

High-dose Chemotherapy Response in Adults with Relapsed/Refractory Small Round Cell Tumours

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ABSTRACT

Objective: To demonstrate the treatment responses, survival analysis, and treatment-related mortality characteristics of high-dose chemotherapy (HDC) in patients with relapsed/refractory Ewing sarcoma (ES), osteosarcoma, rhabdomyosarcoma (RMS) and medulloblastoma (MB).

Study Design: Observational study.

Place and Duration of Study: Department of Medical Oncology, University of Health Sciences, Gulhane School of Medicine, from January 2016 and April 2020.

Methodology: Clinical features and follow-up data of relapsed/refractory ES, osteosarcoma, RMS and MB patients treated with HDC were recorded from the patients' registration database of the hospital. Patients <16 years and those whose medical records were not available were excluded. Progression-free survival (PFS), one-year overall survival (OS) rates and treatment-related mortality (TRM) after the HDC were determined. Ifosfamide, carboplatin and etoposide (HD-ICE) were used as the HDC protocol in all patients.

Results: Thirty-seven adult patients were included. PFS was determined as 2.70 ± 0.97 months, 11.57 ± 3.63 months, 3.47 ± 0.44 months and 2.96 ± 0.91 months, for ES, MB, RMS and osteosarcoma, respectively. One-year OS rate was $44.8 \pm 14.8\%$ for ES; $75 \pm 15.8\%$ for MB. In ES, PFS was found to be better in males than females ($p = 0.025$). No patient died during HD-ICE. Mortality was observed most frequently in the RMS in the first 100 days (25%).

Conclusion: HD-ICE treatment may be an option in relapsed/refractory small round cell tumours (SRCT). Significant progression-free survival can be achieved in patients who received at least two lines of treatment, with acceptable treatment-related mortality.

Key Words: Small round cell tumours, Ewing sarcoma, Osteosarcoma, Rhabdomyosarcoma, Medulloblastoma, High-dose chemotherapy, Autologous stem cell transplantation.

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INTRODUCTION

Small round cell tumours (SRCT) is the term used to describe malignant neoplasms that are highly aggressive. These tumour family members include Ewing sarcoma (ES), osteosarcoma, rhabdomyosarcoma (RMS), medulloblastoma (MB), as well as other tumours.¹ ES and osteosarcoma are the most common primary bone tumours in young adults (<21 years).^{2,3} About 30-40% of ES patients, who achieve remission with first-line treatment, relapse occurs later on.⁴

In primary metastatic ES and recurrent/refractory osteosarcoma or metastatic osteosarcoma, the overall survival (OS) rate is around 20-40%.^{5,6}

RMS is in the most common soft tissue tumours of childhood.^{7,8} In the case of metastasis and other poor prognostic factors (e.g. unfavourable histologies like alveolar RMS), the cure is achieved only about 25%.⁹

Adult MB is exceedingly rare and accounts for <1% of intracranial tumours. Five-year progression-free survival (PFS) rates are reported to be 40-45%. The recurrence rate in adult MB is between 50-60%. The median survival after recurrence is around 15 months.^{10,11}

The rationale for using high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) rescue is based on the fact that SRCTs are chemosensitive. However, HDC eventually causes dose-limiting hematopoietic toxicity. The tolerable dose of chemotherapy is increased through ASCT rescue. Thus, the most severe side effect of dose intensification can be eliminated in a short time.¹²

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Table I: The demographic and disease-related characteristics of the patients.

Features	Ewing Sarcoma (n=20)	Medulloblastoma (n=10)	Rhabdomyosarcoma (n=4)	Osteosarcoma (n=3)
Age (mean \pm SD)	26.85 \pm 8.57	29.40 \pm 8.98	25.25 \pm 2.5	21 \pm 3
Male Gender, n (%)	14 (70%)	4 (40%)	3 (75%)	3 (100%)
Primary tumour location, n (%)				
Extremities	17 (85%)	-	1 (25%)	3 (100%)
Cerebellum	-	10 (100%)	-	-
Stage at the time of diagnosis, n (%)				
Stage 3	5 (25%)	-	1 (25%)	1 (33.3%)
Stage 4	9 (45%)	10 (100%)	3 (75%)	2 (66.6%)
Lung metastases, n (%)	7 (35%)	-	1 (25%)	1 (33.3%)
Radiotherapy, n (%)				
Adjuvant	6 (30%)	10 (100%)	2 (50%)	-
Palliative	5 (25%)	-	2 (50%)	1 (33.3%)
Neoadjuvant Chemotherapy, n (%)	7 (35%)	-	1 (25%)	3 (100%)
Surgery, n (%)	10 (50%)	10 (100%)	1 (25%)	3 (100%)
Adjuvant Chemotherapy, n (%)	19 (95%)	7 (70%)	4 (100%)	3 (100%)
Time to relapse, n (%)				
<2 years	13 (65%)	3 (30%)	3 (75%)	1 (33.3%)
Extrapulmonary relapse, n (%)				
Yes	11 (55%)	-	1 (25%)	1 (33.3%)
Number of lines before HD-ICE treatment, n (%)				
2 lines	17 (85%)	6 (60%)	2 (50%)	3 (100%)
Amount of stem cells given 10 ⁶ /L (mean \pm SD)	3.89 \pm 1.82	4.38 \pm 1.53	3.8 \pm 2.08	5.66 \pm 2.30
Engraftment Time (days) (mean \pm SD)	11.75 \pm 1.97	12.60 \pm 2.91	9.5 \pm 0.57	10.33 \pm 1.52

RT: Radiotherapy, HD-ICE: High-Dose ICE regimen

Table II: The PFS, OS and follow-up characteristics of the patients and characteristics of the patients' toxicity profiles during AHSCT.

Features	Ewing Sarcoma (n=20)	Medulloblastoma (n=10)	Rhabdomyosarcoma (n=4)	Osteosarcoma (n=3)
PFS after first-line treatment (months) (mean \pm SE)	15.02 \pm 0.83	44.98 \pm 13.79	10.45 \pm 5.0	19.46 \pm 7.40
PFS after second-line treatment (months) (mean \pm SE)	10.19 \pm 2.11	3.25 \pm 0.32	2.7 \pm 0.84	7.3 \pm 1.02
The response of the patients after ASCT n (%)				
Complete response	7 (35%)	6 (60%)	1 (25%)	-
Partial response	2 (10%)	2 (20%)	-	-
Stable response	2 (10%)	2 (20%)	1 (25%)	1 (33.3%)
Progressive disease	9 (45%)	-	2 (50%)	2 (66.6%)
PFS after HD-ICE treatment (months) (mean \pm SE)	2.70 \pm 0.97	11.57 \pm 3.63	3.47 \pm 0.44	2.96 \pm 0.91
Chemotherapy after ASCT, n (%)				
Yes	11 (55%)	1 (10%)	2 (50%)	3 (100%)
No	9 (55%)	9 (90%)	2 (50%)	-
One-year OS rate after HD-ICE treatment (% \pm SE)	44.8 \pm 14.8	75 \pm 15.8	75 \pm 21.7	NA
TRM in the first 100 days after HD-ICE, n(%)	4 (20%)	-	1 (25%)	-
Febrile neutropenia, n (%)				
Grade 3	20 (100%)	10 (100%)	4 (100%)	3 (100%)
Hgb <10g/dl, n (%)	20 (100%)	10 (100%)	4 (100%)	3 (100%)
Number of ES units transfused after HD-ICE (mean \pm SD)	3.55 \pm 2.35	6.00 \pm 2.44	2.25 \pm 0.95	1.66 \pm 0.57
After ASCT, the day when thrombocyte <20 000/mm ³ (mean \pm SD)	4.40 \pm 1.18	3.30 \pm 1.25	4.25 \pm 2.21	4.66 \pm 1.15
Number of PAS units transfused after HD-ICE (mean \pm SD)	4.50 \pm 1.98	6.20 \pm 3.01	3.50 \pm 1.00	3.66 \pm 2.08
Nausea, vomiting, n (%)				
Grade 2	5 (25%)	3 (30%)	1 (25%)	2 (66.6%)
Grade 3	6 (30%)	-	-	1 (33.3%)
Diarrhoea, n (%)				
Grade 2	4 (20%)	4 (40%)	-	2 (66.6%)
Grade 3	4 (20%)	1 (10%)	-	-

PFS: Progression-free survival, OS: Overall survival, ASCT: Autologous stem cell transplantation, HD-ICE: High-dose ICE regimen, TRM: Transplantation-related mortality, Hgb: Haemoglobin, ASCT: Autologous stem cell transplantation, ES: Erythrocyte suspension, PAS: Platelet additive solutions.

The effectiveness of ifosfamide, carboplatin and etoposide (ICE) protocol has been demonstrated in many refractory

cancers.^{13,14} There is currently no satisfactory randomised prospective study in the literature on the effect of HDC-ASCT on relapsed/refractory SCRTs, particularly when HDC-ASCT is used as a third-line treatment with a single cycle of ICE for the HDC regimen.

In this study, it was aimed to evaluate the survival and progression of patients with relapsed/refractory SCRTs who underwent ASCT and received high dose ICE (HD-ICE).

METHODOLOGY

This study was designed as a cross-sectional study with a retrospective data collection method. It included 37 patients with relapsed/refractory ES, MB, RMS, and osteosarcoma, older than 16 years, who underwent ASCT with the HD-ICE chemotherapy regimen at Bone Marrow Transplantation Unit, Gulhane Education and Research Hospital between January 2016 and April 2020. Records were assessed for age, gender, primary tumour location, stage at the time of diagnosis, site of metastases on first presentation, lung metastasis situation, previous treatments (radiotherapy, neoadjuvant chemotherapy and adjuvant therapy), relapse time after the first treatment (<2 years or ≥ 2 years), extrapulmonary relapse situation, number of treatment lines before HD-ICE, data of the ASCT (amount of reinfused stem cells, time of engraftment and transplant-related side effects), PFS and one-year OS rate after HD-ICE and TRM until engraftment, and in the first 100 days and the observed side effects profile.

The inclusion criteria were: being ≥ 16 years old, patients who received two lines of chemotherapy due to relapsed/refractory ES, MB, RMS or osteosarcoma patients, and those who received HD-ICE protocol in this centre. Those <16 year and whose medical records were not available, were excluded.

Patients were divided according to their primary diseases. All patients were given HD-ICE protocol with 12 g/m² ifosfamide, 1200 mg/m² carboplatin, and 1200 mg/m² etoposide by dividing the total dose into six days. Stem cell reinfusion was performed on the eighth day after two days of rest. For engraftment definition after ASCT, the day like +10, on which platelet count >20 000/mm³, leukocyte count >4000/mm³ or neutrophil count >2000/mm³ occurs first will be accepted as that day. The primary endpoint was to evaluate the patients' PFS, one-year OS rate, and TRM after HD-ICE. Evaluation of treatment-related side effects was also determined as a secondary endpoint.

The local Ethics Committee approved the study protocol (Approval No. 2020/170). All procedures followed the ethical standards of the Turkish medicine and medical devices agency good clinical practices guidelines and the Declaration of Helsinki.

Statistical analyses was performed using SPSS version 22.0 software (SPSS Inc., Chicago, Illinois). Uniformity of contin-

uous variables to a normal distribution was examined by using the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean \pm standard deviation (SD). Data that was not normally distributed was expressed as median (interquartile range [IQR]). Kaplan-Meier survival function analyses and log-rank tests were used to calculate cumulative survival and treatment correlations. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

There were 37 patients with male predominance in all groups except MB. While primary tumour localisation was detected as extremities in patients with ES and osteosarcoma (85% and 100%, respectively); in rhabdomyosarcoma, the primary origin was most frequently detected in non-extremity tissues (75%). The data of the other clinical characteristics, engraftment days and reinfused stem cell amounts of other patients and the demographic and clinical features of the whole group are presented in Table I.

The PFS results observed after the patients' first- and second-line chemotherapy treatments are presented in Table II.

After HD-ICE, overall response rate (ORR), PFS and one-year OS rate are presented in Table II, and Figures 1, 2 and 3. No patient died during HD-ICE. The most common side effect after HD-ICE was determined as myelotoxicity.

The most common non-myelotoxic side effect was nausea and vomiting. Data on other features of the HD-ICE treatment are presented in Table II.

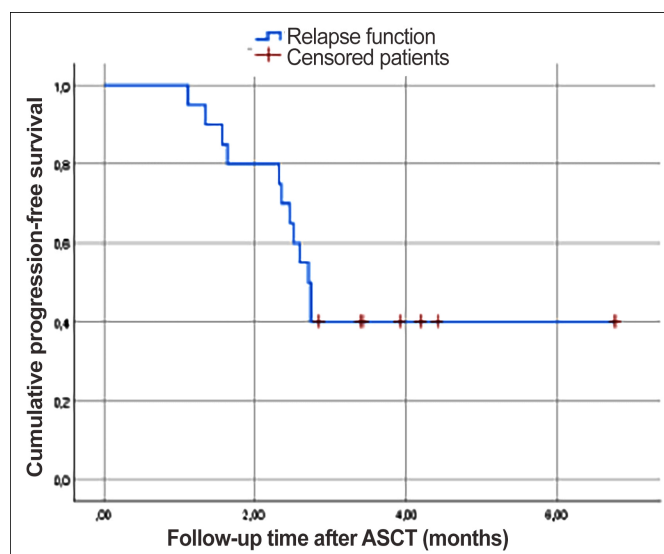


Figure 1: Kaplan-Meier curve of progression-free survival of the patients with Ewing Sarcoma after HD-ICE.

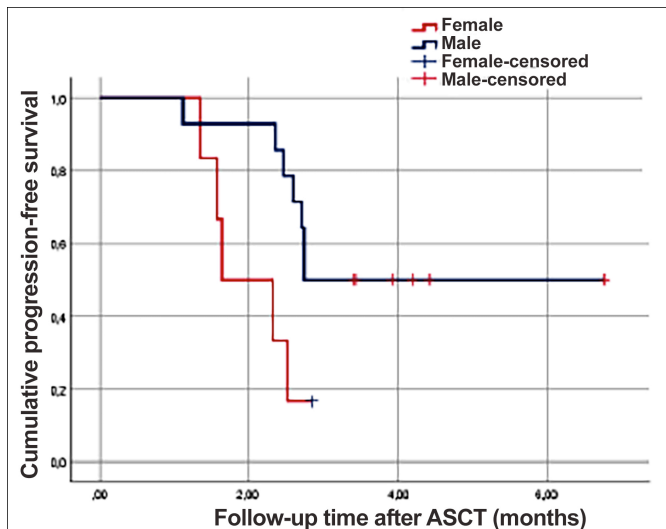


Figure 2: Log-Rank curve of progression-free survival of the patients with Ewing Sarcoma after HD-ICE by gender ($p=0.025$).

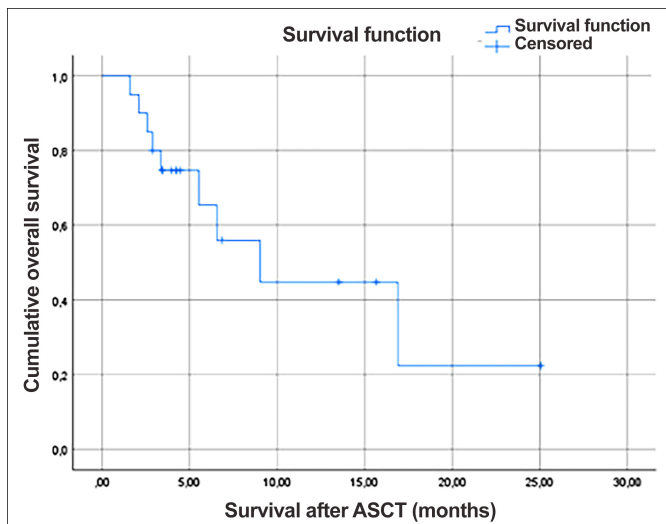


Figure 3: Kaplan-Meier curve of overall survival of the patients with Ewing Sarcoma after HD-ICE.

DISCUSSION

PFS, one-year-OS rate and TRM results of patients with metastatic SRCTs were determined, who underwent HD-ICE and ASCT. An important possibility that excited the authors is the use of only the ICE protocol as the HDC. The number of publications reporting on this protocol is limited. Patients were primarily evaluated in terms of their stages of diagnosis, metastasis status, treatment modalities, relapse times and PFS duration in the first two lines. After this evaluation, response to HD-ICE, PFS, one-year-OS rate, and TRM were determined. Finally, the toxicity profile was evaluated.

There was complete response (CR) in 35% of ES, and the duration of PFS in ES was 2.70 ± 0.97 months. One-year OS rate after HD-ICE was $44.8 \pm 14.8\%$. McTierman and colleagues reported a two-year event-free survival (EFS) of 42.5% with busulfan-based HDC. Patients received HDC-ASCT after the second relapse or after induction therapy

after the first relapse. Approximately half of the patients experienced recurrence after >2 years, and 21% of patients presented with extra-pulmonary relapse.¹⁵ In this study, 85% of patients received HD-ICE after the second recurrence, and 65% of patients had relapsed within two years. Extra-pulmonary relapse was experienced in 55% of patients. Bacci and colleagues described relapse within two years and extra-pulmonary metastases as bad prognostic factors for OS.¹⁶ This may be due to the low PFS duration; and OS rate detected were due to poor prognostic factors. Like that by McTierman and colleagues, in this study, four patients died at similar rates within the first 100 days. Moreover, myelotoxicity was the most common side effect. Death of more patients may be attributed to the higher tumour burden and other poor prognostic factors.

CR was obtained in six patients and partial response (PR) in two patients in the MB group. PFS was 11.57 ± 3.63 months. The one-year OS rate was $75 \pm 15.8\%$. TRM has not been detected. Zia and associates evaluated the effectiveness of HDC-ASCT treatment in six adult relapsed/refractory MB patients. The median duration of response was 13.5 months. Carboplatin, etoposide and cyclophosphamide were used as HDC regimens.¹⁷ TRM has not been reported. The successful results can be achieved with HD-ICE in adult MB.

Matsubara and colleagues reported HDC-ASCT results in 22 advanced RMS patients. Preparation regimens primarily included etoposide, carboplatin and melphalan. They achieved CR in 14 patients and PR in five patients. The five-year OS rate was reported to be 70%.¹⁸ The number of studies evaluating only adults is very small, since this tumour is very rare in adults. Additionally, it is known that older age is one of the worst prognoses in RMS patients. In this study, four adult alveolar-type RMS patients were evaluated, and CR was detected in one patient. PFS duration was determined as 3.47 ± 0.44 months. Although it is difficult to interpret the present data due to the small number of patients, HD-ICE can be preferred in eligible patients.

Arpaci and colleagues reported HDC-ASCT data in 22 high-grade but non-metastatic primary osteosarcoma patients. All patients were operated after HDC-ASCT and received adjuvant chemotherapy after the operation. Significant tumour necrosis was demonstrated in $> 80\%$ of patients with the neoadjuvant HDC approach. The one-year OS and DFS rates are 100% and 94%, respectively. They did not report TRM.¹⁹ Only three adult osteosarcoma patients were examined in this study. Two patients were identified with progressive disease after HD-ICE. PFS was determined as 2.96 ± 0.91 months; TRM was not detected. As a result, this treatment modality still constitutes an experimental method for patients who have poor prognostic factors.

This study has several limitations. In retrospective studies, bias may be encountered due to the low ability to keep records. Although SRCT group tumours are rare in adulthood

and a single-centre experience is presented here, evaluation of OS, PFS and TRM results may be affected by the small number of patients. Retrospective cross-sectional design is the method of this study. Therefore, the results cannot be assumed to be causal.

CONCLUSION

HD-ICE in SRCT is acceptable due to low TRM and manageable side effects. However, given the results of the study endpoints, this approach is still an experimental treatment modality.

ETHICAL APPROVAL:

This study was approved by Institutional Ethics Committee of Ankara Gulhane Training and Research Hospital (Ethics Committee approval No. 2020/170).

PATIENTS' CONSENT:

Because this study was retrospective, the patients' consents were waived.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MBA, IE, RA, GSY, BY, NK: Conception of the work, analysis or interpretation of data for the work, and drafting the work.

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