Original Articles

Autologous stem cell transplantation for multiple myeloma: Long-term results

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ABSTRACT

Background. Survival of myeloma patients has improved considerably in the past decade. However, limited data are available on their long-term outcome. We analysed the data of 225 consecutive patients who underwent autologous stem cell transplantation (ASCT) at our centre.

Methods. Between April 1990 and December 2013, a total of 225 patients with multiple myeloma (median age 53 years, range 27–67 years, 69.3% men) underwent ASCT. High-dose melphalan 200 mg/m^2 was used for conditioning. Before transplant, the patients received induction therapy with novel agents (thalidomide and dexamethasone, or lenalidomide and dexamethasone, or bortezomib and dexamethasone); or vincristine, doxorubicin, dexamethasone; or alkylating agents (vincristine, melphalan, cyclophosphamide and prednisolone; or melphalan and prednisolone). The response to transplant was evaluated using the European Bone Marrow Transplant criteria, and an intention-to-treat analysis was done.

Results. Four-fifths (79.6%) of our patients had Durie Salmon Stage (DSS) IIIA and nearly a quarter (24%) of them had International Stage III disease. Before the transplant, 80.4% of patients had chemosensitive disease. The median interval from diagnosis to transplant was 10 months (range 2–128 months). Following ASCT, 197 (87.5%) patients responded. Complete response was obtained in 54.7%, very good partial response in 19% and partial response in 13.8%. At a median follow-up of 90 months (range 18–266 months), the median progression-free survival (PFS) and overall survival (OS) were 32 and 85.5 months, respectively. The estimated PFS and OS at 10 years were 29.7% and 43.6%, respectively. On multivariate analysis, the presence of extramedullary disease (HR 3.05, $p < 0.001$), and ISS III (HR 0.50, $p < 0.02$) predicted inferior OS. Extramedullary disease at diagnosis (HR 1.585, $p < 0.03$), and more than one regimen pre-transplant (HR 0.53, $p < 0.02$) predicted an inferior PFS. Complete response was a predictor of superior OS and PFS ($p < 0.001$).

Conclusion. Complete response following ASCT is associated with good long-term outcome. Alternative treatment strategies are needed to improve results in patients who fail to achieve CR post-transplant and in those with high-risk disease.

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INTRODUCTION

Management of multiple myeloma has undergone a paradigm shift in the past decade. Currently, all symptomatic patients are treated with initial induction therapy using a combination of novel agents, e.g. immune modulators (thalidomide, lenalidomide), proteasome inhibitors (bortezomib) and dexamethasone. Following 4–6 months of induction therapy, eligible patients (aged 65–70 years or younger) are advised treatment with high-dose melphalan followed by autologous stem cell transplantation (ASCT). This is followed by maintenance therapy using low-dose thalidomide/lenalidomide or bortezomib for 1–2 years.[1–3] A number of non-randomized, randomized,[4–9] population-based studies[10] and meta-analyses[11] have suggested that this approach is associated with higher response rates, and better progression-free survival (PFS) and overall survival (OS). Following transplant, nearly 50% of patients achieve complete response (CR), which in turn is associated with longer OS and PFS. Approximately 15% of these are long-term survivors (beyond 10 years).[12–14] Our initial results with ASCT have been reported earlier.[15,16] We now describe the long-term outcome of 225 consecutive patients of myeloma who had undergone ASCT till December 2013.

METHODS

Between April 1990 and December 2013, a total of 239 patients with plasma cell dyscrasias (225 multiple myeloma) underwent ASCT. We prospectively collected and analysed the data of patients with multiple myeloma who underwent ASCT.

Transplant protocol

Briefly, all patients were initially reviewed in the weekly Bone

Marrow Transplant Clinic in which the procedure, potential risks and benefits were explained to the patients and family members. Pre-transplant evaluation included a detailed history, physical examination, staging according to the Durie and Salmon and the International Staging System (ISS). Details of previous treatment were recorded. The pre-transplant investigations included haemoglobin, total and differential count, renal and liver function tests, bone marrow examination, skeletal survey, and serum and urine electrophoresis, immune-fixation studies, serum β-2 microglobulin and quantitative immunoglobulin levels. Written informed consent was obtained. Regimen-related toxicity was defined as per the Seattle criteria.[17]

Response assessment

Evaluation of response to ASCT was assessed 6 weeks after transplant using the European Group for Blood and Bone Marrow Transplantation (EBMT) criteria.[18] CR was defined as disappearance of monoclonal protein in the serum and urine by immunofixation, maintained for a minimum of 6 weeks, and normalization of the bone marrow (BM) with <5% plasma cells or fewer plasma cells of normal morphology in the BM aspirate. Very good partial response (VGPR) was defined as serum and urine M (monoclonal) component detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M protein and urine M protein <100 mg per 24 hours, maintained for a minimum of 6 weeks. Partial response (PR) required >50% reduction of measurable monoclonal protein or BM infiltration. Progressive disease (PD) was defined as any of the following: (i) an absolute increase of >500 mg of serum M protein per decilitre, as compared with the nadir value; (ii) an absolute increase of >200 mg of urinary M protein in 24 hours; (iii) a new bone lesion or plasmacytoma; (iv) an increase in the size of such lesions; or (v) the development of hypercalcaemia (serum calcium level >11.5 mg/dl). Stable disease (SD) was defined as not meeting the criteria for CR, VGPR, PR or PD.[18] Post-transplant patients were followed up every month for the first year, then every 2–3 months for 3 years, and thereafter every 4–6 months. Follow-up information was available for all patients.

Stem cells

The source of stem cells was the BM in the first 7 patients but in the next 218 patients granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells were harvested. A median of two leukapheresis were done (range 1–3). A sample of stem cells was obtained and total cell counts were determined using an automated cell counter while the differential count was done manually. CD34 cells were labelled with fluorescence 4-conjugated anti-CD34 and analysed using a fluorescence-activated cell sorter scan flowcytometer to obtain absolute CD34 counts. Stem cells were kept at 4 °C or were cryopreserved at –80 °C using cryoprotectant mixture of 7.5% dimethyl sulphoxide (DMSO), albumin and saline. Stem cells were transfused intravenously (i.v.) 24 hours after high-dose melphalan. The viability of cells was determined by the trypan blue dye exclusion test.[15]

Conditioning regimen

The myeloablative regimen consisted of melphalan 200 mg/m^2 slow i.v. push on day 1 followed by forced alkaline diuresis. Patients with renal insufficiency at the time of transplant received melphalan 120–150 mg/m^2. Stem cells were reinfused on day 0 through a central venous catheter (Hickman) preceded by pheniramine maleate 50 mg i.v.

Supportive care and monitoring

All patients received growth factors G-CSF 5 μg/kg daily subcutaneously on day 0, 12 hours after stem cell infusion and onwards until engraftment. Patients were admitted in an isolation room and reverse barrier nursing was practised. All patients received antimicrobial prophylaxis—ciprofloxacin, fluconazole/itraconazole and acyclovir. Packed red blood cells and platelet transfusions were administered to maintain a haemoglobin level of 8 g/dl and a platelet count >20×10^9/L. All the blood products transfused during the post-transplant period were irradiated with 25 Gy. Patients received broad-spectrum antibiotics for fever; amphotericin B was added, if they had persistent fever after 4–5 days of i.v. antibiotics.

Post-transplant maintenance therapy

Until December 2001, patients received maintenance therapy, with interferon-alpha at a dose of 3 million units thrice a week subcutaneously. From January 2002, all patients received thalidomide 50 mg daily for 1 year or more. From 2010 onwards, patients have also received lenalidomide 5 mg daily for 14 days every 28 days or bortezomib 2 mg subcutaneously once or twice a month. Maintenance therapy was initiated on post-transplant day 100 when engraftment was stable. Maintenance therapy was planned for 12 months but was continued for longer periods if patients wanted and if there were no major toxicities and the disease was in remission. Patients also received zoledronic acid 4 mg i.v. once in a month for 6–9 months after diagnosis, then once every 3 months for the initial 2 years, followed by once in 4–6 months indefinitely.

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.[17] The prognostic factors (type of induction therapy, more than one line of induction therapy, presence of extramedullary disease) for response to transplant were analysed 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 censoring. 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 and were compared by the log rank test. The prognostic factors for survival were analysed by Cox regression analysis. Analysis was carried out using SPSS-16 statistical software. The median follow-up for the whole group was 90 months (range 18–272 months). The data were censored on 30 June 2015.

RESULTS

Patient characteristics

The patients' age ranged from 27 to 67 years (median 53 years). There were 156 men and 69 women (Table I). Before transplant, 128 patients had received induction therapy using novel agents (thalidomide and dexamethasone, or lenalidomide and dexamethasone, or bortezomib and dexamethasone), 74 patients had received induction chemotherapy using VAD (vincristine, doxorubicin, dexamethasone) and 23 patients received alkylating agents (VMCP [vincristine, melphalan, cyclophosphamide and prednisolone] or MP [melphalan and prednisolone])-based induction, mainly in the initial years. One hundred and eighty-one patients (80.4%) had chemosensitive disease (including CR, VGPR and PR) before ASCT. The remaining 44 patients (19.6%)

TABLE I. Characteristics of the patients (*n*=225)

Characteristic	*n*	%
Median age (in years)	53	Range 27–67
Men: Women	156: 69	
Durie Salmon Stage		
I–II	12	5.3
IIIA	167	74.2
IIIB	46	20.4
International Staging System		
I	80	36.7
II	86	39.4
III	52	23.9
Ig type		
IgG kappa	105	47.1
IgG lambda	47	21.1
IgA kappa	18	8.1
IgA lambda	14	6.3
Kappa light chain	22	9.9
Lambda light chain	16	7.2
Non-secretory	1	0.4
Mean bone marrow plasma cells % (*n*=223)	40%	Range 1–100
Mean haemoglobin (g/dl)	9.76	Range 3.2–16
Mean serum albumin (g/dl)	3.7	Range 1.8–5.7
Pre-transplant status		
Chemosensitive (CR-63,VGPR-36, PR-82)	181	80.4
Chemoresistant (SD-23, PD21)	44	19.5
Extramedullary disease	55	20.4
Induction regimens		
Alkylating agents	23	10.2
Vincristine, doxorubicin and dexamethasone	74	32.9
Novel agents	128	56.9
Median interval from diagnosis to transplant (in months)	10	Range 2–128

CR complete response VGPR Very good partial response PR partial response SD stable disease PD progressive disease

had either SD or PD at the time of transplant. Forty-six patients had serum creatinine >2 mg/dl at diagnosis (Durie Salmon stage IIIB). The median interval from diagnosis to transplant was 10 months (range 2–128 months) and 131 (58.2%) patients received a single-regimen induction therapy while 94 (41.8%) received more than one regimen of induction therapy.

Response to transplant

The post-transplant response evaluation (day 100±7) revealed CR in 123 (54.7%). Among 123 patients with CR, 63 (51.3%) were in CR pre-transplant (Table II).

Predictors of response

For overall response (CR+VGPR+PR). On univariate analysis, transplant within 12 months of diagnosis, ISS stages I and II, presence of pre-transplant chemosensitive disease (CR+VGPR+PR), induction treatment with novel agents and absolute lymphocyte count (ALC) ≤3000/cmm were associated with a higher response rate. On logistic regression analysis, the presence of extramedullary disease (OR 0.075, p<0.001), treatment with one-induction regimen (p<0.001, OR 2.92, 95% CI 1.56–5.48), and ISS stage (I+II *v.* III) (p<0.006, OR 3.92, 95% CI 1.47–10.44) were predictive factors (Table III).

For complete response. Treatment with novel agents (p<0.003, OR 2.14, 95% CI 1.31–3.52), one-induction regimen (p<0.001, OR 1.98, 95% CI 1.33–2.95) and absence of extramedullary disease (p<0.03, OR 1.99, 95% CI 1.06–3.78) predicted higher probability to achieve CR.

Toxicity to high-dose melphalan

Grade III mucositis (65.7%), nausea/vomiting (21.5%) and diarrhoea (26.8%) were the common regimen-related toxicities. Other toxicities were liver dysfunction grade I (3.1%) and renal dysfunction (25.7%). One-fifth of the patients had evidence of engraftment syndrome as evidenced by weight gain, fever, dyspnoea, pleural effusion, skin rash, and impaired liver and renal functions. This required use of diuretics and low-dose steroids in a few patients.

Sixteen patients (7.2%) died by day 30 post-ASCT and another 3 patients died between days 30 and 100. The causes of death were pulmonary infections (*n*=13, including multi-organ failure in 9 of them), pulmonary embolism (*n*=1), *Pneumocystis carinii* pneumonia (*n*=1), bleeding (*n*=2 including bleeding diathesis in one), and viral infection (H1N1) and acute myocardial infarction in one each. The higher transplant-related mortality was mainly in the initial years and was possibly due to poor case selection, e.g. 7 patients had renal failure at the time of transplant, 2 had rheumatoid arthritis, 2 had paraparesis and 5 patients had PD. Over the years, the mortality has decreased and in the past 2 years there have been no deaths.

Survival

The median PFS and OS for the whole group were 32 and 85.5 months, respectively. Patients who achieved CR had significantly higher PFS (89 months) compared to those with VGPR (20 months) and PR (18 months; p<0.001). The difference in PFS for patients who achieved VGPR and PR was not significant. The median OS for those with CR was 178 months, which is higher than in those with VGPR (71 months) and PR (48 months; p<0.001). There was no difference in OS between VGPR and PR (p=0.43; Table IV). The estimated mean (SE) PFS percentage at

TABLE II. Response to transplant

Pre-transplant status	*n*	Post-transplant response				
		Complete	Very good partial	Partial	Stable disease	Died
Complete response	63	57 (90.5)	2	0	0	4 (6.3)
Very good partial response	36	26 (72.2)	6	1	0	3 (8.3)
Partial response	82	32 (39.0)	25	14	6	5 (6.1)
Stable disease	23	5 (21.7)	8	7	0	3 (13.0
Progressive disease	21	3 (14.3)	2	9	4	3 (14.3)
Total	225	123 (54.7)	43 (19.1)	31 (13.8)	10 (4.4)	18 (8.0)

TABLE III. Factors predicting response to autologous stem cell transplantation

Factor	*n*	Response		p value	Response		p value
		Complete	Others		Overall*	Others	
Age (years)							
≤53	118	57	61	<0.03	100	18	0.127
>53	107	66	41		97	10	
Sex							
Male	156	87	69	0.36	140	16	0.103
Female	69	36	33		57	12	
Interval: Diagnosis to transplant (months)							
≤12	146	92	54	0.001	135	11	<0.003
>12	79	31	48		62	17	
International Staging System (n=223)							
I	82	52	30	0.153	77	5	<0.001
II	89	46	43		82	7	
III	52	25	27		36	16	
I+II	171	98	72	0.15	157	12	<0.001
III	52	25	27		36	16	
Durie Salmon stage							
≤IIIA	179	104	75	<0.03	166	13	<0.001
IIIB	46	19	27		31	15	
*Extramedullary dis*ease							
Present	55	23	32	<0.02	43	12	<0.01
Absent	170	100	70		154	16	
Ig type							
IgG	152	75	77	<0.04	129	23	0.136
IgA	32	21	11		30	2	
Light chains	38	26	12		36	2	
Haemoglobin (g/dl) (n=224)							
≤7	40	16	24	<0.03	29	11	<0.003
>7	184	106	78		167	17	
Serum albumin (g/dl)							
≤3.5	100	44	56	<0.003	81	19	<0.007
>3.5	125	79	46		116	9	
Plasma cell %							
≤40	117	68	55	0.171	105	12	0.203
>40	108	55	53		92	16	
Absolute lymphocyte count (per cmm) at diagnosis (n=187)							
≤3000	155	91	64	0.08	141	14	<0.04
>3000	32	14	18		25	7	
Induction therapy							
Novel agents	128	82	46		115	13	<0.001
VAD	74	36	38		68	6	
Alkylating agents	23	5	18	<0.001	14	9	
Number of regimens used pre-transplant							
One	131	90	41	<0.001	123	8	<0.001
More than one	94	33	61		74	20	
Pre-transplant disease status							
Chemosensitive	181	115	8	<0.001	115	66	<0.001
Chemoresistant	44	8	36		8	36	

* CR+VGPR+PR complete response + very good partial response + partial response VAD vincristine, doxorubicin and dexamethasone

TABLE IV. Survival according to post-transplant response (*n*=207)

Response	*n*	Median PFS (months)*	95% CI	Median OS (months)*	95% CI
Complete	123	89	42–136.1	178	139–217.1
Very good partial	43	20	16.8–23.2	71	45–97
Partial	31	18	15.8–20.2	48	23.4–72.6
Stable disease	10	5	2.0–8.1	9	4.4–13.6

*p<0.001 PFS progression-free survival OS overall survival

5 and 10 years was 38.5 (0.03) and 29.7 (0.04), respectively. The estimated mean (SE) OS percentage at 5 and 10 years was 63.2 (0.03) and 43.6 (0.04), respectively.

Prognostic factors

On univariate analysis factors, Durie Salmon stage ≤IIIA, ISS stages I and II, interval from diagnosis to transplant (≤12 months), serum albumin (>3.5 g/dl), one-induction regimen before transplant

TABLE V. Factors determining progression-free (PFS) and overall survival (OS)

Factor	*n*	Median PFS (months)	95% CI	p value	Median OS (months)	95% CI	p value
Age (years)							
≤53	118	33	24.2–41.8	<0.68	91	60.2–121.8	0.68
>53	107	31	16.3–47.8		79	62.6–95.4	
Sex							
Male	156	34	23.0–45.1	0.38	91	64.3–117.7	0.18
Female	69	28	33		71	32.8–109.2	
Interval: Diagnosis to transplant (months)							
≤12	146	42	29.1–55.0	0.002	106	67.0–145.1	<0.001
>12	79	22	13.6–30.4		51.5	45.1–57.8	
≤10	120	48	34.1–62.0	0.003	125.5	83.3–167.7	0.001
>10 months	105	24	17.8–30.2	0.003	53.5	44.6–62.4	
International Staging System (n=223)							
I	82	34	18.4–49.7	0.12	97	60.8–133.2	0.001
II	89	37	18.1–56.0		52	29.8–74.2	
III	52	24	13.4–35.6				
I+II	171	36	24.1–48.0	0.04	95	74.0–116.0	0.002
III	52	24.5	13.4–35.6		52	34.7–69.4	
Durie Salmon stage							
≤IIIA	179	37	22.9–51.1	<0.001	95	59.0–130.9	0.001
IIIB	46	22	17.2–26.8		37	0–74.01	
*Extramedullary dis*ease							
Present	55	21	12.4–29.6	0.01	40	7.4–72.6	<0.001
Absent	170	37	25.1–48.9		102	64.3–139.7	
Ig type							
IgG	152	28	19.5–36.5	0.32	91	63.9–118.1	0.66
IgA	32	48	35.8–60.2		85	10.6–159.4	
Light chains	38	36	2.4–69.6		72	46.6–97.40	
Haemoglobin (g/dl) (n=224)							
≤7	40	20	11.5–28.5	0.007	37	14.9–59.1	0.002
>7	184	34	20.5–47.5		95	67.03–123.0	
Serum albumin (g/dl)							
≤3.4	86	22	17.6–26.4	0.002	56	33.6–78.4	<0.001
≥3.5	139	43	27.8–58.2		106	55.0–157.0	
Plasma cell %							
≤40	117	36	20.5–51.5	0.48	91	45.1–136.8	0.32
>40	108	30	20.0–40.0		79	44.5–113.5	
Absolute lymphocyte count (per cmm) at diagnosis (n=187)							
≤3000	155	42	30.2–53.8	<0.001	103	60.8–145.2	<0.001
>3000	32	17	12.4–21.6		51	27.0–75.0	
Induction therapy							
Novel agents	128	50	28.6–71.4	0.004	91	48.5–133.5	0.03
VAD	74	31	17.3–44.7		85	55.5–115.5	
Alkylating agents	23	18	11.8–24.2		24	5.2–42.8	
Number of regimens used pre-transplant							
One	131	51	29.3–72.7	<0.001	140	91.8–188.2	<0.001
More than one	94	22	18.2–25.8		51	35.9–66.1	
Two	197	36	24.7–47.3	0.005	95	73.8–116.2	<0.001
More than two	28	18	12.5–23.5		45.5	9.9–81.1	
Pre-transplant disease status							
Chemosensitive	181	48	34.7–61.3	<0.001	95	78.3–111.7	0.005
Chemoresistant	44	18	13.8–22.2		48	27.6–68.4	
Post-transplant response							
Complete response	123	107	54.2–160.0	<0.001	174	137.3–210.7	<0.001
Others	102	16	14.0–18.0	<0.001	31	19.0–43.0	

VAD vincristine, doxorubicin and dexamethasone

and ALC ≤3000/cmm at diagnosis were associated with a better PFS and OS. The presence of chemosensitive disease (CR+VGPR+PR) pre-transplant, treatment with novel agents and achievement of CR post-transplant were also associated with improved PFS and OS (Table V).

Multivariate analysis

On Cox regression analysis for PFS, Durie Salmon stage ≤IIIA, two versus more than two lines of induction therapy before transplant, presence of extramedullary disease, ALC ≤3000/cmm at diagnosis and achievement of CR post-transplant were the predictive factors. For OS, in addition to the above factors, ISS stage I+II *v.* III was a predictor of better outcome (Table VI).

10-year survival according to response

The estimated PFS at 10 years for patients with CR, VGPR and PR were 45.4%, 7% and 0%, respectively (Fig. 1). The estimated OS at 10 years for patients with CR, VGPR and PR were 68.5%, 21% and 21.9%, respectively (Fig. 2). We analysed factors predictive of survival beyond 10 years. For OS, achievement of CR post-transplant ($p<0.005$), absence of extramedullary disease ($p<0.001$), up to two-induction regimens ($p<0.01$), presence of chemosensitive disease ($p<0.05$) and transplant within 12 months of diagnosis ($p<0.08$) were predictive factors.

For PFS, achievement of CR post-transplant ($p<0.001$), absence of extramedullary disease ($p<0.005$), treatment with one line ($p<0.01$) or up to two lines of induction therapy ($p<0.08$), and presence of Durie Salmon stage ≤IIIA were important factors.

Current status

Among 207 patients, 70 patients (33.8%) continue to be alive and progression-free, 27 patients (13%) are alive with disease and are on salvage treatment, 10 patients (4.8%) are alive in second CR following salvage therapy, 7 patients (3.4%) are alive and asymptomatic with serum M protein being positive at a low level. Eighty-five (41%) patients died of PD and its complications. Eight (3.8%) patients died of unrelated causes including a second malignancy in 3 (renal cell carcinoma, myelodysplastic syndrome and acute myeloid leukaemia), and 1 each from a cardiac event, stroke, pulmonary embolism, viral infection (dengue) and acute graft-versus-host disease following salvage ASCT.

DISCUSSION

A better outcome for patients with multiple myeloma following ASCT has been attributed to achievement of CR. This translates into longer PFS and OS. In our study, following transplant, 80% of patients responded, with 54.7% achieving CR. These results are similar to recent studies using novel agents-based combinations for induction and is higher compared to those achieved with conventional chemotherapy earlier (before 2001). In our study, 57% of patients had received novel agents-based induction therapy, and the remaining patients had received either infusional combination of VAD (n=74) or alkylating agent-based (n=23) combination in the initial years. Among novel agents, 74 (32.9%) patients received thalidomide and dexamethasone, 27 got lenalidomide and dexamethasone, and bortezomib and dexamethasone-based combinations. The post-transplant overall

TABLE VI. Predictors of survival: Cox regression multivariate analysis

Prognostic factor	Progression-free survival		Overall survival	
	HR	p value	HR	p value
Presence of extramedullary disease	1.585	0.03	3.053	0.001
Two versus more than two lines of induction therapy pre-transplant	0.534	0.02	0.542	0.07
Durie Salmon Stage (≤IIIA *v.* IIIB)	0.347	0.001	0.365	0.001
International Staging System I+II versus III	–	–	0.503	0.026
Serum albumin (≤3.5 *v.* >3.5 g/dl)	–	–	0.146	0.004
Absolute lymphocyte count at diagnosis(≤3000/cmm *v.* more)	0.414	0.001	0.235	0.001
Post-transplant complete response	0.175	0.001	0.203	0.001

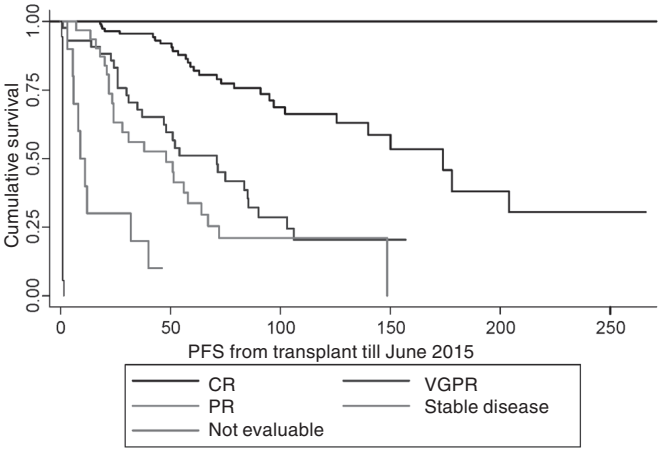

FIG 1. Progression-free survival (PFS) by Kaplan–Meier method (CR complete response VGPR very good partial response PR partial response)

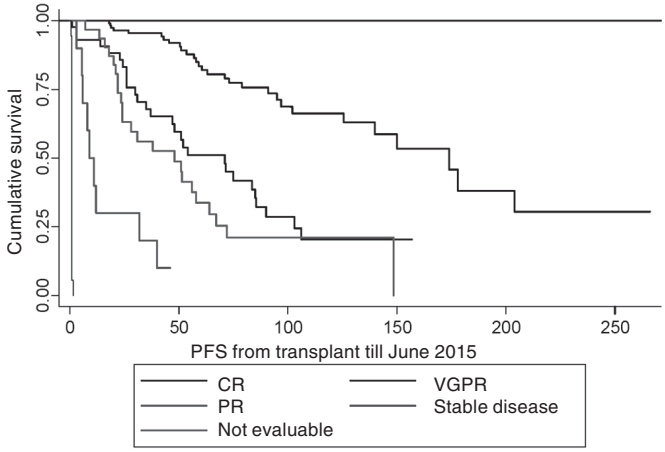

FIG 2. Overall survival (OS) by Kaplan–Meier method (CR complete response VGPR very good partial response PR partial response)

response rate (90.5%, 96.3% and 92.6%, respectively) and CR rate (35.1%, 44.4% and 48.1%, respectively) was not significantly different among the three combinations. Currently, a combination of three drugs is preferred for induction. However, there is no head-to-head comparison of these regimens (bortezomib + lenalidomide + dexamethasone [VRD], bortezomib + thalidomide + dexamethasone [VTD] or bortezomib + cyclophosphamide + dexamethasone [VCD]). In a recent meta-analysis of non-randomized studies, VTD was superior to VCD in rates of CR or near CR ($p<0.002$) and VGPR ($p<0.0001$). However, neurotoxicity was higher with VTD ($p<0.05$).[19] Mai *et al*. reported results of a randomized study comparing VCD with liposomal doxorubicin, bortezomib and dexamethasone (PAD) and the response rate (≥VGPR) was significantly higher in the VCD arm ($p<0.001$) with overall less serious toxic effects.[20]

We found that the probability to achieve CR was higher for patients who received induction with novel agents, in those who received one line of induction therapy before transplant (compared to those who received an additional induction regimen) and in those without evidence of extramedullary disease at diagnosis. The probability to achieve CR post-transplant is related to the pre-transplant disease status and is supported by our observation that 115 of 181 (63.5%) patients with pre-transplant chemosensitive disease (CR + VGPR + PR) achieved CR compared to 8 of 44 (18.1%) patients with chemoresistant (SD or PD) disease ($p<0.01$). Recent studies have suggested that presence of extramedullary disease is associated with shorter PFS and OS and is a marker of high-risk disease.[21] Similar to earlier observations, results of our study support the hypothesis that achievement of CR represents an early index of long-term survival.[13,14,22,23]

Whether additional therapy should be given to improve the response in patients who do not achieve CR or VGPR after 4–6 cycles of the induction regimen is not clear. Vij *et al*. analysed 539 patients, 214 who proceeded directly to transplant while 324 who received additional therapy.[24] The majority of patients received VAD infusional chemotherapy. The PFS at 4 years was 30% for those who received additional therapy compared to 31% for those who did not. The OS was also not significantly different. For 195 patients who had received novel agents as first-line therapy, there was no difference in the OS between patients who received additional therapy compared with those who did not.[24] It has been suggested that post-transplant consolidation using 2–4 cycles (same regimen as used pre-transplant for induction) may help to deepen response with survival benefit.[25]

Few studies have reported long-term outcome for myeloma patients following ASCT.[14] We estimated the 10-year probability of PFS and OS to be 29.7% and 43.6%, respectively. Patients who achieved CR post-transplant had a significantly higher median OS (178 months) and PFS (89 months).

In our study, the median PFS was 42 versus 22 months for those transplanted within 12 months of diagnosis ($p<0.002$). Similarly, OS was 106 versus 51.5 months ($p<0.001$). However, OS was not significantly different in a randomized French study of 200 patients who underwent ASCT either immediately after induction therapy or after they had relapsed. However, patients who were transplanted earlier had a significantly higher median PFS compared to those transplanted later (39 *v*. 13 months, $p<0.01$).[26] Recently, results of the IFM/DFCI-2009 study (The Determination Trial), where VRd (bortezomib, lenalidomide and dexamethasone) induction (3 cycles) followed by randomization to early versus delayed ASCT have been reported.[27] This study included 700 patients and the second interim analysis has shown superior CR rates (58% *v*. 46%, $p<0.01$) as well as better 3-year PFS (61% *v*. 48%) in the early ASCT arm. OS was not significantly different between the two arms and requires longer follow-up. This study has suggested that early ASCT should remain the standard of care for young patients with *de novo* myeloma even with highly active regimens such as VRd.[27]

Maintenance therapy for 1–2 years post ASCT is the present standard of care. This is based on the assumption that it may be more effective in patients with minimal residual disease after transplantation. Currently, low-dose thalidomide (50 mg/day), lenalidomide (5–10 mg daily for 14–21 days a month) or bortezomib (once a month) are being used based on the results of multiple randomized trials. Interestingly, responses improved following maintenance therapy in some patients. Similar observations have been made by others too. Promising results with monoclonal antibodies in recent reports suggest their potential role in maintenance therapy in future studies.[28]

The lack of cytogenetic data is a major limitation of our study. However, long-term results at a median follow-up of 90 months confirm that high-dose chemotherapy supported by ASCT in patients with advanced myeloma is safe, effective and is associated with a high CR rate. Patients who achieve CR post-transplant have a longer survival. Our study also supports the view that early transplant is better. Strategies to improve outcome in patients who fail to achieve CR following transplant and in high-risk patients, e.g. use of consolidation therapy post-transplant to improve outcome are likely to be potential areas of research in future studies.

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