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ORIGINAL ARTICLE

High-dose thiotepa, etoposide and carboplatin as conditioning regimen for autologous stem cell transplantation in patients with relapsed or refractory germ cell tumors

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Summary

Purpose: *As well as standard chemotherapy, autologous stem cell transplantation (ASCT) is also seen as a good therapeutic alternative in the relapsed/refractory germ cell tumors (GCT). The combination of thiotepa, carboplatin and etoposide (TECA) is also one of the high-dose chemotherapy options that can be used before ASCT. Except a phase-II study there are no large studies conducted with the TECA regimen in GCT. In this study, we aimed to evaluate the efficacy and toxicity of the TECA regimen in patients who underwent ASCT.*

Methods: *Patients who underwent ASCT with TECA for relapsed/refractory GCT in our center between 2013-2020 were included in the study.*

Results: *The median age of 15 patients included in the study was 31 years (19-46). The majority of patients (n=12; 80.0%) had a diagnosis of non-seminoma GCT. All of the patients had previously received bleomycin, etoposide, cisplatin (BEP) combination chemotherapy. They were relapsed/refractory to platinums and had at least one distant metastasis. ASCT was administered as a second-line therapy in 12 (80.0%) patients. In all patients etoposide, thiotepa and carboplatin were administered before ASCT as myeloablative therapy. Complete response was obtained in 6 (40.0%) patients and partial response in 5 (33.3%). The objective response rate was 73.3%. Three-year progression-free survival (PFS) was 43.1% and the estimated median PFS was 12.6 months (2.7-41.7). The estimated median overall survival (OS) was 37.3 months and 3-year OS was 54.5%. None of the patients had ASCT-related death.*

Conclusions: *High-dose TECA is an effective and safe myeloablative regimen for ASCT in relapsed/refractory GCT.*

Key words: *germ cell tumors, high dose chemotherapy,TECA stem cell transplantation*

Introduction

Germ cell tumors (GCT) are rare and account for approximately 1% of malignancies in men and approximately 5% of malignant tumors of the ovary in women [1,2]. However, they are the most common malignancies in young men between the ages of 15-35 and 70% of ovarian neoplasms are GCT in young women [3,4]. Although the majority of patients can be cured even in advanced stages, relapse or progression develop and salvage treatments are required in approximately 30% despite platinum-based treatments [5].

Autologous stem cell transplantation (ASCT) which is applied following high-dose chemotherapy seems as a treatment alternative as well as conventional chemotherapy in recurrent or platinum-refractory patients [6-11].

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Carboplatin/etoposide (CE) combination is mostly preferred as high dose chemotherapy regimen before ASCT. However, there is limited experience with regimens including cisplatin, ifosfamide, cyclophosphamide, paclitaxel and thiotepa in different centers [5-11]. The combination of thiotepa, carboplatin and etoposide (TECA) is also one of the high-dose chemotherapy options that can be used before ASCT. Except a phase-II study [12] there are no large studies conducted with the TECA regimen in GCT.

In this study,we aimed to evaluate the efficacy and toxicity of the TECA regimen in patients who underwent ASCT for salvage therapy due to GCT in our center.

Methods

Patients who underwent ASCT with TECA for relapsed/refractory GCT in our center between 2013-2020 were included in the study. The demographic and clinocopathologic characteristics of the patients, International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic risk group, chemotherapy-related complications, the progression and death status were recorded through an electronic registry system.

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

Treatment schedule

TECA was administered before ASCT as follows; etoposide 250 mg/m^2/day (day -6, -5, -4, and -3) intravenously as daily 2-h infusion, thiotepa 166 mg/m^2/day (day -5, -4, and -3) intravenously as daily 2-h infusion, and carboplatin 266 mg/m^2/day (day -5, -4, and -3) intravenously as daily 4-h infusion. CD 34 + stem cells were infused on day 0. With white blood cell (WBC) count fewer than 1000 mm^3, 5μg/kg/day filgrastim was applied at least 24 h after stem cell infusion. Filgrastim was continued to be administered until the WBC was > 1000 mm^3 for three consecutive days. Patients received metoclopramide 20-30 mg/day (day -7 to day +3) intravenously, dexamethasone 8 mg/day (day -7 to day +3) intravenously and granisetron 3 mg/day (day -4 to day +3) intravenously as antiemetic therapy. Fluconazole 200 mg/ day (day -8 to day +30), valacyclovir 2x500 mg/day (day -8 to day +30), metronidazole 3x500 mg/day (day -8 to day +30) and trimethoprim/sulfamethoxazole 2x800 mg/day (two days a week, day -7 to day +30) were given prophylactically to all patients.

In the imaging performed by computed tomography 6-8 weeks after ASCT, the absence of measurable lesions was defined as complete response (CR), while reduction of more than 30% in target lesions was defined as partial response (PR). Stable disease (SD) was defined as less than 30% reduction and less than 20% growth in target lesions in accordance with RECIST 1.1 criteria. Overall response rate (ORR) was defined as the proportion of patients attaining PR or CR.

Statistics

The data were analyzed using the IBM SPSS v.21 (IBM Inc.; Armonk, NY, USA).

The time from ASCT to progression was defined as progression-free survival (PFS) and the time from ASCT to death was defined as overall survival (OS). The Kaplan-Meier method was used for PFS and the long-rank test was used to calculate the median PFS and median OS.

The primary outcome of this study was ORR and the secondary outcomes were PFS, OS, and TECA-related toxicities.

Results

The median age of 15 patients included in the study was 31 years (19-46). Only one (6.6%) patient was female and had a diagnosis of overian germ cell neoplasm. The majority of patients (n=12; 80.0%) had a diagnosis of non-seminoma GCT. All

Table 1. Patient characteristics

	n=15 *n (%)*
Age, years	
Median (range)	31 (19-46)
Gender	
Male	14 (93.3)
Female	1 (6.6)
ECOG performance status score	
0	7 (46.6)
1	8 (53.3)
Malignancy	
Seminoma	2 (13.3)
Non-seminoma	12 (80.0)
Dysgerminoma (ovarian)	1 (6.6)
Site of metastasis	
Lymph node	13 (86.6)
Lung	12 (80.0)
Bone	4 (26.6)
Liver	2 (13.3)
Brain	1 (6.6)
IGCCCG risk clasiffication	
Good	-
Intermediate	5 (33.3)
Poor	9 (60.0)
N/A	1 (6.6)
ASCT sequence	
2nd line	12 (80.0)
3rd line	2 (13.3)
4th line	1 (6.6)

ECOG: Eastern Cooperative Oncology Group, IGCCCG: International Germ Cell Collaborative Group, ASCT: Autologous Stem Cell Transplantation, N/A: not applicable.

of the patients had previously received bleomycin, etoposide, cisplatin (BEP) combination therapy. They were relapsed/refractory to platinums and had at least one distant metastasis. According to IGCCCG risk classification 9 (60.0%) patients were in the poor risk group and 5 (33.3%) in the intermediate risk group. Patient characteristics are shown in Table 1.

ASCT was administered as a second-line therapy in 12 (80.0%) patients and as a third-line therapy in two (13.3%) patients and as a fourth-line therapy in one (6.6%) patient. Stem cell mobilization with granulocyte-colony stimulating factor (G-CSF) was performed after two cycles of paclitaxel, ifosfamide, and cisplatin (TIP) combination chemotherapy in patients treated with ASCT as a second-line treatment. Mobilization was performed with plerixafor after combination therapy with gemcitabine and oxaliplatin in the third-line treatment of GCT with ASCT. A median 7.0×10^6/kg (4.1-14.1) CD 34 + stem cells were collected.

In all patients etoposide, thiotepa and carboplatin were administered before ASCT as myeloablative therapy. Median 6.9×10^6/kg (4.1-8.4) CD 34 + stem cells were infused on day 0.

The median platelet engraftment time was on the 13th day (8-20) and the median neutrophil engraftment was on 10th day (9-21).

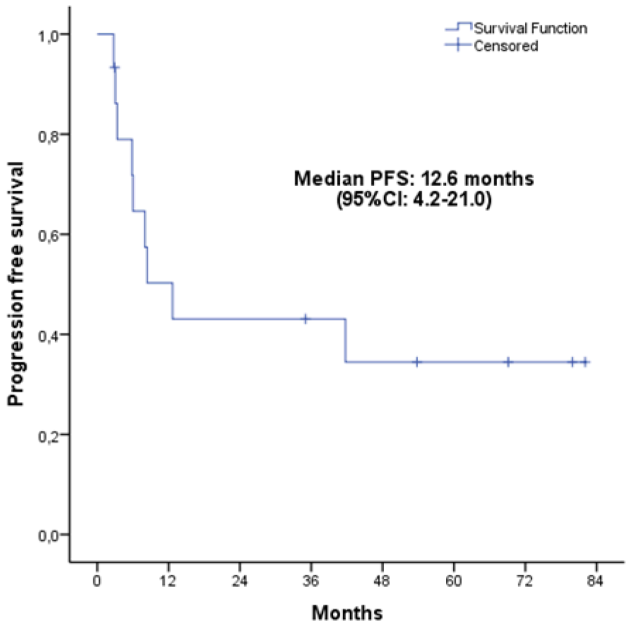

Figure 1. Kaplan-Meier estimates of progression-free survival.

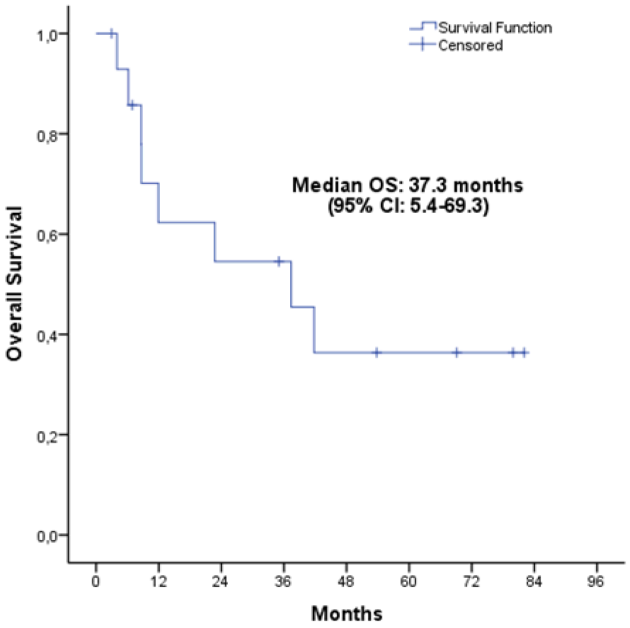

Figure 2. Kaplan-Meier estimates of overall survival.

Table 2. High dose chemotherapy (thiotepa, carboplatin and etoposide combination) related toxicity

	None *n (%)*	*Grade 1* *n (%)*	*Grade 2* *n (%)*	*Grade 3* *n (%)*	*Grade 4* *n (%)*
Nausea	0	9 (60.0)	5 (33.3)	1 (6.6)	-
Diarrhea	3 (20.0)	2 (13.3)	4 (26.6)	6 (40.0)	0
Mucositis oral	3 (20.0)	7 (46.6)	5 (33.)	0	0
Peripheral neurotoxicity	13 (86.6)	1 (6.6)	1 (6.6)		
Febrile neutropenia	1 (6.6)	-	-	14 (93.3)	0
Alanine aminotransferase (ALT) increased	2 (13.3)	1 (6.6)	6 (40.0)	5 (33.3)	1 (6.6)
Aspartate aminotransferase (AST) increased	2 (13.3)	1 (6.6)	6 (40.0)	5 (33.3)	1 (6.6)
Blood bilirubin increased	11 (73.3)	4 (26.6)	0	0	0
Creatinine increased	14 (93.3)	1 (6.6)	0	0	0
Death	15 (100)	-	-	-	-

CR was obtained in 6 (40.0%) patients, PR in 5 (33.3%) and SD in 4 (26.6%) after ASCT. The ORR was 73.3%.

During a median follow-up of 31.3 (2.9-82.0) months, nine patients developed progression and five had no progression. Three-year PFS was 43.1% and the estimated median PFS was 12.6 months (2.7-41.7) (Figure 1). Eight (53.3%) patients died during follow-up. All deaths were associated with disease relapse/progression. The estimated median OS was 37.3 months and 3-year OS was 54.5% (Figure 2).

None of the patients had ASCT-related death. Febrile neutropenia (FN) occurred in 93.3% (n=14) of our patients, and the median time was the 5th day (4-7 days) after ASCT. In our study, grade 2 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase was observed in 6 (40.0%) patients and grade 3 AST/ALT increase in 5 (33.3%). In these patients, the median time to reach the peak of AST/ALT was the 10th day (7-13 days). All ASCT-related toxicities are shown in Table 2.

Discussion

ASCT which was performed after high-dose chemotherapy is seen as a good alternative in the relapsed/refractory GCTs in second and subsequent lines of treatment. Discussions about the chemotherapy regimens preferred before ASCT still continue [13,14]. In this study it was observed that an ORR of 73.3% was obtained with the TECA regimen in relapsed/refractory GCTs.

As a high-dose chemotherapy before ASCT the combination of CE was mostly preferred as the standard regimen in previous studies. In the following years it was aimed to increase the effectiveness by adding agents such as ifosfamide, cyclophosphamide, paclitaxel and thiotepa to these two agents [12,15-21].

In the extensive experience of Indiana University consisting of 184 patients published in 2007 by Einhorn et al, 5-year OS was achieved in 65% with ASCT which was administered after CE in platinum-refractory testicular carcinoma [10]. This good response with CE appears to be the best response achieved with salvage therapies in the literature, better than in our study [17,21]. However, the rate of poor-risk patients in this study is low compared to other studies [10,17,21]. While the rate of patients at poor risk was 100% in the Motzer's study, 69% in our study, and 50% in the Feldman's study, it was significantly lower than in the Einhorn's study, below 40% [10,17,21].

In another retrospective analysis of 48 patients after ASCT with CE regimen, 75% CR was obtained and the 5-year OS was 75% [22]. Although the results seem very successful, all patients in this study consisted of low-risk patients with seminoma histology.

In a phase 2 study evaluating the efficacy and safety of TECA as a high-dose chemotherapy regimen in relapsed/refractory GCT, 62 patients were able to perform ASCT. Two-year event-free survival was 25% and 3-year OS was 30% in this study [12]. In our study, 3-year PFS was 43.1%, and 3-year OS 54.5%. The survival results obtained with the TECA regimen seem better in our study. It was thought that subsequent-lines treatments applied in case of progression or relapse after ASCT, may cause this difference in survival.

In a review of 59 studies published in 2017, standard chemotherapy and high-dose chemotherapy regimens were compared as a salvage therapy in testicular cancer [23]. In the pooled analysis of this review, mean OS was 14.8 months for standard-dose chemotherapy and 24.0 for high-dose chemotherapy. Three-year OS was 45.1% in the standard dose chemotherapy arm and 46.7% in the high-dose chemotherapy arm. In our study median OS and 3-year OS results obtained with the high-dose TECA regimen seem better. In most of the studies included in this analysis, regimens containing carboplatin were preferred, while only a few studies were performed with regimens in which thiotepa was added. Based on this, it is thought that this positive OS difference we obtained in our study may be due to thiotepa.

When the toxicities due to TECA were evaluated, 89% of the patients developed febrile neutropenia (FN) in the pivotal study, which was similar (93.3%) in our study [12]. Rick et al reported that grade 2 peripheral neurotoxicity occurred in 22% of the patients [12]. In our study, this rate was 6.6%. In a German study, while three cycles of TIP were given before TECA, two cycles of TIP were given to the patients in our study. Therefore, our paclitaxel-related neuropathy rates were much lower.

Grade 3 ALT/AST elevation was observed in 15.4% of the patients in the German study, while this rate was 33.3% in our study [12]. This difference was thought to be caused primarily by antibiotics, antiviral and antifugal drugs used in our center due to FN. Since the day of peak value was day 10, it was thought that chemotherapy agents were not the cause of AST/ALT increased. While ASCT-related death developed in only one patient in this study, similarly none of the patients experienced ASCT-related death in our study.

The most important limitations of our study were the retrospective nature and the small num-

ber of patients. However, almost all of the studies investigating high-dose chemotherapy regimens before ASCT consisted of a single center experiences with small patient groups. To the best of our knowledge, except for the pivotal phase-2 study showing the effectiveness of the TECA regimen in GCT, there are no other reports in the literature.

Conclusions

In our study it was observed that the high-dose TECA regimen was an effective and safe myeloablative regimen for ASCT in relapsed/refractory GCTs. Large prospective randomized studies are needed to determine the most effective and safe regimen in this area.

Ethics approval

HSU Dr.A.Y. Ankara Oncology Training and Research Hospital Ethics committee approval was obtained prior to the study (approval number: 2020-08/763).

Conflict of interests

The authors declare no conflict of interests.

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