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Ifosfamide plus Doxorubicin in Previously Untreated Patients with Advanced Soft Tissue Sarcoma

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The objective of this phase II trial was to assess the therapeutic activity and toxicity of doxorubicin plus ifosfamide in previously untreated patients with advanced soft tissue sarcoma. Treatment was doxorubicin 50 mg/m² followed by a 24 h infusion of ifosfamide 5 g/m² plus mesna 2.5 g/m² repeated every 3 weeks until disease progression or unacceptable toxicity occurred. Of 203 patients entered, 175 were evaluable for response. The response rate was 35% (95% CI 28–42%), with 9% of the patients achieving a complete remission and 26% a partial remission. The median time to progression was 29 weeks for all evaluable patients, and 67, 40 and 28 weeks for complete and partial responders and patients with stable disease, respectively. The median duration of survival was 58 weeks. Myelosuppression was the dose-limiting toxicity, resulting in leukopenia (WHO grade 3 and 4) in 73% of evaluable treatment courses. Other side-effects were rare and usually well manageable.
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INTRODUCTION

A LITTLE over half of soft tissue sarcomas (STS) in adults (annual incidence 2–3 per 100 000) arise in the extremities, and local tumour can be controlled in about four-fifths of these cases. However, due to a propensity for early widespread dissemination and a primary resistance to most cytostatic drugs, 5 year survival is only 40–50%. Various cytostatics have been tested by the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) as well as by other investigators. Only doxorubicin and ifosfamide consistently achieve response rates above 20% [1–11]. Initial studies of doxorubicin-containing combinations appeared promising, with response rates of 50–60% [12, 13]. However, these rates could not be reproduced and considerable toxicity was observed in subsequent larger trials [14, 15].

Urothelical toxicity limits the dose of ifosfamide. The development of mesna, which reduces ifosfamide-induced haemorrhagic cystitis, rekindled interest in ifosfamide. Response rates with ifosfamide as a single agent for untreated and pretreated patients with STS ranged from an initial 65% [16, 17] to 18–38% in more recent studies [1–8]. In a randomized phase II trial [7], there was no significant difference between the overall response rates of ifosfamide (18%) and cyclophosphamide (8%); a trend in favour of ifosfamide was observed. 7% of pretreated and 24% of untreated patients responded to ifosamide, compared with 13% and none out of 30 with cyclophosphamide. In addition, ifosfamide was less myelotoxic than cyclophosphamide.

Against this background, in 1984, STBSG started a phase II trial of doxorubicin plus ifosfamide in previously untreated patients with locally advanced or metastatic STS. Our aim was to assess the activity and toxicity of this combination.

PATIENTS AND METHODS

Eligibility

Patients aged 15–70 with WHO performance status 0–2 and a histologically proven locally advanced and/or metastatic sarcoma were eligible. The following histological types of sarcoma were eligible: malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma, fibrosarcoma, leiomyosarcoma, angiosarcoma including haemangiopericytoma, neurogenic sarcoma, unclassified sarcoma, and miscellaneous sarcoma (including mixed mesodermal tumours of the uterus). In addition, patients were required to have adequate renal (serum creatinine below 150 μmol/l), hepatic excretory (serum bilirubin below 20 μmol/l) and bone marrow (leucocytes above 3.5×10^9/l, platelets over 100×10^9/l) function and measurable progressive disease. Osseous metastases and pleural effusions were not considered to be measurable lesions. Other exclusion criteria were: previous chemotherapy, radiotherapy to the sole available index lesion, second primary malignant tumours (except for adequately treated *in situ* carcinoma of the cervix or basal cell carcinoma), central nervous system metastases, or concomitant

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severe medical illness, including psychosis and heart failure. Patients for whom regular follow-up could not be assured were also ineligible. Informed consent was obtained from all patients according to national/institutional guidelines.

Treatment

Therapy was doxorubicin 50 mg/m^2 as an intravenous bolus followed by a 24 h infusion of 3 l of dextrose-saline containing ifosfamide 5.0 g/m^2 and mesna 2.5 g/m^2. 2 h before ifosfamide/mesna, diuresis was initiated with 1 l of dextrose-saline. 200 ml 20% mannitol was infused 1 h before chemotherapy. In addition, an intravenous bolus injection of mesna 600 mg/m^2 preceded the ifosfamide/mesna infusion. After this infusion another 2 l of dextrose-saline containing mesna 1.25 g/m^2 was infused over 12 h.

Treatment courses were repeated every 3 weeks for at least two cycles unless there was rapid disease progression after the first cycle. Patients with an objective remission or stable disease continued treatment until disease progression or unacceptable toxicity occurred.

Treatment modifications were allowed in cases of severe myelosuppression. The initial dose of both drugs was reduced by 20% if leucocytes fell below 1.0 × 10^9/l and/or platelets below 40 × 10^9/l during the previous cycle (monitored by weekly blood counts). Further therapy was delayed by a week if the leucocyte count was under 3.5 × 10^9/l and/or platelets were below 100 × 10^9/l at the time scheduled for the next treatment. The doses of both drugs were reduced by 20% if the treatment was postponed for more than a week on two consecutive courses. In cases of treatment delay of more than 3 weeks without haematological recovery, therapy was stopped (unacceptable toxicity).

Assessments

Baseline studies included history and physical examination, complete blood count (including differential blood count), biochemistry (including liver and renal function) and urine analysis. These tests were repeated before each treatment course. Electrocardiography and chest radiography, if normal before therapy, were repeated every 6 weeks. When required for individual tumour measurement, chest X-rays were done before each course, and other radiographs, computed tomography and ultrasound were repeated every 3–6 weeks. Radionuclide scans for assessment of left-ventricular ejection fraction and bone scans or bone X-rays were optional. Haematuria was assessed before and immediately after the ifosfamide infusion. Blood counts were done weekly after each course, at least during the first two cycles. A new treatment course was not started if serum creatinine was over 150 μmol/l or creatinine clearance was below 60 ml/min.

Evaluation of response and toxicity

Patients were considered evaluable for response if they had received at least two courses of chemotherapy and tumour measurements had been repeated at 6 weeks. However, if tumour progression occurred before the second treatment course could be completed, treatment failure rather than non-evaluability was assumed. Complete response (CR), partial response (PR), no change (NC), and progressive disease (PD) as well as toxicities were defined/graded according to WHO criteria [18]. Objective responses (CR and PR) were reviewed externally.

Histopathology review

A central pathology review was done by two panels consisting of six members each, one for the Northern European institutes, chaired by Professor J. van Unnik, Utrecht, The Netherlands, and one for the Southern European institutions, chaired by Dr G. Contesso, Villejuif, Paris, France. If two members of the panel independently made the same diagnosis as the referring pathologist, this diagnosis was accepted. If there was disagreement, other members of the panel examined the histological sections and a consensus was reached.

Statistics

Patient registration and data analysis were done at the EORTC Data Center. Survival and time to progression curves were calculated with the Kaplan–Meier product limit procedure [19].

Table 1. Reasons for exclusion

Total number of patients entered	203
Patients evaluable for response	175
Ineligible patients	17
Inadequate histopathology	5
Non-measurable disease	4
Performance status > 2 at entry	2
Missing data	2
Previous malignant disease	1
Previous therapy excluded by protocol	1
Previous irradiation of index lesions	1
Age > 70	1
Non-evaluable patients	11
Early death	5
malignant disease	3
toxicity	1
other causes	1
Treatment refusal after first course	3
Inadequate treatment	1
Inadequate follow-up	2

Table 2. Characteristics of evaluable patients

	Responders	Non-responders	Total
Number of patients	61	114	175
M/F	33/28	56/58	89/86
Median age (yr, range)	51 (18–70)	47 (17–69)	49 (17–70)
WHO performance status			
0	20	31	51 (29%)
1	33	63	96 (55%)
2	8	20	28 (16%)
Previous radiotherapy	16	31	47 (27%)
Extent of disease at entry			
Local	16	20	36 (21%)
Metastatic	26	48	74 (42%)
Both	19	46	65 (37%)

Table 3. Response by site

Site	CR	PR	NC	PD	Total	Response (%, 95% CI)	
Primary lesion	6	18	34	8	66	36	(25–48%)
Lung lesions	14	22	52	19	107	34	(25–43%)
Skin + lymph nodes	9	9	17	8	43	42	(27–57%)
Liver	0	1	5	1	7	14	(0–40%)
Other visceral lesions	1	6	12	1	20	35	(14–56%)
Other	2	2	2	3	9	44	(12–77%)

RESULTS

Patients' characteristics

Between June 1984 and January 1986, 203 patients from twenty-five participating institutions in Europe entered the trial. 175 (86%) were evaluable for tumour response and toxicity (Table 1). The characteristics of the evaluable patients are shown in Table 2.

Response

16 patients had a CR (9%, 95% CI 5–13%) and 45 patients (26%) a PR, resulting in an overall response rate of 35% (95% CI 28–42%). As has been observed in previous studies, response was dependent on the initial performance status of the patients: 40% for WHO–0, 35% for WHO–1 and 29% for WHO–2. Stable disease was recorded in 82 patients (47%) and 32 patients (18%) had PD. Responses occurred in all types of lesions with no significant differences with respect to tumour site (Table 3).

The median number of weeks to documentation of an objective response (CR or PR) was 9 (range 3–52); the median time to CR was 16 weeks, and ranged from 5 to 62 weeks, the latter in a patient in whom a CR was recorded after treatment had been stopped. Evaluable patients received a median of 6 treatment cycles (1–17): responders 8 (2–17) and non-responders 4 (1–15). The median cumulative drug doses for all evaluable patients given throughout the treatment period were 254 mg/m^2 for doxorubicin (48–686) and 25.4 g/m^2 for ifosfamide (4.8–75).

The median time to progression for all 175 patients was 29 weeks (Fig. 1; CR 67 weeks, PR 40 weeks [P = 0.5], NC 28 weeks). Of 175 evaluable patients, 42 patients were alive at the time of analysis, 5 patients were lost to follow-up, and 128 patients had died (malignant disease 123 patients, cardiovascular disease 3, other causes 2). The median survival for all evaluable patients was 58 weeks (Fig. 2); for patients with CR 100 weeks, for PR 69 weeks, for stable disease 57 weeks, and for PD 21 weeks.

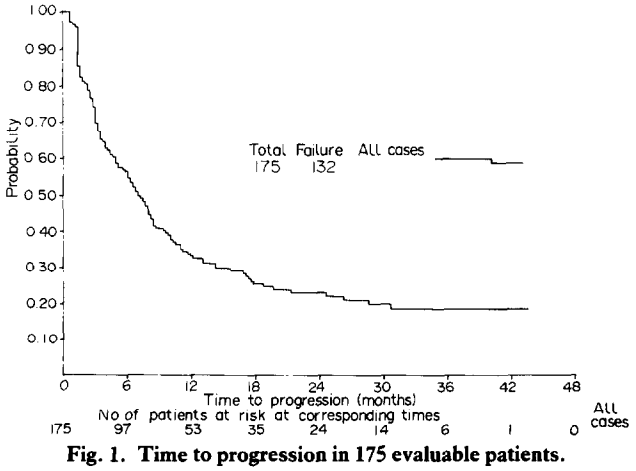

Fig. 1. Time to progression in 175 evaluable patients.

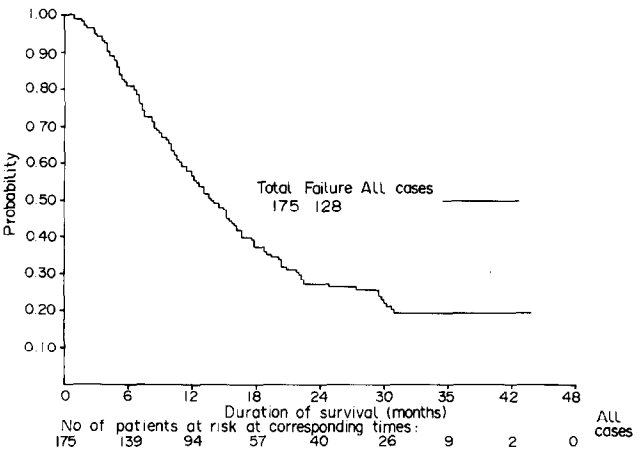

Fig. 2. Duration of survival (all evaluable patients).

Toxicity

Haematological side-effects were analysed in patients for whom weekly blood counts were available (Table 4). Scoring the lowest leucocyte value observed over all treatment cycles in 167 evaluable patients who received a median of 5 treatment courses (range 1–15), 122 patients (73%) had a nadir below 2000/μl, including 56 patients (34%) below 1000/μl.

Thrombocytopenia below 75,000/μl occurred in 2% of the patients after treatment cycles 1 and 2, and in 5% of the patients evaluable for treatment course 3. The lowest values observed were 20,000/μl in 1 patient, and 3000/μl (with less than 100 leucocytes per μl) in a patient who died from severe myelosuppression associated with grade 4 infection after the first treatment course. Non-haematological toxicities, evaluable in 187 patients who received a median of 5 treatment courses (range 1–17) are summarized in Table 5.

Modifications of treatment because of toxicity were required in 271 of 1024 treatment courses (26%) administered to 187 evaluable patients (leucocytopenia 85%, infection 4%, nausea/vomiting 1%, other 10%). Chemotherapy-related side-effects led to treatment being stopped in 20/187 patients (11%): nausea/vomiting (6 patients), leukopenia (4), urothelial toxicity (2), neurological side-effects (2), renal toxicity (1) cardiotoxicity (2) and combinations of these and other toxicities (3).

DISCUSSION

Because of the activity of doxorubicin and ifosfamide as single agents in STS and because our previous trial [7] and other studies [2, 3, 6, 8, 20] did not show complete cross-resistance—at least unidirectionally—between these drugs, the combination was a reasonable choice for advanced STS. Using doxorubicin plus ifosfamide in the present study, we observed a response rate of 35% and the median duration of survival for all patients was

Table 4. Lowest leucocyte value over all treatment courses in 167 evaluable patients

Leucocyte counts (/μl)	WHO grade	No. of patients	
≤ 1000	4	56	(34%)
1001–2000	3	122	(73%)
2001–3000	2	150	(90%)
3001–4000	1	163	(98%)
>4000	0	4	(2%)

*Table 5. Non-haematological toxicities in 187 evaluable patients**

Side-effect	WHO grade 0	1+2	3	4	% grade 3 or 4
Phlebitis	157	29	0	0	0
Nausea/vomiting	8	102	71	5	41
Cutaneous	181	5	0	0	0
Alopecia	12	41	85	46	71
Diarrhoea	158	24	4	0	2
Oral	153	26	5	1	3
Liver	169	17	0	0	0
Renal	180	3	3	0	2
Haemorrhage	179	5	2	0	1
Fever	144	38	3	0	2
Infection	150	24	10	1	6
Cardiac	179	5	2	0	1
Consciousness	172	9	5	0	3
Peripheral neurotoxicity	178	7	1	0	<1
Haematuria	156	26	3	0	2

*Highest grade achieved.

58 weeks. These data accord with other smaller trials. Using doxorubicin 65 mg/m^2 on day 1 and ifosfamide 2.5 g/m^2 on days 1–3, Kircher *et al.* reported a response of 43% in 14 patients [21]. With doxorubicin 50 mg/m^2 administered over 3 days and ifosfamide 7.5 g/m^2 over 5 days, Hartlapp *et al.* reported 3 CRs and 9 PRs (response rate 57%) in 21 patients [22]. Sledge *et al.* [23] observed a 41% response (3 CR, 13 PR) among 42 previously untreated patients with advanced STS. In that study, doxorubicin was administered at 60 mg/m^2 and ifosfamide at 5 g/m^2 over 24 h every 3 weeks. Mansi *et al.* [24], using ifosfamide 5 g/m^2 as a 24 h infusion and doxorubicin at a dose of either 40 or 60 mg/m^2, reported 3 CRs and 8PRs (response rate 22%) in 50 evaluable patients, 8 of whom had been pretreated. Times to progression and duration of survival in that trial were similar to our data.

Except for the 1 toxic death due to severe myelosuppression after the first treatment course, the side-effects from doxorubicin plus ifosfamide as administered in our study were well tolerated in most patients. Major toxicity caused treatment to be stopped in 11% of patients. Myelosuppression was the dose-limiting toxicity, and with regard to the degree and percentage of leukopenia observed, a further increase in the dose of either drug in this schedule cannot be recommended. The results obtained with ifosfamide and doxorubicin were equivalent to those achieved with more toxic combinations [25]. Whether the present combination, however, is preferable to either drug alone or to other regimens (such as cyclophosphamide/vincristine/doxorubicin/dacarbazine) is unclear. Therefore, the therapeutic ratio of doxorubicin plus ifosfamide in advanced STS is being compared in a phase III trial by STBSG with intermittent high doses of doxorubicin alone and with cyclophosphamide/vincristine/doxorubicin/dacarbazine.

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