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Ifosfamide with and without Adriamycin in advanced uterine leiomyosarcoma*

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Summary. Uterine leiomyosarcomas are rare tumours and the results of treatment of advanced disease are poor. Ifosfamide and Adriamycin are both known to be active drugs in soft-tissue sarcomas. We present our experience using ifosfamide alone and in combination with Adriamycin in advanced or recurrent uterine leiomyosarcomas. Ifosfamide alone was given as a 24-h infusion at doses ranging from 5 to 7.5 g/m^2, with mesna rescue. In the combination regimen, ifosfamide was given at a dose of 5 g/m^2 and Adriamycin, at a dose of 40 or 60 mg/m^2. Ten patients were treated with ifosfamide alone, with only one partial response lasting 6 months. In all, 11 patients were treated with ifosfamide and Adriamycin, which resulted in 1 complete response that lasted 11 months. Although many of the patients had extensive disease and some had undergone prior treatment with other chemotherapy, ifosfamide would appear to have only modest activity at the dose and schedule used.

Introduction

Leiomyosarcoma of the uterus is a rare tumour representing 1.3% of all uterine malignancies and about 25% of uterine sarcomas [5]. The prognosis is poor, with survival being related to disease stage and histopathological grade [9]. Over 80% of patients presenting with disease outside the pelvis relapse, the mean time to progression being 9 months [7, 8]. Failures occur predominantly with distal rather than local disease [8]. After recurrence the prognosis is poor, with a median survival of 8 months [3]. Even for patients with stage I disease at presentation, the 5-year survival is only 56% [7].

Treatment of uterine leiomyosarcoma with cytotoxic agents has produced response rates of 25%–30% [2, 6]; the drugs used were the same as those given to treat other soft-tissue sarcomas. Newer agents have been tested but display little evidence of clinical activity [10]; however, ifosfamide has recently been shown to be an active agent in the treatment of soft-tissue sarcoma [1, 11]. We present our experience with ifosfamide given both alone and in combination with Adriamycin in advanced or recurrent uterine leiomyosarcoma.

Patients and methods

Patients. From 1980 to 1988, all patients with biopsy-proven metastatic or locally advanced leiomyosarcoma of the uterus that was not amenable to surgery or radiotherapy were considered for treatment with ifosfamide either alone or in combination with Adriamycin. Those treated between 1984 and 1987 were given the combination, and the remainder received ifosfamide alone in accordance with our current soft-tissue sarcoma protocols. Patients were eligible if they had measurable disease, no chemotherapy within the previous 4 weeks (no prior treatment with ifosfamide at any time), no radiotherapy to the sole index lesion within the previous 8 weeks, no history of cardiac disease, and satisfactory renal function (as judged by normal creatinine levels and/or ethylenediaminetetraacetate (EDTA) clearance of >50 ml/min.

The basic data for the patients are shown in Table 1. The main difference between the two groups of patients was that a greater number in the ifosfamide arm had previously received cytotoxic drugs; they had all progressed on their most recent treatment. These treatments consisted of Adriamycin in one case, cisplatin in three cases, and alkylator combinations in the remaining two. Two patients had been given two previous chemotherapy regimens and both had responded to initial treatment with cyclophosphamide and Adriamycin. No patient had received more than two previous chemotherapy regimens.

Doses and schedules. Ifosfamide was given as an infusion in 3 l dextrose saline over 24 h, with mesna cover [11, 12]. Patients treated with ifosfamide alone received doses of 5 g/m^2, with escalation to 7.5 g/m^2 if toxicity allowed (this was the case in only two patients). Patients given the combination received ifosfamide at a dose of 5 g/m^2 and Adriamycin

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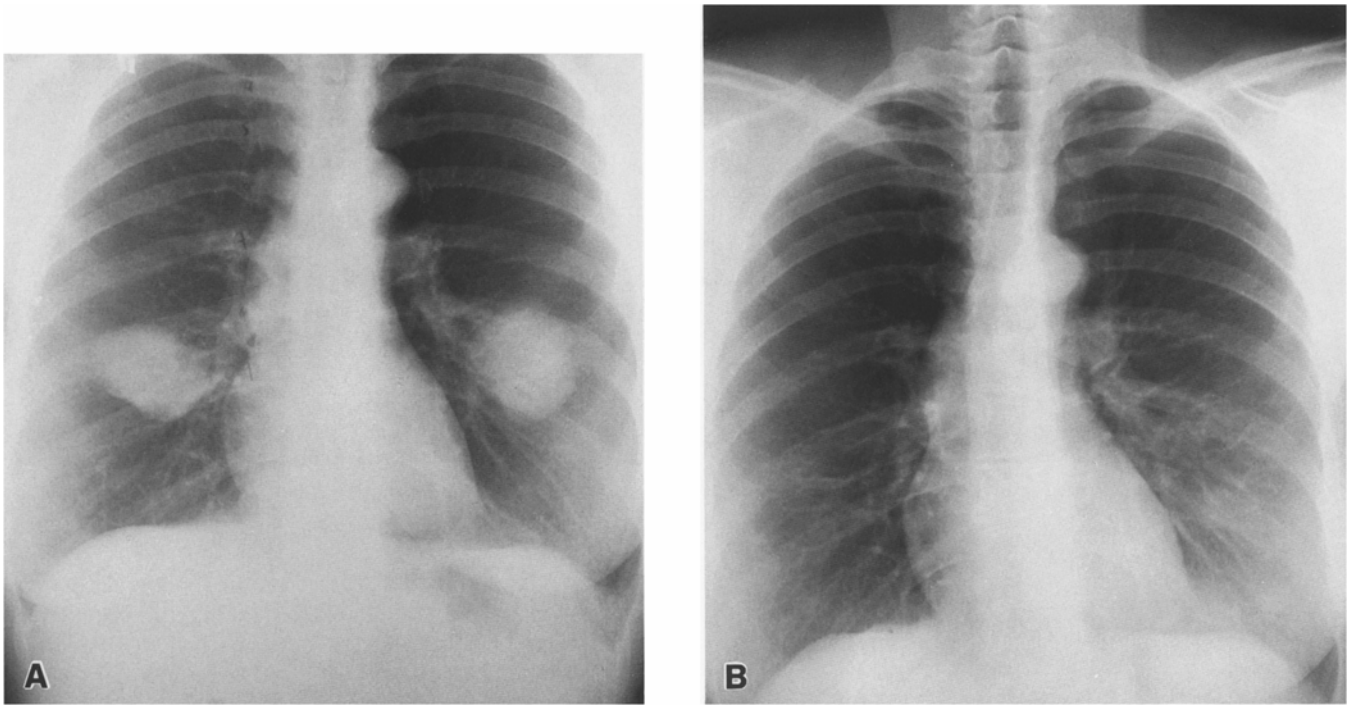

Fig. 1. Chest X-ray showing a complete response of pulmonary metastases to six courses of ifosfamide and Adriamycin

at 40 (two patients) or 60 mg/m^2 (nine cases). Both groups were treated at three-week intervals with a maximum of six courses, provided that haematological parameters were satisfactory (leucocyte count, $>3 \times 10^9$/l; platelets, >100,000/mm^3), renal function was adequate and there was no evidence of cardiac toxicity. Appropriate dose modifications were made to reduce adverse effects. Treatment was discontinued if there was progressive disease or if toxicity was unacceptable.

Evaluation of treatment. Response and toxicity were assessed using the criteria defined by the World Health Organisation [13].

Results

Table 2 shows the sites of disease at chemotherapy, the number of courses given and the responses seen for each type of treatment. There was only one objective response in each arm. The patient who achieved a complete response received six courses of the combination regimen. This patient had bilateral pulmonary metastases (Fig. 1) and, following chemotherapy, was given local radiotherapy to

Table 1. Patient characteristics

Characteristic	Ifosfamide	Ifosfamide + Adriamycin
Total number treated	10	11
Age in years:		
Median	53	47
Range	25–58	34–61
WHO performance status:		
0	2	2
1	6	7
2	1	2
3	1	0
Prior surgery:		
TAH + BSO	8	9
TAH	2	2
Prior radiotherapy	2	0
Prior chemotherapy	4	2
Histological grade:		
High	8	10
Low	2	1

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy

Table 2. Chemotherapy and response

Characteristic	Ifosfamide	Ifosfamide + Adriamycin
Sites of disease at chemotherapy:		
Lung	7	8
Local recurrence	5	7
Liver	2	1
Bone	1	1
Number of courses:		
Median	3	3
Range	1–6	1–6
Responses:		
Complete response	0	1
Partial response	1	0
Stable disease	2	3
Progressive disease	5	6
Not assessable	2	1

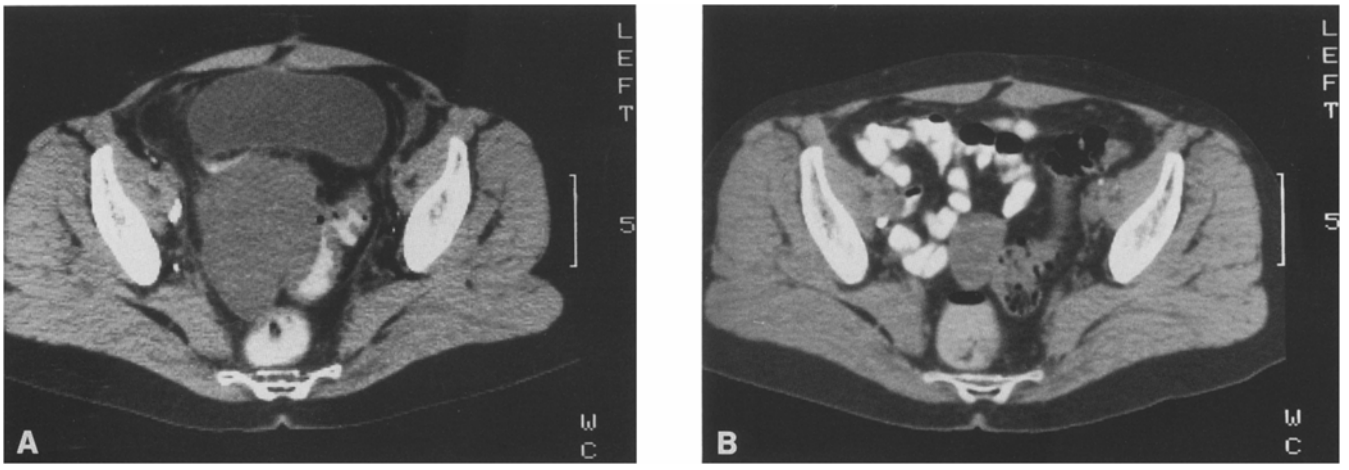

Fig. 2. Computerised tomographic scan of a pelvis, showing a good partial response to five courses of ifosfamide alone

Table 3. Major toxicities

Characteristic	Ifosfamide	Ifosfamide + Adriamycin
Haematuria	0	1
Infection (grade 2 or more)	1	2
Mouth ulceration	0	1
Blood transfusion	0	4
Delay due to myelosuppression	0	0
Neurotoxicity:		
Grade 1	1	2
Grade 4	1	0
Sudden death, cause uncertain	1	1

the sites of previous disease. She remained in complete remission for 11 months before relapsing with disease at other sites. The patient who achieved a partial remission on ifosfamide alone originally had a large pelvic recurrence (Fig. 2), which became amenable to surgical excision after chemotherapy; however, her disease recurred again 6 months later. No response was seen in patients who had received prior chemotherapy.

In the ifosfamide arm there were two patients whose response could not be assessed. A few days after the first treatment, one patient died of probable ifosfamide encephalopathy. The other died suddenly at home, 10 days after her second course of chemotherapy; the cause of death was uncertain (she was known to have a large mediastinal tumour compressing her pulmonary vessels and had not responded to her first course of ifosfamide). Of the patients receiving the combination regimen, one who had rapidly progressive pelvic and pulmonary disease prior to chemotherapy suffered a fatal cardiac arrest, dying in hospital 2 days after completing the first course of chemotherapy.

The major toxicities are shown in Table 3. The only episode of macroscopic haematuria occurred in a patient with tumour invading her bladder; she had experienced haematuria prior to treatment. Infection, mouth ulceration, and blood transfusion were more frequent in patients treated with ifosfamide and Adriamycin. One patient died of neutropenic infection following her third course of combination chemotherapy. Apart from this, however, myelosuppression was not a major problem and did not necessitate treatment delays. In the patient who developed mucositis with her first course of ifosfamide and Adriamycin, the latter drug was stopped and she completed two courses of ifosfamide without problems; all treatment was subsequently stopped due to progressive disease. No dose reductions were necessary in subjects treated with ifosfamide alone, but four patients receiving the combination underwent dose reductions because of toxicity.

Discussion

This study demonstrates that ifosfamide indeed has some modest activity in the treatment of uterine leiomyosarcoma. In four of the patients who received ifosfamide alone, the disease was resistant to other agents, and none of these patients responded to the single agent. It is possible that ifosfamide may be more effective when used as first-line chemotherapy. However, the use of ifosfamide and Adriamycin combined did not lead to an increase in responses, although only two patients had received previous cytotoxic therapy. Overall, this suggests that even in previously untreated patients the activity of ifosfamide is low.

The toxicity of the regimens described is probably acceptable, given that the patients had advanced disease. The patient who developed ifosfamide encephalopathy had known risk factors, namely, extensive pelvic disease with a low serum albumin value [4]. Otherwise, the toxicity of ifosfamide alone was not severe. The toxicity of the combination appeared to be more severe, as would be expected from individual side effects produced by the two drugs.

The number of patients treated in this study was small, but it would appear that ifosfamide used either alone or in combination with Adriamycin does not produce results that are superior to those previously reported for single-agent Adriamycin [6]. Future studies should concentrate on the development of new drugs (or new combinations) or, perhaps, alternative dosing schedules for ifosfamide for the treatment of advanced uterine leiomyosarcoma.

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