Retrospective analysis of patients with relapsed or refractory germ cell tumors treated with autologous hematopoietic stem cell transplantation

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ABSTRACT

Aims: Germ cell tumors (GCT) are the most common malignancies, especially in males of 15 to 35 years of age. Tandem autologous hematopoietic stem cell transplantation (AHSCT) with carboplatin and etoposide (CE) has been performed for many years in relapsed and refractory germ cell patients, but information about AHSCT in patients with germ cell tumors is limited. We aimed to demonstrate some real-life data about patients who underwent AHSCT due to germ cell tumors.

Methods: In this retrospective study, medical records of 20 patients who received CE as high-dose chemotherapy for AHSCT betweeen November 2016 and April 2018 were reviewed. Response rates at 12th month and toxicity profiles were evaluated.

Results: A complete response was obtained in 15% (n=3) and a partial response was obtained in 20% (n=4) of the cases after AHSCT. The survival rate during AHSCT was calculated as 95%. When the progression-free survival time of the patients was examined, the median recurrence time was 6 months (95% CI: 5.08-6.91). The rate of recurrence was 57% in 6 months. Neutropenia, thrombocytopenia and anemia were observed during AHSCT in all patients.

Conclusions: High dose chemotherapy as CE in AHSCT is a safe and effective treatment option in relapsed refractory GCT with an acceptable PFS and mortality rate. Also, high-dose CE was associated with low treatment-related mortality and reasonable side effects in patients with poor prognosis.

Introduction

Germ-cell tumors (GCT) are one of the most common cancers in men between 15 and 35 years of age (1). Patients with metastatic GCT are curable in spite of the metastatic disease (2). The International Germ Cell Cancer Collaborative Group (IGCCCG) has classified metastatic GCT patients into good, intermediate, and poor risk disease according to the specified prognostic criteria (3).

Using cisplatin-based front-line combination chemotherapy, cure rates for good, intermediate, and poor risk disease were approximately 90%, 80%, and 50%, respectively (4). Particularly after the discovery of cisplatin-based chemotherapies, the disease can be cured even if it presents as a metastatic disease by poor prognostic risk factors according to the IGCCCG (5,6).

However, 10 – 20% of these metastatic patients with poor prognosis according to the IGCCC, cannot be cured by standard cisplatin-based chemotherapy (7). For men who relapse within two years after initial (or first-line) chemotherapy, one of these options as standard-dose cisplatin-based chemotherapy, high-dose chemotherapy (HDCT) with autologous hematopoietic stem cell transplantation (AHSCT), or enrollment on a clinical trial are suggested as a salvage treatment. (8). It has been suggested that AHSCT was a good option in patients who were relapsed or refractory to first-line cisplatin-based chemotherapies. Also favorable results were reported when it was used as third-line or later therapy (9).

Also, AHSCT is associated with serious hematologic or non-hematologic toxicities and treatment-related mortalities (10). The high-dose chemotherapy as carboplatin and etoposide is commonly used for AHSCT (11). There is no randomized prospective study of relapsed or refractory GCT in the literature. Therefore, the data about relapsed or refractory GCT are based on retrospective real-life data or meta-analyses.

In this study, we aimed to evaluate the data of AHSCT in patients with relapsed or refractory GCT who received high dose carboplatin and etoposide as HDCT regimen.

Methods

20 patients diagnosed as GCT between November 2016 April 2018 were retrospectively detected from the database of On-

cology Clinics in Gulhane Training and Research Hospital. The study was approved by Gulhane Training and Reseach Hospital Ethics Committee. All of the patients were older than 18 years old. The characteristics of the patients, laboratory findings including beta-human chorionic gonadotropin (β-HCG), lactate dehydrogenase (LDH), and alpha-fetoprotein (AFP) and toxicity profiles of the chemotherapy were documented. All the patients received more than two lines of chemotherapy and they had relapsed or refractory disease after the cisplatin-based chemotherapy.

All the patients underwent chemotherapy regimen as BEP (bleomycin 30 mg/day at D1, 8, 15, etoposide 100 mg/m2/day D1-D5, cisplatin 20 mg/m2/day D1-D5, every 21 days) regimen as first-line therapy for at least three cycles. All the patients received salvage chemotherapy mostly as TIP (paclitaxel 175 mg/m2/day D1, ifosfamide 1000 mg/m2/day D1, 2, 3, mesna 1000 D1, 2, 3, cisplatin 60 mg/m2/day D1, every 12 days) regimen at least three cycles in all patients. Stem cells were collected it by performing subcutaneous injection of granulocyte colony-stimulating factor (G-CSF) of 10 microgram/kg/day on the 5th day of the therapy. HDCT regimen for AHSCT consisted of 700 mg/m2 of carboplatin in combination with 750 mg/m2 etoposide on days 1–3 (12). The patients rested on the days 4 and 5. On the day 6 autologous stem cell was infused to the patients. Patients were treated with G-CSF after the infusion of autologous stem cells. Thrombocyte engraftment was described as thrombocytes more than 20 × 109/l on 3 sequential days and neutrophil engraftment was described as neutrophil number ≥500 × 109/l.

The primary endpoint was to asses the 1-year PFS of the patients. Secondary endpoints were to identify clinical factors prognostic for disease progression after AHSCT and to define the safety and the toxicity profile of the HDCT and AHSCT.

Statistical Analysis

The Statistical Package for Social Science SPSS for Window Version 22.00 (SPSS Inc., Chicago, IL., USA) was used to conduct the statistical analyses. For the descriptive statistics, the discontinuous variables were demonstrated as median and IQR (interquartile range 25% and 75% interquartile range); continuous variables were demonstrated as the mean ± standard deviation or median (minimum, maximum) as appropriate. Numbers and % are used in the representation of categorical variables. Normality of the data was evaluated with the Shapiro Wilk tests. The relationship of the continuous variables between the groups was assessed by Spearman Correlation analysis. The Kaplan-Meier method was used for the survival curves of the cases. Statistical significance was accepted at 95% confidence interval, $p \leq 0.05$ level.

Results

In this study, 20 GCT patients underwent AHSCT with a mean age of 32.75 ± 7.58 years, and almost all (n = 19, 95%) were male. Most of the primary tumor sites were right or left testis (n = 18, 90%). 2 of them originated from extratesticular tissue. The Histological examination revealed that more than half of the tumors (n = 12, 60%) were mixed GCT. The majority of patients had advanced cancer as stage 3A (n = 17, 85%) at the time of diagnosis. Approximately half of the cases (n = 9, 45%) were found to have metastasis to the lymph nodes and one other organ (liver, lung or kidney). Lymphovascular invasion was detected in 75% of the cases (n = 15). All of the patients received chemotherapy before AHSCT. The risk classification of the majority of the cases according to International Germ Cell Cancer Collaboration Group (IGCCCG) was stage 3C (n = 12, 60%). Mean platinum-based treatment refractory period was 6.25 ± 2.66 weeks. The mean duration of relapse after platinum-based treatment until the AHSCT was calculated as 70.55 ± 167.24 weeks (Table 1).

Table 1. The demographic and disease-related characteristics of the patients

Features	n (%)	Mean ± SD	Min-Max
Age (years)	20 (100)	32.75±7.58	21-56
Gender			
Male	19 (95)		
Female	1 (5)		
Primary tumor location			
Testicular (right or left)	18 (90)		
Other (Mediastinal and abdominal)	2 (2)		
Histopathology			
Mix germ cell tumor	12 (60)		
Yolk sac tumor	2 (10)		
Embrional carsinom	2 (10)		
Seminoma	2 (10)		
Teratoma	1 (5)		
Choriocarcinoma	1 (5)		
Stage at the Time of Diagnosis			
≥3A	17 (85)		
2B	2 (10)		
2C	1 (5)		
Site of metastases			
No metastases	1 (5)		
Lymph Node and 1 other organ	9 (45)		
Lymph Node and 2 other organs	4 (20)		
Lymph Node	2 (10)		
Other organs	2 (10)		
Lymphovascular invasion			
Present	15 (75)		
Absent	5 (25)		
IGCCCG Risk Group			
1S	1 (5)		
2B	3 (15)		
2C	1 (5)		
3A	1 (5)		
3B	2 (5)		
3C	12 (60)		
Number of lines before CE treatment			
2 lines	8 (40)		
3 lines	5 (25)		
4 lines	7 (35)		
Refractory period after platinum based treatment (weeks)	20 (100)	6.25 ± 2.66	1-8
The duration of relapse after platinum-based treatment (weeks)	20 (100)	70.55 ±167.25	12.00-572.00

IGCCCG = International Germ Cell Cancer Collaboration Group
CE: Carboplatin, etoposide

Table 2. Descriptive characteristics of the patients during AHSCT and follow-up process

Features	n (%)	Median	IQR
Amount of stem cells given 10^6/L	20 (100)	2.72	2.30-3.71
Engrafment time (days)	20 (100)	12	9.00-12.00
Pre-AHSCT AFP mcg/L	20 (100)	7	5.12-52.50
Post-AHSCT AFP mcg/L	20 (100)	6.50	3.15-56.00
Pre-AHSCT β-HCG mIU/ml	20 (100)	0.5	0.50-94.10
Post-AHSCT β-HCG mIU/ml	20 (100)	0.55	0.50-18.66
Pre-AHSCT LDH IU/L	20 (100)	186.50	172.75-207.00
Post-AHSCT LDH IU/L	20 (100)	190.00	185.50-198.00
The response of the patients after AHSCT			
Stable response	7 (45)		
Complete response	3 (15)		
Partial response	4 (20)		
Progressive disease	4 (20)		
Exitus	2 (10)		
Surgical resection after AHSCT			
Yes	3 (15)		
No	17 (85)		
The best response site after AHSCT			
Lung	4 (20)		
Liver	1 (5)		
LN	8 (40)		
Duration of recurrence of disease after AHSCT (months)	11(55)	4.92	1.92-6.00
Chemotherapy after AHSCT			
Yes	7 (35)		
No	12 (60)		
Febril Neutropenia			
Grade 2	7 (35)		
Grade 3	12 (60)		
Grade 4	1 (5)		
Hgb <10g/dl		9	8.92-9.37
Thrombocyte <20000/mm^3		4000	3250-5000
Bleeding diatesis			
Yes	1 (5)		
No	19 (95)		
Nausea,vomiting			
No	4 (20)		
Grade 1	2 (10)		
Grade 2	8 (40)		
Grade 3	6 (30)		
Diarrhea			
No	5 (25)		
Grade 1	3 (15)		
Grade 2	10 (50)		
Grade 3	2 (10)		
Ileus			
Yes	6 (30)		
No	14 (70)		
Time from diagnosis to AHSCT /month		20.31	11.49-34.48
The duration of follow-up after AHSCT /month		5.21	3.76-10.61
The duration of follow-up after diagnosis /month		26.40	18.54-43.96

AFP: Alpha fetoprotein; AHSCT: Autologous hematopoietic stem cell transplantation; β-HCG: Beta human chorionic gonadotropic hormone; Hgb: Hemoglabin; IQR = interquartile range 25% and 75% interquartile range; LDH: Lactate dehydrogenase

In this study, the median amount of stem cell given was $2.72x10^6$ (2.30-3.71). The average engraftment time was 12 days (9.00-12.00). The median AFP, β-HCG and LDH values before treatment were 7 mcg/L (5.12-52.50), 0.50 mIU/ml (0.50-94.10), and 186.50 U/L (172.75-207.00), respectively. The median AFP, β-HCG and LDH values after treatment were 6.5 mcg/L (3.15-56.00), 0.55 mIU/ml (0.50-18.66), and 190.00 (185.50-198.00), respectively. Complete response was obtained in 15% (n=3) and partial response was obtained in 20% (n=4) of the cases after AHSCT. 5% (n=1) of the patients lost their lives during AHSCT due to progressive disease and bleeding and another patient died within 12 months after treatment. In the study, 85% of the cases (n=17) did not undergo surgical resection after AHSCT. The best response region after AHSCT was lymph nodes (n=8, 40%). The median recurrence time of the disease after AHSCT was 4.92 (1.92-6.00) months and 35% (n=7) of the patients received chemotherapy treatment after AHSCT. In all of the patients, neutropenia, thrombocytopenia, and hemoglobin (Hgb) level less than 10 g/dl were observed during AHSCT. The median Hgb value was 9 (8.92-9.37) g/dl. The mean platelet count of the patients during treatment was 4000 (3250-5000)/mm^3. Neurotoxicity was observed in all cases and 55% (n=11) were grade 1. Ototoxicity was observed in 45% (n=9) of cases during AHSCT and bleeding occurred in 1 patient (5%). Additionally, in 70% (n=14) of the patients had second and third-degree nausea, vomiting and 50% (n=10) of patients had second-degree diarrhea. Additionally, ileus was observed in 30% (n=6) of the patients and renal failure was observed in 15%(n=3) of the patients (Table 2).

The associations among AFP, β-HCG, LDH values of the patients before and after AHSCT and the recurrence time of the disease were examined. There were significant correlations between the pre-treatment and post-treatment measurementsas shown in the Table 3.

Survival analysis of the patients

During the study, one patient died during AHSCT due to progressive disease and bleeding. The survival rate during AHSCT was calculated as 95%. The survival rates of the patients after the first year were not significant because of the low number of patients under follow-up.

When the progression-free survival time of the patients was examined, the median recurrence time was 6 months (95% CI, 5.08-6.91). The recurrence rate was 57% in 6 months. The first-year recurrence rate of patients included in the study was not significant because the number of patients under observation was less than five (Figure 1).

Discussion

As far as we know, there are some studies about AHSCT in patients with relapsed or refractory GCT. According to the literature, cisplatin-based combination chemotherapy cures approximately 80% of patients with metastatic GCT (13). Patients with poor-risk disease have less favorable outcomes and a significant number should relapse and require salvage therapy (14). In the literature mostly all of the patients received one or two cycles chemotherapy. In our study, 60% of patients received 3 or 4 lines chemotherapy. In this respect, it is a rare condition. Our aim is to analyze the efficacy and safety of AHSCT in patients with mostly poor risk according to the IGCCCG.

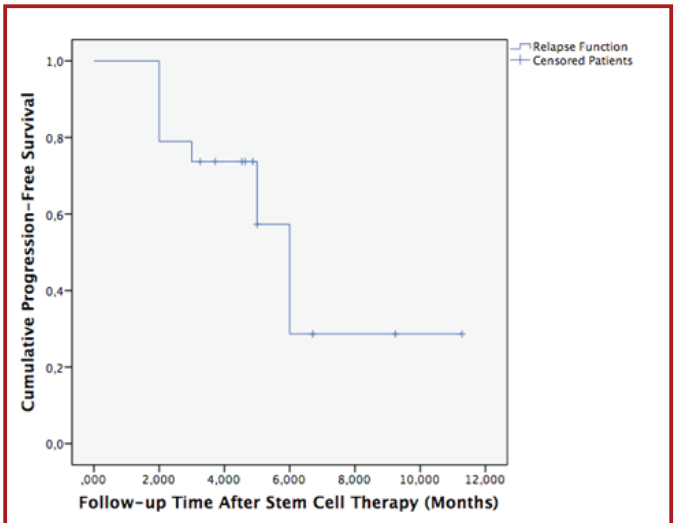

Figure 1. Kaplan-Meier Curve of progression-free survival of the patients with AHSCT

According to the literature, most of the studies consist non-homogenous groups like our study. Mohr M et al. presented in a retrospective analysis of patients with poor or intermediate prognostic factors according to the IGCCCG with GCT CR, PR, and refractory disease were approximately 50%, 35%, and 15%, respectively (15). Additionally, Vaena et al. reported lower response rates with higher mortality rates (8). In our study, in the patient group stable disease, CR, PR, and progressive disease were approximately 45%, 15%, 20 and 20%, respectively. These results were similar to the literature.

Table 3. The correlations among AFP, LDH values of the patients before and after AHSCT and the recurrence time of the disease

	BA AFP	AA AFP	BA β-HCG	AA β-HCG	BA LDH	AA LDH	Relapse time (Months)
BA AFP	1						
AA AFP	0.809**	1					
BA β-HCG	-0.180	-0.222	1				
AA β-HCG	0.024	0.121	0.814**	1			
BA LDH	0.170	0.001	0.067	0.057	1		
AA LDH	0.404	0.399	0.313	0.346	0.540*	1	
Relapse time (Months)	0.300	0.080	-0.491*	-0.460*	0.034	-0.472*	1

AA= After hematopoietic autologous stem cell transplantation, AFP: Alfa feto protein, BA=Before autologous hematopoietic stem cell transplantation, β-HCG: Beta human chorionic gonadotropin, LDH: Lactate dehidrogenase
*p<0.05 **p<0.001

According to the literature ranges of OS (30%–66%) and PFS (25%–50%) rates were reported heterogeneously (16-17). Rick et al. presented the survival rates at 3 years 30% for OS and 25% for event-free survival (18). In our study, in the patient group, PFS was 6 months and the recurrence rate was 57%. The OS could not be calculated due to the short follow-up period. In spite of the fact that this study included a high proportion of patients with poor prognostic factors (stage 3C 60%) at the initiation of AHSCT, the PFS seems superior compared with previous trials evaluating standard-dose salvage chemotherapy.

Many factors were analyzed as possible risk factors affecting relapse time. High serum β-HCG levels and AFP levels, initial IGCCCG risk were represented variables affecting the survival time (19). We found that high levels before and after AHSCT therapy, LDH levels before AHSCT were negatively affected relapse time in the correlation analysis. Our finding may reveal a negative effect of LDH on relapse time. Further investigations with more participants are needed in this area.

Adra et al. presented the treatment-related mortality found to be 2.4% in AHSCT patients (19). Hege et al. also presented treatment-related mortality 5.5% (20). The most common cause of treatment-related mortality was demonstrated as infectious diseases. In the current study treatment-related death was 5% similar to the literature. Eventually, by these results, we think AHSCT as a relatively safe procedure with only 5% death related to transplantation. The most common nonhematologic side effects were vomiting, mucositis and diarrhea as reported before (21). In our study of hematologic adverse events, the most common side effects were neutropenia and thrombocytopenia. Also, these are the most common causes of treatment-related mortality similar to the literature.

Limitations of our study include the small sample size of patients and the heterogeneous patient population with regard to indications for AHSCT and relatively short follow up time. Additionally, it was a retrospective study and there was not a control group. Strengths of the study include new findings that are related to LDH and relapse time. Also, the study consists of a report of rare case series who underwent AHSCT due to relapsed or refractory GCT.

In conclusion, HDCT as carboplatin and etoposide in AHSCT is a safe and effective treatment option in relapsed refractory GCT with an acceptable PFS and mortality rate. Also, high-dose carboplatin and etoposide was associated with low treatment-related mortality and reasonable side effects in patients with poor prognosis. Future prospective randomized studies should reveal more reasonable and effective survival results.

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Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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