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Original article

Phase I multicenter study of combined high-dose ifosfamide and doxorubicin in the treatment of advanced sarcomas

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Summary

Ifosfamide and doxorubicin are the most active agents in the treatment of sarcomas and are characterized by a marked dose-response relationship. The objective of this study was to determine the maximum tolerated dose (MTD) of both agents in combination under granulocyte-macrophage colony-stimulating factor (GM-CSF) cover.

Patients and methods: Thirty-three patients with untreated sarcomas (soft tissue: $n = 20$; gynecological: $n = 11$; bone: $n = 2$) were treated with ifosfamide 12 g/m^2 by continuous i.v. infusion over five days and doxorubicin with dose escalation from 50 mg/m^2 i.v. bolus divided on two days, then to 60 mg/m^2 bolus divided on three days. Ifosfamide was reduced to 10 g/m^2 and doxorubicin was further escalated up to 90 mg/m^2. GM-CSF (5 μg/kg/day subcutaneously) was started 24 hours after chemotherapy and continued for 10 days.

Results: The MTD was reached with the combination of ifosfamide at 12 g/m^2 and doxorubicin at 60 mg/m^2. But with ifosfamide 10 g/m^2 and doxorubicin 90 mg/m^2 the MTD was not obtained. While severe leukopenia and granulopenia were observed at all-dose levels, severe anemia was more frequently related to the highest dose of ifosfamide. Severe thrombopenia and mucositis were more commonly observed at the highest dose of doxorubicin. Ifosfamide 10 g/m^2 and doxorubicin 90 mg/m^2 induced WHO grade 4 leukopenia in 58%, grade 3–4 thrombopenia in 42%, and anemia in 31% of cycles. Mucositis was minor in 50% of cycles. The overall response rate among 31 evaluable patients was 55% (95 confidence interval (CI): 36%–73%), with four (13%) complete responders and 13 (42%) partial responders. Response rates based on soft-tissue sarcomas or gynecological sarcomas alone were similar. Ten patients could be treated by elective surgery and/or radiotherapy. The total group of patients reached a median survival of two years, with 25% (SE 8%) survivors after three years.

Conclusions: The dose level of ifosfamide 10 g/m^2 and doxorubicin 90 mg/m^2 with supportive GM-CSF is manageable in a multicenter setting and should be further tested in regular phase II trials, including patients with gynecological and soft-tissue sarcomas. Transient toxicity with myelosuppression should be accepted in order to obtain a high antitumor activity of this regimen and a potential improvement in survival.

Key words: gynecological sarcomas, high-dose doxorubicin, high-dose ifosfamide, soft tissue sarcomas

Introduction

Improvements in anti-sarcoma therapy have been long overdue [1]. In 40%–60% of patients, curative local treatment is followed by metastatic disease, which has been managed for more than 20 years by single-agent doxorubicin as the standard chemotherapeutic regimen [2, 3]. This approach yields response rates of 20%–25% and a median survival of 12 months. The dose-response relationship is marked, with critical doses of >60 mg/m^2 [4]. Single-agent ifosfamide has been shown to be more active than cyclophosphamide, at a response rate similar to that of doxorubicin in previously untreated patients [5]. Moreover, high-dose ifosfamide ($>$ 10 g/m^2) induces significant anti-tumor activity in patients pretreated with alkylating oxazaphosphorines, which is strongly indicative of a dose-response relationship [6, 7]. The effect of dose on the outcome of sarcomas remained to be tested with high-dose doxorubicin and high-dose ifosfamide combination regimen.

Within the standard dose range, combination of doxorubicin and ifosfamide has resulted in higher response rates than either of them as a single agent. However, there was mainly an enhanced toxicity that was not accompanied by improvement in survival [2, 3, 8]. Presumably the dose of doxorubicin in those regimens was too small to reveal the superiority of combination therapy to single-agent doses. When doxorubicin was increased to 75 mg/m^2 in combination with a standard dose of ifosfamide (5 g/m^2), the response rate improved to 45%, with 10% complete remission and longer response duration [9]. These findings, however, were not confirmed by the preliminary results of a large randomized study [10].

So far, no results have been available on the optimal combination of high-dose doxorubicin and high-dose ifosfamide in previously untreated patients with advanced

sarcoma. The availability of hematopoietic growth factors enabled us to conduct a phase I trial aimed at defining the maximum tolerated dose (MTD) of both agents when given in combination.

Patients and methods

The protocol was in accordance with the Declaration of Helsinki principles and was approved by the competent ethics commission.

Inclusion criteria

Patients were required to have histologically proven advanced soft-tissue, bone or gynecological sarcoma. They were 18–70 years old and had a performance status ≤ 2 according to the Eastern Cooperative Oncology Group (ECOG) criteria [11]. All had normal hematological, renal and hepatic function. Cardiac function was tested by echocardiography or multigated nuclear scan and had to be within the normal range. Previous chemotherapy and CNS metastases were exclusion criteria. A written informed consent was obtained from all patients.

Study design and treatment plan

In order to define the MTD of combined ifosfamide and doxorubicin, the treatment design was to add to a fixed dose of ifosfamide escalating doses of doxorubicin. The first-dose level consisted in ifosfamide 12 g/m^2 as a continuous infusion over five days and doxorubicin 50 mg/m^2 i.v. bolus divided over two days. Planned escalation levels of doxorubicin were 60 mg/m^2 and 75 mg/m^2 i.v. bolus divided over three days. At least, three patients were included at each dose level. If one patient developed dose-limiting toxicity (DLT), three other patients had to be enrolled at the same dose level. The MTD was reached when two patients developed DLT at a particular dose level. Myelosuppression was expected and was not the only criterion for DLT.

DLT criteria were defined as : (a) neutrophil count $\leq 0.1 \times 10^9$/l over more than four consecutive days; (b) platelet count $\leq 25 \times 10^9$/l over more than four consecutive days; (c) any WHO grade 3 or 4 non-hematological toxicity [12] excluding alopecia or nausea and vomiting. The MTD was estimated only during the first cycle of chemotherapy. When it was reached at ifosfamide 12 g/m^2 (and doxorubicin 60 mg/m^2), ifosfamide was reduced to 10 g/m^2 while doxorubicin was further escalated up to 75 mg/m^2 and 90 mg/m^2.

Ifosfamide was administered by continuous i.v. infusion in 2 l/day physiological saline or 5% dextrose. Mesna 2 g/m^2/day was added to the solution over six days. Subcutaneous application of granulocyte macrophage colony stimulating factor (GM-CSF, molgramostim) 5 μg/kg/day was started 24 hours after the end of ifosfamide infusion and continued for 10 days or until neutrophils had reached $\geq 0.5 \times 10^9$/l. The DLT was studied on the first cycle only, but the treatment was continued every three weeks until progression of disease. Dose escalation was not allowed within individual patients. In the subsequent cycles, ifosfamide was reduced by 2 g/m^2 in the event of fever requiring hospitalization and i.v. antibiotics, as well as in the event of grade 3 neurological toxicity or neutropenia and thrombopenia over more than four days. Doxorubicin was reduced by 25% in cases of grade 3 or 4 mucositis, but not down to less than 50 mg/m^2. Doxorubicin had to be stopped in case of $\geq 15\%$ decrease in left ventricular ejection fraction (LVEF). Before each treatment cycle, a creatinine clearance ≥ 60 ml/min. or serum creatinine < 150 μmol/l was required. Prophylactic antiemetic treatment was at the discretion of the physicians in charge.

Response and toxicity assessment

Pretreatment evaluation included full blood count, biochemistry assessment, urinalysis, creatinine clearance, ECG and LVEF, as well as chest X-ray and computerized tomography of chest and abdomen. Full blood count was repeated twice a week during the first cycle of chemotherapy and once a week in the subsequent cycles. Biochemistry, urinalysis and creatinine clearance were performed prior to each cycle. Evaluations after every second cycle included ECG and left ventricular ejection fraction, as well as radiological analysis of response to treatment based on the state of disease defined at presentation.

Toxicity and response were evaluated according to WHO criteria [12], except for neurotoxicity which was measured by M.D. Anderson score [13].

Dose delivery

In order to verify the feasibility of multiple cycles, the delivered dose intensities (mg or g/m^2) for both drugs were evaluated in each cycle at different dose levels. Cumulative dose plots [14] are available for dose level 5, which is recommended for phase II. They show planned and received dose intensity, cumulative intensities at various points of time, and total dose. The cumulative dose (in mg or g/m^2) is plotted against time for each patient. The straight line represents the planned dose intensity. The first dose is the starting point on the drug axis, subsequent doses cumulated against time represent the dose intensity of the drug.

Statistics

Toxicity (nadirs and WHO grades) was described for all cycles to provide a full overview of the frequency of episodes. Statistics however have been calculated by patients due to the correlation between each patient values. The Jonckheere–Terpstra test [15] was used to compare grades of toxicity and response based on dose levels. This test is particularly powerful in comparing progressively increasing dose levels. Hematological nadirs based on dose levels were compared using the test for trend across ordered groups developed by Cuzick [16]. As ifosfamide was reduced while doxorubicin was being escalated, the tests were applied both for ifosfamide levels (12 mg/m^2 vs. 10 mg/m^2) and for doxorubicin levels (60 vs. 75 vs. 90 mg/m^2). Association between fever/infection and dose levels was analyzed using Fisher's exact test.

Survival was measured from the first day of treatment until death or until the day when the patient was last seen alive. Survival was calculated for all 33 cases. Duration of response was measured from initiation of chemotherapy until disease progression or death. Because some patients in remission were subjected to additional procedures like surgery and/or radiotherapy, the duration of response should not be attributed to chemotherapy alone and interpreted with caution Duration of survival and response was estimated using the Kaplan–Meier method [17].

Due to the small sample size, the exact version of each test was used wherever possible. Exact 95% confidence intervals were derived from the binomial distribution. Analyses were carried out with StatXact [18] and STATA [19]. All P-values are for two-sided tests.

Results

Patients

Thirty-three patients were included in the study between January 1993 and November 1994. Two patients could not be analyzed for DLT because of early death due to tumor progression before completing the first treatment cycle. Patient characteristics are listed in Table 1. Their median age was 47 (17–69) years. Of the 31 evaluable patients, 19 had soft-tissue sarcomas, 10 had gynecological sarcomas, and the remaining two patients had bone

Table 1. Patient characteristics.

Number of patients	33
Sex	
Male	10
Female	23
Performance status	
0	18
1	13
2	2
Sarcoma type	
Soft tissue	20
Leiomyosarcoma	5
Synoviosarcoma	3
Liposarcoma	3
Neurofibrosarcoma	2
Other histologies[a]	7
Gynecological	11
Leiomyosarcoma	6
Mixed mesodermal	5
Osteosarcoma	1
Chondrosarcoma	1
Tumor location (one or more per patient)	
Local recurrence	9
Lung	14
Pleura	2
Lymph nodes	8
Liver	5
Bone	4
Other location[b]	10

[a] Other histologies comprise one of each: fibrosarcoma, maligant fibrous histiocytoma, angiosarcoma, rhabdoid sarcoma, rhabdo-myosarcoma, epithelioid sacroma, unclassified.
[b] Other locations include muscle pelvis, retroperitoneum and mediastinum.

Table 2. Dose levels.

Dose level	Ifosfamide (g/m^2)	Doxorubicin (mg/m^2)	Number of patients	Number of cycles
1	12	50	7	24
2	12	60	4	14
3	10	60	6	28
4	10	75	6	24
5	10	90	8	26

sarcomas (osteosarcoma and chondrosarcoma, respectively). Nineteen (61%) had histological grade 3, 10 (32%) had grade 2, and two (6%) had grade 1. Local unresectable recurrence alone was present in four patients and in association with other metastatic sites in five additional ones. Nodal metastases were observed in eight patients of whom four had gynecological sarcomas, one a chondrosarcoma and three a soft tissue sarcoma (epithelioid, $n = 1$; rhabdoid, $n = 1$; liposarcoma, $n = 1$). Patients were treated at the dose levels summarized in Table 2.

Maximum tolerated dose (MTD)

DLT was assessed during the first cycles of treatment only. Eight patients were not monitored twice a week for hematologic toxicity, so that an accurate measurement of the duration of myelosuppression as required in the protocol was not possible. They had to be replaced by fully evaluable ones, to obtain the correct number of patients at each dose level.

At dose level 1 (ifosfamide 12 g/m^2 and doxorubicin 50 mg/m^2) only one out of the six fully monitored patients developed hematologic DLT in the form of granulopenia. The MTD was reached at dose level 2 (ifosfamide 12 g/m^2 and doxorubicin 60 mg/m^2) at which point three patients developed granulopenia that persisted longer than four days, and one of them additionally exhibited grade 3 neurotoxicity.

To allow further escalation of doxorubicin at subsequent dose levels, the total dose of ifosfamide was reduced to 10 g/m^2. No DLT was observed with doxorubicin 60 mg/m^2 at dose level 3. When increased to 75 mg/m^2 at dose level 4, one of the five fully monitored patients developed DLT in the form of granulopenia and thrombopenia. At dose level 5 (ifosfamide 10 g/m^2 and doxorubicin 90 mg/m^2) there was no myelosuppression exceeding four days, but one of the eight patients developed grade 3 mucositis. Further escalation of doxorubicin was beyond the scope of this study and therefore not performed.

Toxicity (all cycles)

After the first treatment cycle during which the DLT was determined, the 31 patients received a total of 116 treatment cycles with a median of two (one to six) cycles per patient. Additional cycles were administered in some cases following surgery and/or radiotherapy and have been included in the toxicity evaluation. The results are summarized in Table 3.

As expected, myelosuppression was the main toxic event. The median nadirs were 0.6 (0.1–7) $\times 10^9/l$ for leukocytes, 0.1 (0–5) $\times 10^4/l$ for granulocytes, 70 (1–425) $\times 10^4/l$ for thrombocytes, and 88 (35–41) g/l for hemoglobin. The duration of leucopenia was a median of four days (one to eight). Treatment was complicated by fever and proven infection in 39% and 33% of cycles, respectively. Fever occurred more frequently in cycles administered at dose levels 1 and 2 (19 of 38, 51%) than at the higher levels (26 of 78, 33%). WHO grade 3 and 4 granulopenia ensued in 70%–95% of all cycles with no significant differences between dose levels. Cases of grade 3 and 4 thrombopenia were evenly distributed across dose levels (31%–58% of cycles), except for a lower incidence at dose level 3 (7%). Severe anemia (WHO grades 3 and 4) occurred in 25%–43% of cycles, again with the lowest incidence at dose level 3.

Mucositis was more frequent at high doses of doxorubicin. It occurred in 54% of cycles at the highest dose level and only in 32% at the initial dose level. CNS toxicity – observable in only six of the 116 treatment cycles – was not a major problem owing to the schedule of ifosfamide administration.

Microscopic hematuria was noted in seven cycles,

Table 3. Toxicity according to dose levels (all cycles; WHO grade 0 not reported).

	Dose levels[a]				
	I (24)	II (14)	III (28)	IV (24)	V (26)
Leucocytes (WHO grade)					
I	1	–	2	–	1
II	4	–	1	1	1
III	4	–	5	7	9
IV	14	14	14	15	15
Granulocytes (WHO grade)					
I	1	–	2	–	–
II	1	1	–	1	1
III	1	–	2	–	5
IV	14	12	16	19	14
Thrombocytes (WHO grade)					
I	5	3	2	4	6
II	2	4	6	4	4
III	2	2	2	8	7
IV	5	5	0	6	4
Hemoglobin (WHO grade)					
I	4	1	7	6	7
II	5	4	7	7	9
III	7	3	6	6	5
IV	3	3	1	1	3
Mucosa (WHO grade)					
I	2	–	5	5	8
II	5	5	1	3	4
III	–	–	–	2	2
IV	–	1	–	–	–
CNS (MD Anderson score)					
I	2	1	1	1	–
II	–	–	–	–	–
III	–	1	–	–	–
IV	–	–	–	–	–

[a] In parentheses = number of cycles.

Table 4. Toxicity according to dose levels (patients; WHO grade 0 not reported).

	Dose levels[a]				
	I (7)	II (4)	III (6)	IV (6)	V (8)
Leucocytes (WHO grade)					
I	–	–	–	–	–
II	–	–	1	–	–
III	1	–	–	–	1
IV	6	4	5	6	7
Granulocytes (WHO grade)					
I	–	–	–	–	–
II	–	–	–	–	–
III	–	–	–	–	1
IV	7	4	6	6	7
Thrombocytes (WHO grade)					
I	2	–	–	1	1
II	1	–	2	–	0
III	0	1	2	2	3
IV	2	3	–	3	3
Hemoglobin (WHO grade)					
I	1	–	–	–	–
II	2	–	3	2	3
III	1	1	1	3	3
IV	3	3	1	1	2
Mucosa (WHO grade)					
I	1	–	3	–	1
II	3	3	1	2	1
III	–	–	–	2	2
IV	–	1	–	–	–
CNS (MD Anderson score)					
I	1	–	1	1	–
II	–	–	–	–	–
III	–	1	–	–	–
IV	–	–	–	–	–

[a] In parentheses = number of patients.

albeit with no clinically relevant increase in serum creatinine.

Toxicity was directly attributable to GM-CSF in 15% of cycles and consisted in fever (15%), flu-like syndrome (8%), myalgia or erythema (12%).

Toxicity (patients)

Table 4 gives a breakdown of toxicity events by patients, based on the highest degree experienced by each patient.

WHO grade 4 granulopenia was present in all patients but one, with no differences between dose levels. Grade 3 and 4 thrombopenia varied across dose levels (29%–100% of patients), with a lower incidence at levels 1 and 3 (29%–33%). There was a trend toward deeper thrombocyte nadirs with increasing doses of doxorubicin ($P = 0.12$). Severe anemia (grades 3 and 4) occurred in 34%–100% of patients, with the lowest incidence at level 3. Hemoglobin nadirs tended to be deeper as the dose of ifosfamide was increased ($P = 0.057$).

Treatment was complicated by fever and proven infection in 87% and 68% of patients, respectively. All patients developed fever at the first two dose levels with ifosfamide at 12 mg/m^2, which was slightly, albeit not significantly, less frequent with ifosfamide at 10 g/m^2 (16 of 20 = 80%; $P = 0.27$). One patient died of septic shock (dose level 5).

Mucositis beyond WHO grade 2 occurred in 16% of patients. CNS toxicity was observed in only four patients and was generally mild, except in one patient who developed grade 3 toxicity with reduced verbal output, comprehension problems and vertigo. Reduction of ifosfamide in the second cycle resulted in grade-1 consciousness problems. One patient showed Fanconi's syndrome-like symptoms.

Twenty-one patients (68%) underwent regular cardiac monitoring. None of them developed clinical heart failure or a significantly reduced left ventricular ejection fraction; however, only three patients received $\geqslant 400$ mg/m^2 of doxorubicin.

In five patients (16%), side-effects and low tolerability necessitated discontinuation of GM-CSF, which was subsequently replaced by G-CSF, that was well tolerated.

Treatment was discontinued in three patients because of toxic events: one patient had febrile granulopenia, grade 4 thrombopenia complicated by retinal hemorrhage (third cycle, dose level 2), and another one had

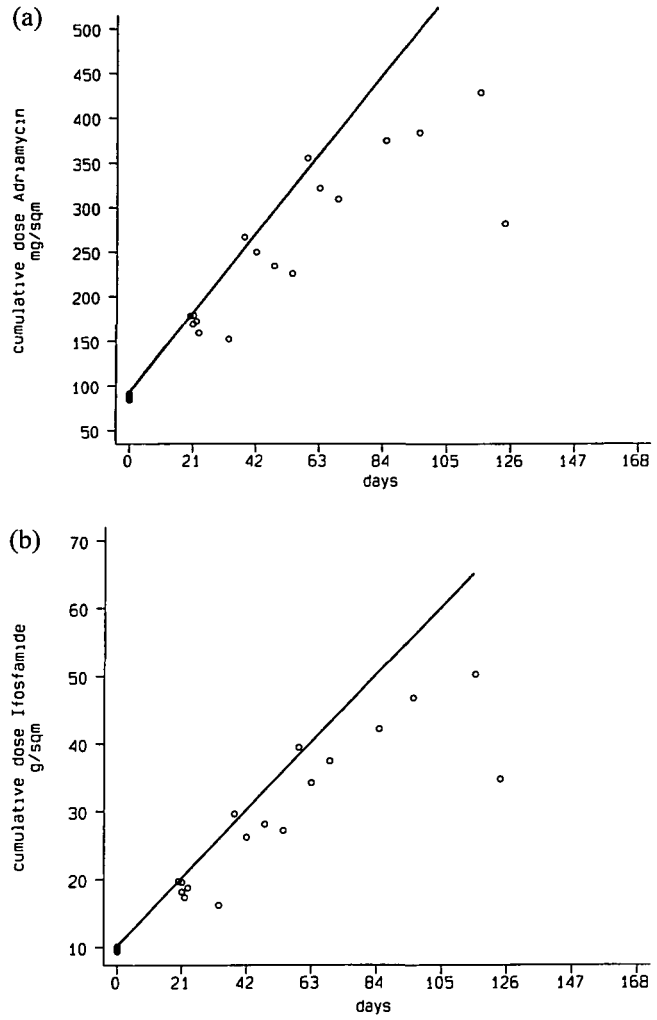

Figure 1 Plots of cumulative doses of (a) ifosfamide and (b) doxorubicin at dose level 5. The first dose (in mg/m^2) is the starting point on the drug axis; subsequent doses are cumulated against time and reflect the dose intensity of the drug. The straight line represents the planned dose intensity, the dots mark the individual doses administered. No lines for individual patients are given to facilitate visual comparison between planned and delivered dose intensities. For both drugs there was a tendency toward dose reduction (up to 20% for ifosfamide and up to 17% for doxorubicin) in the subsequent cycles.

severe sepsis and Fanconi's syndrome-like symptoms while in partial remission (third cycle, dose level 4). The third patient died of septic shock after refusing to be transferred to the hospital while febrile.

Moreover, treatment was discontinued in four patients because of refusal and in two patients because the maximum dose of doxorubicin was reached. Three patients went off treatment thanks to complete remission, and nine because of tumor progression. In 10 patients, clinical response and stabilization of disease allowed elective surgery and/or radiotherapy.

Delivered dose intensity

To assess the feasibility of multiple cycles at the maximum tolerated doses, we studied the median delivered doses (mg/m^{2}or g/m^2) in subsequent cycles at dose levels 2 and 5. At dose level 2, 92% and 97%, respectively, of the scheduled doses of ifosfamide and doxorubicin could be administered. At dose level 5, however, the planned dose of ifosfamide was down by 20% and that of doxorubicin by 17% (Figure 1). This tendency to reduce ifosfamide dosage in later cycles by up to 20% had already been observed at dose level 4, at which time, however, the full dose of doxorubicin was maintained.

Table 5. Response rate based on various characteristics.

			No. of pts	Responses CR	PR	NC	PD
Location of primary							
Soft tissue			19	2	9	5	3
Gynecological			10	2	4	1	3
Bone			2	0	0	1	1
Location of recurrence (one or more per patient)							
Local			9	2	4	1	2
Lung metastases			14	1	6	4	3
Lymph nodes			8	3	1	0	4
Liver metastases			5	0	4	0	1
Bone			4	0	1	2	1
Histology: soft tissue							
Leiomyosarcoma			4	–	3	–	1
Synoviosarcoma			3	–	1	2	–
Liposarcoma			3	–	3	–	–
Neurofibrosarcoma			2	–	–	2	–
Other			6	2	2	1	2
Histology: gynecologic							
Leiomyosarcoma			6	1	3	–	2
Mixed mesodermal			4	1	1	1	1
Grade							
I			2	–	1	–	1
II			10	–	6	4	–
III			19	4	6	3	6
Dose level	Ifo (g/m^2)	Doxo (mg/m^2)					
1	12	50	7	–	3	2	2
2	12	60	4	–	2	1	1
3	10	60	6	1	2	3	–
4	10	75	6	1	4	1	–
5	10	90	8	2	2	–	4
Overall			31	4	13	7	7

Response and survival

Although anti-tumor response was not the primary parameter under study, a summary of sarcoma types and response rates has been compiled in Table 5. The overall response rate was 55% (95% CI: 36%–73%), including four complete responders (13%) and 13 (42%) partial responders. Seven patients (23%) showed stable disease, and another seven patients (23%) showed progressive disease. Response was seen not only in soft-tissue sarcomas but also in six of 10 gynecological sarcomas irrespective of histological features.

As mentioned in the methods section, surgery and/or radiotherapy were proposed to six out of 17 responders,

hence the effect of these additional procedures is also reflected in the duration of response. The median follow-up among survivors was three years. Twelve patients with remission developed disease progression or died. The median duration of response was 19 (1.5–48) months, with 47% (SE 12%) of patients still in remission after two years. Twenty-three out of the total sample of 33 patients have died by the time of this evaluation. The median survival was two years, with 25% (SE 8%) of patients alive after three years. The patients with soft-tissue sarcomas had survived for a median of 28 months, with 33% (SE 12%) alive after three years. Causes of death were for the most part tumor-related. One patient died of toxicity, and three patients died of causes unrelated to tumor or chemotherapy (suicide, $n = 1$; liver cirrhosis, $n = 1$; stroke, $n = 1$).

Discussion

Only few active agents are available for the treatment of sarcomas, and their anti-tumor activity – ranging from 17% to 25% – is limited. Developments that add to the range of active therapeutic strategies have an immediate clinical impact. Higher response rates will benefit patients with locally advanced disease in that they enable higher resection rates. A greater efficacy of active therapeutic regimens may also improve their impact on micrometastatic disease in the adjuvant setting. Furthermore, raising the complete remission rate among patients with advanced metastatic disease will potentially increase the disease-free survival [20].

Combination of active single agents has in some instances brought the response rate up to 30%–35% [3, 8]. This was not reflected, however, in the survival of patients with metastatic disease, possibly because of suboptimal dosages and a low complete remission rate. Both doxorubicin and ifosfamide are known to be characterized by a true dose-response relationship, but owing to the expected hematological toxicity this property has never been fully exploited in combination regimens. Hematopoietic growth factors have been shown to enhance the tolerance to intensive chemotherapy [21] and thus enabled us to re-evaluate the option of applying the maximum tolerated doses in combination.

In the present study we could demonstrate that in combination with ifosfamide 12 g/m^2 the MTD of doxorubicin was 60 mg/m^2. Despite GM-CSF this dose level induced prolonged leukopenia in all analyzed patients, and one patient additionally showed severe neurotoxicity. However, once ifosfamide was decreased to 10 g/m^2 it was possible to further escalate doxorubicin up to 90 mg/m^2 while myelosuppression remained within a tolerable time frame of $\leqslant 4$ days. Only one of eight evaluable patients developed severe mucositis. Doxorubicin dose escalation was stopped at that level, which is now being used in phase II trials. Ifosfamide 10 g/m^2 together with doxorubicin 90 mg/m^2 administrated over multiple (total of 26) cycles induced WHO grade 4 leukopenia in 58% of cycles, with febrile complications requiring antibiotics in seven (27%) cases. Severe grade 3–4 thrombopenia and anemia occurred in 42% and 31% of cycles, respectively. Mucositis was minor in half of them. No neurotoxic events were noticed at that dose level.

Interestingly, there were no major differences in toxicity across the tested dose levels by cycles or by patients. Severe leukopenia and granulopenia were universal. Febrile episodes, on the other hand, were more frequently observed after ifosfamide 12 g/m^2. Similarly, ifosfamide at its highest dose level was associated with a deeper hemoglobin nadir, whereas the maximum dose of doxorubicin led to more severe thrombocytopenia and more frequently caused mucositis.

However, the toxicity of the studied regimen was not significantly different from other modes of combination chemotherapy. Even regimens at standard dose with doxorubicin 60 mg/m^2 and ifosfamide 7.5 g/m^2 has led to substantial grade 3 or higher myelosuppression in 80% of cases, involving a 4% rate of toxic deaths [3]. An even lower dosage of doxorubicin 50 mg/m^2 and ifosfamide 5 g/m^2 induced severe neutropenia in 73% of patients [22].

The standard combination of doxorubicin 60 mg/m^2, ifosfamide 7.5 g/m^2 and dacarbazine 900 mg/m^2 (MAID regimen) led to severe neutropenia in the vast majority of cases, but its duration was reduced by addition of G-CSF from up to 10 days in the absence of growth factors to less than three days [23]. Likewise, the incidence of febrile episodes was reduced with the help of GM-CSF from 58% to 23%. Under the protection of GM-CSF, doxorubicin was increased to 75 mg/m^2 in association with a standard dose of 5 g/m^2 ifosfamide [9]. WHO grade 4 neutropenia was observed in all patients, but its duration varied between three and six days, and the neutropenic infection rate was 14%. Doxorubicin analogues like epirubicin have been thought to be less myelotoxic [24] and to improve the therapeutic index of combination regimens. Grade 4 leukopenia was indeed present in 5% of patients after ifosfamide 5 g/m^2 and epirubicin 100 mg/m^2 [25]. But when ifosfamide 9 g/m^2 was combined with epirubicin escalated from 100 to 140 mg/m^2, grade 3–4 leukopenia was observed in 76%–90%, anemia in 28%–53%, and thrombopenia in 17%–29% of cycles. Under GM-CSF protection the median duration of leukopenia was four to five days, with 43% of patients developing neutropenic fever [26]. Ifosfamide 12.5 g/m^2 and epirubicin 90 mg/m^2 equally induced severe myelosuppression in all patients [27]. The use of hematological stem cells, while failing to reduce the severity of myelosuppression, allowed further escalation of ifosfamide to 17.5 g/m^2 and of epirubicin to 120 mg/m^2, although nephrotoxicity and hepatotoxicity became dose-limiting factors [27]. In this way, the anthracycline analogues had no advantage over doxorubicin in terms of toxicity [28] and, when given at less myelotoxic doses, also had less activity [23].

If myelosuppression must be accepted as inherent in the association of ifosfamide and doxorubicin, the ques-

tion arises whether this translates into a higher remission rate. In some studies, myelosuppression was a significant prognostic factor for response [29]. Thus, for the best results, the most active drugs should be given at doses high enough to eventually induce toxicity [30].

In the study herein reported, the overall response rate was 55%, including 13% complete responders. Other intensive regimens have yielded similar results, with response rates of 45%–69%, including 8%–17% complete responders [9, 26, 31]. Due to the small sample and histological heterogeneity of patients at the various dose levels, we were unable to establish a dose-response relationship even though the number of complete responders was greater at the highest dose of doxorubicin. A similar observation has been made with epirubicin [26]. The high response rate might be due to good patient selection. Although response rates have been related by multivariate analysis to absence of liver metastases, presence of lung lesions, and young age [32], four of our five patients with liver metastases showed partial response.

Overall, 78% of our patients showed response or stable disease. Ten of them could be further treated by surgery and/or radiotherapy in an effort to render them free of disease. The median survival for the total sample (33 cases, including early deaths) was 24 months, and 25% of all patients were alive after three years. The results were even better in the subgroup with soft-tissue sarcomas, where the three-year survival amounted to 33%. Considering the 12-month median survival after standard chemotherapy [2], our results confirm the notion that disease-free status and overall survival can be prolonged by incorporating active chemotherapy in a multimodality approach [20].

Uterine sarcomas are for the most part resistant to chemotherapy [33]. Doxorubicin has some activity in leiomyosarcomas, as have cisplatin and ifosfamide in mixed mesodermal tumors. Combined ifosfamide 5 g/m^2 and doxorubicin 50 mg/m^2 was shown to be toxic and moderately active in metastatic leiomyosarcoma [33]. The response rate in our sample of 10 uterine sarcomas was 60% irrespective of histological subtypes. Such a finding is exceptional given the type of disease and needs to be verified in a larger sample of patients.

To summarize, we were able to demonstrate that the optimal dose combination of doxorubicin and ifosfamide, administered with hematopoietic growth factors, was 90 mg/m^2 and 10 g/m^2 respectively. Myelosuppression was severe but short and could be managed in a multicenter setting. Such a degree of myelosuppression should be regarded as acceptable given the outlook of a high response rate and an improvement in disease-free survival. This clinically relevant antitumor activity now needs to be confirmed in regular phase II trials including patients with both gynecological and soft-tissue sarcomas.

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