Tandem High-dose Chemotherapy Followed by Autologous Transplantation in Patients with Locally Advanced or Metastatic Sarcoma

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Abstract. Background: Patients with locally advanced or metastatic/recurrent soft tissue and Ewing’s sarcoma (EWS) have few treatment options. The purpose of our phase II study was to assess the feasibility, safety and efficacy of tandem high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) in such patients. Patients and Methods: Thirteen patients were enrolled onto this study. The first cycle of HDCT consisted of doxorubicin (150 mg/m²) and ifosfamide (14 g/m²) mixed with mesna (14 g/m²), while the second cycle consisted of melphalan (150 mg/m²) and cisplatin (200 mg/m²). Results: Eleven out of 13 patients were able to complete both cycles of HDCT. No treatment-related mortality occurred and grade 3 or 4 toxicity was clinically tolerable. The 5-year progression-free survival (PFS) and overall survival (OS) for all patients was 23% (confidence interval, CI: 0-46%) and 31% (CI: 14-70%), respectively. Out of the four patients still alive, two had EWS and measurable disease at the time of ASCT and achieved a complete remission, remaining progression free 126 and 155 months after ASCT. Conclusion: Our study demonstrates the feasibility and safety of tandem HDCT in patients with high-risk or metastatic/recurrent sarcoma, with some patients achieving long-term PFS and OS.

Sarcomas comprise a small heterogeneous group of malignant tumors that arise from mesenchymal and neuroectodermal tissue. Approximately 80% of sarcomas originate from soft tissue, the remainder from bone, accounting for 0.7% of all newly diagnosed cancers with an annual incidence of 10,390 cases in the United States (1). Multimodality therapy has become standard treatment providing patients with localized disease and good prognostic features greater than 50% long-term survival. Patients with adverse risk factors, such as unresectable or progressive disease, have a poor prognosis with a median survival of 12 months and less than 10% disease-free survival at 5 years (2). Single-agent chemotherapy with the two most active chemotherapeutic agents, doxorubicin or ifosfamide, offers response rates between 15% and 25% (3). Dose-intensive combination chemotherapy regimens consisting of high-dose ifosfamide, doxorubicin, cisplatin, melphalan, or cyclophosphamide have been tested in the phase II setting resulting in response rates of up to 60% (4). Phase III studies, however, have not confirmed such findings (5, 6). Several reports have demonstrated the feasibility of high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) in patients with advanced sarcomas, some of whom achieve long-term disease-free survival (7, 8). The majority of these reports, however, have focused on the pediatric population with a short-term median follow-up of less than 5 years. Moreover, benefit appears to predominate in patients who are in complete remission prior to undergoing HDCT (9). Whether this benefit is due to HDCT is unclear since long-term survivors have also been reported in patients receiving conventional chemotherapy with or without surgical resection (10).

In this prospective phase II study, we evaluate the feasibility, safety and efficacy of administering two cycles of sequential HDCT consisting of ifosfamide/doxorubicin and melphalan/cisplatin, respectively, followed by ASCT in adult patients with high-risk and recurrent Ewing’s and soft sarcomas.

Patients and Methods

From February 1995 to September 1999, 13 patients were enrolled in this phase II study conducted at the City of Hope Comprehensive Cancer Center. All patients enrolled signed a voluntary Investigational Review Board approved consent form.
Patients. Patients were eligible if they had a diagnosis of soft tissue sarcoma (STS) including rhabdomyosarcoma (RMS), osteosarcoma, Ewing’s sarcoma (EWS), or peripheral primitive neuroectodermal tumor (pPNET), with histological confirmation by the Anatomic Pathology Department at the City of Hope. Patients with primary STS of the extremities were required to have high-grade disease, deep to the fascia, size equal to or greater than 10 cm, or multifocal disease based on surgical pathology. The primary site had to be controlled by surgery and/or radiotherapy. For patients presenting with recurrent high-grade sarcoma, the tumor had to extend at least 10 cm in its greatest dimension, or present in a multifocal manner. Patients with non-extremity STS were eligible if the tumor was 10 cm or greater in size, or of any size with no surgical options for clear margins. Those with metastatic disease were required to have complete or partial response to surgery, chemotherapy, and/or radiotherapy.

Eligibility criteria for patients with primary EWS and pPNET included persistent disease following primary therapy, bulky disease (greater than 10 cm in diameter), or primary disease of the axial skeleton with complete or partial response to primary therapy. Patients with recurrent or metastatic EWS or pPNET were eligible if they had a complete or partial response to chemoradiation or surgery. Furthermore, patients were eligible if they met the following general criteria: no known contraindication to apheresis of up to 16x10⁶ mononuclear cells mobilized by granulocyte colony-stimulating factor (G-CSF)/kg of body weight or contraindication to adequate bone marrow collection; aged 5 to 55 years, with a Karnofsky performance status (KPS) of at least 80%; adequate hepatic function demonstrated by a total bilirubin <1.5 mg/dl and serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) <3 x upper limits of normal; adequate renal function with a creatinine <1.4 mg/dl and measured 24-hour urine creatinine clearance >75 ml/min; an absolute neutrophil count (ANC) >1000/µl, platelets >100,000/µl and hemoglobin >8.5 mg/dl; adequate cardiac function with an ejection fraction of at least 55% by multiple uptake gated acquisition scan (MUGA) or echocardiogram; adequate pulmonary function tests with a forced expiratory volume (FEV₁) >2l at room air, partial pressure of oxygen in arterial blood (Pao₂) >70 mmHg, partial pressure of carbon dioxide in arterial blood (Paco₂) <42 mmHg, and a diffusing capacity of the lung for carbon monoxide (DLCO) >60% predicted; and hepatitis B surface antigen negative, human immunodeficiency virus (HIV) antibody-negative, and hepatitis C antigen-negative if positive for hepatitis C antibody.

Patients were excluded if they had another prior malignancy other than non-melanoma skin cancer or in situ carcinoma of the cervix, histologically confirmed bone marrow metastasis, brain metastasis or CNS dysfunction, hearing loss >40 dB, confirmed pregnancy, history of significant cardiac disease, prior radiation to >20% of the bone marrow-containing axial skeleton or to the left side of the chest wall, prior cisplatin totaling more than 400 mg/m² and doxorubicin greater than 240 mg/m², or more than two prior chemotherapeutic regimens.

Treatment. Each patient who fulfilled the criteria for study entry underwent a computed tomography (CT) scan of the chest, abdomen and pelvis, as well as magnetic resonance imaging (MRI) of the brain, and a bone scan. Collection of peripheral autologous stem cells began at least 4 weeks prior to HDCT. Mobilization of stem cells was generated using G-CSF at a dose of 10 µg/kg/day for 4 consecutive days. On day 5, apheresis was initiated until at least 4x10⁶ CD 34+ cells/kg body weight were collected.

**Cycle 1**

Day –8 through Day –4 (96 h)

- Doxorubicin 150 mg/m² (CI) + Ifosfamide 14 g/m² mixed with mesna (CI)

- Day –3

- Mesna 3.5 g/m² over 24 h

- Day –2

- 12.5% of stem cell reinfused

- Day 0

- 37.5% of stem cell reinfused

**Cycle 2**

Day –11

- Melphalan 75 mg/m² + Cisplatin 100 mg/m²

- Day –10 thru Day –6

- G-CSF 5 µg/kg

- Day –4

- Melphalan 75 mg/m² + Cisplatin 100 mg/m²

- Day –3

- 12.5% of stem cell reinfused

- Day 0

- 37.5% of stem cell reinfused

Figure 1. Treatment algorithm.
received vaginal nystatin suppositories as well as norethindrone acetate 15 mg for those who were menstruating. Between days minus 8 through day minus 4, doxorubicin at 150 mg/m² was given by continuous infusion through a central catheter for 96 hours and ifosfamide at 14 g/m² and mesna at 14 g/m² were mixed together and given intravenously during the same 96-hour period. Hydration consisted of fluid directed at maintaining normal electrolytes and acid-base status, in particular to maintain serum bicarbonate ≥20 mEq/l. Ifosfamide was held daily if urinalysis (UA) detected more than 50 red blood cells (rbc)/high power field (hpf). Ifosfamide was resumed if subsequent UA revealed less than 10 rbc/hpf. Following completion of the ifosfamide infusion, mesna at 3.5 g/m² was given for an additional 24 hours. On day minus 2, 12.5% of the collected apheresis products were reinfused, followed by 37.5% on day 0 (11). G-CSF at 5 μg/kg was given daily following stem cell infusion until the ANC was greater than or equal to 1,000/μl for three consecutive days.

The second cycle of HDCT was initiated no earlier than 4 weeks after day minus 4, doxorubicin at 150 mg/m² was given by continuous infusion through a central catheter for 96 hours and ifosfamide at 14 g/m² and mesna at 14 g/m² were mixed together and given intravenously during the same 96-hour period. Hydration consisted of fluid directed at maintaining normal electrolytes and acid-base status, in particular to maintain serum bicarbonate ≥20 mEq/l. Ifosfamide was held daily if urinalysis (UA) detected more than 50 red blood cells (rbc)/high power field (hpf). Ifosfamide was resumed if subsequent UA revealed less than 10 rbc/hpf. Following completion of the ifosfamide infusion, mesna at 3.5 g/m² was given for an additional 24 hours. On day minus 2, 12.5% of the collected apheresis products were reinfused, followed by 37.5% on day 0 (11). G-CSF at 5 μg/kg was given daily following stem cell infusion until the ANC was greater than or equal to 1,000/μl for three consecutive days.

M: male; F: female; RMS: rhabdomyosarcoma; EWS: Ewing’s sarcoma; STS: soft tissue sarcoma; PNET: peripheral neuroectodermal tumor, MFH: malignant fibrous histiocytoma; HDCT: high-dose chemotherapy; SD: stable disease; PR: partial response; CR: complete response; PD: progressive disease; NED: no evidence of disease; PFS: progressive-free survival; OS: overall survival. *Tumor was completely resected prior to HDCT.

### Results

**Patient characteristics.** Patient characteristics are shown in Table 1. A total of 13 patients (10 males and 3 females) were accrued between February 1995 and September 1999. The median age at transplant was 31 years (range: 21-41). Seven patients presented with EWS or pPNET, four with RMS, and one each with leiomysarcoma and malignant fibrous histiocytoma (MFH). Three of the patients were treated for relapsed disease. Among the patients with EWS or pPNET, three had locally advanced disease (stage III) while the other four presented with metastatic or stage IV disease. Three out of 7 patients with EWS/pPNET had parenchymal organ involvement at the time of study entry. Three patients with RMS had stage IV disease while one had stage III disease. The patient with leiomyosarcoma and the other with MFH each had stage IV disease. All patients enrolled had undergone surgical interventions and received chemotherapy.

**Statistical analysis.** No patients were lost to follow-up. Response to therapy was determined using the World Health Organization (WHO) criteria. The median overall-survival (OS) and progression-free survival (PFS) were calculated from the date of HDCT. Survival curves were calculated using a Kaplan-Meier product-limit method using S-Plus™, version 8.0 (Supplied by Tibco Software, Inc).

### Table 1. Patient characteristics and outcome (n=13).

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<th>Patient number</th>
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<th>Ages (years)</th>
<th>Histological subtype</th>
<th>Primary site</th>
<th>Stage at time of protocol entry</th>
<th>No. of HDCT cycles completed</th>
<th>Tumor status: prior to HDCT</th>
<th>After HDCT</th>
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<td>SD</td>
<td>CR</td>
<td>Dead</td>
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Toxicity. All patients experienced grade 4 leukopenia, neutropenia and thrombocytopenia after HDCT according to the Common Toxicity Criteria Version 2.0 (Table IIa). Median time to ANC recovery to ≥1,000/μl was 9 days for cycle 1 (range: 5-18 days) and 12 days for cycle 2 (range: 9-15 days). Median time to platelet recovery was 6 days for cycle 1 (range: 2-32 days) and 10 days for cycle 2 (range 5-19 days). Grade 3 anemia was seen in 8 patients following cycle 1 and in 3 patients following cycle 2. All 13 patients developed febrile neutropenia during cycle 1, while 9 out of 11 developed it during cycle 2. All patients developed grade 3 mucositis with cycle number 1. There were no treatment-related mortality events in our study, however, two patients were taken off study after completing cycle 1. One patient developed osteomyelitis that required extensive antibiotic treatment while the other developed a drop in her forced expiratory capacity, which did not improve following cycle 1. A full summary of treatment-related side-effects per the Common Toxicity Criteria Version 2.0 and a separate list of toxicities according to the Autologous Bone Marrow Transplantation Toxicity Criteria are presented in Tables IIa and b, respectively.

Response. The median follow-up for those still alive is 132 months (range: 99-155 months). The 5-year PFS and OS for all patients was 23% (CI: 0-46%) and 31% (CI: 14-70%), respectively (Figure 2). There were four long-term survivors and among them, two were in complete response (CR) prior to HDCT while the other two were in partial remission (PR). The 5-year PFS and OS for those with EWS/pPNET was 29% (CI: 0-62%) and 29% (9-92%), respectively. Five of these patients ultimately died due to disease progression; however two patients, both of whom had stage III disease at study onset, are still alive and disease-free, one 126 months and the other 155 months following HDCT. Among the patients with RMS, none were long-term survivors. Three died within 13 months of HDCT, while one lived 44 months post-HDCT. Of note, this patient had stage III disease while the other three had stage IV disease. Figures 3 and 4, respectively, illustrate the PFS and OS in patients with RMS compared to those with other forms of sarcoma. One patient with metastatic MFH is alive and disease free at 99 months post-HDCT while the one patient with metastatic leiomyosarcoma relapsed at 19 months but was salvaged with surgery and radiation and remains alive at 138 months post-HDCT.

Discussion

Survival of most patients with locally advanced, unresectable, metastatic, or recurrent sarcoma is less than 10% at 5 years (9). Until recently, therapy has typically consisted of salvage chemotherapy with poor response rates. Several agents have been found to have modest activity against sarcoma such as doxorubicin, ifosfamide, melphalan and cisplatin. The alkylating agents, in particular, have demonstrated a steep dose response relationship in the treatment of sarcomas. In an attempt to improve the overall survival of patients in this population, HDCT followed by ASCT was investigated as a treatment option.

The optimal myeloablative regimen for metastatic and recurrent sarcoma is unknown. Most series have used some combination of ifosfamide, doxorubicin, melphalan, busulfan and etoposide, with or without total body irradiation. A retrospective review by Landenstein et al. evaluated various regimens used by the European Bone Marrow Transplant Solid Tumor Registry (12). They identified a trend towards improved event-free survival in patients treated with high-
Figure 2. Progression-free and overall survival for the entire cohort.

Figure 3. Overall survival for patients with rhabdomyosarcoma versus all other histologies.
dose busulfan and melphalan alone than with regimens containing total body irradiation (TBI). Burdach et al. detected a similar improvement in patients treated with a regimen that did not include TBI (13).

In our trial, we accrued only high-risk patients based on validated poor prognostic factors or if they had recurrent or metastatic disease. The choice of using the combination of high-dose ifosfamide/doxorubicin for cycle 1 and melphalan/cisplatin for cycle 2, followed by stem cell transplantation, respectively, was based on their known synergistic activity and rare development of drug resistance (14). In addition, these agents demonstrate a steep dose response relationship that we felt would enhance response in the advanced disease setting. The 5-year PFS and OS for all patients was 23% (CI: 0-46%) and 31% (CI: 14-70%), respectively, while the 5-year PFS and OS for those with EWS/pPNET was 29% (CI: 0-62%) and 29% (9-92%), respectively. The regimen was feasible as 11 out of 13 patients were able to successfully complete both cycles of HDCT and grade 3/4 toxicity, including myelosuppression and mucositis, which is expected from HDCT, was clinically manageable; no treatment-related deaths were observed. In this relatively small trial of poor-prognosis patients, 4 out of 13 patients are alive and long-term survivors beyond 5 years, including one patient with relapsed disease. However, none of the patients with RMS and no patient with stage IV EWS were long-term survivors. While the small number of patients treated and heterogeneous histologies included in this study are obvious limitations of our trial, it seems that those with RMS or metastatic/recurrent EWS patients are unlikely to gain significant overall benefit from HDCT followed by ASCT.

Our results appear to complement other studies in the literature that have highlighted the moderate response rates appreciated with HDCT in adult, high-risk sarcoma patients. Blay et al. reported on 30 patients with unresectable or metastatic soft tissue sarcoma using high-dose ifosfamide, etoposide, and cisplatin followed by peripheral blood stem cell transplantation (9). At 94 months follow-up, the 5-year OS was 23% and PFS 21%. The 5-year OS was 75% in those who achieved CR before the start of HDCT compared to 5% who were not in CR. Horowitz et al. described 65 patients with high-risk EWS and RMS, mostly in children, who were treated with total body irradiation (TBI) and a combination of high-dose vincristine, doxorubicin, and cyclophosphamide followed by autologous bone marrow rescue (7). They identified 20 long-term survivors in their cohort but also noted that patients with localized disease fared much better than those with metastatic disease. The six-year event-free survival

Figure 4. Progression-free survival for patients with rhabdomyosarcoma versus all other histologies.
Definite benefit seen in treating patients with HDCT.

After controlling for such bias, there was improved PFS and OS as a form of consolidation therapy after (16). One of the goals of the study was to determine if HDCT patients with recurrent sarcoma, 13 of whom received HDCT eligibility criteria and uniform preparative HDCT regimens. Large multi-institutional cooperative trials using clearly defined HDCT. Such understanding can be achieved only through high-dose therapies may particularly help patients with biology, targeted therapy as well as dose-dense, rather than following HDCT. Indeed, one patient in our study, who was initially a partial responder prior to HDCT, achieved a CR after the first cycle of HDCT and remains a long-term survivor. Based on our experience as well as others, HDCT may offer limited benefit to some patients. Not all sarcomas benefit to the same degree, however, from HDCT and in our series, those with RMS demonstrated an obvious need for alternative options. With better understanding of the specific biology, targeted therapy as well as dose-dense, rather than high-dose therapies may particularly help patients with EWS/pPNET (18).

As our study helps demonstrate, tandem HDCT is feasible and safe but the next step in this area of therapy should be identification of those that are most likely to benefit from HDCT. Such understanding can be achieved only through large multi-institutional cooperative trials using clearly defined eligibility criteria and uniform preparative HDCT regimens.

References


