

Genitourinary Cancer

Autologous Stem Cell Transplantation in Testicular Germ Cell Tumor—Preliminary Experience from a Single Center

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Abstract



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Keywords

- ▶ relapsed germ cell tumor
- ▶ autologous stem cell transplant
- ▶ high-dose chemotherapy
- ▶ high-dose carboplatin and etoposide
- ▶ long-term survival in relapsed GCT

Background Germ cell tumor (GCT) of the testis is one of the highly curable solid organ malignancies. Those who experience relapse after platinum-based chemotherapy can be salvaged with systemic therapy followed by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT). Complete remission can be obtained in approximately 50 to 60% of patients treated with HDCT. Our experience reports the efficacy and safety of HDCT followed by ASCT in relapsed GCT.

Methods Analysis of patient records (2012–2019) showed that three patients had received HDCT and ASCT.

Results All the three patients were treated with BEP (bleomycin, etoposide, and cisplatin) as first-line therapy. HDCT was done in Case 1 after third-line salvage and in other two patients after second-line salvage chemotherapies. High-dose carboplatin and etoposide were used as conditioning regimen. Granulocyte colony-stimulating factor was used for the mobilization of stem cells. After ASCT, complete remission was documented in all the patients. All were alive and disease-free till the last follow-up. Grade 3/4 toxicities including myelosuppression, diarrhea, and mucositis were observed in all three patients.

Conclusion This is the first report from India on HDCT with ASCT in GCT. HDCT/ASCT seems to be feasible, safe, and effective in relapsed testicular GCTs.

Introduction

Germ cell tumor (GCT) of the testis is one of the highly curable solid organ malignancies despite the presence of disseminated disease. Testicular cancer commonly affects males between the ages of 15 and 40 years. They are highly sensitive to platinum-based chemotherapy. Since the use of cisplatin, the cure rates have reached 90 to 95%. None of the other advanced solid tumor malignancies have such high survival. The 5-year disease-free survival of patients

with good, intermediate, and poor-risk disease are 89, 75, and 41%, respectively.^{1,2} Cure rates are still lower in relapsed and refractory patients. Those who experience relapse after platinum-based chemotherapy can be salvaged with another course of platinum-based therapy followed by high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT).³

The outcomes of the HDCT may vary from patient to patient. There are two prognostic scoring systems, namely, the Lorch–Beyer score (LBS) and Einhorn score, of which

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the former one is widely accepted. The benefit of HDCT reduces with increasing risk with both the scoring systems. In the International Prognostic Factors Study Group analysis, patients who had progressed after first-line cisplatin-based chemotherapy had a longer 2-year progression-free survival (PFS) (49.6% vs. 27.8%) and 3-year overall survival (53.2% vs. 40.8%) in the HDCT group compared with the standard-dose chemotherapy group.⁴ The LBS was devised based on this report and four risk groups were identified. The benefit was seen across all risk categories but the magnitude of benefit in survival was high in the very low-risk category (> 70%) compared with the high-risk category (10–15%).^{4,5} In another report, retrospective analysis of patients who were refractory or received two or more lines of chemotherapy, and a scoring system was devised with three risk groups. This study also showed that in patients with intermediate-risk and high-risk score, the 2-year PFS were 60 and 40%, respectively.⁶

With the availability of newer drugs like plerixafor which increases stem cell mobilization and advances in supportive care following HDCT, remission can be achieved in approximately 50 to 60% of relapsed patients treated with HDCT.⁷ There is no published literature from India in this setting. Hence, we present the preliminary experience from our center.

Methods

Data of adult patients with GCT of the testis, who had undergone stem cell transplant from January 2012 to December 2019, were captured from the patient records.

Results

A total of three patients underwent HDCT and ASCT for relapsed GCT during the study period. Baseline patient and treatment characteristics are shown in ▶Table 1. Granulocyte colony-stimulating factor was used for the mobilization of

stem cells. The conditioning regimen used for HDCT was carboplatin at area under the curve 7 daily and etoposide 750 mg/m² daily for 3 days (days –4, –3, –2). The toxicity following HDCT and ASCT are shown in ▶Table 2. The data were censored up to December 2019.

Case 1

A 24-year-old male patient presented with left testicular swelling and back pain. He underwent left high inguinal orchiectomy and was diagnosed as a non-seminomatous GCT of the testis (NSGCT) – stage IIIB with International Germ Cell Cancer Collaborative Group (IGCCCG) classification good risk. He received three cycles of bleomycin, etoposide, and cisplatin (BEP). His markers normalized after two cycles. Following chemotherapy, computerized tomography (CT) scan showed residual retroperitoneal and mediastinal lymphadenopathy. Hence, he underwent retroperitoneal lymph node dissection (RPLND) which had no viable tumor in the specimen. He was kept on follow-up. After 4 months, there was a rise in β -human chorionic gonadotropin (β -HCG). CT scan had shown left para-aortic lymph nodal mass. He received four cycles of vinblastine, ifosfamide, and cisplatin (VeIP) chemotherapy regimen and had a complete response and hence was kept under follow-up. After 5 months, he had a recurrence again in the left para-aortic and left suprarenal region with rising alpha-fetoprotein (AFP) and β -HCG. He received two cycles of irinotecan, paclitaxel, and oxaliplatin (IPO) regimen^{8,9} following which his tumor markers normalized and then he underwent excision of the left suprarenal nodal mass and left adrenalectomy. The histopathology was suggestive of a mixed GCT. He belonged to a very low-risk category as per the LBS. He received high-dose carboplatin and etoposide (HD-CE) followed by ASCT. The patient had febrile neutropenia and grade 4 mucositis during the procedure which was managed conservatively with crystalloids, total parental nutrition, and intravenous antibiotics. Neutrophil and

Table 1 Patient characteristics

	Case 1	Case 2	Case 3
Age at diagnosis (in y)	24	31	31
Age at transplant (in y)	27	33	33
IGCCCG risk	Good	Poor	Intermediate
Prior regimens chemotherapy before ASCT	3	2	2
Einhorn risk score	Intermediate	High	Intermediate
Lorch–Beyer risk score	Very low risk	High	Intermediate
Conditioning regimen	HD-CE	HD-CE	HD-CE
Mobilization regimen	G-CSF	G-CSF	G-CSF
No of days of collection	1	1	1
CD 34 cells ($\times 10^6$ cells/kg)	3.6	5.5	4.06
Day of engraftment neutrophil/platelets (in d)	14/ 17	19/ 22	11/ 17
DFS (mo) till last follow-up	39	22	33

Abbreviations: ASCT, autologous stem cell transplantation; DFS, disease-free survival; G-CSF, granulocyte colony-stimulating factor; HD-CE, high-dose carboplatin and etoposide; IGCCCG, International Germ Cell Cancer Collaborative Group.

Table 2 Toxicity following high-dose chemotherapy (HDCT)

Toxicities	Case 1	Case 2	Case 3
Neutropenia	Grade 4	Grade 4	Grade 4
Febrile neutropenia	Yes	Yes	Yes
Thrombocytopenia	Grade 4	Grade 4	Grade 4
Anemia	Grade 3	Grade 4	Grade 1
Diarrhea	Nil	Grade 2	Grade 3
Vomiting	Grade 1	Grade 2	Grade 2
Mucositis	Grade 3	Grade 3	Grade 3
Neurotoxicity	Nil	Nil ^a	Nil
Ototoxicity	Nil	Nil	Nil
Nephrotoxicity	Nil	Nil	Nil
Hepatotoxicity	Nil	Nil	Nil
Pulmonary toxicity	nil	nil	Nil
Secondary cancers	Nil	Nil	Nil

^aPreexisting neuropathy was not aggravated.

platelet engraftments were observed on the 14th and 17th day, respectively. He is on active follow-up without disease for the past 39 months.

Case 2

A 31-year-old male patient presented with left testicular swelling and underwent a high inguinal orchiectomy. He was diagnosed as NSGCT stage IIIB with IGCCCG intermediate risk. He received four cycles of BEP and then he underwent RPLND followed by staged left lung metastasectomy. There was no viable tumor and he was kept on follow-up. After 1 month, he had rising markers and was found to have a recurrence in the liver and mediastinal lymph nodes. Following two cycles of second-line IPO chemotherapy, he developed grade 3 peripheral neuropathy and hence the chemotherapy was changed and two more cycles of etoposide, ifosfamide, and cisplatin (VIP) regimen were administered. Evaluation by CT scans showed the persistence of mediastinal lymph nodes with few calcifications. Markers were normal. He belonged to the high-risk category as per LBS. Subsequently, he underwent HDCT (HD-CE regimen) and ASCT. He developed grade 2 chemotherapy-induced nausea and vomiting (CINV), grade 2 diarrhea, and grade 3 mucositis which were managed conservatively with appropriate supportive care. Neutrophil and platelet engraftments were observed on the 19th and 22nd day, respectively. He is on active follow-up without disease for the past 22 months.

Case 3

A 31-year-old male patient presented with right testicular swelling and underwent high inguinal orchiectomy. He was diagnosed as NSGCT stage IIIB with IGCCCG intermediate risk. He received four cycles of BEP and had residual disease in the retroperitoneum with normal markers and hence underwent RPLND. There was no viable tumor. The AFP levels

started rising serially after 6 months without detectable disease on imaging. He received one cycle of IPO as second-line regimen. He developed grade 3 diarrhea and hence further therapy changed to paclitaxel, ifosfamide, and cisplatin (TIP) regimen and he received three cycles. CT scan showed no evidence of any disease with normal markers. He belonged to the intermediate-risk category as per LBS. He received HDCT (HD-CE regimen) and ASCT. The patient developed grade 2 CINV, grade 3 diarrhea, electrolyte disturbances, febrile neutropenia, and grade 3 mucositis which were managed conservatively with appropriate supportive care. Neutrophil and platelet engraftments were observed on the 11th and 17th day, respectively. He is on active follow-up without disease for the past 33 months.

Discussion

Although GCT is much less common in India,¹⁰ the proportion of patients with poor-risk disease at presentation is higher and their overall survival is only around 45%. Therefore, there will be a cohort of patients who would benefit from more intensive treatment following a recurrence.¹¹ However, to our knowledge, there are no published reports from India evaluating HDCT and ASCT in this setting.

Patients with recurrent GCT may still be cured in more than 50% of cases with salvage chemotherapy while it is only 10 to 20% among the high-risk group according to the LBS score. Usage of HDCT and ASCT as consolidation after initial first-line therapy in randomized control trials (RCTs) for patients with poor prognostic factors did not demonstrate better outcomes.^{12,13} The exact role and initiation of HDCT and ASCT vary between centers. It is either performed following chemotherapy at first^{14,15} or later recurrences.^{6,16} There is no RCT to substantiate the benefit of HDCT compared with chemotherapy alone in patients with recurrent disease. The ongoing RCT (TIGER trial) is designed to address the benefit of HDCT in patients following the first recurrence after chemotherapy.^{17,18}

The patients in this series belonged to three different risk groups as per LBS (very low, intermediate, and high risk). All are disease-free till now with good quality of life and regular follow-up. Although the follow-up of the patients was not long enough, no second malignancies were detected.

Different regimens such as high-dose VIP¹³; high-dose carboplatin, etoposide, and cyclophosphamide (HD-CEC)¹²; high dose carboplatin, etoposide, and thiotepa (HD-CET)¹⁹; high-dose ifosfamide, carboplatin, and etoposide (HD-ICE)²⁰; and high-dose carboplatin, etoposide (HD-CE) have been employed in various studies. Though there are no direct comparisons between these regimens, the outcomes have been similar. The most common HD-CE regimen was used in all the three patients.^{5,21,22}

HDCT/ASCT is associated with various hematologic or nonhematologic morbidities. The common toxicities are myelosuppression, mucositis, nausea, vomiting, diarrhea, peripheral neuropathy, and otologic abnormalities. Treatment-related mortality reported in the literature is approximately 3 to 8% which was primarily due to renal, hepatic, and pulmonary toxicity.⁶ Second malignancies especially acute leukemia had been reported in < 2% cases.²³⁻²⁵ Our study had similar toxicities as described in the literature with no treatment-related mortality or second malignancies.

It is challenging to treat patients with HDCT and ASCT in resource-constrained settings like India. Lack of financial support, lack of centers with the facility to perform HDCT with ASCT, lack of cryopreservation facility for tandem transplants, noncompliance to treatment, and poor stem cell mobilization due to prior multiple lines to treatment are the potential constraints in offering HDCT to GCT patients. Hence, very few centers routinely do HDCT for GCTs, and consequently, there is no published experience from India in this context.

Despite having only three patients with recurrent GCT, our series has shown an excellent survival (100%) with HDCT and ASCT. The proportion of similar patients who were eligible for HDCT and ASCT during the period was not recorded and contributes to selection bias.

Conclusion

Though the number of patients reported in this series is limited, HDCT with ASCT seems to be safe and effective in relapsed/refractory testicular GCT with durable complete remission achieved in all three patients. Prospective pooled data of all the relapsed GCT patients from multiple centers would need to be analyzed to further ascertain the exact number of patients who would require HDCT after salvage chemotherapy in India.

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Conflict of Interest

None of the authors have any relevant conflicts of interest to declare.

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