A Phase I/II Study of Sequential, Dose-Escalated, High Dose Ifosfamide plus Doxorubicin with Peripheral Blood Stem Cell Support for the Treatment of Patients with Advanced Soft Tissue Sarcomas

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BACKGROUND. This Phase I/II study investigates increasingly high doses of ifosfamide combined with full dose doxorubicin chemotherapy supported with peripheral blood stem cells (PBSC) and granulocyte-colony stimulating factor (G-CSF) in patients with metastatic soft tissue sarcoma (STS).

METHODS. Patients with histologically proven metastatic or advanced adult STS without prior treatment received doxorubicin, 75 mg/m^2, on Day 1 followed by 4-day continuous infusion of ifosfamide at 5 consecutive dose levels starting with 8 g/m^2 and escalating to 16 g/m^2 in increments of 2 g/m^2. Three patients per dose level and a maximum of 5 treatment cycles per level at 3-week intervals were planned. Each cycle was followed by G-CSF and retransfusion of PBSC. PBSC separation was performed prior to chemotherapy by steady state mobilization with G-CSF.

RESULTS. Eighteen patients (median age, 45 years, range, 25–57 years) were included, with 4, 3, 4, 4, and 3 patients assigned to Levels 1–5, respectively. Metastatic sites included the lungs in 12 patients (67%), lymph nodes in 8 patients (44%), and the liver in 5 patients (28%). Nine patients (50%) achieved objective responses with 4 complete responses (22%) and 5 partial responses (28%). Lung metastases and a histology of synovial sarcoma or malignant fibrous histiocytoma were favorable features for response to therapy. The median survival for all patients was 13+ months (range, 3–19+ months). Hematotoxicity was manageable and treatment could be administered at a median interval of 24 days. One case of World Health Organization Grade 3 neurotoxicity occurred. Nephrotoxicity was dose-limiting, with 1 patient in Level 4 (WHO Grade 2) and 2 patients in Level 5 (WHO Grade 3).

CONCLUSIONS. Multiple cycles of dose-intensive therapy with doxorubicin and high dose ifosfamide can be administered safely with PBSC support. Nephrotoxicity is dose-limiting for ifosfamide at total doses of 16 g/m^2. Multiple cycles of high dose chemotherapy at short treatment intervals using ifosfamide at a dose of 14 g/m^2 should be investigated further in a neoadjuvant setting in patients with STS. ***Cancer* 1997;80:1221–7.** © *1997 American Cancer Society.*

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The results of chemotherapy in patients with advanced adult soft tissue sarcomas are still disappointing. Only three drugs have demonstrated single agent activity; doxorubicin and ifosfamide have both shown response rates of 20–30% in nonpretreated patients and dacar-

bazine) has yielded response rates of nearly 20% in pretreated patients.[1,2] Several studies on combination chemotherapy using these three drugs have been performed and increased response rates up to 40% have been reported, but the toxicity induced with this treatment was often substantial.[3,4] Furthermore, despite the high response rates achieved, no clear benefit for overall survival could be demonstrated with combination chemotherapy. Phase III studies comparing combination chemotherapy with doxorubicin alone have shown equivalent overall survival times for single agent chemotherapy in the range of 12 months for patients with metastatic disease.[1]

Clinical studies have demonstrated a dose-response relationship for doxorubicin in patients with soft tissue sarcomas and doses > 60 mg/m^2 every 3 weeks are recommended to achieve improved response rates.[2] However, the escalation of doxorubicin doses to > 80 mg/m^2 will produce severe side effects, particularly mucositis and severe skin toxicity as reported in patients treated with high dose doxorubicin plus granulocyte-colony stimulating factor (G-CSF) for metastatic breast carcinoma.[5]

Based on several clinical studies, a dose-response relationship also has been established for ifosfamide in patients with soft tissue sarcomas.[6–8] Although the use of standard dose ifosfamide (≤ 5 g/m^2) will achieve response rates of approximately 25%, the use of higher doses of ifosfamide may not only achieve higher response rates but also appears to be active in patients already resistant to standard dose ifosfamide treatment.[9] Phase I studies using single agent high dose ifosfamide as a continuous infusion have demonstrated the possibility of administering doses of 16–18 g/m^2, which result in increasing myelotoxicity and reach the dose-limiting nephro- and neurotoxicity of the drug. In a Phase I study by Elias et al., 7 of 20 sarcoma patients pretreated with standard doses of ifosfamide again responded to higher doses of this agent, demonstrating that resistance to ifosfamide can be overcome by dose escalation.[10,11]

A regimen using a full dose of doxorubicin of 75 mg/m^2 plus ifosfamide, 5 g/m^2, given every 3 weeks has been used by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group.[12] In their study a recombinant human growth factor, granulocyte-macrophage-colony stimulating factor (GM-CSF), was used to ameliorate the hematotoxicity after chemotherapy. Severe and dose-limiting hematotoxicity has been reported in regimens using a full dose anthracycline compound in combination with an ifosfamide dose in the range of 10–12 g/m^2.[13] To study the use of doxorubicin at 75 mg/m^2 in combination with dose-intensive ifosfamide therapy at doses ranging from 8–16 g/m^2, the authors have incorporated peripheral blood stem cell (PBSC) transfusion and G-CSF as supportive measures to the administration of multiple cycles of this intensive treatment regimen at 3-week intervals.[14,15] This article presents the results of a Phase I/II study in patients with metastatic adult soft tissue sarcomas to define the maximally tolerated dose (MTD) of ifosfamide in combination with doxorubicin when given at short treatment intervals supported by PBSC.

PATIENTS AND TREATMENT

Eligibility Criteria

Patients entered on this study had a histologically proven diagnosis of adult soft tissue sarcoma with a pathologic grade ≥ 2 and documented progressive metastatic disease. Inclusion criteria required the presence of measurable tumor lesions, age between 18–60 years, a Karnofsky index $\geq 50\%$ and obtaining informed consent from the patient. Prior chemotherapy and concomitant radiation therapy of the indicator lesions were not allowed. Patients were required to have adequate liver (bilirubin $<$ 2-fold of upper normal limit), renal (glomerular filtration rate > 50 mL/minute), and bone marrow function (leukocytes $\geq 3000/\mu$L and thrombocytes $\geq 100{,}000/\mu$L prior to treatment). Ethical approval was given by the Hannover University Medical School ethical committee.

Treatment Regimen

Chemotherapy was comprised of doxorubicin, 75 mg/m^2, given as a 4-hour-infusion on Day 1. Ifosfamide was administered as a continuous infusion over 4 consecutive days starting immediately after doxorubicin administration. The dose of ifosfamide was escalated from dose Level 1 with 8 g/m^2 to a total dose of 16 g/m^2 (dose Level 5) using a dose increase of 2 g/m^2 per dose level. Treatment was scheduled every 21 days for a maximum of 5 cycles. During treatment, diuresis was established using 2 L of dextrose/saline administered 12 hours prior to the start of chemotherapy. Mesna was given at 20% of the dose of ifosfamide at each dose level prior to the start of the continuous ifosfamide infusion and was given at the same dose as ifosfamide at each dose level as a continuous infusion and continued for 12 hours after the end of the 4-day ifosfamide infusion. The daily dose of ifosfamide was diluted in 2 L of dextrose/saline and infusion bags were changed every 24 hours.

In addition sodium bicarbonate (approximately 100 mg/day) was infused during the time of ifosfamide treatment to maintain the urinary pH > 7.5. During treatment daily monitoring of serum potassium, monitoring of urine for hematuria, and body weight mea-

surement were performed. All chemotherapy was administered in the hospital and patients were routinely hospitalized for 5 days during each treatment cycle.

At each dose level the inclusion of three consecutive patients was planned. If no dose-limiting toxicities (World Health Organization [WHO] Grade 3/4 peripheral or central neurotoxicity or WHO Grade 3/4 nephrotoxicity) and no dose-limiting myelosuppression were observed, the next dose level was started. If one case of severe toxicity occurred, the number of patients per dose level was increased by one. If dose-limiting toxicities occurred in two patients at one dose level, study termination was planned at that dose level.

Use of Growth Factors and PBSC

Recombinant G-CSF was given at a dose of 5 μg/kg subcutaneously. after each treatment cycle starting 2 days after the end of the ifosfamide administration (Day 6). G-CSF was continued until leukocytes had reached $> 2000/\mu$L on 2 consecutive days. On Day 6 (at least 24 hours after the end of the ifosfamide administration), PBSC were retransfused for each treatment cycle. Approximately 1×10^6 CD_{34+} cells per kg body weight were used to support hematopoietic recovery for each consecutive treatment cycle. PBSC separation was performed at steady state mobilization with G-CSF, 10 μg/kg, given for 5–6 days prior to the start of chemotherapy. Thus, autologous stem cell support already was available for the first course of high dose doxorubicin/ifosfamide therapy.

Treatment Duration and Assessment of Response

Standard response criteria as defined by the WHO were used. Each patient receiving at least one complete treatment cycle was considered evaluable for response. In case of tumor progression patients were taken off study. Patients with stable disease and tolerable toxicity and patients with partial response (PR) or complete response (CR) after three cycles of chemotherapy were scheduled for a maximum of five cycles. Response duration and survival times were measured from the first day of chemotherapy administration. Adequate radiologic assessments to monitor the metastatic lesions were performed prior to each treatment cycle. Furthermore, full blood count analysis and routine laboratory measurements were performed at least twice weekly and prior to the next treatment cycle. Every two cycles the cardiac ejection fraction was monitored using radioisotope methods. Patients were followed if taken off study or after the completion of five treatment cycles. Patients with PRs and initially nonoperable disease were evaluated for secondary surgical resection of metastatic lesions, if considered clinically useful.

TABLE 1
Characteristics and Response to Therapy of 18 Patients with Soft Tissue Sarcomas Receiving High Dose Ifosfamide and Doxorubicin with PBSC Support

Median age (yrs) (range)	45 (25–57)
Histology (no. of patients) (%)	
Malignant fibrous histiocytoma	5 (28%)
Hemangiopericytoma	4 (22%)
Synovial sarcoma	3 (17%)
Malignant schwannoma	2 (11%)
Leiomyosarcoma	2 (11%)
Mesenchymal sarcoma	2 (11%)
Localization of metastases (no. of patients) (%)	
Lungs	12 (67%)
Lymph nodes	8 (44%)
Liver	5 (28%)
Other	4 (22%)
No. of metastatic lesions (no. of patients) (%)	
1 site	9 (50%)
2 sites	5 (28%)
$\geq$3 sites	4 (22%)
Response to therapy	
CR/NED	4 (22%)
PR	5 (28%)
No change	3 (17%)
Progressive disease	3 (17%)
Stop therapy	2 (11%)
Median no. of cycles given (range)	4 (1–5)

PBSC: peripheral blood stem cells; CR: complete response; NED: no evidence of disease; PR: partial response.

Toxicity was also graded according to WHO criteria. All patients were seen twice weekly for toxicity assessments. Toxicity was calculated as worst toxicity per patient.

RESULTS

Patient Characteristics

Eighteen patients with a median age of 45 years (range, 25–57 years) were included in the study. All patients had metastatic lesions, involving mainly the lungs in 12 patients (67%), lymph nodes in 8 patients (44%), and the liver in 5 patients (28%). Fifty percent of the patients had $\geq$ 2 sites of metastatic disease and none of the patients had the lymph nodes as the only metastatic site. Several histologic subtypes of adult soft tissue sarcomas were present in the study population with malignant fibrous histiocytoma (MFH) and hemangiopericytoma being the most predominant with 5 and 4 patients each, respectively. All lesions were pathologically graded as either Grade 2 or Grade 3. The clinical characteristics of all patients are summarized in Table 1.

Administration of Chemotherapy

The study used 5 dose levels with doxorubicin, 75 mg/m^2, given on Day 1 and a total dose of ifosfamide, 16

TABLE 2
High Dose Ifosfamide and Doxorubicin with PBSC Support: Dosing Schedule, Severe Toxicities, and Responses by Dose Level

Dose level	Dosing schedule		No. of patients	Median treatment interval between cycles (days) (range)	Severe toxicities	Response	
1	Doxorubicin	75 mg/m^2 Day 1	4	24 (21–29)	WHO Grade 3 neurotoxicity	CR	—
	Ifosfamide	8 g/m^2 Days 1–4 ci				PR	1
2	Doxorubicin	75 mg/m^2 Day 1	3	24 (21–35)		CR	2
	Ifosfamide	10 g/m^2 Days 1–4 ci				PR	—
3	Doxorubicin	75 mg/m^2 Day 1	4	24 (21–31)	WHO Grade 3 infection	CR	—
	Ifosfamide	12 g/m^2 Days 1–4 ci				PR	1
4	Doxorubicin	75 mg/m^2 Day 1	4	21 (21–23)	WHO Grade 2 neurotoxicity	CR	1
	Ifosfamide	14 g/m^2 Days 1–4 ci			WHO Grade 2 nephrotoxicity	PR	1
5	Doxorubicin	75 mg/m^2 Day 1	3	25 (21–34)	WHO Grade 3 nephrotoxicity (2 patients)	CR	1
	Ifosfamide	16 g/m^2 Days 1–4 ci				PR	2

PBSC: peripheral blood stem cells; ci: continuous infusion; WHO: World Health Organization; CR: complete response; PR: partial response.

g/m^2, given as continuous infusion on Days 1–4 being dose-limiting at dose Level 5. At dose Levels 1, 3, and 4, four patients each were entered and at dose Levels 2 and 5, three patients each were entered (Table 2). A median of four (range, one to five) cycles per patient were applied. Eleven patients (61%) completed all 5 treatment cycles. The median treatment intervals between cycles ranged from 21–25 days at the different dose levels. The treatment intervals were neither related to the intensity of chemotherapy (dose level) nor did they increase with consecutive cycles of therapy at each level (Table 2).

Response to Therapy and Survival

Approximately 50% of patients responded favorably to therapy with 4 patients (22%) achieving a CR and 5 patients (28%) achieving a PR. Stable disease was present in 3 patients (17%), and 3 patients (17%) had early disease progression during the second, third, and fourth cycle of therapy, respectively. Two patients withdrew from the study early due to toxicity. A tendency toward a higher response rate at higher dose levels was observed; 3 of 3 patients achieved CR/PR at dose Level 5, 2 of 4 patients at dose Level 4, and 1 of 4 patients at dose Level 3. Responses by dose levels are shown in Table 2. Most patients with responses had either lung metastases or lymph node involvement. Only one of five patients with liver metastases achieved a PR. Analyzing the responses by histologic subtype of sarcoma, three of five patients with MFH (one CR and two PR) achieved a response and three of three patients with synovial sarcoma achieved a response (one CR and two PR). Additional responses occurred in patients with hemangiopericytoma (one CR in a patient with a Grade 3 hemangiopericytoma of four patients included with this particular histologic subtype) and with undifferentiated mesenchymal sarcoma (one CR and one PR of two patients). No responses were observed in patients with leiomyosarcomas or malignant schwannomas. The median survival for all patients was 13 months (range, 3–19+ months), and the median progression free survival was 8 months (range, 2–19+ months).

Toxicity

Overall hematologic toxicity with the support of PBSC was manageable. No dose-limiting hematotoxicity was observed and all patients had fully recovered blood counts at the start of the next treatment cycle without the need for prolonged intervals between cycles. After each treatment cycle, a median of 0.9 (range, 0.5–2.4 $\times$ 10^6) $\times$ 10^6 CD_{34+} cells per kilogram were retransfused. The median duration of severe granulocytopenia ($<$ 500/μL) was 4 days (range, 3–5 days) at consecutive dose levels. The median number of days with severe thrombocytopenia ($<$ 20,000/μL) was 2 days (range, 1–3 days), and patients received a median of 1 platelet transfusion per cycle (Table 3). Severe infections (WHO Grade 3/4) occurred in one patient who developed a septic episode related to *Staphylococcus aureus* infection and was subsequently withdrawn from the study.

WHO Grade 3 mucositis was the most severe gastrointestinal toxicity, occurring in 2 patients (11%). Minimal hematuria was observed in 7 patients (39%). Nausea and emesis was tolerable with the use of $5HT_3$-antagonists and prophylactic steroid premedication. Two severe cases of central neurotoxicity were observed with one patient developing psychotic episodes and disturbance of vision and smell (dose Level 4). The patient remained on the study. Another patient developed seizures at dose Level 1 and was withdrawn

TABLE 3
Hematologic Toxicity of High Dose Ifosfamide and Doxorubicin with PBSC Support

	Cycle no.					
	1	2	3	4	5	Total
No. of patients	18	17	16	12	11	18
Median no. of days with granulocytes $< 500/\mu L$	4	3	3	5	4	4 (3–5)
Median no. of days with platelets $< 20{,}000/\mu L$	1	1	2	3	2	2 (1–3)
Median no. of platelet transfusions/per patient	0	1	1	2	1	1 (0–2)

PBSC: peripheral blood stem cells.

TABLE 4
Nonhematologic Toxicity of High Dose Ifosfamide and Doxorubicin with PBSC Support

	WHO toxicity grade			
	1	2	3	4
Nausea/emesis	2 (11%)	8 (44%)	2 (11%)	0
Hematuria	7 (39%)	0	0	0
Neurotoxocity				
Central	7 (39%)	1 (6%)[a]	1 (6%)[b]	0
Peripheral	1 (6%)	0	0	0
Diarrhea	3 (17%)	4 (22%)	0	0
Mucositis	6 (33%)	1 (6%)	2 (11%)	0
Nephrotoxicity	2 (11%)	1 (6%)	2 (11%)[c]	0
Infection/fever	2 (11%)	1 (6%)[d]	1 (6%)[e]	0

PBSC: peripheral blood stem cells; WHO: World Health Organization.
[a] Patient on study (Level 4).
[b] Patient off study (Level 1).
[c] Regarded as dose-limiting toxicity (Level 5).
[d] Patient on study (Level 4).
[e] 1 Patient off study (Level 3).

from the study. At the highest dose level of ifosfamide (16 g/m^2), 2 cases of severe nephrotoxicity occurred. One additional case of Grade 2 nephrotoxicity occurred at dose Level 4; thus, dose Level 5 was regarded as the MTD for this treatment regimen. One of the 2 patients with Grade 3 nephropathy required temporary dialysis; kidney function recovered within 6–8 weeks, whereas the other patient had elevated creatinine levels ($>$ 3.5 mg/dL) that did not recover until he developed disease progression and death. Based on the small number of patients the toxicity profile did not appear different when comparing the first and the subsequent cycles of treatment. Overall, five patients required hospitalization due to toxic complications. A brief summary of side effects is given in Table 4.

DISCUSSION

It was the major objective of this Phase I/II study to establish the MTD of ifosfamide given as a 4-day continuous infusion combined with full dose doxorubicin (75 mg/m^2) administered during consecutive high dose chemotherapy cycles at 3-week intervals with the support of PBSC and G-CSF. The use of PBSC in this treatment approach clearly has allowed treatment at planned intervals without dose-limiting hematotoxicity. In contrast to doxorubicin and ifosfamide followed by GM-CSF as used in a study by the EORTC, no cumulative myelosuppression was observed with each sequential cycle of chemotherapy.[12]

The EORTC study used doxorubicin, 75 mg/m^2, plus 5 g/m^2 of ifosfamide; full recovery of neutrophils was only reached at Days 17–18 after the fourth cycle of treatment. A recent Phase II study using epirubicin, 120 mg/m^2, and ifosfamide doses escalated from 9–12 g/m^2 followed by G-CSF clearly achieved dose-limiting hematologic toxicity with the higher dose of ifosfamide used.[13] Cumulative doses of doxorubicin, 60 mg/m^2, and ifosfamide, 9 g/m^2, supported with G-CSF alone resulted in Grade 4 leukopenia in 100% of patients and Grade 4 thrombocytopenia in 33% of patients.[16] Another study by Italian investigators showed a dose of 11 g/m^2 of ifosfamide combined with 110 mg/m^2 of epirubicin to be the maximally tolerated combination with dose-limiting hematologic toxicity, particularly leukocytopenia found in 5 of 5 patients at this dose level, which also resulted in treatment delays of 1–2 weeks between cycles. [17] Thus, although the schedule of doxorubicin and ifosfamide used in the current study is not myeloablative, the use of PBSC clearly allows the administration of multiple treatment cycles at 3-week intervals without dose-limiting hematotoxicity and without signs of cumulative hematotoxicity. The retransfusion of approximately 1×10^6 CD_{34+} cells/kg after each cycle was sufficient to adequately restore hematopoiesis in this setting and the number of PBSC necessary for 5 cycles of this treatment regimen can be gained easily by 1 or 2 days of apheresis with steady state conditions by priming with G-CSF alone in patients with advanced soft tissue sarcomas.[14,18.]

As observed in other studies of high dose ifosfamide, nonhematologic toxicities become dose-limiting.[6,7,9] Two cases of central neurotoxicity were observed in this study with one of these patients taken off study. However, methylene blue, as recently proposed for the treatment of this toxicity, was not used in this patient.[19] Central neurotoxicity has occurred despite normal serum albumin levels and prophylactic application of sodium bicarbonate with the maintenance of urinary pH levels > 7.5. As previously reported, it is difficult to predict the occurrence of central neurotoxicity related to high dose ifosfamide treatment.[20]

As observed by Elias et al. and LeCesne et al., renal toxicity may become dose-limiting when high doses of ifosfamide in the range of 16–18 g/m^2 are used as a single agent.[9–11] In the current study 3 cases of renal toxicity were observed, 1 at dose Level 4 with 14 g/m^2 of ifosfamide and 2 at dose Level 5 with 16 g/m^2 of ifosfamide. The development of nephrotoxicity after ifosfamide was not related to urothelial toxicity or hematuria, no severe cases of which were observed in the study.

High dose ifosfamide has been used as a continuous infusion given over 3 or 4 days in most studies investigating this treatment approach in patients with adult soft tissue sarcoma.[10,11,13,21] It has been suggested that continuous infusion of ifosfamide decreases toxicity and thereby may increase the therapeutic ratio of the drug. With the higher dose intensities achievable, more responses possibly can be reached with lower toxicity. Pharmacokinetic investigations have demonstrated that continuous infusion of ifosfamide leads to a higher time-concentration curve (area under the curve) and a shorter half-life with a significant increase of the total body clearance of ifosfamide. As an explanation the repetitive use of high doses of ifosfamide may lead to enzymatic autoinduction of metabolic enzymes in the liver.[22] The use of continuous infusion of high dose ifosfamide with mesna uroprotection and G-CSF already has been demonstrated as a safe outpatient regimen during a Phase I study.[21] A dose of 15 g/m^2 single agent ifosfamide given over 4 days as a continuous infusion was identified as the MTD given to outpatients with portable infusion pumps.

The rationale for dose intensification of ifosfamide has been demonstrated clearly in several clinical and preclinical investigations showing that high dose ifosfamide may circumvent resistance to previously administered standard dose ifosfamide treatment.[9] High response rates have been reported with the use of dose intensive ifosfamide regimens, either given alone or in combination with anthracyclines in patients with advanced soft tissue sarcomas. It is of particular interest that certain histologic subtypes, particularly synovial cell sarcomas, appear to achieve high objective response rates whereas other subtypes such as gastrointestinal leiomyosarcomas appear to be completely unresponsive to any type of chemotherapy used.[23] Thus, to compare treatment results of different protocols for soft tissue sarcomas, the distribution of the histologic subentities included needs to be carefully compared. Responses to chemotherapy have been reported in patients, particularly those with MFH and synovial sarcoma.[1,23] In the current study all three patients with synovial sarcoma and three of five patients with MFH responded to treatment.

However, as previously reported in other trials with high doses of ifosfamide,[6,7] the median duration of responses is rather brief, reaching 8 months in the current investigation. Although high response rates may be achieved by sequential high dose therapy with anthracyclines and ifosfamide, there is no evidence that these responses will last longer than after standard treatment and thus will translate into prolonged survival. It needs to be particularly stressed that it is of course very difficult to derive solid, disease specific correlations from a Phase I/II study design with a rather small number of patients included. However, when using intensive sequential high dose chemotherapy as neoadjuvant treatment in patients with potentially resectable metastatic disease and in patients with locally inoperable large soft tissue sarcoma, the benefit of achieving a major response may possibly translate into an improved survival through subsequent surgical resection of the primary tumor and of metastatic lesions. In this respect lung metastases not only appear to be responsive to chemotherapy but also may be a feasible target for postchemotherapy resection. In contrast, the presence of liver metastases, which only will respond poorly to chemotherapy, may indicate a poor prognosis for the patient.[1] Having established the feasibility of the administration of full dose doxorubicin in combination with high dose ifosfamide as sequential treatment given every 3 weeks with the use of PBSC and G-CSF in patients with metastatic disease, the authors believe the recommended dose for future trials is 14 g/m^2 when using the described treatment schedule. This approach should be tested in a neoadjuvant setting during a Phase II study in an attempt to improve survival for this selected subgroup of patients.

REFERENCES

1. Dirix LY, Somville J, Van Oosterom AT. Diagnosis and treatment of soft tissue sarcomas in adults. *Curr Opin Oncol* 1996;8:289–98.

2. Bokemeyer C, Harstrick A, Schmoll HJ. Treatment of adult soft-tissue sarcomas with intensified chemotherapy and haematopoietic growth factors. *Onkologie* 1994;17:216–25.
3. Elias A, Ryan L, Sulkes A, Collins J, Aisner J, Antman KH. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. *J Clin Oncol* 1989;7:1208–16.
4. Bokemeyer C, Harstrick A, Schmoll HJ, Köhne-Wömpner CH, Schöffski P, Poliwoda H. Epirubicin/dacarbazine rapidly alternated with ifosfamide in the treatment of metastatic soft tissue sarcomas. *Ann Oncol* 1992;3:487–8.
5. Bronchud MH, Howell A, Crowther D, Hopwood P, Souza L, Dexter TM. The use of granulocyte colony-stimulating factor to increase the intensity of treatment with doxorubicin in patients with advanced breast and ovarian cancer. *Br J Cancer* 1989;60:121–5.
6. Demetri GD. High-dose ifosfamide in the treatment of sarcomas of soft tissues and bones. *Semin Oncol* 1996;23:22–6.
7. Tursz T. High-dose ifosfamide in the treatment of advanced soft tissue sarcomas. *Semin Oncol* 1996;23:34–9.
8. Cerny T, Leyvraz S, Dazzi H, Varini M, Kroner J, Marti C, et al. Phase II trials of ifosfamide and mesna in advanced soft tissue sarcoma (STS) patients: a definite dose-response relationship [abstract]. *Proc Am Soc Clin Oncol* 1992;11:1416.
9. LeCesne A, Antoine E, Spielmann M, LeChevalier T, Brain E, Toussaint C, et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol* 1995;13:1600–8.
10. Elias AD, Eder JP, Shea T, Begg CB, Frei III E, Antman KH. High-dose ifosfamide with mesna uroprotection: a Phase I study. *J Clin Oncol* 1990;8:170–8.
11. Elias AD, Ayash LJ, Eder JP, Wheeler C, Deary J, Weissman L, et al. A phase I study of high-dose ifosfamide and escalating doses of carboplatin with autologous bone marrow support. *J Clin Oncol* 1991;9:320–7.
12. Steward WP, Verweij J, Somers R, Spooner D, Kerbrat P, Clavel M, et al. 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. *J Clin Oncol* 1993;11:15–21.
13. Palumbo R, Toma S. Feasibility and compliance of epirubicin plus ambulatory continuous infusion ifosfamide at escalation doses in advanced soft tissue sarcomas: a Phase I study. *Eur J Cancer* 1995;31A:1552–3.
14. Bokemeyer C, Kuczyk MA, Köhne H, Einsele H, Kynast B, Schmoll HJ. Hematopoietic growth factors and treatment of testicular cancer: biological interactions, routine use and dose-intensive chemotherapy. *Ann Hematol* 1996;72:1–9.
15. DeVries EG, DeGraaf H, Boonstra A, van der Graaf WT, Mulder NH. High-dose chemotherapy with stem cell reinfusion and growth factor support for solid tumors. *Stem Cells (Dayt)* 1995;13:597–606.
16. Leyvraz S, Bacchi M, Cerny T, Lissoni A, Sessa C, Herrmann R. A phase I trial of intensification of ifosfamide and adriamycin and GM-CSF for the treatment of sarcomas [abstract]. *Proc Am Soc Clin Oncol* 1995;14:515.
17. Buondonna A, Romanini A, Comandone A, Della Palma M, Verusio C, Frustaci S. Increasing continuous infusion (CI) ifosfamide (IFO) and bolus epirubicin (EPI) in soft tissue sarcoma (STS) patients (PTS) [abstract]. *Proc Am Soc Clin Oncol* 1996;15:522.
18. Schwartzberg L, Birch R, Blanco R, Wittlin R, Muscato J, Tauer K, et al. Rapid and sustained hematopoietic reconstitution by peripheral blood stem cell infusion alone following high-dose chemotherapy. *Bone Marrow Transplant* 1993;11:369–74.
19. Küpfer A, Aeschlimann C, Wermuth B, Cerny T. Prophylaxis and reversal of ifosfamide encephalopathy with methylene-blue. *Lancet* 1994;343:763–4.
20. Meanwell CA, Blake AE, Kelly KA, Honigsberger L, Blackledge. Prediction of ifosfamide/mesna associated encephalopathy. *Eur J Cancer Clin Oncol* 1986;22:815–9.
21. Toma S, Palumbo R, Comandone A, Oliva C, Vincenti M, Bumma C, et al. Ambulatory 4-day continuous infusion schedule of high-dose ifosfamide with mesna uroprotection and granulocyte colony-stimulating factor in advanced solid tumours: a phase I study. *Ann Oncol* 1995;6:193–6.
22. Comandone A, Frustaci S, Leone L, Santoro A, Oliva C, Bretti S, et al. Ifosfamide in continuous infusion: the pharmacokinetic profile in patients with soft tissue sarcomas [abstract]. *Eur J Cancer* 1995;31A(Suppl 5):178.
23. Rosen G, Forscher C, Lowenbraun S, Eilber F, Eckardt J, Holmes C, et al. Synovial sarcoma: uniform response of metastases to high-dose ifosfamide. *Cancer* 1994;73:2506–11.