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Original Paper

Ifosfamide and Continuous Infusion Etoposide in Advanced Adult Soft Tissue Sarcoma. A Scandinavian Sarcoma Group Phase II Study

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The purpose of this study was to evaluate tumour response and toxicity to ifosfamide and continuous infusion etoposide in metastatic or locally advanced soft tissue sarcoma, with dose escalations under G-CSF (granulocyte colony-stimulating factor) support. Of 92 eligible patients (median age 51 years), 85% had tumours of high-grade malignancy and 82% had metastatic disease. Chemotherapy, the baseline dose, consisted of etoposide 600 mg/m^2 as a 72 h infusion and ifosfamide 1500 mg/m^2/day for 3 days, followed by G-CSF support (VIG regimen). Stepwise 10% dose escalations were performed depending on haematological toxicity. For patients considered operable after induction chemotherapy, surgical resection of all identifiable residual tumour was attempted. Complete and partial response rates were 11% and 31%, for an overall response rate of 42% (95% CI 31–52%). Forty-eight per cent of courses were dose escalated by a median of 20%. Complete responders had significantly higher, and patients with progressive disease had significantly lower, dose levels than other patients. None of 20 patients with liver metastases responded despite high dose levels. Compared to a preceding pilot study, the addition of G-CSF led to significantly higher dose levels, improved schedule adherence and less haematological toxicity, but no apparent increase in response rate. In view of the modest dose of ifosfamide applied in this study, it is possible that the prolonged infusion of etoposide made a significant contribution to the regimen's antitumour activity, although this can only be determined definitively in a randomised study. © **1997 Elsevier Science Ltd.**

Key words: soft tissue sarcoma, ifosfamide, etoposide, dose intensity, filgrastim, phase specificity, metastasectomy, response

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INTRODUCTION

ADULT SOFT tissue sarcoma (STS) is considered to be moderately sensitive to chemotherapy, with some reports suggesting that tumours of high-grade malignancy respond better than low-grade tumours [1, 2]. Doxorubicin and ifosfamide are generally considered to be the most active agents, and aggressive combination regimens have yielded response rates of around 45% [2–5]. However, the role of chemotherapy in prolonging survival is still undefined both in the primary adjuvant situation and in advanced disease [6–8] and there is a need for the development of new chemotherapy approaches. Etoposide is considered to have low

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activity in adult STS [9–12]. However, a recent study suggested that the activity of etoposide is considerably higher when administered as a prolonged infusion [13], taking advantage of the high cell cycle phase specificity of this agent [14, 15]. Combined with a moderate ifosfamide dose (4500 mg/m^2), etoposide 600 mg/m^2 given as a 72 h infusion yielded a 40% overall response rate in high-grade adult STS [13]. This finding prompted the Scandinavian Sarcoma Group (SSG) to perform a prospective phase II trial to establish the level of activity for this regimen in adult STS. The study also addressed the possibility of dose escalation with the addition of granulocyte colony-stimulating factor (G-CSF) (VIG regimen), and analysed the impact of G-CSF on haematological toxicity, as compared to the preceding single-institution study [13]. Finally, in selected patients, the study analysed disease-free and overall survival after chemotherapy and surgical removal of all identifiable disease.

PATIENTS AND METHODS

Eligibility criteria

The SSG 10/91 study was open to patients aged 15–70 years, with WHO performance status 0–2, histologically proven soft tissue sarcoma and measurable locally advanced or metastatic STS. Before chemotherapy, tumour measurements were to be taken by CT or MRI (magnetic resonance image) scans. Tumours of all malignancy grades were eligible, but small-cell STS (extraskeletal Ewing's sarcoma, primitive neuroectodermal tumours and undifferentiated variants) were ineligible. Patients previously treated with chemotherapy were ineligible, as were patients treated with radiotherapy to the indicator lesion(s) during the preceding 2 months. Other requirements were adequate renal function (creatinine clearance >70 ml/min), WBC count $\geq 3.0 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l.

Patients

From July 1991 to January 1994, 107 patients were entered into the study. Fifteen patients were not eligible due to poor performance status ($n = 3$), non-measurable lesions ($n = 3$), previous chemotherapy ($n = 2$), pathology review showing primary bone sarcoma ($n = 5$) or carcinoma ($n = 2$), leaving 92 eligible patients recruited from 10 Scandinavian institutions (Table 1). There were 47 males and 45 females, with a median age of 51 years (range 15–70) and 92% of the patients had a WHO performance status of 0 (65%) or 1 (27%). The most common histologies were leiomyosarcoma (29%), malignant fibrous histiocytoma (MFH, 25%) and synovial sarcoma (11%) (Table 2) and 85% of the tumours were of high-grade malignancy (Table 3). No patients had received previous radiotherapy to the indicator lesions themselves, but 2 patients had VIG chemotherapy for local recurrences that developed in previously irradiated fields.

Table 1. Number of eligible patients from each participating institution

The Norwegian Radium Hospital, Oslo, Norway	22
Karolinska Hospital, Stockholm, Sweden	19
University Hospital, Lund, Sweden	16
Haukeland Hospital, Bergen, Norway	14
Sahlgrenska Hospital, Gothenburg, Sweden	9
Regional Hospital, Trondheim, Norway	5
Regional Hospital, Karlstad, Sweden	4
Regional Hospital, Tromsø, Norway	1
Ullevål Hospital, Oslo, Norway	1
Regional Hospital, Umeå, Sweden	1
	92

Table 2. Histological classification

	n	(%)
Leiomyosarcoma	27	(29)
Malignant fibrous histiocytoma	23	(25)
Synovial sarcoma	10	(11)
Liposarcoma	6	(7)
Schwannoma	6	(7)
Haemangiopericytoma	3	(3)
Fibrosarcoma	3	(3)
Alveolar cell sarcoma	3	(3)
Clear cell sarcoma	1	(1)
Malignant giant cell tumour of soft tissue	1	(1)
Unclassifiable	9	(10)
Total	92	(100)

The extent of disease is outlined in Table 4. Eighty-three per cent of the patients had metastatic disease and 25% had metastases to multiple sites. The most common metastatic site was the lungs, affecting 46% of all eligible patients. It should be noted that liver metastases were indicator lesions for response in 20 patients (22%) and the liver was the sole metastatic site in 12 patients (13%). As compared to the preceding single-institution study [13], the patients in the present study were similar as regards age, sex, functional status, percentage of patients with metastatic disease and the number of chemotherapy courses delivered. More of the patients in the present study had leiomyosarcomas (29% versus 18%) and liver involvement (22% versus 15%) and 33% of patients in the first study had received previous chemotherapy.

Chemotherapy

The VIG regimen at the baseline dose level consisted of etoposide 600 mg/m^2 administered as a 72 h continuous infusion in 9000 ml of 0.9% saline; ifosfamide 1500 mg/m^2 in 1000 ml 5% dextrose given as daily 2 h infusions for 3 consecutive days, with a mesna dose equalling 20% of the daily ifosfamide dose given at 0, 4 and 8 h; G-CSF (Neupogen, Roche) 5 μg/kg given subcutaneously for 12 days starting 24 h after the termination of chemotherapy. A new VIG course was started on day 21 if the total white blood cell (WBC) count was $\geq 3.0 \times 10^9$/l and the platelet

Table 3. Malignancy grading [43]

	n	(%)
Low-grade tumours	14	(15)
Grade 1	1	(1)
Grade 2	7	(8)
Alveolar	3	(3)
Clear cell	1	(1)
Unspecified low	2	(2)
High-grade tumours	78	(85)
Grade 3	27	(29)
Grade 4	37	(40)
Unspecified high	14	(15)

Table 4. Extent of disease

	n	(%)
Inoperable primary tumour	6	(7)
Local recurrence only	10	(11)
Metastatic disease	76	(83)
Lungs only	30	(33)
Liver only	12	(13)
Abdominal/retroperitoneal only	6	(7)
Soft tissue only	5	(5)
Multiple sites	23	(25)
Concurrent local disease	13	(14)

count was $\geq 100 \times 10^9$/l. If not, the course was delayed until these levels were reached.

Haemoglobin, total WBC count and platelet count were performed on days 8, 12, 15 and 19 after the start of each course. If the WBC nadir was $>1.5 \times 10^9$/l and the platelet nadir was $>70 \times 10^9$/l, the doses of both agents were increased by 10% in the next course (up to a maximum of 140% of the baseline dose). Conversely, if the WBC nadir was $<0.7 \times 10^9$/l, the platelet nadir $<50 \times 10^9$/l, or the patient had neutropenic fever (temperature >38.5°C and WBC 1.0×10^9/l) in the previous course, the doses in the next course were reduced by 20%. Blood sampling and dose modifications were identical to those of the previous study [13].

Response and toxicity evaluation

Clinical response was evaluated by CT or MRI scan according to standard WHO criteria after 3, 6 and 9 courses, and at 3 monthly intervals after the end of chemotherapy. Although only patients receiving at least two chemotherapy courses were considered evaluable for response, response was also analysed on an intention-to-treat basis. Time to progression was calculated from the start of chemotherapy. All eligibile patients who received both chemotherapeutic agents and G-CSF were considered evaluable for dose, toxicity and survival analyses.

In evaluating the relationship between tumour response and chemotherapy dose levels, only the courses given prior to response evaluation were analysed. For patients who were judged to be complete responders with total necrosis of the residual tumour at surgery, all the pre-operative courses were included in the analyis. In patients with stable disease for six courses or more, the first six courses were included in the analysis, but for earlier progression, the first three courses were included.

Surgery

In patients who were considered operable after chemotherapy, surgical resection of all residual disease was attempted. Complete surgery was defined as the removal of all identifiable lesions, with microscopically tumour-free margins.

Statistical analysis

To address the study objectives within an acceptable time frame, the aim was to enter 100 eligible patients into the study. Frequency tables of tumour response and toxicity events were analysed by the chi-square or the Fischer's exact tests, depending on sample size. Chemotherapy dose levels showed a normal frequency distribution and unless otherwise stated, comparisons of dose levels in different groups of patients were performed by two-sided *t*-tests. Survival data were analysed by the Kaplan–Meier method, utilising the log-rank test for comparisons.

RESULTS

Chemotherapy dose levels

One patient was not considered evaluable because G-CSF was not administered. In the remaining 91 patients, a total of 548 VIG courses were administered, with a median of 6 courses per patient (range 1–12). Data on dose levels were available for 526 courses (96%). The mean (±S.D.) dose for all courses was 643 mg ± 82 mg for etoposide and 4829 mg ± 650 mg for ifosfamide, equalling 107.2% ± 13.7% and 107.3% ± 14.5% of the baseline dose levels, respectively. Dose escalation was performed at least once in 70% of the patients; 48% of all courses were dose escalated, which corresponds to 58% of courses given after the initial baseline dose. Judged by the requirements for dose escalation specified in the protocol, 64% of courses from the second course onwards fulfilled these criteria and thus 91% of courses that met the criteria for dose escalation were in fact escalated. Of the escalations performed, 42% were by 10%, 32% by 20%, 21% by 30% and 5% by 40%. Dose reductions by at least 10% below baseline were performed in 11% of the courses and at least once in 29% of the patients (Table 5). Figure 1 shows that the dose levels were similar regardless of the course number in the treatment sequence, with no tendency for declining dose with prolonged treatment.

Tumour response

Of the 92 eligible patients, 86 were considered evaluable for response, 5 patients were considered not evaluable due to treatment with only one VIG course: 1 of these patients developed a generalised exanthema during the first course, 1 developed CNS toxicity, 1 had a severe infection, and 2 patients with baseline performance status WHO 2 had rapid deterioration of their general condition prohibiting further chemotherapy. One patient was considered not evaluable due to the absence of G-CSF administration.

Four patients (5%) were radiologically complete responders (CR), 31 (36%) were partial responders (PR), 29 (34%) had stable disease (SD) and 22 patients (26%) had progressive disease (PD) for an overall response rate (RR) of 41%. However, 4 patients with PR and 1 patient with

Table 5. Haematological toxicity and its consequences

	% of courses affected	% of patients affected at least once
Grade 3–4 leucopenia (nadir $<2.0 \times 10^9$/l)	28	67
Grade 4 leucopenia (nadir $<1.0 \times 10^9$/l)	8	33
Grade 3–4 thrombocytopenia (nadir $<50 \times 10^9$/l)	12	33
Grade 4 thrombocytopenia (nadir $<25 \times 10^9$/l)	2	10
Neutropenic fever	5	19
Course delay by ≥7 days	6	17
Dose reduction by ≥10%	11	29

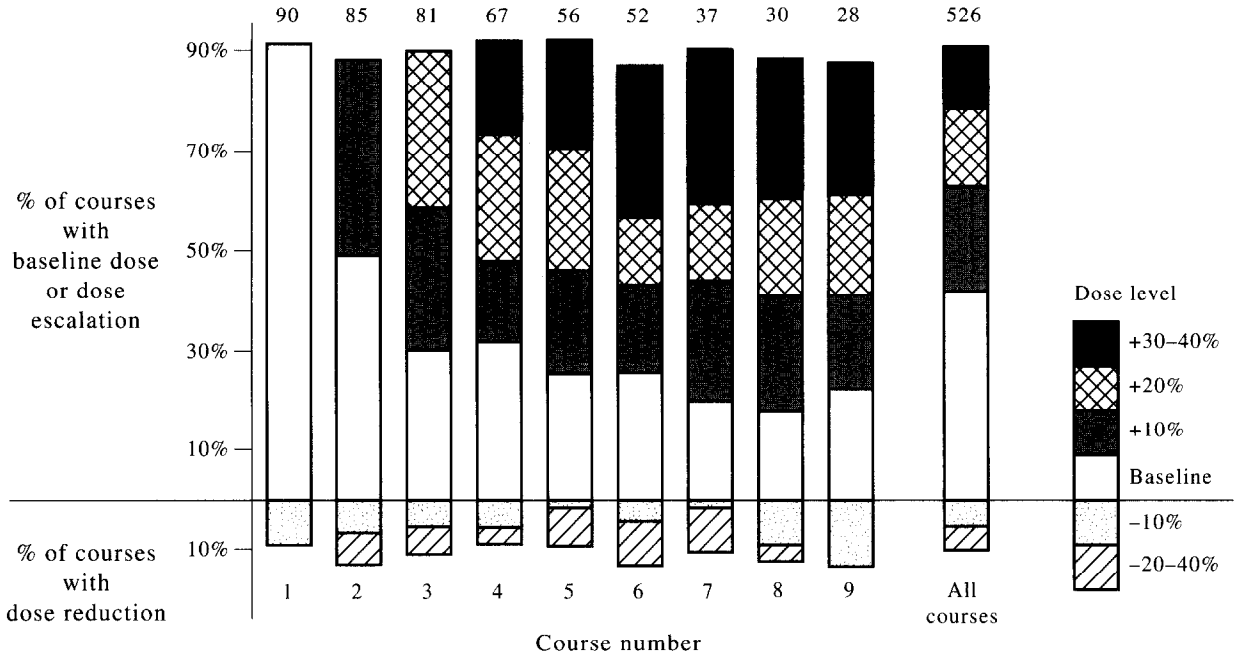

Figure 1. Chemotherapy dose levels by course number in the treatment sequence. Numbers above the bars indicate the number of courses.

SD underwent surgery and had complete necrosis of all residual tumour on histological examination. When these patients are included among the complete responders, the CR rate was 11%, the PR rate 31% and RR 42% (95% CI 31–52%). On an intention-to-treat (all 92 eligible patients), the RR was 39% (CI 29–49%). Seven out of the 36 responders (19%) had less than 50% tumour area reduction after three courses, but went on to PR (WHO criteria) after six courses. The median time to progression in the 19 responders who did not undergo surgery was 10 months (range 3–41+ months).

The response rate for lesions of high-grade malignancy was 47% (34/72), and for low-grade lesions 14% (2/14) ($P = 0.04$). Of 20 patients with liver metastases as their indicator lesions, none responded. Thus, considering only the subgroup of patients with extrahepatic, high-grade lesions, the response rate was 64% (35/55). For those with extrahepatic lesions, the response rate was 55% (36/66). No correlations were found between response rate and histological subtype.

Tumour response in relation to chemotherapy dose

Table 6 outlines clinical characteristics and mean chemotherapy dose levels in the various response categories. When patients with histological complete necrosis were included among the complete responders, CR patients had significantly higher dose levels for both etoposide and ifosfamide than all other patients considered together. CR patients also had significantly higher dose levels than both PR and PD patients when analysed separately and there was a trend in the same direction for comparison with SD patients. Conversely, PD patients had significantly lower dose levels than the rest of the patients considered together, as well as when compared with the SD and CR groups separately.

When each patient's tumour response was plotted on a four-point linear scale (corresponding to PD, SD, PR and CR) and was correlated to the patient's mean dose level prior to response evaluation, no significant overall correlation was found (Spearman coefficient 0.129, $P = 0.24$). However, patients with a mean dose level ≥110% had a sig-

Table 6. Patients' characteristics and chemotherapy dose levels in relation to response category

	CR ($n = 9$)	PR ($n = 27$)	SD ($n = 28$)	PD ($n = 22$)	Liver metastases ($n = 20$)
Median age	46	54	47	49	50
(range)	(26–56)	(15–70)	(19–67)	(27–69)	(23–67)
High-grade tumours	9	25	20	18	17
Metastatic disease	7	23	20	21	20
Etoposide dose level*	111.7†	104.0	107.9	102.1‡	110.1§
	(13.4)	(11.0)	(13.1)	(8.3)	(13.4)
Ifosfamide dose level*	112.9†	104.8	108.0	102.5‡	109.6δ
	(13.0)	(11.7)	(13.4)	(7.9)	(12.7)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. *Mean (S.D.) dose level as percentage of baseline dose for all courses given prior to response evaluation. †$P < 0.003$ for comparison with all other response categories considered together, PR patients and PD patients. ‡$P < 0.005$ for comparison with all other response categories considered together, CR patients and SD patients. §$P = 0.004$ and δP = 0.04 compared to patients without liver metastases.

nificantly lower PD frequency than patients with lower dose levels (3/32 versus 19/54, $P = 0.01$). CR frequencies for the same dose levels were 5/32 and 4/54, respectively ($P = 0.28$). No differences were found in the frequency of PR and SD.

Toxicity

Table 5 outlines the haematological toxicity and its consequences. Leucopenia was more pronounced than thrombocytopenia, with 33% of the patients experiencing grade 4 leucopenia at least once, and 19% experiencing neutropenic fever. The percentage of all courses being associated with grade 4 leucopenia or neutropenic fever was 8% and 5%, respectively. Dose reductions by ≥10% or course delays by ≥7 days were relatively rare (11% and 6% of the courses, respectively). No fatal toxicity was seen and no patient experienced renal toxicity as judged by serum creatinine levels.

The regimen was subjectively well tolerated and 26% of the courses were not associated with any reported gastrointestinal toxicity. Mild nausea or transient vomiting (WHO grades 1–2) was seen in 69% of the courses, whereas more severe vomiting complicated only 5%. Mild to moderate myalgia due to G-CSF was seen in 25% of the courses. Other forms of toxicity included mild to moderate mucositis (2 patients), skin rash (2 patients), mild polyneuropathy (1 patient) and confusion (1 patient). The patient who became confused during the first ifosfamide infusion (interpreted as CNS toxicity) was 1 of 3 patients who terminated chemotherapy after only one course due to toxicity; the other 2 developed a generalised exanthema and a severe infection.

Surgery

Following a median of 4 pre-operative VIG courses (range 2–12), complete surgery was attempted in 34 patients, and was accomplished in 26 (28% of all eligible patients). Of the successfully operated upon patients, 18 (69%) had distant metastases, 5 (19%) had retroperitoneal local recurrences and 3 (12%) had locally advanced primary tumours that were considered inoperable at diagnosis. The tumour sites are summarised in Table 7, showing that 54% of all operated patients had lung metastases (19% in combination with other metastatic sites).

Survival

No patients were lost to follow-up. The median observation time for patients who are still alive was 30 months from the start of chemotherapy (range 21–45 months). The median survival from the start of chemotherapy for all patients was 19 months (95% CI 13–28 months), with projected two- and three-year survival rates of 44% (95% CI 34–54%) and 23% (CI 13–33%), respectively. Patients who underwent surgery had significantly better survival than patients who were not operated upon (Figure 2), and for those who underwent surgery, the two-year overall and disease-free survival rates from the time of surgery was 64% (CI 45–83%) and 34% (CI 15–53%), respectively. The corresponding survival rates for 18 patients operated upon for distant metastases were 66% and 28%, respectively.

Table 7. Patients with complete surgery after pre-operative chemotherapy (numbers of patients)

Metastatic disease	
Lungs only	9
Lungs + other	5
Abdominal/retroperitoneal	2
Liver	1
Soft tissue	1
Retroperitoneal local recurrence	5
Primary tumour	
Extremity	2
Head and neck	1
Total	26

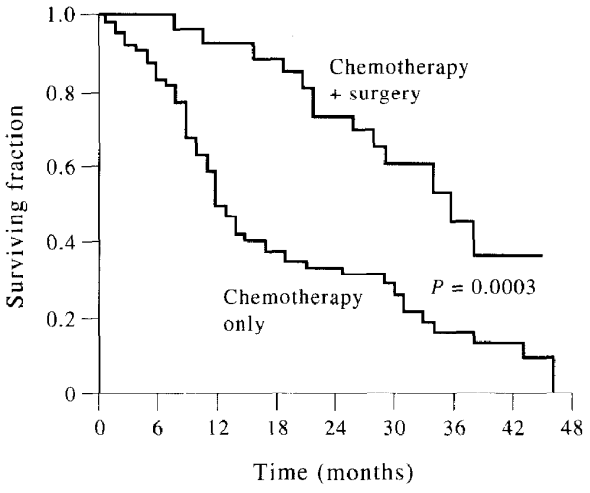

Figure 2. Overall survival from the start of chemotherapy in 26 patients treated by chemotherapy followed by complete surgery, and in 65 patients treated by chemotherapy alone (with the addition of radiotherapy to residual tumour in 2 patients).

Of the 26 patients who underwent complete surgery, 18 relapsed after a median of 8 months (range 1–30 months), and 8 are continuously disease-free after a median of 31 months (range 21–46 months) from the time of surgery. 5 of these disease-free patients had lung metastases, 1 had a retroperitoneal recurrence and 2 had inoperable primary tumours in a proximal extremity. Of the 18 patients who relapsed, 2 obtained a second complete remission following further surgery or doxorubicin-containing chemotherapy plus radiotherapy. One patient who first underwent non-radical surgery was later brought into complete remission by radiotherapy and further surgery. Another 2 patients obtained complete remissions after radiotherapy following VIG chemotherapy. Thus, a total of 13 patients are currently free of identifiable disease at a median 29 months (range 21–41 months) after the start of chemotherapy.

There was no detectable relationship between chemotherapy dose levels and survival, regardless of additional treatment with surgery.

DISCUSSION

The present study demonstrates a high overall response rate (42%) for the present etoposide/ifosfamide combination, and thus confirms the results of the preceding smaller series [13]. Although it is difficult to compare the results of different phase II studies, the present response rate is similar to that reported for the most potent ifosfamide/doxorubicin combinations [2–5]. However, there is still contro-

versy regarding whether combination chemotherapy is in fact superior to single-agent doxorubicin in adult STS. In randomised studies, response rates are commonly lower than in preceding phase II studies, as demonstrated in a recent randomised EORTC study where no difference could be found between doxorubicin alone, a doxorubicin/ifosfamide combination and CYVADIC [16].

Considering the low level of non-haematological toxicity observed in this study, the VIG regimen may be an attractive alternative to doxorubicin-containing chemotherapy. Furthermore, the previous pilot study suggested that VIG appears to be non-cross-resistant with doxorubicin-containing regimens, suggesting that it may be suitable for patients who have failed on anthracycline therapy [13].

The ifosfamide dose employed in the VIG regimen (total 4500 mg/m^2) was considerably lower than in the most active combination regimens for STS [2, 4], suggesting that the dose and mode of administration of etoposide in this study contributed to the observed antitumour effect. Results of previous studies of etoposide in adult STS have classified this agent as having low activity with response rates in the 5–15% range when administered as short-term infusions [9–12]. Others have reported higher activity, but only in combination with high doses of ifosfamide [17] or ifosfamide and hyperthermia [18]. Attempts to increase etoposide activity by prolonged oral administration have failed [19, 20], probably due to inadequate serum levels [21]. Since etoposide exerts its cytotoxic effect only in the late S and G2 phases, prolonged infusions would be expected to yield a higher antitumour effect than bolus infusions, provided the tumour cells are otherwise sensitive to the agent [15, 22–24]. Also, adult STS tumours may have a relatively low S-phase fraction at a given time point and there may be an advantage in administering a prolonged infusion to increase the probability of tumour cells cycling through their sensitive phase during drug exposure [24, 25]. The results of the present study appear to support the concept of prolonged etoposide infusion in soft tissue sarcoma.

However, the relationships between tumour growth rate, cell cycle time and drug sensitivity on the one hand and the phase specificity and effect of a cytostatic agent on the other, are complex. This is illustrated when the present results are compared to a randomised study in small cell lung cancer (SCLC) [26], where etoposide was found to have a dramatic schedule dependency, but with daily 2-h infusions for 5 days being significantly superior to a 24-h continuous infusion. Although this result appears to be in conflict with those of the present study, it may have been influenced by the considerably higher proliferation rate seen in SCLC [27]. Furthermore, it has been shown that in SCLC cells, prolonged exposure to etoposide prolongs or arrests the cell cycle at different phases depending on drug concentration [28], further complicating the relationship. The complexity of the issue is also illustrated by findings in breast cancer, where no difference was found in response rates when etoposide was given as a daily bolus injection or as a prolonged infusion. However, the patients in that study were heavily pretreated with chemotherapy, as the overall sensitivity to etoposide was low in both arms [29].

Although there is no consensus regarding prognostic factors for chemotherapy response in adult STS, some studies have found that liver metastases and tumours of low malignancy grade respond poorly [1, 30]. The present study supports these findings, with a mere 14% response rate in low-grade tumours and 0/20 patients with liver metastases responding. Thus, the overall response rate of 42% was seen despite 22% of evaluable patients having liver metastases, yielding a 55% (36/66) response rate for extrahepatic lesions. Thirteen of the 20 patients with liver metastases had leiomyosarcomas, but the lack of response appears to be related to liver localisation rather than to histology, as 8/12 leiomyosarcomas situated outside the liver responded. It should also be noted that patients with liver metastases had significantly higher chemotherapy dose levels than the other patients (Table 6), excluding low dose as an explanation for poor response.

In general, comparison of results in successive phase II studies should be interpreted with caution. This also applies to the present comparison with the preceding pilot study [13], where the addition of G-CSF significantly reduced haematological toxicity, allowed dose escalation and improved schedule adherence (Figure 3). These findings are nevertheless in accordance with previous results on the effect of growth factor addition to the doxorubicin, ifosfamide and dacarbazine (MAID) and doxorubicin/ifosfamide regimens in adult STS [5, 31]. However, despite the dose intensification in the present study, no increase was seen in the overall response rate (Figure 3). CR patients had significantly higher doses than the other response categories and PD patients had significantly lower dose rates than the rest. Although this may give some support to the existence of a dose–response relationship, the data should be interpreted with caution. The study was not designed to adequately address this issue; there was no general correlation between response and dose level and patients obtaining CR may have received higher dose levels on the basis of improved tolerance.

The study supports the concept that surgical removal of metastatic disease may prolong survival and that some patients may be cured by metastasectomy [32–35]. In other

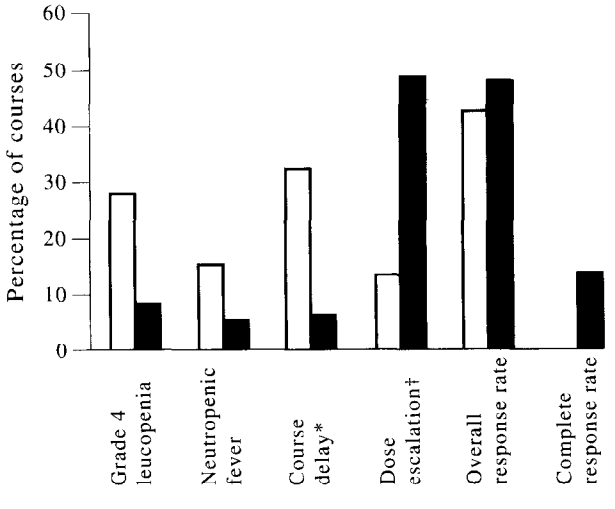

Figure 3. Toxicity, dose levels and response for the present study compared to the preceding pilot study (28 patients treated without G-CSF supplement) [13]. As the pilot study only included high-grade STS, response rates are shown for high-grade lesions only. □, chemotherapy without G-CSF supplement [13]; ■, chemotherapy with G-CSF (present study). *Course delay by 7 days or more. †Dose escalation by 10% or more.

studies on advanced STS, median survival from the start of chemotherapy was usually in the 8–12 months range [36–38]. In the present study, this corresponds well with the group of patients that did not undergo surgery (median survival 12 months, 95% CI 11–15 months). The group treated with surgery in addition to chemotherapy had significantly superior survival (median 36 months, CI 28–45 months, Figure 2), increasing the median survival of the entire study population to 19 months (CI 13–28 months). To what extent the surgical treatment in itself, or merely the process of patient selection for surgery, contributed to this improved outcome remains unclear. The comparison of survival between different studies in advanced adult STS is difficult, as patient selection criteria and treatment strategies vary widely. For example, most other reports on metastasectomised patients are limited to patients with lung metastases, whereas in the present series 9/18 patients who were operated upon had extrapulmonary metastases and 5/18 had metastases to multiple sites (Table 7). These features would normally be regarded as adverse for outcome. Whether chemotherapy contributes to survival in patients with resectable metastases remains to be determined [39–41]. It should be remembered that a few patients with metastatic STS who accomplish complete response on chemotherapy may become long-term survivors without further treatment [2, 42], implying that chemotherapy can eradicate both macroscopic and residual microscopic disease. This question can only be adequately addressed in prospective trials randomising patients to metastasectomy with or without supplemental chemotherapy.

We conclude that the SSG 10/91 trial confirms a high level of activity for the VIG regimen in adult STS. An escalated dose of etoposide administered as a prolonged infusion may increase this agent's activity against STS, taking advantage of phase specificity. Etoposide thus appears to be an underrated agent in adult STS, and previous poor results may be due to suboptimal dose levels and suboptimal modes of administration. The VIG regimen is well tolerated, and the addition of G-CSF appears to reduce haematological toxicity and the incidence of neutropenic fever, to allow dose escalation and to improve schedule adherence.

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