Granulocyte-Macrophage Colony-Stimulating Factor Allows Safe Escalation of Dose-Intensity of Chemotherapy in Metastatic Adult Soft Tissue Sarcomas: A Study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

By W.P. Steward, J. Verweij, R. Somers, D. Spooner, P. Kerbrat, M. Clavel, D. Crowther, J. Rouesse, T. Tursz, E. Tueni, A.T. Van Oosterom, J. Warwick, B. Greifenberg, D. Thomas, and M. vanGlabbeke

Purpose: This study was designed to test the feasibility of administering doxorubicin at an optimal dose-intensity (> 70 mg/m² per 21 days) in combination with ifosfamide under recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) cover in patients with metastatic soft tissue sarcomas.

Patients and Methods: One hundred four eligible patients (of 111 entered) in 16 centers received doxorubicin 75 mg/m² plus ifosfamide 5 g/m² every 3 weeks for up to seven cycles. rhGM-CSF (250 μg/m²) was administered once or twice daily by subcutaneous injections for up to 14 days between cycles of chemotherapy.

Results: Full protocol dose-intensity of chemotherapy was administered to the majority of patients with only 15 of 293 cycles being complicated by febrile episodes that required hospitalization. There were two treatment-related deaths: one from septicemia and one from cardiac failure. The main toxicities attributed to rhGM-CSF were pruritus and rash. A 45% response rate (10% complete remission [CR]) was seen, with a median response duration of 9 months and median survival of 15 months.

Conclusion: This high-dose regimen of chemotherapy was feasible under rhGM-CSF cover and produced a higher response rate and median survival than previously seen by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue Sarcoma Group. A randomized phase III study is now underway comparing this regimen with conventional-dose doxorubicin/ifosfamide to test the dose-response relationship.

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ADULT SOFT TISSUE SARCOMAS have an incidence similar to that of Hodgkin's disease, but result in approximately twice as many deaths per year.[1] The use of radical surgery (often with radiotherapy) at an early stage can be curative in up to 60% of patients. Unfortunately, many patients are diagnosed late or receive inadequate primary surgery such that metastases ultimately occur. Although salvage treatment by excision of the metastases is successful for some patients, the majority will die from progressive disease.

The use of chemotherapy in this situation has been extensively investigated. Only two drugs—doxorubicin (Adriamycin; Adria Laboratories, Columbus, OH) and ifosfamide—have consistently shown single-agent activity in more than 20% of patients who did not receive pretreatment, although results from different series vary widely.[2-4] Such variation is probably due to the heterogeneity of the patient populations treated and the different doses and schedules of administration of chemotherapy. There is increasing evidence of a strong dose-response relationship for doxorubicin in soft tissue sarcomas; the first study to demonstrate this also showed a correlation between dose and survival.[5] To obtain optimal response rates to doxorubicin, it appears to be critical to achieve a dose-intensity of at least 70 mg/m² every 3 weeks. A series of phase I/II studies with ifosfamide from the Dana-Farber Cancer Institute in Boston, MA have shown that this agent also has different activity in soft tissue sarcomas depending on the schedule of administration, with short, daily bolus injections producing higher numbers of responses than continuous 4-day infusions.[6]

In an attempt to improve results of treatment of advanced soft tissue sarcomas, combination chemotherapy is usually administered. The regimen developed in Boston includes ifosfamide (7.5 g/m²), doxorubicin (60 mg/m²), and dacarbazine [5-(dimethyltriazeno)imidazole-4-carboxamide] (MAID) and resulted in a response rate of 49% with 10% complete remissions (CRs).[6,7] This high response

From the Beatson Oncology Centre, Western Infirmary, Glasgow, United Kingdom; Rotterdam Cancer Institute, Rotterdam; Antoni van Leeuwenhoekhuis, Amsterdam, the Netherlands; Queen Elizabeth Hospital, Birmingham, United Kingdom; Centre Eugene, Marquis, Rennes, France; Centre Leon Berard, Lyon, France; Christie Hospital, Manchester, United Kingdom; Centre Rene Huguenin, Saint-Cloud, France; Institute Gustave Roussy, Paris, France; Institute Jules Bordet, Brussels, Belgium; University Hospital, Antwerp, Belgium; Behringwerke, Marburg, Germany; and the European Organization for Research and Treatment of Cancer Data Centre, Brussels, Belgium.

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Address reprint requests to W.P. Steward, MD, Beatson Oncology Centre, Western Infirmary, Glasgow G11 6NT, United Kingdom.

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rate fell to 32% (2% CR) when MAID was compared with doxorubicin and dacarbazine in the American Intergroup study.[8] The European Organization for Research and Treatment of Cancer (EORTC) combined ifosfamide (5 g/m^2) and doxorubicin (50 mg/m^2) as first-line treatment in 175 assessable patients and reported objective responses in 35% (9% CR).[9] A subsequent EORTC three-arm, prospective, randomized study compared this combination with the results of single-agent doxorubicin (75 mg/m^2) and the widely used four-drug combination of cyclophosphamide, vincristine, doxorubicin, and dacarbazine (CyVADIC). An interim analysis of the first 549 patients showed no significant difference in terms of response for any of the options, although toxicity was more severe for CyVADIC,[10] which resulted in early discontinuation of this arm.

It is difficult to interpret the results of this EORTC phase III study, because different doses of doxorubicin were used in the three arms. If the final analysis fails to demonstrate superiority for the combination regimens over single-agent doxorubicin, the reason could be that the former included lower doses of anthracycline. From the extensive experience of our own group and that of others with the combination of ifosfamide and doxorubicin, it was felt that, with conventional supportive measures, escalation of doxorubicin to optimal doses (> 70 mg/m^2) in combination with ifosfamide would not be possible because of the degree of myelosuppression that would occur. The current study was therefore established to determine whether the use of the hematopoietic growth factor, recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF), would allow the safe administration of doxorubicin 75 mg/m^2 with ifosfamide 5 g/m^2 and thereby, if such a regimen was feasible, allow the group to test subsequently whether it would result in a greater response rate in this disease.

PATIENTS AND METHODS

Criteria for Eligibility

Patients were entered onto this study if they had a histologically proven diagnosis of soft tissue sarcoma (excluding Ewing's sarcoma and embryonal rhabdomyosarcoma) and had documented progressive metastatic disease. Entry criteria included the presence of measurable lesions, age limits of 18 to 75 years, and a World Health Organization (WHO) performance status of 0, 1, or 2. No prior chemotherapy should have been given (previous radiotherapy to lesions other than those used to measure response was acceptable). All patients were required to have adequate renal (serum creatinine < 150 μmol/L) and hepatic excretory function (serum bilirubin < 25 μmol/L), and normal bone marrow reserve (leukocytes > 4 × 10^9/L, platelets > 125 × 10^9/L). All patients gave informed consent.

Therapeutic Regimen

Chemotherapy with doxorubicin 75 mg/m^2 was administered as an intravenous push injection followed immediately by ifosfamide administered as a 24-hour infusion at a dose of 5 g/m^2. No dose reductions for prior toxicity were planned in this protocol. Before treatment, a diuresis was established using 1 L of dextrose/saline administered over 2 hours with 200 mL of 20% mannitol infused over 30 minutes. Mesna (2-mercaptoethane sodium sulfonate [600 mg/m^2]) was administered as an intravenous bolus immediately preceding the continuous infusion of ifosfamide. The total dose of ifosfamide was diluted in 3 L of dextrose/saline with 2.5 g/m^2 of mesna. At the end of the ifosfamide infusion, a further 2 L of dextrose/saline containing 1.25 g/m^2 of mesna was infused over 12 hours. *Escherichia coli*–derived rhGM-CSF (Behringwerke, Marburg, Germany) was commenced 24 hours after the end of the ifosfamide infusion at a total daily dose of 250 μg/m^2. The first 52 patients received this as a once-daily subcutaneous injection and the second 59 as every-12-hour divided doses. This was administered for up to 14 days, but was discontinued before then if, after the leukocyte nadir had occurred, the neutrophil count was greater than 10 × 10^9/L. Chemotherapy was repeated at 3-week intervals. Therapy was continued to a maximum of seven cycles or to two cycles beyond documentation of a CR if this occurred before seven cycles had been given. Treatment was only permitted beyond seven cycles (at a cumulative doxorubicin dose of 525 mg/m^2) if cardiac ejection fractions were performed and the resting ejection fraction remained greater than 40%.

Investigations During Treatment

Assessments of response, with repetition of all previously abnormal investigations, were made after the second, fifth, and subsequent alternate cycles of chemotherapy. Full blood counts and differentials were performed on the first, fourth, eighth, 11th, 15th, and 18th days of each cycle of treatment. Full biochemical profiles and liver function tests were performed before each course of chemotherapy.

Definitions of Response, Response Duration, Survival, and Toxicity

Patients were considered assessable for response if they had received a minimum of two cycles of chemotherapy. Response criteria were those defined by WHO.[11] If there was evidence of rapid disease progression (> 50% increase in tumor volume and/or the appearance of new lesions) after the first course, this was classified as treatment failure and therapy was discontinued. Deaths during the first 3 weeks, due to tumor progression without severe toxicity, were classified as early deaths. Response and survival times were measured from the first day of chemotherapy administration. All toxicities were graded according to WHO criteria.[11] Infections were classified as minor if the patient developed symptoms or signs suggestive of localized involvement (predominantly oral candidiasis, upper respiratory tract or urinary tract infection) without accompanying systemic symptoms or signs and for whom oral antibiotics or antifungal agents were prescribed. All patients who were febrile (temperature > 38°C) and neutropenic (granulocytes < 0.5 × 10^9/L) or hypotensive were admitted for intravenous antibiotics and were classified as having major infections.

Statistical Analysis

An analysis of variance (ANOVA) was used to compare data on blood count parameters for all patients during the treatment cycles.

The original patient data were first tested to determine whether the assumptions of normality and equality of variances pertaining to this analysis were satisfied. The raw data did not prove to be suitable, and so a logarithmic transformation was applied to the data using the formula $Y = \log (X + 1)$. Transformations for all but eosinophil values were normally distributed, and analysis was therefore performed on transformed data (information on eosinophils was not calculated). To obtain an overall assessment of the effects of treatment on blood count parameters, a repeated-measures ANOVA was performed using program 5V from the BMDP statistical package. Survival and disease-free survival were estimated by the Kaplan-Meier method.

Quality Control of Data

All information on chemotherapy administration and response was subject to quality control assessment with visits to participating centers by members of the EORTC Quality Assurance Group.[12] Data on eligibility criteria, doses and timings of chemotherapy, toxicity, and laboratory variables were checked with source information in patient case records. Responses were assessed by review of all source material. All histology was independently reviewed by a pathology subcommittee.

RESULTS

Patient Characteristics

One hundred eleven patients from 16 centers in five countries were registered in this study. Seven patients were ineligible, which left 104 eligible and assessable patients. Patient characteristics are listed in Table 1, and reasons for exclusion in Table 2.

Chemotherapy Administered

A total of 293 cycles of chemotherapy were administered, with a median of four cycles being administered to each patient. The full protocol dose of both cytotoxic drugs was administered to the majority of patients on all cycles (Table 3). When doses below those stipulated in the protocol were administered, it was usually the result of an arithmetic error of calculation, with dose reductions only being made on six occasions because of prior toxicity (always due to severe thrombocytopenia). The median total dose of GM-CSF was also 100% of the amount calculated for a 14-day course, although reductions occurred when early discontinuation resulted from a rapid recovery of a neutrophil count greater than 10×10^9/L. The administration schedule of chemotherapy was as intended in the protocol, with a median of 21 days between each course for up to seven cycles of therapy (Table 4). However, there were delays on 94 cycles (32%), and 66% of these delays were for organizational reasons (incorrect readmission dates given, no empty beds, etc), rather than toxicity. Full protocol dose-intensity was therefore administered to the majority of patients and, when treatment delays occurred, these were avoidable in the majority of instances.

Table 1. Patient Characteristics

Characteristic	No.
Total eligible patients	104
Sex (male:female)	53:51
Age (years)	
Median	49
Range	20-73
Performance status	
0	55
1	47
2	2
Prior radiotherapy	27
Extent of disease at entry	
Metastatic only	70
Local and metastatic	34

Table 2. Reasons for Exclusion

Reason for Exclusion	No.
Prior radiotherapy to sole index lesion; withdrawn before any chemotherapy	1
Performance status 3; withdrawn before any chemotherapy	2
Incorrect histology—malignant melanoma	2
Patient failed to attend for follow-up after first course—no information obtained	1
Died of intestinal perforation before receiving chemotherapy	1

Toxicity

Hematologic. Sequential blood counts were recorded between treatment cycles for all patients. The neutrophil and platelet nadirs occurred on days 8 and 11, respectively, after each course (Figs 1 and 2). There was evidence of cumulative myelosuppression with significant decreases of the nadir total leukocyte ($P < .001$), neutrophil ($P < .001$), and platelet ($P < .001$) counts with sequential cycles of chemotherapy. The magnitude of the decrease was greatest for platelets (median nadir platelets after cycles 1 and 6, 122 and 37×10^9/L, respectively). There was also an increased duration of myelosuppression as treatment progressed ($P < .001$ for all parameters). The most important parameter that determined the risk of developing septicemia, duration of neutropenia,[13] showed that the median duration of neutropenia less than 0.5×10^9/L was only 3 days after course 1 and 6 days after course 6. Recovery to neutrophil count greater than 1.5×10^9/L occurred by medians of day 14 after course 1, day 15 after course 2, day 16 after course 3, day 17 after courses 4 and 5, and day 18 after course 6. Comparison of blood counts for the two groups of patients receiving once-daily or every-12-hour GM-CSF showed no significant difference in the depth or duration of thrombocytopenia ($P = .945$) or neutropenia ($P = .896$).

Table 3. Chemotherapy Doses Delivered

Course No.	No. of Patients	Dose of Doxorubicin (mg/m²)		Dose of Ifosfamide (g/m²)		% Patients Receiving Full Dose
		Median	Range	Median	Range	
1	104	75	70-77	5	4.7-5.6	97
2	98	75	60-83	5	4.0-5.5	99
3	81	75	71-78	5	4.9-5.4	99
4	66	75	39-77	5	2.6-5.3	95
5	48	75	51-79	5	3.2-5.3	96
6	35	75	25-77	5	2.5-5.4	97

Nonhematologic. The most frequent nonhematologic toxicities were nausea, vomiting, and alopecia. All patients developed grade III alopecia after three cycles, and 17 patients experienced WHO grade I, 28 patients grade II, and 31 patients grade III nausea and vomiting. Oral mucositis occurred in 28 patients. One patient developed WHO grade II nephrotoxicity, which was reversible after discontinuation of therapy. Cardiotoxicity occurred in three patients who all had normal ECGs before study entry (grade I, one patient; grade II, one patient). One further patient developed severe myocardial ischemia after two cycles and died of cardiac failure. No encephalopathy was seen.

Toxicity related to rhGM-CSF. Injections of rhGM-CSF were generally well tolerated. Fourteen patients developed bone pain (severe in one, mild/moderate in 13), and 16 patients developed mild myalgia and arthralgia. These symptoms were of short duration and were usually controlled by subsequent administration of paracetamol. Thirty-two patients experienced erythema at the injection sites, and two patients developed widespread erythema that prevented further administration of rhGM-CSF.

Infections. Forty-two episodes of infection were documented, but 27 of these were classified as minor and were controlled with oral antibiotics or topical antifungal agents. Fifteen patients required admission for serious episodes of febrile neutropenia and received parenteral antibiotics. Blood cultures and routine bacteriology screens failed to detect responsible organisms in any of these patients, and 13 recovered rapidly after hospitalization. One patient died suddenly 2 days after commencing antibiotics and, unfortunately, no autopsy was performed. He was classified as having died due to infection.

Response and Survival

Forty-seven patients (45%) achieved an objective response (95% confidence interval [CI], 34% to 56%), with 10 (10%) CRs. Sites of response were soft tissue (nine CRs, 18 partial remissions [PRs]), lung (eight CRs, 18 PRs), and liver (one CR, five PRs). The median overall survival was 15 months, and the median duration of remission was 9 months (Figs 3 and 4).

DISCUSSION

Chemotherapy options for the treatment of metastatic soft tissue sarcomas are limited by the scarcity of active agents. Given this constraint, it is essential to ensure that the few drugs that have activity are given in optimal doses and schedules. This study was designed to determine whether it would be possible to exploit the suggested dose-response relationship of doxorubicin in this disease by using it within the optimal dose range (> 70 mg/m²) in combination with the other most active agent—ifosfamide.

Unfortunately, the myelotoxicity of doxorubicin at such doses would preclude its being safely combined with other myelosuppressive agents. Careful monitoring of serial blood counts at 75 mg/m² in patients with breast and ovarian carcinoma showed neutropenia ($< 1.0 \times 10^9$/L) lasting a median of 7 days.[14] Single-agent ifosfamide (5 g/m²) produced WHO grade 3/4 leukopenia in 38% of patients in an earlier EORTC study.[2] The combination of doxorubicin, ifosfamide, and dacarbazine in the MAID regimen caused life-threatening leukopenia in 85% of the 471 cycles administered,[7] and experience with ifosfamide (5 g/m²) plus doxorubicin (50 mg/m²) in more than 450 patients treated in EORTC Soft Tissue and Bone Sarcoma Group studies showed toxicity to include a median neutrophil count of 0.4×10^9/L with 26% of cycles being delayed or dose-reduced because of previous myelosuppression and infection.[9,10] The Royal Marsden Hospital

Table 4. Time Interval Between Chemotherapy Cycles

Course No.	Time Interval (days)		% Patients With Delay
	Median	Range	
1-2	21	19-24	24
2-3	21	19-35	26
3-4	21	20-42	39
4-5	21	21-42	29
5-6	21	20-41	23

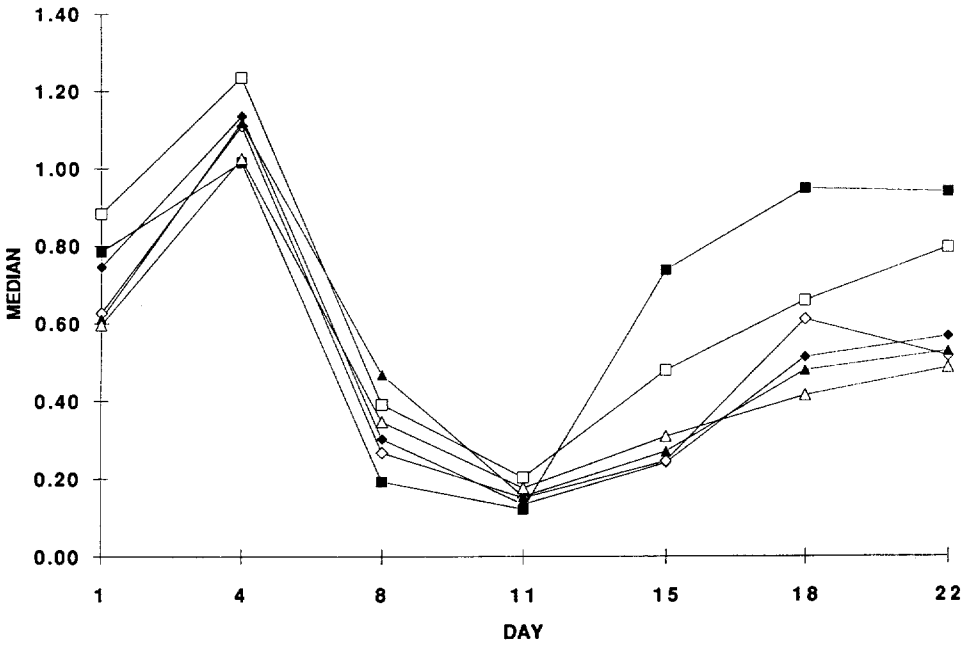

Fig 1. Neutrophil toxicity with sequential cycles of chemotherapy (neutrophil values are logarithmic transformations). Course 1, ■; course 2, □; course 3, ♦; course 4, ◇; course 5, ▲; course 6, △.

combined doxorubicin 60 mg/m^2 with ifosfamide 5 g/m^2 and observed septicemia in 23% of patients, with 55% requiring dose reductions after previous cycles.[15] An identical regimen used in Indianapolis resulted in a median leukopenia of 1.2×10^9/L (the figure for neutropenia was not reported), with 14% of patients experiencing septicemia and 10% discontinuing treatment after the first course because of toxicity.[16]

As a result of this information on hematologic toxicity, it has not so far been possible to determine whether improvements of the outcome for soft tissue sarcomas will occur by escalating the dose of doxorubicin above 70 mg/m^2 in combination with ifosfamide. The availability of hematopoietic growth factors provided the opportunity to test whether such dose escalations would be feasible. rhGM-CSF was among the first of a group of myeloid

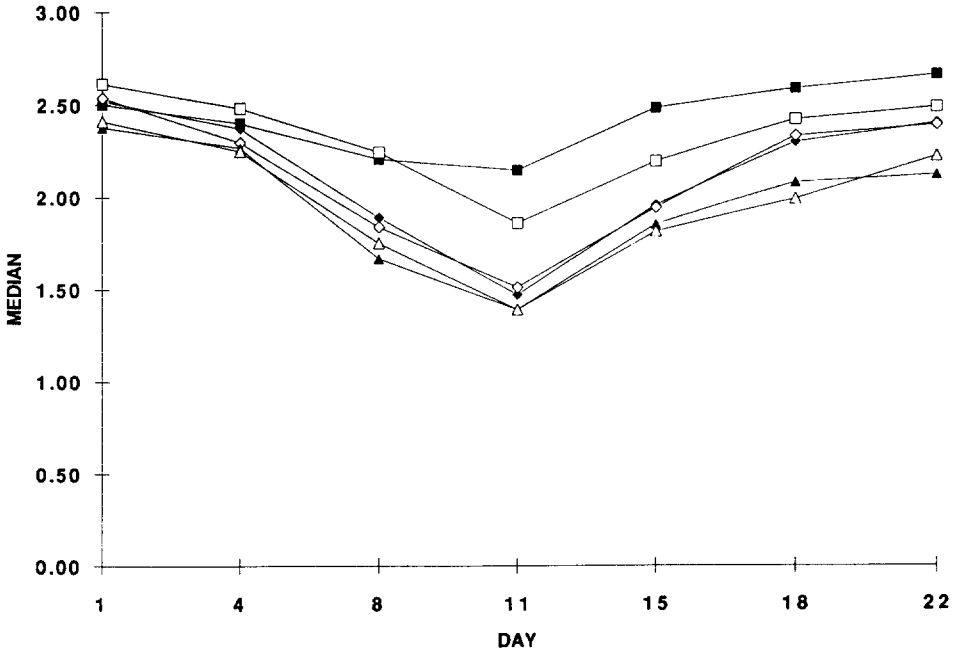

Fig 2. Platelet toxicity with sequential cycles of chemotherapy (platelet values are logarithmic transformations). Course 1, ■; course 2, □; course 3, ♦; course 4, ◇; course 5, ▲; course 6, △.

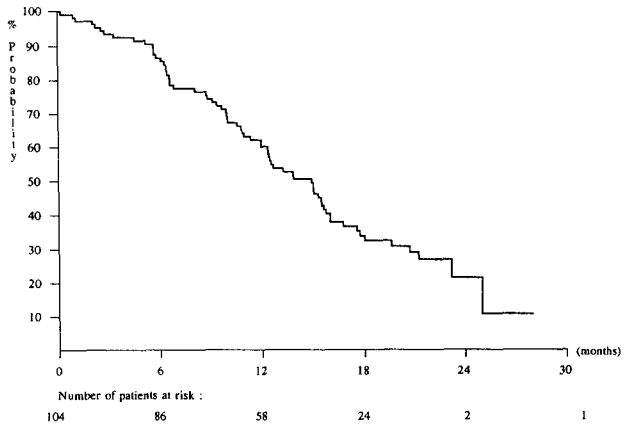

Fig 3. Overall survival.

growth factors to enter clinical testing in 1987. Phase I studies[17,18] confirmed the expectations from in vitro and animal experiments that this agent would increase peripheral leukocyte counts, and several phase II studies of rhGM-CSF administered after chemotherapy have suggested that this agent reduces the degree of cytotoxic-induced myelosuppression[19] and requirement for antibiotics.[20] A similar agent, granulocyte colony-stimulating factor (G-CSF), also appears to reduce the duration of neutropenia after chemotherapy, to reduce the incidence of infection, and to allow safe administration of greater dose-intensity of chemotherapy.[21]

Our results indicate that use of rhGM-CSF between cycles of optimal-dose doxorubicin with ifosfamide allows safe administration of such a regimen. Although patients experienced grade 3/4 neutropenia between each course, the incidence of septicemia was less than in other reports using lower doses of doxorubicin,[7,15,16] with only 15 admissions for intravenous antibiotics during 293 cycles of chemotherapy and one death from infection. Such a protective effect could have been due to the short duration of severe neutropenia or to other effects that rhGM-CSF exerts on neutrophil function.[22] The predominant hematologic toxicity that caused treatment delays or dose reductions was thrombocytopenia. There have been reports of protective effects of rhGM-CSF on platelet toxicity[19,20] and, as a result of one study that suggested this effect to be greater with twice-daily fractionation of administration,[23] the second 59 patients were treated with every-12-hour injections. There was no significant difference in platelet toxicity with the latter scheduling.

All patients had clinically normal cardiac function before study entry and normal ECGs. Three subsequently developed cardiac toxicity, which was mild and reversible in two, but progressed to fatal cardiac failure in one. All had received doses of doxorubicin well below 500 mg/m^2. Administration of rhGM-CSF has been associated with pericarditis and pericardial effusions, although this has only been described at higher doses than used in this study.[17] There was no clinical evidence of pericarditis in any of these patients, although a postmortem examination was not performed on the patient who died.

Encouragingly, full protocol dose-intensity of chemotherapy was administered to the majority of patients for up to seven cycles. The dose was only reduced as a result of prior toxicity on six occasions and, when delays occurred (32% cycles), two thirds of these were for avoidable reasons (predominantly administrative), rather than toxicity. A median of 45% of cycles of doxorubicin and ifosfamide were delayed beyond 21 days in a previous study of our group, despite the lower dose of doxorubicin used (50 mg/m^2) (EORTC Data Center, data on file).

An important aspect of this trial was that it provided a model for development of a strict quality assurance program to check information in patient hospital records with data that were completed on case record forms by participating clinicians. Results of this program will be published in detail separately, but valuable information was obtained, including additional data on laboratory parameters, responses, and reasons for treatment delays. Errors of data transcription were corrected, and a flow sheet was developed for future use by all members to record information on chemotherapy administration and toxicity assessments. A program of site visits to centers contributing to group studies will continue in future trials.

The response rate of 45% in this study was the highest so far seen by our cooperative multinational group for patients with advanced soft tissue sarcomas—10% above

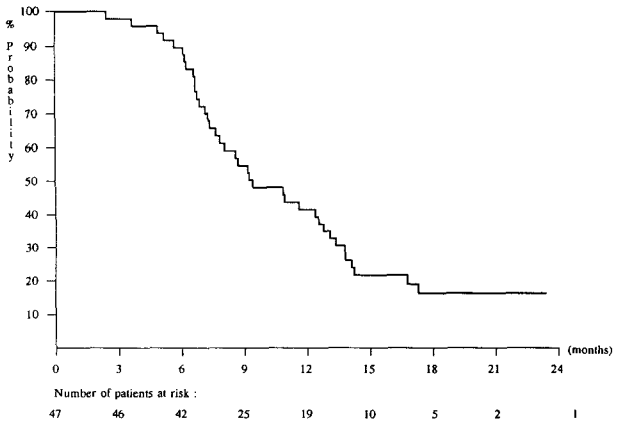

Fig 4. Relapse-free survival for responders.

that seen when ifosfamide was combined with doxorubicin 50 mg/m^2. Both the response duration and survival were also longer. However, an assessment of the activity of this combination was not the main end point of this trial, and historical comparisons are particularly unreliable in this disease. Having demonstrated that this regimen is feasible, it will now be important to compare it with the combination containing doxorubicin 50 mg/m^2 without growth factor support in a randomized phase III study to determine the true value of dose-intensity escalation for such patients. Such a study is now underway, and its results will be awaited with interest.

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