Cancer Chemother Pharmacol (2001) 47: 206–210
DOI 10.1007/s002800000219

ORIGINAL ARTICLE

L. Serrone · M. Zeuli · T. Gamucci
M. Nardi · F. Cognetti

A phase II study of dose-intense ifosfamide plus epirubicin with hematopoietic growth factors for the treatment of patients with advanced soft tissue sarcomas; a novel sequential schedule

Received: 18 July 2000 / Accepted: 3 October 2000 / Published online: 24 January 2001

Abstract *Purpose*: The efficacy and feasibility of a novel sequential schedule of high-dose ifosfamide (HD-IFO) and full-dose epirubicin (EPI) with granulocyte colony-stimulating factor (G-CSF) was evaluated in adult patients with soft tissue sarcomas (STS). *Methods*: Since November 1995, 22 chemotherapy-naive patients have been treated. HD-IFO was given as a continuous infusion at a total dose of 14–18 g/m^2 per cycle, with mesna, over 6 to 8 days, q 3 weeks, twice. EPI was administered subsequently as an IV bolus at a total dose of 120–160 mg/m^2, on days 1–2, q 2 weeks, twice. G-CSF was planned for each course of treatment as a daily subcutaneous injection for 7 days, starting 24 h after the end of the treatment. After the first four cycles, patients were evaluated for surgery and patients with locally inoperable or metastatic disease received further chemotherapy up to a maximum of eight cycles. *Results*: The response of 19 patients could be assessed. One complete response (CR) and six partial responses (PRs) were achieved for an overall response rate of 37% (95% confidence interval, 15–59%). Noteworthy is that two of the six leiomyosarcoma patients responded to the HD-IFO treatment. The median survival period was 15 months. Most common toxicities included myelosuppression, nausea and vomiting, and stomatitis. Six patients were hospitalized for complicated nadir fever. No severe renal and CNS toxicities were seen. Transient gross hematuria occurred in six patients and affected treatment in only one case. There were no treatment-related deaths. *Conclusions*: By the protraction of continuous infusion of HD-IFO over 6 to 8 days, ifosfamide-induced acute renal toxicity is avoided, while G-CSF support allows the delivery of the planned dose intensity in most of the patients. Although manageable in an oncology setting, the hematologic toxicity of such a regimen remains substantial. Moreover, in terms of efficacy and median survival, this regimen showed no benefits over a conventional-dose anthracycline-ifosfamide schema. Further evaluations of this novel ifosfamide-epirubicin schedule are not warranted, even if the HD-IFO regimen could be taken forward specifically for leiomyosarcomas in a phase II trial.

Key words High-dose anthracyclines · High-dose ifosfamide · Sequential chemotherapy · Soft tissue sarcomas

Introduction

Sarcomas are rare tumors for which only a few drugs have shown single-agent activity; doxorubicin and ifosfamide remain the two most active drugs with response rates up to 40% when used in combination [18]. Since clinical studies have demonstrated a dose-response relationship for both doxorubicin and ifosfamide (IFO) in soft tissue sarcoma (STS) patients [2, 3], increasingly higher doses of these two drugs have been tested in the first-line treatment of advanced disease [4, 13]. The anthracycline analog epirubicin (EPI) has been tested in STS patients as a single agent [6] and in combination with IFO as well [20], as an alternative to doxorubicin, in view of the demonstrated antitumor activity and better toxicity profile of EPI [14]. In a pilot study conducted by Frustaci et al. [10], increasing EPI doses were combined with a fixed dose of IFO at 9 g/m^2 over 5 days: at an EPI dose level of 70 mg/m^2/day on days 1–2, only 46% of the patients were able to tolerate full-dose chemotherapy, because of toxicity. A total IFO dose of 10.5 g/m^2 plus an IV bolus EPI dose of 120 mg/m^2 was found to be the maximum tolerated dose (MTD) in a dose-finding study from the Italian Group for Study on Rare Tumours (IGSRT), in which a continuous infusion schedule of ifosfamide, over three days, was adopted [5].

The work was conducted at Regina Elena Institute

L. Serrone (✉) · M. Zeuli · T. Gamucci · M. Nardi · F. Cognetti
Division of Medical Oncology A,
Regina Elena Institute for Cancer Research and Treatment,
Via E. Chianesi, 53, 00144 Rome, Italy
E-mail: lserrone@hotmail.com
Tel.: +39-6-52406775
Fax: +39-6-52273366

Empirical evidence in breast cancer and other solid tumors indicate that sequential, rather than concurrent, administration of drugs may be more effective, since full doses can be more safely administered, supported by hematopoietic factors [7, 21]. This study was designed to evaluate the efficacy and the feasibility of a dose-intense IFO and EPI regimen administered by a novel alternate, sequential schedule in chemotherapy-naive STS patients. Protracting continuous infusion of HD-IFO (14–18 g/m^2) over 6 to 8 days has been shown to attenuate IFO-induced acute renal toxicity while producing a 100% response rate [17].

The promising activity and the acceptable toxicity profile of such a regimen prompted us to investigate this IFO schedule in combination with full-dose epirubicin. To avoid treatment-related hematotoxicity, hematopoietic growth factors (G-CSF) were planned for each course of treatment.

Materials and methods

Criteria for eligibility

Patients were required to have a histologically proven diagnosis of soft tissue sarcoma. Entry criteria included: age between 18 and 70 years, a performance status of ≤2 according to the Eastern Cooperative Oncology Group (ECOG) and an expected survival of ≥3 months. Previous chemotherapy was not allowed. Surgery and/or radiotherapy should have been completed at least 4 weeks before trial entry. All patients were required to have adequate renal (serum creatinine <1.5 mg/dL) and hepatic function (serum bilirubin <1.5 mg/dL), and normal bone marrow reserve (leukocytes ≥4000/μL, platelets ≥100 000/μL). Assessment of cardiac function was performed by pretreatment left ventricular ejection fraction (LVEF) and ECG, and was repeated every EPI cycle. Radiation therapy to the only measurable site of disease, other concomitant cancers, and brain involvement were exclusion criteria. All patients gave their informed consent.

Treatment plan

The treatment plan consisted of high-dose ifosfamide (HD-IFO) infused intravenously (IV) at a dose of 2 g/m^2 over 4 h on day 1, followed by 2 g/m^2 as a 24-h continuous infusion for a total dose of 14 g/m^2 (if age >55 years) or 18 g/m^2 (if age <55 years) per cycle over a 6- to 8-day period. Two cycles were given at 3-week intervals .Twenty-one days after the second HD-IFO cycle, epirubicin (EPI) was given as an IV bolus, at a total dose of 120 mg/m^2 (if age >55 years) or 160 mg/m^2 (if age <55 years) on days 1 and 2 for two cycles repeated every other week. The total daily dose of ifosfamide with an equimolar dose of mesna was diluted in 3 l of dextrose saline, and the infusion bags were changed every 24 h. Antiemetic prophylaxis with HT3 antagonists and corticosteroids was provided for each day of treatment. Hematopoietic support with G-CSF was planned for each patient, starting 24 h after the end of chemotherapy, as a daily subcutaneous injection for 7 days, at a dosage of 300 μg/day. Toxicity was evaluated according to the World Health Organization (WHO) criteria. Ifosfamide infusion was withheld in case of grade 3 or 4 neurologic toxicity or macroscopic hematuria, until toxicity resolved. Hematologic toxicity was evaluated during each cycle: the dose of ifosfamide and epirubicin were reduced by 25% in case of grade 4 myelosuppression with sepsis that required hospitalization and parenteral antibiotics and/or bleeding.

Tumor response was evaluated after a minimum of two courses and every two cycles of chemotherapy with clinical and radiologic assessment based on the extent of the disease defined at presentation, according to WHO criteria.

Time to progression was calculated from day 1 of chemotherapy for patients who received at least one cycle of treatment. Survival was measured from the first day of treatment to death or to date of last follow-up by the Kaplan–Meier method. After the first four courses, patients were evaluated for surgery and/or radiotherapy: patients with locally inoperable or metastatic disease received further chemotherapy according to the response obtained in the previous cycles, up to a maximum of eight cycles.

Results

Patient characteristics

Between November 1995 and December 1999, 22 STS patients were treated. The median age was 52 years (range: 18–69 years) and the median performance status was 1 (range: 0–2). The histologic types are listed in Table 1. The extent of disease at entry was locoregional in nine of the 22 patients (41%) and metastatic in 13 of the 22 patients (59%). The lung was the most common site of metastatic disease. Most of the patients underwent surgery (17 of the 22) and radiotherapy (6 of the 22) as primary treatment and were rendered disease-free for a mean time of 12 months (range: 2–60 months) from initial diagnosis.

Response data

The response of two patients treated for microscopic disease after surgery could not be evaluated, and one

Table 1 Patient characteristics

Total no of patients	22
Age, median	52 years
Range of ages	18–69 years
ECOG performance status	1
Range of ECOG performance status	0–2
Sex (*n*)	
Female	12
Male	10
Histologic types (*n*)	
Leiomyosarcoma	7
Synovial sarcoma	3
MFH	6
Chondrosarcoma	1
Liposarcoma	1
Schwannoma	1
Epithelioid sarcoma	1
Angiosarcoma	1
Phyllodes cystosarcoma	1
Grading (*n*)	
1–2	8
3–4	14
Extent of disease (*n*)	
Locoregional	9
Metastatic	13
Prior therapy (*n*)	
Surgery	17
Radiotherapy	6

MFH malignant fibrous histiocytoma

patient was lost to follow-up after the second course of ifosfamide therapy. Among 19 patients assessable for response, we observed one CR and six PRs, for an overall objective response rate of 37% (95% confidence interval, 15–59%; Table 2). After the first four courses, two patients with locally advanced soft tissue sarcomas (one PR and one SD) received local treatment of the primary tumor by surgery and radiotherapy and were rendered disease-free for 42 and 11 months, respectively. The remaining four patients with localized disease did not undergo surgery, because of unresectable disease. One patient with metastatic synovial sarcoma of the right leg, responsive to the HD-IFO–EPI therapy underwent surgery for lung metastases and relapsed within 12 months. One patient with metastatic malignant fibrous histiocytoma (MFH), rendered disease-free by local treatment of the primary tumor is not assessable in terms of long-term efficacy because of the short follow-up time. The median time to progression and the median survival for all CR, PR, and SD patients were 8 months (range: 3–42 months) and 16.5 months (range: 5+ to 49+ months), respectively. The median overall survival period for all patients was 15 months (range: 3 to 49+ months). Responses according to disease characteristics are listed in Table 3.

Table 2 Clinical responses

Response (WHO)	No of patients (total = 19)	Response rate (%)
CR	1	5
PR	6	32
SD	8	42
PD	4	21

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

Table 3 Responses according to disease characteristics

	No of patients	CR + PR	SD	PD
Histology				
Leiomyosarcoma	6	2	3	1
Synovial sarcoma	2	1	1	–
MFH	5	2	3	–
Chondrosarcoma	1	1	–	–
Others	5	1	1	3
Extent of disease				
Locoregional	6	2	2	2
Metastatic	13	5	6	2

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *MFH* malignant fibrous histiocytoma

Toxicity

All patients but one (21 of 22) were assessable for toxicity (Table 4). A total of 98 courses of chemotherapy was administered with a median of four cycles per patient (range: 2–8). The total ifosfamide (IFO)/epirubicin (EPI) doses delivered per cycle were 14 g/m^2 (IFO) and 120 mg/m^2 (EPI) in 11 of the 22 patients, those aged ≥55 years, and 18 g/m^2 (IFO) and 160 mg/m^2 (EPI) in 10 of the 22 patients, those aged ≤55 years. Hematologic toxicity was the major side effect with grade 3 or 4 neutropenia occurring in 17 of the 21 patients (81%).

Severe thrombocytopenia was unusual (two of the 21 patients) and necessitated platelet transfusion in one case. Severe anemia occurred in six of the 21 patients (29%). There were 17 episodes of infection; in six patients who required hospitalization and received parenteral antibiotics for serious episodes of febrile neutropenia, the dose was reduced by 25%, and in 13% of the cycles, therapy was delayed because of persistent hematologic toxicity. Grade 3 alopecia was universal. Nausea and vomiting were the most common gastrointestinal toxicity (53% of patients), generally mild. Stomatitis was recorded in eight of the 21 patients (38%) and only in one case necessitated parenteral support. No severe metabolic acidosis or acute renal toxicity was noted. Ifosfamide infusion was withheld for gross hematuria in six of the 21 patients, and in one case required treatment interruption. No severe neurologic toxicity was encountered.

Discussion

Results of upfront chemotherapy in adult advanced sarcomas remain disappointing, and the median survival

Table 4 Number of patients experiencing grade 3–4 toxicity

Grade 3–4 toxicity	No of patients (11 pts) (dose: 14 g/m^2 IFO, 120 mg/m^2 EPI)	No of patients (10 pts) (dose: 18 g/m^2 IFO, 160 mg/m^2 EPI)
Hematologic		
Neutropenia	8	9
Thrombocytopenia	1	1
Anemia	2	4
Nonhematologic		
Alopecia	11	10
Stomatitis	–	1
Nausea/vomiting	–	2
Hematuria	–	1
Hepatotoxicity	1	1

IFO ifosfamide, *EPI* epirubicin

period almost invariably does not exceed 12 months [8]. To date, doxorubicin and/or epirubicin and ifosfamide remain the most active drugs with response rates ranging between 15% and 40% for single-agent and combination chemotherapy [1]. Since a steep dose-response relationship has been established for both doxorubicin and ifosfamide in STS patients, escalating doses of these two drugs have been used: doxorubicin doses >60 mg/m^2 and ifosfamide doses >12 g/m^2 every 3–4 weeks appear to be critical to achieve optimal response rates [3, 12]. However, at the dose intensities needed to achieve a meaningful response, treatment-related toxicity is frequently seen: severe neutropenia can lead to febrile episodes and occasionally to life-threatening septic infections and nonhematologic toxicity may become dose-limiting when ifosfamide doses ≥ 12 g/m^2 are administered [9, 15]. Moreover, doxorubicin can potentially cause irreversible cardiac damage as cumulative doses exceed 550 mg/m^2 [22]. Approaches to the reduction of treatment-related toxicities have included the following: the use of the doxorubicin analog epirubicin, in view of its demonstrated antitumor activity and better toxicity profile [14], the administration of ifosfamide by protracted continuous infusion [17], and hematopoietic colony-stimulating factors support [19]. Although many efforts have been made, dose-limiting toxicities are frequently seen with regimens using concomitant full-dose epirubicin at 120–140 mg/m^2 in combination with ifosfamide doses in the range of 9–12 g/m^2 [5, 10, 16]. The delivery of cytotoxic drugs by an alternate or sequential schedule has resulted in a significant increase in the dose intensity administered in patients with solid tumors, when supported by hematopoietic growth factors [7, 21]. In our series, G-CSF support allowed the delivery of the planned dose intensity in 81% of the cycles: dose modifications and delays were necessary in 6% and 13% of the cycles, respectively. Severe hematopoietic toxicity was common and required hospitalization in 28% of the patients. Other toxicities were generally mild. No severe metabolic or acute renal toxicity was encountered. The absence of these complications may be because a daily bicarbonate infusion was systematically administered concurrently with the ifosfamide/mesna infusion. Transient gross hematuria occurred in six patients and only in one case necessitated ifosfamide interruption. Only one episode of neurotoxicity with a mild and transitory dazzling syndrome, which spontaneously resolved, occurred during an ifosfamide infusion in a 60-year old woman with chest liposarcoma with massive liver involvement. No treatment-related deaths occurred. The overall response rate was 37% (95% confidence interval: 15–59%), with only one patient, affected by phyllode cystosarcoma of the right breast with liver and lymph nodes metastases, experiencing complete response after the first four cycles of chemotherapy. Four patients (21%) were rendered disease-free by surgical procedures: three relapsed within 11, 12, and 42 months, and one patient is not assessable because of the short follow-up time. Even though no significant correlation could be detected between response and disease characteristics, such as histologic type and/or extent of disease, because of the small sample size, a noteworthy response rate was obtained in leiomyosarcoma patients: of the six patients, there were two (33%) who experienced partial responses after two HD-IFO cycles. Notably, one patient with localized epithelioid sarcoma, a rare and occasionally aggressive soft tissue malignancy, characterized by its tendency to extend regionally, is, despite not responding to treatment, still alive, at 32 months from the initial diagnosis. This result is in accordance with other reports [11].

In conclusion, although manageable in an oncology setting, the hematologic toxicity of this regimen is substantial. Moreover, this novel dose-intense alternate, sequential ifosfamide-epirubicin schedule showed no advantages in terms of efficacy or long-term and relapse-free survival compared with concurrent, less intensive, anthracycline-ifosfamide schema. While no further evaluations are warranted, the HD-IFO regimen could be taken forward specifically for leiomyosarcomas in a phase II trial.

References

1. Antman KH (1992) Chemotherapy of advanced sarcomas of bone and soft tissue. Sem Oncol 19 (Suppl 6):13
2. Benjamin RS, Legha SS, Patel SR, Nicaise C (1993) Single-agent ifosfamide studies in sarcomas of soft tissue and bone: the MD Anderson experience. Cancer Chemother Pharmacol 31: S174 (Suppl 2)
3. Bokemeyer C, Harstrick A, Schmoll HJ (1994) Treatment of adult soft-tissue sarcomas with intensified chemotherapy and haematopoietic growth factors. Onkologie 17: 216
4. Bokemeyer C, Franzke A, Hartmann JT, Schober C, Arseniev L, Metzner B, Link H, Kanz L, Schmoll HJ (1997) A phase I/II study of sequential, dose-escalated, high dose ifosfamide plus doxorubicin with peripheral blood stem cell support for the treatment of patients with advanced soft tissue sarcomas. Cancer 80(7): 1221
5. Bonadonna A, Romanini A, Comandone A, et al (1996) Increasing continuous infusion ifosfamide and bolus epirubicin in soft tissue sarcoma patients. Proceedings of the American Society of Clinical Oncologists (ASCO) 15: (Abstr 1683)
6. Chevallier B, Montcuquet P, Fachini T, Nguyen Bui B, Kerbrat P, Bastit P, Vo Van ML (1990) Phase II study of epirubicin in advanced soft tissue sarcomas. Bull Cancer 77: 991
7. Culine S, Fabbro M, Assens C, Ychou M, Romieu G, Kramar A, Cupissol D, Pinguet F, Pujol H (1997) Four-step high-dose sequential chemotherapy with haematopoietic progenitor-cell support as induction treatment for patients with solid tumors. Ann Oncol 8: 951
8. Dirix LY, Somville J, Van Oosterom AT (1996) Diagnosis and treatment of soft tissue sarcomas in adults. Curr Opin Oncol 8: 289
9. Elias AD, Eder JP, Shea T, Begg CB, Frei E, Antman KH (1990) High-dose ifosfamide with mesna uroprotection: a phase I study. J Clin Oncol 8: 170
10. Frustaci S, Buonadonna A, Galligioni E, Favaro D, De Paoli A, Lo Re G, Sorio R, Tumolo S, Monfardini S (1997) Increasing 4′-epidoxorubicin and fixed ifosfamide doses plus granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a pilot study. J Clin Oncol 15: 1418
11. Galanis E, Edmonson JH, Papagelopoulos PJ, Nascimento AG (1997) Chemotherapy for advanced epithelioid sarcoma.

Proceedings of the American Society of Clinical Oncology 16: (Abstr 1817)
12. Le Cesne A, Antoine E, Spielmann M, Le Chevalier T, Brain E, Toussaint C, Janin N, Kayitalire L, Fontaine F, Genin J (1995) High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. J Clin Oncol 13: 1600
13. Leyvraz S, Bacchi M, Cerny T, Lissoni A, Sessa C, Bressoud A, Hermann R (1998) Phase I multicenter study of combined high dose ifosfamide and doxorubicin in the treatment of advanced sarcomas. Ann Oncol 9: 877
14. Mouridsen HT, Bastholt L, Somers R, Santoro A, Bramwell V, Mulder JH, Van Oosterom AT, Buesa J, Pinedo HM, Thomas D (1987) Adriamycin versus epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer Clin Oncol 23: 1477
15. Patel SR, Vadhan-Raj S, Papadopolous N, Plager C, Burgess MA, Hays C, Benjamin RS (1997) High-dose ifosfamide in bone and soft tissue sarcomas: results of phase II and pilot studies – dose-response and schedule dependence. J Clin Oncol 15: 2378
16. Reichardt P, Tilgner J, Hohenberger P, Dorken B (1998) Dose-intensive chemotherapy with ifosfamide, epirubicin, and filgrastim for adult patients with metastatic or locally advanced STS: a phase II study. J Clin Oncol 16: 1438
17. Rosen G, Forscher C, Lowenbraun S, Eilber F, Eckardt J, Holmes C, Fu YS (1994) Synovial sarcoma: uniform response of metastases to high-dose ifosfamide. Cancer 73: 2506
18. Schutte J, Mouridsen HT, Stewart W, Santoro A, Van Oosterom AT, Somers R, Blackledge G, Verweij J, Dombernowsky P, Thomas D (1990) Ifosfamide plus doxorubicin in previously untreated patients with advanced soft tissue sarcoma. The EORTC Soft tissue and Bone Sarcoma Group. Eur J Cancer 26: 558
19. Steward WP, Verweij J, Somers R, Spooner D, Kerbrat P, Clavel M, Crowther D, Rouesse J, Tursz T, Tueni E, Van Oosterom AT, Warwick J, Greifenberg B, Thomas D, Van Glabbeke M (1993) 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 Clin Oncol 11: 15
20. Toma S, Palumbo R, Canavese G, Albanese E, Cantoni E, Barisone A, Reggiardo G, Rosso R, Santi L (1993) Ifosfamide plus epirubicin at escalating doses in the treatment of locally advanced and/or metastatic sarcomas. Cancer Chemother Pharmacol 31 (Suppl 2): S222
21. Viens P, Gravis G, Genre D, Bertucci F, Cowen D, Camerlo J, Cappiello MA, Conte M, Finaud M, Chabannon C, Houvenaeghel G, Maraninchi D (1997) High-dose sequential chemotherapy with stem cell support for non-metastatic breast cancer. Bone Marrow Transplant 20: 199
22. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, Muggia FM (1979) Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 91: 710