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A phase II study of ifosfamide in advanced and relapsed carcinoma of the cervix

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Summary. Forty-one patients with advanced progressing carcinoma of the cervix were treated with ifosfamide 1.5 g/m^2 daily in a 30-min infusion for 5 days every 3 weeks. The overall response rate (complete + partial) was 12/39 (31%), or 12/30 (40%) in those who had not recieved previous chemotherapy. Six patients achieved a complete remission of disease and four of these remain disease-free 24-39 months later. Durable response were seen in patients with disease progressing after radical radiotherapy.

Bone marrow suppression was the dose-limiting toxicity and led to dosage modification in 24 patients. Nausea and vomiting was experienced by all patients at some time during therapy and all patients developed alopecia. Mild neurological toxicity occurred in seven patients but severe life-threatening neurotoxicity was not seen with this schedule of administration.

Further studies are needed to identify the optimum dose and schedule of ifosfamide and to ascertain its place in combination therapy.

Introduction

Carcinoma of the cervix is a common cause of death in women and the prognosis of advanced disease has not improved significantly in the last 20 years [9]. Palliation with chemotherapy can be achieved but remissions are usually short. Cis-platin is probably the most active single agent [15]. Squamous tumours from all sites are often resistant to chemotherapy, and in cervix cancer specific adverse factors may occur which render chemotherapy hazardous and the assessment of response to treatment difficult.

Extensive pelvic disease may cause urinary tract obstruction with impairment of renal function, restricting the use of certain cytotoxic drugs. Most patients with advanced cervix cancer have had prior extensive pelvic radiotherapy. This may compromise bone-marrow tolerance of chemotherapy. Extensive fibrosis may follow surgery and radiotherapy, leading to poor tumour vascularity impairing delivery of drugs to the tumour. The fibrosis also hinders the assessment of response by clinical examination and imaging techniques, including computerised tomography (CT).

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Ifosfamide is a highly active oxazophosphorine derivative and structural analogue of cyclophosphamide with notable activity in testicular, ovarian and lung tumours, soft tissue sarcomas and lymphomas [8]. There are differences in the spectrum of activity of ifosfamide in comparison to cyclophosphamide in both experimental and human tumours [7]. In addition, ifosfamide causes relatively less bone marrow suppression. The previously dose-limiting urothelial toxicity can be avoided by the synchronous administration of Mesna (sodium 2-mercaptoethane sulphonate) [3].

The ideal schedule of ifosfamide administration has yet to be defined, and previous experience with ifosfamide in carcinoma of the cervix has until recently been minimal [2]. Costanzi saw responses in squamous cell lung cancer to ifosfamide given as a daily short infusion of 1.5 g/m^2 for 5 days [4]. We have seen responses to the same schedule in various squamous tumours with minimal renal toxicity and only mild subjective toxicity (P. G. Harper, personal communication), and we selected the same schedule for this study.

Patients and methods

Forty-one women with avanced or relapsed carcinoma of the cervix (FIGO stages III or IV) aged 24–67 (median 40) years were entered into the study by the four participating institutions. The median time from diagnosis was 9 (range 0–168) months. Thirty-eight patients had a squamous tumour, three adenocarcinoma of the cervix. Previous treatments are shown in Table 1. Only six patients had not had

Table 1. Previous treatments

$n = 41$	
Wertheim's/total abdominal hysterectomy	15
External beam radiotherapy	32
Caesium insertion	27
Caesium insertion and external beam radiotherapy	24
Previous chemotherapy[a]	9[b]

[a] Platinum + etoposide + bleomycin in five patients; vincristine + bleomycin + methotrexate in one patient; platinum in one patient; carboplatin in one patient; methotrexate in one patient; mitomycin c + bleomycin in one patient

[b] Two patients had received two previous chemotherapy schedules

Table 2. Dosage modifications

1. Haematological			
WBC ($x10^9/l$)	Neutrophils ($x10^9/l$)	Platelets ($x10^9/l$)	Dose
>3.0	>2.5	>120	100%
2.5–3.0	1.5–2.5	100–120	3 days treatment
<2.5	<1.5	<100	delay 1 week
2. Renal			
EDTA/creatinine clearance (ml/min)			Dose
>65			100%
40–65			3 days treatment
<40			none

Table 3. Response data

Evaluable patients – 39		
Non-evaluable patients – 2		
Complete response	6 (15%)	Duration 3, 16[a], 24[b], 28[a,b], 29[b], 39[a,b]
Partial response	6 (15%)	Duration 7, 9, 12[c], 20[b,c], 32[b,c] months (+ 1 lost to follow-up)
No change	4 (10%)	
Progression	23 (59%)	

[a] Pathologically confirmed CR at second-look laparotomy
[b] Remission continues
[c] Remission maintained by radiotherapy following chemotherapy

prior pelvic radiotherapy, and three of these had received chemotherapy as first-line therapy. Three of nine patients had responded to previous chemotherapy (one previously untreated).

Patients were eligible for the study if they were less than 75 years of age with a WHO [16] performance status of <3, had no previous second malignancy other than skin cancer (excluding malignant melanoma), histological proof of the diagnosis and had clinically measurable or evaluable disease. No radiotherapy or chemotherapy was permissible in the previous month. A total white count and platelet count of $>3.0 \times 10^9/l$ and $>120 \times 10^9/l$ respectively, and glomerular filteration rate (GFR), as measured by creatinine or EDTA clearance, of >65 ml/min were mandatory before commencing chemotherapy.

Ifosfamide 1.5 g/m^2 was given as a 30-min infusion in normal saline daily for 5 days. Mesna 400 mg/m^2 was given by bolus injection at the start of the ifosfamide infusions and at 3, 6 and 9 h after each dose. Intravenous hydration was given when necessary to maintain a urine output of at least 2 l/day. Treatment was repeated every 3 weeks for a maximum of six courses or until disease progression. All courses were given on an inpatient basis. Dosage modification in the presence of bone marrow suppression or renal impairment are detailed in Table 2.

Baseline investigations included a full clinical examination, with assessment of pelvic disease by a gynaecologist and under anaesthetic if deemed necessary, full haematological and biochemical screen, creatinine or EDTA clearance, chest radiography, pelvic and abdominal CT or ultrasound, and radionuclide imaging of the skeleton and liver if clinically indicated. Haematological and biochemical measurements were repeated before every course, and scans and X-rays for assessement purposes after the second and final courses. Response to treatment was assessed using the WHO criteria [16]. A complete response implied resolution of all lesions both clinically and radiologically. A partial response was recorded if the size of the products of the perpendicular axes of the lesions had decreased to 50% or less of the original value and no lesion had progressed or new lesion arisen. Progressive disease was indicated by an increase of 25% or more in the size of the products of the perpendicular axes of the lesions or by the appearance of new lesions. Duration of response was defined from the beginning of treatment to the date of observation of progressive disease.

Results

Thirty-nine patients are fully evaluable for response. Two patients are not fully evaluable for response but are evaluable for toxicity. In one patient chemotherapy was changed because of neurotoxicity after two courses without complete assessment of response, and in the second, the patient refused further therapy after one course.

The response data and duration of responses are shown in Table 3. The overall response rate (complete + partial: CR+PR) was 12/39 (31%), or 12/30 (40%) in those who had not received previous chemotherapy. If the two incompletely evaluable patients are included the response rates fall to 29% and 39%. None of the nine patients previously treated with chemotherapy responded objectively, but two had a subjective response: one of breathlessness for 2 months despite progressive disease on chest X-ray, and the other, with stable disease, of haematuria for 6 months.

Response was seen in both irradiated and non-irradiated sites. Response in pelvic disease was seen in 9/28 (32%) of irradiated sites and two of seven patients (29%) who had not been irradiated. Response in distant disease was seen in five of 27 sites (lung two, distant lymph nodes two, skin one). A further six distant sites were not assessed because of evidence of progression in the pelvis. No patients with progressive pelvic disease had concurrent regression of distant disease. Symptomatic improvement of pain, leg oedema, haematuria or vaginal discharge was seen in 14 of 33 patients (42%). In three patients CR was confirmed pathologically, two by laparotomy and one by needle biopsy. Three previously untreated patients who only achieved PR subsequently received pelvic radiotherapy with conversion in two to clinical CR.

The median time to objective response was 12 weeks (range 3–17 weeks). The median duration of response has not been reached and exceeds 20 months (range $3-39^+$ months). The median duration of survival for all patients is 9 months (range $1-39^+$ months).

Toxicity

Bone marrow suppression was the dose-limiting toxicity, and was particularly severe in this group of patients, This may be attributable to previous pelvic radiotherapy. The haematological toxicity is shown in Table 4. Four patients developed non-fatal septicaemia. Twenty-four patients required dosage modifications or delay of treatments at

Table 4. Haematological toxicity

(n = 41)					
WHO grade worst course	0	1	2	3	4
Haemoglobin	28	8	5	0	0
WBC	21	5	8	3	4
Platelets	39	1	1	0	0

Table 5. Ifosfamide dosage

	Proportion of projected dose received			
	81%–100%	61%–80%	41%–60%	21%–40%
Number of patients	19	7	14	1
Responding patients	5	3	4	0

Table 6. Gastrointestinal toxicity

WHO grade	0	1	2	3	4	
Nausea/vomiting	15	32	70	14	6	All courses
	0	6	22	9	4	Worst course
Stomatitis	38	2	1	0	0	

some time during therapy because of bone marrow suppression.

The median number of courses received was three (range one to nine). Two patients received more than the planned six courses. The percentage of the projected dose received is shown in Table 5 for all patients and seperately for responding patients. No cumulative toxicity occurred.

All patients experienced nausea and vomiting at some time during therapy and this was severe despite prophylactic anti-emetic therapy in 13 patients (see Table 6). Two patients stopped therapy because of intolerable vomiting. Stomatitis was infrequent and mild, and diarrhoea did not occur.

Ifosfamide-induced renal impairment was not encountered with this schedule of administration. Renal function did deteriorate in five patients but all had progressive disease and known urinary tract obstruction. Mesna prevented haemorrhagic cystitis; no macroscopic haematuria occurred and only four patients developed microscopic haematuria.

Neurological toxicity was recorded in seven patients. Six had a decrease in their level of consciousness, one becoming briefly unconscious and responsive only to pain. The electroencephalogram (EEG) in the most severely affected patient showed a marked generalised abnormality. EEGs were not performed in the other patients. One patient experienced hallucinations and two developed abnormal movements. Both of the latter had received phenothiazines to control vomiting.

All patients receiving more than one course of ifosfamide developed either moderate (WHO grade II) or total (WHO grade III) alopecia.

Discussion

The mortality from carcinoma of the cervix has fallen in both the UK and the USA over the last 30 years. The detection of lesions at an earlier stage by screening the "at-risk" population, rather than changes in surgical or radiotherapeutic techniques, has probably accounted for most of this improvement. Furthermore, the prognosis in stage III and IV disease remains poor, with 5-year survival of 20% and 5% respectively [13]. The prognosis appears to be worse in younger patients [10] and it is perhaps in this group that the benefits of chemotherapy may be most easily demonstrated.

Ifosfamide had a 31% objective response rate in this fairly young group of patients, 40% when only patients receiving ifosfamide as first-line therapy are considered. This is comparable with the very best of other active single agents [1, 15]. Durable responses were seen, with seven patients remaining in remission for more than 12 months. In three patients CR was pathologically confirmed at laparotomy. Our results are similar to those achieved by Meanwell et al. [11] with ifosfamide 5 g/m^2 over 24 h, but on our schedule there was no life-threatening neurotoxicity.

Useful remissions with combination chemotherapy have recently been achieved in carcinoma of the cervix. The combination of cisplatin, vinblastine and bleomycin, (PVB) produced a response rate of 66% as first-line therapy for locally advanced carcinoma of the cervix [5]. Our response rate with single-agent ifosfamide was not as high, but responses were of similar duration.

Haematological and gastrointestinal toxicity was often severe and appeared to be greater than observed in other squamous cancer treated with the same regime (P. G. Harper, personal communication). The previous extensive pelvic radiotherapy would appear to contribute to the severe marrow suppression. The renal toxicity observed by Stuart-Harris et al. [14] with a similar dose given as a 24-h schedule for soft tissue sarcomas was not seen in this study.

Mild neurological toxicity, with transient somnolence, confusion, motor unrest and emotional lability the most common manifestations, occurs in about 10% of patients treated with ifosfamide [6]. Recently a life-threatening encephalopathy in patients with carcinoma of the cervix treated with ifosfamide and Mesna has been reported [11, 12]. The neurotoxicity in this cohort of patients was mild but the possibility of severe encephalopathy remains a concern.

Preliminary results from pharmacokinetic studies of different ifosfamide schedules reveal acceleration of ifosfamide metabolism and a progressive increase in alkylating activity from day 1 to day 5 with the schedule of administration which we emloyed. (L. Lewis, personal communication). The pharmacokinetics of ifosfamide may be of relevance in explaining the different spectrum of toxicity seen in our study.

Further studies are required to identify the optimum dose and schedule of ifosfamide. The response we have seen are encouraging for a single agent, with complete and durable responses in patients with disease progressing after radical radiotherapy. The 5-day schedule we have used may be associated with less severe neurological toxicity than the 1-day schedule, but is costly in terms of gastrointestinal toxicity, bone marrow suppression and inpatient care.

We believe that further investigation of scheduling is important to optimise the use of ifosfamide and to ascertain its place in combination therapy. The addition of ifos-

famide to other drugs active in cervial carcinoma [5] may further improve the response rate in this disease, particularly in previously untreated patients.

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