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Cyclophosphamide versus ifosfamide: preliminary report of a randomized phase II trial in adult soft tissue sarcomas*

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Summary. One hundred and seventy-one patients with advanced soft tissue sarcoma entered a randomized cross-over phase II study comparing cyclophosphamide (CYCLO) with a new analogue, ifosfamide (IFOS), both administered as 24 h i.v. infusions every 3 weeks. The doses used were CYCLO 1.5 g/m^2 and IFOS 5 g/m^2, with provision for dose escalation. All patients received mesna 400 mg/m^2 as an i.v. bolus 4 hourly × 9 doses, commencing at the start of the oxazophosphorine infusion. Patients who had received previous chemotherapy were eligible provided this did not include a classical alkylating agent. There were 22 patients who were ineligible, and response could not be evaluated in 12 additional patients. IFOS produced two complete and ten partial remissions, for an overall response rate of 18%. CYCLO was significantly ($P = 0.04$) less active, producing one complete and five partial remissions, an overall response rate of 9%. Stabilization of disease was similar in both arms (27% and 24% respectively), but fewer patients showed progression on IFOS. The response rate was higher (20% vs 5%) for patients who had not received previous chemotherapy, and also for female compared with male patients (21% vs 5%). When only patients who had not received previous chemotherapy were considered, the respective response rates for IFOS and CYCLO were 24% and 15%. There were no responses in previously treated patients receiving CYCLO. There were four partial responses in 33 patients crossing from CYCLO to IFOS, but no responses in 18 patients receiving CYCLO after IFOS. Leucopenia was significantly more pronounced ($P = 0.0004$) with CYCLO, both after the first course and throughout treatment, although the incidence of severe infections, 6%, was the same in both arms. Nausea and vomiting were more severe with IFOS ($P = 0.022$), but other toxicities were mild. Grade 1 or 2 bladder (haematuria) or renal (rise in serum creatinine) toxicity was slightly more frequent with IFOS (7 vs 3 patients) and was a reason for stopping treatment for one patient in each arm. Three episodes of mild to moderate drowsiness after IFOS were reported, but no severe encephalopathy. A higher response rate with less myelosuppression suggests that IFOS may have advantages over CYCLO in combination with such active agents as adriamycin.

Introduction

Despite encouraging early results, there has been little recent progress in the development of chemotherapy for advanced soft tissue sarcomas in adults. Adriamycin, identified as an active agent in the early 1970s [5, 18], is the backbone of all effective combination regimens [2–4, 7–9, 18], but despite extensive testing of more than 30 agents [2–4, 7–9], no other drug has confirmed single-agent activity of greater than 20%. Response rates for combination chemotherapy are in the range of 30%–50%, but complete durable remissions are rare [2–4, 7–9, 18].

On the basis of its significant activity in childhood rhabdomyosarcoma [5], cyclophosphamide (CYCLO) has frequently been incorporated into combination chemotherapy for advanced adult sarcomas, although single-agent data in this context are scarce. Ifosfamide (IFOS) is an analogue of CYCLO, introduced in 1977, which has significant activity in a wide range of tumour types [6]. The frequent occurrence of haemorrhagic cystitis and occasional renal failure dampened enthusiasm, outside Germany, for the use of this drug. Interest has been rekindled by the development of mesna (sodium 2 mercapto-ethanesulphonate), a thiol compound which detoxifies the oxazaphosphorine metabolite acrolein [12, 19, 20].

In light of early favourable reports in the German literature [13–15], investigators at the Royal Marsden Hospital [21] undertook a phase II study of IFOS 5–8 g/m^2 every 3 weeks, using a 24 h infusion schedule. They reported an overall response rate of 38% in 42 evaluable patients. Equally exciting results (overall response 50%) were observed in a smaller series of 16 patients treated in Manchester [11]. The purpose of the present study conducted by the Soft Tissue and Bone Sarcoma Group of the EORTC was to confirm these results in a larger series of patients and determine whether IFOS was more active than the parent compound CYCLO. Additional aims were to generate single-agent data for CYCLO and evaluate the relative toxicities of the two analogues.

Patients and methods

Between October 1982 and May 1984, 171 patients were entered from 18 participating centres. Copenhagen, Milan,

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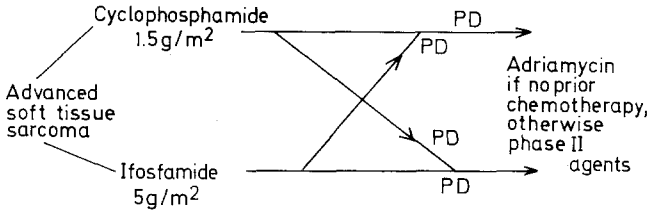

Fig. 1. Treatment regimens, both given as 24 h infusions with Mesna 400 mg/m^2 i.v. bolus 4 hourly × 9

Manchester, Birmingham and Amsterdam contributed 60% of the total patients accrued. The treatment regimens are shown in Fig. 1. Eligibility criteria included histologically proven soft tissue sarcoma, inoperable locally advanced or metastatic disease which had progressed in the last 2 months and was measurable, age 15 years or above and adequate haematological, hepatic and renal (serum creatinine < 0.15 mmol/l) function. All patients gave informed consent. Reasons for exclusion were performance status lower than 2 (WHO), severe concomitant illness or CNS metastases, radiotherapy at any time to the sole index lesion or chemotherapy within the past 4 weeks, and a history of other cancer. Patients who had received prior chemotherapy were eligible, provided they had not received a classical alkylating agent (excluding DTIC).

A total of 136 patients were considered to be evaluable, 68 in each arm. Reasons for exclusion are shown in Table 1. Patient characteristics are described in Table 2. Patients were evenly distributed between the two arms with respect to age, performance status, prior chemotherapy or radiotherapy and presence of distant metastases. However, there were more female patients in the IFOS group (59%) than in the CYCLO group (44%). There was a history of previous chemotherapy in 56 patients, 67% of whom had received only one drug (usually an anthracycline) and only 12.5% of whom had received three or more drugs. Of 22 receiving CYCLO and 18 receiving IFOS, 3 and 5, respectively, had responded to prior chemotherapy. On pathological review, leiomyosarcoma, was the commonest histological subtype (26%), with a wide range of other cell types.

The criteria used for asessing response and toxicity are those defined by the WHO [22].

Results

The overall results are summarized in Table 3. IFOS produced two complete remissions (CR) and ten partial remissions (PR), giving an overall response rate of 18%, compared with 1 CR and 5 PR with CYCLO, for an overall response rate of 9% ($P = 0.04$). Preliminary data show that the duration of response ranged from 1 to 18 months for IFOS and 2 to 5 months for CYCLO.

The response rate was higher – 20% vs 4% – for patients who had not received prior chemotherapy (Table 4). In addition, female patients achieved remission significantly more often than male patients (21% vs 5%). Among the patients who had not received previous chemotherapy, the respective response rates for IFOS and CYCLO were 24% and 15% (Table 5). There were no responses in previously treated patients receiving CYCLO. Higher response rates

Table 1. Reasons for exclusion

Ineligible	22	Non evaluable	12
Pathology	8	Early death	7
Prior alkylator	4	Refusal	2
Not measurable	5	Wrong treatment	2
No data	3	Lost to follow-up	1
Raised creatinine	2		

Table 2. Patient characteristics

	CYCLO	IFOS
Mean age	48 years	50 years
Sex female	44%	59%
Previous XRT	31%	32%
Previous chemotherapy	43%	40%
Metastases	91%	91%
PS 0–1	75%	79%

Table 3. Overall response

Response	CYCLO	IFOS
CR	1	2
PR	5	10
NC	24	27
PD	38	29
Total	68	68
Overall response	9%	18%
95% CI	2%–16%	9%–27%
P trend	0.04	

were evident in females patients in both IFOS and CYCLO arms (Table 5), but only in the CYCLO arm was this difference significant ($P = 0.03$). There was no relationship between response rate and performance status. The effects of the crossover to the other analogue after failure of initial chemotherapy was evaluated in 51 patients. There were 4PR in 33 patients crossing from CYCLO to IFOS, and no responses in 18 patients receiving CYCLO after IFOS.

An intriguing finding (Table 4) was that patients treated in Great Britain seemed to have a higher response rate (27% vs 9%; $P = 0.08$) than those treated in other European countries. Britain entered 22% of the evaluable patients. A number of prognostic factors were examined. More patients in Britain received escalated doses of chemotherapy, particularly in the CYCLO arm. Despite this, white cell count nadirs were lower (data not shown) for patients treated on the Continent, probably reflecting a more extensively pretreated population. However, British patients had lower performance statuses at entry. There was no difference in extent of disease according to country.

The difference in response rate according to country was only apparent in the IFOS arm and disappeared if only patients who had received no previous chemotherapy were considered (Table 6). Britain entered slightly more female patients and 87% had not received previous chemotherapy, compared with 51% for the rest of Europe. Thus,

Table 4. Response according to prior chemotherapy, institution and sex

Response	Prior chemo		Institution		Sex	
	No	Yes	GB	C	Male	Female
CR	2	1	1	2	1	2
PR	14	1	7	8	2	13
NC	25	26	9	42	26	25
PD	39	28	13	54	37	30
Total	80	56	30	106	66	70
Overall response	20%	4%	27%	9%	5%	21%
95% CI	10–28%	0–9%	11–42%	3–14%	0–10%	11–30%
P trend	0.16		0.08		0.01	

GB, Great Britain; C, Continent (rest of Europe)

Table 5. Response by treatment related to prior chemotherapy and sex

		Response rate %	
		CYCLO	IFOS
Prior chemo	Yes	0	7
	No	15	24
Sex	M	0	11
	F	20	23
No prior chemotherapy – Men		56%	
Women		61%	

Table 6. Response by treatment related to institution and prior chemotherapy

		Response rate %	
		CYCLO	IFOS
Institution (all pts)	GB	14	38
	C	7	12
Institution (no prior chemotherapy)	GB	17	36
	C	15	19
No prior chemotherapy	GB	87%	
	C	51%	
Female sex	GB	63%	
	C	48%	

GB, Great Britain; C, Continent (rest of Europe)

Table 7. Leucopenia all courses (77% Evaluable)

	WBC NADIR $\times 10^9$/l					
	<1.0	<2.0	<3.0	<4.0	>4.0	Total
CYCLO	10	23	13	5	2	53
IFOS	3	14	19	10	7	53

P for trend 0.004 CYCLO more leucopenia

the higher response rate according to country would seem to be a spurious finding.

The median number of courses per patient was 2.5 (range 1–12) for CYCLO and 3.0 (range 1–15) for IFOS. Similar proportions of courses, 16% and 10%, were modified in both arms because of toxicity. Leucopenia was significantly more pronounced with CYCLO (Table 7), both after the first course and throughout treatment. This was most marked in patients who had received previous chemotherapy. Serious infections occurred in approximately 6% of patients, with no difference between the two drugs. IFOS appeared to have a cumulative effect on the white cell count. This was not true of CYCLO, probably because early leucopenia led to dose reductions. In the CYCLO arm there was one death due to infection during drug-induced leucopenia. Thrombocytopenia was rare.

Table 8. Other toxicities, 145 Evaluable patients

	WHO Toxicity				
	0 C/I	*1* C/I	*2* C/I	*3* C/I	*4* C/I
Nausea, vomiting[a]	7/1	31/29	22/25	11/17	0/1
Renal, bladder	70/66	1/3	1/4		
Infection	65/63	3/5	3/4	1/1	
Cerebral	72/70	0/2	0/1		

C/I, cyclophosphamide/ifosfamide

Three patients left the study because of toxicity: CYCLO leucopenia, bladder
IFOS renal

[a] *P* trend 0.022; IFOS more nausea, vomiting

Although there was provision for dose escalation if the nadir white count was above 2.0 $\times$ 10^9/l, only 18% of such patients actually had an appropriate increase in dose. Surprisingly, as CYCLO was more myelosuppressive, dose escalation was performed in this arm for a larger proportion (25%) of patients.

IFOS caused significantly more nausea and vomiting than CYCLO (Table 8). Grade 1 or 2 renal and/or bladder toxicity occurred in seven patients receiving IFOS, compared with three receiving CYCLO, and was a reason for stopping treatment for one patient in each arm. Three episodes of mild to moderate drowsiness with IFOS were reported, but no severe encephalopathy. Alopecia was seen in all patients receiving more than one course of either analogue.

Discussion

Response rates for IFOS in adult soft tissue sarcomas have ranged from 22% to 67% [1, 6, 11, 13–15, 21] in other

published studies, most of which have included patients previously treated with chemotherapy. The overall response rate in this study was 18%, but in patients not previously exposed to chemotherapy it was 26%, a result which is in the same range as our previous results with adriamycin [10, 17]. The dose actually administered in this study was lower than in two other recent phase II trials [1, 21], and this, together with the potential heterogeneity of the patient populations with sarcoma, may account for the lower remission rate.

CYCLO has marginal activity in previously untreated patients, perhaps comparable with that of DTIC. Its use in combination cannot be recommended, in view of the marked myelosuppression associated with modest activity. In contrast, IFOS was significantly more active in all patients and produced remissions in previously treated patients, including those resistant to CYCLO. Although this suggests a lack of cross-resistance, at least in one direction, a dose-response effect cannot be excluded, as the dose of IFOS was 3.3 times that of CYCLO. The mild myelosuppression associated with the dose of IFOS used in this study would permit its use in combination with myelosuppressive agents, such as adriamycin, without modification.

Although nausea and vomiting were more severe with IFOS than with CYCLO, these side-effects rarely limit the use of a cytotoxic agent and are largely alleviated by modern antiemetic regimens. Alopecia was universal with both drugs. The urothelial damage produced by IFOS has been largely obviated by the use of mesna. In a few cases, haematuria could be linked to omission of one or more doses of Mesna, and in our current study we are exploring the use of higher doses of mesna given by continuous infusion. Irreversible renal failure was not seen in this study.

Although encephalopathy is a well-recognized complication of IFOS therapy [6, 16], only 3 episodes of drowsiness in 68 patients were observed in this study. This contrasts with an incidence of 26% in the study of Antman et al. [1], in which higher doses of IFOS, 8–10 g/m^2, were used.

In summary, ifosfamide is an active drug in adult soft tissue sarcomas, which has moderate and manageable toxicity. With the use of mesna, bladder and renal toxicity are minimal and are no longer dose-limiting. Combinations of adriamycin and IFOS are of considerable interest, and the relatively mild myelosuppression observed in this study suggests that minimal compromise of single-agent doses will be necessary. The EORTC Sarcoma Group is currently exploring this area.

References

1. Antman KH, Montella D, Rosenbaum C, Schwen M (1985) Phase II trial of Ifosfamide with Mesna in previously treated metastatic sarcoma. Cancer Treat Rep 69: 499–504
2. Bonadonna, G, Santoro A (1982) Bone and soft tissue sarcomas. in: Pinedo HM (ed) Cancer chemotherapy 1982, chap 22, The EORTC Cancer Chemotherapy Annual, vol 4, Excerpta Medica, Amsterdam, pp 373–396
3. Bonadonna G, Santoro A (1983) Bone and soft tissue sarcomas. In: Pinedo HM, Chabner BA (eds) Cancer chemotherapy, chap 24, The EORTC Cancer Chemotherapy Annual, vol 5. Elsevier, Amsterdam, pp 430–445
4. Bonadonna G, Santoro A (1984) Bone and soft tissue sarcomas. In: Pinedo HM, Chabner BA (eds) Cancer chemotherapy, chap 25, The EORTC Cancer Chemotherapy Annual, vol 6. Elsevier, Amsterdam, pp 436–449
5. Bonadonna G, Beretta G, Tancini G, Brambilla, C, Bajetta, E, De Palo GM, De Lena M, Fossati-Bellani F, Gasparini M, Valagussa, P, Veronesi U (1975) Adriamycin (NSC-123127) studies at the Istituto Nazionale Tumori Milan. Cancer
6. Brade WP, Herdrich K, Varini M (1985) Ifosfamide – pharmacology, safety and therapeutic potential. Cancer Treat Rev 12: 1–47
7. Bramwell VHC, Pinedo HM (1979) Bone and soft tissue sarcomas. In: Pinedo HM (ed) Cancer chemotherapy 1979, chap 20, The EORTC Cancer Chemotherapy Annual, vol 1. Excerpta Medica, Amsterdam, pp 424–450
8. Bramwell VHC, Pinedo HM (1980) Bone and soft tissue sarcomas. In: Pinedo HM (ed) Cancer chemotherapy 1980, chap 21, The EORTC Cancer Chemotherapy Annual, vol 2. Excerpta Medica, Amsterdam, pp 393–414
9. Bramwell VHC, Pinedo HM (1981) Bone and soft tissue sarcomas. In: Pineda HM (ed) Cancer chemotherapy 1981, chap 21, The EORTC Cancer Chemotherapy Annual, vol 3. Excerpta Medica, Amsterdam, pp 409–424
10. Bramwell VHC, Mouridsen HT, Mulder JH, Somers R, Van Oosterom AT, Santoro A, Thomas D, Sylvester R, Markham D (1983) Carminomycin vs Adriamycin in advanced soft tissue sarcomas: an EORTC randomized phase II study. Eur J Cancer Clin Oncol 19: 1097–1104
11. Bramwell VHC, Crowther D, Deakin DPD, Swindell R, Harris M (1985) Combined modality management of local and disseminated adult soft tissue sarcomas: a review of 257 cases seen over 10 years at the Christie Hospital & Holt Radium Institute, Manchester. Br J Cancer 51: 301–318
12. Brock N, Pohl J (1983) Detoxification as a principle to increase the drug's therapeutic range in cancer chemotherapy, Ifosamide and Mesna. In: 13th Interntional Congress on Chemotherapy, Vienna, Austria, 1983, pp 123–137
13. Czownicki A, Utracka-Hutka B (1977) Contribution to the treatment of malignant tumors with Ifosfamide. In: Burkert H, Voight HC (eds) Proceedings, International Holoxan Symposium, Düsseldorf. Asta-Werke, Bielefeld, pp 109–111
14. Hoefer-Janker H, Scheef W, Günther U, Hüls W (1975) Erfahrungen mit der fraktionierten Ifosfamide Stoßtherapie bei generalisierten malignen Tumoren. Med Welt 26: 972–979
15. Klein HO 1982) High dose Ifosfamide and Mesna continuous infusion over 5 days – a phase I/II trial. In: Proceedings, 13th International Cancer Congress, 1982
16. Meanwell CA, Blake AE, Blackledge G, Blake DR, Honisberger L, Williams AC, Latief TN, Mould JJ, Shaw IC, Spooner D, Jones SR (1985) Encephalopathy associated with Ifosfamide/Mesna therapy. Lancet 1: 406–407
17. Mouridsen HT, Somers R, Santoro A, Mulder JH, Bramwell VHC, Van Oosterom AT, Sylvester R, Thomas D (1984) Adriamycin vs 4'epiadriamycin in advanced soft tissue sarcomas: An EORTC randomized phase II study. In: Bonadonna G (ed) Advances in anthracycline chemotherapy: epirubicin. Masson Italia, Milan, pp 105–109
18. Pinedo HM, Kenis Y (1977) Chemotherapy of advanced soft tissue sarcoma in adults. Cancer Treat Rev 4: 67–86
19. Scheef W, Klein HO, Brock N, Burkert H, Günther U, Hoeferjanker, H, Mitrenga D, Schnitker J, Voigtman R (1979) Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphorines: preliminary results. Cancer Treat Rep 63: 501–505
20. Scheef W, Soemer G (1981) The treatment of solid malignant tumors with holoxan and uromitexan. In: Burkert H, Nagel GA (eds) New experience with the oxazophosphamines, with special reference to the uroprotector uromitexan. Karger, Basel, pp 12–20
21. Stuart-Jarris RC, Harper PG, Parsons CA (1983) High-dose alkylation therapy using Ifosfamide infusion with Mesna in the treatment of adult advanced soft tissue sarcoma. Cancer Chemother Pharmacol 11: 69–72
22. World Health Organization (1979) Handbook for reporting results of cancer treatment. WHO, Geneva (Offset publication no 48)