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A phase II study of ifosfamide/mesna with doxorubicin for adult soft tissue sarcoma

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Summary. In a phase II study, 16 adult patients with locally advanced or metastatic soft tissue sarcomas were treated with i.v. infusions of ifosfamide/mesna 5 g/m^2 plus i.v. doxorubicin 40 mg/m^2. Courses were given every 3 weeks up to a maximum of six courses in responding patients. Six patients (37.5%) had either complete (1 patient) or partial responses (5 patients). Confidence limits for this response rate were 15.2%–64.5% (95% confidence level). There was one toxic death in association with encephalopathy, renal and bone marrow failure. Unilateral pneumothoraces occurred in 2 patients with large pulmonary metastases. Recurrent severe ifosfamide/mesna encephalopathy occurred in 2 patients at risk for this complication; patients who develop severe ifosfamide/mesna encephalopathy should not be retreated with this drug. Ifosfamide/mesna with doxorubicin is an active combination to treat adult soft tissue sarcoma but, despite the feasibility of the combination, sequential monotherapy with these drugs might provide similar or better clinical benefit.

Introduction

Soft tissue sarcomas comprise a heterogenous group of malignant tumours of mesenchymal and neuroectodermal origin that account for about 1% of all malignant tumours in adults. Effective chemotherapy for sarcomas has been limited by a lack of active drugs in association with toxicity of therapy.

Doxorubicin, when used to treat soft tissue sarcoma, has yielded objective response rates as low as 9% [9] and as high as 70% and has been the most active single agent in the treatment of adult soft tissue sarcoma [16].

Ifosfamide, a cyclophosphamide analogue, has shown significant single-agent antitumour activity in advanced adult soft tissue sarcoma, both in untreated and in chemotherapy-pretreated patients [1, 3, 18]. Ifosfamide was more effective and caused less leucopenia than cyclophosphamide in a randomized phase II trial in adult soft tissue sarcomas [4]. Ifosfamide's major toxicity is haemorrhagic cystitis, which can be circumvented by the concomitant use of the uroprotector mesna [6]. We therefore combined ifosfamide and mesna given as infusions with bolus i.v. doxorubicin to treat advanced adult soft tissue sarcoma in a phase II trial.

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Patients and methods

Sixteen consecutive patients with histologically proven locally advanced or metastatic soft tissue sarcoma not amenable to surgery or radiation therapy were entered into study. No patient had documented bone metastases. Patient's characteristics and histological diagnoses are shown in Table 1. Patient's performance, response to therapy and toxicity were graded by World Health Organization (WHO) criteria [21].

Ifosfamide was given as a 24-h i.v. infusion of 5 g/m^2 in 3 l dextrose saline preceded by 1 g/m^2 i.v. bolus of mesna. Starting at the same time as ifosfamide, mesna 4 g/m^2 BSA was given by infusion over a 32-h period. Doxorubicin 40 mg/m^2 was given by i.v. bolus injection. Courses in general were given every 3 weeks, up to a maximum of six courses per patient. One patient, because of progressive disease, received only one course; the other 15 patients had a minimum of two courses. Table 2 shows details of courses and doses of ifosfamide/mesna and doxorubicin. Before each treatment, full blood counts and renal and hepatic biochemical indices, including serum albumin levels, were estimated. Nadir haematological and biochemical estimates were not routinely made. Response was assessed by serial clinical examinations, chest X-rays (CXR), and computed tomographic and ultrasound scans where appropriate. Routine antiemetics were given with each che-

Table 1. Patients' characteristics and histological diagnoses

Median age (range) in years	52 (18–76)
Median performance status	1 (0–2)
Male patients	8
Female patients	8
Histological diagnosis	
Leiomyosarcoma	8
Malignant fibrous histiocytoma	3
Liposarcoma	2
Fibrosarcoma	1
Rhabdomyosarcoma	1
Schwannoma	1
Previous non-surgical treatments	
Radiotherapy	2
Chemotherapy	1[a]

[a] Chemotherapy in this one case consisted of courses of actinomycin D, vincristine, methotrexate and cyclophosphamide in combination, followed by single-agent mitomycin C

Table 2. Courses and doses of ifosfamide/mesna and doxorubicin, given every 3 weeks

Total number of courses	61[a]
Median (range)	3 (1–6)
Doxorubicin dose	40 mg/m^2[b]
Ifosfamide dose	5 g/m^2[c]

[a] Six courses (10%) were delayed more than 3 weeks, but only on one occasion was a course delayed for more than 4 weeks
[b] Two patients had reduced doses of doxorubicin during 12 courses, in one because of advanced age (76 years) and in the other patient, who had an oesophageal stricture, to ameliorate emesis
[c] One elderly patient in addition to reduced doxorubicin doses had dose reductions in all 6 courses of ifosfamide

motherapy course, 13 patients receiving oral dexamethasone 4 mg q.d.s. for 1 day and oral domperidone 30 mg q.d.s. for 2 days or longer. Three patients were given metoclopromide, chlorpromazine or prochlorperazine in various combinations.

Results

There was one histopathologically confirmed complete response and five partial responses; thus, 6 of 16 patients (37.5%) had objective responses. The confidence limits for this response rate were 15.2%–64.5% (95% confidence level). Details of responding patients are shown in Table 3.

One elderly patient remains in partial response after more than 41 months, despite dose reductions to 70% of the projected doxorubicin dose and to 43% of the projected ifosfamide dose because of age. This response was complete on clinical examination but, because of minor persisting abnormalities on serial computed tomographic scans, was designated as partial. One other male patient with a locally advanced gastric leiomyosarcoma had a minor objective response, less than partial, and received six courses of therapy. No other patients showed objective response.

Table 4. Maximum episodes[a] of WHO-graded toxicity during 61 courses

	Grade 1	Grade 2	Grade 3	Grade 4
Serum urea	1	–	–	1
Serum creatinine	–	1	–	–
Haematuria	1	–	–	–
Nausea/vomiting	6	17	23	–
Alopecia	2	4	10	–

[a] Serum alkaline phosphatase, bilirubin and alanine transferase were normal throughout treatment courses

Toxicity

Full blood counts and serum urea, creatinine, bilirubin, alkaline phosphatase and alanine transferase investigations were performed before each treatment cycle, revealing mild or no toxicity except in one patient. Maximum episodes of WHO-graded toxicity are shown in Table 4.

In addition to WHO-graded toxicity, two patients (12.5%), both with large pulmonary metastases, developed unilateral pneumothoraces. One patient with responding pulmonary metastases developed a pneumothorax after five courses of treatment. The other, a non-responding patient, developed cavitation but no shrinkage of a large pulmonary metastasis and a pneumothorax after two courses.

Two patients (12.5%) developed ifosfamide/mesna encephalopathy.

One woman (aged 44) with metastatic liposarcoma who responded to treatment developed mental confusion, emotional lability and visual hallucinations after the first course. This patient had previously undergone nephrectomy before chemotherapy in an attempt to debulk the disease. A similar reversible encephalopathic event occurred after the second course, after which no further ifosfamide was given and doxorubicin was continued alone to a total of six courses. The other female patient developed reversible confusion, tremor and visual hallucinations after the second course, but after the third ifosfamide/mesna and adria-

Table 3. Responding patients

Histology and sites of disease	Response	Sex	Age	Response duration in months[a]	Outcome and major toxicity
Uterine leiomyosarcoma recurrent in pelvis/intestines	CR	F	53	2.5+	Encephalopathy and treatment related death. No viable tumour at autopsy
Malignant fibrous histiocytoma of mediastinum/SCF node metastases[b]	PR	F	23	6+	Consolidation radiotherapy to residual diseases after 6 courses of chemotherapy
Malignant fibrous histiocytoma of thigh with pulmonary metastases	PR	M	53	4.5	Pneumothorax and refusal of further chemotherapy after 5 courses
Liposarcoma with multiple skin, node, pulmonary and intra-abdominal/pelvic metastases	PR	F	44	15	Encephalopathy
Uterine leiomyosarcoma with pelvic metastases	PR	F	42	9	–
Retroperitoneal liposarcoma[c]	PR	F	76	41+	–

[a] Response estimated from initiation of chemotherapy until detected relapse
[b] Complete resolution of SCF node metastases after chemotherapy only and continued slow resolution of mediastinal tumour on serial computed tomography 16 months after initiation of chemotherapy
[c] Dose reductions of both doxorubicin and ifosfamide because of age

mycin course these features progressed through mutism, the patient later falling into a trance-like state associated with developing renal failure and pancytopenia, which resulted in septicaemia and death. The neurological abnormalities reversed before the patient's demise. During treatment, this patient's illness was complicated by episodes of klebsiella urinary infection and postoperative abdominal wall sinus infection, which may have been sources of septicaemia. Autopsy revealed acute renal tubular necrosis and no histological evidence of residual active tumour; treatment-related death was considered probable. In this patient, the only one in the study to have had prior chemotherapy (mitomycin C), this had been discontinued because of deteriorating biochemical estimates of renal function, but these biochemical abnormalities had reversed before the administration of ifosfamide/mesna plus doxorubicin.

All patients developed moderate to severe false-positive ketonuria on urine testing during ifosfamide/mesna therapy. This mesna-induced phenomenon has been reported previously [8].

Discussion

We have found that ifosfamide/mesna with doxorubicin is an active combination in the treatment of adult soft tissue sarcoma. Responses occurred in patients with leiomyosarcomas, liposarcomas and malignant fibrous histiocytomas, relatively common types of adult soft tissue sarcomas [3]. Responses occurred in primary sites and in soft tissue, pulmonary and visceral metastases. One young patient with a primary malignant fibrous histiocytoma of the mediastinum and supraclavicular node metastases had a substantial response to chemotherapy. Malignant fibrous histiocytoma arising from the mediastinum is exceedingly rare [15], and its sensitivity to cytotoxic chemotherapy was previously unknown.

A prospective multinational phase II study is in progress to evaluate ifosfamide 5 g/m^2 plus mesna as a 24-h infusion combined with adriamycin 50 mg/m^2 every 3 weeks to treat advanced adult soft tissue sarcoma. The result of the final analysis is not yet available, but on preliminary analysis there is a 24% response rate (confidence limits 10%–39%) [10]. Wiltshaw et al. [20] treated 66 soft tissue sarcoma patients with ifosfamide 5 g/m^2 plus mesna and a further 50 patients with additional adriamycin. The dose of adriamycin varied from 40 to 60 mg/m^2, and the study was not randomized. Objective remissions occurred in 17 of 63 (27%) assessable patients given ifosfamide/mesna and in 17 of 47 (36%) patients given ifosfamide/mesna plus adriamycin. Despite the percentage increase in responses with the addition of adriamycin, myelosuppression was greater in the group that received both cytotoxic drugs, and the 95% confidence limits of the percentage responses overlapped widely, being 16.5%–39.6% for ifosfamide/mesna and 22.6%–51.4% for the combination cytotoxic group. Stuart-Harris et al. [18] found that 15 of 40 patients (95% confidence limits 22.7%–54.2%) responded to high-dose ifosfamide/mesna without additional cytotoxics. A recent randomized comparison of three adriamycin regimens in metastatic soft tissue sarcoma showed that the addition of DTIC to adriamycin significantly increased both the response rate and the toxicity of treatment but did not increase survival [2]. These data and our own collected in a small number of patients suggest that, although the addition of adriamycin to ifosfamide is feasible and may lead to modest increases in response rates, there is as yet no evidence that any survival benefit accrues to offset the potential for increased toxicity. Since ifosfamide/mesna is active in patients progressing despite prior chemotherapy [1, 3, 18], it could be used after prior adriamycin therapy. The sequential use of these drugs might confer better survival benefit than concomitant combination therapy, but this concept would need to be tested in a comparative randomized study.

Encephalopathies and pneumothoraces are uncommon chemotherapy-related toxicities, but were the major toxicities in our study. Pneumothorax occurred in only 2 patients with large pulmonary metastases; it thus seems that this subgroup of patients may be particularly at risk of developing pneumothorax during therapy.

The single treatment-related death previously reported [7], although caused by septicaemia with renal and bone marrow failure, was associated with severe encephalopathy which tended to mask the developing lethal toxicities. The encephalopathy was typically ifosfamide-associated, and this drug may also have caused the renal failure. The severe myelosuppression in this case was probably caused by the addition of adriamycin to the combination. Bremner et al. [5] record a toxic death in a patient who became comatose after ifosfamide but also developed renal and bone marrow failure. Meanwell et al. [13] describe two deaths in patients with ifosfamide-associated encephalopathy. In one patient the encephalopathy masked colonic perforation, and a fatal gram-negative septicaemia in association with leucopenia ensued. In the other case, death was ascribed directly to the encephalopathy.

Many studies have reported cerebral effects associated with ifosfamide therapy [1, 5, 18, 19], which has been more precisely defined by Meanwell et al. [11]. Cerebral toxicity ranging from disturbance of mood and consciousness through motor disturbances, including seizures and cranial nerve palsies, has since been described in both adults [13] and children [17]. Discriminant function analysis has identified low serum albumin concentration, high serum creatinine concentration and the presence of pelvic tumour as pretreatment parameters that increase the risk of severe encephalopathy, and a nomogram using these parameters has been constructed [12]. Our two female patients who developed severe clinical encephalopathy had a history of renal disease and intra-abdominal/pelvic disease, and the two had the lowest serum albumin levels of the study group. Additionally, these two patients had the highest and third highest pretreatment serum creatinine levels of the study group, but the levels were below the upper limit of normal for our institution. Application of the nomogram to these patients would have excluded one patient only from ifosfamide therapy, i.e., the patient who had a less than 0.20 probability of remaining free from severe encephalopathy [14]. The other patient, who suffered a toxic death, had a probability of between 0.20 and 0.40 of remaining free from severe encephalopathy. It is possible to preclude ifosfamide therapy for some patients with high risk factors for ifosfamide-associated encephalopathy using the nomogram devised by Meanwell et al., but not all high-risk patients can be confidently detected. Patients who develop severe but reversible encephalopathy after ifosfamide should not be retreated with that drug.

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