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A phase II study of ifosfamide in the treatment of recurrent sarcomas in young people

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Summary. We have evaluated the activity of ifosfamide in 75 patients with recurrent sarcomas and pediatric solid tumors. All patients had previously received cyclophosphamide in combination with other chemotherapeutic agents. Ifosfamide was administered as a continuous 5 day infusion at a dose of 1800 mg per M^2, except in the last 14 patients who received the drug as a daily one hour infusion at the same dose level. Partial response was observed in 9 of 20 patients with Ewing's sarcoma, 2 of 9 patients with rhabdomyosarcoma, 3 of 17 patients with osteogenic sarcoma and 4 of 29 patients with various other neoplasms. A further 6 patients had stable disease, defined as the absence of progression for at least 6 cycles of therapy. Thus overall response rate was 24%, with the highest response rate of 45% being observed in Ewing's sarcoma. Toxicity was acceptable, although there was quite marked leucopenia (median nadir 700) with less profound thrombocytopenia (median nadir 87000). Sepsis occurred in 3 patients but no patient died as a result of infection. Hematuria occurred in 43% of patients who did not receive mesna, and in 26% of patients who did, although prior pelvic irradiation was found to be a significant risk factor for hematuria. Only 1 of 14 patients whithout prior pelvic irradiation or hematuria developed hemorrhagic cystitis when treated with ifosfamide and mesna. Confusional states developed in 6 patients. We conclude that ifosfamide is an active agent in patients with relapsed sarcomas and childhood solid tumors, even when such patients have been previously treated with cyclophosphamide.

Introduction

Sarcomas which occur predominantly in young people, such as Ewing's sarcoma, rhabdomyosarcoma, and osteosarcoma, are initially responsive to a variety of cytotoxic drugs, and cure can be achieved with a combination of therapeutic modalities. Patients who relapse or who fail to achieve remission, however, have an extremely poor prognosis, and further therapy is at best palliative.

One of the most useful agents in the treatment of these diseases is cyclophosphamide, an oxazaphosphorine. Ifosfamide, another oxazaphosphorine, has not been as widely used, although it is clearly active in a broad range of human cancers [4, 6, 10]. In several animal tumors ifosfamide appears to be a more active drug than cyclophosphamide, suggesting that the two drugs differ in their spectrum of activity [5].

A deterrent to the use of ifosfamide has been the associated high incidence of hemorrhagic cystitis, and it is probably for this reason that the drug has not been as widely used as its congener, cyclophosphamide. In recent years, reports from Europe have indicated that the sulfhydryl compound, mesna (2-mercaptoethanesulfonate), can succesfully prevent this complication [3], a finding which has led to renewed interest in ifosfamide. It is important to determine whether ifosfamide has any advantages over cyclophosphamide, and whether there is cross-resistance between these drugs in various tumors.

As a preliminary step to answering these questions, we have carried out a phase II trial to determine the activity of ifosfamide in previously treated patients with sarcomas, particularly Ewing's sarcoma, rhabdomyosarcoma, and osteosarcoma. All the patients had previously received intensive chemotherapy with cyclophosphamide-containing regimens, in some cases including total-body irradiation and autologous bone marrow reinfusion. We were particularly interested to observe the activity of ifosfamide in patients clearly refractory to cyclophosphamide and to determine the frequency of hemorrhagic cystitis in this patient group, which included a proportion of patients who had received pelvic irradiation and were therefore considered to be at particularly high risk for this complication. Furthermore, if mesna is highly effective in the prevention of hemorrhagic cystitis, it should permit the subsequent treatment of patients with oxazaphosphorines even when there is a previous history of cyclophosphamide-induced hematuria.

Patients and methods

We have treated 78 patients with ifosfamide. The histological diagnoses for evaluable patients are shown in Table 1. All patients had previously received chemotherapy that included cyclophosphamide, and 37 had also been treated with radiotherapy to known sites of disease. In addition, 9 had also completed the intensive component (which included total-body irradiation and autologous bone marrow reinfusion) of a primary protocol used in patients with selected poor-risk sarcomas, including Ewing's sarcoma, rhabdomyosarcoma, neuroepithelioma and undifferentiat-

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Table 1. Histological diagnoses

	Number
Ewing's sarcoma	20
Rhabdomyosarcoma	9
Undifferentiated sarcoma	3
Osteogenic sarcoma	17
Synovial cell sarcoma	7
Neuroblastoma	4
Neuroepithelioma	3
Wilm's tumor	3
Malignant fibrous histiocytoma	4
Leiomyosarcoma	2
Fibrosarcoma	1
Chondrosarcoma	1
Schwannoma	1
Total	75

ed sarcomas [9]. A summary of prior treatment regimens is provided in Table 2. All patients had either failed to achieve remission with their prior therapy or had relapsed after a period of complete remission. The vast majority had extensive disease at the time of treatment with ifosfamide, lung metastases being the most frequent manifestation of recurrence.

We initially used ifosfamide as a 5-day continuous infusion at a dose of 1800 mg/m^2 daily. Courses were repeated as soon as marrow recovery, defined as a total granulocyte count of 1500/mm^3, was reached – in most patients between 3 and 4 weeks. We chose this regimen because of previously published data indicating that continuous infusions of ifosfamide produce less hemorrhagic cystitis [11]. Since mesna has not yet been approved as a uroprotective agent by the USA Federal Drug Administration (FDA), we initially decided to use this agent, with FDA approval, only for patients who developed hematuria while receiving ifosfamide. More recently, in view of our positive experience with mesna, we adopted an ifosfamide regimen suitable for outpatient administration. Instead of being given continuously, ifosfamide was infused i.v. over a 1-h period daily for 5 days, and mesna uroprotection was given routinely. The last 14 patients have been treated in this way.

Mesna was administered as an equi-dose infusion added to the same bottle as ifosfamide in patients receiving a continuous infusion. In patients receiving hourly infusions mesna was given in five doses, each being 20% of the daily ifosfamide dose. In the latter case, the first dose was added to the bottle containing ifosfamide and subsequent doses were administered every 4 h, either i.v. or p.o. Regardless of the drug regimen used, mesna was given for a further 18 h after the completion of ifosfamide administration.

A dose escalation up to 2400 mg/m^2 was included in the protocol for patients who tolerated ifosfamide well, but in practice this was rarely used. Only 8% of courses were delivered at either 2100 mg/m^2 or 2400 mg/m^2, and 11% were delivered at lower doses (1200 and 1500 mg/m^2) because of previous excessive toxicity at higher dose levels.

All patients were treated with at least two courses of ifosfamide unless immediate rapid progression occurred or clinical events prevented the administration of further drug. Ifosfamide was continued in all patients as long as disease progression was not observed.

Partial response was defined as a reduction in two perpendicular diameters of at least 50% for all measurable tumors; complete response as the disappearance of all disease measured clinically and radiologically; and stable disease as the absence of progression for at least six courses of therapy.

Hematuria was defined as grade I if 5–40 red blood cells were observed per high-power microscope field (HPF), grade II if more than 40 red blood cells per HPF were observed, and grade III (gross) if visible hematuria was observed by the patient or staff.

Results

Response

In all, 78 patients were entered into the study, 3 of whom were inevaluable for response because of failure to complete one cycle of therapy. The median age of all patients was 21 years, the age range being 9 months to 64 years. The male to female ratio was 1.7:1. Response to ifosfamide according to tumor type is shown in Table 3. Overall, 18 (24%) of the 75 evaluable patients achieved partial remission status, and a further 6 (8%) had stable disease (as defined in *Methods*). Thus, 32% of this heavily pretreated group of patients benefited significantly from ifosfamide therapy.

Six patients, who were given additional local therapy (4 underwent surgical tumor resection and 2, irradiation) after achieving partial remission, were rendered disease-free and have been followed up for periods ranging from 6 to 27 months. Five of these patients remain disease-free at

Table 2. Previous chemotherapy in patients treated with ifosfamide

Ewing's sarcoma, Rhabdomyosarcoma, Neuroepithelioma, Undifferentiated sarcomas	Cyclophosphamide, actinomycin D/adriamycin, vincristine
Osteosarcoma	Cyclophosphamide, actinomycin D, bleomycin, methotrexate, *cis*-platinum, adriamycin
Neuroblastoma	Cyclophosphamide, vincristine, *cis*-platinum, DTIC
Differentiated sarcomas	Cyclophosphamide, adriamycin

Table 3. Response to ifosfamide according to disease category

	Total	PR	SD	PR+SD	(%)
Ewing's sarcoma	20	9	1	10	(50)
Rhabdomyosarcoma	9	2	0	2	(22)
Undifferentiated sarcomas	3	1	0	1	(33)
Osteosarcoma	17	3	2	5	(29)
Synovial cell sarcoma	7	1	3	4	(57)
Neuroblastoma	4	0	0	0	(0)
Neuroepithelioma	3	1	0	1	(33)
Other histologies	12	1	0	1	(8)
Total	75	18	6	32	(32)

Table 4. Incidence and degree of hematuria in different patient groups

	Patients with hematuria						
	Number	Microscopic evidence	%	Gross	%	Total	%
Ifosfamide alone	52	11	22	11	22	22	43
Pelvic irradiation	10	3	30	4	40	7	70
Previous hematuria	4	1	25	1	25	2	50
Neither	40	7	18	7	18	14	35
Ifosfamide and mesna	23	5	22	1	6	6	26
Pelvic irradiation	8	4	50	1	12	5	62
Previous hematuria	4	1	25	0	0	1	25
Neither	14	1	8	0	0	1	8

Some patients had both previous pelvic irradiation and previous hematuria

the present time, including the longest survivor. In two patients ifosfamide converted an unresectable tumor mass to a resectable one.

Toxicity

Ifosfamide was well tolerated. Only one patient had severe emesis, which invariably commenced prior to the administration of ifosfamide and was therefore felt to have a large psychogenic component. Most patients were able to continue to eat during the 5-day treatment period. Forty patients were followed closely for hematological toxicity and biochemical toxicity, which are summarized in Tabel 4. The median nadir white blood cell count was 700, with a range of 100–3700/mm^3. The median nadir platelet count was 87000, with a range of 8000–536000/mm^3. Fever during a period of neutropenia occurred in 22 of 255 cycles (9%) delivered; sepsis developed in three patients. Serum transaminases became elevated in 43% of patients, although in no case above 250 u/l. Mild bilirubin elevations occurred in three patients after ifosfamide, and pre-existed in two other patients. Serum creatinine elevations occurred in three patients, to a maximum of 3.6 mg/dl. Two of these patients became significantly acidotic, and in one glycosuria and aminoaciduria were also observed. These renal function changes were reversed within a few weeks.

Of the 78 patients, 6 developed a transient confusional state with disorientation and a variably disturbed level of conciousness: 1 of these patients had an intracranial tumor, and 4 others were receiving narcotic analgesics. There were no consistent electrolyte changes. In all cases the confusional state was fully reversible, although 1 patient died from tumor progression before complete resolution had occurred. In 3 of these patients further ifosfamide was given in the absence of narcotics, with no recurrence of CNS toxicity. Two patients developed mild peripheral neuropathy, which did not require modification of therapy. In 1 of these the neuropathy was unilateral and developed in the same limb as that previously affected by a peripheral neuropathy resulting from radiation and vincristine.

Hematuria was detected in 22 (43%) (half of whom had gross hematuria) of the patients who did not receive mesna and 6 (26%) of those who did (17% of whom had gross hematuria). However, it is clear that previous pelvic irradiation significantly increased the risk of hematuria, since 66% of patients in whom the bladder had been irradiated developed hematuria despite receiving mesna. The influence of mesna could still be discerned, however, since 40% of the irradiated patients treated without mesna and only 12% of those treated with mesna had gross hematuria (Table 4). Moreover, 12 patients who developed hematuria during treatment with ifosfamide alone were subsequently treated with mesna and ifosfamide. None had hematuria with subsequent cycles.

Discussion

We conclude from our data that ifosfamide is an active agent in a variety of bone and soft tissue sarcomas. The best response rate was seen among patients with Ewing's sarcoma, in which almost 50% of patients had partial responses. Patients with differentiated sarcomas, however, did poorly. Our results are similar to those of Stuart-Harris et al., who treated 67 patients with soft tissue sarcomas with infusions of 5–8 g/m^2 ifosfamide over 24 h and recorded 16 responses (24%), including 6 complete responses [11]. Whether there is any advantage of one regimen over another will await more detailed comparisons, and probably additional trials. Early results obtained with ifosfamide in combination with other drugs, e.g., vincristine and *cis*-platinum, in untreated and relapsed solid tumors and soft tissue sarcomas in childhood are promising [7, 8, 12] and indicate that further trials of such combinations should be undertaken.

Although we cannot comment on the relative activities of ifosfamide versus cyclophosphamide from our results, it is clear that ifosfamide can produce responses in patients previously treated with cyclophosphamide. Moreover, at the time of protocol entry all our patients had progressive tumor and were receiving, or had very recently received, cyclophosphamide-containing regimens. Thus, the possibility that ifosfamide is a more active drug than cyclophosphamide in the tumors represented here must be considered and is worthy of study. A randomized trial of ifosfamide versus cyclophosphamide in sarcomas is currently in progress in Europe, and preliminary results favor ifosfamide [2]. Ifosfamide is also worthy of consideration for inclusion in phase III protocols for the tumors included in this trial.

Mesna, although not commercially available in the USA, is clearly an effective uroprotective agent and should be used routinely with ifosfamide-containing regimens, since hemorrhagic cystitis is otherwise a dose-limiting toxicity for ifosfamide. This drug was otherwise well tolerated, apart from the uncommon CNS toxicities encountered. These appeared in our series to be much more likely in patients simultaneously receiving narcotic analgesics.

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