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Short report

High-dose ifosfamide plus adriamycin in the treatment of adult advanced soft tissue sarcomas: Is it feasible?

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Summary

Background: Adriamycin (ADM) and ifosfamide (IFO) are the two most active agents in the treatment of soft tissue sarcomas (STS) with a clear dose-response relationship. We evaluated the feasibility and toxicity of a high-dose IFO-plus-ADM combination.

Patients and methods: Fourteen patients with advanced disease and nine patients in adjuvant setting received IFO 12.5 g/m^2 in 120-hour continuous infusion with Mesna uroprotection and ADM 20 mg/m^2 on days 1–3 and G-CSF every three weeks.

Results: Twenty-three patients received 89 chemotherapy cycles (70 cycles at full dose). Seventeen patients received the planned treatment, and nine patients required dose reductions. We observed grade 3–4 neutropenia in 52 cycles (59%)/20 patients; grade 3–4 thrombocytopenia in 16 cycles (18%)/nine patients; grade 3–4 anaemia in 24 cycles (27%)/11 patients. Eight patients experienced febrile neutropenia and six patients required blood transfusions.

Conclusions: While feasible, this regimen showed heavy toxicity. Nevertheless, 74% of the patients were able to complete the planned treatment. Adjustment of the schedule of IFO continuous infusion to improve this combination is currently under investigation.

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

Introduction

Only a few drugs have shown activity in the treatment of soft tissue sarcomas (STS). Doxorubicin (ADM) has yielded a response rate of 15% to 35%, with a proven dose-response relationship.

Ifosfamide (IFO) has shown an 18%–20% response rate as both first- and second-line treatment in metastatic STS when administered at standard doses (5 g/m^2), and promising response rates ranging from 17% to 66% at higher dose, with a proven dose-response relationship.

Trials testing full doses of an anthracycline in combination with maximal doses of IFO are not homogeneous: data concerning response are few and inconclusive, although response rates of 50%–63% have been reported [1–6]. The highest reported dose of IFO in combination with an anthracycline without peripheral blood stem cell support was 12.5 g/m^2 and the two reports testing this regimen showed different toxicity results [2, 6]. We decided therefore to assess the feasibility and toxicity of a regimen combining high-dose. IFO (12.5 g/m^2) and standard-dose ADM (60 mg/m^2).

Patients and methods

From May 1995 through February 1997, 23 patients with Soft Tissue Sarcoma (STS), 10 men and 13 women, aged 15 to 69 years (median age 45 years), entered the study. A total of 89 cycles of chemotherapy were administered, 70 cycles at full dose and 19 cycles at reduced doses. Fourteen patients had advanced disease and nine were treated in an adjuvant setting. Only one of 23 patients was pretreated with anthracycline; since relapse occurred more than six months after treatment discontinuation, he has not been considered anthracycline-resistant.

Histologic subtypes were leiomyosarcoma (ten patients), alveolar rhabdomyosarcoma in adults (three patients), liposarcoma (two patients), other STS (eight patients). All STS were high or intermediate grade.

Sites of primary tumour in patients with advanced disease were as following: the extremities (four patients), gluteal region (three patients), gastro-intestinal/retroperitoneal (three patients), breast (two patients), pelvis (one patient), mediastinum (one patient). Exclusion criteria included ECOG performance status >2, age over 70 years, CNS involvement or other health problems that might prevent full compliance with the study. Informed consent was obtained from all patients.

IFO 12.5 g/m^2 continuous-infusion over 120 hours with Mesna uroprotection (175% IFO dose) and adriamycin 20 mg/m^2 i.v. bolus on days 1–3, plus 3000 ml of glucosate solution 5%, desametasone 8 mg and granisetron 3 mg daily, were administered every three weeks. Prophylactic G-CSF 5 mg/kg s.c. was given daily on days 7–14.

Four cycles of treatment in the adjuvant setting were planned, six cycles for responding patients and four for patients with stable disease.

Toxicity was evaluated according to WHO criteria; a complete blood cell count was performed twice a week.

In the presence of grade 4 thrombocytopenia, grade 3–4 febrile neutropenia (T > 38 °C) requiring hospitalisation, grade 1 neutropenia after treatment delay ≥2 weeks or leucoencephalopaty, a 20% reduction of the total dose of IFO (except in one patient, who received a dose reduction of 25% of both drugs) was performed for all subsequent cycles.

Drop-out occurred if the same toxicity occurred despite dose reduction or if >grade 1 haematological toxicity persisted after treatment delay ≥2 weeks or because of grade 3–4 neutropenia associated with fever for over a week.

Results

Overall toxicity

Twenty-three patients received 89 cycles of chemotherapy, 70 of the cycles at full dose.

Seventeen patients (74%) completed the treatment as planned. Interruption of the treatment program in the remaining six patients was according to drop-out criteria in three cases and because of patient refusal in three cases. Overall, nine patients required dose reductions; two of them had to discontinue treatment altogether before completion.

Grade 3–4 haematological toxicity is reported in Table 1.

Four patients required hospitalisation because of febrile neutropenia (T > 38 °C > 48 hours); none of them experienced infection or sepsis, haemorrhaged or required platelet transfusion.

One patient developed acute leukoencephalopathy, grade 3 mucositis occurred in three patients (13%)/five cycles (6%). All patients experienced grade 2 alopecia.

No renal toxicity nor grade 3–4 nausea or vomiting were reported.

Table 1. Overall toxicity (89 cycles, 23 patients).

Toxicity	Grade 3 (WHO)		Grade 4 (WHO)	
	Cycles *n* (%)	Patients *n* (%)	Cycles *n* (%)	Patients *n* (%)
Neutropenia	14 (16)	5 (22)	38 (43)	15 (65)
Thrombocytopenia	12 (13)	6 (26)	4 (4)	3 (13)
Anemia	19 (21)	7 (30)	5 (6)	4 (17)
Neurotoxicity	–	–	1 (1)	1 (4)
Mucositis	5 (6)	3 (13)	–	–
Renal toxicity	–	–	–	–
Nausea vomiting	–	–	–	–

Other events	Cycles *n* (%)	Patients *n* (%)
Febrile neutropenia	13 (15)	8 (35)
Blood transfusions	10 (11)	6 (26)

Table 2. Toxicity: full-dose regimen schedule (70 cycles, 23 patients).

Toxicity	Grade 3 (WHO)		Grade 4 (WHO)	
	Cycles *n* (%)	Patients *n* (%)	Cycles *n* (%)	Patients *n* (%)
Neutropenia	11 (16)	5 (22)	30 (43)	15 (65)
Thrombocytopenia	9 (13)	5 (22)	3 (4)	3 (13)
Anemia	13 (19)	7 (30)	4 (6)	3 (13)
Neurotoxicity	–	–	1 (1)	1 (4)
Mucositis	5 (7)	3 (13)	–	–
Renal toxicity	–	–	–	–
Nausea vomiting	–	–	–	–

Other events	Cycles *n* (%)	Patients *n* (%)
Febrile neutropenia	11 (16)	7 (30)
Blood transfusions	5 (7)	5 (22)

Full-dose regimen toxicity

All 70 full-dose cycles, administered to 23 patients, were evaluable for toxicity.

Grade 3–4 haematological toxicity is reported in Table 2.

No cumulative neutropenia can be detected; 16 grade 3–4 episodes occurred during the first 23 cycles of treatment.

Because of febrile neutropenia four patients required hospitalisation. Three patients (14%) experienced grade 3 mucositis.

Responses

All 14 patients with advanced disease were evaluable for response. We observed two complete and five partial responses with a 50% overall response rate (confidence interval (CI): 23%–77%); six patients had stable disease and one patient progressed.

With a median follow-up of nine months (range two to 25+), the median survival has not yet been determined; the median time to progression was nine months (range six to 15) in eight patients; six patients are still in response (range 4+–9+).

Discussion

The main purpose of this study was to evaluate the feasibility and toxicity of a poly-chemotherapy regimen containing IFO 12.5 g/m^2 and ADM 60 mg/m^2 associated with G-CSF, every three weeks.

Of 23 patients in the group, 17 (74%) received the planned treatment, while six had to discontinue treatment before completion of the schedule. Moreover, seven of 17 and two of six patients had dose reductions during treatment.

Myelosuppression was the predominant toxicity observed. Febrile neutropenia occurred in eight patients (35%)/13 cycles (15%), four of them requiring hospitalisation. Nine patients (39%) experienced grade 3–4 thrombocytopenia in 16 cycles (18%), six of them requiring blood transfusions. There were no deaths, sepsis or bleeding complications. As for the 70 full-dose cycles, febrile neutropenia occurred in 11 cycles (16%), whereby four patients required hospitalisation and five received blood transfusions.

In three cases the interruption of treatment before completion was due to neutropenia, while in the remaining three such interruptions were due to the patients' refusal.

Overall, as a consequence of treatment toxicity, both drugs were administered at 85% of the planned dose-intensity:

The data on the efficacy of the studied treatment are inconclusive because of the heterogenicity of the population and the limited number of patients with advanced disease. Among the 14 patients evaluable, we obtained two complete responses, five partial responses, and only one disease progression.

Literature data on the toxicity of regimens containing high-dose IFO and an anthracycline do not identify any one less-myelotoxic combination, since different doses of anthracycline and IFO have been used in the few reported experiences [2–6]. Few studies have been reported using a schedule similar to the one we tested.

A dose-finding study by the Italian Group for the Study of Rare Tumours (IGSRT) on advanced adult STS found a maximal tolerable dose of IFO 10.5 g/m^2 in three days plus epirubicin 120 mg/m^2 [1].

Reichardt reported grade 3–4 haematotoxicity in all 46 patients with advanced STS treated with a schedule containing IFO 12.5 g/m^2 and EpiADM 90 mg/m^2 [2].

Nevertheless, in a dose-finding study on metastatic breast cancer [6], authors recommended total IFO and ADM doses equal to those used in our schedule after five levels of IFO dose-escalation.

From these data it follows that future studies on the treatment of STS should aim to reduce the haematological toxic effects of the combination of h.d. IFO and full-dose anthracycline to increase its feasibility.

The most interesting possibility for reducing the toxicity of our combination consists of a modification in the administration schedule for IFO, using a prolonged out-patient infusion of a daily low dose [7–9].

Out-patient 10-day continuous infusion of IFO 13 g/m^2 [9] administered by portable pump showed a 30% Grade 3–4 neutropenia; even lower myelosuppression was registered in preliminary data by the IGSRT by a further prolongation of the infusion, whereby IFO 1 g/m^2 was administered daily over a 14-day period every three weeks, without growth factor support [10].

Another interesting research approach would be to combine with high-dose IFO the liposomal formulation of ADM, which has show minimal myelosuppression in the absence of growth factor support. However, only a few preliminary data on liposomal doxorubicin activity in STS are as yet available [11, 12] and we cannot assess its role in the management of these tumours.

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