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Original Articles

High-dose alkylation therapy using ifosfamide infusion with mesna in the treatment of adult advanced soft-tissue sarcoma

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Summary. *In a phase II study, 42 patients with advanced soft-tissue sarcoma were treated with ifosfamide by 24-h infusion and mesna by 4-h IV bolus, repeated every 3 weeks. Ten patients received ifosfamide 5.0 g/m², 20 had the dosage increased to 8.0 g/m², and 12 received 8.0 g/m² from the outset. Mesna was given in doses of 400 mg/m² or 600 mg/m². Of 40 patients evaluable for response, six (15%) achieved complete response and nine (23%) partial response. The overall response rate was 38%. The median duration of response was 11 months. Treatment was associated with falls in peripheral WBC and alopecia in all patients. Most experienced severe nausea and vomiting. In seven nephrotoxicity developed, and two of these died of renal failure. Renal tubular defects and cerebral effects also occured. Mesna largely prevented haemorrhagic cystitis. Ifosfamide offers a new alternative to previous chemotherapy for advanced soft-tissue sarcoma, but alterations in dose or method will be necessary to reduce toxicity.*

Introduction

Ifosfamide is an alkylating agent chemically similar to cyclophosphamide [3]. Although cyclophosphamide is regarded as an active agent in the treatment of advanced soft-tissue sarcoma and has been used extensively to this purpose in combination chemotherapy, there are insufficient single-agent data to predict an accurate response rate for cyclophosphamide alone in the treatment of soft-tissue sarcoma in adults. The dose-limiting toxicity for both cyclophosphamide and ifosfamide has been haemorrhagic cystitis due to urothelial damage. The urothelial damage is thought to be produced by acrolein [5], which is a metabolite produced during the metabolism of both cyclophosphamide and ifosfamide. Mesna (2-mercaptoethane sodium sulphonate) has recently been introduced. This agent binds acrolein [12] and is reported to prevent urothelial damage [4]. The advent of mesna has enabled higher doses of ifosfamide or cyclophosphamide to be given without urothelial damage.

Ifosfamide has been reported to be an active agent in the treatment of soft-tissue sarcoma in several previous studies from Germany and France [6, 8, 11, 13, 16]. Although ifosfamide was used at high dosage levels, the studies were of large groups of patients with different malignancies. An accurate assessment of the response rate for adults with soft-tissue sarcoma is not possible because of the small number of soft-tissue sarcoma patients, differing schedules of treatment, and the concurrent use of sensitizing doses of radiotherapy in the treatment of some patients in these trials. In addition, mesna was not administered in the majority of these studies.

We decided to conduct a phase II study of high-dose ifosfamide to assess its activity and toxicity in the treatment of soft-tissue sarcoma, using concurrent mesna to determine whether urothelial toxicity could be adequately prevented. Because pharmacokinetic studies had shown that a greater proportion of ifosfamide was metabolized when it was given in divided doses than with single high-dose administration [1] and a preliminary study had shown that high doses of ifosfamide were well tolerated when given by a 24-h infusion [4], we elected to use ifosfamide by infusion over a 24-h period.

Materials and Methods

Patients. Between October 1980 and September 1982, 42 consecutive patients with biopsy-proven metastatic or locally advanced soft tissue sarcoma, not amenable to surgery or radiation therapy, were entered into the study. The histological diagnoses are shown in Table 1. Twenty-five patients were female and 17 were male; the median age was 44 years (age range 17–73 years). Karnovsky performance status ranged from 30–100, with a mean of 75. Eight patients had a performance status of less than 70 on entry to the study.

Table 1. Histological diagnoses recorded in study patients

Histological diagnosis	No. of patients
Leiomyosarcoma	10
Epithelioid leiomyosarcoma	2
Undifferentiated sarcoma	6
Malignant fibrous histiocytoma	4
Malignant giant cell tumour of soft parts	1
Fibrosarcoma	3
Cystosarcoma phylloides	1
Embryonal rhabdomyosarcoma	2
Alveolar rhabdomyosarcoma	1
Liposarcoma	3
Spindle cell sarcoma	3
Haemangiopericytoma	2
Müllerian adenosarcoma	1
Alveolar soft-part sarcoma	1
Synovial sarcoma	1
Chordoid sarcoma	1

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Table 2. Responding patients

Response	Courses	Histological diagnosis	Sex	Age	P.S.[a]	Time to first response	Response duration	Max. dose received (g/m^2)
CR	9	Leiomyosarcoma	F	46	100	Inevaluable	73/52 relapsed	5
CR	4	Undifferentiated	M	41	60	3/52	49/52 relapsed	8
CR	4	Alveolar rhabdomyosarcoma	M	61	80	2/52	29/52 relapsed	5
CR	9	Malignant giant cell Tumour of soft parts	F	26	100	3/52	39/52+	8
CR	6	Cystosarcoma phylloides	F	31	100	3/52	37/52+	8
CR	4	Synovial sarcoma	M	57	90	3/52	10/52	8
PR	8	Leiomyosarcoma	F	37	80	8/52	51/52 relapsed	8
PR	9	Haemangiopericytoma	M	18	50	2/52	50/52 relapsed	8
PR	5	Spindle cell sarcoma	F	44	70	3/52	33/52 relapsed	8
PR	7	Epithelioid leiomyosarcoma	F	55	30	3/52	32/52 relapsed	7
PR	6	Undifferentiated	F	31	70	3/52	19/52 relapsed	5
PR	5	Liposarcoma	F	48	60	3/52	19/52 relapsed	8
PR	3	Embryonal rhabdomyosarcoma	M	21	50	3/52	10/52 relapsed	5
PR	9	Leiomyosarcoma	F	27	90	6/52	67/52+	8
PR	5	Malignant fibrous histiocytoma	M	32	100	3/52	31/52+	8

[a] Performance status

Fourteen patients had received prior chemotherapy. Informed consent was obtained from all patients.

Dose and Schedule. The first 10 patients were treated with a dosage of 5.0 g/m^2 every 3 weeks. The next 20 patients were treated with 5.0 g/m^2 for their first course, escalating to 8.0 g/m^2 (maximum 12.0 g) on the second and subsequent courses if toxicity allowed. The remaining 12 patients received 8.0 g/m^2 (maximum 12.0 g) from the outset of therapy. Patients received between one and 11 courses of therapy, with a mean of 4.3 courses. Ifosfamide was given as an infusion in 3 l of dextrose saline over 24 h. Because of possible anti-diuretic hormone-like activity of ifosfamide, diuresis was initiated with 1 l of dextrose saline given in 2 h prior to the chemotherapy infusion. In addition, 30 min prior to chemotherapy 200 ml 20% mannitol was given. To prevent urothelial toxicity, mesna (400 mg/m^2 or 600 $mg/^2$, depending on ifosfamide dosage) was given by IV 4-h bolus, to a total of nine doses, commencing immediately before the chemotherapy infusion.

Fluid output was carefully monitored during treatment, and if the urine output fell to less than 100 ml/h, frusemide 40 mg was given by IV bolus as required. After the start of the ifosfamide infusion, 4-h specimens of urine were examined for the presence of microscopic (Bili-Labstix) or macroscopic haematuria. Anti-emetics (chlorpromazine, prochlorperazine, metoclopramide, or levonantradol) were given as required.

Investigations. Full blood counts were carried out at weekly intervals during treatment. Before treatment and at 3-weekly intervals the following were also checked: Plasma urea and electrolytes, serum creatinine, bilirubin, alanine transferase, alkaline phosphatase, gamma-GT, and chest X-ray. Skeletal X-rays, computerized tomography, isotope or ultrasound scans, or other investigations, were carried out as indicated.

Criteria for Assessment of Response and Toxicity. All courses of therapy have been assessed for toxicity. Two patients were considered inevaluable for response; one was withdrawn after the second course of therapy because of toxicity and the other was subsequently excluded because of radiotherapy to a sole index lesion available in the 4 weeks prior to entry on the study. Response was defined according to standard WHO criteria [17].

Table 3. Response by site of disease (40 patients)

	No. of patients	Response
Local recurrence	17	3
Metastatic disease		
Soft tissue	5	2
Nodes	2	2
Lung	24	10
Pleura	2	1
Bone	4	2
Liver	7	0
Bone marrow	1	1

Results

Response

Of the 42 patients, 40 are therefore evaluable for response: six (15%) achieved a complete response and nine (23%) a partial response, giving an overall response rate of 38%. One of the complete responders and four of the partial responders had received prior chemotherapy. Details of responding patients are shown in Table 2. Notably, an equal response rate was observed in patients who had received prior chemotherapy (5 of 13; 38%) and those who were previously untreated (10 of 27; 37%). During therapy nine patients (22%) showed no change, whilst 16 (40%) showed disease progression. Response according to sites of disease is given in Table 3.

Time to Achieve First Response

Response was achieved within 3 weeks in 12 patients, 6 weeks in one patient, and 9 weeks in one further patient. It was not possible to determine time to first response in one patient as

Table 4. WBC nadirs during ifosfamide therapy

Dose	Patients	Courses	> 3,000/mm^3	2,000–3,000/mm^3	1,000–1,900/mm^3	< 1,000/mm^3	Mean
5 g/m^2	26	39	23	12	3	1	4,000/mm^3
8 g/m^2	26	76	18	18	26	14	2,100/mm^3

the index lesion could only be measured by computerized tomography and this was not repeated until after the fourth course of therapy. Mean time to first response for the group of 14 responders was $3^1/_2$ weeks.

Overall Duration of Response

Of the six complete responders, two remain in remission at 39 and 37 weeks; three have relapsed following remissions of 73, 49, and 29 weeks. One patient died in complete remission at 10 weeks, but autopsy showed no evidence of residual disease and he has been reported as a toxic death. Of the nine partial responders, two remain in remission at 67 and 31 weeks. The other seven have relapsed following response durations of 10–51 weeks (see Table 2). The median duration of response for all responders was 11 months. Actuarial survival curves have shown that the median survival for nonresponders is 7 months, whilst median survival for responders has not been reached but is in excess of 18 months.

Response in Relation to Previous Cyclophosphamide Therapy

Ten patients had received prior combination chemotherapy regimens containing cyclophosphamide in a dose of 600 mg/m^2 by IV bolus; three had achieved response, four had shown progressive disease, one had been classified as no change, and two were inevaluable for response. Of this total of 10 patients who were subsequently treated with ifosfamide, three achieved response. One patient who had failed to achieve response with a cyclophosphamide-containing regimen subsequently responded to ifosfamide. None of the patients who were treated with ifosfamide have subsequently been treated with cyclophosphamide.

Subjective Toxicity

Two patients experienced nausea only during therapy. The remaining 40 patients had nausea and vomiting, which was most severe during the last 8 h of therapy. Of these, 21 patients vomited less than five times during each cycle of therapy, but the remaining 19 had severe vomiting which responded poorly to anti-emetic therapy. In these patients vomiting was similar in severity to that seen with high-dose cisplatin therapy.

Objective Toxicity

Haematological Toxicity. Nadir counts were obtained in 26 patients at each dose level during a total of 115 courses of ifosfamide (Table 4). Mean white blood count nadir at 5 g/m^2 was 4,000/mm^3 (range 200–11,200/mm^3) and at 8 g/m^2 was 2,100/mm^3 (range 600–6,100/mm^3).

Four cycles of treatment were delayed because of leucopenia (WBC < 3,000/mm^3) in three patients and infection in one. A further patient who had previously had a nephrectomy needed her treatment intervals extended to 4 weeks for each of her nine courses, because of leucopenia following each cycle.

There were six episodes of neutropenic infection, all successfully treated with antibiotics. Thrombocytopenia of less than 100,000/mm^3 occurred in four patients during a total of 14 cycles. Mean platelet nadir in these patients was 78,000/mm^3. Haemoglobin values remained stable throughout.

Haematuria. Forty-one patients were assessed over 168 courses for the presence of haematuria. Microscopic haematuria was detected by dipstick testing (Bili-Labstix) during 41 courses (24.4%), but was not confirmed by microscopy. Macroscopic haematuria occurred during five courses (2.9%). Of these five courses, insufficient mesna was given during two and a urinary tract infection was detected during two other courses. No precipitating factors could be identified in the one remaining course.

Nephrotoxicity. Evidence of nephrotoxicity was assessed during the study using plasma urea and electrolytes and serum creatinine determinations, carried out at 3-weekly intervals. Ten patients also had creatinine clearance estimations performed before and during therapy. Seven patients showed evidence of deterioration in renal function during or after treatment. The maximum doses of ifosfamide per course in these patients had been 8 g/m^2 in five patients, 7 g/m^2 in one patient, and 5 g/m^2 in the remaining patient. Two patients, both receiving therapy for hypertension, developed irreversible renal failure following 21 g and 31.5 g ifosfamide, respectively. At post mortem the kidneys in both showed evidence of acute tubular necrosis. Renal impairment developed in a further three patients. The first had pre-existing obstructive hydronephrosis but developed renal parenchymal damage after 66 g ifosfamide; the second developed urate nephropathy associated with treatment (maximum 5 g/m^2 of ifosfamide per course) and the third patient developed renal tubular acidosis, after 96 g ifosfamide, which progressed into chronic renal failure. Transient rises in plasma urea and serum creatinine were observed in two additional patients after 35 g and 132 g ifosfamide. In both therapy was stopped and renal function gradually returned to normal.

Clinical evidence of tubular damage was also seen. Transient glycosuria developed in two additional patients, in both of whom glucose tolerance tests gave normal results.

Other Toxicities. All patients developed severe alopecia. Hair regrew following the cessation of therapy in all patients.

One patient developed severe drowsiness during therapy with 8 g/m^2 of ifosfamide. Initially this was attributed to anti-emetic medication but drowsiness recurred on the subsequent course and necessitated a dose reduction.

Thrombophlebitis near the treatment site was also occasionally seen. One toxic death occurred during the study. This patient, who had achieved complete response, had severe diarrhoea and vomiting at home following his fourth course of therapy. He died before readmission, but autopsy showed no precipitating cause of death, and no residual tumour.

Discussion

The assessment of clinical trials in the treatment of soft-tissue sarcoma is difficult, as the histological classification embraces a wide variety of rare mesenchymal tumours whose natural history is variable. This problem is further compounded by factors such as the histological grade, size of the tumour, and age [10] and performance status of the patient [2], all of which may affect the response to therapy. Nevertheless, the term soft-tissue sarcoma is useful as it draws together these diseases, enabling further experience to be gained in their management.

Local surgery is usually the first line of therapy, but once metastatic disease has occurred or if the primary tumour is not amenable to local surgery or radiotherapy, then chemotherapy may offer the only hope of palliative or even curative therapy. The most active single agent is probably adriamycin, but the range of reported response rates is wide, between 9 [7] and 70% [15]. When the world literature was reviewed in 1977 [10], the overall response rate for adriamycin in a total of 357 patients was 27%. The efficacy of adriamycin is apparently increased when it is used in combination with cyclophosphamide, vincristine, and dacarbazine (CYVADIC). The value of cyclophosphamide in this combination is difficult to assess, as although cyclophosphamide is proven to be an active agent in the treatment of soft-tissue sarcoma in children, there are scant single-agent data concerning its use in adults.

Prior to this study there were insufficient data to predict a reliable response rate for ifosfamide. In our series of adult patients, single-agent ifosfamide has achieved a response rate of 38%, including a complete remission rate of 15%. In previous studies with single agents, complete remissions have rarely been achieved. It is interesting to note that the complete response rate that we have achieved in adults is similar to the reported complete response rates attained with three- or four-drug combination chemotherapy (VADIC, 9%; CYVADIC, 15%) [10].

The previous dose-limiting side-effect of ifosfamide was haemorrhagic cystitis caused by acrolein [5], and various hydration regimens have been used to ameliorate this. Mesna is said to act by binding with acrolein [12]. In our study, macroscopic haematuria occurred in only five of 168 courses, and in only one could it be attributed to a failure of mesna protection. The major toxicity in this study was renal parenchymal and tubular damage. Two patients died and five developed significant renal impairment. This high incidence of renal parenchymal damage may be due to the use of ifosfamide as a 24-h infusion, although acute tubular necrosis has also been reported following large single bolus injections [14]. It appears, therefore, that urothelial and renal parenchymal damage are produced by different mechanisms. It is important to note, however, that recent work has shown that 70% of a bolus injection of mesna is excreted in the first 2 h after administration [9] and therefore our use of 4-h bolus injections of mesna may have left the renal tract unprotected for 2 h. More frequent injections, or continuous infusion, of mesna warrant further investigation. Other side-effects encountered were tolerable, and myelosuppression was not a serious problem with the doses used.

The majority of responding patients (11 of 15) responded at the lower dose of 5 g/m^2 and no further responses were seen at the higher dose. It appears that 5 g/m^2 is a satisfactory dose and escalation to 8 g/m^2 is not necessary.

Ifosfamide is an important new agent for the treatment of soft-tissue sarcoma in adults, but changes in dose or method will be necessary to reduce toxicity. Its activity should be compared with cyclophosphamide in future studies, but its relatively mild myelosuppression would make it more suitable than cyclophosphamide for use in combination therapy.

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References

1. Allen LM, Creaven PJ, Nelson RL (1976) Studies on the human pharmacokinetics of isophosphamide (NSC-109724). Cancer Treat Rep 60: 451
2. Bramwell V, Mouridsen H, Somers R, van Oosterom A, Sylvester R, Thomas D, Markham D, Crowther D, Pinedo H (1982) The influence of scheduling and performance status (P.S.) on chemotherapy of advanced soft-tissue sarcoma with cyclophosphamide (CY), vincristine (V), adriamycin (A), and DTIC (DIC). Proc Am Soc Clin Oncol 1: 23
3. Bremarer DN, McCormick JStC, Thomson JWW (1974) Clinical trial of isophosphamide (NSC-109724) – Results and side-effects. Cancer Chemother Rep 58: 889
4. Bryant BM, Jarman M, Ford HT, Smith IE (1980) Prevention of isophosphamide-induced urothelial toxicity with 2-mercaptoethane sulphonate sodium (Mesnum) in patients with advanced carcinoma. Lancet II: 657
5. Cox PJ (1979) Cyclophosphamide cystitis – Identification of acrolein as the causative factor. Biochem Pharmacol 28: 2045
6. Drings P, Fritsch H (1972) Experiences with ifosfamide in high individual doses in metastasising solid tumours. Verh Dtsch Ges Inn Med 78: 166
7. Hahn RG, Ahman DA, Bisel HF (1973) A phase II study of adriamycin (NSC 123127) therapy for metastatic or inoperable sarcoma. Cancer Chemother Rep 57: 102
8. Hoefer-Janker H, Scheef W, Günther U, Hüls W, Vahlensieck W, Brühl P (1975) Results obtained with fractionated ifosfamide massive-dose treatment in generalized malignant tumours. Med Welt 26: 972
9. Ormstad K, Orrenius S, Lastbom T, Uehara N, Pohl J, Stekar J, Brock N (1983) Pharmacokinetics and metabolism of sodium 2-mercaptoethane-sulfonate in the rat. Cancer Res 43: 333
10. Pinedo HM, Kenis Y (1977) Chemotherapy of advanced soft-tissue sarcomas in adults. Cancer Treat Rep 4: 67
11. Ritter S, Schröder HJ (1977) Clinical experience with the cytostatic ifosfamide. Med Welt 28: 1395
12. Scheef W, Klein HO, Brock N, Burkert H, Günther U, Hoefer-Janker H, Mitrenga D, Schnitker J, Voigtmann R (1979) Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphorines: Preliminary results. Cancer Treat Rep 63: 501
13. Schnitker J, Brock N, Burkert H, Fichtner E (1976) Evaluation of a cooperative clinical study of the cytostatic agent ifosfamide. Arzneim Forsch 26: 1783
14. Van Dyk JJ, Falkson HC, Van Der Merwe AM, Falkson G (1972) Unexpected toxicity in patients treated with iphosphamide. Cancer Res 32: 921
15. White DR, Cooper MR, Spurr CL (1975) A comparison of single and three-day dosage schedules of adriamycin in adult solid tumours. Proc Am Soc Clin Oncol 16: 250
16. Wicart L (1976) Ifosfamide in the treatment of solid tumours and their metastases. Nouv Press Med 5: 996
17. World Health Organization (1979) WHO Handbook for reporting results of cancer treatment. WHO, Geneva (offset publication no. 48)

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