Original article

Annals of Oncology 13: 161–166, 2002
DOI: 10.1093/annonc/mdf004

Phase I study of twelve-day prolonged infusion of high-dose ifosfamide and doxorubicin as first-line chemotherapy in adult patients with advanced soft tissue sarcomas

T. De Pas[1]*, G. Curigliano[1], G. Masci[1], C. Catania[1], A. Comandone[2], C. Boni[3], A. Tucci[4], O. Pagani[5], E. Marrocco[1] & F. de Braud[1] on behalf of the Italian Sarcoma Group

[1]Division of Medical Oncology, European Institute of Oncology, Via Ripamonti 435, 20141 Milan; [2]Division of Medical Oncology, Hospital Gradenigo, Torino; [3]Medical Oncology Service, Arcispedale S. Maria Nuova, Reggio Emilia; [4]Medical Oncology, Hospital Cardarelli, Napoli, Italy; [5]Oncology Institute of Southern Switzerland, Bellinzona and Mendrisio, Switzerland

Received 14 March 2001; revised 3 August 2001; accepted 17 August 2001

Purpose: To determine whether a prolonged 12-day continuous infusion allows the administration of high-dose ifosfamide (IFO) with an acceptable toxicity profile when combined with full-dose doxorubicin (Adriamycin®; ADM) as first-line chemotherapy in patients with advanced soft tissue sarcomas.

Patients and methods: Escalating doses of continuous infusion IFO (8–15 g/m^2) given on days 1 to 12 in combination with ADM 75 mg/m^2 given on day 8 and prophylactic granulocyte colony-stimulating factor support were administered every 4 weeks to 35 chemonaïve patients with advanced soft tissue sarcomas.

Results: The maximum tolerated dose was IFO 15 g/m^2. Hematological toxicity was the main dose-limiting toxicity and was dose dependent. Furthermore, thrombocytopenia was cumulative. Grade 4 (WHO) neutropenia and thrombocytopenia were recorded in 48% and 14% of courses, respectively. Eight patients experienced febrile neutropenia. A partial response was observed in 16 out of 30 assessable patients [53%, 95% confidence interval (CI) 25–63]; median time to progression was 25 weeks (range 4–91).

Conclusions: This study proved that a prolonged 12-day continuous infusion allows an increase in the total IFO dose that can be safely combined with ADM. A multicentric phase II study by the Italian Sarcoma Group to assess its antitumor activity is currently ongoing in patients with advanced soft tissue sarcomas.

Key words: chemotherapy, continuous infusion, high dose, ifosfamide, soft tissue sarcomas

Introduction

The outcome of advanced, inoperable soft tissue sarcomas is still disappointing and minimal impact on overall survival is obtained by systemic chemotherapy.

Ifosfamide (IFO) and doxorubicin (Adriamycin®; ADM) are the most active agents, the response rate reported by several studies being 15% to 35% with single-agent ADM and 18% to 20% with standard dose IFO (5 g/m^2), with a confirmed dose–response relationship for both drugs [1–3].

Non-randomized studies testing the combination of high-dose IFO (>9 g/m^2) and anthracycline have been performed in soft tissue sarcomas, with overall response rates of 50% to 67% [4–7]. However, most of these trials were complicated by serious clinical and hematological toxicity, undermining the real benefit of these treatments.

In our previous study we found IFO 12.5 g/m^2 as a 120-h continuous infusion combined with ADM 60 mg/m^2/q3 weeks to be very effective as first-line chemotherapy in patients with soft tissue sarcomas [5]. Nevertheless, the severe toxicity observed led us to develop a new schedule, further prolonging the continuous infusion of IFO as a possible method of reducing side effects [5] while maintaining dose intensity. This approach was based on pharmacological data and early clinical trials showing that a prolonged infusion of IFO can significantly reduce treatment-related side effects [8]. Moreover, although the fractionated administration of IFO has been shown to be more effective than a single dose [8], because of the saturable mechanism of activation of the drug, at present no standard way to administer IFO has been generally

**Correspondence to:* Via Ripamonti 435, 20141 Milan, Italy.
Tel: +39-02-57489460; Fax: +39-02-57489457;
E-mail: tommaso.de-pas@ieo.it

approved, and phase III trials comparing continuous infusion to fractionated bolus of a similar dose of IFO have not been conducted.

Preliminary data on a prolonged infusion of IFO at a dose of 1 g/m^2 daily are available by the Italian Group on Rare Tumors. This new schedule showed a favorable toxicity profile, with a median of 15 treatment days, the absence of granulocyte colony-stimulating factor (G-CSF) support notwithstanding, and a reported 24% response rate, with responses observed also in the subgroup of highly IFO-pre-treated patients [9].

In the present study we evaluated the toxicity and antitumor activity of escalating IFO doses as a 12-day continuous infusion in combination with full-dose ADM and G-CSF support, given every 4 weeks as first-line chemotherapy in advanced soft tissue sarcoma patients.

Patients and methods

Eligibility criteria

Patients with histologically proven intermediate- to high-grade metastatic or locally advanced soft tissue sarcomas, previously untreated with chemotherapy were eligible for this study. Patients with lung metastases suitable for pre-operative chemotherapy were also included in the study. Additional eligibility criteria were: adequate bone marrow (absolute neutrophil count $>1.5 \times 10^9$/l and platelet count $>100 \times 10^9$/l); hepatic (AST, ALT <2 times upper normal limits and total bilirubin <1.25 times upper normal limits) and renal (serum creatinine <1.25 times upper normal limits and/or creatinine clearance ≥60 ml/min) functions; age between 18 and 65 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; life expectancy >3 months; and written informed consent.

Exclusion criteria were: prior radiotherapy to more than 30% of bone marrow reserve; symptomatic cardiac disease; left ventricular ejection fraction <50% (US-cardiogram); previous or concurrent other malignancies; uncontrolled infections. The protocol was approved by the local ethics committees.

Pre-treatment evaluation

Pre-treatment evaluation included: complete medical history and physical examination; complete blood cell count; a full chemistry profile; electrocardiogram (ECG) and US-cardiogram; chest X-ray and computed tomography (CT) scan; abdomen CT scan.

Treatment schedule, toxicity and response evaluation

The dose-escalation schedule is listed in Table 2. IFO was administered intraveneously (i.v.) on an out-patient basis via a portable pump as a 24-h continuous infusion for 12 consecutive days (days 1–12), every 28 days, together with equal mesna dose. IFO and Mesna were diluted in a cassette containing IFO/mesna and this device was changed on day 8. ADM was administered as an i.v. bolus injection after prophylactic antiemetic premedication (dexamethasone 8 mg i.v. and granisetron 3 mg i.v.) on day 8. No prophylactic antiemetic therapy was planned during IFO administration. A daily oral hydration with at least 1500 ml of liquids was recommended. During treatment, a complete blood cell count on days 1, 8, 10 and 12 and biweekly thereafter, serum creatinine on day 8 and a complete chemistry profile on the first day of each cycle were performed. G-CSF (300 μg) was routinely administered on days 14–18 and continued until white blood cell count reached 10.0×10^9/l.

Patients with measurable disease treated for at least two cycles and patients progressing at any moment after starting the treatment were considered evaluable for response. All patients with measurable disease underwent complete tumor-response assessment every two cycles. A maximum of six cycles was planned, according to the physician's discretion and patient's request, in both responders and in patients with stable disease. WHO criteria for toxicity and response were used [10]. Response duration was defined as the time from the start of treatment to the date on which progressive disease was first noted.

Treatment was repeated on day 28 if absolute neutrophil count and platelets were $>1.5 \times 10^9$/l and $>100 \times 10^9$/l, respectively, and in the absence of non-hematological toxicity grade >1. Otherwise, treatment cycles were delayed for a maximum of 1 week and then definitively stopped if these conditions were still not satisfied on day 35, and toxicity considered to be dose limiting. ADM was administered on day 8 in order to prevent myelosuppression and only if absolute neutrophil count and platelets were $>1.5 \times 10^9$/l and $>75 \times 10^9$/l, respectively, with non-hematological toxicity grade <2 (excluding nausea/vomiting and alopecia). Otherwise, treatment was discontinued and toxicity considered to be dose limiting. IFO infusion was discontinued until the beginning of the subsequent cycle in case of grade 3/4 neutropenia or thrombocytopenia. If this toxicity occurred before ADM administration, treatment was permanently discontinued and toxicity considered to be dose limiting.

Once dose-limiting toxicity (DLT) occurred, no dose-reduction criteria were provided, but a 25% reduction of IFO dose was recommended.

Dose-finding procedures and DLT

At each dose level a minimum of three patients were entered. Accrual at any given level was increased to six patients if DLT occurred during one of the first two cycles. Maximum tolerated dose (MTD) was defined as the dose level at which DLT occurred in two out of three or in ≥3 out of six patients during one of the first two cycles. Toxicity was considered dose limiting when one or more of the following occurred: ANC $<0.5 \times 10^9$/l lasting >7 days; febrile neutropenia (fever ≥38.5°C with grade 4 neutropenia or febrile grade 3 neutropenia requiring i.v. antibiotics or hospitalization); platelets $<25 \times 10^9$/l; mucositis grade >2; anthracycline-related cardiac toxicity (congestive heart failure, left ventricular ejection fraction absolute reduction >10% associated to values of <50% confirmed 3–5 days later, ischemic cardiopathy or clinically relevant rhythm alterations); ADM administration withheld because of toxicity; treatment delay of >1 week on day 28.

Dose intensity

Dose intensity (mg/m^2/week) is calculated by the following formula: total milligrams of drug per body surface area/total days of therapy/7, where total days is the number of days between day 1 of the first cycle and day 28 of the last cycle.

Results

Patient characteristics

Between August 1997 and September 1999, 35 consecutive patients from four institutions were enrolled in this study

(Table 1). Median age was 55 years (range 21–68); six patients had received prior radiotherapy for primary tumor and two patients for metastatic disease.

Table 1. Patients' characteristics (n = 35)

	No. of patients
Age	
Median	55 (years)
Range	21–68 (years)
Sex	
Male	13
Female	22
ECOG performance status	
0/1	30/5
Histology	
Leiomyosarcoma	11
Liposarcoma	4
Histiocytoma	2
Hemangioendothelioma	2
Chondrosarcoma	2
Primary pleural fibrous malignant tumor	2
Unclassified sarcomas	7
Rhabdomyosarcoma[a]	1
Renal carcinoma[a]	1
Others	3
Status	
First diagnosis	14
Relapse	21
Site of target lesions	
Primary	7
Local relapse	7
Lung	15
Liver	10
Bone	3
Other	14
Grading	
1	5
2	7
3	13
NA	10
Site of primary	
Extremities and girdles	5
Retroperitoneal	6
Gastrointestinal	3
Uterus	4
Thoracic wall	4
Other	12

[a]Assessable for toxicity.

Dose levels and toxicity

IFO doses were escalated from 8 to 15 g/m^2/12 days, in combination with ADM 75 mg/m^2, through six dose levels. Once the MTD was defined at level 6 (IFO 15 g/m^2/12 days), the accrual of patients treated at level 5 (IFO 13 g/m^2/12 days) was expanded up to a total of 10 patients.

Thirty-four patients were assessable for toxicity, as treatment was discontinued before the second cycle in one patient, due to refusal. A total of 107 treatment cycles were administered: 105 and 103 were evaluable for hematological and non-hematological toxicity, respectively. Patients received a median of three cycles (range 1–6).

DLT and hematological toxicity

The MTD was reached at the 6th dose level (IFO 15 g/m^2/12 days) as five out of six patients experienced DLT. Overall, a total of nine DLTs, all but one hematological, were registered, eight occurring at the three highest dose levels (Table 2). No correlation between hematological toxicity and prior radiotherapy was observed.

Neutropenia occurred at all dose levels, appeared to be dose dependent, but not cumulative, grade 3/4 occurring in 71% of first cycles and in 48% of all cycles, respectively. Eight patients experienced febrile neutropenia, seven of them as DLT (grade 3 febrile neutropenia lasting 1 day not requiring i.v. antibiotics or hospitalization in one patient).

Thrombocytopenia was dose dependent, grade 4 occurring only at the three highest levels, and cumulative as well, grade 4 occurring in 6% of first cycles and in 14% of all cycles, respectively.

Grade 4 neutropenia and thrombocytopenia occurred in 23 and three patients, respectively, with a median time of occurrence on day 18 (range 11–21 and 17–21, respectively) and with a median length of 3 (range 2–11) and 7 (range 4–10) days, respectively; the median nadir values were: absolute neutorophil count 0.24 (range 0.03–0.48) $\times$ 10^9/l and platelet count 17 (range 9–19) $\times$ 10^9/l.

Three patients treated at the three highest levels required blood transfusions after the first or second treatment cycle.

Non-hematological toxicity

Non-hematological toxicity, including mucositis, was mild to moderate, non-cumulative and not clearly dose dependent, except for nausea/vomiting that required treatment discontinuation (one patient) and dose modification (one patient) at levels 5 and 6, respectively.

No patient suffered CNS toxicity. No patient developed urinary tract toxicity, namely hemorrhagic cystitis, or nephrotoxicity: one grade 4 episode of fatigue was registered.

Dose intensity

Taking into account dose reductions for each drug as well as any delay in drug administration, the actual delivered dose

Table 2. Dose-limiting toxicity at first/second cycles and reason for treatment delay or dose modification over all 105 cycles

Dose level	IFO g/m^2/12 days	No. of patients	Dose limiting toxicity (no. of patients)	Reason of delay or modification (no. of patients) all cycles
1	8	6	Leucopenia requiring treatment delay >1 week (1)	Leuconeutropenia (1)
2	9	3	–	–
3	10	4	–	Grade 3 anemia (1)
4	12	6	Grade 4 febrile neutropenia + grade 4 thrombocytopenia (1)	Grade 4 febrile neutropenia (1)
			Grade 4 febrile neutropenia (1)	
5	13	10[a]	Grade 4 febrile neutropenia + grade 4 thrombocytopenia (1)	Grade 3 nausea/vomiting (1)
6	15	6	Grade 4 febrile neutropenia (3)	
			Grade 4 febrile neutropenia + grade 4 thrombocytopenia (1)	
			Grade 4 vomiting + grade 4 fatigue (1)	

[a]Nine patients evaluable for MTD: one patient refusal during 2nd cycle.

intensities of both IFO and ADM calculated according to the start dose were >93% of the intended dose intensity, at all dose levels. Namely it was 97% for both IFO and ADM at dose level 5.

Antitumor activity

Thirty patients were evaluable for response, while reasons for non-evaluability were: required treatment interruption for toxicity after the first cycle without evidence of progression (two patients); non-measurable disease (one patient); and inelegibility due to wrong histological diagnosis in two patients (one rhabdomiosarcoma and one renal cell carcinoma). Responses were seen at all dose levels, with no clear evidence of a dose–response relationship. Objective responses were observed in 16 patients [RR: 53%; 95% confidence interval (CI) 25% to 63%], including three complete responses; eight patients had stable disease and six patients had disease progression. The analysis of response by site and histology also showed major tumor responses among the traditionally chemoresistant subgroup of patients, with a response rate of 30% and 27% in liver metastases and in patients with leiomyosarcoma, respectively.

Median time to progression was 25 weeks (range 4–91). Responses were observed after a median of two cycles (range 2–4), with responders receiving a median of three cycles (range 2–6). Median response duration was 27 weeks (range 12–90).

Discussion

We performed a dose-finding study to define MTD of IFO given as a 12-day continuous infusion when combined with a fixed dose of ADM 75 mg/m^2 given as a single i.v. bolus injection on day 8, with prophylactic G-CSF every 4 weeks. Six dose levels were evaluated, with IFO dose escalating from 8 to 15 g/m^2/12 days.

At IFO 15 g/m^2/12 days, five out of six patients experienced DLT. One dose below MTD (IFO 13 g/m^2/12 days and ADM 75 mg/m^2) was associated with an acceptable toxicity. Since clinical responses were also observed at this dose level, this is recommended for further clinical evaluation.

Despite prophylactic use of G-CSF, myelosuppression was the main DLT. Hematological toxicity was dose dependent and thrombocytopenia was dose dependant and cumulative. No infection-related complications were observed.

Major responses were observed at all dose levels (overall response rate 53%, 95% CI 25–63%) and median time to progression was 25 weeks (range 4–91).

The number of patients at the respective dose levels was too small to allow any conclusion on a dose–response relationship.

Our results support the hypothesis that the administration of high-dose IFO by a 12-day continuous infusion could overcome the very high toxicity associated with a shorter infusion of similar doses of IFO combined with anthracyclines.

Due to severe thrombocytopenia and mucositis, the MTD of a 3-week schedule by the Swiss Group for Clinical Research (SAKK) [11] was reached at IFO 12 g/m^2 given as a 5-day continuous infusion combined with ADM 60 mg/m^2. The Spanish Group for Research on Sarcomas (GEIS) found IFO 10–12 g/m^2 given as a 5-day continuous infusion combined with ADM 50 mg/m^2 to be limited by severe hematological, cardiological and neurological toxicity [12]. Moreover, grade 3/4 thrombocytopenia was registered in half of the patients treated with standard-dose IFO (5 g/m^2) given as 24-h continuous infusion in combination with ADM 75 mg/m^2/q3 weeks in a European Organisation for Research and Treatment of Cancer (EORTC) phase III study [13].

Reichardt found a 3-week schedule with IFO 12.5 g/m^2, given as a 5-day continuous infusion combined with epirubicin 90 mg/m^2, given as a 48-h continuous infusion to be burdened by severe hematological toxicity in 46 patients with advanced soft tissue sarcomas; 83% and 35% of patients

Table 3. High-dose (≥9 g/m^2) IFO combined with anthracyclines in patients with advanced soft tissue sarcomas: dose-escalation studies

Author	Dose escalation[a]	Schedule[a]	MTD[a]	Comments
Bokemeyer [6]	IFO: 8–16	IFO: 96 h (ci)	IFO: 16	PBSC support
	ADM: 75	ADM: d 1(b)	ADM: 60	Nephrotoxicity was dose limiting
		q3 weeks		
Leyvraz [11]	IFO: 10–12	IFO: 120 h (ci)	IFO: 12	IFO 10 + ADM 90 was not MTD
	ADM: 50–90	ADM: dd 1,2 (b)	ADM: 60	
		q3 weeks		
Frustaci [18]	IFO: 9–10,5	IFO: 86 h (ci)	IFO: 10,5	
	EpiADM: 120	EpiADM: dd 1,2 (b)	EpiADM: 120	
		q3 weeks		
Frustaci [19]	IFO: 9	IFO: 120 h (ci)	IFO: 10	
	EpiADM: 100–140	EpiADM: dd 1,2 (b)	EpiADM: 140	
		q3 weeks		
Current study	IFO: 8–15	IFO: 12 days (ci)	IFO: 15	
	ADM: 75	ADM: d 8 (b)	ADM: 75	
		q4 weeks		

[a]Prophylactic G-CSF was given in all studies.
IFO, ifosfamide (g/m^2); ADM, doxorubicin (mg/m^2); EpiADM, epirubicin (mg/m^2); ci, continuous infusion; b, bolus; PBSC, peripheral blood stem cells; q3 weeks, administered once a day on days 1 to 3, repeated every 3 weeks.

suffering from grade 4 neutropenia and grade 4 thrombocytopenia, respectively [14].

The results of high-dose IFO plus anthracyclines dose-escalation studies are reported in Table 3.

The present study compares favorably in terms of toxicity with our previous experience [5]. In that study only 74% of the 23 patients treated with IFO 12.5 g/m^2 as a 120-h continuous infusion combined with ADM 60 mg/m^2/q3 weeks were able to complete the planned treatment.

While treating with IFO at the dose-intensity level recommended for future phase II studies (3.25 g/m^2/week), obtained by giving a higher total dose of IFO each cycle than that currently used in clinical practice, we hypothesize that the total dose of IFO represents by itself an essential feature for treating soft tissue sarcomas, as indicated by several studies showing an IFO total dose–response relationship. Moreover, there is evidence that high doses of IFO, even if administered continuously over several days, also obtain an antitumor effect in patients unresponsive to standard dose IFO-containing regimens [15–17].

A 12-day continuous infusion allows an increase of the total IFO dose that can be safely combined with ADM. The combination of ADM 75 mg/m^2 with IFO 13 g/m^2/12 days is feasible and effective for patients with soft tissue sarcomas. Further investigation is warranted, and a multicentric phase II study by the Italian Sarcoma Group (ISG) to confirm its antitumor activity is currently ongoing.

References

1. Borden EC, Amato DA, Rosenbaum C et al. Randomized comparison of three adriamycin regimens for treatment of metastatic soft tissue sarcomas. J Clin Oncol 1987; 5: 840–850.
2. Antman KH, Ryan K, Elias A et al. Response to ifosfamide and mesna in 124 previously treated patients with metastatic or unresectable sarcoma. J Clin Oncol 1989; 7: 126–131.
3. Tursz T. High dose ifosfamide in the treatment of advanced soft tissue sarcomas. Semin Oncol 1996; 23 (Suppl 7): 34–39.
4. Reichardt P, Tilgner J, Hohenberger P, Dorken B. Dose-intensive chemotherapy with ifosfamide, epirubicin, and filgrastim for adult patients with metastatic or locally advanced soft tissue sarcoma: a phase II study. J Clin Oncol 1998; 16: 1438–1443.
5. De Pas T, 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.
6. Bokemeyer C, Franzke A, Hartmann J et al. A phase I/II study of sequential, dose-escalated, high dose ifosfamide plus doxorubicin peripheral blood stem cell support for the treatment of patients with advanced soft tissue sarcomas. Cancer 1997; 80: 1221–1227.
7. De Pas T. Comments on: Should patients with advanced soft tissue sarcomas be treated with chemotherapy? Eur J Cancer 1999; 35: 327.
8. De Pas T, Curigliano G, Catania C et al. Ifosfamide in the elderly: clinical consideration for a better drug management. Crit Rev Oncol Hematol 2000; 33: 129–135.
9. Frustaci S, Comandone A, Bearz A et al. Efficacy and tolerability of an ifosfamide continuous infusion in soft tissue sarcomas patients. Proc Am Soc Clin Oncol 1993; (Abstr 1998).
10. Beacon HJ, Thompson SG. Multi-level models for repeated measurement data: application to quality of life data in clinical trials. Stat Med 1996; 15: 2717–2732.

11. Leyvraz S, Bacchi M, Cerny T et al. for the Swiss Group for Clinical Research (SAKK). Phase I multicenter study of combined high-dose ifosfamide and doxorubicin in the treatment of advanced sarcomas. Ann Oncol 1998; 9: 877–884.
12. Buesa JM, Lopez-Pousa A, Martin J et al. Phase II trial of first-line high-dose ifosfamide in advanced soft tissue sarcomas of the adult: a study of the Spanish Group for Research on Sarcomas (GEIS). Ann Oncol 1998; 9: 871–876.
13. Le Cesne A, Judson I, Crowther D et al. Randomised phase III study comparing conventional-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol 2000; 14: 2676–2684.
14. Reichard P, Tilgner J, Hohenberger P, Dorken B. Dose-intensive chemotherapy with ifosfamide, epirubicin, and filgrastim for adult patients with metastatic or locally advanced soft tissue sarcoma: a phase II study. J Clin Oncol 1998; 16: 1438–1443.
15. Elias AD, Eder JP, Shea T et al. High dose ifosfamide with mesna uroprotection: a phase I study. J Clin Oncol 1990; 8: 170–178.
16. Le Cesne A, Antoine E, Spielmann M 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. Benjamin RS, Legha SS, Patel SR, Nicaise C. Single agent ifosfamide studies in sarcomas of soft tissue and bone: the MD Anderson experience. Cancer Chemother Pharmacol 1993; 31 (Suppl 2): S174.
18. Frustaci S, Buonadonna A, Romanini A et al. Increasing dose of continuous infusion ifosfamide and fixed dose of bolus epirubicin in soft tissue sarcomas. A study of the Italian Group on Rare Tumors. Tumori 1999; 85: 229–233.
19. Frustaci S, Buonadonna A, Galligioni E et al. Increasing 4′-epidoxorubicin and fixed ifosfamide doses plus granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a pilot study. J Clin Oncol 1997; 15: 1418–1426.