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Efficacy of High Dose Chemotherapy in Adult Patients with Relapsed or Refractory Ewing Sarcoma

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Abstract

A rare condition in adults, Ewing sarcoma (EWS) has no standard treatment during the relapse–refractory period. In our study, we aimed to identify the treatment-related side effects of high-dose chemotherapy (HDC) and salvage autologous stem cell transplantation (ASCT) in adult patients with relapsed or refractory EWS and their survival rates. In a retrospective study, we recorded the clinical characteristics of patients with relapsed or refractory EWS treated with HDC in the hospital's patient registry to determine their objective response rate (ORR), progression-free survival (PFS), 6-month PFS rate, overall survival (OS), 6-month OS rate, transplantation-related mortality (TRM) and treatment-related side effects. In our sample of 29 patients (72.4% male), the mean age was 26.41 years (SD=9.35). The most common primary tumour site was the lower extremities (31%), 69% of patients had lung metastases, and 48.1% had undergone surgical resection, adjuvant radiotherapy and chemotherapy. The ORR to HDC was 31%. Median PFS (IQR) was 5.35 (6.79) months (95% confidence interval =4.23–8.28), whereas the 6-month PFS rate was 38.9%. Median OS (IQR) was 9.46 (14.45) months (95% confidence interval = 8.52–15.82), whereas the 6-month OS rate was 68.1%. Mortality from HDC or other causes occurred in five patients within the first 100 days after ASCT. Grade 3 febrile neutropenia and thrombocytopenia were present in all patients until engraftment following ASCT. Amongst adults with relapsed or refractory EWS, HDC has successful survival and response rates and a manageable side-effects profile

Keywords: Ewing sarcoma, high-dose chemotherapy, autologous stem cell transplantation

Introduction

While sarcomas represent less than 1% of all malignancies in adults, approximately 15% of sarcomas are bone sarcomas (1,2), amongst which Ewing sarcoma (EWS) is the most frequently observed. A malignancy that often originates from bone and soft tissue (3), EWS is more common in children and young adults than in adults.

Although current treatments for local EWS have survival rates exceeding 70% (4,5), survival rates for relapsed or refractory EWS are not as high. In fact, the 3-year survival rate for patients who are metastatic at diagnosis and treated according to conventional chemotherapy protocols is 10–30% (5,6). The survival rates for patients with relapsed or refractory EWS are even worse despite combined systemic treatments, with a 5-year survival rate following first-line therapy of less than 20% (6,7). Moreover, given the lack of standard treatment for patients with relapsed or refractory EWS, adults with such EWS represent a patient group whose treatment needs remain unmet.

High-dose chemotherapy (HDC) followed by salvage autologous stem cell transplantation (ASCT) is frequently used to treat haematological and various solid malignancies. With a treatment rationale based on elevating responses by increasing the dosage in chemosensitive tumours, the method achieves successful survival responses against many malignancies, including lymphomas, multiple myeloma and germ cell tumours (8,9). Beyond that, the myelotoxicity-related side effects of HDC can be eliminated when coupled with salvage ASCT. Amongst patients with EWS, HDC is a treatment modality whose role has been investigated mostly retrospectively, frequently with regimens containing busulfan and melphalan (10,11), which have different severe side effects as well as risk myelotoxicity. By contrast, studies on systemic treatments for EWS with more manageable toxicity have been rare.

Meanwhile, the efficacy of chemotherapy combining ifosfamide, carboplatin and etoposide (ICE) has been demonstrated in numerous

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relapsed and refractory malignancies (8,9). However, few studies on the ICE protocol's effectiveness when applied as HDC in patients with relapsed or refractory EWS have been conducted (12). Given those trends, it remains necessary to identify HDC protocols with more manageable toxicity in patients with relapsed or refractory EWS whose prognosis is poor, especially if they have received both radiotherapy and multiple systemic treatments.

In response, in our study we aimed to identify the survival rates, post-transplant side effects and mortality of a single HDC ICE and salvage ASCT protocol in patients with relapsed or refractory EWS.

Materials and Methods

Our study was designed to follow a cross-sectional working method with retrospective data collection from the medical records of patients with relapsed or refractory EWS in a tertiary hospital between January 2017 and August 2021. To be included, patients needed to be at least 18 years old, to have relapsed or refractory EWS and to have received HDC–ASCT. Patients less than 18 years old or with insufficient medical records were excluded. The study was approved by the local ethics committee (ethics board 2021/96).

Each patient's age, gender, stage of EWS at diagnosis, primary origin of EWS and previous treatments (i.e. surgery, radiotherapy and neo/adjuvant chemotherapy) were recorded. Next, the presence of pre-HDC lymph nodes, bone, liver and lung metastases were determined, and the number of systemic chemotherapy lines in the relapsed or refractory period before HDC was recorded. Once data related to ASCT (i.e. amount of reinfused stem cells, engraftment time and side effects of HDC) were integrated into the database, the best objective response obtained after HDC was recorded. Complete remission (CR) indicated the disappearance of all clinically and radiologically detectable lesions, partial response (PR) indicated a reduction in tumour burden exceeding 20%, and progressive disease indicated tumour growth exceeding 20%. Any other response was classified as stable disease.

Progression-Free Survival (PFS) was defined as the time from hdc date to local or distant recurrence or death. By contrast, overall survival (OS) was calculated as the time from the first day of HDC to the date of either the patient's last follow-up examination or death. Meanwhile, the objective response rate (ORR) was calculated as the sum of the complete and partial responses achieved, and the 6-month PFS rate and 6-month OS rate were obtained from Kaplan-Meier survival analysis. Last, transplantation-related mortality (TRM) was evaluated as mortality within the first 100 days of HDC.

For HDC, all patients received the ICE protocol, which prescribed a total dose divided across 6 days of 12 g/m² ifosfamide and mesna, 1200 mg/m² carboplatin and 1200 mg/m² etoposide. After 6 days of treatment, stem cell reinfusion was performed over 2 d. For engraftment after ASCT, the platelet count had to be >20,000/mm3, the leukocyte count >4000/mm³ and the neutrophil count >2000/mm³.

The percentages of totals were used in descriptive statistics. The normal distribution of continuity variables was evaluated using the Kolmogorov–Smirnov test, and normally distributed data were expressed as M±SD. Data that did not have normal distribution were expressed as the median interquartile range (IQR). Survival rates and graphics were evaluated with Kaplan–Meier analysis. All statistical analyses were performed in SPSS version 22.0 (IBM, Armonk, NY, USA), and all p values less than .05 were considered to be statistically significant.

Results

In our sample of 29 patients (72.4% male), the mean age was 26.41 years (SD=9.35). The most common primary tumour site was the lower extremities (31%), and most patients had been diagnosed with early-stage EWS (55.1%). Lymph nodes metastases were present in 86.2% of the patients and lung metastases in 69.0%. Whereas 48.1% of patients had undergone surgical resection, adjuvant radiotherapy or chemotherapy before developing relapsed or refractory EWS and thus becoming candidates for HDC therapy, 25 patients (86.2%) had received two or fewer lines of systemic chemotherapy before HDC. The mean total (SD) amount of stem cells reinfused to patients during ASCT was 4.08 (±1.62)×106/mm3, while the mean (SD) day of engraftment after ASCT was Day 12.1 (2.11). The patients' characteristics are presented in Table 1.

For all patients, the ORR to HDC was 31%. Median PFS (IQR) was 5.35 (6.79) months (95% confidence interval =4.23–8.28), whereas the 6-month PFS rate was 38.9%. Median OS (IQR) was 9.46 (14.45) months (95% confidence interval =8.52–15.82), whereas the 6-month OS rate was 68.1%. Mortality from HDC or other causes occurred in five patients within the first 100 d after ASCT. However, none of the patients had mortality during ASCT until discharge. Grade 3 febrile neutropenia and thrombocytopenia were observed in all patients until engraftment following ASCT. The treatment's side effects and the patients' responses to treatment are presented in Table 2 and Figures 1 and 2.

Table 1. Demographic and clinical characteristics of the patients

Features	n:29
Gender	
Male, n (%)	21 (72.4)
Age, mean (range)	26.41 (17-55)
Primary origin of tumor, n (%)	
Lower Extremities	9 (31)
Vertebrae	8 (27.6)
Upper Extremities	4 (13.8)
Pelvis	4 (13.8)
Other	4 (13.8)
Stage at Diagnosis, n (%)	
≤ Stage 2	16 (55.1)
≥ Stage 3	13 (44.9)
Site of Metastases, n (%)	
Lymph nodes	25 (86.2)
Bone	23 (79.3)
Lung	20 (69)
Liver	4 (13.8)
Brain	2 (6.9)
Neoadjuvant Chemotherapy, n (%)	8 (27.6)
Surgery, n (%)	14 (48.3)
Adjuvant Chemotherapy, n (%)	14 (48.3)
Adjuvant Radiotherapy, n (%)	14 (48.3)
Number of systemic treatment lines before HDC, n (%)	
≤ 2 lines	25 (86.2)
> 2 lines	4 (13.8)
Amount of stem cells given 10^6/L, mean (SD)	4.08 (1.62)
Engrafment day, mean (SD)	12.1 (2.11)

HDC: High Dose Chemotherapy, SD: Standard Deviation

Table 2. Treatment-related characteristics of the patients

Features	n: 29
Best Objective Response, n (%)	
Complete Response	4 (13.8)
Partial Response	5 (17.2)
Stable Disease	6 (20.7)
Progressive Disease	14 (48.3)
PFS, median (IQR), months	5.35 (6.79)
6 months PFS rate, % (SE)	38.9 (9.4)
OS, median (IQR), months	9.46 (14.45)
6 months OS rate, % (SE)	68.1 (8.8)
TRM in the first 100 days after HDC, n(%)	5 (17.2)
Febrile Neutropenia, n (%)	29 (100)
Anemia, n (%)	
-Grade 2	18 (62.1)
-Grade 3	11 (37.9)
Thrombocytopenia, n (%)	
-Grade 4	29 (100)
Diarrhea, n (%)	
-Grade 1	11 (37.9)
-Grade 2	11 (37.9)
-Grade 3	7 (24.1)

PFS: Progression Free Survival, IQR: Interquartile range , SE: Standard Error, OS: Overall Survival, TRM: Transplantation related mortality, HDC: High Dose Chemotherapy

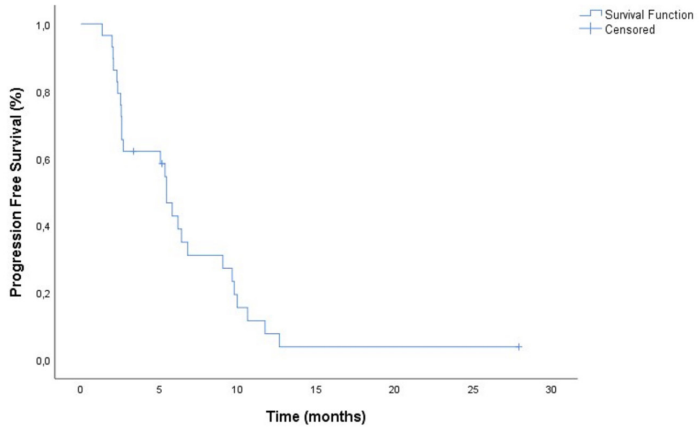

Figure 1. Median progression-free survival curve after HDC

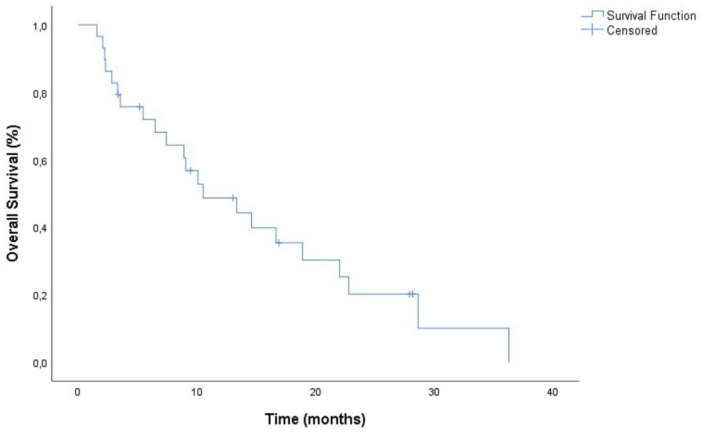

Figure 2. Overall survival curve after HDC

Discussion

Despite having various systemic treatment options, EWS is a disease with a poor prognosis, especially in the relapse–refractory period, and especially affects young people (13,14). Although immunotherapy agents are increasingly replacing conventional chemotherapies to treat oncological diseases (15), whole sarcomas represent malignancies in which immunotherapy-class agents have not been dominant or especially successful as with other solid malignancies. At the same time, next-generation sequencing methods increasingly used to evaluate the nature of malignancies in daily oncological practice and to pinpoint potential driver mutations offer a major advantage to patients with sarcoma (16). However, such methods remain extremely expensive and are not easily accessible for everyone.

Included in the family of small round-cell tumours, EWS is known to have chemosensitivity (17), and in vitro data have shown a steep dose-response relationship for both the toxic and therapeutic effects of some chemotherapeutic agents. It has also been reported that tumour toxicity can increase in a nearly linear manner with the increased dose of chemotherapy in patients with EWS (18). With salvage ASCT, however, the myeloablation caused by such dose increases can be reversed.

Despite recent studies on using HDC and salvage ASCT to treat patients with recurrent EWS, the effectiveness of treating EWS with salvage-based methods remains unclear (19). Moreover, most of those studies did not involve following a standard HDC protocol. Added to that, such studies involving adult patients have been few because EWS is most frequently observed in children.

We performed our study at one of the few transplantation centres in Turkey that provides HDC treatment to patients who have received systemic treatment for relapsed or refractory EWS. A significant PFS and OS were detected after HDC, a relatively heavy treatment modality, amongst patients who had received adjuvant radiotherapy for their bones, mostly in a bone marrow production area, and who received adjuvant chemotherapy followed by chemotherapy with palliative intent.

In Pawlowska et al.'s recent study (20)—a work with one of the longest follow-up periods published—most of the study groups were of paediatric age, and tandem transplantation was performed in a significant portion of the patients. In Turkey, however, tandem transplantation is not covered by health insurance, and patients with EWS can receive transplantation only once. Even so, most patients in their study were male, and the primary origin was bone, as consistent with our sample. The overall rates of patients with lung metastases were similar to ours as well. The authors used busulfan, melphalan and topotecan as an HDC regimen in a significant proportion of their patients. OS was 46% at 10-year follow-up and 42% at 15-year follow-up, and the authors attributed the leading cause of such long survival to patients who did not exhibit a progressive response prior to transplantation.

In other studies, evaluating the efficacy of HDC for advanced EWS, the 5-year OS has generally been 15-45% (21,22). Bacci et al. shared data regarding 33 patients with recurrent EWS treated with HDC, who had a PFS of 21.2% at 5 years and approximately half of whom had a pre-HDC response (CR/PR). Also, almost all of the patients who received HDC but did not respond were without a pre-HDC CR/PR response. (23). Therefore, HDC may not be particularly effective against diseases that do not respond to first-line salvage treatment after relapse. On the contrary, HDC may be more beneficial as part of consolidation therapy after conventional

chemotherapy for improving OS and PFS.

Published studies on HDC used in patients with EWS in the past four decades have evaluated different conditioning regimens; however, the number of studies evaluating the efficacy of the ICE protocol for HDC in such patients has been limited. Van Winkle et al. reported a response rate of 51% in their study using the ICE protocol in paediatric patients (8). The comparatively low response rate in our study may be due to the different characteristics of our patients.

In our study, TRM was observed in five patients (17.2%) within the first 100 days. TRM may vary depending on patients' clinical characteristics and the preparation regimen used. Pawlowska et al. reported a 3.7% mortality rate associated with the preparation regimen (20), while Meyers et al. reported TRM of 13% (24).

Our results have some limitations. First, we performed a cross-sectional analysis of the data, which precluded establishing any causal links amongst the results. Second, even if advanced EWS is a rare malignancy in adulthood, the number of patients in our sample was relatively low, which reduces the generalizability of the results to different populations. Third, the probability of error in data quality is relatively high in retrospective studies, and neither our study's follow-up intervals nor follow-up times could be controlled.

Conclusion

In conclusion, although patients with advanced EWS have a poor prognosis with conventional chemotherapy, HDC-ICE treatment has successful survival and response rates in chemosensitive adults with relapsed or refractory EWS. Prospective randomised controlled studies are nevertheless needed to identify patients with poor prognoses who may benefit from HDC.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The study was approved by the local ethics committee of SBU Gülhane Training and Research Hospital clinical trials (ethics committee 2021/96).

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