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A phase II study of ifosfamide in endometrial cancer*

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Summary. Around 32% of all patients with endometrial carcinoma relapse after primary therapy. The outlook for these patients is poor. Ifosfamide (IFX) has activity in a number of gynaecological malignancies and was selected for evaluation in this disease. The aims of this study were to assess the activity and toxicity of IFX in recurrent endometrial carcinoma no longer amenable to radical local treatment. In all, 16 evaluable patients with symptomatic advanced metastatic or recurrent disease entered a phase II study of this drug. Patients received IFX (5 g/m^2) as a 24-h infusion, with mesna (8 g/m^2) given during and for 12 h following IFX to prevent urothelial toxicity. Treatment was repeated every 21 days. Two patients showed evidence of response [one complete response (CR) of 3 months and one partial response (PR) lasting 5 months]. Most patients experienced nausea and vomiting, and WHO grade 3/4 alopecia invariably occurred after two or more cycles. Four patients developed severe (grade 3/4) IFX/mesna CNS toxicity, and four other patients had mild (grade 1/2) CNS toxicity. Significant myelosuppression was seen in 3/41 cycles. Haematuria was uncommon and invariably mild. There were two toxic deaths (one due to grade 4 CNS toxicity and one due to septicaemia). IFX has activity in endometrial carcinoma, but responses are of limited duration and toxicity is considerable.

Introduction

Adenocarcinoma of the endometrium has become the most common gynaecological malignancy in many countries. Although early-stage disease has a favourable prognosis, around 32% of all patients relapse after primary therapy [3]. The outlook for patients with advanced, metastatic or recurrent disease is poor. A number of single-agent and combination chemotherapeutic regimens have shown activity in this disease, but responses are usually of short duration and there is considerable haematological toxicity with some combinations [9]. Many patients are frail, often with intercurrent illness, and are unsuitable for such intensive chemotherapy.

Ifosfamide (IFX) is an oxazaphosphorine derivative and structural analogue of cyclophosphamide, an agent with activity in endometrial carcinoma that has shown greater activity than cyclophosphamide against a number of malignancies [1, 5, 7]. IFX produces less myelosuppression than cyclophosphamide and the dose-limiting toxicity, haemorrhagic cystitis, can be virtually eliminated by concurrent administration of mesna [4]. IFX was therefore selected for evaluation in this disease. The aims of this study were to assess the activity and toxicity of IFX in patients with advanced, metastatic or recurrent endometrial carcinoma no longer amenable to radical local treatment.

Patients and methods

A total of 16 evaluable patients with symptomatic, progressive endometrial carcinoma no longer amenable to radical surgery or radiotherapy were entered into this phase II study. Patient characteristics are shown in Table 1. In all patients, renal function was normal (serum creatinine levels of <120 mmol/l, serum urea values of <8.0 mmol/l, creatinine clearance of >50 ml/min) and bone marrow reserve was adequate (WBC count, $>3.5 \times 10^9$/l; platelet count, $>100 \times 10^9$/l; haemoglobin concentration, >10.0 g/l). None of the patients had been treated with hormones or chemotherapy for at least 3 weeks or with radiotherapy for at least 6 weeks prior to study entry. Before treatment, evaluable sites of disease were identified and documented using plain radiography, abdominal ultrasonography and computed tomography. Corroborative clinical measurements were made by the investigators.

After prehydration with 1 l dextrose saline over 2 h, patients were treated with IFX (5 g/m^2) given as an infusion in 3 l dextrose saline over 24 h. Treatment was repeated every 21 days. Mesna (1 g/m^2 as a bolus at the start of the IFX infusion and 5 g/m^2 added to the IFX infusion solution) was given before and during treatment with IFX, followed by a further 3 g/m^2 in 1 l dextrose saline infused over 12 h to prevent serious

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Table 1. Patient characteristics and responses

Median age (range)		62 (35– 71) years
Median Karnofsky performance status (range)		80 (40–100)
Median time to relapse (range)		10 (6– 52) months
Histology	Adenocarcinoma	13
	Adenosquamous	3
Differentiation	Good	3
	Moderate	4
	Poor	8
	Unknown	1
Original stage	I	11
	II	3
	IV	2
Previous treatment	TAH BSO	15
	Radiotherapy:	
	vaginal stock	7
	external beam	8
	Progestogens	12
	Tamoxifen	1
	Cytotoxics	1
Disease sites	Central pelvic	7
	Pelvic/para-aortic nodes	9
	Lung/liver	3
	Intraperitoneal	1
	Skin	4
Response to ifosfamide	CR	1
	PR	1
	SD	12
	PD	2

TAH BSO: Total abdominal hysterectomy + bilateral salpingo – oophorectomy

Table 2. Toxicity (percentage of cycles affected)

Toxicity	WHO grade:				
	0	1	2	3	4
Anemia	56	39	2	0	2
WBC	90	0	5	2	2
Platelets	98	0	2	0	0
Nausea and vomiting	5	10	72	13	0
Alopecia	7	4	37	52	0
Infection	93	0	5	0	3
Central nervous system	80	10	2	0	8
Haematuria	83	10	7	0	0
Renal	95	2	2	0	0

and delayed urothelial toxicity. No dose reductions were carried out, but treatment was delayed for 1 week if there were signs of bone marrow suppression or renal impairment (parameters lower than the pre-treatment values listed). Patients were given a minimum of two cycles of treatment before evaluation of response, unless there was obvious disease progression or toxicity precluded further treatment. If no evidence of disease progression was seen, a maximum of five treatment cycles were given. Response, duration of response, survival and toxicity were defined according to UICC and WHO criteria [8], apart from CNS toxicity, which was graded according to the criteria of Meanwell et al. [6]. Data were recorded on pro forma sheets and stored on a computer at the West Midlands Cancer Research Campaign Clinical Trials Unit. All analyses were carried out using the Biomedical Statistical Programmes software package [2]. Follow-up is complete for all patients up to March 1, 1989.

Results

Overall, 2 patients showed evidence of response [1 complete (CR) and 1 partial response (PR)]; 2 patients developed disease progression during treatment, and the remaining 12 showed evidence of disease stabilization. In the two patients who responded to treatment, the durations of response were 12 and 19.7 weeks. The overall median survival was 5 months (range, 0.5–25+ months) from the start of treatment. Toxicity consisted of nausea and vomiting, which was experienced by most patients, and alopecia, which invariably occurred after two or more cycles (Table 2). There were two deaths attributable to toxicity. One patient died of a neutropaenic septicaemia after only one course of treatment, but severe myelosuppression was rarely a problem in the remaining patients; the second toxic death was due to severe IFX/mesna-associated CNS toxicity. Two other patients developed grade 4 and one patient, grade 3 CNS toxicity, all recovered spontaneously. Mild degrees of CNS toxicity were suspected in an additional four patients.

Discussion

The outlook for patients with advanced metastatic or recurrent endometrial carcinoma is poor. Traditionally, this group of patients has been treated with palliative radiotherapy and hormonal therapy. Treatment with progestogens and antioestrogens, which have minimal toxicity, produces a response in around 50% of patients with well-differentiated tumours; however, a substantial proportion of patients who develop recurrence have poorly differentiated disease that is unlikely to respond to hormonal manipulation. This has prompted interest in systemic chemotherapy in the latter group of patients. A number of single-agent and combination chemotherapeutic regimens have shown activity in this disease, but responses are usually of short duration and toxicity is often considerable [9].

Many patients are unsuitable for intensive chemotherapy because they are frail, often with intercurrent illness, and may have co-existent medical disorders such as diabetes or cardiovascular or renal disease. Cyclophosphamide has activity against endometrial carcinoma; it was therefore logical to evaluate IFX, which has shown even greater activity in a number of malignancies and produces less myelosuppression than cyclophosphamide, in this setting. Although 2 responses were seen in the 16 patients (12.5%) entered into the study, continuation to the planned total recruitment of 30 patients was limited by the considerable toxicity that was encountered. In summary, IFX appears to have some activity as a single agent in patients presenting with recurrent endometrial adenocarcinoma, but at the cost of considerable toxicity.

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