Outcomes of Autologous Stem Cell Transplantation (ASCT) in Relapsed/Refractory Germ Cell Tumors: Single Center Experience from Turkey

Fatih Yildiz[1]*, Ayse Durnali[1], Emrah Eraslan[1], Aysegul Ilhan[1], Gulnihal Tufan[1], Ferit Aslan[2], Ulku Yalcintas Arslan[1], Necati Alkis[1], Umut Demirci[1], Fevzi Altuntas[3], Berna Oksuzoglu[1]

Purpose: Germ cell tumors (GCTs) are rare and highly curable malignancies. However, salvage treatments for relapsed or refractory disease are needed in approximately 20-60% of the patients. As salvage therapy, autologous stem cell transplantation (ASCT) administered after high-dose chemotherapy (HDCT) may be a feasible option as well as standard dose chemotherapy (SDCT). This study aimed to evaluate the efficacy and toxicity of ASCT in salvage therapy of GCTs retrospectively.

Materials and Methods: Male patients older than 18 years of age who underwent ASCT due to a relapsed/refractory GCT were included in the study.

Results: The median age of 18 patients included in the study was 28 (19-46). The majority of patients (n:16, 88.8%) had non-seminomatous GCT histology. All of the patients had relapsed or refractory GCTs and received bleomycin, etoposide, cisplatin (BEP) combination therapy previously. Half of the patients were in the poor risk group. ASCT was administered as a second-line therapy in 14 (77.7%) patients and third-line therapy in four (22.2%) patients. There is no ASCT-related exitus. Febrile neutropenia (FN) developed in almost all patients. Complete response (CR) was obtained in 7 (38.8%) patients, partial response (PR) in four (22.2%) patients after ASCT. The 2-year progression free survival (PFS) was 44.4% and the median PFS was 8.7 (2.7-12.6) months. Median overall survival was 22.7 (3.9-41.7) months and 3 years OS was 50.0%.

Conclusion: In conclusion, ASCT was found to be an effective and safe treatment option in salvage therapy of GCT patients in our study.

Keywords: germ cell tumor; autologous stem cell transplant; high dose chemotherapy; testiculer cancer

INTRODUCTION

Germ cell tumors (GCTs) are rare but the most common malignancy in men aged between 15-35 years[1,2]. The most common primary site of GCTs is testis and they are divided into two histological main types: seminoma and non-seminoma. GCTs have been considered as one of the most curable solid malignancies with the advances in treatment approaches during last four decades[3-7].

GCTs can be highly curable with platinum-containing combination regimens even in the advanced stage with visceral metastases and high serum tumor markers. However, approximately 20% of patients in the good risk group and 60% in the intermediate and poor risk group develop progression despite platinum-based chemotherapy and salvage treatments are required[3-13].

In second-line and subsequent-line salvage therapy for recurrent or platinum refractory patients autologous stem cell transplantation (ASCT) applied following high-dose chemotherapy (HDCT) is a treatment option as well as standard dose chemotherapy (SDCT) [2,4,6,9,14-20].

In this study we aimed to evaluate the efficacy and toxicity of ASCT in salvage therapy of GCTs retrospectively.

MATERIALS and METHODS

The patients diagnosed with GCT in our center between 2010 and 2019 were retrospectively reviewed. Male patients older than 18 years of age who underwent ASCT due to a relapsed/refractory GCT were included in the study. Demographic and clinicopathological features of the patients, International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic risk group, conditioning regimens for ASCT, ASCT-related complications, the date of disease progression and death were recorded by using patient files and computer-based registries.

Complications after ASCT were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

The data were analyzed using the IBM Statistical Package for Social Sciences (SPSS®) v.21 (IBM Inc.; Ar-

[1]University of Health Sciences, Dr. A.Y Ankara Oncology Research and Education Hospital, Oncology Department, Ankara/Turkey.
[2]Medical Park Ankara Hospital, Oncology Department, Ankara/Turkey.
[3]University of Health Sciences, Dr. A.Y Ankara Oncology Research and Education Hospital, Hematology Clinic and Bone Marrow Transplantation Unit, Ankara/Turkey.
*Correspondence: University of Health Sciences, Dr. A.Y Ankara Oncology Research and Education Hospital, Oncology Department, Ankara/Turkey. Tel: +90 506 366 51 81. E mail: dr.fatihyildiz@hotmail.com;
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Table 1. Patient characteristics.

	n: 18	%
Age		
Median (range) – yr	28 (19-46)	
Gender		
Male	18	100
ECOG performance status score		
0	7	38.8
1	11	61.1
Malignancy		
Seminoma	2	11.1
Non-seminoma	16	88.8
Primary tumor site		
Testis	15	83.3
Mediastinum	2	11.1
Retroperitoneal	1	5.5
Site of metastasis		
Lymph node	18	100
Lung	11	61.1
Bone	3	16.6
Liver	3	16.6
Brain	2	11.1
IGCCCG classification		
Good prognosis	3	16.6
İntermediate prognosis	6	33.3
Poor prognosis	9	50
ASCT sequence		
2nd line	14	77.7
3rd line	4	22.2

ECOG: Eastern Cooperative Oncology Group
IGCCCG: International Germ Cell Cancer Collaborative Group
ASCT: Autologous Stem Cell Transplant

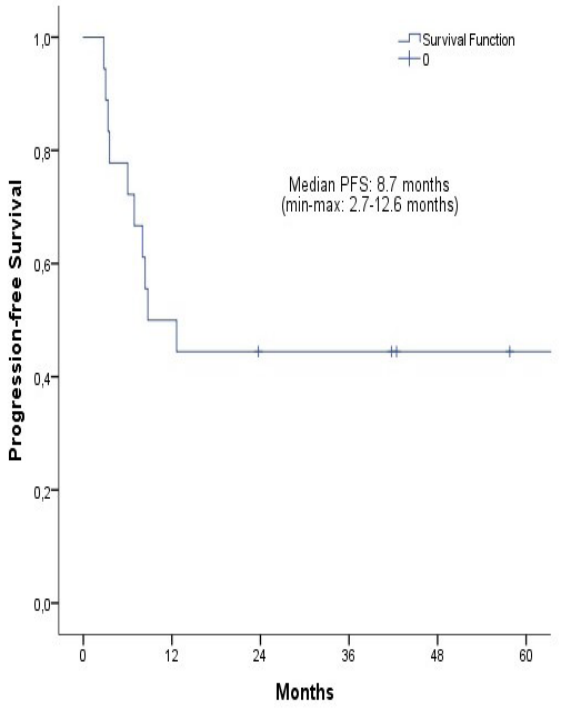

Figure 1. Progression-free survival with autologous stem cell transplantation.

monk, NY, USA).
The time from ASCT to progression was defined as progression free survival (PFS) and time from ASCT to death as overall survival (OS). Kaplan-meier survival curve was used for PFS and OS, long-rank test was used for median PFS and OS.

RESULTS

The median age of 18 patients included in the study was 28 (19-46). The majority of patients (n:16, 88.8%) had non-seminomatous GCT histology and the most common primary tumor site is testis (n: 15, 83.3%). Patient characteristics are shown in **Table 1**.
All of the patients had relapsed or refractory GCTs and received bleomycin, etoposide, cisplatin (BEP) combination therapy previously. According to IGCCCG risk classification half of the patients were in the poor risk group. Eight (44.4%) patient had non-pulmonary visceral metastasis. ASCT was administered as a second-line therapy in 14 (77.7%) patients.
As myeloablative regimen before ASCT, 13 (72.2%) patients received etoposide (250 mg/m2, days 1-4), thiotepa (166 mg/m2, days 2-4), carboplatin (266 mg/m^2, days 2-4) combination (TECA regimen) and 5 (27.7%) patients received etoposide (100 mg/m2, days 1-6), ifosfamide (2500 mg/m2, days 1-6), carboplatin (250 mg, days 1-6) combination (ICE regimen).
Two cycles of paclitaxel, ifosfamide, and cisplatin combination (TIP regimen) were used for conditioning regimen before TECA. CD 34 + stem cell mobilization was achieved with plerixofor in two (11.1%) patients and granulocyte colony stimulating factor (G-CSF) in remaining patients.
Median 6.8 X 106/kg (4.7-14.1) CD 34 + stem cells were collected and median 6.5 X 106/kg (4.7-8.4) CD 34 + cells were infused. There is no ASCT-related exitus. Febrile neutropenia (FN) developed in almost all patients. All ASCT-related toxicities are shown in **Table 2**.
Complete response (CR) was obtained in 7 (38.8%) patients, partial response (PR) in four (22.2%) patients after ASCT.

Table 2. Autologous stem cell transplantation related toxicity.

	None	Any Grade
Nause	0	18 (100%)
Diarrhea	2 (11.1%)	16 (88.8%)
Mucositis oral	4 (22.2%)	14 (77.7%)
Febrile neutropenia	1 (5.5%)	17 (94.4%)
Alanine aminotransferase (ALT) increased	0	18 (100%)
Aspartate aminotransferase (AST) increased	0	18 (100%)
Blood bilirubin increased	16 (88.8%)	2 (11.1%)
Creatinine increased	15 (83.3%)	3 (16.6%)
Death	18 (100%) -	

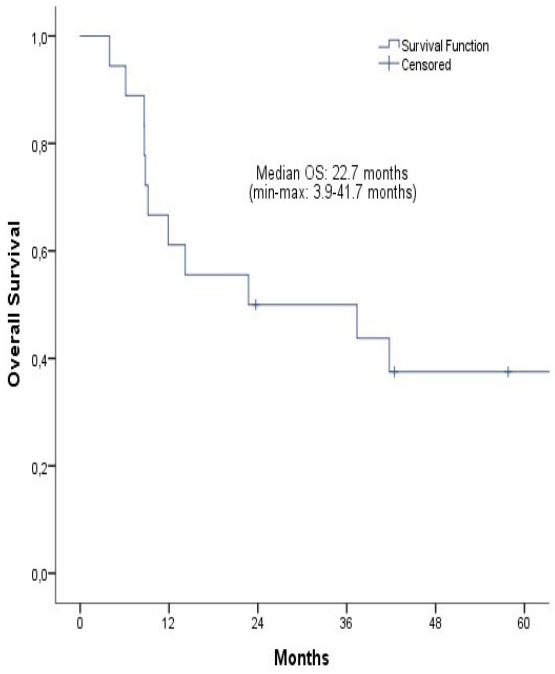

Figure 2. Overall survival with autologous stem cell transplantation.

Median follow-up was 23.7 months. During the follow-up period 11 (61.1%) patients had progressive disease. The 2-year PFS was 44.4% and the median PFS was 8.7 (2.7-12.6) months (**Figure 1**). Eleven (61.1%) patients died during follow-up. Median OS was 22.7 (3.9-41.7) months and 3 years OS was 50.0% (**Figure 2**).

DISCUSSION

GCTs are rare and highly curable malignancies. However, salvage treatments for relapsed or refractory disease after platinum-based treatments are needed in approximately 20-30% of the patients. As salvage therapy, ASCT administered after HDCT may be a feasible option. In this study, we aimed to evaluate the efficacy and toxicity of ASCT in patients with GCTs, mostly non-seminomatous histologic type and in intermediate/poor risk group.

Pico and colleagues' phase 3 trial is one of the rare prospective studies comparing HDCT with SDCT. In this study, one cycle HDCT/ASCT which administered after three cycles SDCT was compared with four cycles SDCT. According to the results of this study, ASCT was not superior to SDCT[15].

In retrospective analysis of Beyer, HDCT and SDCT for salvage treatment in non-seminomatous GCTs were compared. Approximately 10% absolute improvement was observed in 2-year survival in favor of ASCT[17].

The thought that single-dose HDCT might not be effective, led to the studies that investigate the effectiveness of two-cycle HDCT. ASCT was performed after two cycles of HDCT for relapsed/refractory GCTs in the series of 184 patients published by Einhorn et al. in 2007. ASCT applied as a second-line treatment in the majority of patients. They reported that 63% of patients were disease free at the end of four years. But, in this study 78% of the patients were platinum-sensitive and approximately 40% of patients were in the good-risk group according to IGCCCG[14].

In Indiana University's other experience consisting of 364 patients announced in 2017, after ASCT therapy, 2-year PFS and OS of patients with relapsed/refractory GCTs were 60 % and 66% respectively. Performing ASCT in the third-line and later-lines, intermediate and poor risk group were found to be associated with poor PFS in this trial[2]. Approximately 40% of patients were in good risk group and more than 70% were sensitive to platinum in these two studies of Indiana University. Therefore 2-year PFS seems better than that of in our study.

In the phase 2 study of Feldman and colleagues, 108 patients with relapsed/refractory GCTs were administered 3 cycles of carboplatin/etoposide (CE) and ASCT following 2 cycles of paclitaxel/ifosfamide. Complete response (CR) was obtained in 42% of patients and the 5-year OS was reported as 52%. In this study, most of the patients had non-seminomatous histology and were in intermediate and poor risk group. The response rates obtained in this patient group seem to be quite good[16]. Considering the toxicity, treatment-related death of 2%, appears to be similar to other regimens.

In another retrospective analysis of 48 patients, after ASCT with CE regimen, 75% CR was obtained and the 5-year OS was reported as 75%[18]. Although the results seem very successful, all patients in this study were in low-risk group with seminomatous histology.

In the phase 2 study which evaluating the efficacy and safety of TECA as a high dose chemotherapy regimen in relapsed/refractory GCTs, 62 patients were treated with ASCT. Two-year event-free survival (EFS) was 25% and 3-year OS was 30% in this study[19]. TECA was preferred as the myeloablative regimen in the majority of our patients. However, the OS results which we obtained seems better than this phase 2 study. This OS difference may be due to the different subsequent treatment choices administered after progression.

In a review of 59 studies, published in 2017, SDCT and HDCT regimens were compared as salvage therapy in testicular cancer. In the pooled analysis of this review, mean OS was reported as 14.8 months for SDCT and 24.0 months for HDCT. Three-year OS was 45.1% in the SDCT arm and 46.7% in the HDCT arm(20). The 3-year OS reported in this review was similar to our result.

When the toxicities were evaluated, it is remarkable that there was no ASCT-related death in our study. In Feldman and Adra's studies, 2%-2.4% ASCT-related death was reported[2,16]. Grade 4 neutropenia after HDCT was observed in almost all patients in all studies[2,14-19]. Similarly, in our study, FN after ASCT developed in all patients except one. Grade 3 and higher HDCT-related hepatic/renal toxicity reported as 3.3% in the wide experience of Indiana University[2]. In our study, while HDCT-related grade 3 nephrotoxicity was not experienced, up to 30% hepatotoxicity occurred. This high rate of hepatotoxicity may be the result of FN protocol of our center, which includes antibiotic, antiviral and antifungal treatments.

The limitations of our study were retrospective nature and small number of patients. Due to rarity of this disease, as far as we know , there is no previous larger study evaluating ASCT efficacy in poor-risk group and

there is no experiences about using the thiotepa combination regimen as high-dose chemotherapy for relapsed/refractory GCTs treatment.
In conclusion ASCT was found to be an effective and safe treatment option in salvage therapy in our study, including mostly intermediate and high-risk non-seminomatous GCT patients. To evaluate the role of ASCT for the treatment of GCT, prospective studies with larger number of homogeneous patients groups are required.

CONFLICT ON INTEREST

No conflict of interest was declared by the authors.

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