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Treatment of Advanced Soft Tissue Sarcomas With Ifosfamide and Doxorubicin Combination Chemotherapy

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Our objective was to assess the efficacy of a standard dose ifosfamide and doxorubicin containing regimen in the treatment of advanced soft tissue sarcomas. Forty consecutive patients with a median age of 35.5 years were treated. Ifosfamide was administered at a dose of 2.5 g/m^2/day as 72-hour continuous infusion with mesna at the same dosage and schedule. Doxorubicin was given at the dose of 60 mg/m^2/day as 2-hour infusion on day 1. Six patients had a complete response (15%), and 9 (22.5%) had a partial response, fourteen patients (35%) stable disease, and 11 (27.5%) did not respond to chemotherapy. The median duration of response was 13 and 5 months for the complete and partial responders, respectively. The median survival was 37 months. Febrile neutropenia was encountered in 9 cases (22.5%). The present ifosfamide and doxorubicin combination is a moderately effective and well-tolerable regimen in the treatment of advanced soft tissue sarcomas.

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KEY WORDS: doxorubicin; ifosfamide; soft tissue sarcoma

INTRODUCTION

The optimal treatment for soft tissue sarcomas often requires a multidisciplinary approach consisting of histopathology, surgery, radiotherapy, and chemotherapy. Histopathological examination provides diagnostic and prognostic classification that guides the choice of subsequent treatment. Surgery, whenever technically possible, is the mainstay of treatment. Radiotherapy can be employed preoperatively, postoperatively, or as a palliative procedure. Currently, it is generally accepted that chemotherapy has a role in advanced soft tissue sarcomas particularly in inoperable locally advanced or metastatic disease, whereas the use of chemotherapy in the adjuvant setting is not yet justified.

Ifosfamide and doxorubicin are considered the most active agents in the treatment of soft tissue sarcomas, with response rates ranging from 15–35% [1–4]. Furthermore, there is a proven dose-response relationship for both drugs. Combination of high-dose ifosfamide (> 10 g/m^2/cycle) and doxorubicin (> 60–75 mg/m^2/cycle) has a modest advantage in overall response compared to standard doses of these agents. Such activity, however, is associated with notable toxicity and is unlikely to result in substantial gain in quality-of-life-adjusted survival time [5–7]. As a consequence, colony-stimulating factors are generally integrated into these high-dose protocols, but the cost-benefit ratio is still a matter of debate. In the present study, we administered a regimen of a standard dose of ifosfamide and doxorubicin in the treatment of soft tissue sarcomas. Our primary objective was to assess the efficacy of this regimen, with an attempt to compare

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our results with the ifosfamide and doxorubicin protocols reported in the literature in terms of efficacy and safety.

MATERIALS AND METHODS

From October 1993 to February 1998, 40 consecutive patients with a histopathologic diagnosis of soft tissue sarcoma were entered into this study. Eligibility criteria included locally advanced or metastatic nonosseous sarcoma, with bidimensionally measurable disease, Karnofsky performance status of at least 60, anticipated life expectancy of at least 3 months, left ventricular ejection fraction > 50%, leukocyte count > 4,000/mm^3, platelet count > 100,000/mm^3, and serum levels of creatinine and bilirubin < 1.5 mg/dl. The tumor grade was assessed by an experienced pathologist, based upon histologic and other features of tumor. Once the type of tumor was established, the accepted histologic criteria of malignancy, such as cellularity, cellular pleomorphism, and mitotic activity were determined [8]. Malignant mesothelioma and Kaposi sarcoma were not included.

Ifosfamide was administered at 2.5 g/m^2/day as a 72-h continuous infusion with mesna at the same dosage and schedule, for uroprotection. Doxorubicin was given at 60 mg/m^2/day as a 2-h infusion on day 1. In the absence of disease progression, chemotherapy was planned to be repeated every 3 weeks for a total of six cycles. In patients with a continuing response, two additional cycles were administered. An adequate evaluation for response required at least two courses of therapy. Complete response (CR) was defined as the total disappearance of the tumor and partial response (PR) was defined as >50% reduction in the sum of the diameters of all measurable lesions and the absence of any new lesions for at least 2 months; stable disease (SD), a disease status with no change for at least 2 months; and progressive disease (PD), > 25% increase in the sum of the diameters of all measurable lesions. In addition to physical examination and plain radiographs, ultrasonography, computed tomography, or magnetic resonance imaging was used when appropriate to evaluate the response.

Toxicities were graded according to World Health Organization (WHO) criteria [9]. Any side effects observed by the physician and/or the patients were recorded. Complete blood count was performed out at least on weekly basis in asymptomatic patients, and the doses of ifosfamide and doxorubicin were adjusted accordingly. Chemotherapy was delayed for 1 week when neutrophil count was $\leq$ 2,000/mm^3, and if it was still low after 1 week, the doses of both chemotherapeutic agents were reduced to 75% of the original dose. The dose was also reduced by 25% if the neutrophil count dropped to < 1,000/mm^3 or the platelet count to <50,000/mm^3 any time between the cycles.

The primary end point of the study was the objective response rate, defined as the percentage of the patients in the group who achieved a complete and partial response. The secondary end points included progression-free survival, survival from the time of entry, and toxicity. Differences among variables were evaluated using the χ^2 test. Logistic regression was used to assess the ability of patient covariates to predict the probability of objective response, defined as CR or PR. Survival rates were calculated by the method of Kaplan and Meier [10], and were compared by the log-rank test. Progression-free survival was calculated from date treatment started until the date disease progressed, relapsed, or the patient died of the disease. The Cox proportional-hazards regression model was used to perform comparisons after adjustment for the baseline characteristics and to investigate the prognostic value of the baseline variables.

RESULTS

In total, 40 patients with soft tissue sarcoma were included in this study. Thirteen patients (32.5%) were female and 27 (67.5%) were male. The ages of the patients ranged from 16 to 63 years, with a median of 33.5 years. Most patients (87.5%) had a WHO performance status of 0 or 1. All patients were anthracycline naive. One had received steroids, cyclophosphamide, colchicine, and interferon-α2b for the treatment of Behçet's disease, which was diagnosed 20 months earlier. Another had rheumatoid arthritis prior to the diagnosis of leiomyosarcoma. Most of the tumors were localized in the extremities, abdomen, or pelvis. Initial presentation was hypercalcemia in a patient with clear cell sarcoma. Patient characteristics including the tumor histopathology are presented in Table I. A complete resection of the tumor was performed in 27 patients (67.5%).

A total of 204 treatment cycles was administered to our patients (median, 6; range, 2–8). All patients completed two cycles of therapy and were evaluable for response. In addition to chemotherapy, 18 patients received radiotherapy. Among these, radiotherapy was used to treat primary tumor in 16 cases and metastatic sites in 2 cases. Six patients had a complete response (15%), and 9 (22.5%) had a partial response (Table II). Fourteen patients (35%) had stable disease, and 11 (27.5%) did not respond to chemotherapy. The median duration of response was 13 and 5 months for the complete and partial responders, respectively (7 months for the whole group). The objective response (CR+PR) rate in patients who were previously treated was 38.7% (12/31 cases). The objective response (CR+PR) rate for patients who received prior radiation was 40% (4/10 cases). Complete responses were achieved in 1 sarcoma (type not designated), 1 leiomyosarcoma, 2 rhabdomyosarcomas, 1 synovial sarcoma, and 1 clear cell sarcoma. Partial responses were observed in 2 sarcomas (type not designated), 1 leiomyosarcoma, 2 liposarcomas, 1 angiosarcoma, 1 malignant schwannoma, 1 clear cell sar-

TABLE I. Patient Characterictics in Soft Tissue Sarcoma

No. of patients entered	40
Age, years	
Median	33.5
Range	16–63
Sex	
Female	13
Male	27
Performance status	
WHO 0	16
WHO 1	19
WHO 2	5
Primary site	
Head and neck	3
Thorax	3
Abdomen and gastrointestinal tract	10
Pelvis and genitourinary tract	8
Vertebral column and medulla spinalis	2
Limbs	14
Histologic subtype	
Sarcoma, type not designated	7
Leiomyosarcoma	6
Liposarcoma	5
Rhabdomyosarcoma	5
Fibrosarcoma	3
Synovial sarcoma	3[a]
Angiosarcoma and hemangiopericytoma	2
Malignant schwannoma	2[b]
Clear cell sarcoma	2
Epitheloid sarcoma	1
Malignant fibrous histiocytoma	1
Aggressive fibromatosis	1
Extraskeletal chondrosarcoma	1
Alveolar soft part sarcoma	1
Grade	
Low-intermediate	13
High	23
Not available	4
Group	
Locally advanced	13
Metastatic	27
Previous therapy	
Surgery	27
Radiotherapy	10
Chemotherapy	8

[a]One patient had prior Behçet's disease.
[b]One patient had prior von Recklinghausen's disease.

coma, and 1 epitheloid sarcoma. Responses according to the histopathologic diagnosis were presented in Table III.

Among the poor and nonresponders, 7 patients (3 with SD and 4 with PD) received high-dose ifosfamide (14–18 mg/m^2/cycle) as a salvage therapy. Only 1 patient achieved a PR and another had SD.

None of the pretreatment characteristics analyzed by logistic regression analysis was predictive of a response to ifosfamide and doxorubicin ($P < 0.05$). The median survival was 37 months. We were not able to identify any pretreatment characteristics reaching statistical significance in the univariate and multivariate analyses, which were performed to assess the prognostic value of the

TABLE II. Therapeutic Results to Treatment for Soft Tissue Sarcoma*

Response data	No. responding (%)	Median duration of CR/PR (months)
Complete response	6 (15)	13
Partial response	9 (22.5)	5
Stable disease	14 (35)	NA
Progressive disease	11 (27.5)	NA
Overall response	15 (37.5)	7

*NA: not applicable.

TABLE III. Response by Histologic Subtype in Patients With Soft Tissue Sarcoma*

Histologic subtype	No.	CR	PR	SD	PD
Sarcoma, type not designated	7	1	2	2	2
Leiomyosarcoma	6	1	1	1	3
Liposarcoma	5		2	3	
Rhabdomyosarcoma	5	2		1	2
Fibrosarcoma	3			2	1
Synovial sarcoma	3	1		2	
Angiosarcoma and hemangiopericytoma	2		1		1
Malignant schwannoma	2		1	1	
Clear cell sarcoma	2	1	1		
Epitheloid sarcoma	1		1		
Malignant fibrous histiocytoma	1				1
Aggressive fibromatosis	1			1	
Chondrosarcoma	1			1	
Alveolar soft part sarcoma	1				1
Total	40	6	9	14	11

*CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

baseline variables on the progression-free and overall survivals. Lungs were the most common metastatic site (54.5%), followed by the liver (12.1%) and bones (12.1%).

All 40 patients were evaluable for toxicity. The general condition of the patients remained good; asthenia, anorexia, or weight loss was encountered only in a few cases. Alopecia (17 cases), nausea and vomiting (14 cases), and leukopenia (13 cases) were common. Febrile neutropenia was encountered in 9 cases (22.5%). Although grade 4 thrombocytopenia did occur, it was uncommon and also usually of brief duration. Reversible abnormalities of liver function were seen in 2 patients. Severely impaired renal function was not observed. A single episode of gross hematuria occurred. Two patients had mild to moderate somnolence. One patient had hallucinations during the infusion of ifosfamide. Another patient was found to have depression after 2 cycles of therapy. Patients were also monitored closely for cardiac toxicity. Only 1 patient exhibited a significant decrease in left ventricular ejection fraction to < 40%. There was no death from cardiac toxic effects. Progressive disease (n = 3) and treatment related sepsis (n = 1) were the causes of death in 4 of 5 patients who had passed away.

DISCUSSION

Although mesenchymal tissues amount for > 50% of the body weight, only approximately 1% of all malignant tumors are sarcomas [11], and 85–90% of them are soft tissue in origin. Sarcomas can originate in any area of the body and from any origin; however, they most commonly arise in the soft tissue of the extremities, trunk, retroperitoneum, or head and neck area.

A growing number of studies have convincingly documented that histopathologic grade is the most important factor influencing the outcome in soft tissue sarcomas. Sarcomas are a heterogeneous group of diseases and patients treated in small studies will have wide variety of histologic subtypes and grades, which makes interpretation of response rates and survivals very difficult. There are some tumors, however, that are considered highly malignant, regardless of their grade. The most common of these are rhabdomyosarcoma, synovial sarcoma, and certain types of angiosarcoma [8,12]. The present study failed to document any difference in terms of response rate and outcome according to the histology and grade, but the numbers are too small to draw a firm conclusion.

As adult soft tissue sarcomas are among the most chemoresistant of all malignancies, it is important to know the limitations of chemotherapy as well as its potential value [7]. The goal of therapy for patients with advanced disease is primarily palliative, where only a small fraction of patients achieve complete remission. Therefore, it is questionable whether asymptomatic patients should be offered chemotherapy or watchful waiting. On the other hand, it is noteworthy that any degree of improvement or stabilization of previously advancing disease can extend the progression-free survival, thus the symptom-free period.

In recent years, ifosfamide was proven to be effective in the treatment of most soft tissue sarcomas [3,13,14]. Ifosfamide is less myelosuppressive than its parent compound cyclophosphamide but is more urotoxic. However, with the introduction of uroprotector mesna in the 1980s, urotoxicity is now largely avoidable. While the results of pharmacokinetic studies indicate that ifosfamide is probably best administered in divided doses over several days, whether the daily dose should be given in continuous or in a short infusion remains an unresolved issue. It has been shown that renal and nonrenal clearance do not change with age [15]. Thus, elderly patients apparently do not need dose reductions/modifications. Doxorubicin also has significant activity in a broad range of tumors, both as a first-line agent and in the treatment of refractory tumors [1,2], and it was the backbone of most combinations used in patients with soft tissue sarcomas before the advent of ifosfamide. Therefore, it seems reasonable to combine ifosfamide and mesna with doxorubicin in the treatment of these tumors [16].

Numerous combination regimens had been tried in the treatment of soft tissue sarcomas in recent past. However, the results obtained are not uniform and guiding. For instance, CyVADIC (cyclophosphamide, vincristine, doxorubicin, dacarbazine) was widely used and in initial studies high response rates of $\geq$ 50% were achieved. But, subsequent studies failed to confirm such a high response rate, furthermore in a recent European Organization for Research and Treatment of Cancer (EORTC) study CyVADIC was not superior to single agent doxorubicin or to ifosfamide and doxorubicin in terms of response rates and survival. Myelosuppression and cardiotoxicity were more frequent in the ifosfamide and doxorubicin arm [17]. The SWOG (Southwest Oncology Group) and CALGB (Cancer and Leukemia Group B) compared the combination of mesna, doxorubicin, ifosfamide, and dacarbazine (the MAID regimen) with the combination of doxorubicin and dacarbazine. The MAID regimen showed a significantly higher response rate without a survival benefit [18].

After the advent of ifosfamide, we initially designed a pilot study with single agent ifosfamide (3 g/m^2 for 5 days) in advanced refractory sarcomas [19]. All 20 patients enrolled in the mentioned study had previously received doxorubicin- and/or cyclophosphamide-based chemotherapies. Ending up with only 2 partial responses, we concluded that ifosfamide alone at this dose and schedule was not very promising in refractory sarcomas as a second-line therapy. Thereafter, we decided to use the most active two drugs in the first-line therapy of advanced soft tissue sarcomas, and we initiated the present protocol. At the same time, we started another study with ifosfamide (2 g/m^2 for 5 days) and etoposide (120 mg/m^2 for 3 days) in advanced sarcomas refractory to cyclophosphamide and doxorubicin. The latter study, comprising 26 patients, yielded encouraging results, a 29.1% CR and 12.5% PR rate with a median time to treatment failure of 13.3 months [20]. In the present study, all patients were anthracyline naive, the overall response rate was 37.5% (including 15% CRs), and stable disease was achieved in another 35% of the patients. In those with objective response, the median time to treatment failure was 7 months. Of note, the majority of cases (63.8%) have had high-grade tumors in which pathological grading was available. In this respect, the results obtained in this study are acceptable. Table IV provides some of the selected phase II and III trials using standard doses of doxorubicin and ifosfamide in the treatment of soft tissue sarcomas. Our results are comparable to these studies and the toxicity profile is acceptable. Recent studies focus on high-dose ifosfamide and reported results are generally superior to the standard ifosfamide-doxorubicin combination regimens; however, as one might expect, toxicity is also of concern. At the time this study was originally designed, the results of the

TABLE IV. Doxorubicin (DOX) + Ifosfamide (IFO) Response Rates in Phase II/III Studies*

Author Year [reference]	Dosage (mg/m^2/3 weeks)	No. of patients	CR (%)	PR (%)	RR (%)
Mansi 1988 [21]	DOX: 40 IFO: 5,000	28	4	3	7
	DOX: 60 IFO: 5,000	22	9	32	41
Schütte 1993 [22]	DOX: 40–60 IFO: 5,000	41	5	24	29
Schütte 1990 [16]	DOX: 50 IFO: 5,000	175	9	26	35
Loehrer 1989 [23]	DOX: 60 IFO: 5,000	42	7	29	36
Weh 1990 [24]	DOX: 30×2 IFO: 2,500 × 4	44	16	27	43
Steward 1993 [25]	DOX: 75 IFO: 5,000 + GM-CSF	104	10	35	45
Edmonson 1993 [26]	DOX: 30 ×2 IFO: 3,750 × 2	88	3	31	34
Current study	DOX: 60 IFO: 2,500 × 3	40	15	22.5	37.5

*CR: complete response, PR: partial response, RR: response rate, GM-CSF: granulocyte-macrophage colony-stimulating factor.

high-dose ifosfamide-doxorubicin regimens were not published.

The main limitations of this study are the small sample size, and the doses of ifosfamide and doxorubicin, which are lower than what is typically used for monotherapy with either agent. In rare tumors such as soft tissue sarcomas, nonrandomized studies are useful to show whether new treatments are effective. However, major decisions in treatment policy should be tailored by randomized trials. Another interesting approach would be to combine ifosfamide with the liposomal formulation of doxorubicin, which has shown minimal myelosuppression, to find out whether it yields a better response rate than this scheme.

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