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Original Paper

Dose-intensive First-line Chemotherapy with Epirubicin and Continuous Infusion Ifosfamide in Adult Patients with Advanced Soft Tissue Sarcomas: a Phase II Study

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This phase II study was designed to verify the activity and safety of an intensive epirubicin/ifosfamide schedule in untreated soft tissue sarcoma (STS) patients by using both the agents at the identified maximal tolerated doses. 39 adult patients were treated with epirubicin at 55 mg/m^2, on days 1 and 2 (total dose per cycle 110 mg/m^2) combined with ifosfamide at 2.5 g/m^2 days 1–4 (total dose per cycle 10 g/m^2), with equidose mesna uroprotection and G-CSF support. Treatment was given on an ambulatory basis, at 3-week intervals. The overall objective response (OR) rate was 59% (95% confidence interval, CI, 43–72%), with 5 complete responses (13%) and 18 partial responses (46%); 12 partial responders were rendered disease-free following surgery. The median survival time was 19 months, being 23 and 13 months, respectively, for responding and non-responding patients. The median time to response was 40 days (range 21–60). Treatment-related toxicity was overall acceptable. The OR of 59% was the highest ever reported in our consecutive studies in advanced STS, confirming that improved therapeutic efficacy can be obtained with intensified regimens in such a disease; both the response duration and survival were also longer. The observed activity proved to be interesting with regard to the high response rate in the lung (86%), as well as the proportion of patients rendered disease-free by early surgery after the achievement of a partial response (55%). Both these findings may be important in the multimodality approach to patients with lesions potentially resectable for cure.

Key words: epirubicin, ifosfamide, intensified regimens, soft tissue sarcomas
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INTRODUCTION

ADULT ADVANCED soft tissue sarcomas (STS) are rare mesenchymal neoplasms characterised by a high morphological and clinical heterogeneity, as well as a limited responsiveness to most chemotherapy agents. Only two drugs, doxorubicin and ifosfamide, have consistently shown single agent activity in more than 20% of untreated patients [1]. In an attempt to improve results of treatment of advanced STS, one line of investigation has been to combine the two single-most active agents into the same regimen, addressing the hypothesis that certain malignant cells may be resistant to one agent and sensitive to another. By the beginning of the 1980s, several phase II studies of different anthracycline–ifosfamide combinations were reported from trials in STS. Although limited by the overlapping toxicities (most importantly, myelosuppression), the association of doxorubicin (or its epimer epirubicin) and ifosfamide has been shown to increase overall objective response (OR) rates from 20% to 35–45% [2–4]. Despite clear evidence of higher activity for combination strategies compared with single agents, a decade later no benefit has yet been proven over single-agent doxorubicin in promoting median survival, which rarely exceeds 10–12 months [5, 6]. Given the limited chemotherapy options

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against STS, clinical research has focused on the analyses of dose–response and schedule–response relationships of the known effective drugs; the availability of haematopoietic growth factors allowed dose-intensified regimens. Sarcomas represent an attractive clinical model system for such investigations. A body of data support the existence of a dose–response correlation for doxorubicin in STS, and dosages of at least 70 mg/m^2 every 3 weeks appear to be critical for obtaining optimal OR rates to doxorubicin [7, 9]. Recently, a relationship between dose and clinical response has been strongly suggested for ifosfamide; OR rates ranging from 17 to 45% have been reported for doses higher than 12 g/m^2/course in monochemotherapy on different series of advanced, anthracycline-refractory STS patients [10–13].

Since the mid-1980s, we have investigated the activity of the epirubicin–ifosfamide combination in patients with advanced STS, specifically focusing on the hypothesis that the dose and dose intensity of delivered chemotherapy might enhance the probability of achieving ORs in such a disease. At the time our investigation began, a few reports were available concerning epirubicin dose intensification [14–17]. In sequential multi-institutional studies performed by our group we observed increasing OR rates with increasing doses of epirubicin, given in combination with a fixed dose of ifosfamide; in addition, high-dose intensity of the anthracycline was found to be statistically significantly correlated with OR rate and overall survival [18, 19]. Thus, we attempted to increase the ifosfamide dose, administering the drug by continuous infusion (c.i.) with haematopoietic growth factor support. In a first phase I study, ifosfamide at 15 g/m^2/course with equidose mesna was identified as the maximum tolerated dose (MTD) for an ambulatory monochemotherapy regimen in pretreated patients [20]; a later phase II trial tested such a schedule on a series of 38 advanced, anthracycline and/or ifosfamide pretreated STS patients; an OR rate of 39% was observed [21]. The next logical step was to combine the two agents at the identified MTDs. We conducted a pilot study on 17 chemotherapy-naïve STS patients; ifosfamide at 10 g/m^2/course proved to be the recommended dose given in association with a fixed dose of 110 mg/m^2/course of epirubicin [22]. Having demonstrated that this regimen was feasible, we designed the present phase II study to verify the activity and toxicity of such intensified combination as a first-line therapy in patients with advanced and/or metastatic STS.

PATIENTS AND METHODS

Patients with histologically verified, locally advanced inoperable and/or measurable metastatic STS were enrolled. The protocol was approved by the ethical committee and oral informed consent was obtained from all patients. Adequate renal (serum creatinine level ≤ 150 mmol/l), hepatic (bilirubin level ≤ 20 mmol/l), bone marrow (leucocyte count $> 3.5\times10^9$/l and platelet count $\geq 100\times10^9$/l) and cardiac (normal ECG and echography with left ventricular ejection fraction [LVEF] > 60%) functions were required. All patients had to be chemotherapy naïve; previous radiotherapy to lesions other than those used to measure response was acceptable.

Epirubicin was given at a dose of 55 mg/m^2/day as a short intravenous (i.v.) bolus on days 1 and 2. Ifosfamide was administered at a dose of 2.5 g/m^2/day over 4 consecutive days by c.i. (total dose 10 g/m^2/cycle), as previously described [20–22]. One-third of the drug daily dose was given intravenously over 4 hours, then the c.i. ifosfamide was administered through a portable infusion pump. Mesna was infused at equimolar doses along with ifosfamide, both in the bolus and c.i. administration. An additional 2.5 g/m^2/day of mesna was given on day 5, due to its brief half-life. G-CSF support was given from day 6 to day 12 as a daily subcutaneous (s.c.) injection of 200 μg. Treatment was given in an outpatient setting; courses of chemotherapy were repeated at 3-week intervals. Toxicity was monitored by clinical and laboratory evaluations on day 21 of each cycle, according to WHO criteria [23]. Full biochemical profiles and urinary renal function tests were performed weekly and complete blood cell count was performed every 2 days until recovery from the nadir values for granulocytes and/or platelets. Cardiological monitoring included ECG tracing before each cycle and determination of left ventricular ejection fraction (LVEF) by echocardiography every two cycles. No dose reductions for prior toxicity were planned in this protocol. Treatment was continued to a maximum of six cycles or to two cycles beyond documentation of a complete response, if this occurred before the fourth cycle. Exclusion from the study occurred if there was a reduction in LVEF below 50% or more than 20% in relation to the pretreatment level. Patients were also excluded from further treatment if disease progression occurred. Patients were considered assessable for response if they received a minimum of two cycles of chemotherapy. Responses were evaluated after the second, fourth and subsequent alternate cycles of chemotherapy, with repeated clinical and appropriate radiological assessments (CT and/or magnetic resonance imaging (MRI)) based on the extent of the disease defined at presentation. Complete response (CR) was defined as the disappearance of all known lesions after two separate measurements at least 4 weeks apart. Pathological complete response (pCR) was defined as no viable tumour in the resected specimen that represented the residual radiological abnormality. Partial response was defined as a > 50% reduction in the sum of the products of the perpendicular diameters of measurable lesions without the appearance of new lesions for at least 4 weeks. Stable disease (SD) was defined as a decrease of less than 25% or an increase of less than 25% with no new lesions and progressive disease (PD) as an increase > 25% or the appearance of new lesions. Response duration was computed from the initiation of treatment to the first evidence of progressive disease for all responsive patients. Survival was measured from the first day of treatment to death or last patient observation. Time to progression, response duration and survival were calculated using the Kaplan–Meier method.

RESULTS

From July 1994 to December 1995, 39 consecutive patients were entered into the study; all eligible and treated patients were also assessable for response and toxicity. Patient characteristics are listed in Table 1. All patients had one or more measurable lesions either locally (13 primary and 10 relapse, with or without metastases) or at different metastatic sites; 14 patients (36%) entered the study affected with lung metastases only.

The responses to treatment are shown in Table 2. An overall response rate of 59% (95% confidence interval, CI, 43–72%) was obtained, with 5 CRs (13%) and 18 PRs (46%). In the remaining patients, 14 SD (36%) and 2 PD (5%) were observed. 2 patients with synovial sarcoma of the

Table 1. *Patient characteristics*

Characteristics	*n* (%)
Entered/assessable	39
Age, years	
Median	46
Range	19–71
Performance status	
0	14 (36)
1	19 (49)
2	6 (15)
Histological subtype	
Malignant fibrous histiocytoma	14 (36)
Leiomyosarcoma	10 (26)
Synovial sarcoma	7 (18)
Liposarcoma	3 (8)
Angiosarcoma	3 (8)
Rhabdomyosarcoma	2 (5)
Histological grading	
1	3 (8)
2	15 (38)
3	21 (54)
Disease status at start of chemotherapy	
Primary	
Without metastases	6 (15)
With metastases	7 (18)
Local relapse	
Without metastases	4 (10)
With metastases	6 (15)
Metastatic disease only	
Lung	14 (36)
Liver	2 (5)

lower limb achieved a pCR. One of these patients is still in CR off chemotherapy 23 months from the date of response; the other relapsed 19 months later and is currently alive with disease 26 months from the date of response. 3 other patients with lung as the only site of disease obtained a CR: 2 of these patients are presently disease-free after 17 and 21 months from the date of response; the remaining patient relapsed in the lung after 14 months, then was subjected to surgical resection of lung metastases and is currently free of disease 12 months from surgery. Following chemotherapy, 13 patients (including the patient with CR with lung as the only site, mentioned above) underwent surgery to remove either local or metastatic disease. 8 patients with disease localised to the lung underwent metastasectomy after obtaining a PR. 6 of these patients are alive and disease-free at more than 14 months of follow-up; the other 2 patients relapsed in the lung after 9 and 12 months from surgery, underwent surgery again and are currently disease-free. 4 additional patients who entered the study with 'primary without metastases', underwent compartmental resection (2 patients) or wide excision (2 patients) after obtaining a PR at the second to third cycle of therapy. These are also currently disease-free.

Although each histological type is limited in number in the presented series, the analysis of response according to histological subtypes indicates that 6 of the 7 (86%) patients with synovial sarcomas and 8 of the 14 patients (57%) with malignant fibrous histiocytomas obtained an objective tumour regression. Responses were observed over the full range of disease sites, but lung metastases appeared to be highly chemosensitive, because 12 of the 14 patients (86%) with disease in the lung experienced an OR and 14 of the 23 responders (61%) had lung involvement. The median time to response was 40 days (range, 21–60 days, 2–3 cycles).

The overall duration of response is difficult to assess because many patients received surgery consolidation or switched to other individualised treatments. The median duration of CRs was 16 months (range, 14–23+ months). Of the 18 partial responders, 10 underwent surgical debulking of the residual lesions after 2–3 cycles of chemotherapy and 4 were given consolidation radiation therapy; in the remaining 4 patients, the PR lasted from 9 to 14+ months. Median response duration for SDs was 8 months (range, 5–12+ months). 2 patients progressed while on therapy and were

Table 2. *Objective responses according to disease characteristics*

	CR (%)	PR (%)	SD (%)	PD (%)	OR (%)
Overall ($n = 39$)	5 (13)	18 (46)	14 (36)	2 (5)	23 (59)
Histology					
MFH ($n = 14$)	2 (14)	6 (43)	5 (36)	1 (7)	8 (57)
Leiomyosarcoma* ($n = 10$)	1 (10)	3 (30)	6 (60)	–	4 (40)
Synovialsarcoma ($n = 7$)	2 (29)	4 (57)	1 (14)	–	6 (86)
Liposarcoma ($n = 2$)	–	1 (50)	1 (50)	–	1 (50)
Angiosarcoma ($n = 4$)	–	3 (75)	1 (25)	–	3 (75)
Rhabdomyosarcoma ($n = 2$)	–	1 (50)	–	1 (50)	1 (50)
Histological grading					
1 ($n = 3$)	–	2 (67)	–	1 (33)	2 (67)
2 ($n = 15$)	1 (7)	5 (33)	8 (53)	1 (7)	6 (40)
3 ($n = 21$)	4 (19)	11 (52)	6 (29)	–	15 (71)
Status at entry					
Primary without metastases ($n = 6$)	2 (33)	4 (67)	–	–	6 (100)
Relapse without metastases ($n = 4$)	–	2 (50)	2 (50)	–	2 (50)
Primary with metastases ($n = 7$)	–	1 (14)	5 (71)	1 (14)	1 (14)
Relapse with metastases ($n = 6$)	–	1 (17)	4 (67)	1 (17)	1 (17)
Lung only ($n = 14$)	3 (21)	9 (64)	2 (14)	–	12 (86)
Liver only ($n = 2$)	–	1 (50)	1 (50)	–	1 (50)

MFH, malignant fibrous histiocytoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response. *4 leiomyosarcomas originated from the GI tract, with 2 PRs.

given second-line chemotherapy; one of these patients died of cerebral metastases after 8 months and the other died of renal failure 10 months later because of retroperitoneal disease progression. The overall median survival time was 19 months (range, 8–26+ months), being 23 and 13 months for responding and non-responding patients, respectively ($P < 0.05$ by Mantel–Cox). In patients subjected to surgery, the median survival ranged from 15+ to 26+ months.

A total of 167 cycles of chemotherapy were given, the median number of courses given being 4 (range, 3–6 per patient). Median dose intensity of ifosfamide was 6.69 g/m^2/week and for epirubicin 36.6 mg/m^2/week. The regimen was well tolerated; no toxic death occurred and no patient required hospitalisation because of treatment-related side-effects. Neutropenia was by far the most relevant haematological toxicity. Overall, 73% of chemotherapy courses were associated with neutropenia of any grade, but in only 5 patients (7% of courses) was it of grade 4 (Table 3). The median neutrophil count was 2150 (range, 450–4100). The median granulocyte nadir occurred on days 10–12 and the mean recovery time from grade 4 nadir was 4 days (range, 2–8 days). Except for 1 patient in which treatment was delayed for 1 week because of persistent neutropenia, complete recovery by day 21 was the rule. Thrombocytopenia was less frequent and severe and occurred in 13 patients overall (21% of cycles), but never reached WHO grade 3. Anaemia was unusual and only 3 patients (8%) showed haemoglobin levels of less than 9.5 g/dl during treatment. 5 patients experienced febrile neutropenic episodes during 7 of 167 cycles (4%), usually of brief duration (median 4 days, range 2–6 days) and in all cases controlled with oral antibiotics.

Apart from alopecia which was universal, nonhaematological toxicities were uncommon and mild. During the study period, no clinical symptoms of congestive heart failure or ECG abnormalities were observed. A pathological decline in left ventricular ejection fraction (LVEF) as previously defined was observed in one patient at the multigated angioscintigraphy (MUGA) scan 12 days after the fifth course of therapy, with a LVEF decrease from baseline 66 to 42%; additional follow-up LVEF measurements 40 days later (51%) and 6 months later (62%) showed normalisation. Nausea and vomiting was generally mild on standard antiemetic regimens (13% of grade 3 and 87% of grade 1–2). 5 patients had grade 1–2 mucositis and self-limited mild/moderate diarrhoea occurred in 6 patients (13%). No symptom of central nervous system toxicity was observed. In 3 patients grade 1 transient haematuria occurred at the second and third cycles of therapy, in one case associated with reversible proteinuria. Overall, 7 cycles (4%) were complicated by reversible elevations in serum creatinine, while subclinical serum electrolyte abnormalities were detectable during therapy in 32% of patients; in no case was i.v. replacement required. No toxicities attributed to G-CSF administration were registered.

DISCUSSION

Full dose anthracycline alone or in combination with ifosfamide represent the standard first-line chemotherapy in adult STS. The combination of these two drugs in front-line treatment of STS has been shown to improve response rates significantly in both phase II and prospective randomised studies [2–5], but a survival advantage has yet to be demonstrated [6, 7]. In an attempt to improve on previous results, a recent trend in modern oncology has been to administer higher than standard doses of chemotherapy [24]. Sarcomas, historically considered chemoresistant tumours, tend to exhibit relative chemosensitivity to high-dose cytotoxic chemotherapy. The concept of increasing the dose intensity of chemotherapy in STS has come into question with the suggestion that a critical interval exists, from 50 to 75 mg/m^2, in the dose–response curve for doxorubicin [8, 9]. In view of the above, in the past decade our own investigation has focused on determining whether improved therapeutic efficacy could be shown with more intensive therapy in STS, by using the two most active agents in combination within the optimal identified dose ranges. Addressing the hypothesis that 'high dose intensity leads to better end results', in our dose-escalation studies epirubicin was chosen because of its lower toxicity compared with the parent compound doxorubicin [25]. A two-step approach was performed in our consecutive trials, by escalating epirubicin to the MTD (when given with concurrent ifosfamide), and then escalating ifosfamide to a new MTD for the two-drug combination. Studies that have evaluated this topic in STS are limited. The early reported data on a possible dose–response relationship for epirubicin in

Table 3. *Toxicity*

	By patient ($n = 39$)								By course ($n = 167$)							
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Haematological																
Leuconeutropenia*	11	28	15	38	8	21	5	13	28	17	62	37	20	12	12	7
Thrombocytopenia	8	21	5	13	–	–	–	–	19	11	16	10	–	–	–	–
Anaemia	16	41	3	8	–	–	–	–	24	14	5	3	–	–	–	–
Nonhaematological																
Heart-function	1	3	–	–	–	–	–	–	1	1	–	–	–	–	–	–
Creatinine	5	13	–	–	–	–	–	–	7	4	–	–	–	–	–	–
Haematuria	3	8	–	–	–	–	–	–	3	2	–	–	–	–	–	–
Proteinuria	2	5	–	–	–	–	–	–	2	1	–	–	–	–	–	–
Nausea/vomiting	25	64	9	23	5	13	–	–	73	44	82	49	12	7	–	–
Mucositis	3	8	2	5	–	–	–	–	5	3	4	2	–	–	–	–
Diarrhoea	4	10	2	5	–	–	–	–	7	4	5	3	–	–	–	–
Alopecia	5	13	8	21	26	67	–	–	20	12	32	19	104	62	–	–

*Febrile neutropenic episodes, 7 cycles (4%), 5 patients (13%).

patients with STS were by our group; for the first time in such a disease a higher dose intensity of the delivered anthracycline was found to correlate significantly with the probability of response and overall survival in consecutive phase II trials [18, 19, 26]. However, until now no randomised study has been conducted that confirmed the dose-dependent activity of epirubicin. Concurrently, the availability of haematopoietic growth factors provided the opportunity to administer full protocol dose intensity of chemotherapy (doxorubicin 75 mg/m^2 plus ifosfamide 5 g/m^2, every 3 weeks) to most patients of a large EORTC study [27], in which an interesting OR rate of 45% (10% CRs) was observed. Dose escalation of ifosfamide has been studied only in more recent years, but a body of evidence became quickly available for a clear direct dose–response relationship [10–12], also suggesting the possibility that high doses of the agent could circumvent the resistance to standard doses [13]. Concurrently with this evidence, we were evaluating the feasibility of an ambulatory regimen of high-dose c.i. ifosfamide with equidose mesna and G-CSF support in a pilot study on 32 pretreated patients; ifosfamide at 15 g/m^2/course was identified as the MTD [20]. Subsequently, we found that ifosfamide and epirubicin were well tolerated in combination doses of 10 g/m^2 and 110 mg/m^2, respectively [22]; thus, our current reported phase II study was designed to verify the activity of such intensified schedule in untreated STS patients.

In our previous study on 45 patients with advanced sarcomas, we were able to obtain a dose intensity of 30 mg/m^2/week, corresponding to the highest tested epirubicin level (80–100 mg/m^2/course), in combination with a fixed ifosfamide dose of 6 g/m^2/course; the overall OR rate of 38%, reaching 44% in the subset of untreated patients [19]. Compared with that experience, the ifosfamide dose in the present study was 67% higher, while epirubicin dose exceeded only 10% of the previous dosage; median dose intensities were 6.6 g/m^2/week and 36.6 mg/m^2/week, respectively. In a recently reported Italian study, the same drug combination, with epirubicin escalated up to 140 mg/m^2/cycle combined with ifosfamide at 9 g/m^2/cycle, produced an OR rate of 54% on a series of 38 STS patients, suggesting a clear dose–response relationship for epirubicin [28]. It is noteworthy that in this pilot trial the first and second epirubicin tested dose levels produced only 17 and 33% ORs, respectively, whilst 100% of patients (13/13) responded to the third level of 140 mg/m^2, corresponding to a dose intensity of 40 mg/m^2/week. In our study, the response rate of 59% (23/39) was obtained with a 21% lower dosage of epirubicin, whilst ifosfamide dose was 11% higher. These differences are difficult to explain because of the small evaluated series in uncontrolled studies; in rare diseases like STS, patient selection may be sufficient to make two series differ in activity and historical comparisons are particularly unreliable. Moreover, theoretically one could speculate that the ifosfamide dose might play a role in the different reported response rates, considering that even slight differences in drug doses may be critically important when a combined regimen is given. In fact, although different groups have reported their experience on the MTD of ifosfamide and epirubicin as single agents [10–17, 29], the optimal dose and schedule of the two drugs in association have not been exhaustively investigated, nor has the potential impact of different administration modalities on the regimen activity been recognized (i.e. c.i. versus repeated i.v. bolus). Likewise, whether further dose increments of epirubicin could produce increased response rates cannot be determined by the available evidence. It should be pointed out that all published data on epirubicin/ifosfamide combination in STS are uncontrolled, and schedule differences significantly confound analysis of dose–response relationship. However, no definitive conclusions can be drawn from the only two reported randomised trials on high doses of epirubicin in STS patients. In a large phase III trial by the EORTC Soft Tissue and Bone Sarcoma Cooperative Group, no significantly higher activity of epirubicin at 150 mg/m^2/course was found compared with standard dose doxorubicin, despite a higher myelotoxicity [30]. A more recent controlled study compared epirubicin alone at 180 mg/m^2 per cycle versus epirubicin-cisplatin combination in chemotherapy-naïve STS patients, showing a response rate of 29 and 54%, respectively; these results indicate low activity of high-dose epirubicin monotherapy, in agreement with previous data [15–17], whilst suggesting an interesting synergism of action in the epirubicin–cisplatin combination.

The response rate of 59% in the present study was the highest seen so far by our cooperative group for patients with advanced STS, 15% above that seen when ifosfamide at 6 g/m^2/course was combined with epirubicin at 100 mg/m^2/course [19]. Both the response duration and survival were also longer. We would stress that such a good activity was associated with an overall acceptable toxicity; in no case was hospitalisation required because of treatment-related side-effects and in only 1 patient therapy had to be postponed by 1 week due to haematological toxicity. As demonstrated in our previous study [22], the tested regimen was feasible on an ambulatory basis and the adopted system of using portable infusion pumps again was confirmed to allow good patient compliance [20, 21].

Two other aspects deserve to be emphasised in the present study: the high response rate in the lung and the short time to response observed in responding patients. As previously reported by others, we found that lung lesions showed a higher OR rate compared with other sites of disease. Overall, 86% of patients with lung metastases (12/14) obtained an OR, which was complete in 3 cases (27%) and 6/9 (67%) partial responders were rendered disease-free by lung metastasectomy. All these patients are presently alive at more than 26 months follow-up. The median time to response in our trial ranged from 21–60 days (median 40 days), which means 2–3 courses of therapy. Both these findings may be of importance on the final outcome of patients with advanced STS, considering that the main prognostic factor at this moment is probably whether surgery is possible. In fact, if it is true, as it seems, that in a highly selected population with isolated resectable lung metastases curative-intent surgery represents the main therapy [32, 33], a higher proportion of patients exists which can be rendered disease-free by surgery after chemotherapy, i.e. patients achieving a clinical PR following first-line therapy. In this setting, we do believe that the goal of the maximal achievable response in the shorter possible time should be pursued to favour early surgery. However, the suggested better outcome of STS patients with isolated lung metastases needs to be confirmed on larger series; at present, only the absence of liver or bone metastases has been found to be significantly correlated with the probability of response to chemotherapy in a large analysis of prognostic factors performed by EORTC on over 1700 patients [34].

The question of whether chemotherapy could ever cure patients with adult-type STS remains an unresolved and critical issue. While many consider chemotherapy of metastatic STS as mere palliation [35], others have evaluated the role of high-dose chemotherapy with myeloablative regimens followed by bone marrow transplantation or peripheral-blood progenitor cell support [36, 37]. Given the limited chemotherapy options for the treatment of advanced STS, it appears essential that the few drugs that have activity are given in optimal doses and schedules. The belief, possibly mistaken, that adults with advanced STS inevitably fare badly can lead to the use of suboptimal chemotherapy dose intensity or duration. Thus, it is possible that the adjuvant regimens tested to date have not been adequate to affect overall survival [38]. Alternatively, an increased response rate in advanced STS may not translate into a survival advantage, especially if the response rate is substantially less than 50%. Therefore, the exact role of dose intensity in STS will remain unanswered until randomised trials show a benefit in survival for responding patients. In the meantime, we believe that the peculiar biology of these tumours can justify the attempt of achieving an OR, in the absence of corresponding evidence of a survival advantage, in at least two subsets of advanced STS patients: those with locoregional advanced disease and those with lung metastases. Our's and others' experience demonstrate that intensified regimens can produce increased OR rates in such a population, in a proportion of cases associated with prolonged disease-free intervals. Despite the difficulties of interpreting the ultimate significance of clinical response, an improvement in response rates can actually be considered a reasonable intermediate goal for clinical research; more information about the increased activity of higher doses of the best agents (i.e. anthracyclines, ifosfamide) could translate into new trials on patients with early stage, resectable disease, as well as in the adjuvant setting. In this view, studies would be appropriate to investigate further the impact of prognostic factors for chemotherapy response in advanced STS; the assessment that factors affecting response rate are probably different from those that predict survival could be useful in selecting patients to be offered dose-intensive chemotherapy with curative intent, as some data suggest [39, 40].

The overall results of the present study are highly encouraging and compare favourably with those recently reported with more aggressive intensified schedules [41–43]. Currently, we can stress the feasibility and activity of the treatment, which has been shown to represent the 'best' first-line chemotherapy in our own hands. It remains unclear whether further escalation of the dose of this particular combination can be achieved by adding haematopoietic stem-cell support. At the present time, we are conducting a phase II study of sequential chemotherapy in untreated STS patients to evaluate the ability to mobilise peripheral-blood progenitor cells with a short intensive programme of epirubicin–ifosfamide combination, in which both agents are given by c.i. at their individual MTD.

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