Improving Outcome of Hodgkins Disease with Autologous Hematopoietic Stem Cell Transplantation

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Abstract We report analysis of all consecutive Hodgkins disease patients undergoing autologous hematopoietic stem cell transplant from September 1999 to December 2014. Out of total 38 patients 26 were males and 12 were females. 32 were adults and 6 were pediatric (<18 years). None were elderly. Median age was 28 years (9–61). All received BEAM protocol as conditioning regimen. Median engraftment time for granulocytes was 12 and 14 days for platelets. Thirty three (86.84 %) patients achieved complete remission out of which 8 (24.24 %) had further relapse. Transplant related mortality occurred in 4 (10 %) patients. Finally 26 (78.78 %) patients were disease free at median follow up of 60 months and median disease free survival (DFS) was 35 months. DFS was 66.66 and 65 %, respectively on 3 and 5 years. While overall survival was 70.83 and 70 % on 3 and 5 years, respectively.

Keywords Hodgkins · Autologus · Stem cell · Transplantation

Introduction

High dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (ASCT) is the standard treatment for relapsed or refractory Hodgkin lymphoma (HL).

Methods

Design retrospective. *Setting* Gujarat Cancer Research Institute (GCRI). *Period* September 1999–December 2014.

Transplant Protocol

Baseline blood investigations: complete blood counts, biochemistry and HIV, HbsAg, HCV, pulmonary function test and 2D echocardiography.

Preparation

All patients received granulocyte colony stimulating factor (G-CSF) 300 mcg/kg every 12 hourly total nine doses before stem cell collection. Target stem cell collection was greater than 10×10^8 MNC/kg.

Cryopreservation was done by dump freezing at -80°C with dimethyl sulfoxide as cryopreservative (with plasma). Vitality testing was not done routinely. It was only randomly done with trypan blue.

G-CSF was administered post transplant to improve the neutrophil engraftment.

Procedure

Written and informed consent of all patients and their relatives is taken explaining the risk and benefits of transplants. All the patients were admitted to bone marrow transplantation unit before starting conditioning regimen and it was provided with high efficiency particulate air filters.

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HDCT

All patients received BEAM protocol (BCNU, etoposide, cytarabine and melphalan) followed by stem cell rescue.

Antimicrobial Prophylaxis

All patients received

- Isolation till day +30 post transplant.
- Oral cavity, skin and perianal hygiene.
- Tab albendazole 400 mg single dose on –9.
- Tab cotrimoxazole DS alt day from day-14 to day-2 and then from engraftment till 6 months.
- Single donor platelet (SDP) if platelet count (PC) is $<20 \times 10^9/L$ and PCV if HB is <8.0 g.

Statistical Analysis

It was done by SPSS 20 software.

Results

Table 1 shows baseline characteristics of the patients and Table 2 shows details of prior therapy. Out of 38 patients 26 were males and 12 were females. Thirty two were adults and 6 were pediatric. All patients received two–five cycles of chemotherapy. At the time of transplantation 4 patients were with second remission, 6 were with third remission and 28 were primary refractory. Table 3 shows outcomes of salvage chemotherapy prior to transplantation. Table 4 shows the gross details of the observation and results in this study.

For refractory cases median time period for diagnosis to transplant was 12 (range 6–16) months and for relapse cases 25 (range 7–36) months.

Median cell dose (harvested and infused) was 6.5×10^8 MNC/kg body weight (range $5-10 \times 10^8$).

Engraftment

Granulocyte engraftment was defined as three consecutive days with absolute neutrophil count $>0.5 \times 10^9/L$ or 1 day with a count of $>1 \times 10^9/L$. Platelet engraftment was defined as PC $>20 \times 10^9/L$ on three consecutive days.

Table 4 shows that median interval of engraftment for granulocytes was 12 (7–26) days and median interval of platelet engraftment was 14 (7–15) days. Four patients received eltrombopag for delayed thrombocytopenia to tide over the bleeding crisis when SDP was not available.

Haematological Recovery

Response to Transplant

Thirty three (86.84 %) patients achieved complete remission at 100 days (CR). At present 26 (78.78 %) patients are disease free. Median disease free survival (DFS) is 35 months and median overall survival (OS) is 52 months. DFS was 66.66 and 65 % respectively on 3 and 5 years (Fig. 1). While OS was 70.83 and 70 % on 3 and 5 years, respectively. Transplant related mortality (TRM) was 4 (10 %). and another six patients had relapsed Hodgkins disease. No patient was offered second transplant.

Remission was assessed by CT scan in 20 patients and it was assessed by PET CT scan in 18 patients. Out of these 18 patients 6 were PET CT uptake negative before transplantation and 12 were PET CT uptake positive. Five out of 6 (83.33 %) PET negative patients achieved long term DFS but only 6 out of 12 (50 %) PET positive patients achieved long term DFS.

Toxicity/Complications

All patients had febrile neutropenia and mucositis (grades 3 and 4 in 12), vomiting (grades 3 and 4 in 15). Eighteen (47.36 %) patients had diarrhea (grades 3 and 4). Twelve (31.57 %) patients had bleeding. Seven (18.42 %) patients had pneumonia. No patient had had secondary MDS, AML or other malignancy.

Bacterial Infection

Cultures (blood/urine/stool) was positive in 12 (31.5 %) patients.

Fungal Infections

Fungus was isolated in only 3 (7.8 %) patients. However antifungal treatment was received by 24 (63.31 %) patients as a part of management of febrile neutropenia.

TRM

The causes of transplant-related deaths included infection (N = 2), idiopathic pneumonitis (N = 1), and hemorrhage (N = 1).

Discussion

HL is a highly curative malignancy. It has excellent prognosis with chemotherapeutic agents with or without radiotherapy. Relapsed and refractory HL has poor

Table 1 Baseline characteristics of the patients

Characteristics	N
Sex	
Males	26
Females	12
Age	
Median	28
Range	9–16
Performance status	
0	24
1	14
Subtypes	
Classical	3
Mixed cellularity	19
Nodular sclerosis	12
Lymphocyte depleted	4
Biology	
Relapsed	33
Refractory	5
Stages	
1	2
2	20 (11 B symptom)
3	12 (8 had B symptom)
4	26 (5 B symptoms)
B symptoms	24
Induction chemotherapy	
ABVD	34
MOPP	4
Salvage chemotherapy	
DHAP	18
COPP	10
GDP	12
ICE	14
MINE	17
GEMOX	3
Previous lines of chemotherapy	
2	10
3	21
4	2
5	4
Number of chemotherapy cycles	8–18
Previous IFRT	10
At the time of HSCT number of patients with CR/persistent disease	
CR	9
PR/persistent disease	29
PET CT scan after salvage chemotherapy but before ASCT (N = 18)	
PET CT positive	6
PET CT negative	12
Comorbidities	
HbsAg+	8 (all on lamivudin)
Single kidney	2

Table 2 Patient details and prior therapy

Number of patients	38
Months from diagnosis to transplantation in primary refractory cases, median (range)	12 (6–16) months
Months from relapse to transplantation in relapsed cases, median (range)	25 (7–36) months
Number of prior lines of therapy, median (range)	3 (2–5)
Prior autograft (%)	0
Disease status at transplantation	
Chemosensitive	10 (26.31 %)
Chemo-resistant	28 (73.68 %)
Untested relapse	0

Table 3 Outcome of salvage regimens prior to autologous stem cell transplantation

	N	Complete response (%)	Overall response (%)
DHAP	18	28 (N = 5)	83.33 (N = 15)
COPP	10	30 (N = 3)	60 (N = 6)
GDP	12	25 (N = 3)	66.66 (N = 12)
ICE	14	28.5 (N = 4)	78 (N = 11)
MINE	17	11.7 (N = 2)	70.5 (N = 12)
GEMOX	3	33.33 (N = 1)	66.66 (N = 2)

Table 4 Results

Milestones	Outcome/interval
Nadir of neutropenia (range)	Day +4 to day +8
G-CSF support (N = 38)	Day +4 to day +14
Granulocyte engraftment	Median 12 days (7–26)
Platelet engraftment	Median 14 days (7–50)
Eltrombopag support (N = 4)	Day +10 to day +20
Complete remission	33 (86.84 %)
PET CT scan (N = 18)	90 days
Median DFS	35 months
3 year DFS	66.66 %
5 year DFS	65 %

prognosis and ASCT is the treatment of choice for these patients. With better supportive care measures morbidity and mortality rates associated with this therapy have decreased with successful results and increase in DFS rates [1–3].

In the limited stage only 10 % of patients have treatment failure with combined modality while in advanced stage 20–30 % patients have treatment failure. Generally 10 % patients have persistent disease. ASCT remains the treatment of choice for these patients [4, 5].

Current Indications for ASCT in Hodgkin's Disease

In first complete remission (CR1) ASCT is generally not recommended (category 1), in chemosensitive relapse or

any $\geq$ CR2 it is standard treatment (category 1) and it in refractory disease it is a clinical option (category 2) [6].

We have done transplantation of only 38 patients of Hodgkins disease in 16 years because transplantation is not a government funded procedure in this institute and patient has to bear all the cost. Due to financial constraints many patients receive multiple lines of chemotherapy rather than transplantation.

One would like to see the reason for good results in the poor risk subset. First the sample size is small. Besides, it may be due to better patient selection, i.e., those with good performance (ECOG PS 0, 1, 2) and without infection. The outcome in chemo-resistant Hodgkins disease remains significantly poor than that in chemosensitive disease. Similar good outcomes are also reported by some other authors [7–13].

Figure 1 shows the graphic representation of OS and DFS in all patients. Figure 2 shows that 5 year progression free survival (PFS) of chemosensitive (PFS = 70 %) patients was more than double that compared to chemo-resistant cases (PFS = 30 %).

Patients who did not achieve remission or relapsed were put on palliative chemotherapy. Three patients showed CR with lenalidomide (out of total six received lenalidomide) with median DFS of 3 months till date. Second transplantation was not done.

For the patients with CR >2 years the long term outcomes were good (5 year OS 80 %). Majority of the relapses were documented within 1 year. Median time to progression was 7 months and median survival time from second relapse was 24 months. Those patients who had relapse within 6 months had particularly poor prognosis.

Our data is comparable with international outcomes and reported Indian outcomes (Table 5).

Conclusion

- Patients of relapsed or refractory HL were heavily pretreated (8–18 courses of chemotherapy; with IFRT in some patients).

Fig. 1 Overall survival (OS) and disease free survival (DFS) of post HSCT Hodgkins disease patients versus time

Fig. 2 Progression free survival of chemosensitive disease and that of chemoresistant disease

Table 5 Comparison with international and Indian data of outcome

	N	Arm	Outcomes
Relapsed/chemosensitive			
BLNI 1993 [7]	20	BEAM	CR = 74 %, TRM = 10 %, 3 year PFS = 53 %
GSHG 2002 [8]	61	BEAM	CR = 85 %, TRM = 2 %, 3 year PFS = 55 %
Josting et al. [9]	112	BEAM	RR = 91 %, CR = 83 %, mortality = 20 %, 3 year PFS = 72 %, 3 year OS = 80 %
Kumar et al. (India) [10]	19	CBV, BEAM	CR = 84.4 %
GCRI	10	BEAM	CR = 100 %, TRM = 0 %, 3 year PFS = 80 %, 5 year PFS = 70 %
Chemorefractory			
Chopra et al. [11]	155	BEAM	CR = 28 %, TRM = 10 %, 5 year PFS = 50 %, 5 year OS = 55 %
Sweetenham et al. [12]	175	BEAM	CR = 30 %, TRM = 14 %, 5 year PFS = 32 %, 5 year OS = 36 %
Kumar et al. (India) [10]	6	CBV, BEAM	CR = 16.6 %
GCRI	28	BEAM	CR = 30 %, TRM = 14 %, 3 year PFS = 47 %, 5 year PFS = 30 %

- Despite the multiple lines of chemotherapy pre HSCT, results are good and acceptable (CR = 86.84 % with TRM = 10 %).
- Primary refractory disease seems to have much worse biology as compared to relapsed disease.
- Number of patients referred in first relapse is small (10.5 %) and majority of the patients (73.68 %) had persistent disease. Therefore, there is still scope of improvement in results.
- Patients should be counseled at baseline itself regarding the role of HSCT in case of relapse or primary refractory disease.

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