Original Article

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A Retrospective Study of Patients with Recurrent or Refractory Testicular Germ Cell Tumors Treated with High-dose Chemotherapy and Autologous Peripheral-blood Stem-cell Transplantation Single-center Experience

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Abstract

Objective: Patients with recurrent metastatic germ cell tumor (GCT) can be treated with second-line or even third-line regimens; 20-30% of testicular GCT (TGCT) relapse or become refractory after first-line therapy and optimal treatment for this group is not very well defined.

Materials and Methods: We presented the analysis of the efficacy of high-dose chemotherapy and peripheral-blood stem-cell transplantation in patients treated between 2016 and 2019. Five patients with five autologous stem-cell transplantations (ASCT) were analyzed retrospectively. All patients were treated with bleomycin, etoposide, cisplatin as first-line therapy and paclitaxel, ifosfamide, cisplatin was given as salvage chemotherapy. Stem–cell collection was performed with granulocyte stimulating factor. ASCT was performed with carboplatin (700 mg/m^2) and etoposide (750 mg/m^2). The results were provided as median (min-max).

Results: After ASCT, all patients were in complete remission (CR). The follow-up after ASCT was 12 months. At the 12-month follow-up, four patients were still alive and in CR, and only one patient died at 6th month after ASCT due to recurrence. Grade 2/4 toxicities were observed in five patients. Only one patient died due to complications of transplantation.

Conclusion: Although the number of the patients in this study was limited, ASCT seemed to be a safe and effective treatment modality in recurrent refractory non-seminomatous TGCT, and treatment-related mortality was very low in this heavily pretreated group.

Keywords: High-dose chemotherapy, autologous stem–cell transplantation, efficacy, germ cell tumors

Introduction

Testicular cancer is one of the most common solid tumors affecting men between the ages of 15 and 40. Testicular germ cell tumors (TGCT) consist of 95% of all testicular cancers (1). The International Germ Cell Cancer Collaborative Group (IGCCCG) classifies patients with metastatic GCT into good, intermediate, and poor risk disease on the basis of specified prognostic criteria (2). According to IGCCCG, the good risk category represents 60%, intermediate risk represents 26%, and poor risk represents 14% of patients with metastatic GCT. The cure rates in treatment with cisplatin-based front-line combination chemotherapy are found to be 90%, 84%, and 51% in good, intermediate, and poor risk disease, respectively (3). After treatment with first-line chemotherapy, more than 80% of patients with good risk and 50%-60% of patients with poor risk have long-term remissions. Patients with relapse after initial chemotherapy can still be treated with salvage chemotherapy, and the most effective regimen for these patients is not clear. The 5-year overall and disease-free survival rates for patients with poor prognosis are 41% and 48%, respectively, after standard-dose chemotherapy. Salvage therapy alternatives have gained importance in this 20-30% of patients who are refractory or have recurrence after the initial chemotherapy. High-dose

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chemotherapy with autologous stem–cell transplantation (ASCT), mostly performed as tandem transplantation, is an alternative in recurrent or refractory cases (4).

The second-line standard-dose chemotherapy options include etoposide plus ifosfamide plus cisplatin (VIP), vinblastine plus ifosfamide plus cisplatin, or paclitaxel plus ifosfamide plus cisplatin (5,6,7). High-dose chemotherapy (HDCT) followed by bone marrow transplantation was first investigated at the University of Indiana in 1986 (8). In previous series of 184 consecutive patients with recurrent metastatic GCT treated with HDCT and peripheral-blood stem-cell transplantation (PBSCT) between 1996 and 2004, long-term disease-free survival was achieved in 70% of patients in the second-line setting, and in 45% of patients who received a third-line or subsequent regimen (9). Memorial Sloan Kettering Cancer Center pioneered another widely used HDCT regimen, which incorporates paclitaxel and ifosfamide as induction chemotherapy and stem-cell mobilization followed by high-dose carboplatin and etoposide with PBSCT for three cycles (10). The high-dose chemotherapy was mainly based on carboplatin and etoposide as high as 1500 mg/m^2 and 1500 mg/m^2 (11). Other conventional-dose combination chemotherapies may also be used as salvage therapies. They are mostly based on ifosfamide and cisplatin with the addition of a third agent. The third agent may be vinblastine, etoposide, or paclitaxel. Combination chemotherapy with gemcitabine, etoposide and ifosfamide is another salvage therapy (11). There are contradictory statements in the literature about the superiority of ASCT over other salvage chemotherapies. While Pico et al. (12) could not demonstrate a survival benefit of addition of ASCT to VIP/VeIP (vinblastine, ifosfamide, cisplatin) chemotherapies, Lorch et al. (13) showed an improvement in overall survival (OS) when ASCT was performed.

In this study, we aimed to evaluate ASCT data in patients with recurrent or refractory non-seminomatous testicular stem cell.

Materials and Methods

Patients who had metastatic GCT that progressed after one or more standard cisplatin-etoposide-based combination chemotherapy regimens were scanned retrospectively. After the approval of the institutional review board 2018/354, we conducted a retrospective analysis of five patients with recurrent/refractory GCT who received HDCT and PBSCT between 2016 and 2019 in our hospital.

Patients ≥18 years of age at the time of ASCT were enrolled in the study. Patient characteristics and laboratory findings including beta-human chorionic gonadotropin (β-HCG), lactate dehydrogenase (LDH) and alpha-fetoprotein (AFP) were documented. Clinical data were retrieved from clinical records of the patients. All patients had metastatic disease and they were classified as poor or intermediate risk group according to the IGCCC (2).

Treatment Protocol

All patients were treated with BEP (bleomycin 30 mg/day at D1, 8, 15, etoposide 100 mg/m^2/day D1-D5, cisplatin 20 mg/m^2/day D1-D5, every 21 days) as first-line therapy for two or more cycles. TIP (paclitaxel 175 mg/m^2/day D1, ifosfamide 1000 mg/m^2/day D1,2,3, mesna 1000 D1,2,3, cisplatin 60 mg/m^2/day D1, every 12 days) regimen was given as salvage second-line chemotherapy for at least two or more cycles in all patients. Peripheral-blood stem–cells were harvested after stimulating the bone marrow using granulocyte colony-stimulating factor (G-CSF). Stem–cell harvesting was performed by subcutaneous injection of G-CSF at 10 micrograms/kg/day started for 5 days and stem cell collection was performed on the 5th day. Only one patient received TIP before harvesting CD 34+ stem–cell, G-CSF at 10 micrograms/kg/day started on the 5th day of the therapy. ASCT consisted of 700 mg/m^2 of carboplatin in combination with 750 mg/m^2 etoposide on days 1-3 (9). Patients were treated with G-CSF after 5th day of transplantation. Patients received bacterial, viral and fungal prophylaxis according to the following regimen: levofloxacin 500 mg orally once a day, acyclovir 400 mg orally twice a day, fluconazole 400 mg orally once a day. Prophylactic antiemetic drugs were also added to the standard therapy in all patients. Platelet and red blood cells were transfused to maintain 10×10^9/L and 6 g/dL levels, respectively. Patients were treated according to neutropenic fever guidelines. Thrombocyte engraftment was defined as thrombocytes more than 20×10^9/L for three consecutive days and neutrophil engraftment was defined as neutrophil number ≥500×10^9/L.

Response Evaluation

The radiologic response to treatment was evaluated with positron emission tomography-computed tomography (PET/CT) before ASCT and two months after ASCT.

Biochemical evaluation was performed with tumor markers, LDH, β-HCG and AFP that were measured after each course of chemotherapy and approximately two months after ASCT.

Responses were classified as complete response (CR) and partial response (PR), and CR was evaluated with PET/CT of the disease together with tumor markers within normal range. PR was defined as PET/CT of the disease with an evidence of response. PR was divided into PR with negative tumor markers (tumor markers within normal range) and PR with positive tumor markers (high tumor marker levels) (14). Progressive disease (PD) was accepted as more than 25% increase in PET/CT measurable mass or more than 10% increase of elevated tumor markers. Stable disease was classified as a response that did not fit the criteria of PR or PD (15).

Intoxications were evaluated according to World Health Organization criteria.

Results

Patient and Disease Characteristics

We retrospectively analyzed five ASCT in five patients with refractory or recurrent non-seminomatous TGCT. The median age at diagnosis was 36 years (range, 29-58 years). In one patient, tandem transplantation was performed. In four patients, one cycle of ASCT was performed. According to the IGCCC, five patients were classified as intermediate and poor risk group. LDH levels at diagnosis were above the normal limits. Also, AFP and beta-HCG were normal or high at diagnosis. All patients

were at advanced stage with lymph node metastasis and organ metastasis including lung and liver. Five patients had remission, PR, or CR after three or more cycles of BEP. The characteristics are shown in Table 1. TIP regimen was administered as first-line salvage to all patients before ASCT. The median line of chemotherapy before ASCT was seven (range, 5-11). Four patients were transplanted as first salvage therapy and one patient was treated with ASCT as tandem transplantation.

Three patients were treated with radiotherapy before ASCT. Radiotherapy was performed due to pulmonary and/or lymph node metastasis in these patients. The median time to ASCT was 8 months (range, 7-12 months). In four patients, remission (PR or CR) was achieved before ASCT. Only one patient was refractory before ASCT. In the PR group, all patients had normal levels of AFP and beta-HCG.

Table 1. The Characteristics of the patients	
	n %
Age (median, range)	36 (29-58)
IGCCC	
Intermediate	2 (40)
Poor	3 (60)
At The diagnosis (level-median range)	
ß-HCG	4 (80)
AFP	3 (60)
LDH	3 (60)
Lymph node metastasis	5
Organ metastasis	
Lung	2 (40)
Brain	None
Liver	1(20)
Bone	None
Multiple organ	3 (60)
Remission after first line	
PR	4 (80)
CR	1 (20)
Refractory	
Number of chemotherapy linesbefore ASCT (median, range)	7 (5-11)
Response before ASCT	
PR	2 (40)
CR	2 (40)
Refractory	1 (20)
Before ASCT (level-median range)	
Beta HCG	1 (20)
LDH	All patients level were in normal range
AFP	1 (20)
IGCCC: International Germ Cell Consenus Classification, ß-HCG: Beta-human-chorionic gonadotropin, AFP: Alpha Fetoprotein, LDH: Lactate Dehydrogenase, PR: Partial response, CR: Complete response, ASCT: Autologous stem cell transplantation	

The median number of stem cells collected per patient was 5.5×10^6/kg (range, 4.2-8.11×10^6/kg).

Safety and Efficacy

Neutropenic fever episodes were observed in all patients during transplantation procedures, and they were treated according to neutropenic fever guidelines. Only one patient experienced Grade 4 mucositis that required total parenteral nutrition. Table 2 summarizes the toxicities. Transplantation-related mortality was observed in one patient. He died due to uncontrolled infection, sepsis and multiorgan failure during the neutropenic period.

The median number of transfused thrombocyte apheresis and red blood cell was 1 (range, 1-5) and 1 (range, 1-5), respectively. Thrombocyte and neutrophil engraftments were observed at a median of 11 day (range, 10-20) and 10 day (range, 9-20), respectively. Engraftment failure was not documented. During the median 12-month follow-up period, we did not observe any secondary malignancy. After ASCT, all patients were in CR.

Discussion

In the last decade, there have been several reports published on the use of HDCT with ASCT in recurrent/refractory GCTs. These reports are consistent in providing information about the

Table 2. Toxicities associated with autologous stem cell transplantation (n=5)	
Toxicity	**n**
Neutropenia fever (yes/no)	5
Apheresis thrombocyte transfusion (median, range)	1 (1-5)
Erythrocyte transfusion (median, range)	1 (1-5)
Mucositis	
Grade 1/2	4
Grade 3/4	1
Diarrhea	
Grade 1/2	5
Grade 3/4	None
Neuropathy Grade 1	None
Hearing loss Grade 1	5
Requirement for TPN 1	
Requirement for oral nutrition solutions	4
Requirement for intensıve care unit	1
Toxic hepatitis	
Grade 1/2	None
Grade 3/4	None
Renal toxicity	
Grade 1/2	None
Grade 3/4	None
TPN: Total parenteral nutrition	

superiority of HDCT compared to conventional chemotherapy. However, reports have great variability in patient selection, prior treatments, selection of conditioning regimen and variability of the doses within the same regimen. In addition, some reports in the literature describe the effectiveness of a single HDCT cycle, while others use a tandem transplant strategy (9,16,17,18).

In the literature, most of the studies consisted of heterogeneous patient groups with poor or good prognostic factors or including both seminomatous and non-seminomatous (4,15,19,20). In this regard, our study group was relatively homogenous, consisting of only recurrent or refractory primary non-seminomatous TGCTs. We aimed to analyze the efficacy and safety of ASCT in this patient group. Nowadays, cisplatin-based combination chemotherapy will cure 83% of patients with metastatic GCT (21). Ninety percent of patients with IGCCCG good risk disease will achieve cure with primary treatment chemotherapy. Patients with intermediate and poor risk disease have less favorable outcomes and a significant proportion will relapse and require recovery therapy. ASCT can be considered as a relatively safe procedure with only one death related to transplantation (20%).

The most common non-hematologic side effects were mucositis and diarrhea. While prophylactic antiemetic therapy was given in all patients, Grade 3-4 nausea or vomiting was not documented. Among hematologic adverse events, the most common one was neutropenia. In a retrospective study consisting of 364 recurrent metastatic GCT patients treated with ASCT, the treatment-related mortality was found to be 2.4% (nine patients). Infection was the most common cause of treatment-related mortality (19). In another prospective study, the treatment-related mortality was 5.5% in primarily treated patients and 8.3% in recurrent group (4). The vast majority of patients had oropharyngeal mucositis, diarrhea and febrile neutropenia as non-hematologic toxicities, as in our results (4).

In the long-term follow-up, one of the most important adverse side effects were secondary malignancies. There are conflicting data in the literature about secondary malignancies, including acute leukemia. Adra et al. (19) reported that five patients developed secondary leukemia within a range of 17–120 months after transplantation, but no acute leukemia was reported in another study (4). Also, solid tumors were reported in the literature after ASCT (19). In our study, , no secondary malignancy or leukemia was observed during a median follow-up of 12 months.

In a retrospective study of patients with poor or intermediate prognostic factors according to the IGCCC including seminomatous and non-seminomatous subtypes, CR, PR and RD rates were 50%, 36%, and 14%, respectively (19). In another study in 2003, lower response rates and higher mortality rates were reported (21). Yilmaz et al. (22) reported that CR and PR rates were 47.3% and 31.5%, respectively, after ASCT. The median OS and progression-free survival (PFS) were 18 (range, 0-37.4 months) and 7 (range, 0-15months) months, respectively. The estimated 2-year OS was 47.4% and PFS was 35.3%. Although the number of patients (19 patients) in this study was limited, they accepted that ASCT was a safe and effective treatment modality in recurrent and refractory non-seminomatous TGCT with an acceptable OS, PFS and mortality rates.

A wide range of OS (30-66%) and PFS (25-50%) rates were reported in the literature (23,24,25). In a study by Rick et al. (23), TIP chemotherapy followed by one cycle of high-dose carboplatin and etoposide with stem cell transplantation was evaluated. The 3-year survival rates were 30% for OS and 25% for event-free survival. Our estimated rates at 1-year seemed to be similar to the estimated rates at 3-years in this analysis. In a retrospective analysis of 364 patients, 2-year PFS and OS were 60% and 66%, respectively. We think that such changes in these rates may be related to several factors. The first reason is that most of the patients (n=303) in this study were transplanted as a first salvage therapy. Only six of 364 (1.6%) patients were heavily treated. However, in our study, all patients were heavily treated with equal or more than three or more lines of chemotherapy. The second reason is that the cohort of 364 patients consisted of both seminoma and non-seminoma patients, but we only enrolled nonseminoma patients. Finally, the third reason is that 151 of 364 patients were classified as good prognosis according to the IGCCCG. In our study, we only included patients with intermediate and poor prognostic factors.

Several causes have been investigated as possible risk factors affecting PFS and OS. We think that high beta HCG, AFP levels, response of the patient before and after ASCT, LDH levels before ASCT negatively affected the response of the patients. However, in the multivariate analysis, only high LDH levels were associated with poor OS rates. High serum beta HCG levels and AFP levels, initial IGCCCG risk and the time of ASCT (second vs third or later) were possible variables, but it could not be confirmed with other study data (26). We could not demonstrate the statistical difference of variables in multivariate analysis possibly due to small sample size.

There is also conflicting data in the literature about the exact time of the ASCT in GCT. It can be performed as a first-line, second-line therapy or it can be an alternative therapy in heavily treated refractory patients. Although high-survival rates (more than 70%) were documented in the literature when ASCT was performed as first-line therapy in patients with poor prognostic factors (14), the role of ASCT as a first-line treatment in patients with poor prognostic markers is not clear. The International Prognostic Factors Study Group offered data of 1594 patients with GCT, who have progressed after at least three cycles of cisplatin-based chemotherapy. Patients were treated with standard dose or ASCT as first salvage therapy. 2-year PFS (49.6% vs 27.8%; $p<0.001$) and 5-year OS (53.2% vs 40.8%; $p<0.001$) were significantly longer in the ASCT group than in the standard-dose group (26). However, the exact time and the number of ASCT should be determined with Phase III large cohort prospective studies.

Study Limitations

There are some limitations in our study such as small number of patients and retrospective nature of the study. There was also no control group as the study was a retrospective study.

Conclusion

GCTs have an excellent prognosis with platinum-based therapy in recurrent or refractory patients. There are many reports in the literature on the use of HDCT and ASCT in improving the outcome in patients with relapsed GCTS or platinum-refractory disease and patients with poor prognostic features. However, reports have great variability in patient selection, prior treatments, selection of the conditioning regimen and variability of the doses within the same regimen.

In conclusion, HDCT followed by PBSCT is a safe and effective treatment modality in recurrent/refractory non-seminomatous TGCT. Patients with platinum-refractory or recurrent disease and patients with poor prognostic features are primary candidates for HDCT. Treatment with high-dose carboplatin and etoposide was associated with low treatment-related mortality. Nevertheless, final results of ongoing phase III randomized trials are needed to define the role of HDCT as a part of initial treatment of extragonadal GCT with poor prognosis.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Dr. Sadi Konuk Training and Research Hospital Research Committee (no: 2018/354).

Informed Consent: All patients were informed verbally and in writing, and gave written informed consent before the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ş.İ.G., E.G., Design: Ş.İ.G., E.G., Data Collection or Processing: Ş.İ.G., E.G., Analysis or Interpretation: Ş.İ.G., E.G., Literature Search: Ş.İ.G., E.G., Writing: Ş.İ.G., E.G.

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