High-Dose Chemotherapy in the Treatment of Relapsed Osteosarcoma: An Italian Sarcoma Group Study

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Purpose: **To study the feasibility and activity of two courses of high-dose chemotherapy (HDCT) in patients with osteosarcoma in metastatic relapse.**

Patients and Methods: **Patients with high-grade osteosarcoma in metastatic relapse (multiple metastases or solitary metastasis at intervals of less than 30 months) were eligible for study. High-dose chemotherapy consisted of carboplatin and etoposide followed by stem-cell rescue. A second course was planned 4 to 6 weeks after the first. Surgery was performed before or after HDCT.**

Results: **Thirty-two patients were enrolled onto the study. At the end of the treatment, 25 patients were in complete remission (CR), six were alive with disease progression, and one died of toxicity. At present, 14 patients are alive with a median survival time of 23 months from study entry: four are in first CR, three are in second CR, and one is in fourth CR. Six patients are alive with disease. Eighteen patients (56%) died: 17 of disease and one of toxicity. Transplantation-related mortality was 3.1%. The relapse or progression disease rate was 84.4%. The 3-year overall survival rate is 20% and the 3-year disease-free survival rate is 12%.**

Conclusion: **HDCT combined with surgery is feasible and can induce CR in a large portion of patients. Two points, however, need to be considered: only patients who are chemosensitive to induction treatment can obtain CR after HDCT, and the length of remission is short, because most patients relapse. Thus novel strategies are needed to maintain the remission status or to treat patients who do not respond to induction treatment.**

J Clin Oncol 20:2150-2156. *© 2002 by American Society of Clinical Oncology.*

THE PROGNOSIS OF patients with high-grade osteosarcoma has greatly improved over the past 25 years, with overall survival rates increasing from 15% to 70%. This improvement is attributed to (1) the effect of preoperative chemotherapy,[1-4] (2) the introduction of aggressive chemotherapy with various combinations of high-dose methotrexate, doxorubicin, cisplatinum, and ifosfamide,[5-8] (3) the identification of the relationship of dose-response between methotrexate, doxorubicin, cisplatinum, and osteosarcoma cells,[9,10] and (4) the recognition of the main prognostic factor, such as the histologic response to preoperative chemotherapy, which might change postoperative chemotherapy.[11,12]

The prognosis of patients with osteosarcoma in metastatic relapse is very poor, with overall survival rates between 0% and 50% after metastasectomy and aggressive second-line chemotherapy.[13-17] In an attempt to improve survival for patients in metastatic relapse, the Italian and Scandinavian Sarcoma Group devised a prospective phase II protocol with high-dose chemotherapy (HDCT) and peripheral-blood stem-cell (PBSC) reinfusion.[18,19] This approach seems attractive for the pharmacokinetic data available in osteosarcoma patients,[20,21] but the nonhematopoietic toxicity of methotrexate, doxorubicin, cisplatinum, and ifosfamide[9,22-24] makes these agents unsuitable for dose escalation in HDCT. For HDCT, we chose carboplatin and etoposide because of their suitable toxicity profile. Recent data indicate considerable activity of etoposide against bone and soft tissue sarcomas when it is administered in a long-term infusion, taking advantage of the phase specificity of this agent.[25,26] Carboplatin has also been shown to have antitumor activity in osteosarcoma.[27-31]

PATIENTS AND METHODS

Selection of Patients

Patients with high-grade osteosarcoma in metastatic relapse were considered eligible for this protocol if they had multiple metastases or solitary metastasis at intervals of less than 30 months from diagnosis, were younger than 40 years of age, and had normal hepatic and renal function, a WBC count greater than 3.0×10^9/L, and platelets greater than 100×10^9/L. Before entering this protocol, patients underwent a physical examination, a chest computed tomography, and a radionuclide bone scan. Careful enumeration and measurement of all metastatic sites was required. All patients or their legal guardians signed a

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Submitted June 15, 2001; accepted January 21, 2002.

Supported in part by the Italian Association for Cancer Research, Milan, Italy (E.M. and M.A).

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0732-183X/02/2008-2150/$20.00

10.1200/JCO.2002.08.081

document of informed consent consistent with local institutional review board guidelines.

Treatment

Mobilization of PBSCs was performed using cyclophosphamide 4 g/m^2 (day 1) and etoposide 100 mg/m^2 over 1 hour every 12 hours (days 2, 3, and 4; total dose, 600 mg/m^2). Granulocyte colony-stimulating factor 10 μg/kg/d was started 48 hours after chemotherapy. The CD34$^+$ cell number required for two re-infusions was 5×10^6/kg.

High-dose chemotherapy consisted of a 2-hour infusion of carboplatin 375 mg/m^2/d for 4 days and continuous-infusion etoposide 450 mg/m^2/d for 4 days. PBSCs were infused 48 hours after the end of HDCT. The first cycle of HDCT was planned 1 to 2 weeks after mobilization and the second cycle, 4 to 6 weeks after the first. The protocol outline is shown in Fig 1.

Granulocyte colony-stimulating factor 5 μg/kg/d was administered from day +1 until the neutrophil count was more than 1×10^9/L for 3 consecutive days. Patients were nursed in a single room at positive air pressure and received oral nonabsorbable antibiotics (gentamicin and nystatin). *Pneumocystis carinii* prophylaxis was performed with nebulized pentamidine 300 mg every 3 weeks from the first day of HDCT.

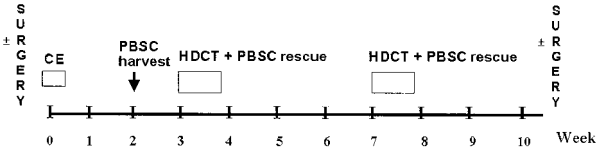

Fig 1. Protocol outline. CE, cyclophosphamide 4,000 mg/m^2 (day 1); etoposide 200 mg/m^2/d (days 2, 3, and 4). HDCT: etoposide 1,800 mg/m^2 (4 days continuous intravenous infusion), carboplatin 1,500 mg/m^2 (4 days). PBSC rescue at 48 hours after termination of chemotherapy. When possible, surgery was performed within 3 weeks before CE or 4 to 6 weeks after the second transplantation.

The surgical management of the metastatic sites was left to the discretion of the individual surgeon. However, surgical removal of all metastatic sites was strongly encouraged.

Toxicity

Extra-hematopoietic toxicity was graded according to the Bearman score.[32]

Table 1. Patient Characteristics at Study Entry

Patient No.	Sex	Site at Diagnosis	First-Line Therapy	Age at Study Entry (years)	No. of Relapses	Months From Diagnosis	Site of Relapse (last)	No. of Lung Metastases	Mono- or Bilateral Lung Metastases
1	F	Tibia	NEO*5*	14	I	24	Lung	13	Bilateral
2	M	Fibula	Pilot ISG-SSG I	13	I	22	Lung	2	Monolateral
3	F	Fibula	Pilot ISG-SSG I	14	I	17	Lung	1 (13 cm)	Monolateral
4	M	Humerus	Pilot ISG-SSG I	12	I	15	Lung	13	Bilateral
5	M	Femour	Pilot ISG-SSG I	13	I	21	Lung	2	Monolateral
6	F	Femour	Pilot ISG-SSG I	8	I	22	Lung	2	Monolateral
7	M	Femour	ISG-SSG I	13	I	12	Lung	5	Bilateral
8	M	Tibia	ISG-SSG I	13	I	15	Bone + lung	2	Monolateral
9	M	Humerus	ISG-SSG I	9	I	18	Lung	2	Monolateral
10	M	Tibia + fibula	NEO*5*	23	I	52	Lung	4	Monolateral
11	M	Tibia	ISG-SSG I	12	I	10	Lung	2	Bilateral
12	F	Tibia	Pilot ISG-SSG I	20	I	23	Lung	2	Bilateral
13	M	Femour	Pilot ISG-SSG I	16	I	19	Lung	4	Bilateral
14	M	Tibia	ISG-SSG I	22	I	18	Lung	5	Bilateral
15	M	Femour	ISG-SSG I	36	I	18	Lung	7	Bilateral
16	M	Femour	ISG-SSG I	17	I	16	Lung	5	Bilateral
17	M	Fibula	NEO4	25	I	41	Lung	3	Monolateral
18	M	Tibia	Pilot ISG-SSG I	26	I	34	Lung	2	Bilateral
19	F	First cervical vertebra	NEO*5*	38	I	45	Lung	2	Monolateral
20	M	Tibia	Pilot ISG-SSG I	21	I	27	Bone + lung	20	Bilateral
21	F	Femour	ISG-SSG I	21	I	12	Lung + lymph node	1	Monolateral
22	F	Femour	NEO*5*	13	II	31	Lung	4	Bilateral
23	F	Fibula	NEO*5*	15	II	26	Bone + lung	1	Monolateral
24	F	Fibula	Pilot ISG-SSG I	16	II	23	Lung	7	Bilateral
25	F	Radius	NEO4	14	II	35	Bone		
26	M	Femour	ISG-SSG I	15	II	15	Lung	7	Bilateral
27	F	Fibula	Pilot ISG-SSG I	12	II	31	Lung	3	Bilateral
28	F	Humerus	NEO*5*	7	II	49	Lung + lymph node	1 (15 cm)	Monolateral
29	F	Humerus	ISG-SSG I	23	II	21	Lung	2	Bilateral
30	M	Tibia	NEO*5*	17	III	39	Lung	3	Monolateral
31	M	Femour	ISG-SSG I	18	III	32	Lung	1 (paracardiac)	Monolateral
32	M	Tibia	ISG-SSG I	17	III	29	Lung	3	Bilateral

Abbreviations: F, female; M, male; ISG-S G, Italian and Scandinavian Sarcoma Group.

Table 2. Characteristics of Previous Relapses in Patients With More Than One Relapse Before Study Entry

Patient No.	Time From Diagnosis to First Relapse (months)	Site of First Relapse	Therapy for First Relapse	Time From First to Second Relapse (months)	Site of Second Relapse	Therapy for Second Relapse	Time From Second to Third Relapse (months)
22	26	Lung	Surgery	5	Lung		
23	19	Bone	Surgery	7	Bone + lung		
24	20	Lung	Surgery	2,5	Lung		
25	35	Lung	Surgery	42	Bone		
26	9	Lung	Surgery	6	Lung		
27	18	Lung	Surgery	13	Lung		
28	45	Lymph node	Surgery	4	Lung + lymph node		
29	14	Lung	Surgery	7	Lung		
30	30	Bone	Surgery	4	Lung	Surgery	5
31	24	Lung	Surgery	4,5	Lung	Surgery	3
32	20	Lung	Surgery	6	Lung	Surgery	3

Clinical Response

Response of lung metastases was assessed radiologically by computed tomography scan. Isotope bone scans were also performed to monitor bone metastases.

Definitions of response were as follows: complete remission (CR), radiologic disappearance of all evidence of metastasis; partial response (PR), ≥ 50% reduction in the tumor diameters at all sites; stable disease (SD), less than 50% decrease or less than 25% increase in the size of one or more lesions; and progressive disease (PD), more than 25% increase in the size of one or more of the metastases.

Statistical Analysis

Survival analysis was carried out using the Kaplan-Meier method.[33] Event-free survival was defined as the time from the day of transplantation until disease progression or any other cause of death.

Table 3. Outcome of Treatment With Primary and Secondary Surgery, Mobilizing Cycle, and HDCT in All Patients

Patient No.	Outcome After Primary Surgery	Disease Status After Mobilizing Cycle	Disease Status After HDCT	Status at the End of Treatment With Secondary Surgery	Months From End of Treatment to Relapse	Follow-Up and Months From Study Entry
1	CR	CR	CR	CR	3	Dead, 15
2	CR	CR	CR	CR	9,5	Dead, 28
3	CR	CR	CR	CR	6	Dead, 10
4	CR	CR	CR	CR	13	Dead, 29
5	CR	CR	CR	CR		Alive 1st CR, 36+
6	CR	CR	CR	CR	8	Dead, 14
7	PR	PR	PD	PD		Dead, 11
8	NA	SD	PD	PD		Dead, 12
9	NA	SD	SD	CR		Alive 1st CR, 22+
10	CR	CR	CR	CR		Alive 1st CR, 20+
11	NA	SD	SD	CR		Alive 1st CR, 7+
12	NA	SD	PD	PD		Dead, 11
13	NA	SD	SD	CR	5	Alive PD, 26+
14	NA	SD	SD	CR	10	Alive 2nd CR, 24+
15	NA	SD	SD	CR	4	Dead, 16
16	CR	CR	CR	CR	7	Dead, 18
17	NA	PR	PR	CR	13	Alive PD, 19+
18	NA	SD	SD	CR	9,5	Dead, 25
19	CR	CR	CR	CR	8	Dead, 21
20	NA	SD	PD	PD		Alive PD, 13+
21	PR	PR	PR	CR	3	Dead, 8
22	NA	PR	PR	PD		Dead, 13
23	NA	SD	PD	PD		Dead, 29
24	NA	PR	CR	CR	13	Dead, 33
25	CR	CR	CR	CR	15	Alive 4th CR, 30+
26	PR	PR	CR	CR	6	Alive PD, 25+
27	NA	SD	SD	CR	13	Alive 2nd CR, 20+
28	CR	CR	CR	CR	5	Alive PD, 17+
29	NA	SD	Dead	Dead		Dead, 3
30	NA	PR	CR	CR	12	Dead, 39
31	NA	PR	CR	CR	4	Alive PD, 11+
32	NA	SD	SD	CR	2	Alive 2nd CR, 8+

Abbreviation: NA, not assessable.

RESULTS

Thirty-two Italian patients (19 male and 13 female) were enrolled onto this study. At the time of study, median patient age was 15 years (range, 8 to 38 years). The site of relapse was mainly the lung. Twenty-one patients were in first relapse at a median of 20 months (range, 10 to 52 months) from diagnosis. All except one had two or more mono- or bilateral metastases. Eight patients were in second relapse at a median of 28.5 months (range, 15 to 77 months), and three patients were in third relapse at 29, 32, and 39 months from diagnosis (Tables 1 and 2).

Surgery was performed in 14 patients before chemotherapy (primary surgery). Surgery was complete in 11 of these patients.

After the mobilizing cycle, 29 patients achieved the required $CD34^+$ cell number (median, 12.1 $\times$ 10^6/kg; range, 5.52 to 25.5) with a median of two aphereses (range, one to six). Three patients failed ($CD34^+$ 0, 1.29, and 2.41 $\times$ 10^6/kg) and received only one course of HDCT (in the first two patients bone marrow was added). Another patient received only one course because she had veno-occlusive disease after the first course and died of multiple organ failure.

As of April 1, 2001, 28 patients had undergone two courses of high-dose carboplatin and etoposide, whereas four patients had one course, for a total of 60 courses.

A median of 10 days (range, 7 to 14 days) was required to reach a granulocyte count greater than 0.5 $\times$ 10^9/L, a median of 11 days (range, 8 to 16 days) was required to reach a granulocyte count greater than 1 $\times$ 10^9/L, a median of 12 days (range, 4 to 30 days) was required to reach a platelet count greater than 25 $\times$ 10^9/L, and a median of 15 days (range, 7 to 30 days) was required to reach a platelet count greater than 50 $\times$ 10^9/L. The median time for hematologic recovery was similar (no significant difference) after the first and the second course of high-dose carboplatin and etoposide.

Severe nonhematologic toxicity, according to the Bearman score, was present in only five courses: grade 3 stomatitis was present in four courses and grade 3 hepatic toxicity was present in one course. There was no significant difference in nonhematologic toxicity between the first and the second course of chemotherapy.

As shown in Table 3, 11 of 32 patients were in CR before HDCT, whereas 21 patients underwent HDCT with evident disease. After the mobilizing cycle, 11 patients were in CR, eight were in PR, and 13 had SD. After HDCT, 15 patients were in CR, three were in PR, eight had SD, five had PD, and one patient died of toxicity. Four additional CRs were obtained with HDCT among the eight patients in PR after induction chemotherapy. None of the 13 patients in SD entered a remission after HDCT. Surgery was performed in 11 patients after HDCT (secondary surgery) and was definitive in 10 patients. Surgery was not performed in five patients because of PD and in four patients because of CR. At the end of treatment, 25 patients were in CR and six had PD.

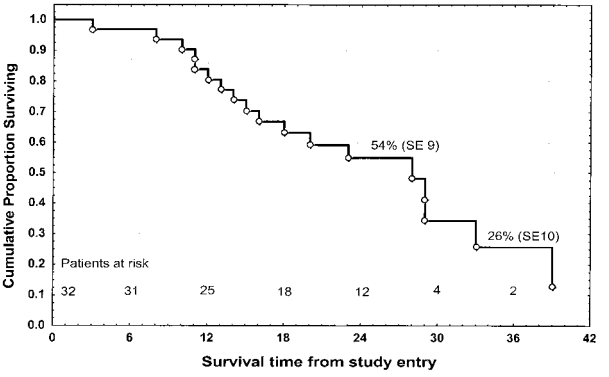

Fig 2. Overall patient survival from the day of CE treatment. ○, Dead.

As of April 1, 2001, 14 patients (43.7%) are alive, with a median survival time of 20 months from study entry (range, 7 to 36 months): four are in first CR at a median of 21 months (range, 7 to 36 months) from study entry, three are in second CR at 8, 20, and 24 months, and one is in fourth CR at 30 months. Six patients are alive with disease at 18 months (range, 11 to 26 months). Eighteen patients (56%) died: 17 of disease at 16 months from study entry (range, 8 to 39 months) and one of toxicity at 3 months (multiple organ failure). Transplantation-related mortality was 3.1%. The relapse or PD rate was 84.4%: 21 patients (65.6%) relapsed with a median time of 8 months (range, 2 to 15 months) and six patients (18.8%) did not respond to treatment.

The 3-year overall survival rate is 20% (Fig 2) and the 3-year disease-free survival is 12% (Fig 3). The median follow-up time is 18.5 months (range, 3 to 39 months).

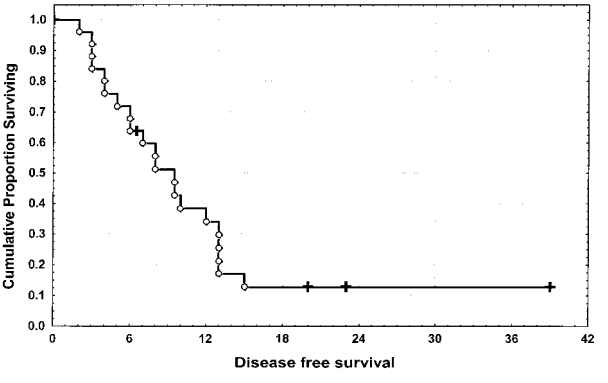

Fig 3. Disease-free survival. ○, Relapse; +, disease-free.

DISCUSSION

The outlook for patients with high-grade osteosarcoma in metastatic relapse remains poor. When the lung is the only site of the disease recurrence, a surgical approach in which all metastases are removed has been advocated as potentially curative, with a reported 5-year survival rate from the first thoracotomy of 23% to 50%.[13,34-41] The prognosis of these patients is correlated with the relapse-free interval from initial diagnosis, the number and the sites of the metastases, and the complete metastasectomy.[13] Incomplete surgery or development of bone metastases carries a worse prognosis, with a 0% 4-year overall survival rate.[39]

Chemotherapy in the management of metastatic osteosarcoma has no proven benefit, especially in heavily pretreated patients.[35,40-44] However, a number of regimens have been reported to have been used in these situations, and the published data are difficult to analyze.[25,45-47] There are but isolated reports of the use of HDCT in patients with metastatic osteosarcoma.[18,19,27,48,49]

In an attempt to improve the survival of patients affected by high-grade osteosarcoma in metastatic relapse, the Italian and Scandinavian Sarcoma Group devised a phase II protocol that consists of high doses of carboplatin and etoposide and PBSC reinfusion. Each of these agents has considerable activity against osteosarcoma and a suitable toxicity profile. Dose-limiting toxicity consists of stomatitis and diarrhea for high-dose etoposide and neuropathy, nephrotoxicity, and hepatic toxicity for high-dose carboplatin. Toxicity data on double high-dose treatment using carboplatin and etoposide are derived from phase I/II studies on adult germ cell tumors and from one pediatric study on mixed tumors. In one study, high-dose therapy was a part of the primary therapy.[50] In the other three, high-dose therapy was a part of salvage therapy, usually after extensive use of chemotherapy containing platinum.[27,51,52]

The patients enrolled onto this study do not have a good prognosis. Twenty-one patients were in first relapse at a median of 20 months from diagnosis. All of these patients except one had two or more mono- or bilateral metastases. Eight patients were in second relapse with bilateral metastases of the lung (five patients), lung and bone (one patient), lung and lymph nodes (one patient), and bone (one patient). Three patients were in third relapse.

The first-line therapy is shown in Table 1. The patients in second or in third relapse received surgery. Therefore, all patients were heavily pretreated, even though a single course of cyclophosphamide and etoposide allowed an adequate collection for two re-infusions. Only three patients failed to achieve the required number of $CD34^+$ cells, and they received just one course of high-dose carboplatin and etoposide. During the mobilizing cycle, no patients had PD and five patients were in PR.

After carboplatin and etoposide administration, trilineage engraftment was promptly observed in all patients, and there was no significant difference between the first and the second course of chemotherapy. Furthermore, our results showed that a two-drug conditioning regimen containing carboplatin and etoposide is well tolerated. We observed severe extra-hematopoietic toxicity in only five courses: severe stomatitis requiring morphine in four courses and severe hepatic toxicity in one course (this patient died of multiorgan failure only 3 months after study entry). After two cycles of HDCT, five patients were in PD, five were in PR, and four were in CR. At the end of treatment, with primary or secondary surgery, there were 25 patients in CR and six in PD. It is important to note that most of these patients had received cisplatin in first-line therapy and such patients may develop resistance to platinum agents. Such acquired cross-resistance after exposure to cisplatin has been reported in an osteosarcoma cell line.[53] Twenty one patients (65.6%) relapsed, with a median time of 8 months.

In conclusion, combining surgery with HDCT can render a large proportion of patients disease-free. The evidence that patients in PR after induction therapy can reach CR after HDCT indicates that this procedure may be useful for these patients. Additional maintenance treatment or completely novel strategies, such as nonmyeloablative allogeneic transplantation, need to be explored to eliminate minimal residual disease. For patients in SD after primary treatment, HDCT seems scarcely efficacious. For these chemoresistant patients, completely new strategies are warranted.

ACKNOWLEDGMENT

We thank Andrew M. Garvey, BA(Hons), Licentiate of Trinity College London(Teaching English as a Second or Foreign Language) for editorial assistance.

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