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Research paper

Limiting factors for autologous transplantation among transplant-eligible multiple myeloma patients: Lesson from a Tertiary Cancer Centre in rural India

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ABSTRACT

There is limited data from low and middle income countries on the exact proportion of Myeloma patients undergoing transplant even if they are eligible for the same. In this retrospective analysis of all newly diagnosed transplant eligible Myeloma treated between January 2011 to June 2017, number of patients undergoing transplant were recorded and among those not opting for transplant, reasons for the same were noted. Among 89 eligible patients, 23 (26%) patients could undergo transplantation. Most common reasons for not undergoing transplant were fear of the complications in 42 (47%) and financial reasons in 41 (46%) of patients. The transplanted group had better progression free survival when compared against the non-transplanted group (3 year PFS of 80% versus 36%, HR = 0.09, 95%CI 0.02–0.4, p = 0.001). Future studies may be conducted to arrive at measures, for correcting the transplant related concerns and fears, through psycho-social interventions.

1. Introduction

Induction chemotherapy followed by autologous stem cell transplantation is the standard of care in newly diagnosed transplant eligible Myeloma patients [1–4]. Even with many recent advances in the field, majority of patients with Multiple Myeloma eventually develop relapsed refractory disease [5]. High dose Melphalan followed by autologous stem cell transplantation improves progression free survival (PFS)compared to conventional chemotherapy (median PFS 41–43 months versus 22–29 months) [1,4]. This holds true even in the era of novel agents incorporated in to the treatment regimens [6,7]. However this treatment modality is limited by factors such as age and cost of treatment, the latter being more relevant in developing countries [8].

There is limited published data, from developing countries including India, regarding the exact proportion of Myeloma patients undergoing autologous stem cell transplantation even if they are eligible for the same. Moreover, data from India on comparison of survival characteristics between patients undergoing autologous transplantation and those undergoing chemotherapy alone, among transplant eligible Myeloma patients is scarce. Hence we decided to find out the proportion of patients who undergo transplantation and survival impact of undergoing autologous stem cell transplantation.

2. Methods

In this retrospective study, all cases of newly diagnosed Multiple Myeloma, who were transplant eligible, diagnosed and treated between January 2011 to June 2017 were included. An official approval from the institutional review board was obtained before the start of the study.

All the patients had received induction chemotherapy for at least 4–6 cycles. Every transplant eligible patient will be seen in the clinic for detailed pre-transplant counselling explaining all the benefits and risks involved. Thereafter, for those opting transplantation, autologous stem cells were infused after conditioning chemotherapy with high dose Melphalan. If any patient was not willing for transplant, reasons for the

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same were documented in the respective case record. Patients not opting transplantation were continued on the induction regimen till a minimum of 9–12 cycles or till progression /toxicity develops. If the induction regimen was Lenalidomide plus Dexamethasone, the same was continued as long as there is response, unless the patient develops toxicity. In case of other regimens, post induction, patients were put on maintenance treatment until progression or development of unacceptable levels of toxicity.

Baseline characteristics of all patients were documented. Number of patients undergoing transplantation were noted and among those not opting for transplantation, reasons for the same were noted. Response assessments were done as per the International Myeloma Working Group (IMWG) criteria [9,10]. For calculating survival duration, date of progression and date of death or date of last follow up of each patient were noted.

Information extracted from previous case records were entered in EpiData Entry (version 3.1) and analysed using both EpiData Analysis (version 2.2.3.187) and the R software v 3.5.2. For finding out the differences in continuous variables between the transplanted and non transplanted patient groups, either Student *t*-test (if parametric distribution) or Mann Whitney U test (if non-parametric distribution) were used. To compare differences in categorical variables, Fisher exact test was used. For calculating survival duration, date of progression and date of death or date of last follow up of each patient were noted. Median follow up was calculated using Kaplan Meier (KM) curves by reversing event and censor codes. Overall survival was calculated from date of diagnosis to date of death or date of last follow up. Progression free survival was calculated from date of diagnosis to the date of progression or date of last follow up. Survival was analysed by KM curves and Cox proportional hazards (CPH) model.

3. Results

A total of 89 patients were eligible for the study as per inclusion criteria. Median age of the entire group was 57 (range 32–66) years. Females constituted just more than half of the entire group (49 patients, 55%). Thirty patients (34%) had some form of comorbidities with diabetes being the most common, noted in 17 (19%) patients. Around two third of the patients (61, 68%) were having good performance status with Eastern Cooperative Oncology Group performance status (ECOG PS) < 2, at the time of diagnosis. Other baseline characteristics were as described in Table 1.

Of the 89 patients, only 23 (26%) patients underwent autologous stem cell transplantation. Fifty nine patients were diagnosed before 2015 and the rest 30 from 2015 onwards. Nine patients out of 59 (15%) opted transplant before 2015 whereas 17 out of 30 (57%) underwent transplant since 2015. The most common reasons for not undergoing transplantation were fear of the complications related to transplantation in 42 (47%) patients and financial reasons in 41 (46%) patients. Median age of the patients in the transplanted and the non-transplanted groups were 52 years and 60 years respectively ($p < 0.001$). Table 2 shows the comparison of baseline characteristics between the transplanted and non-transplanted patient groups. Transplant related mortality (TRM) was 0%. Details regarding grade III/IV adverse events of transplant are shown in Table 3.

Median follow up was 51 months. Median overall survival (OS) was not reached for the entire cohort. The median progression-free survival (PFS) for the entire cohort was 39 months. Estimated 3-year OS and PFS were 77% (95% CI 68–87) and 51% (95% CI 41–63)respectively. There was a trend toward improved OS in patients who underwent transplantation when compared against those who did not (3-year OS of 92% versus 73%), although it did not reach statistical significance (HR = 0.15, 95%CI 0.02–1.1, p = 0.07) (Fig. 1). Patients who underwent transplantation had significantly better PFS compared with the patients who did not (3-year PFS of 80% versus 36%, HR = 0.09, 95%CI 0.02–0.4, p = 0.001) (Fig. 2).

Table 1
Baseline characteristics.

	N	%
Age in Years		
Median	57	
Range	32–66	
Sex		
Male	40	45
Female	49	55
ECOG PS[a]		
0	1	1
1	60	67
2	18	20
3	8	9
4	2	2
ISS[b] stage(n = 77)		
Stage 1	20	26
Stage 2	24	31
Stage 3	33	43
LDH[c] (n = 75)		
High	24	32
Normal	51	68
Ind Rx[d] regimen (n = 86)		
Len dex[e]	39	45
MPT[f]	19	22
CyBorD[g]	26	30
Thal dex[h]	2	2
EOI[i] response(n = 87)		
sCR[j]	9	10
CR[k]	13	15
VGPR[l]	34	39
PR	17	20
Stable disease	2	2
Progression	12	14

[a] ECOG PS = Eastern Cooperative Oncology Group Performance status.
[b] ISS = International Staging System.
[c] LDH = Lactate Dehydrogenase.
[d] Indnuction Rx = Induction Treatment.
[e] Len dex = Lenalidomide dexamethasone.
[f] MPT = Melphalan Prednisolone Thalidomide.
[g] CyBorD = Cyclophosphamide BortezomibDexamethasanoe.
[h] Thal dex = Thalidomide dexamethasone.
[i] EOI = End of induction.
[j] sCR = Stringent complete response.
[k] CR = Complete response.
[l] PR = Partial response.

4. Discussion

Real world data from low and middle income countries regarding the exact proportion of Multiple Myeloma patients undergoing transplantation, even if they are eligible, are scarce. In our cohort, consisting of patients from a tertiary centre in public sector, we could find that nearly 75% of the transplant eligible patients didn't actually undergo the procedure. A previously reported Indian study had found that the proportion of patients undergoing transplant was only 6%, even though this proportion is of the entire newly diagnosed patients without dividing them in to transplant eligible or not [11]. However the median age of the entire group in that study was 54 years implying that a good number of patients would have been transplant eligible. Data in this regard is much different from western world [12,13]. An observational cross sectional study conducted across seven European countries revealed that more than 70% of transplant eligible patients actually underwent transplant [12]. The second study from selected Central and Eastern European countries reported that 55% of transplant eligible patients did receive it [13]. The wide variation in these proportions between Indian settings and the Western world can be explained by the differences in the social and economic backgrounds.

In our study group, fear and concerns regarding the complications related to the transplantation was one of the major reasons for not

Table 2
Comparison of characteristics between transplanted and non-transplanted groups.

Variable		Transplanted (N = 23)		Non-transplanted (N = 66)		p value
		N	%	N	%	
Age in years						
	Median	52		60		< **0.001***
	Range	32-63		44-63		
Sex						
	Male	14	35	26	65	0.07
	Female	9	18	40	82	
LDH(n = 75)						
	High	5	21	19	79	0.90
	Normal	10	20	41	80	
ECOG PS						
	0/1	19	31	42	69	0.09
	> =2	4	14	24	86	
ISS Stage (n = 77)						
	I	4	20	16	80	0.59
	II	7	29	17	71	
	III	6	18	27	82	
EOI response (n = 87)						
	sCR	9	40	0	0	< 0.001
	CR	4	17	9	14	
	VGPR	6	26	28	44	
	PR	4	17	13	20	
	Stable disease	0	0	2	3	
	Progression	0	0	12	19	

LDH = Lactate Dehydrogenase, ECOG PS = Eastern Cooperative Oncology Group Performance status, ISS = International Staging System.
* Statistically significant ($p < 0.05$). EOI = End of induction, sCR = Stringent complete response, CR = Complete response, PR = Partial response.

Table 3
Adverse events /toxicity of stem cell transplant (grade III/IV), N = 22.

Event		Number	Percentage
Any event(all grades)		22	100
Blood disorder			
	Anemia	1	4
	Neutropenia	22	100
	Thrombocytopenia	22	100
Gastro-intestinal disorders			
	Mucositis	6	27
	Diarrhea	2	9
Infection			
	Febrile neutropenia	9	40
	Sepsis	1	4
	UTI	4	18
General			
	Fatigue	17	77
Others (one case of SVT, one case of C.diff diarrhea)		2	9

UTI-Urinary tract infection, SVT-Supraventricular tachycardia, C.diff-Clostridium difficile.

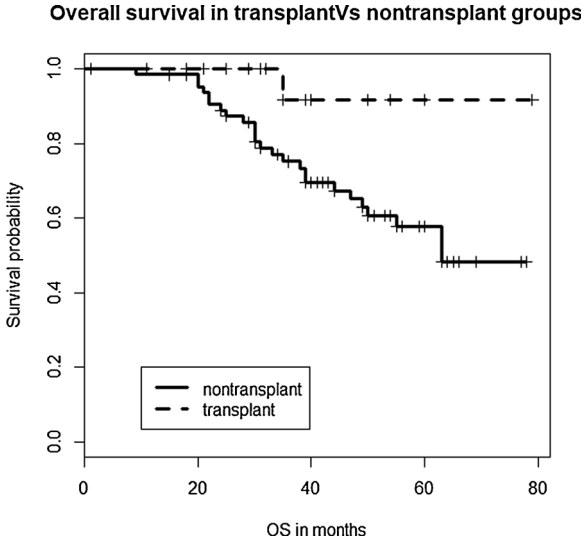

Fig. 1. Overall Survival in Transplant Vs Non-transplant groups.

opting autologous transplantation. Adverse event profiles and transplant related mortality (0%) in the present study were almost similar to published literature even though febrile neutropenia and fatigue were on the higher side [14]. Disease or treatment related anxiety and distress is a documented problem in Myeloma patients undergoing transplantation [15,16]. Sherman et al. had reported that nearly 40% patients had clinically significant levels of anxiety and depression and around 37% patients had cancer related distress at the time of stem cell collection in Myeloma patients [17]. In a study by the Nordic Myeloma Group on Health Related Quality of Life in Myeloma patients, which compared quality of life in patients undergoing transplant with that in patients undergoing conventional chemotherapy, it was reported that patients in the transplant group had more sleep disturbance than the conventional chemotherapy group at 1 month after start of induction chemotherapy [18]. National comprehensive cancer network had proposed that “distress” should be considered as sixth vital sign to highlight on the importance of emotional concerns that cancer patients go through often [19].

The second major reason for not proceeding with transplantation in the present study was non affordability. Average cost of autologous transplant for Myeloma in our setting is USD 6000. Estimated cost of chemotherapy per patient in non- transplant group for a period of one year is around USD 3600. Percentage of patients opting for transplant was much higher (57%) from 2015 onwards compared to those who were before 2015 (15%). This is because the state Government had announced the availability of ‘Sukrutham scheme’, offering financial aid, for all cancer patients from the end of 2014 onwards. In the absence of significant Government supports, and limited insurance coverage options in the country, treatment cost has to be borne by the individual itself which poses significant financial issues for the person and the entire family [20]. It has been very well described that cancer affected households have to spend an additional 36–44% of annual household expenditure of matched controls for the treatment of cancer

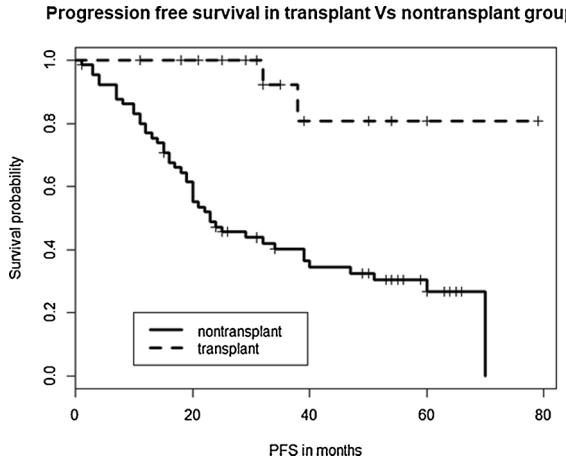

Fig. 2. Progression Free Survival in Transplant Vs Non-transplant groups.

[21].

Randomised controlled trials have shown that high dose Melphalan followed by autologous stem cell rescue improves progression free survival in Multiple Myeloma compared against conventional chemotherapy [1–4]. We were able to get similar finding in our study also, with the transplanted group having superior PFS. There are various Indian retrospective studies describing outcome of autologous transplantation in myeloma patients [22–24]. However there was no head to head comparison, in any of these Indian studies, between transplanted and non transplanted groups either in a prospective or in a retrospective manner.

We agree that our study has some limitations such as being a retrospective, single-centre study with small sample population. Moreover, the number of patients who underwent transplantation was less as compared to the number of patients who did not undergo transplantation which could have influenced the statistical conclusions. Also every patient didn't have cytogenetics/FISH studies performed for risk stratification at diagnosis and hence this aspect was not considered in the study. However, this study could shed some light on the real world data on the actual proportion of transplant-eligible patients who undergo transplantation in a developing country. Given the findings in our study, every transplant centre should have provisions for proper psychosocial counselling and education to alleviate fears and concerns. Moreover measures have to be taken from the side of authorities to arrange for more government funds to support transplant for the needy patients. Fear and concerns on the complications of transplant being the main reason for not opting for transplantation, future studies can be conducted for identifying and addressing the reasons behind such fears through psychosocial interventions and, thus, persuade them to opt for transplantation and regain better health.

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Availability of data and materials

The data are available with the corresponding author and can be shared on request.

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