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Cyclophosphamide versus Ifosfamide: Final Report of a Randomized Phase II Trial in Adult Soft Tissue Sarcomas

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Abstract—*Ifosfamide (IFOS)* 5 g/m^2 *and its parent analog Cyclophosphamide (CYCLO)* 1.5 g/m^2 *were studied in a randomized phase* II *study, accruing* 171 *patients with advanced soft tissue sarcoma. Both drugs were administered as* 24 hr *infusions, every* 3 weeks, *with comcomitant Mesna* 400 mg/m^2 *i.v. bolus* 4 *hourly* × 9 *doses. Twenty-four patients were ineligible and* 12 *were not evaluable. The groups were well matched for age, previous chemotherapy* (42% *of the total) or radiotherapy, the presence of distant metastases and performance status, but there were more females* (59% *vs.* 45%) *in the IFOS arm.*

Among the 68 *evaluable patients receiving IFOS, there were* 2 *CR,* 10 *PR (overall response* 18%), 27 *SD and* 29 *PD. For CYCLO, the corresponding results in* 67 *patients were* 1 *CR,* 4 *PR (overall response* 8%), 23 *SD and* 39 *PD. Using the chi-square test the* P *values for response rate and linear trend were* 0.13 *and* 0.04 *respectively. Response rates were higher for females* (20% *vs.* 5%, P = 0.01) *and patients who had not received previous chemotherapy* (19% *vs.* 4%, P = 0.01). *Fourteen of the* 17 *responses came from a group of* 43 *females, who had not received previous chemotherapy, for whom the overall response rate was* 37.5%. *Remissions were noted in only* 4 *histological subtypes (centrally reviewed material), i.e.,* 5 *of* 17 *synovial sarcomas,* 7 *of* 13 *mixed mesodermal sarcomas and* 2 *of* 7 *fibrosarcomas. One of the* 31 *leiomyosarcomas responded to Cyclophosphamide. Durations of response did not differ significantly between the* 2 *arms—median* 26, *range* 10–81+ *weeks.*

Leucopenia was significantly more severe on CYCLO, particularly in patients who had received previous chemotherapy (P = 0.007). *Serious infections occurred in approx.* 7% *of patients with no difference between the two drugs, although there was one toxic death on CYCLO. Nausea and vomiting were significantly worse on IFOS and alopecia, related in extent to dose, was seen in both arms. Other side-effects, such as hematuria or rises in serum creatinine and encephalopathy, were infrequent and mild.*

A higher response rate with less myelosuppression suggests that IFOS may have advantages over CYCLO in combination therapy.

INTRODUCTION

FOR EXTREMITY soft tissue sarcomas, a multidisciplinary approach to management has resulted in impressive rates of local control of the order of 80–90% [1–3]. However more than 50% of soft tissue sarcomas occur at non-extremity sites, and inoperable disease or local recurrence remains a significant problem. In addition metastasis, which seems to correlate with a higher histological grade, occurs in 30–50% of individuals [4–6].

Drugs, such as Actinomycin-D, Cyclophosphamide and Vincristine, found to be active in pediatric rhabdomyosarcomas, have been less useful for adult sarcomas. The introduction of

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Adriamycin in the early 1970s generated considerable interest and early trials reported reponse rates ranging from 9 to 70% [7, 8]. More recent studies in large series of patients not previously exposed to chemotherapy have established the response rate for high intermittent doses of Adriamycin (> 70 mg/m^2 every 3 weeks) to be between 25 and 30% (9–14%). In sequential studies, the South West Oncology Group built up the combination of Cyclophosphamide, Vincristine, Adriamycin and DTIC (CYVADIC), initially reporting an overall remission rate of 59% [15]. Other groups re-evaluating this regime, have generally reported poorer results [16–18]. In the succeeding 10 years, the larger published series of Adriamycin combinations have not identified a more active regime and combinations lacking Adriamycin have rarely been effective.

Complete remission rates in all studies have been below 20% and durable remissions (in excess of 2 years) have been infrequent. Despite extensive testing of more than 30 agents (9–14%) Adriamycin has been the only drug with established single agent activity in excess of 20%.

Cyclophosphamide (CYCLO) has frequently been incorporated into combination chemotherapy for advanced adult sarcomas [19]. The rationale for its inclusion in these regimes is a reported activity in excess of 50% in childhood embryonal rhabdomyosarcomas, but data on the single agent activity of Cyclophosphamide in adult sarcomas are scarce [8].

Ifosfamide (IFOS) is an analog of Cyclophosphamide, which was first synthesized in 1965 by Asta Research Laboratories in West Germany [20]. IFOS differs chemically from CYCLO by the transfer of one 2-chloroethyl group from the nitrogen mustard moiety of the molecule to the cyclic phosphamide nitrogen atom of the oxazaphosphorine ring. In experimental animal tumors, IFOS has a similar spectrum of activity to CYCLO, and acute and chronic toxicities are qualitatively similar. In the Yoshida ascitic sarcoma of the rat, the curative action of IFOS was more cumulative than that of CYCLO whereas the opposite was true for toxicity, suggesting possible advantages for repeated administration of IFOS over several consecutive days, or for prolonged i.v. infusions [21, 22].

IFOS entered clinical trial in Europe in 1967 and demonstrated activity in a wide range of tumors [23]. Unfortunately dose limiting hemorrhagic cystitis and occasional renal failure prevented more widespread use of the drug. The recent (1980) development of Mesna (sodium 2 mercapto-ethane-sulphonate), a thiol compound which detoxifies the urotoxic oxazaphosphorine metabolite Acrolein, has permitted the use of higher doses of IFOS, with myelosuppression being the dose limiting toxicity [24, 25].

In the German literature, Ifosfamide has been reported to have considerable activity in soft tissue sarcomas. Using a schedule of 60 mg/kg/day × 5 i.v., Hoefer-Janker *et al.* [26] reported 1 CR and 11 PR (67% overall response) in 18 soft tissue sarcomas. Most patients had received prior radiotherapy or chemotherapy. Klein *et al.* [27] and Czownicki *et al.* [28] also reported significant activity. The first study in soft tissue sarcomas, using IFOS with comcomitant Mesna, was reported by Stuart-Harris *et al.* from the Royal Marsden Hospital [29]. Forty-two patients received IFOS 5–8 g/m^2 as a 24 hr infusion every 3 weeks with comcomitant Mesna 400–600 mg/m^2 4 hourly × 9 i.v. and a forced diuresis. Of 40 patients evaluable for response, 6 (15%) achieved a complete remission (CR) and 9 (23%) a partial remission (PR) for an overall response rate of 38%. The median duration of response was 11 months. Equally favorable results, 3 CR and 5 PR in 16 patients (9 had received previously chemotherapy), were reported from Manchester [30].

Reviewing these results, the Soft Tissue and Bone Sarcoma Group of the EORTC decided that a randomized phase II trial studying CYCLO and IFOS would have the advantages of:

(1) Generating single agent data for Cyclophosphamide at maximally tolerated intermittent i.v. doses.
(2) Confirming the efficacy of IFOS, and suggesting whether this might be sufficiently superior to CYCLO to justify the inclusion of IFOS in combination chemotherapy for soft tissue sarcomas instead of CYCLO.

The dose and schedule of IFOS was based on that used in the Royal Marsden study [22] and a dose of CYCLO, that was likely to produce a comparable degree of myelosuppression, was selected and given in an identical manner (i.e., as a 24 hr infusion with comcomitant Mesna).

MATERIALS AND METHODS

Criteria for eligibility

Patients, age 15–70 years, with histologically proven advanced and/or metastatic soft tissue sarcoma were eligible for this study. Entry criteria included measurable progressive disease and a WHO performance status of 0, 1 or 2. Recurrent tumor in irradiated areas was not permitted as the sole evaluable lesion, and pleural effusions or bony metastases were not considered to be measurable. Other criteria for exclusion were prior treatment with classical alkylating agents (excluding DTIC), a previous or concomitant different malignant tumor, any serious concurrent disease, and central

nervous system metastases. Prior to entry patients were required to have adequate renal (serum creatinine < 150 μmol/l) and hepatic excretory function (serum bilirubin < 20 μmol/l) and bone marrow reserve (leucocytes > 3.5×10^9/l and platelets > 100×10^9/l). Informed consent was obtained from all patients.

Trial design

After stratification by institution and exposure (or not) to previous chemotherapy, patients were centrally randomized to receive Cyclophosphamide or Ifosfamide (NSC-109724). At the investigator's discretion, there was provision for patients showing disease progression, after 2 or more courses, to cross to the other drug. For patients showing response or disease stabilization, a minimum of 6 courses was recommended, further therapy then being at the discretion of the investigator. Patients showing progression on both drugs were taken off study.

Therapeutic regimes

Both drugs were administered as 24-hr intravenous infusions, the respective doses being Cyclophosphamide 1.5 g/m^2 and Ifosfamide 5 g/m^2, repeated every 3 weeks.

A diuresis was established with 1 l. of 5% Dextrose/0.9% sodium chloride (dextrose saline) given over 2 hr prior to treatment and 200 ml of 20% Mannitol infused over 30 min, using a Y connection, starting 1 hr prior to chemotherapy. The total dose of each drug was diluted in 3 l. of dextrose saline and infused over 24 hr. This was followed by 2 l. of dextrose saline over 12 hr.

Mesna was administered as an i.v. bolus 400 mg/m^2 every 4 hr for 9 doses, commencing at the start of the oxazophosphorine infusion.

Dose modifications during treatment

Reduction. The initial dose was reduced by 25% for WBC nadir < 1.5×10^9/l or platelet nadir < 50×10^9/l during the previous cycle. Treatment was delayed by 1 week if the WBC was < 3×10^9/l and/or platelets < 100×10^9/l at the time scheduled for the next cycle. If treatment was delayed 3 weeks without hematological recovery, the patients went off study. Subsequent doses were reduced by 25% if treatment was delayed for 2 consecutive courses. Chemotherapy was not given if the serum creatinine was above 150 μmol/l at the time of retreatment.

Escalation. If the WBC nadir > 2.0×10^9/l, platelet nadir > 100×10^9/l, serum creatinine < 120 μmol/l, there was no microscopic or macroscopic hematuria and no cerebral symptoms, there was provision for dose escalation of Cyclophosphamide to 2.5 g/m^2, and Ifosfamide to 8 g/m^2 (maximum 12 g) in subsequent courses together with concomitant increases in Mesna to 600 mg/m^2/dose.

Pretreatment and follow-up investigations. Baseline studies included history and physical examination, WHO performance status, tumor measurements, complete blood count including differential white count, biochemical profile (urea and electrolytes, creatinine, calcium, bilirubin, alkaline phosphatase, alanine, aminotransferase, aspartate aminotransferase), chest radiograph and electrocardiogram. Other investigations (e.g., isotope scan, computer assisted tomography, etc.) to monitor disease status were performed as indicated. Weekly blood counts were required after treatment for at least the first 2 cycles, and all baseline investigations were repeated after 2 courses of chemotherapy and at the time of discontinuation or cross-over to alternative therapy.

Definitions of response

Patients were considered evaluable for response if they had received a minimum of 2 courses of chemotherapy and tumor measurements had been repeated at 6 weeks. Response criteria were those defined by WHO [31]. If there was evidence of rapid progression (> 50% increase in tumor area and/or the appearance of new lesions) after the first course, this was classified as treatment failure and therapy was discontinued. Any demise during the first 3 weeks, due to tumor progression without severe toxicity, was classified as early death.

Toxicity

All toxicities were graded according to WHO criteria [31].

Central pathology review

A central pathology review was carried out by two panels consisting of six members each, one for the Northern European Institutes, chaired by Professor J. Van Unnik, Utrecht, The Netherlands, and one for the Southern European Institutes, chaired by Dr. G. Contesso, Villejuif, Paris, France. If two members of the panel independently made the same diagnosis as the referring pathologist this diagnosis was accepted. If there was disagreement, other members of the panel examined the histological sections and a consensus diagnosis was reached.

Statistical design

An initial patient entry of 29 evaluable patients in each arm was required, with termination of the study if 3 or fewer responses were reported in

Table 1. Reasons for exclusion

Total number of patients entered	171		
Evaluable patients	135		
Ineligible	24	*Non-evaluable*	12
Pathology	9	*Early death	8
Prior alkylating agent	4	Refusal	2
Not measurable	5	Wrong treatment	2
No data	4		
Raised creatinine	2		

*3 CYCLO
5 IFOS

Table 2. Characteristics evaluable patients

	CYCLO	IFOS
Age median	47 yrs	49 yrs
Sex—female	45%	59%
Previous radiotherapy	31%	31%
Previous chemotherapy	43%	41%
Metastases	91%	91%
Performance status 0–1	76%	79%
Total patients	68	67

either arm. The study would have likewise been terminated if no responses had been obtained in the first 19 patients treated on either arm. This plan ensured that if either oxazophosphorine analog had a true response rate of at least 25%, the probability of rejecting it from further study was approx. 0.05. Since responses were seen in both arms, study accrual was extended to screen the drugs both in patients with and without previous chemotherapy and to attempt an actual comparison of the therapeutic effectiveness of the drugs.

The response rates were compared using the classical chi-square test for the comparison of proportions and the chi-square test for linear trend (or average response). Survival and time to progression curves were calculated using the Kaplan–Meier technique, and compared using the log-rank test [32].

RESULTS

Over a 20-month period from October 1982, 171 patients from 18 European centers entered this randomized study. Twenty-four patients were considered to be ineligible and 12 others were not evaluable, for reasons shown in Table 1. Thus, 135 patients could be evaluated for response, 67 on CYCLO and 68 on IFOS, and their characteristics are shown in Table 2. Apart from the fact that more females were randomized to the IFOS arm, the groups were well balanced.

Table 3. Cell type on histological review

	Number of cases CYCLO	IFOS
Leiomyosarcoma	15	16
Synovial sarcoma	8	9
Fibrosarcoma	3	4
Malignant fibrous histiocytoma	3	4
Undifferentiated	5	2
Neurofibrosarcoma	3	2
Liposarcoma	2	2
Angiosarcoma	1	2
Rhabdomyosarcoma	0	2
Unclassified	7	2
Mixed mesodermal sarcoma	5	8
Endometrial stromal sarcoma	3	2
Miscellaneous	4*	1†
Total	59	56

*Epithelioid, cytosarcoma phyllodes, malignant mesenchymoma, mixed leiomyosarcoma and adenocarcinoma.
†Ewing's soft tissue.

Table 4. Chemotherapy dose/schedules

	CYCLO	IFOS
Total patients	67	68
Total courses	238	279
Doses (g/m^2)		
mean	1.6	5.1
range	1.3–2.3	4.0–7.2
Number of courses		
median	2.5	3.0
range	1–13	1–15
Courses modified (toxicity)	49 (21%)	28 (10%)

Fifty-seven (42%) patients had received previous chemotherapy, of whom 68% had received only one drug (usually an anthracycline analog) and only 12.5% had received 3 or more drugs. Three of 25 on CYCLO and 5 of 25 on IFOS had responded to previous chemotherapy, while 7 had received adjuvant treatment. Histological material has been reviewed for 114 (84%) of the 135 evaluable cases, and the cell types are shown in Table 3. Table 4 gives information on drug doses and the number of courses administered in each arm, as well as treatment modifications according to toxicity. Nine patients on CYCLO and 6 on IFOS only received one course of chemotherapy because of rapid disease progression. Dose escalations by at least 20% of the starting dose were performed in 16 patients on CYCLO and 11 patients on IFOS. However, in only 6 patients on CYCLO and 3 patients on IFOS did this reach the recommended levels of 2.5 and 8 g/m^2 respectively.

Table 5. Overall response

Type response	CYCLO	IFOS
	No.(%)	No.(%)
CR	1 (1.4)	2 (2.9)
PR	4 (6.0)	10 (14.7)
NC	23 (34.3)	27 (39.7)
PD	39 (58.2)	29 (42.6)
Total	67 (100)	68 (100)
Overall response	5 (7.5)	12 (17.6)
Chi-square test		*P Value*
response rate		0.13*
linear trend		0.04

*0.15 if adjustments are made for the prognostic factors, sex and previous chemotherapy.

Considering all evaluable patients, IFOS was marginally more active than CYCLO, overall response rates being 18 vs. 8%, $P = 0.04$, for linear trend (Table 5). Three of the 12 responses on IFOS were at the escalated dose level (8 g/m^2) and 1 of the 5 responses on CYCLO was at 2.5 g/m^2. Response rates were higher in patients who had not received prior chemotherapy (Table 6), 25% for IFOS and 13% for CYCLO. Considering only patients who had received previous chemotherapy, there were no responses to CYCLO, whereas 2 (7%) patients responded to IFOS. Neither of these had responded to the previous anthracycline containing chemotherapy regime. Fifty-one patients received the other analogue after failure of initial chemotherapy. There were 3 PR in 33 patients crossing from CYCLO to IFOS, and no responses in 18 patients receiving CYCLO after IFOS. Remissions were more frequent in female patients (20% vs. 5%, Table 6). Performance status did not influence response rates. Fourteen of the 17 responses came from a group of 43 female patients who had not received previous chemotherapy. The overall response rate for this group was 33%, with 37.5% responding to IFOS and 26.3% to CYCLO, $P = 0.65$ (Table 6). In contrast there were only 3 responders in the group comprising all the males, and females who had received previous chemotherapy. Comparison of the overall response rates adjusted for sex and previous chemotherapy further reduces the significance of the response rate comparison between the two analogs to 0.15 (Table 5). It is interesting to note that responses were mainly observed in three cell types (reviewed material)—in 5 of 17 synovial sarcomas, 7 of 13 mixed mesodermal sarcomas (one being a mixed leiomyosarcoma and adenocarcinoma of the uterus) and 2 of 7 fibrosarcomas. One of the 31 leiomyosarcomas responded to Cyclophosphamide. Analyzing this further, 4 of 8 mixed mesodermal sarcomas responded to IFOS, and one of the 3 responses on cross-over from CYCLO to IFOS was of this cell type. Five of nine synovial sarcomas responded to IFOS and a further response was noted on cross-over. Of the remaining 3 responses on IFOS, 1 was a fibrosarcoma and the other 2 could not be reviewed. The third response after cross-over was in a low grade endometrial stromal sarcoma. For CYCLO, 2 of 5 mixed mesordermal sarcomas responded, as did the mixed leiomyosarcoma/adenocarcinoma referred to above. The remaining 2 responses occurred in a fibrosarcoma and a leiomyosarcoma.

Responses were seen most frequently at the primary site (5 of 38 cases) or in lung (14 of 88 cases). There were no responses in lymph nodes, liver or bone (19, 14 and 10 cases respectively). Durations of response in the 17 responders did not differ significantly between the 2 arms (median 26 weeks), ranging from 13 to 64+ weeks on CYCLO

Table 6. Response by treatment related to previous chemotherapy and sex

Group	Total patients C/I†	Response No. C/I	CR+PR (%) (C/I)	Significance *P Response rate	Linear trend
Previous chemotherapy	29/28	0/2	(0/7)	0.01	0.27
No previous chemotherapy	38/40	5/10	(13/25)		
Male	37/38	0/3	(0/11)	0.01	0.02
Female	30/40	5/9	(17/23)		
Previous chemotherapy or male	48/44	0/3	(0/7)	<0.001	0.001
No previous chemotherapy and female	19/24	5/9	(26/38)		

*Chi-square test.
†C/I = Cyclophosphamide/Ifosfamide.

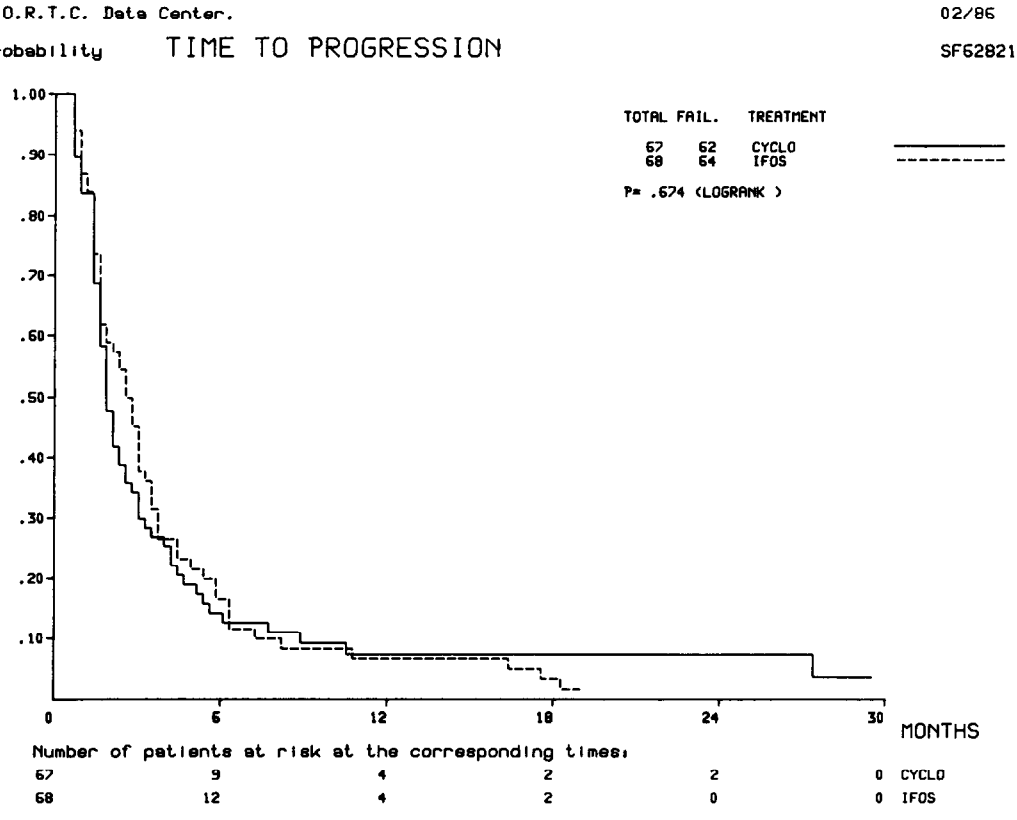

Fig. 1. Time to progression by treatment groups (all evaluable patients).

and 10–81+ weeks on IFOS ($P = 0.29$). There were no differences between the two arms in time to progression or survival both for responders and all evaluable patients (Figs. 1 and 2). Female patients had a longer time to progression ($P = 0.012$) but survival was less influenced by sex ($P = 0.11$). Perhaps not surprisingly, time to progression ($P = 0.026$) and survival ($P = 0.001$) were better for patients with higher performance statuses. There was one toxic death on CYCLO due to infection associated with myelosuppression. Two patients in each arm died at home in between treatments, but there was insufficient information to determine the exact cause of death.

Leucopenia was significantly greater on 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 approx. 7% of patients with no difference between the two drugs. Although IFOS appeared to have a cumulative effect on the white cell count, this was not apparent for CYCLO, probably because leucopenia in early courses led to dose reductions. Thrombocytopenia was rare.

Nausea and vomiting were significantly worse on IFOS (Table 7).

Renal toxicity was rare. IFOS treatment was discontinued in one patient because of a rise in creatinine associated with glycosuria and proteinuria, after course 7. Four patients receiving IFOS and 2 receiving CYCO developed hematuria (macroscopic 5, microscopic 1) in 1 or more courses. In at least 2 cases this was related to a missed injection of Mesna. CYCLO was discontinued because of repeated episodes of dysuria/hematuria in 1 patient who had received previous bladder irradiation. Chemotherapy with CYCLO was discontinued in one other patient because of repeated episodes of neutropenic fever. Significant alopecia, related in extent to the number of courses, was seen in both arms. Three episodes of mild to moderate drowsiness on IFOS were reported, but no severe encephalopathy.

DISCUSSION

Although the response rate to IFOS was superior to that on CYCLO, the difference was not significant particularly when adjustments were made for prognostic factors such as sex and previous chemotherapy. Both drugs were active in previously untreated females, but virtually inactive in males or those who had received previous chemotherapy. This was a phase II study screening for activity of these 2 analogs, and although numbers were expanded when activity was identified, the eventual accrual was insufficient to constitute a formal phase III comparison.

The response rate for IFOS was disappointing by comparison with other studies. Using an ident-

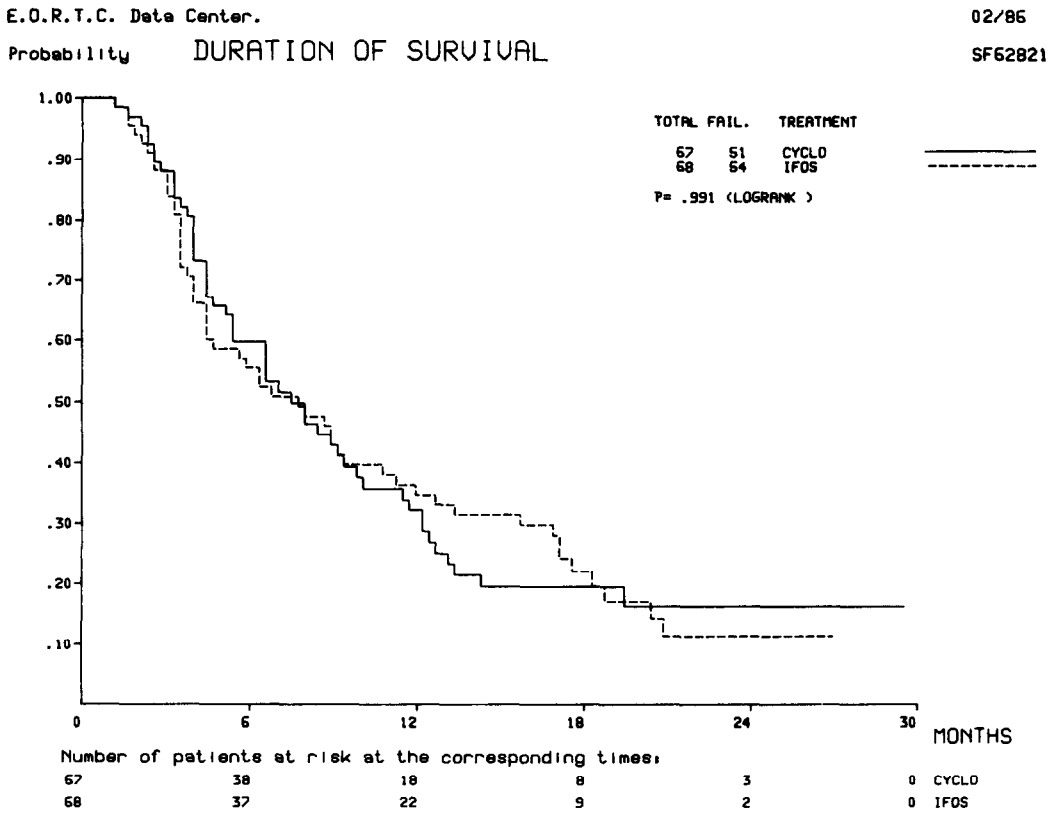

Fig. 2. Duration of survival by treatment groups (all evaluable patients).

Table 7. Toxicity

	WHO grade toxicity						
	1&2		3		4		Total patients
Type toxicity	No.*	C/I(%)	No.	C/I (%)	No.	C/I (%)	evaluable
Nausea/vomiting	52/51	(75/73)	10/17	(14/24)		0/1	69/70
Diarrhea	5/7	(7/10)	1/0			0/0	70/70
Renal/bladder	2/6	(3/9)	0/0			0/0	70/70
Infections	7/8	(10/11)	1/1			0/0	70/70
Hemorrhage	3/2	(4/3)	0/1			0/0	70/70
Cerebral	3/2	(4/3)	0/0			0/0	70/70
Leucopenia							
no previous chemo†	11/13	(37/19)	10/9	(33/31)	7/2	(23/7)	30/29
previous chemo‡	7/16	(30/70)	13/4	(56/17)	3/1	(13/4)	23/23

*C/I = Cyclophosphamide/Ifosfamide
P for trend †0.03
‡0.007

ical dose schedule, Stuart-Harris *et al.* [29] reported a remission rate of 38% in 42 evaluable patients and Bramwell *et al.* [30] described a 50% response rate in 16 patients. A different schedule was employed in the study of Antman *et al.* [33] 2–2.5 g/m^2/d × 4, and achieved 10 PR in 28 patients (36%). In addition to variations in patient population which make all comparisons between small studies difficult, the discrepancy in results may be partly attributable to differences in dosage. In the Marsden study [29], 29% of patients started at, and 48% had their dose escalated to, 8 g/m^2 whereas in the current study only 4% of patients had the same dose escalation. However Stuart-Harris *et al.* [29] commented that the majority of responses in their study (11/15) were seen at 5 g/m^2 and further responses were not seen after dose escalation. In contrast, all patients in the Boston study [33] received 8–10 g/m^2/course, considerably more drug than in the present study. It is also possible that a different spread of histological subtypes, with the inclusion in other studies of a greater proportion of sarcomas that are generally sensitive to alkylating agents (e.g., rhab-

domyosarcomas, Ewing's and undifferentiated sarcomas) accounts for these differences.

The response rate for IFOS in previously untreated patients was 25%, and all previously published studies have reported response rates in excess of 20% [26–30, 33, 34]. This establishes IFOS as one of the two agents demonstrating significant activity in adult soft tissue sarcomas, the other being Adriamycin. In view of the limited data available on IFOS, it is not possible to rank the efficacy of these two drugs, nor is this of major importance compared with exploration of their potential in combination.

The low response rate on IFOS in patients who had received prior chemotherapy also contrasts with the equivalent response rates in untreated and previously treated patients observed in other studies [29, 33]. The patients in the current study were not heavily pretreated (only 12.5% had received 3 or more drugs) and it is difficult to account for this difference. CYCLO was totally inactive in previously treated patients. In common with other studies [29, 33] we observed responses on IFOS in patients resistant to CYCLO. Although this suggests a lack of cross-resistance between the 2 analogs, a dose response effect (the IFOS dosage in the present study was 3.3 × that of CYCLO) cannot be excluded.

Responses were more frequent in females particularly in the CYCLO arm. This apparent superiority of response rate in females may be due to the fact that almost half of the responses occurred in mixed mesodermal sarcomas of the uterus, which would not occur in male patients. Wiltshaw *et al.* [35] found that 16 of 17 complete remitters, in sequential series of combination chemotherapy in their institution, were female and the majority had local disease in the pelvis. Nine of the 14 responding females in the current study had disease arising in pelvic organs, mainly uterus (as did 2 of the responders on cross-over) but only 4 had local recurrences, the remainder having metastases. A higher response rate in females has not been a feature of other EORTC studies and may well be a chance finding.

In this study the response rate for CYCLO in previously untreated patients was 13%. This suggests that it has activity in the same range as DTIC [36] although no randomized comparison has been performed. DTIC has shown activity in previously treated patients, which was not observed for CYCLO in this study. As CYCLO produces significant myelosuppression its limited activity probably does not justify its use in combination, where the dose of active myelosuppressive agents such as Adriamycin may have to be reduced.

In most chemotherapy trials, no significant differences in response according to histological subtype have emerged, because of the relatively low response rates and the small numbers in each group [18, 37, 38], and this caveat applies to the present study. Nevertheless, it is surprising that there was only 1 response among 31 leiomyosarcomas. This contrasts with data for combination chemotherapy [18, 30, 38]. Although it is possible that leiomyosarcomas are particularly resistant to alkylating agent therapy, it seems more likely that this finding is an artifact of small numbers. It is intriguing that 12 of the 14 responses in tumors of known histology occurred in synovial or mixed mesodermal sarcomas. In the study reported by Stuart-Harris *et al.* [29], the only synovial sarcoma included achieved a CR. One mixed mesodermal sarcoma did not respond. There appeared to be no synovial or mixed mesodermal sarcomas entered into the study reported by Antman *et al.* [33]. Other reported studies of IFOS do not give sufficient details of histological types included to allow further comment. Response rates for uterine mixed mesodermal sarcomas to Adriamycin containing regimes have generally been lower than those achieved for sarcomas of other histological types/site [39, 40]. In the study of Omura *et al.* [39] Adriamycin and DTIC seemed more effective than Adriamycin alone for mixed mesodermal sarcomas. *Cis*-platinum seemed to have some activity even in a heavily pretreated population of mixed mesodermal sarcomas [41] and Seltzer *et al.* reported 5 responses in 6 patients [42] given Adriamycin and *cis*-platinum. It is possible that mixed mesodermal sarcomas respond better to regimes that include an alkylating agent (or a drug with a similar mechanism of action). Although these findings on histological review may well have occurred by chance, as the numbers of each cell type are small and the response rates low, nevertheless they may well be worth pursuing in future studies.

Myelosuppression was dose-limiting for CYCLO in this study. White cell count nadirs below 2.0×10^9/l were observed in 62% of patients at some time during treatment, and although dose escalation was possible, this dose was rarely maintained in subsequent courses and dose reductions for myelosuppression were common. In contrast, leucopaenia was much less common on IFOS and dose escalations could have been performed more frequently. The reasons for failing to escalate IFOS doses, in the absence of toxicity, are not clear but may have related to the nephrotoxicity and encephalopathy reported in an earlier study [29]. Although nausea and vomiting were more severe than on CYCLO, this toxicity could not be termed dose limiting. This leaves considerable potential for the use of IFOS at full doses in combination

with myelosuppressive agents such as Adriamycin.

Although occurring more frequently on IFOS, hematuria and rises in serum creatinine were minor and temporary in this study. CYCLO had to be discontinued in 1 patient who had received previous bladder irradiation, and IFOS was discontinued after 7 courses in 1 patient who showed mild persisting renal impairment. In the Marsden study [29], 7 patients developed nephrotoxicity, 2 of whom died in renal failure. Nephrotoxicity was not reported in the Boston study [33]. Higher doses of Mesna by continuous infusion are being explored in current EORTC studies.

Encephalopathy, manifest as hallucinations, somnolence, confusion rarely progressing to coma and death, have been described in patients receiving IFOS [43] with an incidence ranging from 6 to 70%. In a review of 9 series involving 1046 patients the incidence was 12.6%. In the Boston study [33], 5 of the first 11 patients became somnolent or developed visual hallucinations. After a reduction in the use of i.v. antiemetics and major narcotics, single episodes of encepathalopathy were seen in 5 of 27 patients. One of 42 and 3 of 32 respectively developed encephalopathy in the studies conducted at the Marsden [29] and in Manchester (unpublished data). In the current study only 3 patients developed mild cerebral symptoms which rapidly resolved. Awareness of the problem with restriction of sedatives and the lower dose may be responsible for this low incidence.

In summary, our results support the conclusions of others that IFOS is an active drug in adult soft tissue sarcomas, which is only moderately myelosuppressive. Bladder and renal toxicity were found to be minimal with the use of Mesna and were not dose limiting. The optimum dose/schedule has not been established but it seems likely that the dose/schedule of IFOS employed in the current study could be used, in combination with myelosuppressive agents, without modification.

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