HIGH DOSE IFOSFAMIDE, DOXORUBICIN, DACARBAZINE AND G-CSF FOR PATIENTS WITH METASTATIC OR LOCALLY ADVANCED SOFT TISSUE SARCOMA

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ABSTRACT

Objective: A pilot study to test the feasibility and efficacy of high dose IFO and standard dose ADR and DTIC with G-CSF support in treatment of advanced soft tissue sarcoma (STS). Methods: 35 patients of no prior chemotherapy with metastatic or locally advanced unresectable STS were treated by this regimen, including 18 rhabdomyosarcomas, 7 malignant fibrous histiocytomas, 2 neurofibrosarcomas, 2 fibrosarcomas, 2 leiomyosarcomas, 2 synoviosarcomas, and 2 malignant hemangiopericytomas. IFO dose was 2 g/m^2 on day 1–5 (with mesna uroprotection), ADR 50mg/m2 on day 1 and DTIC 250 mg/m^2 on day 1–5. G-CSF (2 μg/kg/d) was administered on day 6 to 15 or until recovery of leukocytes account. The cycles were repeated every 3 weeks. Result: There were five complete responses (CR including pathologic CR) and eleven partial responses for overall 46% objective response rate. Most responses were observed within two cycles. The median survival was 15 months. Following CR, two patients remain disease free at 45 and 28 months, respectively. 6/120 (5%) cycles were complicated by grade IV neutropenia, 46/120 (38%) cycles had grade III neutropenia. No patients had treatment-related deaths. Nonhematologic toxicity consisted predominantly of anorexia and vomiting. No other severe toxicities were seen, especially no severe cardiotoxicity. Conclusion: This regimen is well tolerated and has substantial benefits for patients with advanced soft tissue sarcomas.

Key word: Soft tissue sarcoma, Ifosfamide, high dose, Chemetherapy.

SOFT TISSUE SARCOMAS (STS) account for approximately 1% of adult malignancies and 15% of pediatric malignancies. The use of radical surgery is the most effective method for treatment of early stage STS. Unfortunately, many patients are diagnosed late or receive inadequate primary surgery so that metastases ultimately occur. Although salvage treatment by excision of the metastases is successful for some patients, the majority will die from progressive disease.

Doxorubicin (Adriamycin, ADR) is the most active single agent in soft tissue sarcomas, with a response rate of 15% to 35% in various studies.[1] Ifosfamide (IFO) is a cyclophosphamide analog with one chloroethyl group shifted to the ring nitrogen atom. In European and American phase II trials reporting on more than 300 patients with previously treated sarcomas, the mean response rate was 22% for ifosfamide alone and it has shown an passive lack of cross-resistance with ADR.[2,3] There are increasing evidences of a strong dose-response relationship for ADR and IFO in STS. Dacarbazine (DTIC) alone has response rate of 16% in STS. The addition of DTIC to doxorubicin has been evaluated in some randomized trials, with a trend toward an increased response rate for the combination in the studies.[4] In an attempt to improve results of treatment of advanced soft tissue sarcomas, combination chemotherapy is usually administered. The combination regimen of doxorubicin/ dacarbazine/ ifosfamide may produce a higher response rate in STS.[5] However, the myelosuppression of this regimen is significantly more intense than that produced by the single agent or by the two drug combination. This study was therefore planned to determine whether the use of the hematopietic growth factor, recombinant human granulocyte-clone-stimulating-factor (rhG-CSF) would allow the safe administration of IFO 10g/m^2 with ADR and DTIC of standard dose, and whether it would result in a greater response rate in soft tissue sarcoma.

PATIENTS AND METHODS

Clinical Data of Patients

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All patients had a histopathologically confirmed STS with metastatic or locally advanced disease. Entry criteria included the presence of measurable lesions and performance status (ECOG standard) from 0 to 2. No prior chemotherapy should be given. All patients were required to have adequate renal and hepatic excretory function, and normal bone marrow reserves (leukocytes>4×10^9/L, platelets>100×10^9/L), and no evidence of congestive heart failure.

Between January 1993 and January 1997, 39 patients were enrolled. Two patients did not have sarcomas (lymphoma) and two had performance status 3. Thus, 35 patients were fully eligible. Among these 35 assessable patients, 27 (77%) were males and 8 (23%) were females. The median age was 38 (range, 3 to 62), with 21 (60%) patients older than age 14 and 14 (40%) patients less than or equal to age 14. Twelve patents (34%) had inoperable primary tumors only. The other twenty-three patients had metastases with or without recurrent or residual primary disease. Nine patients had received prior radiotherapy for the primary tumor. The location of the primary tumor was in an extremity in twelve (34%), truncal in five (14%), head and neck in eight (23%), retroperitoneal in seven (20%), mediastinal in one (3%) and gastro-intestinal in two (6%). All patients had a histopathologically proven diagnosis of STS including. 8 rhabdomyosarcomas; 7 malignant fibrous histiocytomas; 2 neurofibrosarcomas; 2 fibrosarcomas; 2 leiomyosarcomas; 2 synoviosarcomas; and 2 malignant hemangiopericytomas.

Chemotherapy Regimen

Chemotherapy with doxorubicin 50 mg/m^2 was administered as an intravenous push injection for day 1, followed immediately by ifosfamide (2 g/m^2) and DTIC (250 mg/m^2) administered as a continuous infusion separately daily for 5 days. The use of ifosfamide was accompanied by intravenous (IV) mesna 400 mg/m^2 immediately preceding and then 4 and 8 h after IFO administration. G-CSF was started 24 h after the end of the IFO infusion at a total daily dose of 2 μg/kg. This was administered for up to 14 days, but was discontinued before then if, after the leukocyte nadir had occurred, the leukocyte count was greater than 10×10^9/L. Chemotherapy was repeated every 3 weeks, but was delayed 1 week if the WBC or platelet count was <3×10^9/L or <100×10^9/L, respectively. Therapy was continued to a minimum of two cycles and a maximum of six cycles. Patients were considered assessable for response when they had received a minimum of two cycles of chemotherapy. Response criteria were those defined by WHO. Response and survival time was measured from the first day of chemotherapy administration. Full blood counts and differentials were performed two times each week of treatment. Full biochemical profiles and liver function tests were performed before each course of chemotherapy. All toxicities were graded according to WHO criteria.

RESULTS

Response

A total of 120 cycles of chemotherapy were administered in this study, with a median of 4 cycles (range, 2 to 6) being administered per patient. Of the 35 eligible patients, 2 had complete response and 14 had partial response. Following partial response, the residual disease of 8 patients was surgically removed. Two had lung metastases resected and 6 had primary tumor resected. Three of eight patients had pathologically negative (pathologic CR) of tumor resected. These patients would receive two courses of chemotherapy after the operation. The complete response rate (including pathologic CR) was 14% and the total response rate was 46% (Table 1).

Survival

Of the 35 eligible patients, 24 (69%) died (Figure 1). The median survival was 15 months (ranged from 5 to 46+ months). The patients older than age 14 had 16 months (ranged from 6 months to 46+ months) of median survival, and the patients of less than or equal age 14 had 13 months (ranged from 5 to 38+ months) of median survival. Following CR, two patients remain disease free at 45 and 28 months, respectively. Of the 8 patients who had received an operation again, 4 have relapsed in a prior site of disease and 4 remains disease free. The median survival and the longest disease-free period for these eight are 26 months (ranged from 13 to 46+months) and 46+ months, respectively.

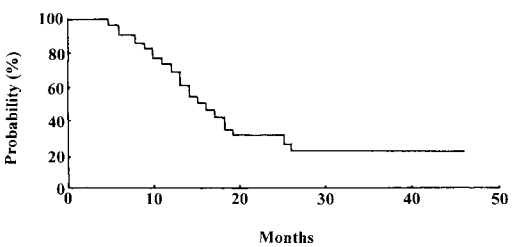

Fig. 1. Overall survival

Toxicity

A total of 35 patients received chemotherapy of 120 cycles. Toxicity from 120 cycles was available for analysis (Table 2). No patient had treatment-related death. Nadir leukocyte counts less than 2.0×10^9/L were observed in 52 (43.3%) of the 120 cycles. Platelet count below 50×10^9/L was observed in two patients, and platelet transfusions were required in these patients. No

bleeding complications were observed. Sight side effect on the hemoglobin concentration was noted. Leukopenic fever was seen in 13 of 120 cycles, and cultures confirmed a bacterial infection in five cycles.

Table 1. Response to Treatment of different Types

	CR	PR	S	PD	Total
Rhabdomyosarcoma	4	6	5	3	18
Malignant fibrous histiocytoma	1	3	1	2	7
Neurofibrosarcoma	0	0	1	1	2
Fibrosarcoma	0	0	2	0	2
Leiomyosarcoma	0	1	1	0	2
Synoviosarcoma	0	1	0	1	2
Malignant hemangiopericytoma	0	0	2	0	2
All groups	5	11	12	7	35

CR: complete response; PR: partial response; S: stable; PD: progressive disease.

Table 2.Chemotherpy-related toxicities from 120 cycles

Side effect	WHO grade					Grade 3+4 (%)
	0	1	2	3	4	
WBC	19	21	28	46	6	43.3
Platelets	104	6	7	3	0	2.5
Hemoglobin	96	18	6	0	0	0
Infection	102	10	5	3	0	2.5
Nausea/vomiting	30	38	35	17	0	14.2
Diarrhoea	104	12	4	0	0	0
Mucositis	110	6	4	0	0	0
Haematuria	114	4	2	0	0	0
Liver	107	8	5	0	0	0
Renal	113	4	3	0	0	0
Cardiac	112	6	2	0	0	0
Neurotoxicity	116	3	1	0	0	0

Nonhematologic toxicity was relatively mild. Nausea and vomiting was severe in five patients despite antiemetic therapy. Oral mucositis occurred in 14 cycles. No severe cardiotoxicity was detected clinically. Macroscopic hematuria occurred in 6 cycles. All patients developed grade II–III alopecia after two cycles. Milder somnolence in two patients was resolved within 1 to 2 days. No hallucinations, confusion, stupor or seizures were observed.

DISSCUION

The patients with inoperable or metastatic STS have a poor prognosis. Recent studies document survival duration of approximately one year from the initiation of therapy.[1] Surgical resection of pulmonary metastases can be curative in some patients, particularly those with a few isolated, slowly growing nodules. But, radical surgery is not fit for treatment of most advanced sarcomas.

Chemotherapy options for the treatment of advanced STS are limited by the scarcity of active agents. ADR and IFO are only two drugs, which have consistently shown single-agent activity in more than 20% of the patients who did not receive pretreatment. There is evidence of a strong dose-response relationship for ADR or IFO in STS.[6] Randomized trial by Edmonson has demonstrated that IFO plus ADR produced a significantly higher response rate (34%) than ADR alone.[7] The regimen developed in Boston which includes standard-dose ifosfamide, doxorubicin and dacarbazine (MAID) resulted in a high response rate of 49% with 10% complete remissions.[8]

Unfortunately, the combination of the MAID regimen caused life-threatening leukopenia in 85% of the 471 cycles administered,[9] and experience with ifosfamide (5 g/m^2) plus doxorubicin (50mg/m2) in more than 450 patients treated in EORTC Soft Tissue and Bone Sarcoma Group studies showed toxicity to include a median neutrophil count of 0.4×10^9/L with 26% of cycles being delayed or dose-reduced because of previous myelosuppression and infection.[10] G-CSF appears to reduce the duration of neutropenia after chemotherapy, to

reduce the incidence of infection, and to allow safe administration of greater dose-intensity of chemotherapy.[11] The availability of hematopoietic growth factors provided the opportunity to test whether escalating agent-dose for treating sarcoma would be more effective and feasible.

Our study demonstrates a response rate of 46% (14% CR rate) and a median duration of survival of 15 months for the combination of IFO (10 g/m^2), ADR (50 mg/m^2), DTIC (1250 mg/m^2) and G-CSF for patients with metastatic or locally advanced STS. With IFO 2.5 g/m^2, ADR 20 mg/m^2 and DTIC 300 mg/m^2 on day 1–3, Anthony Elias et al. reported a response rate of 47% (10% CR) in 108 patients.[9] Using IFO 7.5 g/m^2, ADR 60/m2 and DTIC 1000mg/m2, Karen Antman et al reported 4 CRs and 51 PRs (response rate 32%) in 170 patients.[5] Response rate and duration of survival in this trial were similar to our data.

Our results indicate that use of G-CSF between cycles of high-dose ifosfamide and doxorubicin and dacarbazine allows safe administration of such a regimen. Although patients experienced 43% grade III/IV leukopenia of all courses, the incidence of leukopenia was less than what was in other similar trials and there was no treatment-related death. Nonhematologic toxicity was relatively mild and well tolerated in most patients.

In our study, of the eight PR patients who received another operation, four have relapsed in a prior site of disease and four remains disease free. The median survival and the disease-free time period for these eight is 26 months (ranged from 13 to 46+ months) and 46+ months, respectively. An improved response rate may be particularly important in the management of borderline resectable lesions or pulmonary metastases in a neoadjuvant approach, particularly in younger patients. The role of chemotherapy before surgical resection of borderline resectable lesions or pulmonary nodules needs further exploration.

REFERENCES

[1]. Brennan MF, Casper ES, Harrison LB. Cancer principles and practice of oncology. 5th ed. Philadelphia: PA Lippincott, 1997: 1738.

[2]. Benjamin RS, Legha SS, Patel SR, et al. Single-agent ifosfamide studies in sarcomas of soft tissue and bone: the M.D.Anderson experience. Cancer Chemotherapy Pharmacol 1993; 31:S174.

[3]. Antman KH, Montella D, Rosenbaum C, et al. Phase II trial of ifosfamide with mesna in previously treated metastatic sarcoma. Cancer Treat Rep 1985; 69:499.

[4]. Borden EC, Amato D, Enterline HT, et al. Randomized comparison of Adriamycin regimens for treatment of metastatic soft tissue sarcomas. J Clin Oncol 1987; 5:840.

[5]. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcoma. J Clin Oncol 1993; 11:1276.

[6]. Antman KH. Chemotherapy of advanced sarcomas of bone and soft tissue. Semin Oncol 1992; 12:13.

[7]. Edmonson JH, Ryan LM, Blum RH, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol 1993; 11:1269.

[8]. Antman KH, Elias A. Dana-Farber cancer institute studies in advanced sarcoma. Semin Oncol 1990; 17:7.

[9]. Elias A, Ryan L, Sulkes A, et al. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unrespectable sarcoma and no prior chemotherapy. J Clin Oncol 1989; 7:1208.

[10]. Schitte J, Mouridsen HT, Stewart W, et al. Ifosfamide plus doxorubicin in previously untreated patients with advanced soft tissue sarcoma. Eur J Cancer 1990; 26:558.

[11]. Steward WP Verweij J, Somers R, 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 Clinical Oncol 1993; 11:15.