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CLINICAL TRIAL REPORT

Gunnar Sæter · Kristian Talle · Øyvin P. Solheim

Treatment of advanced, high-grade soft-tissue sarcoma with ifosfamide and continuous-infusion etoposide

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Abstract A total of 33 patients (median age, 44 years) with high-grade, adult soft-tissue sarcoma were treated with etoposide given at 600 mg/m^2 in a 72-h continuous infusion and ifosfamide given at 1500 mg/m^2 per day for 3 days every 3 weeks. Dose escalation/reduction was protocolled depending on the level of hematological toxicity observed in the preceding course. Overall, 90% of patients had metastatic disease, and the most common histologies were malignant fibrous histiocytoma and leiomyosarcoma. A median of 5 (range, 1–9) courses were given. Of 30 patients who were evaluable for response, 12 (40%) obtained a partial remission, and the median time to progression was 8 (range, 4–13) months. Grade 3–4 leukopenia and thrombocytopenia were seen after 89% and 8% of the courses, respectively; neutropenic fever was seen in half of the patients (15% of courses); and 32% of courses had to be postponed by 7 days or more due to myelosuppression. Dose reduction to below the standard had to be performed in 46% of courses, and dose escalation was achieved in only 13%. The reduced toxicity seen after the addition of granulocyte colony-stimulating factor (G-CSF) in five patients indicates that growth-factor support may enhance the dose intensity of the regimen. The results indicate significant activity for this regimen in adult soft-tissue sarcoma, which may in part be a result of the escalated dose and prolonged mode of administration of the phase-specific agent etoposide. As a result of this pilot series, a phase II study with ifosfamide, etoposide, and G-CSF in advanced adult soft-tissue sarcoma has been initiated by the Scandinavian Sarcoma Group.

Key words Etoposide · Ifosfamide · Soft-tissue sarcoma

G. Sæter (✉) · Ø. P. Solheim
Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, N-0310 Oslo 3, Norway

K. Talle
Department of Radiology, The Norwegian Radium Hospital, Montebello, N-0310 Oslo, Norway

Introduction

Adult soft-tissue sarcoma (STS) is considered to be moderately sensitive to chemotherapy, with maximal reproducible response rates being around 45% for aggressive regimens containing doxorubicin and ifosfamide [2, 4, 10, 17]. However, no randomized trial to date has convincingly demonstrated that adjuvant chemotherapy prolongs overall survival [5, 13], and the need for new regimens of increased potency is evident.

Etoposide given as a short-term infusion has shown low activity in adult STS [9, 15, 18, 19]. However, the mechanism of action of etoposide involves high cell-phase specificity [6, 7], and a randomized study in small-cell lung cancer has demonstrated a dramatic schedule dependency for this drug [16]. To evaluate this aspect in advanced adult STS, The Norwegian Radium Hospital has initiated a pilot study for the Scandinavian Sarcoma Group, employing a combination of etoposide given in a 72-h infusion and ifosfamide. Furthermore, due to the indications for a dose-response relationship in STS [3, 17], stepwise dose escalation was intended, based on the level of bone marrow toxicity.

Patients and methods

Patients

From April 1989 to April 1994, 33 patients with metastatic or locally advanced, high-grade adult STS were entered into the study. Patients with round-cell, juvenile tumors (rhabdomyosarcoma, primitive neuroectodermal tumor, extraskeletal Ewing's sarcoma) were ineligible. There were 18 men and 15 women aged a median of 44 (range, 19–73) years. In all, 29 patients (88%) had a WHO performance status of 0–1 and 4 patients (12%) had WHO 2. The most common histologies were malignant fibrous histiocytoma and leiomyosarcoma (Table 1). All patients had STS of high-grade malignancy [1], with 15 tumors being classified as grade IV and 13, as grade III; 5 tumors could not be subgraded.

Overall, 91% of the patients had metastatic disease (lung metastases in 61%, liver metastases in 15%; Table 2). In all, 11 patients

Table 1 Histological subclassification

Malignant fibrous histiocytoma	9 patients
Leiomyosarcoma	6
Synovial sarcoma	5
Angiosarcoma	3
Hemangiopericytoma	2
Malignant schwannoma	2
Fibrosarcoma	1
Liposarcoma	1
Mixed tumor (mesenchymoma)	1
Unclassifiable	3
Total	33 patients

Table 2 Extent of disease

Inoperable primary tumor	3
Metastatic disease	30
Lung metastases alone	18
Lung + other	2
Liver	5
Soft tissue	4
Intraabdominal	1

(33%) had received previous chemotherapy, in all but 1 case involving doxorubicin-containing regimens (CYVADIC in 6 patients); only 1 patient had responded to this treatment.

Chemotherapy

Etoposide (600 mg/m^2) was given as a 72-h continuous infusion. Ifosfamide (1500 mg/m^2 per day for 3 days) was given as a 2-h infusion, with a mesna dose in milligrams equal to 20% of the daily ifosfamide dose being given at 0, 4, and 8 h. This regimen was repeated every 3 weeks for a maximum of nine courses. Chemotherapy was started provided that total leukocyte (WBC) and platelet (PLT) counts were above 3.0×10^9/l and 100×10^9/l, respectively.

WBC and PLT counts were performed on days 8, 12, 15, and 19 after the start of chemotherapy. If nadirs for WBC and PLT were above 1.5×10^9/l and 70×10^9/l, respectively, the doses for both agents were escalated by 10% in the next course, up to a total of 130% of the standard dose. In the presence of WBC nadir below 0.7×10^9/l, a total PLT nadir below 50×10^9/l, or febrile neutropenia (temperature, >38.5 °C; WBC, $<1.0 \times 10^9$/l), doses were reduced by 10%–20% in the next course.

In an attempt to facilitate dose escalations, granulocyte colony-stimulating factor (G-CSF; Neupogen Roche, Basel, Switzerland) was given to five patients at a dose of 5 μg/kg for 12 days starting at 24 h after the completion of chemotherapy.

Evaluation of response

Response evaluation was performed according to WHO criteria after three, six, and nine courses and then every 3 months after the termination of therapy. As a measure of response duration, time to progression was employed, i.e., the time from the start of chemotherapy to disease progression.

Results

Chemotherapy dose level and treatment intensity

A total of 179 courses were given, 17 of which were given with G-CSF cover. A median of 5 (range, 1–9) courses were given. Without G-CSF, dose reduction was necessary in 46% of the courses, affecting 54% of the patients at least once. Dose reduction by more than 20% was seen in 8/28 patients (29%). Dose escalation could be performed in 13% of the courses (18% of patients), in half of these by 10% and in half by 20%–30%. Treatment intervals had to be postponed by 7 days or more in 32% of courses (64% of patients).

Table 3 indicates that the addition of G-CSF may allow increased chemotherapy doses and improve treatment intensity, but the numbers are too low to reach statistical significance. The groups treated with and without G-CSF were comparable with respect to sex, age, performance status, and previous chemotherapy, but the G-CSF-treated patients were somewhat older (4/5 versus 10/28 being over 60 years old).

Treatment response

Three patients were not evaluable for response, in two cases due to early death (one due to toxicity and one due to unrelated causes) and in one case due to radiotherapy to the indicator lesion. Two patients received only one course due to rapid deterioration of their general condition; these are included among the nonresponders.

Of the 30 evaluable patients, 12 (40%) obtained a partial remission; no complete responder was seen. Four of the responders had surgical removal of all identifiable residual disease. The remaining eight responders had a median time to progression of 8 months (range, 4–13 months). Eleven patients (37%) obtained stabilization of their disease and 7 (23%) showed tumor progression. No response was seen among the five patients with liver metastases.

Table 3 Chemotherapy dose levels and treatment intervals

	Treatment interval of ≥4 weeks		Dose reduction of ≥10%		Dose escalation of ≥10%	
	% Of courses	% Of patients	% Of courses	% Of patients	% Of courses	% Of patients
Without G-CSF (28 patients, 162 courses)	32	64	46	54	13	18
With G-CSF (5 patients, 17 courses)	9	20	33	20	33	60

Table 4 Hematological toxicity and infectious complications

	Grade 3–4 leukopenia		Febrile neutropenia		Grade 3–4 thrombocytopenia	
	% Of courses	% Of patients	% Of courses	% Of patients	% Of courses	% Of patients
Without G-CSF (28 patients, 162 courses)	89*	96**	15	54	8	18
With G-CSF (5 patients, 17 courses)	36*	40**	13	20	42	40

*P <0.0001, Chi-square test; ** P = 0.007, Fisher's exact test

Of ten evaluable patients who had received previous chemotherapy (nine doxorubicin-containing regimens; six CYVADIC), six responded. Only one of the responders had previously responded to chemotherapy (CYVADIC).

Toxicity

Without G-CSF, grade 3–4 leukopenia (WBC nadir, $<2.0 \times 10^9$/l) was seen in 89% of the courses and at least once in 96% of the patients. Grade 4 leukopenia (nadir, $<1.0 \times 10^9$/l) was seen in 28% of the courses and 71% of the patients. Febrile neutropenia complicated 15% of courses and was seen in 54% of the patients (Table 4). At the standard dose level, grade 3–4 leukopenia was seen after 81% of the courses and grade 4 leukopenia, after 26%. Grade 3–4 thrombocytopenia (platelet nadir, $<50 \times 10^9$/l) was seen after 11% of the courses. Blood transfusion due to chemotherapy-induced anemia (hemoglobin level, <10.0 g/100 ml) was indicated after 20% of the courses. G-CSF appeared to reduce significantly the incidence of grade 3–4 leukopenia, but the incidence of febrile neutropenia was similar (Table 4).

Two women aged 65 years who had a WHO performance status of 0–1 suffered unexpected deaths during treatment; one died of sepsis at 25 days after the start of her first course, and one apparently died from an acute myocardial infarction at 2 weeks after her third course. One patient had a transient serum creatinine rise (maximal level, 130 μmol/l) following her eight course. No other organ toxicity was seen. The regimen caused total alopecia in all patients but, in general, induced only grade 1 gastrointestinal toxicity.

Discussion

This study indicates that the present etoposide/ifosfamide regimen may have a level of activity in adult STS (40% overall response rate) comparable with that of the most potent ifosfamide/doxorubicin combinations [2, 4, 10, 17]. Furthermore, the response seen in 5/9 previously doxorubicin-treated patients indicates that the regimen may be non-cross-resistant with doxorubicin. The ifosfamide dose given in our study was considerably lower than that employed in some other active combination regimens (total, 4500 versus 7500 mg/m^2 [2, 10], indicating that etoposide may be a significantly active agent in the present dose and mode of administration. Previous studies using conventional doses of etoposide given as short-term infusions in adult STS have indicated only low to modest activity, with responses being in the 5%–15% range [9, 15, 18, 19]. Other investigators have reported higher activity, but only for etoposide given in combination with high doses of ifosfamide [14] or ifosfamide and hyperthermia [11]. Attempts to increase etoposide activity by prolonged oral administration have failed [8, 12]. We believe that the activity seen in the present study was in part due to the administration of an escalated etoposide dose as a prolonged infusion, possibly taking advantage of the phase specificity of this drug. Etoposide may thus be an underrated agent in STS. On the basis of this pilot series, a prospective multicenter phase II study has been initiated by the Scandinavian Sarcoma Group. In that study, G-CSF has been added to the current regimen to facilitate dose escalation and the exploration of a possible dose-response relationship.

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