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High-dose chemotherapy followed by autologous stem cell transplant for multiple myeloma: Predictors of long-term outcome

Lalit Kumar[1], Dev Ramavath[1], Babita Kataria[1], Akash Tiwari[1], Abhishek Raj[1], Santosh Kumar Chellapuram[1], Anjali Mookerjee[1], Ranjit Kumar Sahoo[1], Prabhat S. Malik[1], Atul Sharma[1], Ritu Gupta[2], Om dutt Sharma[2], Ahitagni Biswas[3], Rakesh Kumar[4] & Sanjay Thulkar[5], for AIIMS Myeloma Group

Departments of [1]Medical Oncology, [2]Laboratory Oncology, [3]Radiation Oncology, [4]Nuclear Medicine & [5]Radio-diagnosis, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

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***Background & objectives*: Survival of patients with multiple myeloma (MM) has improved in the past two decades following use of novel agents and autologous stem cell transplantation. To determine predictors of long-term outcome, data of MM patients who underwent autologous stem cell transplantation (ASCT) at a tertiary care centre in north India were retrospectively analyzed.**

***Methods*: Between 1995 and 2016, 349 MM patients underwent ASCT. Patients' median age was 52 yr, ranging from 29 to 68 yr, 68.2 per cent were males. Thirty three per cent patients had international staging system (ISS) Stage III and 68.5 per cent had received novel agents-based induction. High-dose melphalan (200 mg/m^2) was used for conditioning; patients with renal insufficiency (estimated glomerular filtration rate <40 ml/min) received melphalan 140-150 mg/m^2.**

***Results*: Post-transplant, 317 of 349 (90.8%) patients responded; complete [complete response (CR)] −213 (61%)], very good partial response (VGPR) −62 (17.8%) and PR in 42 (12%)]. Induction with novel agents, pre-transplant chemosensitive disease, transplant in first remission and serum albumin (≥3.5 g/dl) were predictors of significant response. At a median follow up of 73 months, median overall survival (OS) was 90 months [95% confidence interval (CI) 70.8-109.2], and progression-free survival (PFS) was 41 months (95% CI 33.0-49.0). On multivariate analysis, achievement of CR post-transplant, transplant in first remission, ISS Stages I and II (vs. III), absence of extramedullary disease and serum albumin ≥3.5 g/dl were predictors of prolonged OS. For PFS, achievement of post-transplant CR and transplant in first remission were predictors of superior outcome.**

***Interpretation & conclusions*: Treatment with novel agents, achievement of complete remission post-transplant, ISS Stages I and II, absence of extramedullary disease and transplant in first remission were predictors of long-term survival for patients with MM.**

Key words Autologous stem cell transplantation - long-term outcome - multiple myeloma - predictors - prognostic factors - response to transplant

Multiple myeloma (MM), a clonal plasma cell malignancy accounts for approximately 10 per cent of haematologic malignancies. Compared to industrialized nations, myeloma occurs a decade earlier in India, at a median age of 55 yr[1]. Present management of myeloma patients includes novel agents (immunomodulators - thalidomide, lenalidomide, proteasome inhibitors - bortezomib)-based initial (induction) therapy for 4-6 months followed by autologous stem cell transplantation (ASCT) in patients aged ≤65-70 yr without major co-morbidities. This is followed by low-dose maintenance therapy with either lenalidomide or thalidomide or bortezomib for two years. For elderly patients (≥65-70 yr) or those not suitable for ASCT induction, therapy is given for 6-9 months followed by maintenance therapy. The ASCT is an integral component of myeloma management and has contributed to survival improvement in the past two decades[2]. Initial transplant studies have used conventional chemotherapy before ASCT. A number of randomized studies[3-7] and meta-analyses[8] have confirmed that ASCT is associated with deepening of response rate and improved progression-free survival (PFS) in most and overall survival (OS) in some studies compared to conventional cytotoxic chemotherapy. Subsequently, these results were confirmed in recent randomized studies[9-14] using novel agents-based induction before ASCT further augmenting responses with improvement in survival. While enough experience with ASCT for long-term outcome has been reported from developed countries[15-20], comprehensive information from resource-limited setting like ours, on the long-term outcome following transplant is limited[21]. We have reported our initial experience for MM patients transplanted till the year 2014[22]. Here we report an updated follow up with long-term outcome on patients with MM transplanted between 1995 and 2016 as well as comprehensive analysis of prognostic factors associated with long-term survival.

Material & Methods

The data on 349 consecutive MM patients, who underwent ASCT at Institute Rotary Cancer Hospital, All India Institute of Medical Sciences (AIIMS), New Delhi, India, between 1995 and December 2016 were analysed. The study was approved by the Ethics Committee of AIIMS. The patients' characteristics are shown in Table I. The median age was 52 yr ranging from 29 to 68 yr; 236 (67.6%) were males, 34.7 per cent had international staging system (ISS) Stage III disease and 24.4 per cent had Stage IIIB by Durie-Salmon

Table I. Characteristics of the patients included in the study

Variable	All patients (n=349), n (%)
Age (yr)	
Median	52
Range	29-68
Gender	
Male	236 (67.6)
Female	113 (32.4)
International staging system (ISS)	
I	103 (30.0)
II	121 (35.3)
III	119 (34.7)
Durie-Salmon staging system (DSS)	
≤IIIA	263 (75.6)
IIIB	85 (24.4)
Ig type (n=342)	
IgG	204 (59.6)
IgA	57 (16.7)
Light chain	81 (23.7)
Extramedullary disease (EMD)	
Yes	80 (22.9)
No	229 (77.1)
Haemoglobin (g/dl)	
≤10	201 (57.6)
>10	148 (42.4)
Serum albumin (g/dl)	
<3.5	140 (40.1)
≥3.5	59.9 (59.9)
BM-PC% (n=348)	
<40	180 (51.7)
≥40	168 (48.3)
Calcium (mg/dl) (n=324)	
≤11.4	296 (91.4)
≥11.5	28 (8.6)
eGFR (ml/min)	
<40	86 (24.6)
≥40	263 (75.4)
Induction treatment	
Novel agents	251 (71.9)
VAD	75 (21.5)
Alkylating agents	23 (6.6)
Pre-transplant status	
Sensitive (CR+VGPR+PR)	291 (83.4)

Contd...

Variable	All patients (n=349), n (%)
Resistant (stable+progressive disease)	58 (16.6)
Interval (months)	
≤12	220 (63.0)
>12	129 (37.0)
Induction regimen (n=348)	
One line	223 (64.1)
>One line	125 (35.9)

BM-PC, bone marrow plasma cell; eGFR, estimated glomerular filtration rate; VAD, vincristine, adriamycin and dexamethasone; Ig, immunoglobulin; CR, complete response; PR, partial response; VGPR, very good partial response

staging (DSS). Eighty one (23.6%) patients had light chain myeloma, 251 (71.9%) received novel agents for induction, 75 (21.5%) received [vincristine, adriamycin and dexamethasone (VAD) as continuous infusion] and the remaining 23 (6.6%) received alkylating agents-based induction regimens. One hundred twenty five patients (36%) had received more than one induction regimen before transplant. Median interval from diagnosis to transplant was 10 months, ranging from 2 to 128 months.

Novel agents-based induction therapy: Among 251 patients, 178 (71.9%) had received two drug combination (thalidomide+dexamethasone, n=92, lenalidomide+dexamethasone, n=54 and bortezomib+dexamethasone, n=32), 71 (20.3%) patients received three-drug combination [VTd (bortezomib+thalidomide+dexamethasone) n=23, VRd (bortezomib+thalidomide+ dexamethasone) n=23, VCd (bortezomib+cyclophosphamide+ dexamethasone) n=21, PAd (liposomal doxorubicin, bortezomib and dexamethasone) n=1 and 3 patients received thalidomide-based combinations]. Two patients received four-drug VTCd (bortezomib+thalidomide+cyclophosphamide+dexamethasone)-based combination.

Transplant protocol: Granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood stem cells (CD34+ $\geq 2\times10^6$/kg) were collected. For conditioning, high-dose melphalan (200 mg/m^2) was administered; patients with renal impairment (RI) received melphalan[23] in dose of 140-150 mg/m^2. This was followed by stem cells infusion. Fifty six patients received stem cells cryopreserved at −80°C, the remaining 293 patients received stem cells stored at 4°C. Transplant response evaluation was done on day 100 ± one week as per European Group for Blood and Marrow Transplant (EBMT) criteria[24]. Patients were advised maintenance therapy using low-dose thalidomide (50 mg daily) or lenalidomide (5-10 mg/day) for 21 days every month or injection bortezomib 2 mg subcutaneously twice a month. In addition, patients with adequate estimated glomerular filtration rate (eGFR) (≥60 ml/min)[23,25] also received injection zoledronic acid once in three months for first two years then once in six months indefinitely along with calcium and vitamin D supplement.

Statistical analysis: An intention-to-treat analysis was done. Descriptive statistics (median and range) were calculated for all variables. Response to transplant was defined as per the EBMT criteria[24]. The prognostic factors for response to transplant were analyzed by Pearson Chi-square test and binary logistic regression analysis. OS was defined as the time from date of transplant until death or date of censor (December 31, 2017). PFS was calculated from date of transplant to disease progression or death (regardless of the cause of death). Survival curves were plotted according to the method of Kaplan and Meier[26] and were compared by the log-rank test. The prognostic factors for survival were analyzed by Cox regression analysis. Analysis was carried out using SPSS-16 statistical software (IBM, Atlanta, USA). The median follow up for the whole group was 73 months (range 12.50-292 months).

Results

A total of 213 (61%) patients achieved complete response (CR), 62 (17.8%) had very good partial response (VGPR), 42 (12.0%) partial response (PR) and 14 (4.0%) patients had stable disease. Eighteen (5.2%) patients died of transplant-related complications (before day 100).

Post-transplant complete response (CR) rate according to pre-transplant status: Among patients with pre-transplant VGPR, 70 (42/60) per cent achieved CR post-transplant, CR rate was 45.5 per cent for those in PR, 23 per cent for those with stable disease and 12.5 per cent for patients with progressive disease pre-transplant (Table II).

Post-transplant response rate according to primary induction regimen: Overall response rate (CR+VGPR+PR) was higher for patients who

Table II. Response to transplant in patients

Pre-transplant	Number of patients, n (%)	Post-transplant				
		CR, n (%)	VGPR	PR	Stable	Died
CR	119 (34.1)	110 (92.4)	4	-	1	4
VGPR	60 (17.2)	42 (70.0)	14	1	-	3
PR	112 (32.1)	51 (45.5)	30	20	6	5
Stable	26 (7.4)	6 (23.1)	10	7	-	3
Progressive disease	32 (9.2)	4 (12.5)	4	14	7	3
Total, n (%)	349	213 (61.0)	62 (17.8)	42 (12.0)	14 (4.0)	18 (5.2)

Abbreviations are as given in Table I

received novel agents (92.8%) versus VAD (92.0%) versus alkylating agents (65.2%), $P<0.001$ [novel agents vs. VAD ($P<0.02$), novel agents vs. alkylating agents ($P<0.001$), VAD versus alkylating agents, ($P<0.01$)]. Corresponding CR rates were 68.1 per cent versus 48.0 per cent versus 26.1 per cent ($P<0.001$). Among novel agents, there was no significant difference in the response rate between those who received doublet (n=178) versus triplet (n=73) (CR 68.8 vs. 71.2%, $P=0.223$).

Predictors of transplant response: Patients with pre-transplant chemosensitive disease (CR+VGPR+PR, $P<0.001$), induction with novel agents ($P<0.001$), transplant in first remission compared to those who underwent transplant after salvage induction ($P<0.001$), those who received one line of induction therapy ($P<0.001$) and serum albumin >3.5 g/dl at diagnosis ($P<0.02$) had higher probability of response to transplant.

Day 100 transplant-related mortality (TRM): Eighteen (5.2%) patients died before day 100 due to transplant-related complications. Low haemoglobin (Hb) (<10 g/dl) ($P<0.05$), low serum albumin (<3.5 g/dl) ($P<0.005$), low eGFR <40 ml/min^{25}, ($P<0.01$), Durie-Salmon Stage IIIB ($P<0.01$) and transplant during second or subsequent remission after salvage induction ($P<0.05$) were predictors of higher mortality. Transplant-related mortality (TRM) was higher for patients transplanted before 2005 compared to those transplanted between 2006-2010 and 2011-2016; 9/81 (11.1%) versus 3/80 (3.8%) versus 6/188 (3.2%), $P<0.02$ (Table III).

Survival: Median OS and PFS from date of transplant for all patients was 90 months [95% confidence interval (CI) 70.8-109.2] and 41 months (95% CI 33.0-49.03),

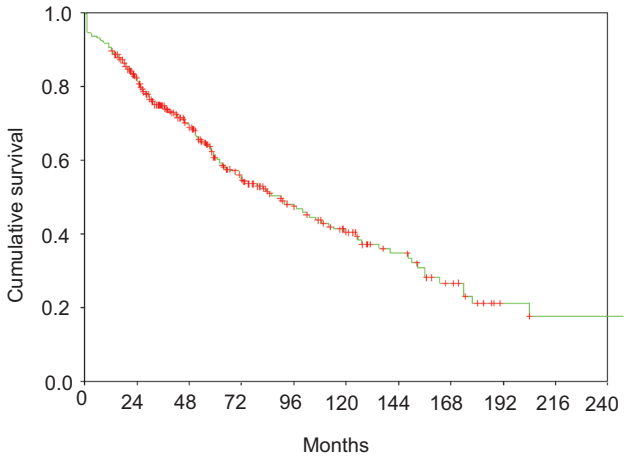

Fig. 1. Overall survival for patients from date of transplant.

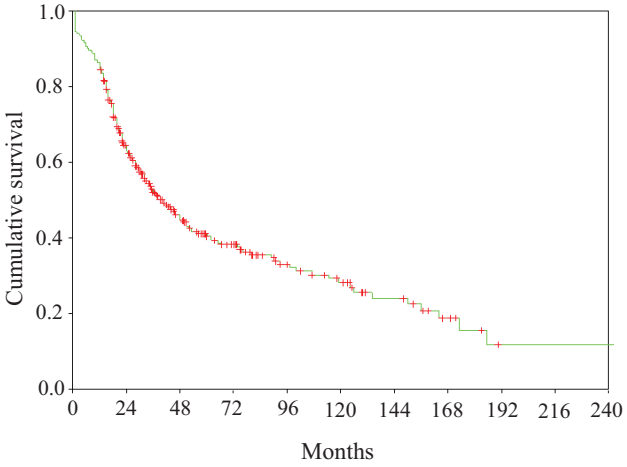

Fig. 2. Progression free survival for patients from date of transplant.

respectively (Figs. 1 and 2). The estimated OS and PFS at 2, 5, 10 and 15 yr was 81.4 versus 64.6 per cent, 60.8 versus 40.6, 40.4 versus 28.2 per cent and 17.7 versus 15.6 per cent, respectively.

Table III. Predictors of transplant related mortality

Factor	n	Day 100 mortality, n (%)	*P* value
Age (yr)			
≤52	177	11 (6.2)	0.254
>52	172	7 (4.1)	
Gender			
Male	236	9 (3.8)	0.08
Female	113	9 (8.0)	
International staging system (ISS) (n=343)			
I	103	2 (1.9)	0.229
II	121	7 (5.8)	
III	119	8 (6.7)	
Durie-Salmon staging system (DSS) (n=348)			
≤IIIA	263	9 (3.4)	0.01
IIIB	85	9 (10.6)	
Extramedullary disease (EMD)			
Yes	80	5 (6.3)	0.39
No	269	13 (4.8)	
Induction therapy			
Novel agents	251	10 (4.0)	0.13
VAD	75	5 (6.7)	
Alkylating agents	23	3 (13.0)	
Number of regimens			
One line	223	8 (3.6)	0.06
>One line	125	10 (8.0)	
Myeloma type (n=342)			
IgG	204	15 (7.4)	0.09
IgA	57	2 (3.5)	
K+L	81	1 (1.2)	
Interval (months)			
≤12	220	10 (4.54)	0.33
>12	129	8 (6.2)	
Haemoglobin (g/dl)			
≤10	201	14 (7.0)	0.05
>10	148	4 (2.7)	
Serum albumin (g/dl)			
<3.5	140	13 (9.3)	0.005
≥3.5	209	5 (2.4)	
BM-PC% (n=348)			
≤40	180	10 (5.6)	0.46
>40	168	8 (4.8)	
Baseline eGFR (ml/min)			
≤40	86	9 (10.5)	0.01
>40	263	9 (3.4)	
Serum calcium (n=324) (mg/dl)			
≥11.5	28	3 (10.7)	0.13
<11.5	296	12 (4.1)	
Pre-transplant status			
Sensitive (CR+VGPR+PR)	291	13 (4.5)	0.16
Resistant (stable+progressive disease)	58	5 (8.6)	
Transplant in first remission versus during second remission	245 104	9 (3.7) 9 (8.7)	0.05
Melphalan dose (n=347) (mg/m^2)			
≤140	35	2 (5.7)	0.56
>140	312	16 (5.1)	
Year of transplant			
Till 2005	81	9 (11.1)	0.02
2006-2010	80	3 (3.8)	
2011-2016	188	6 (3.2)	

P value calculated by Chi-square test. Abbreviations are as given in Table I

Predictors of overall survival (OS): *Univariate analysis*: Patients with ISS Stages I and II (*P*<0.001), Durie-Salmon Stages IIIA (*P*<0.001), absence of extramedullary disease (*P*<0.001), serum albumin (≥3.5 g/dl) (*P*<0.001), eGFR at diagnosis (≥40 ml/min) (*P*<0.001), pre-transplant chemosensitive disease (*P*<0.001), novel agents-based induction (*P*<0.004), achievement of CR post-transplant (*P*<0.001), transplant within 12 months of diagnosis (*P*<0.001) and those who had received one line of induction therapy (*P*<0.001) and patients with transplant in first remission had better OS (Table IV).

Predictors of progression-free survival (PFS): Patients with DSS Stage IIIA (*P*<0.02), transplant within 12 months of diagnosis (*P*<0.03), novel agents-based induction (*P*<0.001), pre-transplant chemosensitive disease (*P*<0.001) and achievement of CR post-transplant (*P*<0.001) were associated with superior PFS. The presence of extramedullary disease (*P*<0.001), transplant in second or subsequent remission post-salvage therapy (*P*<0.001), Hb ≤10 g/dl (*P*<0.05) and albumin <3.5 g/dl (*P*<0.001) were predictors of inferior PFS (Table V).

Multivariate analysis for overall and progression-free survival: Serum albumin (<3.5 g/dl), presence of

Table IV. Predictors of overall survival: Univariate analysis

Factor	Variable	No. of patients	Median OS	95% CI	*P* value
Age (yr)	≤52	177	90.0	52.2-127.8	0.897
	>52	172	85.5	65.3-105.7	
Gender	M	236	91	65.5116.4	0.229
	F	113	85.5	33.5-137.5	
ISS (n=343)	I	103	127	73.9-180.0	0.001
	II	121	91.50	76.8-106.2	I Vs II=0.31
	III	119	59.0	44.8-73.2	II Vs III-0.006
					I Vs III=0.0002
DSS (n=348)	≤IIIA	263	97.0	69.3-125.0	0.001
	IIIB	85	60.5	43.7-77.3	
EMD	Yes	80	42.5	19.5-65.5	0.001
	No	269	102.0	80.6-123.4	
Albumin (g/dl)	≥3.5	140	59.0	37.6-80.4	0.001
	<3.5	209	114.5	75.1-154.0	
Hb (g/dl)	≤10	201	71.5	41.2-101.8	0.07
	>10	148	97.0	58.7-135.3	
BM-PC% (n=348)	≤40	180	100.0	57.9-142.1	0.260
	>40	168	79.0	56.4-101.6	
Ig type (n=342)	IgG	204	96.0	66.8-125.2	0.48
	IgA	57	79.0	51.2-106.8	
	K + L	81	83.5	44.2-122.7	
Induction	Novel	251	91.5	67.4-115.6	0.004
	VAD	75	85.5	54.4-116.6	
	Alkylating agents	23	24.0	9.1-39.0	
Regimen (n=348)	One line	223	124.5	87.7-161.3	0.001
	>One line	125	50.5	35.8-65.2	
eGFR (ml/min)	<40	86	60.5	43.5-77.5	0.001
	≥40	263	97.0	69.93-124.1	
Pre-transplant status	Sensitive (CR+VGPR+PR)	291	102.0	82.9-121.1	0.001
	Resistant (stable+progressive disease)	58	48.0	29.2-66.8	
Interval diagnosis-transplant (months)	≤12	220	106.0	78.9-133.0	0.001
	>12	129	59.0	41.9-76.0	
CD34+ cells ($\times 10^6$/kg)	≤4.0	240	91.5	68.9-114.1	0.10
	>4	68	106.0	58.1-153.9	
Post-transplant response	CR	213	150.0	123.5-184.8	0.001
	Others	136	32.0	22.6-41.4	
Transplant in remission	1st remission	245	125	96.6-154.4	0.001
	Post-salvage	104	37	23.0-51.0	

ISS, international staging system; DSS, Durie-Salmon staging system; BM-PC, bone marrow plasma cell; EMD, extra-medullary disease; Hb, haemoglobin; VAD, vincristine, adriamycin and dexamethasone; Ig, immunoglobulin; OS, overall survival. Abbreviations are as given in Table I

extramedullary disease and ISS Stage III were predictors for inferior OS. Achievement of CR post-transplant and transplant in first remission were predictors for superior OS. Achievement of CR post-transplant and

Table V. Predictors of progression-free survival: Univariate analysis

Factor	Variable	Median PFS	95% CI	*P* value
Age (yr)	≤52	36.0	25.5-46.4	0.817
	>52	44.0	29.8-58.1	
Gender	Male	45.5	35.4-55.6	0.179
	Female	35.0	24.2-45.8	
ISS	I	53.0	16.7-89.3	0.070
	II	44.0	34.8-53.1	
	III	30.0	20.3-39.5	
DSS	≤IIIA	44.0	33.8-54.2	0.02
	IIIB	30.0	15.9-44.1	
EMD	Yes	24.0	15.5-22.5	0.001
	No	46.0	36.0-56.0	
Albumin (g/dl)	≥3.5	28.0	18.3-37.7	0.001
	<3.5	52.0	27.5-76.5	
Hb (g/dl)	≤10	34.0	24.9-43.1	0.05
	>10	51.0	38.2-64.0	
BM PC%	≤40	50.0	21.8-78.2	0.211
	>40	35.0	26.2-43.8	
Ig type	IgG	41.0	28.2-53.8	0.571
	IgA	41.0	33.1-48.9	
	K + L	38.0	0.44-75.6	
Induction	Novel	50.0	35.1-64.8	0.001
	VAD	31.0	16.9-45.1	
	Alkylating agents	18.0	11.7-24.3	
Regimen	One line	62.0	34.0-90.0	0.001
	>One line	22.0	18.2-25.2	
Pre-transplant status	Sensitive (CR+VGPR+PR)	51.0	38.5-63.5	0.001
	Resistant (stable+progressive disease)	18.0	12.8-23.2	
Interval diagnosis-transplant (months)	≤12	48.0	38.3-57.7	0.03
	>12	28.0	19.7-36.3	
CD34 + cells ($\times 10^6$/kg)	≤4	39.0	31.2-46.7	0.24
	>4	51.0	30.1-71.9	
Post-transplant response	CR	91.0	60.9-121.0	0.001
	Others	16.0	14.5-17.5	
Transplant remission	1st remission	62.0	41.0-82.9	0.001
	Post-salvage	20.0	14.8-25.2	

Abbreviations are as given in Table IV

transplant in first remission were predictors for superior PFS (Table VI).

Current status: In a follow up of patients done in 2018, 184 of 349 patients (52.7%) were alive; 134 (38.4%)

Table VI. Multivariate analysis for overall and progression free survival

Variable	*P* value	Hazard	95% CI
OS			
Serum albumin	0.01	1.620	1.12-2.336
EMD	0.005	1.835	1.207-2.79
Stage ISS I + II versus III	0.009	0.598	0.405-0.881
Primary versus post-salvage transplant	0.001	0.502	0.342-0.737
Post-transplant CR	0.001	0.382	0.262-0.556
PFS			
Primary versus post-salvage transplant	0.017	0.652	0.459-0.926
Post-transplant CR	0.001	0.245	0.180-0.334

Abbreviations are as given in Table IV

progression free, 25 (7.2%) with disease and were on salvage therapy, 17 (4.9%), were in second CR after salvage therapy and eight (2.3%) patients had low level serum M spike, <1 g/dl (MGUS like). A total of 164 (47.1%) patients died; these included – 18 (5.2%) deaths before day 100 (TRM), 129 (37.0%) due to progressive disease and its complications and 17 patients (4.9%) due to unrelated reasons. Causes included second malignancy in five (myelodysplastic syndrome – 1, acute myeloid leukaemia – 1, renal cell cancer – 1, hepatocellular carcinoma – 1, carcinoma tongue – 1), dengue fever in two, coronary artery disease in six, cerebral haemorrhage, Alzheimer's disease, acute graft versus host disease and ventilator-associated complications in one patient each. Status was unknown for one patient.

Discussion

Post-transplant high CR rate, higher median OS (90 months) and PFS (41 months) with 10 yr survival rate of 40.4 and 28.2 per cent, respectively, are important findings in the present study. More than one-third of patients had high-risk disease at diagnosis. Post-transplant overall response rate (90.8%) was high in the present study; this was similar to earlier observations[13,14,22]. Conversion to post-transplant CR from pre-transplant response - very good PR (70%), PR (45.5%) and 23 per cent CR in those with stable disease reflected contribution by transplant in augmenting the response already achieved with pre-transplant therapy. Post-transplant CR rate was not significantly different between doublet versus triplet regimen. At present, it is recommended to use triplet (three-drug combinations)[2,13]; however, there is no direct comparison between different triplets being used currently (VTD vs. VRD vs. VCD). There is also suggestion that four cycles of induction may be adequate and more may not be better[27].

A median OS and PFS of 90 and 41 months\in our study is similar to earlier studies[15-20] reporting long-term transplant results. An estimated OS at 10 and 15 yr (40.4 and 17.7%, respectively) indicated prolonged survival in some patients. Similarly, PFS of 15.6 per cent at 15 yr was indicative of a functional cure in a subgroup of patients. A long-term follow up is still needed in the absence of a plateau in survival curve[28]. Achievement of CR post-transplant and transplant in first remission were important predictors of OS and PFS. For those who achieved CR, median OS was 150 months (95% CI 123.5-184.8), significantly higher to those with VGPR and PR. These findings were similar to earlier studies[29]. Achievement of CR post-transplant has been identified as an important marker of long-term survival and is considered to be a desirable goal. Recent studies have suggested that achievement of 'nil' minimal residual disease (MRD) status on multiparameter flow cytometry is a better surrogate marker of long-term survival[30].

In the present study, 'day +100' TRM was 5.2 per cent; this was higher than the current standard of one per cent or less[13]. Important predictive factors of higher mortality were low serum albumin (<3.5 g/dl) and low estimated GFR (<40 ml/min) at diagnosis and transplant in second or subsequent remission. A reduction in TRM could be due to a combined effect of better case selection, better supportive care and use of novel agents leading to higher response rates including CR which resulted in better depth of response post-transplant and better PFS and OS. Five patients (5/18) had graft failure; three of these had CD34+ stem cells <2 million and two patients had 3.38 and 6.70 million, respectively. In the present study, 56 patients received stem cells cryopreserved at −80°C, the remaining 293 patients received stem cells kept at 4°C. There was no difference in outcome OS and PFS in the two groups. This was consistent with earlier observations from our centre[22] and those reported recently[31]. No difference was observed in outcome of patients who received ≤4 million CD34+ stem cells or more.

Lack of cytogenetic/FISH (florescent *in situ* hybridization) data was an important limitation of the present study for most patients.

In conclusion, the findings of the present study showed higher response rate to transplant translating into improved progression free and overall survival. Reducing TRM to <1 per cent and further improvement in CR rates and long-term survival remain desirable goals in future studies.

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For correspondence: Dr Lalit Kumar, Department of Medical Oncology, Room 234, IRCH Building,
All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: lalitaiims@yahoo.com