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Early versus delayed autologous stem cell transplantation in patients receiving novel therapies for Multiple Myeloma

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Abstract

Autologous stem cell transplant (ASCT) is an effective treatment for multiple myeloma (MM). However the timing of ASCT in the era of novel agents (lenalidomide, thalidomide, bortezomib) is unknown. We retrospectively reviewed the outcome of MM patients who received novel agent based induction treatment and received first ASCT within 12 months of diagnosis (early ASCT, N = 102), or at a later date (late ASCT, N = 65). Median time to ASCT was 7.9 months vs. 17.7 months in the early vs. late ASCT. The 3 and 5 yr overall Survival (OS) from diagnosis was 90 and 63% versus 82 and 63% in early and late ASCT respectively (P=0.45). Forty-one and 36 patients in the early and late ASCT have relapsed or progressed with median time to relapse of 28 and 23 mos (p=0.055). On multivariable analysis, factors predictive of increased risk for progression were ISS stage III (p=0.007), and < VGPR post-ASCT (p<0.001). Factor predictive of worst outcomes for OS was being on hemodialysis (p=0.037). No superiority of one agent was seen. In summary, early or late ASCT is a viable option for MM patients receiving induction treatment with novel targeted therapies.

Keywords

Multiple Myeloma; Transplantation; Bortezomib; Lenalidomide

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AUTHORSHIP

Contribution: N.C.D., P. E., and Y.E. collected data; N.C.D., L.W., G.P. and Y.E. analyzed results and made the figures; JCB, SD, CH, and DB were involved with treatment of patients on this study, reviewed versions of the paper and approved the final version. NH performed the cytogenetics reported, reviewed the manuscript and approved the final version; N.C.D. and Y.E. designed the research and wrote the paper.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no competing financial interests.

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INTRODUCTION

Multiple myeloma (MM) represents approximately 10% of all hematologic malignancies with over 20,000 new diagnoses and greater than 10,000 deaths in the United States per year [1]. The introduction of high dose therapy (HDT) and autologous stem cell transplant (ASCT) in the 1980s was a major advancement in MM treatment. Major randomized trials demonstrated improved progression free survival (PFS) and overall survival (OS) with ASCT compared to conventional therapy [2,3], while others showed only improved PFS with no significant survival benefit [4,5]. A large scale meta-analysis of randomized trials demonstrated improved PFS but no overall survival between the two groups [6]. Because of the improved PFS resulting in prolonged time off treatment without symptoms with improved quality of life, ASCT has become an integral part of treatment in patients with newly diagnosed MM. An early transplant was shown to significantly improve the period of time without symptoms, treatment and treatment related toxicity [4,7].

Over the last decade, there has been remarkable improvement in PFS and OS with the introduction of the novel agents – thalidomide, lenalidomide and bortezomib- in the treatment of MM, first for relapsed and refractory disease, and more recently as upfront therapy [8–15]. The percentage of patients expected to achieve a very good partial response (VGPR) or higher before transplant has increased from 20% with vincristine, adriamycin, and dexamethasone (VAD) [16] to as high as 67% with novel agent based therapy [17]. Even as novel agents have gained widespread use, early ASCT continues to be standard of care in transplant eligible patients based on current guidelines, and in clinical practice [18]. However, there is an increasing trend towards delaying ASCT. Hence the timing of ASCT in the era of these novel agents is an important question. To date, there is no published randomized trial addressing this issue. We therefore reviewed the outcomes of MM patients seen at the Ohio State University between 2002 and 2009 who received induction treatment with novel agent-based therapy and compared those who had ASCT within 12 months (early ASCT) to those who had ASCT at a later date (late ASCT) from time of diagnosis.

PATIENTS AND METHODS

Patients

Between August 2002 and December 2009, 317 patients who met the diagnostic criteria for symptomatic multiple myeloma underwent HDT and ASCT at The Ohio State University Medical Center. Patients were eligible for ASCT if they had an ECOG performance status of 0–2, stable or better disease response, adequate cardiac (left ventricular ejection fraction ≥45%), pulmonary (diffusing capacity of the lung for carbon monoxide ≥50%), hepatic (bilirubin, transaminases < 2 times upper limit of normal) function and no uncontrolled infection. Only patients (n=167) who received thalidomide, bortezomib or lenalidomide based therapy (named as the novel agents) and who did not receive consolidation or maintenance therapy after ASCT were included in this analysis. The main reason for late ASCT was late referral by treating physician.

Hematopoietic Stem Cell Collection

G-CSF-mobilized peripheral blood progenitor cells were collected using standard mobilization protocol and apheresis techniques. All patients signed informed consent according to our institutional and the National Marrow Donor Program guidelines. The study was approved by the Institutional Review Board at The Ohio State University.

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Preparative Regimen and Supportive Care

All patients received conditioning regimen with melphalan 200mg/m^2 except for patients with CrCl < 50ml/min including patients on hemodialysis, in which case melphalan140 mg/m^2 was given. Patients received infection prophylaxis with antiviral (valacyclovir) and antifungal (fluconazole). Filgrastim 5ug/kg was administered subcutaneously daily from day 1 after ASCT until recovery of absolute neutrophil count (ANC) to >1.5 × 10^9/L for 3 days. Blood products were irradiated and leukopore filtered. Antiviral was continued for 3–6 months after neutrophil recovery.

Engraftment, Response and Outcome

Response, relapse and disease progression were defined based on the international myeloma working group response criteria (IMWG)[19]. Patients were classified into high risk (FISH detection of t(4;14), t(14;16), t(14;20), deletion 17p, conventional karyotyping of hypodiploidy or deletion 13), or standard risk (all others)[20]. Neutrophil engraftment was defined as the first of 3 consecutive days with an ANC≥0.5 × 10^9/L. Failure to engraft by day 30 was considered primary graft failure. Platelet engraftment was defined as the first of 7 consecutive days with a platelet of ≥ 20 × 10^9/L without platelet transfusion.

Statistical Methods

Primary endpoints were OS and PFS. Secondary endpoints were relapse and treatment related mortality (TRM). OS was measured from the day of MM diagnosis to death from any cause, with censoring performed at date of last contact. PFS was determined from the day of stem cell infusion to the day of documented relapse or progression. Death from any cause other than relapse was classified as TRM. Actuarial survival curves were estimated using the method of Kaplan-Meier. The univariate associations between survival curves and other categorical variables were determined with the log-rank test. Covariates identified as having an influence on survival by univariate analysis (p-value <0.05) were analyzed using Cox proportional hazards model. Step-down regression method was used to build parsimonious statistical models. Patient characteristics were also summarized (median and range for continuous variables, frequency for categorical variables). Categorical variables were analyzed by the Fisher's exact or chi-square test, whichever was appropriate. Bonferroni method was used to adjust for multiplicity[21]. Statistical data was analyzed using the commercial statistical package SAS for Windows® Version 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance was determined at the 0.05 level.

RESULTS

Patient Characteristics

Out of 317 MM patients who underwent first ASCT, 150 were excluded (94 patients did not receive novel agent-based induction therapy, 4 patients were on study incorporating Allogeneic SCT after ASCT, and 52 patients participated on CALGB 100104 study incorporating lenalidomide versus placebo as maintenance post ASCT). Of the167 remaining patients, we compared the outcomes of those who received ASCT within 12 months of diagnosis (early ASCT, N=102) to those who received ASCT at a later date (late ASCT, N=65). No patient received maintenance treatment post ASCT. Patient baseline characteristics at diagnosis are summarized in Table I. There was no statistically significant difference between the groups in age, race, gender, performance status, comorbidity index score, stage of disease at diagnosis, cytogenetic and fluorescent in-situ-hybridization (FISH), or dose of melphalan conditioning. In the early group 46% of patients were in VGPR or greater at the time of ASCT compared to 30% in the late gp (p=0.036). The median time from diagnosis to transplant was 7.9 months (range 3.5–12) in the early ASCT and 17.7

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months (range 12.3–89.4) in the late ASCT. As first line therapy, 69% of early ASCT vs 55% of late ASCT received 2-drug therapy and 31% vs 45% received 3-drug therapy. Forty three patients in the late ASCT received a second line therapy. Nine (8.9%) patients in early ASCT and 7 (10.8%) in late ASCT were on dialysis. More patients in the late ASCT had thalidomide based induction therapy (66%), whereas more patients in the early ASCT had bortezomib based induction (63%), with both groups equally exposed to lenalidomide based induction therapy.

Engraftment

All patients achieved engraftment except one patient who died 7 days post transplant. Median time to neutrophil and platelet engraftments was 11 and 13 days respectively.

Response

After a median follow up of 30.5 months (range 7–94) from diagnosis and 23.2 months (range 0.2–83) from ASCT in the early ASCT and 52 months (range 20–183) from diagnosis and 29 months (3.0–93) from ASCT in the late ASCT, the overall response rate post ASCT (ORR = CR +VGPR + PR) was similar (99% vs. 97%, p=0.56), but with a statistically significant greater proportion of patients in the early ASCT obtaining CR (50% vs. 28%, p=0.007) (Table II). In the early ASCT, 77% of patients obtained a VGPR or better response post ASCT compared to 55% in the late ASCT (p=0.003). In both groups, the number of patients obtaining a CR post ASCT increased by at least 3 fold from pre-ASCT status. The 100 day and 1 year NRM were 3%(3 patients) and 4% (4 patients) in the early ASCT vs.0 and 1.5% (1 patient) in the late ASCT. All patients died of Infection.

Relapse, Progression-Free and Overall Survival

At the time of this analysis, 41 patients (40%) and 36 patients (55%) in the early and late ASCT respectively had relapsed (p=0.055), with a median time to relapse of 28 months and 23 months respectively. Of the 15 patients (15%) in the early ASCT and 25 (38%) patients in late ASCT who died, 11 (73%) and 23 (92%) were due to disease progression (Table II). There was no statistical significance in PFS or OS between the two groups (Figures 1 and 2). The median PFS was 28 months versus 18 months in the early versus late ASCT respectively, with 1, 3, and 5 year PFS of 80, 32, and 25% versus 66, 28, and 23% (p=0.11). The median OS from time of diagnosis was not reached (NR) in the early ASCT versus 75 months in the late ASCT, with 1, 3, and 5 year OS of 96, 90, and 63% versus 100, 82, and 63% (p=0.45) respectively. High risk patients who had early ASCT (N=31, median PFS=25 months) had a statistically significant improved PFS compared to those who had late ASCT (N=20, median PFS=11 months, p=0.049), but no difference in OS (p=0.59) (Figures 3A and 3B). There was no difference in PFS or OS for standard risk patients between the two groups (data not shown).

Prognostic Factors

On univariate analysis, factors predictive of increased risk of progression post transplant were: 2 or more previous therapies before ASCT, pre and post transplant response less than VGPR, DS and ISS stage III, deletion 13 by karyotype, and high risk cytogenetics (del p53, complex karyotype, t(4;14), t(14;16)) (Table III). There was no statistical difference in PFS with regards to sex (M vs. F), race, age (≤60 vs.>60), smoking history (≤10 pk yr vs.>10), conditioning regimen (melphalan 200 vs.140), initial creatinine level (≤2 vs.>2), histological type, beta 2 microglobulin (≤3.5 vs.>3.5), ejection fraction (≤50 vs.>50), comorbidity index score (≤2 vs.>2), or hemodialysis status. In the overall survival analysis, factors predictive of increased mortality were deletion 13 by karyotype and hemodialysis (Table III). On multivariable analysis, factors predictive of increased risk for progression were ISS stage III

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(p=0.007), and < VGPR post-ASCT (p<0.001), and factors predictive of worst outcomes for OS were observed in patients on hemodialysis(p=0.037). There was no superiority of one novel agent over another.

DISCUSSION

In our retrospective analysis, we chose 12 months from diagnosis as a cut-off for early ASCT since older studies and current on-going trials specify first ASCT within 12 months from diagnosis (e.g. BMT-CTN 0702 trial). All our patients received only novel agent based regimens and none received consolidation or maintenance treatment post ASCT to avoid biases between the two groups. Although not statistically significant, probably due to the number of patients, there was a difference in PFS of a median of 10 months between the 2 groups, with the early ASCT having a longer PFS than the late gp (28 mos vs. 18 mos), however, no statistically significant differences in OS between the two groups was seen. This correlated with findings by Kumar et al[22]. Using the same ASCT criteria as ours in a retrospective analysis of patients who received initial therapy with novel agents, they reported a 4 year OS from diagnosis of 67.8% in the early ASCT compared to 63.6% in the late ASCT (p=0.5). Our 3 year OS were 90 and 82% respectively(P=0.45). Their study however did not report if any patient received consolidation or maintenance treatment post ASCT. The only randomized study presented as an abstract reported an PFS advantage for early tandem ASCT but no OS benefit when compared to combination melphalan, prednisone and lenalidomide(MPR)[23]. In this study, after receiving 4 cycles of lenalidomide and dexamethasone, patients were randomized to MPR versus tandem ASCT using melphalan 200 mg/m^2. They reported an 18 months PFS of 78% in the tandem arm versus 68% in the MPR arm (p=0.006), but no OS benefit (95% vs. 91%) and increased grade 3–4 toxicity in the tandem arm (p<0.001). In contrast, in a post-hoc analysis of the ECOG E403 study comparing lenalidomide with high-dose dexamethasone vs. lenalidomide with low-dose dexamethasone, Siegal et al reported an increased survival probability for patients less than 65 years old who elected for early ASCT after 4 cycles of induction treatment with a 3-year OS of 94% vs. 78% for those who continued protocol therapy[24]. However, it was unclear what circumstances led to the decision for delay transplantation in the other group and they admitted that differences in OS seen between the groups may have been influenced by factors such as performance status, comorbidities, and initial response to therapy.

Although there were no statistically significant differences in overall PFS and OS, several features were in favor of early ASCT. Early ASCT patients obtained a statistically significant better response rate post SCT (77% ≥ VGPR) as compared to late ASCT patients (56%, p=0.0066). This may have translated into a better quality of life although this was not assessed in our retrospective study. Our results support findings of other studies showing that first ASCT improves upon the responses seen with induction using the novel agents[16,25]. The study by Harousseau et al showed a 52% VGPR or better with induction treatment with bortezomib plus dexamethasone which improved to 89% post first ASCT as compared to 21.5% and 55.6% respectively with vincristine, adriamycin and dexamethasone[25]. Our study also showed that patients who went to ASCT within 12 months of diagnosis with a ≥ VGPR with induction treatment, had the best disease free benefit post transplant (p=0.035). Our results are comparable to prior studies demonstrating that pre-ASCT response is an important prognostic factor to post-ASCT response, PFS and OS even in patients without exposure to novel agents[26–28]. It has also been shown that the depth of response obtained after ASCT is one of the most robust predictor of PFS and OS[28–30]. Our study confirms that for patients who obtained less than a VGPR post ASCT, the risk of progression was three times higher than those who had a VGPR or better. In particular, patients with CR post ASCT had statistically improved PFS (p <0.001) and OS (p=0.0043). The role of a second ASCT or consolidation may play a significant impact in these patients.

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In conclusion, we found no statistically significant differences in PFS and OS between the early versus late ASCT groups. . A major limitation of this study is that we do not know the reason(s) for the late referral for patients in the late ASCT. Reasons could be patient initial refusal, physician preference because patients were doing well with induction or initial feeling that patients may not be good candidates for ASCT. Also, this study is a retrospective analysis and likely the number of patients may not be powered to attain statistical significance. We excluded patients who received maintenance treatment post ASCT as this was not balanced between the two groups. Although retrospective, these data support the ongoing prospective randomized trial examining this important question (NCT01191060, NCT 1208662, and NCT00551928).

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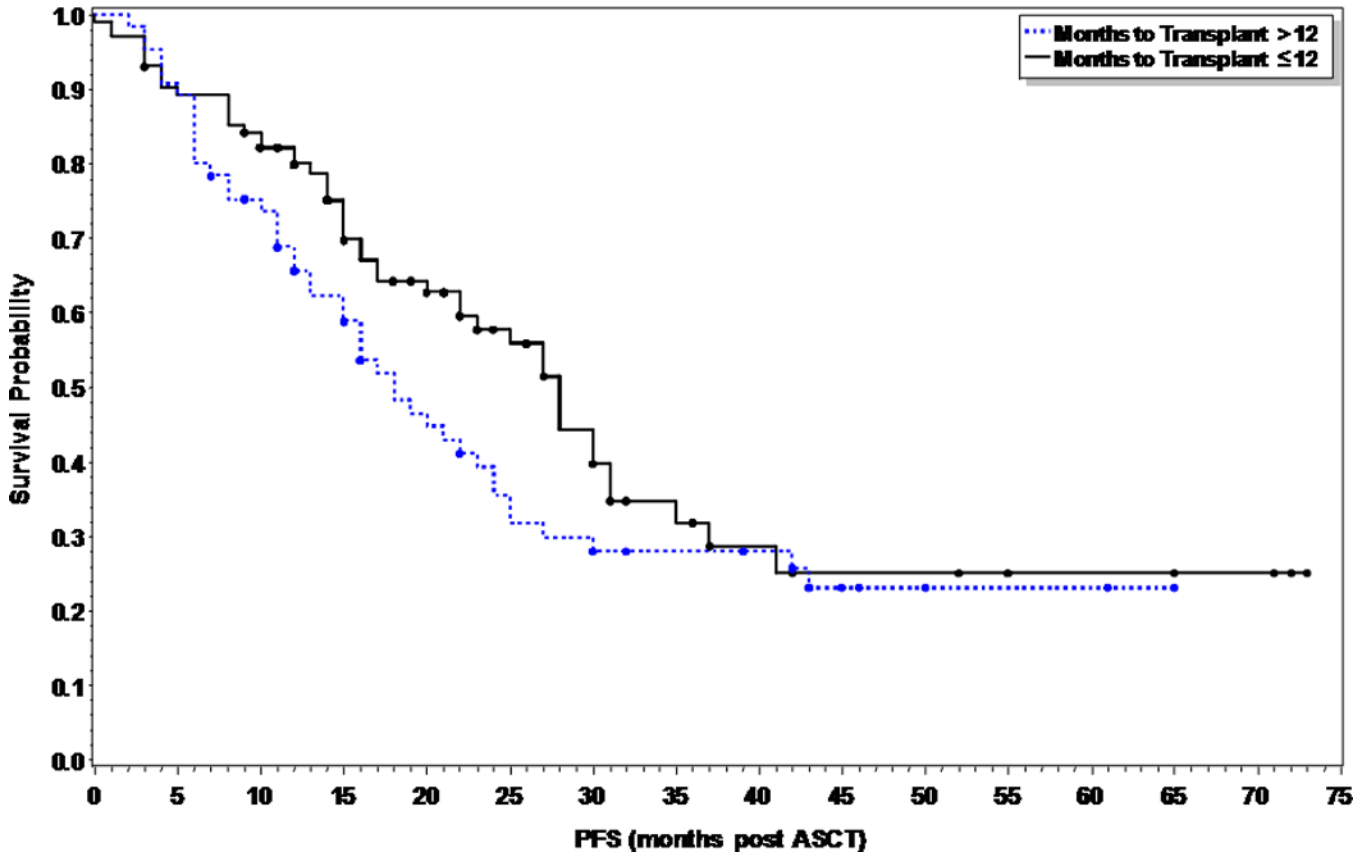

Figure 1.
Progression free survival comparing early vs. delayed first ASCT in multiple myeloma patients (p=0.11).

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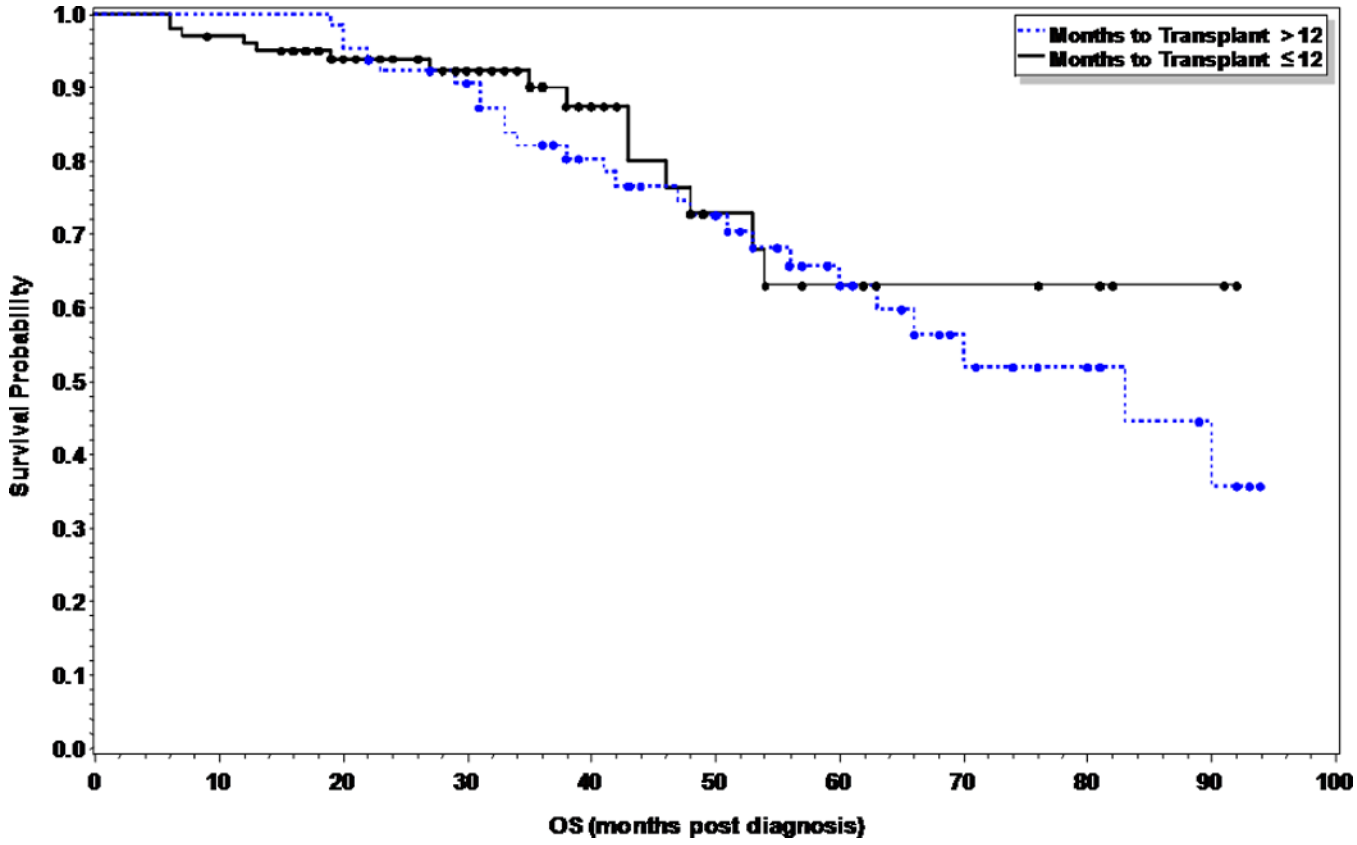

Figure 2.
Overall Survival comparing early vs. delayed first ASCT in multiple myeloma patients (p=0.45).

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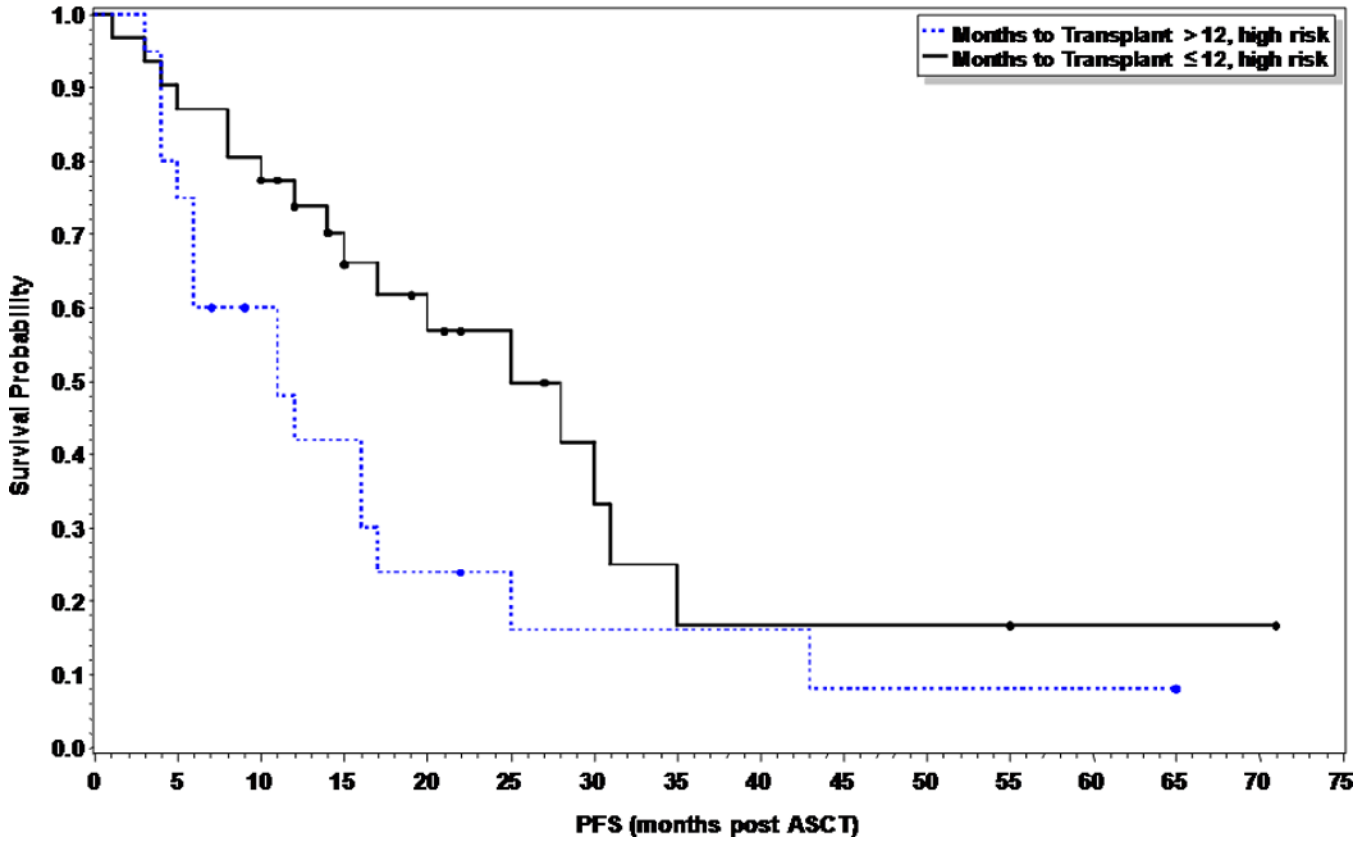

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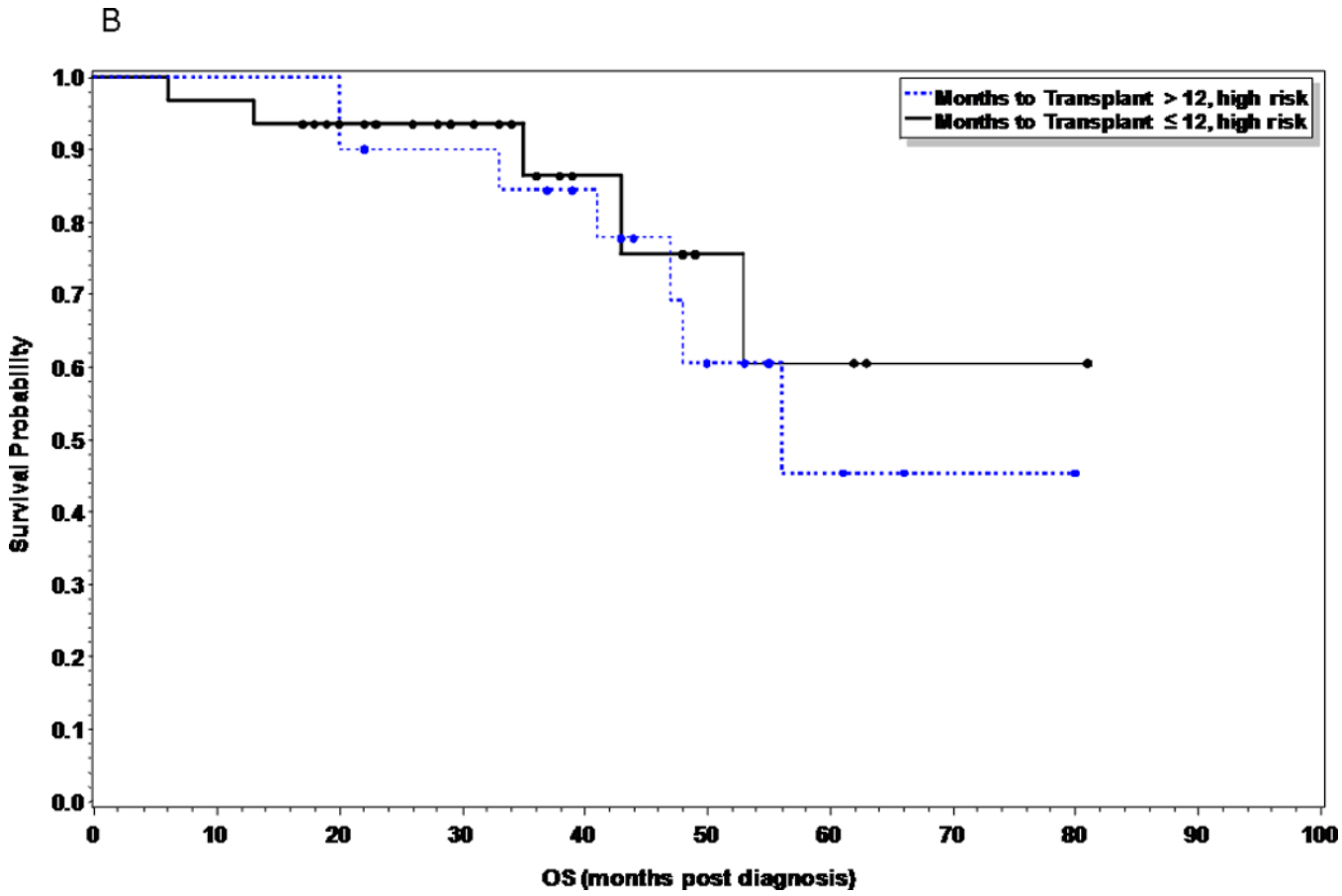

Figure 3.

Progression free survival comparing early vs. delayed first ASCT in high risk multiple myeloma patients (p=0.049).

B. Overall Survival comparing early vs. delayed first ASCT in high risk multiple myeloma patients (p=0.59)

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Table I

Patient Baseline Characteristics

	SCT≤ 12 mos		SCT>12 mos		
	N=102 or 61%	**%**	**N=65 or 39%**	**%**	**P value**
Age					
Median	56.6		55.3		
Range	29 – 76		41–80		
Age>60/≤60	30/72	29/71	20/45	31/69	0.85
Sex Male/Female	59/43	58/42	39/26	60/40	0.78
Race AA/C/O	23 / 78 / 1	23 /76 /1	12 /53/ 0	18/82/0	0.73
KPS Median (range)	80 (60 –100)		90 (70–100)		
NCI-CI Median (range)	3 (0–7)		3 (0–6)		
β2M > 3.5	31/71	43	18/47	38	0.71
DS Stage 3	80	78	50	77	0.73
DS 1and 2	22		15		
ISS stage 1/2/3	23/30/22	23/29/22	14/15/12	22/23/18	0.91
ISS stage unknown	27	26	24	37	
Melphalan 140/200	19/83	19/81	11/54	17/83	0.78
Prior treatment 1/2/3/4/5	74/27/1	73/26/1	22/22/15/4/2	34/34/23/6/2	
Prior treatment 1/>1	74/28	73/27	22/43	34/66	<0.001
Thalidomide	39	38	43	66	
Bortezomib	64	63	32	49	
lenalidomide	34	33	18	28	
Standard/High Risk Cytogenetic	67/31	68/32	40/20	67/33	0.82
p53 deletion	13	13	5	8	0.44
deletion 13 karyotype	11	11	7	11	0.91
deletion 13 FISH	32	31	24	37	0.33
hyperdiploid	24	23	15	23	0.91
Complex Karyotype	21	21	14	21	
Disease Subtype					
IgG	53	52	41	63	0.024
IgA	20	20	11	17	

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	SCT≤ 12 mos		SCT>12 mos		
	N=102 or 61%	**%**	**N=65 or 39%**	**%**	**P value**
Light chain only	25	24	7	11	
Nonsecretory	4	4	2	3	
Others/unknown			4	6	
Disease Status at SCT					
CR	17	17	4	6	0.12
VGPR	30	29	15	23	
CR+VGPR	47	46	19	30	0.036
PR	43	42	34	52	
SD	12	12	11	17	
Unknown/not evaluated			1		

Mos stands for months; SCT stem cell transplant; AA African American; C Caucasian; O other; KPS karnofsky performance score; BMI body mass index; β2M beta-2 microglobulin; DS durie salmon; ISS international scoring system; FISH florescent in-situ hybridization; CR complete response; VGPR very good partial response; PR partial response; SD stable disease.

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Table II

Response, Mortality, Relapse

	SCT ≤12 mos		**SCT >12 mos**		
		%		**%**	**P value**
	N= 102		**N=65**		
Median Time from Dx to SCT	7.9 mos		17.7 mos		
Range	3.5–12.0 mos		12.3–89.4 mos		
Median follow up from Dx	30.5 mos		52 mos		
Range	7–94mos		20–183 mos		
Median Follow up from SCT	23.2 mos		29 mos		
Range	0.2–83 mos		3.0–93 mos		
Response					
ORR	100	99	63	97	0.56
CR	51	50	18	28	0.007
VGPR	27	27	18	28	
CR+VGPR	78	77	36	55	0.003
PR	22	22	27	41	
SD	1	1	2	3	
100 day NRM	3	3	0	0	
1 yr NRM	4	4	1	1.5	
Total Death	15	15	25	38	0.001
Death due to disease progression	11 (73%)		23 (92%)		
Other	4 (27%)		2 (8%)		
# Relapse/ Progression of Disease	41	40	36	55	0.055
Median time to relapse/progression	28 mos		23 mos		
Median OS from Dx (Range)	NR (6–92)		83 mos (19–179)		0.45
1 yr OS from Dx	96%		100%		
3 yr OS from Dx	90%		82%		
5 yr OS from Dx	63%		63%		
Median PFS (Range)	28 mos (0–73)		18 mos (2–91)		0.11
1 yr PFS	80%		66%		
3 yr PFS	32%		28%		

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	SCT ≤12 mos	%	SCT >12 mos	%	P value
	N= 102		**N=65**		
5 yr PFS	25%		23%		

Mos stands for months; SCT stem cell transplant; Dx diagnosis; ORR overall response rate; CR complete response; VGPR very good partial response; PR partial response; SD stable disease; NRM non relapse mortality; OS overall survival; PFS progression free survival.

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Table III

Univariate Analysis for Progression Free Survival and Overall Survival

PFS variable	**HR**	**p-value**
Number of prev therapy >1 vs 1	1.60	0.02
Pre-SCT response Others vs. CR+VGPR	1.67	0.018
Post-SCT response Others vs. CR+VGPR	2.79	<0.001
Pre-SCT response Others vs. CR	2.49	0.015
Post-SCT response Others vs. CR	3.63	<0.001
Durie salmon 3 vs.1 or 2	1.80	0.033
Complex Karyotype No vs. yes	0.63	0.042
Del 13 Karyotype No. vs. yes	0.56	0.035
High risk FISH/Karyotype No vs. yes	0.65	0.041
ISS 1 vs. 2/3	1 vs. 2: 0.89 1vs. 3: 0.49 2 vs. 3: 0.56	0.038
OS Variable		
Pre-SCT response Others vs. CR	1.74	0.35
Post-SCT response Others vs. CR	3.10	0.0043
Del 13 Karyotype No vs. yes	0.44	0.045
HD No vs. yes	0.36	0.018

HR stands for hazard ratio; prev previous; SCT stem cell transplant; CR complete response; VGPR very good partial response; PR partial response; SD stable disease; NRM non relapse mortality; OS overall survival; PFS progression free survival; FISH florescent in-situ hybridization; ISS international scoring system; HD hemodialysis.