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Review

Myeloablative therapy against high risk Ewing's sarcoma: A single institution experience and literature review

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ABSTRACT

Background: Attempts to improve survival outcomes of patients with high risk Ewing's sarcoma (ES) have focused on chemotherapy dose intensification strategies.
Aim: The objective of this study is to retrospectively evaluate clinical characteristics and outcome of pediatric patients with high risk ES treated at a single institution.
Materials and methods: From 1995 to 2008, seventeen patients (male:female, 14:3) were treated with dose-intensive therapy in our institution. Median age at diagnosis was 10 years (range: 2–15). Seven patients had metastases at diagnosis (lung in 6 cases and bone in one case). Eleven patients presented with unresectable disease. Fifteen (88.2%) received the Spanish Society of Pediatric Oncology protocol which includes six cycles of vincristine, doxorubicin, ifosfamide and etoposide. Two out of the six cases that were resectable received postoperative radiation. In addition, eleven patients received definitive radiation therapy. Finally, twelve (70.5%) out of 17 patients received myeloablative therapy with melphalan/etoposide. The rest of patients (N = 5) received busulfan/melphalan.
Results: Median follow-up was 78 months (range: 15–155 months). Initial responses were complete in all patients, but 9 of them developed progression disease. Seven patients became long-term event-free survivors. No patient died of toxicity after transplantation. The 2- and 5-year overall survival rates for all patients were 93% and 73%, respectively. Event-free survival rates were 74% and 54% at 2 and 5 years, respectively.
Conclusion: This single-institution experience suggests that myeloablative therapy against high risk ES is effective and safe.

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1. Background

Ewing's sarcoma (ES) is characterized by a chromosome 22 rearrangement, arises from bone or soft tissue, and predominantly affects children and young adults.[1,2] The overall incidence of ES seems to remain unchanged in the last decades.[3] Multimodality treatment programs achieve event-free survival (EFS) rates of 60%. An axial skeleton location and metastatic disease at diagnosis are well recognized adverse factors.[4,5] Up to one third of the patients whose metastases are limited to the lungs and/or pleura become long-term survivors with conventional chemotherapy, surgery, and radiotherapy. Results are worse in patients with metastases to the bone and/or bone marrow (BM). Recognition of this problem, combined with improvements in supportive measures[6] that decrease toxicity risks,[7] has led to a great interest in applying chemotherapy dose intensification strategies to improve the prognosis of this subset of patients.

Autologous stem cell transplantation (ASCT) has been employed as consolidation therapy for children with a variety of high-risk solid tumors.[8–11] The rationale for this approach is that many of these tumors are sensitive to chemotherapy and radiation, but because of steep dose–response curves to both treatment modalities, relatively small dose reductions can result in sharp decreases in log tumor cell kill. Phase I and II studies have demonstrated the activity of high-dose melphalan against tumors refractory to intensive conventional chemotherapy.[12,13] The dose-limiting toxicity of alkylating agents, such as melphalan, busulfan and thiotepa is myelosuppression. This problem can be circumvented by rescue with ASCT, thereby allowing a 3–10-fold dose escalation of those agents.[14]

2. Aim

The objective of this study is to retrospectively evaluate our single-institution experience of clinical characteristics and outcomes of pediatric patients with high risk ES treated with myeloablative therapy.

3. Materials and methods

3.1. *Patients*

We studied 17 patients with high-risk ES diagnosed from 1995 to 2008, most of whom (88.2%) were treated according the Spanish Society of Pediatric Oncology (SEOP) protocol.[15] All patients underwent myeloablative consolidation. Considerations for high risk recurrence and indication for dose-intensive/myeloablative therapy against Ewing's sarcoma were: (1) patients with non-metastatic axial skeleton tumors; (2) patients with lung/pleural metastasis, if they disappeared at week 18 after neoadjuvant chemotherapy; (3) patients with multicentric tumor or with BM metastasis if there was a response $\geq$50% at week 18 after neoadjuvant chemotherapy.

The median age for all patients (male:female, 14:3) was 10 years (range: 2–15). The primary tumor involved the bone in all patients (Table 1). Eleven (64.7%) presented with unresectable disease at diagnosis. Pathologic criteria for ES were typical histologic appearance plus immunohistochemical, ultrastructural, or chromosomal findings consistent with the diagnosis of ES. Staging studies included a technetium-99m bone scan, computed tomography or magnetic resonance imaging, and

Table 1 – Patients with newly diagnosed ES treated with dose-intensive/myeloablative therapy.

Patient No./sex	Age (years)	Site of disease at diagnosis (primary/distant)	Local treatment	Source of stem cells	Follow-up, time from diagnosis (transplant) (months)
1/M	12	L-spine/lung	Surgery	PB	PD (L), 20 (15)
2/M	13	Pelvis/lung	RT	PB	PD (LNA), 34 (20)
3/F	10	Calcaneus	Surgery	PB	CR, 21 (17)
4/M	10	Pelvis/lung	RT	PB	PD (L), 18 (7)
5/F	13	Scapula/lung	Surgery	BM	PD (B), 72 (62)
6/M	13	Pelvis	RT	PB	CR, 133+ (124+)
7/M	7	Pelvis/lung	RT	PB	PD (B), 112 (104)
8/M	10	Rib	Surgery, RT	PB	CR, 111+ (100+)
9/M	7	Pelvis	RT	PB	CR, 106+ (97+)
10/M	3	L-spine	RT	BM	PD (B), 31 (21)
11/F	3	Pelvis	RT	PB	PD (B), 31 (21)
12/M	10	Femur	Surgery, RT	PB	PD (L), 39 (24)
13/M	2	L-spine/bone	Surgery	PB	CR, 66+ (59+)
14/M	11	L-spine	RT	PB	CR, 19+ (16+)
15/M	15	Pelvis/lung	RT	PB	PD (L), 15 (8)
16/M	8	Pelvis	RT	PB	CR, 16+ (7+)
17/M	8	L-spine	RT	PB	CR, 15+ (7+)

Abbreviations: M, male; F, female; B, bone metastasis; L, lung metastasis; BM, bone marrow; PB, peripheral-blood; LNA, location not available; CR, complete response; PD, progressive disease; RT, local radiotherapy.

histochemical evaluations of bilateral bone marrow aspirations and biopsies. The TNM classification according the American Joint Committee on Cancer 2002 staging system[16] for bone cancer was as follows: 10 T1 and 7 T2; 17 N0; 10 M0, 6 M1a and 1 M1b.

3.2. Treatment

Informed consents for all treatments were obtained in accordance with institutional review board guidelines. The SEOP[15] protocol included six induction cycles of vincristine (1.5 mg/m^2, day 1), doxorubicin (20 mg/m^2, days 1–3. Alternating with actinomycin D 0.5 mg/m^2 before 2001), ifosfamide (2 g/m^2 before 2001 and 3 g/m^2 after 2001, days 1–3) and etoposide (150 mg/m^2, days 1–3). Resectable tumors were removed after cycle 6. Consolidation chemotherapy was delivered after surgery or after induction chemotherapy in unresectable cases, and consisted of one cycle of vincristine 1.5 mg/m^2, actinomycin 0.75 mg/m^2 and cyclophosphamide 1500 mg/m^2. After consolidation chemotherapy, patients received myeloablative therapy followed by ASCT. Unresectable cases were treated by radiation therapy for local control which was delivered 8 weeks after the ASCT. The radiotherapy dose to the primary site was 48 Gy in once-daily 1.8–2 Gy for postoperative radiation therapy and 55.2 Gy in the setting of radiotherapy as the sole modality for local control. The target volume encompassed the entire site as delineated at diagnosis, plus 4-cm margins craniocaudal and 2-cm in the other directions. Metastatic sites were irradiated at the discretion of the treating physician.

Two cases were treated with a different protocol because they received the ASCT before the SEOP protocol was implemented at our institution. One of them was treated according the T-9 protocol which consisted of five cycles of actinomycin D, doxorubicin, cyclophosphamide, vincristine, methotrexate, and bleomycin administered over a period of 45 weeks[17] and the other one following the Memorial Sloan-Kettering Cancer Center P6 protocol,[18] which includes cycles of cyclophosphamide, doxorubicin, vincristine and cycles of ifosfamide/etoposide.

According to the SEOP protocol, the myeloablative regimen recommended is (stem-cell rescue was on day 0): busulfan (150 mg/m^2/day po, days −6 to −3)/melphalan (140 mg/m^2 by 30-min infusion on day −2). In our institution the regimen delivered was (stem-cell rescue was on day 0): busulfan (days −7 to −4; 4 mg/kg po every 6 h if >6 years old or 10 mg/kg po bid if ≤6 years old; the prescription for intravenous administration was: 1 mg/kg every 6 h if <9 kg; 1.2 mg/kg every 6 h if ≥9 kg and <16 kg; 1.1 mg/kg every 6 h if ≥16 kg and <23 kg; 0.95 mg/kg every 6 h if ≥23 kg and <34 kg; 0.8 mg/kg every 6 h if ≥34 kg)/melphalan (140 mg/m^2 by 30-min infusion on day −2). A regimen of melphalan (35 mg/m^2/day by 30-min infusion on days −7 to −4)/etoposide (60 mg/kg IV, day −3) was used ($N = 5$) instead of the previously mentioned regimen in patients receiving pulmonary radiation or if they had received radiation therapy to the thorax or pelvis, due to potential increased toxicity that could result from busulfan.

Patients given PBSCs ($N = 15$) received the highest number of nucleated cells (median: 5.5×10^8 kg^{-1}, range: 0.49–10.2); the median number of nucleated cells was 0.3×10^8 kg^{-1} (range: 0.3–0.36) when the source of stem cells was the BM ($N = 2$). The highest median CD34$^+$ cells/kg was contained in the PB products (median: 4×10^6 kg^{-1}, range: 1.8–12.6); the CD34$^+$ cells/kg in BM products ranged from 0.91×10^6 kg^{-1} to 1×10^6 kg^{-1}.

3.3. Statistical analysis

Data regarding transplant patient characteristics, post transplant follow up and outcomes were retrospectively collected by our institutional data base. The Kaplan–Meier product limit method was used to estimate survival. The criteria used to determine objective tumor response for target lesions were adapted from the original WHO Handbook and were recorded as follows[19]: complete response (CR)—defined as disappearance of all target lesions; partial response—defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease (PD)—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD)—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the start of treatment.[20]

4. Results

4.1. Response

Initial responses to the SEOP protocol were CR in all patients; the earliest PD was in patient number 15 (Table 1). Nine patients developed distant recurrences after completing the SEOP protocol. The sites of recurrence were the bone alone ($N = 3$), the lung alone ($N = 3$), the bone and primary site ($N = 1$), and the lung and the primary site ($N = 1$). The location of distant progression of one patient was not reported. Eight patients died from tumor progression 18 to 143 months after diagnosis (Table 1).

Among the 12 patients (70.5%) treated with melphalan/etoposide, seven died after recurrence (three relapsed 2–8 months after transplantation), while four patients remained in CR after 5 years. In contrast, among patients treated with busulfan/melphalan, there were two relapses at 2–5 years after transplantation.

4.2. Survival outcome

Nine of seventeen patients are alive and with no evidence of disease, with seven being disease-free for more than 5 years (five of these patients received radiation therapy, four as definitive local treatment and one postoperatively). Only one of these patients had distant involvement at diagnosis (bone metastasis). The median follow-up for all patients was 78 months (range: 15–155 months). The 2- and 5-year overall survival (OS) rate for all patients was 93% (95% CI: 81–105%) and 73% (95% CI: 51–95%), respectively (Fig. 1). EFS was 74% (95% CI: 52–96%) and 54% (95% CI: 30–78%) at 2- and 5-year, respec-

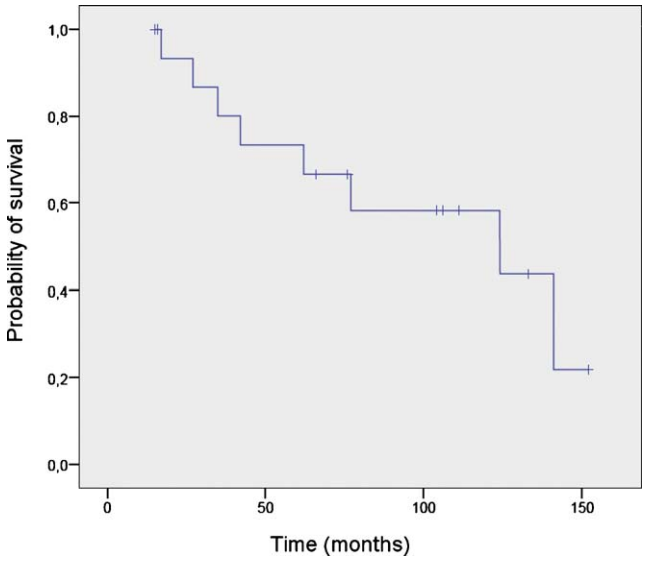

Fig. 1 – Kaplan–Meier estimate of overall survival for all patients.

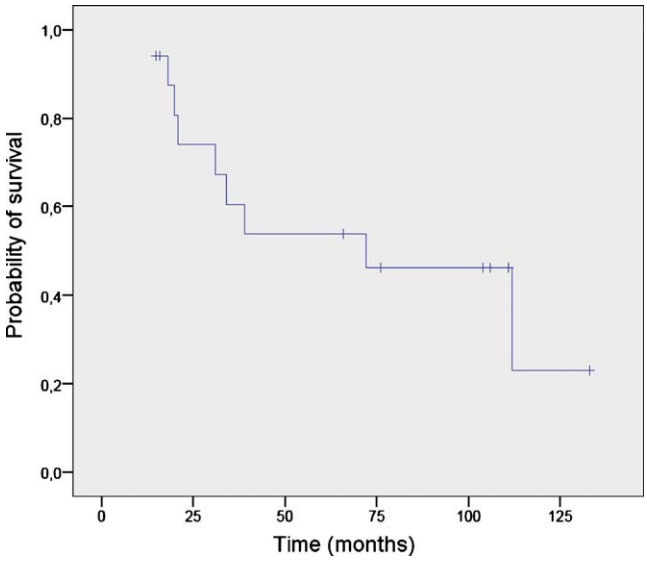

Fig. 3 – Kaplan–Meier curve for distant progression-free survival for all patients.

tively (Fig. 2). The local control rate was 94% (95% CI: 84–104%) at 2- and 5-year, respectively. Finally, we observed that 2- and 5-year distant progression-free survival rate (Fig. 3) was 74% (95% CI: 52–96%) and 54% (95% CI: 30–78%), respectively.

5. Discussion

The Ewing's family of tumors comprises 16% of primary malignant bone tumors. This tumor is chemosensitive, and multimodal therapy has significantly improved outcome for patients with ES.[21] Despite these encouraging results, subgroups of patients who have a poor prognosis can be identified (survival of 10–30% at 3 years). Poor prognostic features at initial presentation include metastatic disease, particularly those with bone or BM involvement, bulky disease (48 cm diameter)

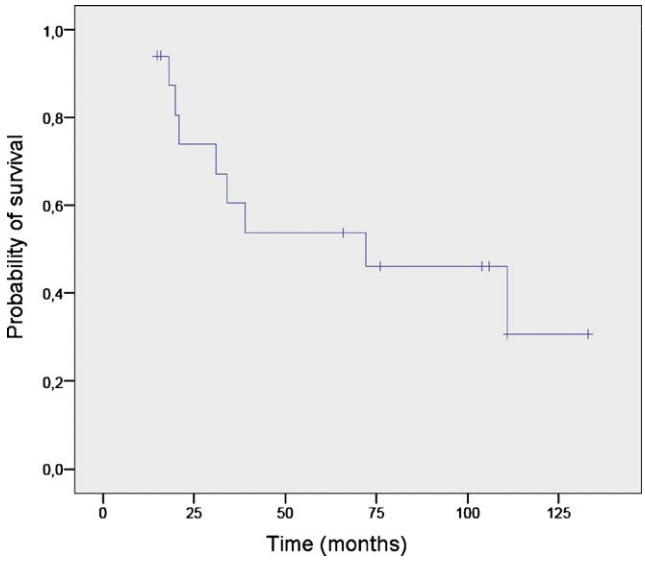

Fig. 2 – Kaplan–Meier curve for event-free survival.

at diagnosis, primary tumor involving axial or proximal locations (femur and humerus), shorter interval of EFS between diagnosis and relapse[22] and age older than 16 years.[23] We attempted to improve the prognosis in a cohort of patients with high risk ES by using high-dose chemotherapy to achieve remission followed by myeloablative therapy to consolidate the disease response. Among our 17 patients, six patients were prolonged (more than 5 years) relapse-free survivors. The SEOP induction regimen and local treatment was successful at achieving a complete response in all patients. However, the myeloablative regimen failed to maintain remissions in patients who had metastases to the lung at diagnosis. We observed an EFS rate of 74% at 2 years. The recent addition of ifosfamide and etoposide to conventional therapy has resulted in higher EFS rates in patients with local disease.[21,24]

EFS rates reported in the current study are difficult to compare to those reported by others[25–27] due to the differences in the definition of high-risk patients and the differences in the megatherapy procedure. Successive studies at the National Cancer Institute used a regimen that included relatively high doses of doxorubicin (75–90 mg/m^2) and cyclophosphamide (1800 mg/m^2) first as a short-term induction preliminary to total body irradiation (TBI) based consolidation[28] and then intercalated with multiple cycles of ifosfamide (9 g/m^2)/etoposide (300 or 500 mg/m^2).[29] This change from a short-term induction with end-intensification to prolonged treatment with active combinations yielded similar early response rates and no improvement in EFS. Successive studies by cooperative groups in the United States were marked first by the addition of ifosfamide (9 g/m^2)/etoposide (500 mg/m^2) to standard-doses of vincristine (1.5 mg/m^2), doxorubicin (75 mg/m^2), dactinomycin (1.25 mg/m^2), and cyclophosphamide (1.2 g/m^2),[19] and then by major increases in alkylator dosing with cycles that included high-dose cyclophosphamide (2.2 or 4.2 g/m^2) alternating with cycles that included high-dose ifosfamide (14 or 12 g/m^2).[30,31] Prolonged[30] or short-term[31] use of these regi-

mens, or end-intensification with TBI (12 Gy) plus melphalan (180 mg/m^2)/etoposide (750 mg/m^2),[31] did not improve EFS. Prolonged use of the protocol with augmented alkylator dosing resulted in a 22.7% cumulative risk of secondary leukemia at 4 years.[32] In studies from the United Kingdom that used prolonged treatments with modest dosing, improvement in outcome was attributed to the replacement of low-dose cyclophosphamide (0.6 or 1.0 g/m^2) by higher relative dosing of ifosfamide (6 or 9 g/m^2).[33–35] In the large series of ES patients who received transplants in first remission[36,37] induction protocols, myeloablative regimens, and sources of stem cells varied greatly. Poor outcome was seen with the use of the active agents for Escyclophosphamide, ifosfamide, doxorubicin, dactinomycin, vincristine, and etoposideat standard dosages for prolonged periods of time (United Kingdom Children's Cancer Study Group,[34] European Intergroup Cooperative Ewing's Sarcoma Study [EICESS][36]) and at higher dosages in intensive regimens for short (Children's Cancer Group [CCG][31]) or prolonged (Intergroup Ewing's Sarcoma Studies [IESS],[30] St Jude[38]) periods of time. No improvements in EFS rates occurred with successive cooperative group (US,[30,31] German[36]) or large single-institution (St Jude[38]) studies that used increasingly aggressive chemotherapeutic approaches. Inclusion of ifosfamide with (IESS,[30,31] St Jude,[38] EICESS[36,39]) or without etoposide did not affect outcomes, nor did consolidation of remission with myeloablative chemoradiotherapy (CCG,[31] EICESS[36]). The impact of megatherapy on prognosis is obscured by the long-term survival with conventional chemotherapy of some of these patients.

The importance of studying an unselected rather than a selected group of patients when assessing treatment efficacy has been emphasized elsewhere.[8] Although reports on myeloablative therapy do not give posttransplant EFS rates for ES patients who had bone/BM metastases at diagnosis, 20–25% of these patients who receive transplants in first remission may become long-term survivors.[36,40,41] Moreover, marrow ablative conditioning regimens prior to stem cell with melphalan or busulfan-based combinations could be the most efficient myeloablative scheme.[42] Evidence of ES dose-responsiveness, the feasibility of dose-escalated conventional chemotherapy, and the recognition of ifosfamide/etoposide as an active combination in this disease has led to several studies aimed at exploiting these findings (without using myeloablative consolidation). A variety of myeloablative regimens without TBI have been tried against ES but none as the planned consolidation in a prospective study of newly diagnosed patients. Melphalan has long been the most commonly used agent in myeloablative end-intensification approaches to ES. Exploratory studies on its use in high doses found activity against refractory, large localized, and disseminated ES.[43] Drabko et al.[11] reported a probability of 2-year OS of 0.68 and DFS of 0.63 in high-risk ES patients treated with melphalan-based megachemotherapy. Melphalan has often been combined with etoposide for synergistic antitumor effect. A de-emphasis on the use of that combination may be warranted in view of the preliminary analysis of the 20-year European Bone Marrow Transplantation Registry experience which yielded results suggesting an advantage to the use of busulfan. Oberlin et al. published the impact of high-dose busulfan plus melphalan as consolidation in metastatic Ewing tumors in France.[44] Seventy-five unselected patients with newly diagnosed metastatic ES received high-dose chemotherapy. The 5-year EFS rate for all 97 patients was 37% and the OS rate was 38%. Patients obtained from the Center for International Blood and Marrow Transplant Research with localized and metastatic disease who received ASCT as first-line therapy had 5-year EFS of 51% and 60%, respectively.[45]

The source of stem cells in most of the patients of our study was PBSCs. Both autologous BM and PBSCs were sources of stem cells in most myeloablative studies in the literature involving ES; the use of PBSCs was stipulated in the CCG study of unselected patients.[31] An advantage of one autologous stem-cell source over another was not evident. Nevertheless, it is of interest to note that the degree of tumor contamination seems to be lower in PBSC than in BM harvest.[46,47] The consensus of two workshops on high-risk ES was that allografting conferred no benefit, although a very limited experience with allogeneic BM rescue was deemed favorable in a single-institution study (three of six patients relapse-free; no further details).[37] In vitro studies suggest that pharmacologic purging may reduce the content of tumor cells in an autograft, but cyclophosphamide derivatives have been withdrawn from clinical use. Immunologic purging has not been described for ES but a monoclonal antibody for that purpose has been identified and is being studied in a clinical trial.[48]

6. Conclusion

This single-institution experience in the context of findings reported in the literature suggest that (a) distant and local relapse remain the main obstacles to improving outcomes in patients with high risk ES, (b) consolidation treatment by megatherapy contributes to improved EFS rates in high-risk patients compared with the historical experience, (c) a major impact on prognosis awaits the introduction of entirely novel therapies, and (d) major questions for the future to be addressed prior to randomized studies include agreement on the definition of high-risk patients and the most efficient megatherapy procedure. Continued investigation of ASCT as a consolidation therapy in patients with high risk ES, a larger number of study patients, and long-term clinical results are needed.

Conflict of interest statement

The content has not been published or submitted for publication elsewhere and all persons listed as authors have given their approval for the submission of the paper. Authors declare that we do not have any financial support or relationships that may pose conflict of interest.

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