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A phase II study of ifosfamide and cisplatin chemotherapy for metastatic or relapsed carcinoma of the cervix

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Summary. A total of 44 women received a combination of ifosfamide (1.5 g/m^2 daily $\times 5$) and cisplatin (50 mg/m^2 on day 1 only) as first-line chemotherapy for recurrent or metastatic carcinoma of the cervix. In all, 12/42 (38%) evaluable patients responded, with the median duration of response being 7 months. Bone marrow and gastrointestinal toxicity were frequently severe. There were 3 septic deaths. Although cisplatin plus ifosfamide is an active combination against this disease, these results suggest that it is no more so than either drug used alone.

Introduction

In recent years chemotherapy has increasingly been used to palliate advanced carcinoma of the cervix. A number of single agents have shown useful activity and this has encouraged investigators to study the role of combination chemotherapy in both palliation and, in patients at high risk of recurrence, as an adjunct to radiotherapy and surgery.

Ifosfamide is one of the most active agents against cervical cancer and achieves a response rate of 33%–40% in previously untreated patients [5, 8]. This appears to be independent of the schedule used. The 5-day schedule previously used by this group achieved several prolonged responses, with a median duration of remission of 20 months [5]. Furthermore, severe ifosfamide-induced neurotoxicity, which was first described in patients with cervical cancer who received ifosfamide over 24 h [7, 8], did not occur on this schedule. Cisplatin is the other most active single agent against cervix cancer [2, 9]. Unlike ifosfamide, it is relatively non-myelosuppressive and may be given without compromising the dose of ifosfamide. Cisplatin and ifosfamide was therefore a logical cytotoxic combination.

We report herein the results of a phase II study of cisplatin and ifosfamide in patients with recurrent or metastatic squamous carcinoma of the cervix. The ifosfamide schedule was identical to that used in the single-agent study [5].

Patients and methods

A total of 44 women with recurrent (n = 38) or metastatic (n = 6) squamous carcinoma of the uterine cervix were entered into the study by the five participating institutions. The median age was 49 years (range, 28–67 years). The median time from diagnosis to relapse was 12 months (range, 0–194 months). In all, 37 patients had undergone previous pelvic irradiation and 9 previous surgery (followed by radiotherapy in 8 subjects and surgery alone in 1 case). Overall, 35/37 previously irradiated patients had recurrence of disease within the irradiated area, and 15 subjects had disease in non-irradiated sites. No patient had received previous chemotherapy.

Patients were eligible for the study if they were <75 years of age, with a WHO performance status of <3, had histological proof of squamous carcinoma of the cervix that was measurable or evaluable and had had no prior malignancy (excepting non-melanomatous skin cancers). A total white blood cell (WBC) and platelet count of $>3.0\times10^9$/l and $>100\times10^9$/l, respectively, and a glomerular filtration rate (GFR) of >45 ml/min as measured by chromium-labelled ethylenediamine-tetraacetic acid (EDTA) or creatinine clearance were mandatory before treatment was started.

Ifosfamide (1.5 g/m^2) was given daily for 5 days as a 30-min intravenous infusion in 500 ml normal (0.9%) saline. After saline and mannitol prehydration, cisplatin was given over 6 h on day 1 only at a dose of 50 mg/m^2 in 1 l normal saline. Mesna (400 mg/m^2) was given as an intravenous bolus injection before the start of the ifosfamide treatment and was continued as an infusion over 8 h at a dose of 1 g/m^2 on each of the 5 days. Treatment was given every 3 weeks on an inpatient basis for a maximum of 6 courses or until disease progression. All patients received combination antiemetics.

Treatment was modified according to the usual haematological and renal parameters. If the WBC was $<3.0\times10^9$/l or the platelet count, $<100\times10^9$/l, chemotherapy was delayed for 1 week. If the GFR was between 45 and 59 ml/min, both the cisplatin and ifosfamide doses were reduced by 25%; if it fell below 40 ml/min, treatment was stopped.

Baseline investigations included a full clinical examination, with assessment of pelvic disease being carried out by a gynaecologist, includ-

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Table 1. Response data

Evaluable patients (n = 42):	
Complete response	2 (5%)
Partial response	14 (33%)
No change	6 (14%)
Progressive disease	16 (38%)
Early death	4 (10%)
Non-evaluable patients (n = 2)	
Refused treatment	2

Table 2. Dose intensity and response

	Dose intensity[a] 81%–100%	61%–80%	41%–60%	<40%
All patients:				
Ifosfamide (*n*)	23	9	10	2
Cisplatin (*n*)	30	11	3	0
Responding patients:				
Ifosfamide (*n*)	7	5	4	0
Cisplatin (*n*)	9	6	1	

[a] % DI for ifosfamide = $\frac{\text{cumulative total dose/m}^2 \text{ (in g) of ifosfamide} \times 3 \times 100}{7.5 \times \text{number of weeks scheduled for treatment}}$

% DI for cisplatin = $\frac{\text{cumulative total dose/m}^2 \text{ (in mg) of platinum} \times 3 \times 100}{50 \times \text{number of weeks scheduled for treatment}}$

ing examination of patients under anaesthesia, if necessary; haematological and biochemical screening; EDTA or creatinine clearance; chest radiography; and pelvic and abdominal computerised tomography (CT). Haematological and biochemical measurements were repeated at each course. Radiological tests and gynaecological examination were repeated after the third and sixth courses to assess response to treatment. Follow-up gynaecological assessment was only rarely performed with patients under anaesthesia.

The objective response to and the toxicity of treatment were assessed using WHO criteria [10]. Duration of response was defined as the time from the beginning of treatment to the first observation of progressive disease. To obtain data on subjective response, the presence of symptoms such as pain, leg oedema and vaginal discharge was recorded and changes in these symptoms were noted after each course.

The dose intensity (DI) of cisplatin and ifosfamide was calculated. The planned DI (100%) was 50 mg/m^2 cisplatin and 7.5 mg/m^2 ifosfamide every 21 days. Both dose reductions and delays were taken into account in calculations of the actual DI, which was expressed as a percentage of the planned DI.

Results

In all, 42 patients were evaluable for response to treatment and all 44 were evaluable for toxicity; 2 subjects refused further therapy before a treatment response could be determined. The median number of chemotherapy cycles received was 3 (range, 1–6); 8 patients received only 1 course and 12 completed the planned 6 courses.

A response was seen in 16/42 (38%) patients (Table 1). In 2 cases the response was considered to be complete, although this was not pathologically confirmed. The median duration of response was 7 months (range, 3–12 months). Responses in both non-irradiated and irradiated

Table 3. Toxicity data[a]

	WHO grade[b] 0	1	2	3	4	NK
Haematological:						
WBC	7	6	11	8	9	3
Haemaglobin	14	21	5	1	0	3
Platelets	38	2	1	0	0	3
Nausea and vomiting (n = 44):	1	3	17	20	1	2
Stomatitis (n = 44):	31	10	2	0	0	1
Neurological[b]:	11	21	7	1	3	1

[a] Data represent the worst cycle for 44 patients

[b] 0 = alert
1 = transient drowsiness
2 = somnolence for <50% of waking hours
3 = somnolence for >50% of waking hours
4 = coma
NK = not known

sites were seen but were more frequent in the former (9/15; 60%) than in the latter (10/32; 31%). A symptomatic response, with improvement in pain, leg oedema, vaginal discharge or breathlessness was seen in 22 (50%) patients. In all, 39 (89%) subjects died and the median duration of survival was 8 months (range, 0–22 months). The response to treatment did not appear to be influenced by the dose intensity of either cisplatin or ifosfamide; 4/12 patients receiving <60% of the planned dose of ifosfamide and 7/14 receiving <80% of the planned dose of cisplatin responded (Table 2).

Bone marrow suppression was the dose-limiting toxicity (Table 3), with 17 (39%) patients experiencing WHO grade 3 or 4 leucopaenia. In all, 9 subjects had an episode of septicaemia, which was fatal in 3 cases (7%). In 29 patients (66%), bone marrow suppression resulted in a treatment delay or dose reduction at some time during treatment. A total of 21 patients (48%) experienced severe (WHO grade 3 or 4) nausea and vomiting despite prophylactic combination antiemetics, and this occurred in 27% of all cycles. Stomatitis and diarrhoea were uncommon. Alopecia occurred in all patients.

Neurotoxicity was difficult to assess accurately because of the confounding influence of antiemetic treatments. However, severe impairment of conscious level occurred in four patients, resulting in discontinuation of treatment in three cases. Four subjects showed a significant deterioration in renal function (doubling of serum creatinine), which was shown to be secondary to progressive hydronephrosis in three patients.

Discussion

Several recent studies have confirmed the activity of single-agent chemotherapy against advanced cervical cancer [2, 5, 8, 9]. Ifosfamide and cisplatin appear to be the most active of these agents and both can provide useful palliation in advanced recurrent disease. Response rates achieved with combination chemotherapy appear to be higher [6], and there is considerable interest in the feasi-

bility of incorporating chemotherapy into the primary treatment of bulky early or advanced cervical cancer. Before any adjuvant treatment can be evaluated, its activity against advanced disease must be tested and the "optimal" regimen, selected. Indeed, the West Midlands Gynaecological Cancer Group (WMGCG) has published preliminary results of a combination of bleomycin, ifosfamide and cisplatin (BIP) and reported a 73% response rate in recurrent disease and a 79% response rate when this regimen was given prior to radidotherapy [3]. The present study showed ifosfamide and cisplatin to be an active combination, with a response rate of 38%; however, this is similar to the objective response rate seen with either drug alone [2, 5, 8, 9].

In our previous study of ifosfamide alone, using an identical ifosfamide schedule, a 31% (12/39) overall response rate was achieved. As nine patients had previously been treated with chemotherapy, the response rate in patients receiving ifosfamide as first-line therapy was 40% (12/30). Furthermore, the median duration of response in the ifosfamide and cisplatin study was only 7 months as compared with that of 20 months obtained with ifosfamide alone. It is theoretically possible that the use of mesna to protect the urothelial tract could inhibit the activity of cisplatin. Mesna is known to reduce some of the gastrointestinal toxicities of cisplatin in mice [1], and although there is no evidence that mesna inhibits the antitumour activity of cisplatin in the L1210 tumour, further investigation of this potential interaction is needed.

In most other respects our two studies using ifosfamide were similar. The number of previously irradiated patients, sites of disease, age and performance status were comparable. Although the addition of cisplatin appeared to increase the haematological toxicity, a similar dose intensity of ifosfamide was possible. As in the previous study, response did not appear to be related to dose intensity.

Gastrointestinal toxicity was moderately severe despite prophylactic combination antiemetics and led to refusal of further treatment by two patients. Bone marrow suppression was particularly severe, with 39% of patients developing WHO grade 3 or 4 leucopenia and 3 cases of fatal septicaemia.

Neurotoxicity is a complication of ifosfamide that is more frequently being recognised. A severe encephalopathy occurred in three patients, one of whom died before recovering from a neutropaenic infection; thus, it was felt unwise to continue with treatment in the other two. It is unclear whether cisplatin increases the risk of neurotoxicity; however, a pilot study of ifosfamide plus cisplatin at 100 mg/m^2 was abandoned after two episodes of severe neurotoxicity were observed in the first six patients (unpublished observations).

The present study did not address quality of life. However, the gastrointestinal toxicity, coupled with the inevitable alopecia and prolonged inpatient time necessary for treatment administration and management of neutropaenic infection, makes it unlikely that treatment improved the quality of life of our patients. Although this is speculative, we doubt that, even in patients achieving a response, the few months of disease control outweighed the "Costs" of treatment. We accept that it may be imprecise to draw conclusions based on a retrospective comparison. Nevertheless, these results have dissuaded us from continuing with this combination in the neoadjuvant situation.

The 73% response rate achieved with BIP chemotherapy by the WMGCG is impressive, and a recent multivariate analysis of prognostic factors in patients treated both in London and in the West Midlands showed that treatment type was the most powerful predictor of response, with BIP chemotherapy being superior to ifosfamide given either alone or in combination with cisplatin [4]. In the absence of obvious differences in patient selection, it has to be assumed that either bleomycin is more active against cervix cancer than has previously been recognised or the difference in drug scheduling between the WMGCG study and our own is important.

In conclusion, we cannot recommend treatment of advanced cervical cancer with this schedule of ifosfamide and cisplatin. The addition of cisplatin apparently increased the toxicity without improving the response rate.

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