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Ifosfamide plus mesna with and without adriamycin in soft tissue sarcoma

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Summary. Early results with ifosfamide plus mesna in soft tissue sarcoma showed an initial response rate of 38% in 42 patients. All these patients treated at The Royal Marsden Hospital plus 30 more (total 67) have now been analysed. Single doses of 5 or 8 g/m^2 ifosfamide were given over 24 h by infusion in dextrose saline together with 400 mg/m^2 or 600 mg/m^2, respectively, of mesnum every 4 h to give a total of 9 doses. A diuresis of 200 ml/hour was maintained during therapy. Treatment was repeated 3-weekly. CR was seen in 6 and PR in 10 patients.

More recently doxorubicin was added to ifosfamide therapy in an attempt to improve on these results. At first only 20 mg/m^2 doxorubicin was given but this was escalated to 40 mg/m^2 and 60 mg/m^2. Mesna has been given in higher dosage (5 g/m^2 over 24 h), but otherwise the schedule is as above. In all 60 patients have been treated and most are now evaluable for response.

Encephalopathy has been seen with both regimens. The incidence and patient characteristics are reported.

Introduction

Soft tissue sarcomas, especially in adults, remain a difficult group of rare tumors to treat with chemotherapy. Despite early enthusiasm for single agents such as adriamycin and for combination chemotherapy regimens such as CyVADic, with time and larger numbers of patients the complete response rate has remained stubbornly in the 10%–15% range. Since only patients achieving complete remission (CR) can expect real therapeutic benefit and since combination chemotherapy adds to side-effects and toxicity, many medical oncologists now recommend only single-agent therapy. In our own unit we recently studied ifosfamide in this context, following the encouraging results from Germany [2, 4].

Our initial results in 42 patients treated with 5 or 8 g/m^2 ifosfamide plus 400 or 600 mg/m^2 of mesna for urothelial protection showed that 15% achieved CR and 23%, partial regression (PR) [7]. Eleven patients had received previous chemotherapy, but this did not appear to affect the response rate. Furthermore, the study revealed that response rate was no higher with 8 g/m^2 than with 5 g/m^2, although the toxicity, especially renal, was enhanced at the higher dosage [7]. Lastly, although PR and CR were not achieved immediately, regression was measurable after the first course of treatment if remission was going to occur.

With this previous experience in mind and our belief that adriamycin was the best single agent other than ifosfamide, a study was begun using the two agents together.

This report compares the results obtained with ifosfamide alone in 66 patients (including the previously reported 42 cases) with a further 50 patients treated with the combination.

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Methods

Ifosfamide was given as a 24-h infusion in 3 l dextrose saline at a dose of 5 g/m^2. Mesna was infused with the ifosfamide at 5 g/m^2, at a dose of 1 g/m^2 for each 1 l of saline. The last 1 g/m^2 was given over 8 h in dextrose saline after completion of the ifosfamide infusion. Adriamycin was given into a fast-flowing drip at the beginning of the ifosfamide infusion. The dose was 40 mg/m^2 in the earlier cases, later being escalated to 60 mg/m^2.

Treatment was repeated at 3-week intervals provided that leucocyte and platelet counts had returned to near-normal levels and renal function remained normal (urea <7.5 mmol/l and creatinine <105 mol/l). At least two course were given provided that progressive disease was not seen, and if response occurred a total of six treatments was administered. All patients had measurable and evaluable disease; none had a second tumour or evidence of cardiac disease. Histology was reviewed in all cases. Initially, all had an EDTA clearance done to assess renal function.

Eligibility

Patients with a histological diagnosis of soft tissue sarcoma with measurable and inoperable primary tumours not amenable to local radiotherapy and patients with metastatic sarcoma were included. Prior chemotherapy and/or radiotherapy did not exclude patients provided that the treatment was completed more than 6 weeks before the start of this regimen and, in the case of radiotherapy, measurable and untreated disease was still present. Patients were excluded if they had a history of cardiac disease or evidence of renal impairment (EDTA clearance <50 ml/min) or were older than 75 years. A low performance status alone did not exclude any patient.

Results

There were 66 patients who received ifosfamide alone and 50 were given additional adriamycin. Of these 50 patients, 21 received less adriamycin than 60 mg/m^2. Age range was similar in the two groups but the proportion of female patients was higher in the ifosfamide study (62% compared with 42%). On the other hand, more patients had received previous chemotherapy in the ifosfamide/adriamycin group (30%) than in the ifosfamide alone series (16%) (Table 1). Histological features were similar (Table 2), though there were proportionally slightly more tumours of young people, such as Ewing's tumour and rhabdomyosarcoma, in the combination group. Table 2 also shows that responses occurred in all the more common histological tumour types.

Remissions were seen in 17 cases in each group, i.e., in 27% with ifosfamide alone and 36% for the combination. The complete remission rates were similar, at 9.5% and 13% (Table 3).

It is of interest that responses occurred in patients previously treated with other drugs. There were two complete and five partial regressions in 15 previously exposed patients given ifosfamide and adriamycin. In the single-agent group there were one complete regression and four partial regressions in 13 previously treated cases.

Not all patients in the combination group had the full dose of adriamycin. Of the 21 cases receiving less than 60 mg/m^2 the response rate was 28.5%, and in the remaining 29 cases the response rate was 38%. It seems unlikely that this is a real difference, but it needs verification.

Duration of response appears to be longer for ifosfamide alone, but this is because the single-agent study has had longer to run. Thus, the responses to the combination are continuing in 10/17 patients, while responses to ifosfamide as a single agent are continuing in only 5/17 patients (Table 4).

Toxicity

Since the maximum dose of ifosfamide and the mesna protocol were changed in the second study, comparison of toxicity of the two regimens is not entirely reasonable. However, comparison of the protocols as a whole, bearing in mind that nadir blood counts were not taken routinely, indicates that the toxicities were very similar.

Haematuria and renal toxicity were lower in the combination group, almost certainly because of a reduction in the total dose of ifosfamide together with an increase in the total dose of mesna. Almost all the renal toxicity in the first study was seen in patients given 8 g/m^2.

Bone marrow toxicity was increased with the addition of adriamycin, but this was rarely severe. Febrile episodes occurred on only two occasions and purpura was not seen. There was one attack of herpes zoster during treatment and one patient had extravasation of adriamycin subcutaneously; again, this was not severe (Table 5).

A rash was seen in one patients probably due to ifosfamide. Central nervous system toxicity was seen in one patient receiving ifosfamide alone and three with added adriamycin. All had pelvic tumours and none showed response to their first dose of chemotherapy. The toxicity varied from drowsiness with incontinence over a 24-h period to fits or loss of consciousness and gag reflex lasting 24–26 h.

Table 1. Sequential phase II studies. Soft tissue sarcoma (STS)

	Ifosfamide alone	Ifosfamide + Adriamycin
Total no.	66	50
Sex F/M	41/25	21/29
Age (median)	41	41
(range)	5–73	10–72
Previous chemotherapy	13	15

Table 2. Histology and response

Histology	Ifosfamide alone		Ifosfamide + Adriamycin	
	Total no.	No. responding	Total no.	No. responding
Leiomyosarcoma	16	3	11	2
MFH & Fibrosarcoma	10	1	11	2
Undifferentiated	11	2	6	3
Liposarcoma	5	2	3	1
Synoviosarcoma	1	1	4	2
Epithelioid	1	0	2	0
Other	9	4	4	1
Embryonal/Rhabdo	5	1	5	4
Ewings	5	2	4	2
Mesothelioma	3	1	0	0

Table 3. Response rates

	Ifosfamide alone		Ifosfamide + Adriamycin	
	No.	%	No.	%
CR	6	9.5	6	13
PR	11	17.5	11	23
NR	46	73.0	30	64
NA	3	–	3	–
Overall response rate	27%		36%	

NR = no response; NA = not assessable

Table 4. Length of response

Ifosfamide alone	3, 4+, 5, 5, 6, 7, 7, 8, 9+, 11+, 12, 15, 16, 16, 21, 32+, 39+ *Median* 9–12 m *Alive in remission* 5/17
Ifosfamide + Adriamycin	2+, 2+, 3, 3+, 4, 4+, 4+, 5, 5+, 6, 6+, 7, 8, 8+, 9+, 10, 12+ *Median* 5–6 m *Alive in remission* 10/17

Table 5. Toxicity

	Ifosfamide alone	Ifosfamide + Adriamycin
Alopecia	90%	100%
Nausea and vomiting	95%	100%
Measurable haematuria	10%	4%
Renal toxicity	13%	6%
Leukopenia (< 2,000)	16%	28%
Thrombocytopenia (< 100,000)	1.5%	2%
CNS toxicity	1.5%	6%

Although highly dangerous, the toxicity was not fatal in any case. In all, EDTA clearance was relatively low (55–80 ml/min) and the leucopenia which followed was unusually severe, suggesting prolonged exposure. In one patient stomatitis was seen. Three patients had a CT scan done following the episode but none were abnormal. This toxicity has been reported by others [6] following 24-h infusion of ifosfamide, and it seems unlikely that adriamycin was responsible for the additional cases seen with the combination. It is more likely that in this patient population large pelvic masses relatively low EDTA clearance and a poor performance rating are the major contributory factors.

Conclusions

There have been several reports confirming the usefulness of high-dose ifosfamide in the treatment of soft tissue sarcoma both in adults [1, 3] and in young people [5], and responses can be produced even in patients previously treated with cyclophosphamide. Nevertheless, the response rates are no higher than with other chemotherapeutic agents used singly or in combination. The addition of adriamycin, another agent likely to produce around 30% responses, might be expected to give additional benefit without unacceptable toxicity.

Our study suggests that adriamycin by bolus injection up to 60 mg/m^2 will not increase the response rate by an amount sufficient to justify the added toxicity and expense. However, larger patient numbers will be needed and a randomized study would show whether there are small but worthwhile therapeutic advantages.

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