Cancer Chemother Pharmacol (1998) 41: 513–516

CLINICAL TRIAL REPORT

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High-dose-intensity combination chemotherapy for advanced sarcomas: a pilot study

Received: 29 July 1997 / Accepted: 23 October 1997

Abstract A new polychemotherapy schedule involving high dose intensity and shortened intervals has been developed for patients with advanced sarcomas. Mesna at 2500 mg/m^2 for 3 days, epidoxorubicin at 60 mg/m^2 on day 1, ifosfamide at 2500 mg/m^2 for 3 days, and dacarbazine at 450 mg/m^2 for 2 days were given every 2 weeks to a consecutive series of 20 patients. All patients received granulocyte colony-stimulating factor (G-CSF; Filgrastim) subcutaneously at 300 μg from day 5 to day 12 of each cycle. The treatment was feasible and toxicity was acceptable, with grade IV myelotoxicity being observed only in one case. In all, 6 of 14 evaluable patients had an objective response; the median survival was 12 months. Toxicity was milder than that observed for the classic combination MAID, and the planned dose intensity was maintained in the majority of cases.

Key words Sarcomas · Chemotherapy dose intensity · G-CSF

Introduction

The combination of anthracyclines and ifosfamide with or without dacarbazine represents one of the most commonly employed chemotherapy regimens in advanced sarcomas. Such regimens may yield a response rate in the range of 40% with a median survival of 12 months, but the reported toxicity is severe and sometimes life-threatening [1]. Considering the palliative intent of chemotherapy in advanced sarcomas, the availability of regimens capable of inducing tumor regression without producing severe toxicity should be considered a high-priority objective.

The recent development of the concept of dose intensity has stimulated efforts to increase chemotherapy's effectiveness by increasing the doses of antiproliferative agents and/or by shortening the intervals of administration [2, 3]; furthermore, the availability of hematopoietic growth factors has rendered safer the administration of dose-intense chemotherapy [4].

In this trial we evaluated a new treatment schedule for advanced sarcomas based on the acceleration of chemotherapy given at 2-week intervals with the support of granulocyte colony-stimulating factor (G-CSF; Filgrastim) to avoid severe neutropenia.

Patients and methods

To be eligible for this trial, patients were required to have a histologically confirmed sarcoma (excluding Ewing's sarcoma, mesothelioma, paraganglioma, osteosarcoma, and neuroblastoma) with advanced locoregional tumors or distant metastases that were not amenable to potentially curative surgery. Patients had to be chemotherapy-native and less than 75 years old; normal hepatic and renal function (as evaluated by means of serum creatinine and serum bilirubin) and normal cardiac function (on the basis of clinical examination and EKG) were also required. Since the main aim of the study was to investigate the feasibility and toxicity of the new schedule, the presence of measurable lesions was not considered an inclusion criterion.

Patients were scheduled to receive at least four cycles of the following regimen (accelerated MEID): mesna given at 2500 mg/m^2 (500 mg^2 given i.v. immediately before ifosfamide infusion and 1000 mg/m^2 given orally at 4 and 8 h thereafter) on days 1–3, epidoxorubicin given at 60 mg/m^2 by bolus i.v. on day 1, ifosfamide given at 2500 mg/m^2 by 2-h i.v. infusion on days 1–3 and dacarbazine given at 450 mg/m^2 by 1-h i.v. infusion on days 1 and 2). G-CSF at 300 μg was given s.c. from day 5 to day 12 of each cycle.

Cycles were repeated every 14 days, provided that bone marrow recovery had occurred; treatment was delayed until recovery in case of a WBC count of $< 3.0 \times 10^9$/l and/or a platelet count of $< 100 \times 10^9$/l on the planned day for recycle. Otherwise, WBC and platelet values were assessed weekly until recovery and then chemotherapy was given. If the delay lasted 3 weeks or more the patient was withdrawn from the study. Dexamethasone and ondansetron as antiemetics were employed in all cases.

Discontinuation of treatment was planned in case of tumor progression or grade IV toxicity (excluding hair loss). The planned dose intensity (amount of drug delivered per unit of time) was 3750 mg/m^2 per week for ifosfamide, 30 mg/mg^2 week for epidoxorubicin, and 450 mg/mg^2 per week for dacarbazine. In no case was the

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treatment delay or dose reduction (the latter being applied only in one case) differentiated for the agents employed; as a consequence, the ratio between the actually delivered dose intensity and the planned dose intensity was the same for each drug. Continuation of chemotherapy for more than four cycles was planned on an individual basis for patients who acceptably tolerated and positively responded to treatment.

Clinical examination, hemogram and blood chemistry were performed every 2 weeks during treatment. For the patients with measurable lesions an evaluation of tumor response was performed according to WHO criteria [5] using computerized tomography or ultrasound scans every month. Toxicity was graded according to the WHO scale [5]. Informed consent was obtained in all cases.

Results

A total of 20 patients entered the trial and received 99 cycles of accelerated MEID (mean 5 cycles; range 2–7 cycles). Characteristics of the patients are listed in Table 1.

One patient suffered from grade IV neutropenia and thrombocytopenia after the second cycle and was withdrawn from the study. One patient received only two cycles because of disease progression. In all, 18 patients received at least 4 cycles of chemotherapy (7 cycles in 1 case, 6 cycles in 9 cases, 5 cycles in 2 cases, and 4 cycles in 6 cases). Of the 18 patients who were given 4 cycles or more, 9 received an actually delivered/planned dose intensity ratio of 1.0; another 3 patients had a ratio of 0.8–1, and 6 had a ratio of <0.8. Only 14 patients had fully evaluable lesions; one complete response and five partial responses were seen (all the responding patients had a dose intensity ratio of >0.8). The median survival for the whole group was 12 months (range 3–24 months).

Toxicity appeared milder than that reported in trials including the MAID combination (Table 2). In particular, no toxic death was observed, and admission to the hospital due to toxic effects of chemotherapy was never necessary. Hemoglobin concentrations declined during subsequent cycles, and five patients had to receive one or more red-blood-cell (RBC) transfusions (Table 3).

Table 1 Characteristics of the patients

Number	20
M/F	6/14
Median age (range)	59 (26–75) years
Median performance status (range)	1 (1–2)
Histologic subtypes:	
Malignant fibrous hystiocytoma	1
Leiomyosarcoma	6
Liposarcoma	3
Malignant schwannoma	1
Extraskeletal chondrosarcoma	2
Fibrosarcoma	1
Epithelioid cell sarcoma	1
Endometrial stroma sarcoma	3
Undifferetiated sarcoma	2
Extent of disease:	
Locoregional disease	6
Locoregional disease + metastases	1
Metastases	13
Measurable disease	14

Table 2 Toxicity as determined 14 days after the previous cycle

Toxic effects	Patients (*n*) WHO grade			
	0	1	2	3–4
Nausea/vomiting	–	17	2	1
Alopecia	–	4	4	12
Stomatitis	12	5	3	–
Infections	18	1	1	–
Diarrhea	18	1	1	–
Neurotoxicity	18	1	1	–
Cardiac toxicity	19	1	–	–
Constipation	–	2	–	–
Anemia	6	6	8	–
Leukopenia	2	10	7	1
Thrombocytopenia	19	–	–	1

Platelet transfusions were required in one case. Two episodes of infection with fever but without neutropenia and one episode of fever with neutropenia were registered. Since blood counts were performed routinely only on the 1st day of each cycle, clinically irrelevant decreases may have been missed. In spite of antiserotoninergic premedication, the majority of patients suffered from mild to moderate nausea and/or vomiting.

Discussion

Sarcomas are a large family of neoplastic diseases that are only moderately responsive to chemotherapy. Among the older agents, only doxorubicin and ifosfamide yield a 20% response rate, whereas dacarbazine shows a 15% response rate and other cytotoxic agents are substantially inactive. Chemotherapy is commonly employed as palliative treatment in advanced sarcomas, whereas neoadjuvant or adjuvant treatment must yet be considered investigational.

Adjuvant chemotherapy after resection of the primary tumor seemed to prolong the distant and local disease-free survival in a large trial comparing CYVADIC (cyclophosphamide, vincristine, doxorubicin, and dacarbazine) with no treatment; in this trial the overall survival was not prolonged by chemotherapy [6]. In a recent large, randomized EORTC trial, Santoro et al. [7] demonstrated that single-agent doxorubicin might be considered the standard treatment for advanced disease; indeed, the addition of ifosfamide to doxorubicin or the combination CYVADIC did not result in a statistically significant difference in terms of overall survival in spite of higher response rates (21.3% for doxorubicin alone versus 25.2% for doxorubicin and ifosfamide versus 26.8% for CYVADIC). In 1989, Elias et al. [1] published the results of a phase II study on the combination of mesna, doxorubicin, ifosfamide, and dacarbazine (MAID), reporting a 47% response rate. The doses planned in this trial were 60, 7500, and 900 mg/m^2 for doxorubicin, ifosfamide, and dacarbazine, respectively. Subsequently, Antman et al. [8] carried out an intergroup randomized study of MAID versus the doxorubicin-dacarbazine combination. The

Table 3 Treatment and hematologic parameters (*Pt* Patient, *Cy* number of cycles, *DI* ratio between planned and actually delivered dose intensity, *Hb* hemoglobin/d1, *WBC* white blood cells $\times 10^9$/l, *N* neutrophils $\times 10^9$/l, *Plt* plateletes $\times 10^9$/l)

Pt	Cy	DI	Before first cycle			Before last cycle		
			Hb	N	Plt	Hb	N	Plt
1	5	1.0	13.6	1.7	170	12.8	10.2	173
2	7	1.0	12.7	7.4	350	11.6[a]	1.8	199
3	6	0.85	13.8	10.5	205	9.9[a]	2.7	134
4	4	1.0	12.4	7.2	212	11.7	14.2	209
5	4	0.70	12.5	5.9	210	9.0	2.3	124
6	4	1.0	11.7	4.5	255	10.2	4.6	198
7	6	1.0	13.8	2.7	179	10.6	4.3	117
8	4	0.7	10.5	6.3	270	9.5	3.4	233
9	6	1.0	14.9	8.7	311	13.5	2.5	169
10	6	1.0	11.7	8.4	278	9.4	6.9	112
11	6	0.85	11.3	3.0	193	10.5[a]	2.4	237
12	6	1.0	11.8	4.2	262	9.5	8.1	152
13	6	0.7	16.4	3.7	167	13.3	2.1	169
14	4	0.5	11.5	4.7	403	13.1	5.3	422
15	2	–	11.5	4.0	224	10.0[a]	5.1	259
16	6	1.0	14.9	8.7	247	13.2	3.1	201
17	6	0.5	13.2	6.1	326	12.9	3.2	202
18	4	0.7	12.6	4.8	302	9.1[a]	2.8	145
19	2	–	13.2	6.8	326	12.9	2.4	132
20	5	0.85	12.6	4.9	284	9.8	2.9	124

[a] Patients who received RBC transfusions

increase in response rate observed for the ifosfamide-including regimen was achieved at the expense of a high level of toxicity: 134/170 patients treated with MAID suffered from severe neutropenia and 7/170 patients died with grade 4 myelosuppression.

In the present trial we investigated the activity and toxicity of a new schedule based on dose intensification, rendered possible by the supportive use of G-CSF. Dose intensity, i.e., the dose delivered per unit of time, has been demonstrated to be directly correlated with the activity of a number of cytotoxic drugs in several experimental and clinical models [2, 3]. With regard to sarcomas, several studies have shown a direct correlation between response and dose for doxorubicin [9–11]; moreover, high doses of ifosfamide have yielded a high rate of response in phase II studies [12, 13]. The issue of dose intensity in human cancer was the focus of some retrospective analyses by Hryniuk and Bush [2], who showed a direct relationship between the clinical response and the average relative dose intensity (a mean of the dose intensities of each drug in different regimens) and between survival and the average relative dose intensity for several cytotoxic drugs and schedules in breast and other cancers. Other retrospective studies have analyzed the impact of the actually delivered dose intensity of chemotherapy in large series of patients, again showing a correlation between dose intensity and outcome [14].

There are basically two ways to increase the dose intensity of a regimen: the first is to increase the dose of the drugs for each cycle, and the second is to shorten the intervals between cycles. Since the administration of hematopoietic growth factors allows faster marrow recovery after chemotherapy [15, 16], we employed G-CSF to accelerate the chemotherapy. A similar approach has been applied in breast cancer by the administration of cyclophosphamide, epidoxorubicin, and fluorouracil every 14 days [15, 16] and in ovarian cancer by the administration of cyclophosphamide, epidoxorubicin, and cisplatin every 14 days [17]. Lalisang et al. [18] demonstrated that chemotherapy acceleration resulted in a more pronounced dose intensification with respect to increase in the doses per cycle. With regard to sarcomas, hematopoietic growth factors allowed only a limited increase in dose intensity when they were used to escalate the dose of anthracycline or of other drugs given at conventional intervals [19–22].

In the present study we applied a regimen with a planned dose intensity 50% greater than that used in the conventional MAID regimen with regard to ifosfamide and dacarbazine, thanks to a 2-week interval between cycles. The results of an EORTC randomized trial [23] comparing doxorubicin and epidoxorubicin at equimolar doses (75 mg) in advanced soft-tissue sarcomas show no statistically significant difference in response rate between the two compounds. Thus, the planned dose intensity of anthracycline in our study may also be considered increased by 50%; nevertheless, it has been observed that the maximum tolerated doses of epidoxorubicin are in the range of 120–150 mg and further intensification of epidoxorubicin, also in the context of combination chemotherapy, may be considered [21, 24, 25].

Our regimen was feasible. Only one case of grade IV myelotoxicity was observed; the marrow toxicity was largely milder than that observed in other studies using conventional doses and schedules [1], and the severe pattern of toxicity observed in studies employing the classic regimen MAID [8] was not observed. Furthermore, in the MAID studies, treatment delays and dose reductions were very frequently necessary, resulting in decreases in dose intensity, whereas $>80\%$ of the planned dose intensity was maintained in the majority of patients in our study. Since dose intensity remained high

in our study, we may presume that both the schedule and the myeloprotection provided by Filgrastim rendered the combination safer.

This study demonstrates that a high-dose-intensity regimen based on the combination of ifosfamide, dacarbazine, and an anthracycline given at shortened intervals with the support of G-CSF may be safely given to advanced sarcoma patients. On the basis of these results, the new schedule may be taken into consideration in further studies of efficacy.

References

1. Elias A, Ryan L, Sulkes A, et al. (1989) Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. J Clin Oncol 7: 1208–1216
2. Hryniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2: 1281–1288
3. Tannock IF, Boyd NF, DeBoer G, Erlichman C, Fine S, Laroque G, Mayers C, Perrault D, Sutherland H (1988) A randomized trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for patients with metastatic breast cancer. J Clin Oncol 6: 1377–1387
4. Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Dabbara I, Kris M, Grous J, Picozzi V, Rausch G, Smith R, Gradishar W, Yahanda A, Vicent M, Stewart M, Galspy J (1988) Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small cell lung cancer. N Engl J Med 325: 164–170
5. World Health Organization (1979) Handbook for reporting results of cancer treatment. WHO Offset Publication 18. World Health Organization, Geneva
6. Bramwell V, Rouesse J Steward W, Santoro A, Schraffortd-Koops H, Buesa J, Ruka W, Priario J, Wagener T, Burgers M, Van Unnik J. Contesso G. Thomas D, Van Glabbeke M, Markman D, Pinedo H (1994) Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma – reduced local recurrence but no improvement in survival: a study of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 12: 1137–1149
7. Santoro A, Tursz T, Mouridsen T, Verweij J, Steward W, Somers R, Buesa J, Casali P, Spooner D, Rankin E, Kirkpatrick A, Van Glabbeke M, Van Oosterom A (1995) Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 13: 1537–1545
8. Antman K, Crowley J, Balcerzack P, Rivkin SE, Weiss GR, Elias A, Natale RB, Cooper RM, Bazlogie B, Trump DL, Dozoshow JH, Aisner J, Pugh RP, Weiss RB, Cooper BA, Clamond GH, Baker LH (1993) An intergroup randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol 11: 1276–1285
9. Bodey GP, Rodriguez V, Murphy WK, Burgess A, Benjamin RS (1981) Protected environment-prophylactic antibiotic program for malignant sarcoma: randomized trial during remission induction chemotherapy. Cancer 47: 2422–2429
10. Pinedo HM, Bramwell VHC, Mouridsen HT, Somers R, Vendrik CP, Santoro A, Buesa J, Wagener T, Oosterom AT van, Unnik JA van (1984) CYVADIC in advanced soft tissue sarcoma. A study of the EORTC Soft Tissue and Bone Sarcoma Group. Cancer 53: 1825–1832
11. Schoenfeld D, Rosenbaum C, Horton J, Wolter JM, Falkson G, De Conti RC (1982) A comparison of Adriamycin versus vincristine and Adriamycin and cyclophosphamide for advanced sarcoma. Cancer 50: 2757–2762
12. Miser JS, Kinsella TJ, Triche TJ, Tsokos M, Jarosinski P, Forquer R, Wesley R, Magrath I (1987) Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. J Clin Oncol 5: 1191
13. La Cesne A, Antoine E, Spielmann M, Le Chevalier T, Brain E, Toussaint C, Kayitalire L, Fontaine F, Gemin J, Vanel D, Contesso G, Tursz T (1995) High-dose ifosfamide: circumvention of resistance to standard dose ifosfamide in soft tissue sarcomas. J Clin Oncol 13: 1600–1608
14. Pronzato P, Campora E, Amoroso D, Bertelli G, Botto F, Conte PF, Sertoli MR, Rosso R (1989) Impact of administration-related factors on outcome of adjuvant chemotherapy for primary breast cancer. Am J Clin Oncol 12: 481–485
15. Ardizzoni A, Venturini M, Sertoli MR, Giannessi PG, Brema F, Danova M, Testore F, Mariani GL, Pennucci MC, Queirolo P, Silvestro S, Bruzzi P, Lionetto R, Latini F, Rosso R (1994) Granulocyte-macrophage colony stimulating factor (GM-CSF) allows acceleration and dose-intensity increase of CEF chemotherapy. A randomised study in patients with advanced breast cancer. Br J Cancer 69: 385–391
16. Venturini M, Del Mastro L, Testore F, Danova M, Garrone O, Lanfranco C, Latini F, Sertolli MR, Lionetto R, Queirolo P, Ardizzoni A, Rosso R (1996) Erythropoietin and granulocyte-macrophage colony stimulating factor allow acceleration and dose escalation of cyclophosphamide/epidoxorubicin/5-fluorouracil chemotherapy: a dose finding study in patients with advanced breast cancer. Cancer Chemother Pharmacol 38: 487–494
17. Pronzato P, Bertelli G, Vigani A, Vaira F (1996) A feasibility study of accelerated polychemotherapy with cisplatin, epidoxorubicin and cyclophosphamide (PEC) in advanced ovarian cancer. Br J Cancer 73: 1425–1427
18. Lalisang RI, Wils JA, Nortier HW, Burghoults JT, Hupperets PS, Erdkamp FL, Schouten HC, Blijham GH (1997) Comparative study of dose escalation versus interval reduction to obtain dose intensification of epirubicin and cyclophosphamide with granulocyte colony-stimulating factor in advanced breast cancer. J Clin Oncol 15: 1367–1376
19. Frustaci S, Buonadonna A, Galligioni E, Favaro D, DePaoli A, Lo Re G, Sorio R, Tumolo S (1997) Increasing 4-epidoxorubicin and fixed ifosfamide doses plus granulocyte-macrophage colony-stimulating factors in advanced soft tissue sarcomas: a pilot study. J Clin Oncol 15: 1418–1426
20. Hicks LG, Balcerzack S, Zalupski M (1996) GM-CSF did not allow doxorubicin dose escalation in the MAID regimen: a phase I trial. A Southwest Oncology Group study. Cancer Invest 14: 507–512
21. Toma S, Palumbo R, Canavese G, Albanese A, 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: S222–S227
22. Steward WP, Verwej 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 (!993) Granulocyte macrophage colony stimulating factor allows dose 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: 15–21
23. Mouridsen HT, Bastholt L, Somers R, Santoro A, Bramwell V, Mulder JH, Van Oosterom AT, Buesa J, Pinedo HM, Thomas D, Sylvester R (1987) Adriamycin versus epiribicin in advanced soft tissue sarcomas. A randomized phase II/III study of the EORTC Soft Tissue and Bone Sarcomas Group. Eur J Cancer Clin Oncol 23: 1477–1483
24. Hichisht T, Cunningham O, Haydock A, et al (1989) Experience with intermediate dose (110–120 m^2) epirubicin. Cancer Chemother Pharmacol 24: 61–64
25. Tjuljandin SA, Dog RG, Sobol MM (1990) Pharmacokinetics and toxicity of two schedules of high dose epirubicin. Cancer Res 50: 5095–5101