

Autologous Stem Cell Transplant in Multiple Myeloma: Excellent Safety and Efficacy Possible in a Non University Hospital of Developing Country

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Introduction

Background: There have been major advances in past decade in the continuum of therapy for transplantation-eligible multiple myeloma patients. For patients requiring therapy, recommended induction treatment consists of triple drug regimens followed by the collection of hematopoietic stem cells. For transplantation-eligible patients, high-dose melphalan followed by autologous stem cell transplant (HSCT) remains the standard regimen as it helps in increasing both the frequency and depth of responses leading to improved outcomes [1-3]. Autologous HSCT has thus become the standard approach after induction therapy for myeloma patients [4].

However in a developing country like India there are very few centres, only about 40 in whole of India, performing regular transplant [5,6]. Also, the total number of transplants performed is only about 1000 per year in India. Reasons for this low number of patients undergoing transplant includes lack of basic infrastructure and misconceptions regarding safety, efficacy and cost of this procedure both in general public & medical fraternity including oncologists. Also there are very few publications from developing countries including India about the outcome of this therapy, which again prevents doctors to consider it in their patients [5-7]. Due to above reasons we thought of analysing our transplant results and share it with medical fraternity. Here we describe our experience with autologous HSCT in multiple myeloma patients.

Methods

This analysis includes patients with multiple myeloma undergoing Autologous HSCT at our Institute from 2007 to November 2013. The total number of patients undergoing transplant for multiple myeloma was 31. Twenty three patients had undergone Autologous HSCT in first line setting while the rest 8 patients were treated after relapse of their disease.

The induction therapy included regimens combining dexamethasone with bortezomib & lenalidomide (or thalidomide). Mobilization therapy (Table 1) consisted of G-CSF stimulation in the dose of 10 mcg/kg/day. Apheresis was initiated on Day 4 or 5, depending on number of CD 34 positive stem cells in peripheral

blood. The conditioning regimen included melphalan in a standard dose 200 mg/m² in 23 patients while it was reduced to 140 mg/m² in the remaining 8 patients in view of old age (defined as over 60 years) or other comorbidity. The transplant procedure was followed by the administration of G-CSF in the dose of 5 mcg/kg in 17 patients. The prophylactic measures included anti-infection therapy with cefixime 200 mg twice daily orally plus acyclovir and fluconazole. The substitution with blood derivatives was indicated in patients with asymptomatic course and hemoglobin and platelet levels under 7 g/dl and 10 × 10⁶/cumm respectively.

Engraftment was defined as the increase in neutrophil and platelet levels exceeding 0.5×10⁶/cumm and 20×10⁶/cumm without following decrease, respectively. The toxicity was assessed according to NCI-CTC scale [8].

The responses were assessed by International Myeloma Working Group uniform response criteria [9]. The outcomes that we assessed included response rates, overall survival (OS, an interval from stem cell transfer to death or date of the last assessment) and event-free survival (EFS, an interval from the date of stem cell transfer to progression, death or the date of the last assessment).

Results

Baseline patient's & transplant characteristics are shown in Table 1 and 2 respectively. Out of 31 patients 26 were male and 5 were female with a median age of 52 years. Most patients were having Ig G type of M component (N=17) and Durie Salmon stage (DSS) 3 disease on presentation (N=18). Serum Creatinine levels were normal in 15 patients while 14 patients were having altered baseline renal functions. Most patients had achieved CR or VGPR before undergoing transplant on induction therapy (N=23) while 8 patients were having PR.

Transplant procedure followed was as described above in methods section. Median CD 34 cell dose was 1.96x10⁶/kg. Median day of neutrophil engraftment was day +14 and median day of discharge was Day +16. Febrile neutropenia developed in total 16 patients (51.6%) and one patient also developed fungal infection. For these 31 patients, transplant related mortality is 0% at both 30 days and 100 days.

		N	%	Median	Range
No of transplants	Total	31	100		
Mobilisation regimen	GCSF	31	100		

Conditioning regimen (Melphalan Dose)	200 mg/m ²	23	74.2		
	140 mg/m ²	8	25.8		
No of CD 34+ cells in graft 106/kg				1.96	1.1-4.9
Day of neutrophil engraftment				+14	10-26
Day of discharge				+16	12-33
Febrile neutropenia		16	51.6		
Fungal infection		1	3.2		
30 day TRM		0	0		
100 day TRM		0	0		

Table 1: Transplant Characteristics GCSF- Granulocyte Colony Stimulating Factor, TRM: Transplant Related Mortality

Characteristics		No of patients (%)	Median	Range
Sex (male/female)		26/5		
Age (year)			52	40-66
M component	IgG	17		
	IgA	3		
	IgD, IgM	0		
	LC	8		
	Non secretory	0		
Disease status at transplant				
	CR	11 (35.5)		
	VGPR	12 (38.7)		
	PR	8 (25.8)		
S. Creatinine at diagnosis (mg/dl)				
	Not available	2 (6.5)		
	<1	15 (48.3)		
	1.1 – 2	11 (35.5)		
	>2	3 (9.7)		
Stage at diagnosis DSS criteria				
	I	6 (19.4)		
	II	7 (22.6)		
	III	18 (58.1)		

Table 2: Baseline Patient's Characteristics Dss, Durie Salmon Staging

Transplant Outcome Analysis

Median follow-up of all 31 patients is 19 months (range of 4 to 72 months). 9 patients currently have follow up of ≥ 36 months. Out of these 9 patients, 8 are in CR and 1 in PR at the time of analysis.

Due to small sample size & very wide range of follow up duration, the median EFS of all patients is not statistically analysable. However for the 9 patients who have ≥ 36 months of follow-up, median EFS is 51 months. Similarly, median OS of these 9 patients is 51 months.

Our data also confirms the benefit of autologous HSCT in increasing depth of response in myeloma patients. 10 out of 12 (83%) patients having VGPR before transplant have achieved CR after transplant. Also 3 out of 8 (37%) patients having PR before transplant have achieved CR with transplant. At the time of analysis, 23 patients (74.2%) are in CR, 4 (12.9%) are in PR and remaining 4 (12.9%) have expired. At median follow-up of 19 months OS is 87%.

Major side effects during and after transplants are shown in Table 4. As previously mentioned febrile neutropenia developed in 16 patients (51.6%) and one patient also developed fungal infection. Other than this, 2 patients have developed features resembling graft versus host disease (GVHD) which were restricted to gastrointestinal system and are similar to condition described in few publications [10].

Other toxicities not shown in Table 4 include oral mucositis of grade 2 in two patients and grade 3 in one patient. Low incidence of oral mucositis in our patients can be explained by strict adherence to continuous ice sucking during melphalan infusion, which is one of the few proven prophylactic measures for oral mucositis [11] (Table 3).

Current disease status	No patients	of %
Complete response [CR]	23	74.2
Partial response [PR]	4	12.9
Expired	4	12.9
Total	31	100.0

Table 3: Current Disease Status of Patients

Major Complications	No of patients
GI GVHD like syndrome	2
Fungal Infection	1
GI side effects (diarrhea grade 2+3)	2+3
Neuropathy	1

Table 4: Toxicity Analysis GI: Gastro-Intestinal, GVHD: Graft versus Host Disease

Discussion

Our centre is performing autologous HSCT for multiple myeloma since year 2007 and our analysis of these 31 patients shows results comparable to international and other Indian centres results (Table 5) [12-16]. One Indian study described by Lalit Kumar et al showed median EFS & OS of 42 months & 71 months respectively. Similarly

most of the international trials from IFM group have shown EFS of 1.9 to 4.8 years & OS of 3.9 to 9.0 years. Long-term follow-up of our all patients is still limited, but initial trends in the outcome are encouraging. This can be suggested by median EFS (51 months) & OS (51 months) for nine of our patients who have follow-up of 36 months or more. As the follow-up of other patients will increase, our survival data will become mature and more definite results will be analysed. Our data supports the current role of autologous HSCT in myeloma patients both in first and second line settings. Post autologous HSCT, most of our patients are in disease remission and treatment free.

Study	EFS median	OS median
Our Analysis		
Patients ≥ 36 months follow up (N-9)	4.2 years (51 months)	4.2 years (51 months)
Indian study (AIIMS) [16]	42 months	71 months
N=108, median follow-up of 70 months		
International trials-IFM 90,99,94.TT1/2) [12-15]	1.9 to 4.8 years	3.9 to 9.0 years

Table 5: Outcome comparison with other studies, EFS: Event Free Survival, OS: Overall Survival

Complications profile related to transplant is also comparable to other institutes data with exception of very low incidence of oral mucositis. Other studies have shown average 50 to 70% overall incidence of oral mucositis with 15 to 25% having severe form, however our data shows that only 3 (9.6%) patients had developed grade 2+3 oral mucositis [12-16]. Most important intervention which has helped in preventing oral mucositis in our patients is strictly following continuous ice sucking during Melphalan infusion, a proven intervention [11].

Till now we are able to achieve a 0% 30 day & 100 day TRM. We believe that this excellent safety profile is because of factors like stem cell unit having rooms with HEPA filter and positive pressure [17,18], hospitalist concept in patient care where a critical care specialist is an integral part of our transplant team, nursing staff dedicated to transplant unit and strict adherence to infection control measures including protective isolation.

Finally it can be concluded that autologous HSCT, which is already a standard of care in developed countries as post induction therapy in multiple myeloma patients, is also feasible in a non-university hospital of developing country with excellent safety and efficacy comparable to a transplant centre in a developed country.

In Indian perspective our results can help patients in multiple aspects like prolonged treatment free interval leading to good quality of life, ease in follow-up after achieving disease control (as our patients have to travel long distances for subspecialty care) and cost effectiveness (as cost of Autologous HSCT for myeloma is approximately 10000 USD, whereas cost of chemotherapy for about 9 months is approximately 7500 USD) [19]. Also setting up a strong autologous HSCT program can serve as a step towards developing allogeneic HSCT centre.

In conclusion, by initiating measures as we have done, even large multispecialty private hospitals in developing world can achieve good results allowing wider availability of this type of important treatment. Also, this would allow hospitals to slowly start Allogeneic HSCT, as in our experience, for a number of other diseases. Sharing of best practices should happen to increase number of transplant centres in India and other developing countries.

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