PERGAMON

European Journal of Cancer 38 (2002) 2397–2406

European Journal of Cancer

www.ejconline.com

Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients

A.T. van Oosterom[a,*], H.T. Mouridsen[b], O.S. Nielsen[c], P. Dombernowsky[d], K. Krzemieniecki[e], I. Judson[f], L. Svancarova[g], D. Spooner[h], C. Hermans[i], M. Van Glabbeke[i], J. Verweij[j], for the EORTC STBSG

[a]*Department of Oncology, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium*
[b]*Department of Oncology, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark*
[c]*Center for Bone- and Soft Tissue Sarcomas, Aarhus University Hospital, Noerrebrogade 44 DK-8000 Aarhus C, Denmark*
[d]*Department of Oncology, Herlev University Hospital, Herlev Ringvej, DK-2730 Herlev, Copenhagen, Denmark*
[e]*Maria Sklodowska-Curie Memorial Cancer Institute Krakow, Garncarska 11, PL-31 115 Krakow, Poland*
[f]*Sarcoma Unit, The Royal Marsden NHS Trust, Fulham Road 203, London SW3 6JJ, UK*
[g]*National Cancer Institute, Klenova 1, SK-833 10 Bratislava, Slovakia*
[h]*Queen Elisabeth Hospital, Edgbaston, Birmingham B15 2TH, UK*
[i]*EORTC Data Center, Avenue E. Mounier, 83/11, B-1200 Brussels, Belgium*
[j]*Rotterdam Cancer Institute (Daniel Den Hoed Kliniek and University Hospital Rotterdam), Groene Hilledijk 301, NL-3008 AE Rotterdam, The Netherlands*

Received 28 June 2002; received in revised form 15 July 2002; accepted 2 September 2002

Abstract

The aim of this phase II study was to evaluate the efficacy and toxicity of two regimens of ifosfamide in metastatic soft tissue sarcoma patients given as first- and second-line chemotherapy. Two different schedules of ifosfamide were investigated in a randomised manner: Ifosfamide was given either at a dose of 5 g/m^2 over 24 h (5 g/m^2/1 day), every 3 weeks or at a dose of 3 g/m^2 per day, administered over 4 h on three consecutive days (3 g/m^2/3 days), every 3 weeks. Both schedules were given as first-line or second-line chemotherapy. A total of 182 patients was entered, 103 in first- and 79 in second-line, of whom 8 patients were ineligible, 5 in the first- and 3 in the second-line study. Most patients had a leiomyosarcoma, 46 of the 98 in the first-line and 34 of the 76 in the second-line. The two study arms were well balanced in both the first- and second-lines with respect to sex, age and performance status. In first-line treatment, 5 g/m^2/1 day yielded five partial responses (PR) (Response Rate (RR) 10%), versus 12 PR (RR 25%) for the 3 g/m^2/3 days. As second-line treatment, the 24-h infusion yielded: one CR and one PR (RR 6%) and the 3-day schedule one CR and two PR (RR 8%). Survival did not differ between the two regimens. The major World Health Organization (WHO) grade 3 and 4 toxicities encountered were: leucopenia in 19% of all courses in the first-line and 32% in the second-line with the 5 g/m^2/1 day, while for the 3 g/m^2/3 days schedule the rates were 57 and 63% respectively. Grade 3 or 4 infections were seen in 4% of patients treated with 5 g/m^2/1 day first-line and 10% of patients given 3 g/m^2/3 days, both as first- and second-lines. No such infections were seen in patients receiving 5 g/m^2/1 day as second line treatment. In advanced soft-tissue sarcomas in the first-line, ifosfamide 3 g/m^2, given over 4 h on three consecutive days, is an active regimen with acceptable toxicity while the 5 g/m^2 over 24 hours schedule resulted in a disappointing response rate.

Keywords: Chemotherapy; Advanced soft tissue sarcoma; Ifosfamide

* Corresponding author. Tel.: +32-1634-6900; fax: +32-1634-6901.
E-mail address: allan.vanoosterom@uz.kuleuven.ac.be (A.T. van Oosterom).

0959-8049/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0959-8049(02)00491-4

1. Introduction

Soft-tissue sarcomas are rare tumours of mesenchymal origin [1]. They account for approximately 1% of all malignancies. There are multiple histological subtypes which are usually grouped for the purpose of treatment under the heading of soft-tissue sarcomas [2]. In the majority of study protocols, most soft-tissue sarcomas are considered as one group, despite their distinct differences in biological behaviour depending on their specific histological characteristics [3].

Local treatment strategies for patients with sarcomas of the soft tissues have evolved over the past decades into modern combined modality therapy resulting in improved local control and survival rates. Notwithstanding optimal surgery and adjuvant radiotherapy the combined local and distant failure rate at 5 years is 40% and 50% at 10 years [4].

Despite many small and some large studies, of which all patient data have been pooled in a recently published meta-analysis, adjuvant chemotherapy at best seems to have a minor impact on improved local control and a questionable effect on survival [5].

For metastatic disease over the last 25 years, approximately 100 small non-randomised and three large randomised studies [6–8] employing different combinations have been published. The American Intergroup randomised doxorubicin/DTIC versus MAID (mesna, doxorubicin, ifosfamide/DTIC) [7] while Eastern Cooperative Oncology Group (ECOG) randomised doxorubicin versus doxorubicin + ifosfamide versus doxorubicin + mitomycin C (MMC) + cisplatin (CDDP) [8]. Both studies resulted in higher response rates for the combinations, but median survival was equal in all study arms and always less than 12 months. The latter has also been found by the European Organization for Research and Treatment of Cancer (EORTC) in the largest study ever performed in soft tissue sarcomas which compared the Cyvadic regimen (cyclophosphamide, vincristine, doxorubicin, DTIC) versus doxorubicin + ifosfamide versus doxorubicin single agent [6].

Of all the drugs studied, basically only doxorubicin and ifosfamide resulted in response rates of around 25% if the drugs were given at full dosage [9]. Several studies with different anthracyclines have not proven their superiority in the response rate over doxorubicin 75 mg/m^2 given every 3 weeks, neither has any of the tested analogues shown superiority over doxorubicin in terms of therapeutic index [10,11].

Following the demonstration that mesna could control the urotoxicity of ifosfamide [12], several small-sized non-randomised studies have shown response rates up to 40% depending on the ifosfamide schedule [13]. The EORTC Soft Tissue and Bone Sarcoma Group (STSBG) decided in the early 1980s to perform a randomised study in non-pretreated patients comparing the parent compound cyclophosphamide, at a dose of 1500 mg/m^2, with ifosfamide, at a dose of 5 g/m^2 given over 24 h [14]. The latter schedule was selected because it was conveniently given over 24 h resulting in a short stay in hospital. Ifosfamide was more active than cyclophosphamide, with response rates of 25 and 10%, respectively, and showed less haematological toxicity. After treatment with cyclophosphamide, ifosfamide still resulted in a 15% response rate, while patients who failed ifosfamide did not show any response to subsequent cyclophosphamide. This led to the adoption by the EORTC STSBG of ifosfamide given at 5 g/m^2 as a continuous infusion over 24 h as their standard second-line treatment. In a subsequent phase II study by the group, the combination of doxorubicin 50 mg/m^2 with 5 g/m^2 ifosfamide yielded a response rate of 32% [15]. However, as discussed above, a randomised phase III study showed single agent doxorubicin, at a dose of 75 mg/m^2, to be equivalent to the combination of doxorubicin + ifosfamide or Cyvadic in terms of progression-free and overall survival while being less toxic [6]. More recently, phase II studies employing higher doses of ifosfamide ranging from 12 to 18 g/m^2, have reported substantially higher response rates, even in patients previously treated with ifosfamide [16–21]. In many of these studies, ifosfamide was given as a continuous infusion. Given this background, the EORTC STSBG decided to compare the standard regimen of ifosfamide 5 g/m^2 given over 24 h (5 g/m^2/1 day) with ifosfamide given at a dose of 3 g/m^2 over 4 h daily for three consecutive days (3 g/m^2/3 days). The present paper describes the results of this study.

2. Patients and methods

2.1. Eligibility criteria

All patients were required to have a histologically-confirmed diagnosis of soft-tissue sarcoma excluding Ewing's sarcoma, embryonal rhabdomyosarcoma, mesothelioma, paraganglioma, chondrosarcoma, neuroblastoma and osteosarcoma. Patients had either locally recurrent disease not amenable to potentially local therapy or metastatic disease without Central Nervous System (CNS) involvement, with measurable lesions showing evidence of progression within 6 weeks prior to treatment. Osseous lesions and pleural perfusions were not considered measurable. Minimal size of measurable lesions were: for lung metastases $\geqslant$2.0 cm on chest X-ray, superficial lymph nodes $\geqslant$2.5 cm, skin and or subcutaneous metastases $\geqslant$2.5 cm, lymph node metastases in the mediastinum and in the retroperitoneal region $\geqslant$2.5 cm as measured by Computed Tomography (CT) scan and liver metastases $\geqslant$2.5 cm as measured by CT scan.

Other inclusion criteria included: age 15–75 years, World Health Organization (WHO) performance status $\leqslant 2$ [25]. Patients in the first-line study should have had no prior chemotherapy. In the second-line study, patients had either doxorubicin 75 mg/m^2 or epirubicin 150 mg/m^2, which had to be discontinued for more than 3 weeks. Radiotherapy was accepted only if given to lesions other than the index lesions. Patients had to have adequate renal (serum creatinine level $\leqslant 150$ μmol/l), hepatic (bilirubin level $\leqslant 25$ μmol/l and albumin $\geqslant 25$ g/l) and bone marrow (leucocyte count $\geqslant 4.0\times10^9$/l and platelet count $\geqslant 100\times10^9$/l) function. No other severe medical illness should be present, including psychosis or cardiovascular disease. Patients should not have had other primary malignant tumours (except adequately treated *in situ* carcinoma of the cervix or basal cell carcinoma of the skin). Informed consent had to be obtained from all patients according to the local and national rules and the regulations of each participating institution.

2.2. Study plan and conduct

The study opened in February 1992 as a second-line study for patients failing in protocol # 62901 comparing doxorubicin 75 mg/m^2 given on day 1 with epirubicin 150 mg/m^2 given on 1 day or on three consecutive days at 50 mg/m^2/day [23]. The minimal response rate of interest was 20%. In addition, the duration of response and acute and chronic toxicities of the two therapeutic arms would be assessed according to optimal Bayes restricted sampling plan. A total of 44 patients had to be randomised in each arm of the 3-day or 24-h ifosfamide regimens and a regimen would be rejected from further analysis if less than six responses were observed [24]. If no responses were observed among the first 21 patients in either of the two treatment arms, the study would be closed. After the closure of the EORTC study # 62901, the study was extended to include patients treated with ifosfamide as first-line, using the same statistical considerations.

2.3. Treatment plan

Each patient was randomly assigned either to ifosfamide 5 g/m^2, given as a 24-h infusion (5 g/m^2/1 day) or to ifosfamide 3 g/m^2/day, given over 4 h on three consecutive days (3 g/m^2/3 days). All cycles were to be repeated every 3 weeks.

At least two cycles were given, except in cases of rapid disease progression. Cycles were restarted provided the leucocyte count was $>4.0\times10^9$/l, and platelet count $>100\times10^9$/l at the date planned for the next cycle. Patients with grade 1 myelosuppression at the time of retreatment, had a 10% dose reduction while in patients with grade $\geqslant 2$ toxicity treatment was delayed 1 week until recovery to grade 1 or better. If the start of a cycle had to be postponed for more than 3 weeks, the patient went off-study. A second dose modification was based on nadir values. Patients with white blood cell nadirs $<0.5\times10^9$/l or platelet nadirs $<50\times10^9$/l had a 20% dose reduction independent of the blood count on the day of retreatment.

2.4. Treatment duration

If a complete response was achieved treatment was to be continued for another two courses. If a partial response or no change was observed, treatment could be continued until disease progression or unacceptable toxicity or patient refusal.

2.5. Therapeutic regimens

In the 5 g/m^2/1 day schedule, patients were pre-treated with 1 l of dextrose/saline over 2 h with 200 ml of 20% mannitol infused over 30 min. Mesna (2-mercaptoethane sodium sulphonate) 600 mg/m^2 was administered as an intravenous (i.v.) bolus immediately preceding ifosfamide. Mesna was added at a dose of 2.5 g/m^2 to the ifosfamide/dextrose/saline solution, and at the end of the ifosfamide infusion, an additional 2 l of dextrose/saline containing 1.25 g/m^2 of mesna was given over 12 h.

In the 3-day schedule, the ifosfamide 3 g/m^2 was infused over 4 h on three consecutive days. The ifosfamide was dissolved in 125 ml sterile water per gram ifosfamide. The total dose was further diluted in 1 l of dextrose/saline. Mesna 600 mg/m^2 was given as an i.v. bolus directly before the mesna/ifosfamide infusion. Mesna was added at a dose of 1.5 g/m^2 to the ifosfamide/dextrose/saline solution. At 4 and 8 h after the end of the infusion, patients received mesna 500 mg/m^2 and 1 l of fluid orally. In this way, it was possible to give the treatment, if required, on an outpatient basis. Antiemetics were prescribed according to local conventions.

2.6. Follow-up evaluation during treatment

Blood counts and urine analysis were performed weekly. Responses were evaluated clinically at every cycle and radiologically every other cycle.

2.7. Definitions of response, survival, and toxicity

Patients were considered assessable for response if they had received at least two cycles of chemotherapy. Response criteria were those as defined by the WHO [25]. For all responding patients, the hospital records and available films were reviewed by two independent investigators as previously described by Van Glabbeke [26], and a response was accepted only if the two independent investigators reached a consensus. In cases of no consensus, the worse response category was assigned.

The time to progression was defined as the time from the date of randomisation to the date of first documented progression. Patients for whom the best overall response was 'progression' were considered as failures at the first disease evaluation. Response duration was the time from the date of randomisation to the first evidence of progression for all responsive patients. Progression-free survival was the time from the date of randomisation to the date of first progression for responding and stable-disease patients, while it was considered as zero for patients who progressed during the first two treatment cycles. Overall survival was the time from the date of randomisation to the date of death regardless of the cause of death. All toxicities were graded according to WHO criteria [25].

2.8. Statistical analysis

Patients were prospectively randomised by the EORTC Data Center in Brussels. In this phase II study, the only purpose of randomisation was to control for possible selection biases: the 5-g schedule was intended as an internal standard. It was not intended to formally compare the two regimes, neither to expand the study as a phase III trial. Randomisation was stratified by centre, and by treatment (first-line versus second-line). The statistical analysis was performed according to the 'intent-to-treat' principle. Response rates based on either all eligible patients or all evaluable patients were reported with their exact 95% confidence intervals (CIs). Response rates to the two therapeutic regimens were compared in both strata by the exact one-sided Fisher's test. Time to progression and overall survival were estimated in each stratum and in each therapeutic arm by the Kaplan–Meier method. No formal comparisons were performed, because the trial was designed as a phase II trial, with an insufficient power for such comparisons.

2.9. Quality control

Histopathological diagnoses were reviewed by an independent pathology panel in the majority of eligible patients as described earlier by the group [27]. Methods of quality control have been detailed elsewhere [28].

3. Results

3.1. Patient characteristics

From March 1992 to November 1994, 79 patients were entered in the second-line study by 18 institutions in nine countries. Three patients were not eligible for the following reasons: inadequate histopathology, no measurable target lesion and brain metastasis.

The first-line study started in March 1994 and closed June 1996. 103 patients were entered by 17 institutions in eight countries of whom 5 were ineligible due to inadequate histopathology (1), prior treatment not permitted by the protocol (1), no measurable target lesions (2) and previous other malignant disease (1) (Fig. 1).

Patient characteristics are listed in Table 1 for both second-line and first-line treatments. The characteristics were evenly distributed in the two treatment arms. In the second-line study, 18 patients had had adjuvant treatment. The majority (58) had been pretreated for advanced disease; some (19) also had adjuvant chemotherapy. Drugs used were either doxorubicin (37) or epirubicin (39). In the first-line study, no patients had had prior chemotherapy, but one had had an isolated limb perfusion with interferon and melphalan (thus excluding systemic exposure).

Most patients had leiomyosarcoma (80 of the 174 = 46%). For all major histological types, there was a good balance between the different regimens in both randomised studies.

The localisation of the different lesions was very well balanced over the regimens and studies (Table 2), i.e. recurrent primaries, lung and liver metastases.

3.2. Treatment compliance

In the second-line study, the patients in the 5 g/m^2/1 day regimen arm received a median of three cycles (range 1–16) and in the 3-day regimen, a median of four cycles (1–11). The relative median dose intensity achieved was 97% (83–111%) and 93% (61–107%), respectively. Non-pre-treated patients in the 5 g/m^2/1

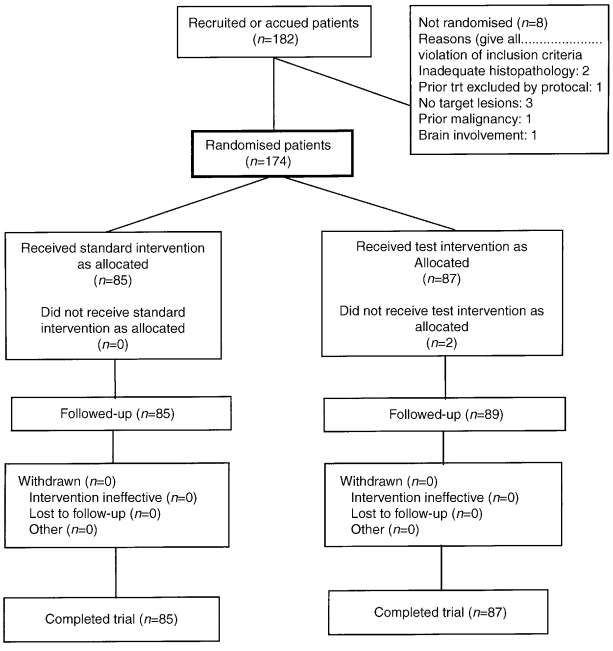

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [30]).

Table 1
Patients' characteristics at randomisation

	First-line study		Second-line study		
	5 g/m^2×1 day (N=49)	3 g/m^2×3 days (N=49)	5 g/m^2×1 day (N=36)	3 g/m^2×3 days (N=40)	Total (%)
Characteristics at entry					
Sex					
Male	24	22	16	20	
Female	25	27	20	20	
Age (years)					
Median (range)	52 (22–75)	55 (30–73)	51 (24–75)	50 (22–73)	
WHO performance status					
0	10	15	10	15	
1	39	34	26	25	
Histologic type					
Leiomyosarcoma	20	26	17	17	80 (46%)
Liposarcoma	6	5	5	5	21 (12%)
Synovial sarcoma	7	5	2	3	17 (10%)
Malignant fibrous histiocytoma	3	3	2	6	14 (8%)
Miscellaneous sarcomas	9	8	6	9	32 (18%)
Unclassified sarcoma	4	2	4	–	10 (6%)
Prior treatment					
Prior radiotherapy					
No	33	33	24	28	
Yes, excluding haematopoietic sites	13	10	11	10	
Yes, including haematopoietic sites	3	6	1	2	
Prior chemotherapy					
No	49	49	–	–	
Yes, adjuvant	–	–	9	9	
Yes, for advanced disease	–	–	26	31	
Yes, both	–	–	1	–	
Prior chemotherapy					
Doxorubicin (as single agent)	–	–	18	19	
Epirubicin (as single agent)	–	–	18	21	

Table 2
Localization of lesions

	First-line study		Second-line study	
	5 g/m^2/1 day (N=49)	3 g/m^2/3 days (N=49)	5 g/m^2/1 day (N=36)	3 g/m^2/3 days (N=40)
Primary tumour or recurrence	22 (45%)	24 (49%)	18 (50%)	18 (45%)
Lung metastases	29 (59%)	25 (51%)	19 (53%)	21 (53%)
Liver metastases	6 (12%)	6 (12%)	8 (22%)	8 (20%)
Other types of lesions	20 (41%)	18 (37%)	17 (47%)	17 (43%)

day schedule received a median of two cycles (1–14) with a median dose intensity of 99% (46–179). 2 patients randomised to this regimen received the 3-day regimen, which explains the 179% dose intensity. Patients treated with the 3 g/m^2/3 days regimen received a median of four cycles (1–17), with a median dose intensity of 94% (33–104). In conclusion, in both treatment arms in both studies the relative dose intensities are very near to 100% (Table 3).

3.3. Response rate

Overall response data are shown in Table 4. In the second-line study, the response rate in eligible patients was 6% (95% CI 1–19%) for the 5 g/m^2/1 day and 8% (95% CI 2–20%) for the 3 g/m^2/3 days regimen. The median time to progression (Fig. 2) was 6 weeks in the 5 g/m^2/1 days versus 14 weeks in the 3 g/m^2/3 days schedule.

Table 3
Dose intensity of the second-line and first-line studies

Ifosfamide	Patients	Cycles	Total dose (g/m^2)	Duration (days)	Relative dose intensity (%)
Second-line					
5 g/m^2/1 day	36	3 (1–16)[a]	12.6 (4.9–78.9)	58 (21–357)	97 (83–111)
3 g/m^2/3 days	40	4 (1–11)	29.8 (5.9–89.1)	84 (21–245)	93 (61–107)
First line					
5 g/m^2/1 day	49	2 (1–14)	10 (4.8–94.4)	43 (21–317)	99 (49–179)
3 g/m^2/3 days	47	4 (1–17)	35.3 (3.0–147.7)	91 (21–548)	94 (33–104)

[a] Median, range.

Table 4
Overall response rate

Response rate	First-line study		Second-line study	
N (%)	5 g/m^2/1 day (*N* = 49)	3 g/m^2/3 days (*N* = 49)	5 g/m^2/1 day (*N* = 36)	3 g/m^2/3 days (*N* = 40)
Complete response	–	–	1 (3)	1 (3)
Partial response	5 (10)	12 (24)	1 (3)	2 (5)
No change (⩾6 weeks)	17 (35)	14 (29)	10 (28)	20 (50)
Progression	22 (45)	15 (31)	23 (64)	14 (35)
Early death due to progressive disease	–	2 (4)	1 (3)	1 (3)
Early death due to toxicity/failure	2 (4)	1 (2)	–	–
Other failures	3 (6)	5 (10)	–	2 (5)
			–	–
Response rate (eligible-WHO)	5 (10%)	12 (25%)	2 (6%)	3 (8%)
Confidence interval (95%)	3–22%	13–39%	1–19%	2–20%
Response rate (evaluable)	5 (11%)	12 (28%)	2 (6%)	3 (8%)
Confidence interval (95%)	4–25%	15–44%	1–19%	2–21%

WHO, World Health Organization.

In the first-line study, response rates in the 5 g/m^2/1 day and 3 g/m^2/3 days groups were 10% (3–22) and 25% (13–39) respectively. Similarly the median time to progression was 11 and 14 weeks, respectively (Fig. 3).

3.4. Survival

In the pretreated patients, the estimated median survival was 45 weeks in the 5 g/m^2/1 day group and 36 weeks in the 3 g/m^2/3 days group (Fig. 4). In the first-line study, the estimated median survival was 52 weeks in the 5 g/m^2/1 day group and 44 weeks in the 3 g/m^2/3 days group (Fig. 5). At 2 years, the median survival was 25% in both arms. None of the survival parameters differed between the two treatment schedules.

3.5. Toxicity

The haematological toxicities are presented in Table 5. There was a difference in the white blood cell and neutrophil counts between the two treatment arms, 5 g/m^2/1 day versus 3 g/m^2/3 days, both in the second- and the first-line studies. The 3 g/m^3/3 days regimen resulted in substantially more patients experiencing low white blood cell and neutrophil counts.

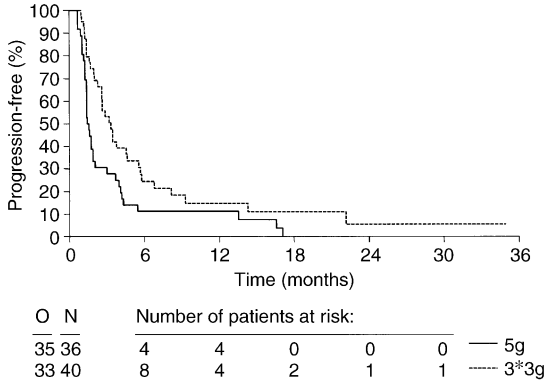

Fig. 2. Time to progression (second-line study). O, observed; N, number.

In the second-line study, more patients had grade 3 and 4 thrombocytopenia in the 3 g/m^2/3 days group, whereas in the first-line study the platelet nadirs did not differ. Anaemia was also more frequent with the 3 g/m^2/3 days regimen, both in first- and second-line treatments.

The distribution of the nadirs is given in Table 6. Platelet and haemoglobin nadirs were similar in the two groups whereas nadirs for leucocytes and neutrophils were lower for the 3 g/m^2/3 days regimen compared with the 5 g/m^2/1 day regimen.

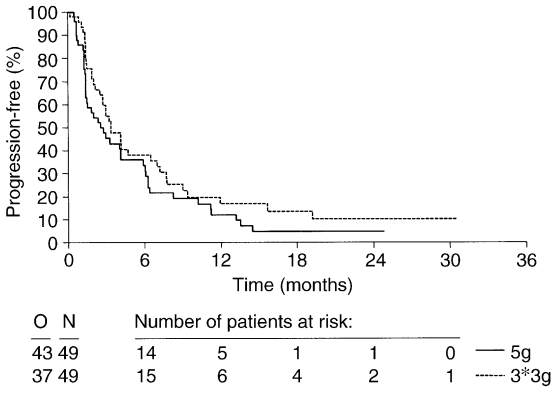

Fig. 3. Time to progression (first-line study).

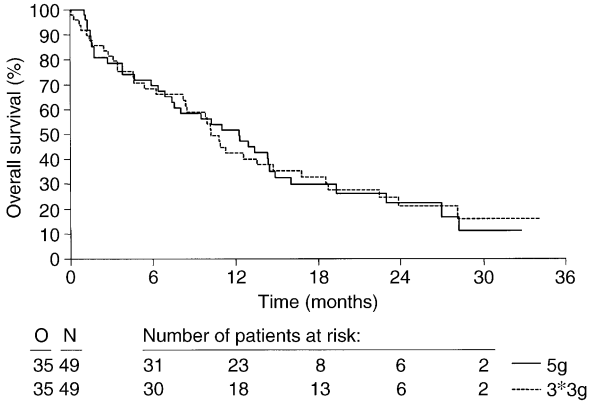

Fig. 5. Overall survival (first-line study).

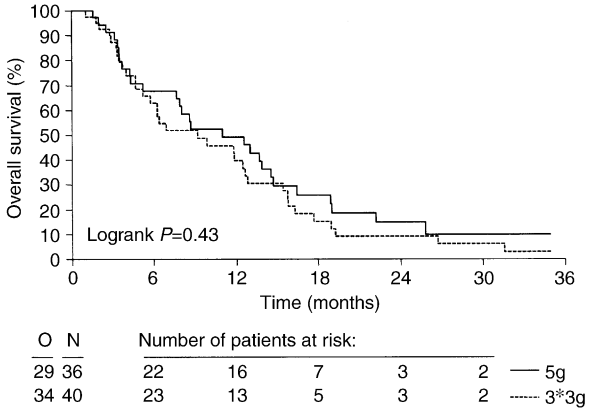

Fig. 4. Overall survival (second-line study).

The non-haematological toxicities are presented in Table 7. The majority of patients in the second-line study entered with alopecia caused by the prior treatment. There was a trend for all toxicities to be more frequent in the 3 g/m^2/3 days group than in the 5 g/m^2/1 day group. The rate of severe infections was relatively low considering the high rate of severe neutropenia. All other types of organ toxicities were very rare.

The reasons for treatment discontinuation are given in Table 8. Most patients went off study because of progression or relapse. The number of patients that went off study, because of toxicity or patients' refusal, was substantially higher for the 3 g/m^2/3 days regimen (25%) than the 5 g/m^2/1 day regimen (11%) in the second-line study, whereas the difference was less remarkable in the first-line study.

Table 5
Haematological toxicities (worst WHO grade per patient)

	First-line study				Second-line study			
	5 g/m^2/1 day ($N \leqslant 48$)		3 g/m^2/3 days ($N \leqslant 47$)		5 g/m^2/1 day ($N \leqslant 37$)		3 g/m^2/3 days ($N \leqslant 41$)	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
WBC								
3	2	(4)	11	(23)	10	(27)	10	(24)
4	7	(15)	16	(34)	2	(5)	16	(39)
Neutrophils								
3	3	(7)	5	(12)	5	(19)	8	(31)
4	6	(13)	19	(44)	3	(12)	12	(46)
Platelets								
3	1	(2)	1	(2)	1	(3)	3	(7)
4	1	(2)	1	(2)	–	(0)	3	(7)
Haemoglobin								
3	3	(6)	6	(13)	1	(3)	6	(15)
4	–	(0)	1	(2)	1	(3)	2	(5)

WHO, World Health Organization; WBC, white blood cells.

Table 6
Distribution of nadir values

	First-line study		Second-line study	
	5 g/m^2/1 day $N \leqslant 48$	3 g/m^2/3 days $N \leqslant 47$	5 g/m^2/1 day $N \leqslant 37$	3 g/m^2/3 days $N \leqslant 41$
WBC (10^9/l)				
Median (range)	3.05 (0.10–10.60)	1.50 (0.20–8.90)	3.20 (0.20–7.70)	1.50 (0.00–10.00)
Neutrophils (10^9/l)				
Median (range)	1.99 (0.01–14.62)	0.60 (0.00–6.52)	1.78 (0.05–7.81)	0.52 (0.00–5.25)
Platelets (10^9/l)				
Median (range)	218(12–571)	203 (16–415)	212 (38–439)	175 (14–482)
Haemoglobin (mmol/l)				
Median (range)	6.80 (4.30–12.20)	6.50 (0.70–8.30)	6.50 (2.80–9.20)	6.00 (2.80–8.20)

Table 7
Non-haematological toxicities grade 3/4 observed ($N = 177$ treated patients with toxicity)

	First-line study				Second-line study			
	5 g/m^2/1 day ($N \leqslant 50$)		3 g/m^2/3 days ($N \leqslant 49$)		5 g/m^2/1 day ($N \leqslant 37$)		3 g/m^2/3 days ($N \leqslant 41$)	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Alopecia								
3	6	(13)	14	(30)	14	(44)	26	(65)
4	–	(0)	–	(0)	2	(6)	–	(0)
Nausea/vomiting								
3	5	(10)	5	(10)	3	(9)	6	(15)
4	–	(0)	–	(0)	–	(0)	1	(2)
Neurotoxicity								
3	3	(6)	5	(11)	1	(3)	1	(2)
4	–	(0)	–	(0)	–	(0)	1	(2)
Infection								
3	1	(2)	2	(4)	–	(0)	4	(10)
4	1	(2)	3	(6)	–	(0)	–	(0)

Table 8
Reason for treatment discontinuation

Reason off study	First-line study		Second-line study	
N (%)	5 g/m^2/1 day ($N = 49$)	3 g/m^2/3 days ($N = 49$)	5 g/m^2/1 day ($N = 36$)	3 g/m^2/3 days ($N = 40$)
Progression/relapse	29 (59)	27 (55)	29 (81)	25 (63)
Toxicity	3 (6)	9 (18)	1 (3)	5 (13)
Patient refusal	7 (14)	3 (6)	3 (8)	5 (13)
End of protocol treatment	7 (14)	4 (8)	2 (6)	3 (8)
Intercurrent death	–	1 (2)	–	–
Other	3 (6)	5 (10)	1 (3)	2 (5)

4. Discussion

In drug development, drugs are traditionally identified as active only if they show at least a 20% response rate in an adequate number of patients. In adult soft-tissue sarcomas, only doxorubicin given at a dose of at least 70 mg/m^2, and ifosfamide reach this goal (9–14). Despite the fact that ifosfamide would be considered by many to be 'an old drug', the optimal dose regimen has still not been established. If given over 24 h, a dose of 5 g/m^2 can not be exceeded owing to encephalopathy, as has been shown by Wiltshaw and colleagues [12]. If given over several days by a fractionated schedule, the maximum dose per cycle varies between 6 g/m^2 over 2 days to 18 g/m^2 over 6 days. Generally, it can be stated that a dose of 3 g/m^2/day can not be exceeded in such

fractionated schedules. For continuous infusion this is less clear. In any case, mesna is always required to prevent urothelial toxicity.

In the mid-1980s, the EORTC STBSG determined the dose of 5 g/m^2 by 24-h infusion to be an acceptable palliative treatment. In the outpatient setting, more prolonged infusions can only be given using portable pumps or a longer stay in hospital is required. A 3 g/m^2 infusion given over 4 h or less each day can be given on an outpatient basis, but the time spent in hospital is still substantial. The question addressed in this study was whether the larger dose thus achieved was worthwhile. When given as second-line treatment, the response rates for both 5 g/m^2/1 day and 3 g/m^2/3 days were disappointingly low. Several explanations for this low response rate can be given. In the studies performed in the early 1980s, it was not part of routine practice to carry out an independent response review, neither in the EORTC STBSG nor in any other group. The response rate is always 20–30% lower if such an external review is performed [26,29]. In addition, the substantially higher proportion of patients with leiomyosarcomas, a sarcoma type that is relatively resistant to any type of chemotherapy, in the present study compared with our previous studies, can partly explain the lower response rate.

However, the important finding in the current study was the response rate observed with the 3 g/m^2/3 days regimen when used as first-line therapy. The response rate was 28% in evaluable patients i.e. in the same range as that of doxorubicin if given at the optimal dose. This higher response rate, however, did not translate into a longer time to progression and better survival. However, randomised phase II studies such as this are not formally powered to compare therapeutic arms and give information on improved survival. Although haematological toxicity in the 3 g/m^2/3 days groups was higher this did not result in more infections and can thus be judged as acceptable. Therefore, the response and toxicity data with this regimen need to be re-analysed once data in a larger patient group have been accrued. This can be done once the data of the current study of the group comparing doxorubicin 75 mg/m^2 with ifosfamide 3 g/m^2/3 days become available. An important question not answered by the present study is whether infusion duration affects either efficacy or toxicity with ifosfamide. The data in the literature are quite conflicting. In non-randomised studies, the suggestion is made that short duration infusion therapies result in a similar activity, but more toxicity compared with a continuous infusion [13,16,17,19]. The follow-up study of the EORTC STSGB compared ifosfamide given at 3 g/m^2 over 4 h on three consecutive days, as in this study, with 9 g/m^2 given by continuous infusion over 3 days and doxorubicin 75 mg/m^2 as a control arm, has just been closed and the data are being analysed.

In the light of the data obtained in the present study, one might question whether the dose and schedule of administration of ifosfamide used in previous combination studies with doxorubicin was optimal. It is acknowledged that single agent doxorubicin remains the standard therapy for palliation of metastatic disease. However, in situations where it is important to maximise the likelihood of response, e.g. when treating preoperatively, optimal treatment is perhaps more likely to be a combination of doxorubicin given at 60–75 mg/m^2 with ifosfamide at 3 g/m^2 on three consecutive days, or with both agents fractionated over 3 days. Several recent studies have used this type of regimen and all reported substantial higher response rates ranging from 32 to 46% [19–22]. However, these studies have all been performed as single institution studies where selection of the patients is less strict than in randomised multicentre studies and in which external response review has not been performed. Hopefully, ongoing studies will identify the optimal mode of administration of ifosfamide and it will then be possible to determine the most appropriate combination regimen.

In the meantime, novel agents that have more selective targets need to be investigated for activity against soft tissue sarcomas since it is unlikely that substantial higher response rates or improvements in survival will result from varying the dose and schedule of doxorubicin and ifosfamide.

5. Participating centres

Next to those of the authors, these included: City Hospital, Nottingham, UK (P. Woll); Ist. Di Oncologia, Valencia, Spain (A. Poveda); King Faisal Hospital, Riyadh, Saudi Arabia (R. Wiersbicki, A. Ezzat); Inst. Jules Bordet, Brussels, Belgium (J. Kerger); Christie Hospital, Manchester, UK (J. Radford, D. Crowther); Universitair Ziekenhuis, Antwerpen, Belgium (A.T. van Oosterom); Hôpital Universitaire Erasme, Brussels, Belgium (D. Gangji); Cancer C. Sklodowska Curie, Warsaw, Poland (W. Ruka); Universitätskliniken, Graz, Austria (Ploner, Samonigg); Radboud Hospital, Nijmegen, The Netherlands (G. Van Hoesel); Univ. Hospital, Odense, Denmark (L. Bastholt).

References

1. Enzinger FM, Weiss SW. General considerations. In Enzinger FM, Weiss SW, eds. *Soft Tissue Tumors*, 3rd ed. St. Louis, Mosby, 1995, 1–16.
2. Weiss SW. *Histopathological Typing of Soft Tissue Tumors*, 2nd ed. (WHO International Histopathological Classification of Tumors). Berlin, Springer Verlag, 1994.
3. Van Glabbeke M, van Oosterom AT, Oosterhuis JW, *et al.* Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2.185 patients treated with

anthracycline-containing first-line regimens—a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group study. *J Clin Oncol* 1999, **17**, 150–157.
4. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1.041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol* 1996, **14**, 1679–1689.
5. Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet* 1997, *350*, 1647–1654.
6. Santoro A, Tursz T, Mouridsen H. Doxorubicin *versus* CYVADIC *versus* doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas. A randomized study of the European Organization for Research and Treatment of Cancer, Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1995, **13**, 1537–1545.
7. Antman K, Crowley J, Balcerzak SP, *et al*. An intergroup phase III randomised study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol* 1993, **11**, 1270–1285.
8. Edmonson JH, Ryan LM, Blum RH, *et al*. Randomized comparison of doxorubicin alone *versus* ifosfamide plus doxorubicin or mitomycin, doxorubicin and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol* 1993, **11**, 1269–1275.
9. Verweij J, Mouridsen HT, Nielsen OS, *et al*. The present state of the art in chemotherapy for soft tissue sarcomas in adults: the EORTC point of view. *Crit Rev Oncol Haematol* 1995, **20**, 193–201.
10. Borden EC, Amato DA, Rosenbaum C, *et al*. Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. *J Clin Oncol* 1987, **5**, 840–850.
11. Mouridsen HT, Bastholt L, Somers R, *et al*. Adriamycin *versus* epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer Clin Oncol* 1987, **23**, 1477–1483.
12. Wilshaw E, Westbury G, Harmer C, *et al*. Ifosfamide plus mesna with and without adriamycin in soft tissue sarcoma. *Cancer Chemother Pharmacol* 1986, **18**(Suppl. 2), 10–12.
13. Antman KH, Ryan L, Elias A, Sherman D, Grier HE. Response to Ifosfamide and Mesna: 124 previously treated patients with metastatic or unresectable sarcoma. *J Clin Oncol* 1989, **7**, 126–131.
14. Bramwell VHC, Mouridsen HT, Steward W, *et al*. Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. *Eur J Cancer Clin Oncol* 1987, **23**, 311–321.
15. Schutte J, Mouridsen HT, Steward W, *et al*. Ifosfamide plus doxorubicin in previously untreated patients with advanced soft tissue sarcoma. *Eur J Cancer* 1990, **26**, 558–561.
16. Le Cesne A, Antoine E, Spielmann KM, *et al*. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol* 1995, **13**, 1600–1608.
17. Elias AD, Ryan L, Sulkes A, *et al*. Response to mesna, doxorubicin, ifosfamide in 108 patients with metastatic sarcoma and no prior chemotherapy. *J Clin Oncol* 1989, **7**, 1208–1216.
18. Palumbo R, Palmeri S, Antimi M, *et al*. Phase II study of continuous-infusion high-dose ifosfamide in advanced and/or metastatic pretreated soft tissue sarcomas. *Ann Oncol* 1997, **8**, 1159–1162.
19. Reichardt P, Tilgner M, Mapara MY, Hohenberger P, Dörken B. Dose-intensive chemotherapy with or without stem cell support for adult patients with advanced soft tissue sarcoma: final results of a phase II study and preliminary results of a phase I/II study. *Proc Am Soc Clin Oncol* 1997, **16**, 1791.
20. De Pas I, De Braud F, Orlando L, *et al*. High-dose ifosfamide plus adriamycin in the treatment of adult advanced soft tissue sarcomas: is it feasible? *Ann Oncol* 1998, **9**, 917–919.
21. Bokemeyer C, Franzke A, Hartmann JT, *et al*. A phase I/II study of sequential, dose-escalated high dose ifosfamide plus doxorubicin with peripheral blood stem cell support for the treatment of patients with advanced soft tissue sarcomas. *Cancer* 1997, **80**, 1221–1227.
22. Frustaci S, Buonadonna A, Favaro D, *et al*. Effectiveness of intensive chemotherapy in metastatic soft tissue sarcomas and ability to mobilize PBPC. *Proc Am Soc Clin Oncol* 1994, **13**, 1650.
23. Nielsen OS, Dombernowsky P, Mouridsen H, *et al*. High dose epirubicin is not an alternative to standard-dose doxorubicin in the treatment of advanced soft tissue sarcomas. A study of the EORTC Soft Tissue and Bone Sarcoma Group. *Br J Cancer* 1998, **78**, 1634–1639.
24. Sylvester RJ. A Bayesian approach of the design of phase II clinical trials. *Biometrics* 1998, **44**, 833–836.
25. World Health Organization. WHO Handbook for Reporting the Results of Cancer Treatment. *Offset Publication 40*. Geneva, WHO, 1979.
26. Van Glabbeke M, van Oosterom AT, Steward W, Verweij J, Mouridsen H. Selection of large and objectively measurable target lesions in EORTC phase II trials: impact on recruitment and response rate. *Eur J Cancer* 1993, **14**, 1943–1947.
27. van Unnik JA, Coindre JM, Contesso C, *et al*. Grading of soft tissue sarcomas: experience of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 1993, **29**, 2089–2093.
28. Vantongelen K, Rotmensz N, van der Schueren E, *et al*. Quality control of validity of data collected in clinical trials. *Eur J Cancer Clin Oncol* 1989, **8**, 1241–1247.
29. Thiesse P, Ollivier L, Di Stefano-Louineau D, *et al*. Response rate accuracy in oncology trials: reasons for interobserver variability. *J Clin Oncol* 1997, **15**, 3507–3514.
30. Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.