Eleven patients had a blood transfusion. Alopecia was common, and nausea and vomiting, though frequent, usually mild. Cardiological toxicity was observed in one patient only. She developed congestive cardiac failure after an acute myocardial infarction. This regimen is active in advanced ovarian cancer that has not responded to prior treatment and warrants further study combination with other active drugs as a first-line regimen for ovarian cancer.

Introduction

The majority of patients with epithelial ovarian cancer present with late-stage disease that is not amenable to complete surgical excision [4]. Epithelial ovarian cancer is chemosensitive, and therefore chemotherapy is important in the management of this disease. Although objective response rates of up to 90% can be achieved wih platinum-containing combination regimens [9], the majority of patients relapse after primary treatment. At this stage ovarian cancer is relatively resistant to further treatment and the responses obtained of short duration [10]. There is therefore a need for effective, yet non-toxic, second-line regimens. It is also important in this situation to evaluate innovative combinations which might incorporated into potentially more active primary regimens.

Epirubicin (4'-epidoxorubicin) is a derivative of adriamycin (doxorubicin). It has been shown to have activity comparable with that of its parent compound in ovarian cancer [7, 8] though there is less haematological and cardiac toxicity [3]. Mitomycin C is moderately active in ovarian cancer, both as a single agent [1] and in combination [5]. There is evidence to suggest that the combination of mitomycin C and adriamycin is active in disease resistant to other regimens [11]. Our aim was to evaluate the effectiveness of the combination of epirubicin and mitomycin C as a relatively non-toxic regimen that could be administered on a outpatient basis to patients in whom disease had progressed during, or relapsed after, prior therapy.

Patients and methods

Thirty-three patients were recruited into this study between January 1986 and August 1987. Their characteristics are shown in Table 1. Entry criteria included histologically confirmed epithelial ovarian cancer that had not responded to prior treatment, no medical or cardiac contraindications to treatment, no history of other malignancy other than non-melanomatous skin cancer, no anticancer treatment for at least 3 weeks before entry to the study, and informed consent. All patients had measurable and evaluable disease.

All patients had received at least one previous treatment regimen, and 5 had also failed second-line therapy. The group included 4 patients with primary drug resistance, the remaining patients having relapsed after an initial response. There were 15 patients who had been treated previously with three or more anticancer drugs. Of 32 patients who had previously received cisplatin, 13 had also received 150 mg/m^2 adriamycin as part of platinum-combination primary; the 8 patients who had received mitoxantrone also included 2 who had also had adriamycin. No patient had received prior radiotherapy.

Epirubicin and mitomycin C were administered at doses of 65 mg/m^2 and 4 mg/m^2, respectively, each as a separate bolus over 1–2 min via a fast-following 0.9% saline infusion. The treatment was repeated every 4 weeks up to a maximum of eight courses or until there was evidence of progression.

The sites of evaluable disease and the methods of assessment are detailed in Table 1. Clinical examination was performed at each treatment cycle. Examination under anaesthesia was not performed for clinical assessment of response. When necessary radiological assessment was repeated, usually after two treatment cycles and at the end of drug treatment. Responses were assessed using International Union Against Cancer criteria [6]. Acute toxicity was assessed using World Health Organization criteria [6].

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Table 1. Pretreatment characteristics of 33 evaluable patients

Median age in years (range)	54	(30–74)
Median interval from diagnosis to study in months (range)	14	(4–57)
Baseline performance score (WHO)		
1	6	
2	24	
3	3	
Histological classification		
Serous	20	
Mucinous	3	
Endometroid	9	
Undifferentiated	1	
Histological differentiation		
Well	3	
Moderate	15	
Poor	14	
Unknown	1	
Types of previous therapy		
Cisplatin	32	
Alkylating agent	23	
Adriamycin	13	
Mitoxantrone	8	
No. of previous treatment regimens		
1	28	
2	5	
No. of previous drugs		
1	1	
2	17	
3	2	
4 +	13	

Evaluable disease and mode of baseline assessment

	CT Scan	US Scan	Clin	Total
Pelvic mass	7	4	7	18
Abdominal mass	3	2	5	10
Liver metastases	2	1	0	3
Skin metastases	0	0	1	1
Lymph nodes	0	0	1	1

Table 2. Characteristics of responders and non-responders

	Responders	Non-responders
n	10	23
Median relapse-free interval weeks after first treatment (SE)[a]	70 (18.9)	27 (4.8)
EM given as third-line therapy[b]	1	4
Reponse to first-line therapy[c]		
CR	6	10
PR	3	5
Static	0	2
Progression	0	4
Not evaluable	1	2
Site of evaluable disease		
Pelvis	7	11
Abdomen	2	8
Liver	0	3
Skin	0	1
Lymph gland	1	0
Tumor size < 5 cm[c]	5	5

[a] $\chi_1^2 = 12.531$; $P = 0{,}004$ [Mantel-Cox log rank test]
[b] $\chi_1^2 = 0.291$; NS
[c] $\chi_1^2 = 3.210$; NS (First-line responders V first-line non-responders; non-evaluable patients excluded)
[d] $\chi_1^2 = 1.376$; NS

Table 3. WHO toxicity grades epirubicin and mitomycin C ($n = 29$)[a]

	0	1	2	3	4	Pre-existing
Nausea/vomiting	1	10	14	4	0	–
Alopecia	3	4	6	8	0	8
Diarrhoea	17	6	3	3	0	–
Infection	21	3	1	2	2	–
Anaemia	14	8	3	3	1	–
Leucopenia	20	1	2	4	2	–
Thrombocytopenia	26	1	2	0	0	–

[a] Values = no. of patients

Results

Response

Four patients achieved complete response and six patients achieved partial response. Response was assessed objectively using CT scan [4] or ultrasound [4] in all but 2 cases. Three patients had stable disease while they were receiving treatment. Twenty patients had disease progression, and eight of these had only one course of treatment. The overall response rate was 30% (95% confidence limits 19%–41%). The median duration of response was 20 weeks (range, 9–53).

The characteristics of the responding and non-responding patients are summarized in Table 2. No responses were seen in patients who had failed to respond to primary chemotherapy. The relapse-free interval after primary chemotherapy was significantly longer in those patients who responded to the study treatment than in those who did not. Neither the site nor the size of disease influenced response. Three responses, including one complete response, were seen in patients who had been previously treated with adriamycin. The intervals from the last dose of adriamycin to the commencement of epirubicin and mitomycin C were 92, 98, and 119 weeks.

Toxicity

Toxicity is summarized in Table 3. This was assessed in 29 patients. It was not possible to assess toxicity in 4 patients, because of early death from progressive disease. There were no treatment-related deaths. Nausea and vomiting, though almost universal, were mild; only 4 patients experienced emesis that required fluid replacement therapy. Alopecia was also common. Nadir counts were not routinely performed. There were eight episodes of infection in association with leucopenia $< 2 \times 10^9$ WBC/l, including four instances of septicaemia. Two patients had recorded thrombocytopenia $< 100 \times 10^9$ platelets/l. Eleven patients had a total of 14 blood transfusions for anaemia. Four courses of treatment (3 patients) were delayed by a week due to myelosuppression. Myelosuppression did not appear to be cumulative, though only 10 patients received more than three courses. There were no dose reductions.

Skin extravasation occurred in 6 patients, though severe tissue necrosis and ulceration was seen in only 1 patient, who also experienced a local recall phenomenon on further treatment given into the contralateral arm. There

was no evidence of cardiac toxicity. One patient developed congestive cardiac failure following an acute myocardial infarction after a cumulative dose of 390 mg/m^2 epirubicin and 24 mg/m^2 mitomycin C. A further 6 patients who had received more than 390 mg/m^2 underwent left ventricular ejection fraction measurement using echocardiography and there was no evidence of cardiotoxicity. Neither pulmonary nor neurological toxicity was observed.

Discussion

This study shows that the combination of epirubicin and mitomycin C is active in the management of previously treated ovarian cancer and has acceptable toxicity. The response rates observed using the combination of epirubicin and mitomycin C in pretreated patients are greater than reported for either drug given as a single agent at higher dosage [1, 8], suggesting a synergistic interaction. Although we observed responses in patients who had relapsed after adriamycin-containing combination regimens, no patient had received more than 150 mg/m^2 of adriamycin. This enhanced activity was gained without increased toxicity. Although a synergistic increase in cardiotoxicity has been reported in patients receiving adriamycin and mitomycin [2], we found no evidence of cardiotoxicity using epirubicin and mitomycin at the doses employed in the study.

This study demonstrates the activity of this regimen in patients with advanced ovarian cancer after previous chemotherapy. Combination of this chemotherapeutic regimen with other active drugs such as cisplatin should be considered for study as a first-line combination regimen for ovarian cancer.

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