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TANDEM HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION IN GERM CELL TUMOR— EXPERIENCE FROM A TERTIARY CARE CENTER FROM SOUTH INDIA

Oncology

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ABSTRACT

Background: The use of high-dose chemotherapy with autologous hematopoietic cell transplantation is well established as a potentially curative approach in patients with relapsed or refractory disease in testicular Germ cell tumours after initial cisplatin-based chemotherapy. The use of tandem transplant with high-dose carboplatin and etoposide conditioning has been a tried and is a feasible option in relapse setting.Overall, HDCT and Autologous stem cell transplant can offer cure rates of up to 60% in the relapsed GCT setting. Data on Tandem HDCT and ASCT is very limited in Indian subcontinent. Hence we report our experience with respect to safety, efficacy and tolerability, survival outcomes of HDCT/ ASCT in patients with relapsed GCT. **Methods:** Patients who were diagnosed with relapsed or refractory Germ cell tumours and underwent Tandem HDCT and ASCT were analysed from patient records from 2013 to 2020. **Results:** Both our patients received BEP (bleomycin, etoposide, and cisplatin) as first-line therapy. HDCT was done after 2nd line salvage chemotherapies in both patients. Both patients were treated with 2 courses of High-dose carboplatin (700mg/m2) and etoposide(750mg/m2) as conditioning regimen followed by stem cell rescue(CD34+ stem cells yield – 5 to 6x106 cells/kg) 3-4 weeks apart. Grade ¾ toxicities including myelosuppression, diarrhea, mucositis were observed in both patients. After ASCT both patients were followed up with imaging and serial monitoring of tumour markers. 1st patient died 3 months after ASCT due to disease relapse and our 2nd patient was disease free for 22 months, after which he developed progressive disease in brain and succumbed to disease. **Conclusion:** This is the first report from India on tandem HDCT with ACST in relapsed GCTs. Tandem HDCT/ASCT seems to be safe and feasible option in relapsed/ refractory testicular GCT's.

KEYWORDS

Testis , Germ cell tumour, relapse, Tandem transplant

INTRODUCTION

Testicular cancer accounts for 1-2% of all malignancies in men .Ninety five percent of all testicular cancers are germ cell tumours. Among these, about 50% are non –seminomatous germ cell tumours (NSGCT). The age standardized incidence rate of testicular cancer in India is 0.5 per 100,000 population, while its 6.7 and 5.6 per 100,000 population for Europe and United states respectively[1] .Globally, India has the lowest incidence, hence Indian data on testicular germ cell tumours are sparse. Testicular cancer affects males between ages of 15 to 40 yrs. They are highly sensitive to platinum based chemotherapy. The current standard of care in first line therapy is combination chemotherapy with four cycles of cisplatin, etoposide and bleomycin(BEP). The International Germ Cell Consensus (IGCC) Classification distinguishes patients with non-seminomatous germ cell tumours (NSGCT) with a good, intermediate or poor prognosis, with a reported 5-year overall survival of 92%, 80% and 48%, respectively[2] . Despite high rates of platinum sensitivity, upto 40% of men with intermediate or poor risk advanced GCT will require salvage treatment[3]. The prognosis for relapsed / refractory male GCTs is not very good and seems poor, and such patients can be offered treatment options with 2nd and 3rd line chemotherapy with an intent to cure.The current standard of care for salvage of relapsed / refractory GCT is either conventional dose chemotherapy consisting of cisplatin, ifosfamide, vinblastine, paclitaxel or etoposide or high dose chemotherapy (HDCT) with autologous hematopoietic stem cell transplantation (ASCT). In 1980's high dose combination chemotherapy followed by autologous stem cell rescue was found to be effective in treatment of relapsed hematologic malignancies.

Investigators at Indiana university administered HDCT with Carboplatin plus Etoposide in 1986 in patients with relapsed GCTs, and that experience resulted in complete remission rates of 63% at 2 years and long-term disease-free survival achieved was 70% in second-line setting, and 45% in third-line or later regimen[4] . Furthermore the study enrolled another 180 patients, all of whom received tandem HDCT with carboplatin plus etoposide followed by PBSC rescue and 2-year progression-free survival (PFS) was 63% in patients who received 2nd line therapy and 49% in third line or later therapy [5].Currently, there are no randomized data to validate the optimal sequencing of these approaches and the number of transplantations (single transplant [ST] versus tandem transplant [TT] versus triple transplant) in the salvage setting.

However the largest study reported from North America compared outcomes in patient who received single versus tandem transplants, which resulted in superior outcomes in terms of PFS and OS for Tandem transplants than single transplant[6].

Indian data on relapsed GCTs is limited due to its low incidence. There is no Indian literature on Tandem HDCT and ASCT to our knowledge. Hence we report our experience from a tertiary care centre in treating patients with relapsed GCTs with Tandem HDCT and stem cell rescue.

METHODS:

All patients profiles from January 2013 to December 2021, who underwent tandem HDCT followed by ASCT were retrieved from patients records .

RESULTS :

A total of 2 patients were analyzed from patients records from 2013 to 2021 who underwent tandem HDCT and ASCT for relapsed GCTs. Baseline patient and treatment related characteristics are recorded in table 1. HDCT was offered after 2nd line salvage chemotherapies in both patients. Both patients were treated with 2 courses of High-dose carboplatin (700mg/m2) and etoposide (750mg/m2) as conditioning regimen followed by stem cell rescue(CD34+ stem cells yield – 5 to $6x10^6$cells/kg) 3-4 weeks apart .

Grade ¾ toxicities including myelosuppression, diarrhea, mucositis were observed in both patients and are shown in table 2 .

1st patient died 3 months after ASCT due to disease relapse and our 2nd patient was disease free for 22 months, after which he developed progressive disease in brain and succumbed to disease

Case 1

A 24yr old presented with complaints of left testicular swelling. He underwent left high inguinal orchidectomy. Post operative histopathology was suggestive of choriocarcinoma, biphasic .Post operative Beta HCG was 102,330 IU/ml . CT thorax was suggestive multiple enhancing nodular lesions in bilateral lung fields .Hence he was diagnosed with non-seminomatous GCT of the testis (NSGCT) – stage IIIC with International Germ Cell Cancer Collaborative Group (IGCCCG) classification poor risk. He received 2 cycles of bleomycin / etoposide / cisplatin (BEP) followed by etoposide / cisplatin (EP) as bleomycin was omitted due to pulmonary toxicity. His tumour markers normalised prior to 4th cycle of chemotherapy followed by which he was kept on follow up. His tumor markers were repeated after 1 month of completion of chemotherapy. There was rise in Beta HCG levels (30 IU/ml), which gradually increased over a period of 2 weeks (980 IU/ml). PET CT showed multiple scattered lung nodules with no significant FDG uptake. He received 3 cycles of 2nd line salvage chemotherapy with TIP (paclitaxel / ifosfamide/ cisplatin) regimen. He then received received tandem high-dose carboplatin and etoposide (HD-CE) followed by ASCT. He tolerated 1st transplant fairly well with grade 3/4 febrile neutropenia, anemia, thrombocytopenia and mucositis with appropriate supportive care. Neutrophil and platelet engraftments were observed on day 15 and day 18 respectively. He received 2nd transplant 4 weeks apart from 1st transplant with similar toxicity profile and engraftments. He was kept on follow up, with serial monitoring of tumor markers. His Beta HCG increased at 3 months follow up and patient progressed with disease and succumbed after 6 months post transplant.

Case 2:

Patient presented with retroperitoneal mass with beta -HCG (>6lakh). He was diagnosed with Extragonal non-seminomatous GCT (NSGCT) – stage IIIC with International Germ Cell Cancer Collaborative Group (IGCCCG) classification poor risk. Sites of metastasis includes brain, retroperitoneum, lung, mediastinum, liver. He received 3 cycles of BEP and 1 cycle of EP in view of bleomycin induced lung toxicity. He had persistent disease after 4 cycles of chemotherapy. He then received 2nd line salvage chemotherapy with 2 cycles of IPO (Irinotecan / paclitaxel / oxaliplatin). Beta HCG normalized post 2 cycles IPO .

He then received tandem high-dose carboplatin and etoposide (HD-CE) followed by ASCT. He tolerated 1st transplant fairly well with grade 3/4 febrile neutropenia, anemia, thrombocytopenia and mucositis with appropriate supportive care. Neutrophil and platelet engraftments were observed on day 14 and day 17 respectively. He received 2nd transplant 4 weeks apart from 1st transplant with similar toxicity profile and engraftments. He was kept on regular follow up, with serial monitoring of tumor markers. He then had progressive disease in brain with persistent elevation of Beta HCG and expired due to disease .He was disease free for 22 months post transplant.

DISCUSSION

Cisplatin-based combination chemotherapy is the mainstay for advanced GCT transforming incurable disease into one of the most curable neoplasms.The treatment of relapsed GCT's is complex and optimal treatment is still ambiguous.Well established data is available from developed countries with mature outcome data.Treatment options aiming at cure are either conventional chemotherapy or HDCT followed by ASCT.

Multiple large retrospective studies, including a recent series of nearly 1600 patients, have all suggested a benefit in both PFS and OS and favoured HDCT over CDCT as initial salvage chemotherapy[7].

The preferred initial salvage approach for patients with relpased GCT who progressed after 1st line cisplatin based chemotherapy is still not clear due to lack of randomized trials and data. Treatment strategies vary throughout the world and hence obtaining uniformity worldwide is difficult .

Indiana university and few German centers administer high-dose chemotherapy as initial salvage chemotherapy to all patients whereas others use HDCT only in the third-line setting after failure of initial salvage (2nd line treatment) with CDCT.

Given the efficacy of both CDCT and HDCT in the first line salvage setting and in particular, the excellent outcomes with HDCT for patients with unfavorable features several studies have attempted to compare these two strategies to establish the optimal initial salvage approach. However the timing, sequencing and initiation of HDCT followed by stem cell rescue varies between centers.Post HDCT followed by ASCT, treatment related mortality has been less than 5% and long term disease free survival is between 40% to 70%.

One prior randomized trial (IT-94 study, Pico et al, was conducted to investigate the role of high dose therapy in relapsed disease but unfortunately was inadequately designed[8]. They compared four cycles of VIP or VeIP (arm A) with three such cycles followed by one cycle of high-dose carboplatin, etoposide, and cyclophosphamide with ASCT (arm B) , this trial demonstrated no clinical benefit with initial salvage HDCT despite significant EFS benefit . The study only used 1 cycle of HDCT whereas 2 or 3 cycles of HDCT are considered necessary for optimal benefit. The ongoing RCT (TIGER trial) is designed to address this issue and test the benefit of HDCT in GCT patients with 1st relapse. Furthermore, In India, there are only a few published reports available on NSGCT. There are 2 large retrospective data studying Prognostic factors and outcomes in relapsed patients who were treated with conventional chemotherapy as 2nd or 3rdline [9,10]. Those are also limited by improper risk stratification or treatment details and minimal outcome data .

The only transplant data published in India is from prestigious Cancer institute from southern India reported good survival outcomes , safety profile and feasibility in 3 patients who underwent HDCT followed by single transplant recently [11].

The majority of patients from India present with a high burden of disease belonging to poor risk according to IGCCCG risk stratification[12] .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.

We report outcomes in 2 of our patients who belonged to poor risk and relapsed after 2 lines of chemotherapy and were offered HDCT and tandem transplant based on considerable evidence. Although both patients died due to disease relapse, one patient had significant Disease free survival of 22 months.

Feasibility and safety outcomes of Tandem transplant were good in our patients and there were no treatment related mortality. Treatment of relapsed GCT is difficult especially in country like India due limited resources , rarity of the disease and lack of financial support for the patients. Due to the complexity in performing tandem transplants not many institutions administer HDCT and ASCT . As a result of which, there is no published experience from India. Hence our data is unique in this context.

CONCLUSION

This is the first report from India on tandem HDCT with ACST in relapsed GCTs .Tandem HDCT/ASCT seems to be safe and feasible option in relapsed/ refractory testicular GCT's as there were no treatment related mortality. Given the low incidence, complexity of its management and multimodality treatment , mature prospective data is required to substantiate the use of HDCT /ASCT for relapsed GCT 's in India.

Table 1 : Patient characteristics

	Case 1	Case 2
Age at diagnosis	27yrs	29yrs
Age at transplant	27yrs	30yrs
IGCCCG risk	Poor risk	Poor risk
HISTOLOGY	Choriocarcinoma	NSGCT
1ST Line chemotherapy	BEP x 2 cycles EP X 2 cycles	BEP x 3 cycles EP x 1 cycle
2nd line chemotherapy	TIP X 3 cycles	IPO X 2 cycles
Einhorn risk score	Low risk	Intermediate risk
Lorchbeyer risk score	High risk	High risk
Organ involvement	Lungs	Lung , retroperitoneum, brain, mediastinal

Mobilising regimen	G-CSF and Plerixafor	G-CSF and Plerixafor
Conditioning regimen	HD -carboplatin / etoposide	HD -carboplatin / etoposide
No of days of collection	3 days	2 days
Mononuclear cell count (x108 cells / kg)	7x108 cells /kg	5x108 cells/kg
C D 34 cells (x 106/kg)	Not done	6.6x106 cells /kg
1st tandem transplant	Yes	Yes
Day of engraftment	Day 14	Day 13
2ndtrandem transplant	Yes	Yes
Day of engraftment	Day 15	Day 14
Interval between 1 st and 2nd transplant	31 days	28 days
DFS (mo) till last follow up	3 months	22 months

Table 2 : Toxicity profile

Toxicities	Case 1	Case 2
Neutropenia	Grade 4	Grade 4
Febrile neutropenia	Yes	Yes
Thrombocytopenia	Grade 4	Grade 4
Anemia	Grade 3	Grade 4
Mucositis	Grade 3	Grade 3
Diarrhea	Grade 2	Grade 3
Neuropathy	Nil	Nil
Hepatotoxicity	Nil	Yes
Nephrotoxicity	Nil	Nil
Pulmonary toxicity	Nil	Yes
Ototoxicity	Nil	Nil
Requirement of TPN	Yes	Yes
Miscellaneous	Nil	Nil

REFERENCES:

1. Madhavan Nair L, Jagathnath Krishna K, Kumar A, Mathews S, Joseph J, Vadakkumparambil James F. Prognostic factors and outcomes of nonseminomatous germ cell tumours of testis—experience from a tertiary cancer centre in India. ecancermedicalscience. 2020 Nov 18;14.
2. vanDijk MR, Steyerberg EW, Habbema JDF. Survival of non-seminomatous germ cell cancer patients according to the IGCC classification: An update based on meta-analysis. European Journal of Cancer [Internet]. 2006 May 1 [cited 2022 Sep 20];42(7):820–6.
3) Kilari D, D'Souza A, Fraser R, Qayed M, Davila O, Agrawal V, et al. Autologous Hematopoietic Stem Cell Transplantation for Male Germ Cell Tumors: Improved Outcomes Over 3 Decades. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation [Internet]. 2019 Jun 1;25(6):1099–106.
4) Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-Dose Chemotherapy and Stem-Cell Rescue for Metastatic Germ-Cell Tumors. New England Journal of Medicine. 2007 Jul 26;357(4):340–8.
5) Adra N, Abonour R, Althouse SK, Albany C, Hanna NH, Einhorn LH. High-Dose Chemotherapy and Autologous Peripheral-Blood Stem-Cell Transplantation for Relapsed Metastatic Germ Cell Tumors: The Indiana University Experience. Journal of Clinical Oncology [Internet]. 2017 Apr 1 [cited 2021 Nov 4];35(10):1096–102.
6) Kilari D, D'Souza A, Fraser R, Qayed M, Davila O, Agrawal V, et al. Autologous Hematopoietic Stem Cell Transplantation for Male Germ Cell Tumors: Improved Outcomes Over 3 Decades. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation [Internet]. 2019 Jun 1;25(6):1099–106.
7) Lorch A, Bascoul-Mollevi C, Kramar A, Einhorn L, Necchi A, Massard C, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology [Internet]. 2011 Jun 1 [cited 2022 Sep 23];29(16):2178–84. Available from: https://pubmed.ncbi.nlm.nih.gov/21444870/
8) J. L. Pico, G. Rosti, A. Kramar et al., "A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours," Annals of Oncology, vol. 16, no. 7, pp. 1152–1159, 2005
9) Nair LM, Krishna KJ, Kumar A, Mathews S, Joseph J, James FV. Prognostic factors and outcomes of nonseminomatous germ cell tumours of testis—experience from a tertiary cancer centre in India [Internet]. ecancer.org. 2020 [cited 2022 Sep 20].
10) Saju SV, Radhakrishnan V, Ganesan TS, Dhanushkodi M, Raja A, Selvaluxmy G, et al. Factors that impact the outcomes in testicular germ cell tumors in low–middle-income countries. Medical Oncology. 2019 Feb 6;36(3).
11) Selvarajan G, Jayachandran PK, Rajan AK, Kesana S, Kannan K, Sagar TG, et al. Autologous Stem Cell Transplantation in Testicular Germ Cell Tumor—Preliminary Experience from a Single Center. South Asian Journal ofCancer. 2021 Apr;10(02): 97–101.
12) Joshi A, Zanwar S, Shetty N, Patil V, Noronha V, Bakshi G, Prakash G, Menon S, Prabhash K. Epidemiology of male seminomatous and nonseminomatous germ cell tumors and response to first-line chemotherapy from a tertiary cancer center in India. Indian J Cancer [serial online] 2016 [cited 2022 Sep 24];53:313-6