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Outcomes with Autologous Stem Cell Transplant vs. Non-transplant Therapy in Patients 70 Years and Older with Multiple Myeloma

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Abstract

We evaluated 79 patients with multiple myeloma (MM) ≥ 70 years referred to our blood and marrow transplant clinic, within 1 year of diagnosis from 2010–19, for consideration of autologous stem cell transplant (ASCT). Thirty-eight (48%) of 79 patients underwent ASCT. ASCT was not pursued in 41 (52%) patients due to: patient or physician preference in 80% (n=33) or ineligibility in 20% (n=8). Baseline characteristics of patients in the 2 groups were similar. Median PFS from treatment start amongst patients undergoing ASCT (n=38) vs. not (n=41) was 41 months vs. 33 months, p=0.03. There was no difference in OS, with estimated 5-year OS of 73% vs. 83%, respectively (p=0.86). Day +100 transplant related mortality was 0%. ASCT was an independent favorable prognostic factor for PFS in multivariate analysis, after accounting for HCT-CI score, performance status, hematologic response and maintenance. Finally, patients ≥ 70 years undergoing ASCT had similar PFS compared to a contemporaneous institutional cohort of patients<70 years (n=631) (median PFS from transplant: 36 vs. 47 months, p=0.25). In this retrospective analysis, ASCT was associated with low TRM and better PFS in fit older adults with MM compared to non-transplant therapy, with comparable benefits as seen in younger patients.

Keywords

multiple myeloma; elderly; stem cell transplant; 70 years

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Introduction

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been considered the standard of care first-line therapy for eligible multiple myeloma (MM) patients for more than three decades[1–4]. Multiple myeloma is mainly diagnosed in older patients with a median age at diagnosis of 70 years old[1]. With an expected MM incidence rising by 57% from 2010 to 2030[2], the number of older patients being considered for ASCT will continue to increase. Unfortunately, most randomized studies evaluating ASCT in MM only included patients <65 years old[3, 4]. However, retrospective studies have shown that patients over 65 years old who undergo ASCT have good survival outcomes with acceptable toxicities[5–18]. Patient selection remains one of the crucial aspects of ASCT.

The main advantage of transplant in the era of novel agents is improved progression-free survival (PFS)[19, 20]. There has been no prospective randomized study amongst patients ≥ 70 years old with MM comparing ASCT to non-ASCT approaches. The objective of this single-center retrospective study was to compare the safety and efficacy of ASCT to non-ASCT treatment in patients ≥ 70 years old with MM.

Methods

Study design

We conducted a single center, retrospective study examining outcomes of ASCT versus non-ASCT based treatment in patients with MM who were ≥ 70 years old. Patients who were ≥ 70 years old, with a diagnosis of multiple myeloma based on the International Myeloma Working Group consensus criteria[21] and referred within 1 year after their diagnosis for ASCT for a transplant consult at Stanford University Medical Center between January 1, 2010, and November 1, 2019 were included in this study. We excluded patients who received a second or a tandem autologous transplantation. Patients who underwent transplant were treated with a high dose melphalan (140–200 mg/m^2) +/− BCNU (300–350 mg/m^2) preparative regimen. ASCT was primarily done as an outpatient transplant per institutional guidelines. This study was approved by the institutional review board.

High-risk cytogenetics was defined by detection of t(4;14), t(14:16), t(14:20), del 17p or amplification 1q by fluorescence in situ hybridization (FISH). Treatment response at time of transplantation was evaluated based on the International uniform response criteria for multiple myeloma[22]. The International Staging System (ISS)[23] for multiple myeloma prognosis and the Hematopoietic cell transplantation comorbidity index (HCT-CI)[24, 25] were calculated for each patient with the available data. Patients were divided into three HCT-CI risk groups: low (score 0), intermediate (score 1–2) and high risk (score ≥ 3). Reasons not to undergo transplant were either transplant ineligibility, patient choice or physician recommendation despite patient being deemed eligible. Time to next treatment (TTNT) was defined as the time from start of treatment to start of next treatment or death, whichever occurred earlier. Progression-free survival was defined as the time from start of treatment to disease progression or death, regardless of the cause of death. Overall survival (OS) was defined as the time from start of treatment to death from any cause. Data for both OS and PFS were censored at the time of last follow-up in patients who had not experienced events.

We defined transplant related mortality (TRM) as death from any cause related to the transplant.

Finally, progression free survival outcomes from transplant of patients 70 years or above undergoing ASCT were compared to a contemporaneous cohort of patients <70 years (n=631) who underwent ASCT for myeloma at our institution from 2010–19. Inclusion criteria for selecting this cohort of younger patients were similar to that described above and patients were within one year of myeloma diagnosis.

Statistical Analysis

Statistical analyses were run using the JMP pro 14 software. Univariate analysis was done using Chi-Square and Fischer's exact tests for categorical variables and Wilcoxon Rank Sum/Kruskal Wallis test for continuous variables. TTNT, PFS and OS were calculated with the Kaplan-Meier method. The log-rank test was used to evaluate the differences between groups. PFS and OS were adjusted for the following factors with Cox proportional hazard method: HCT-CI, high-risk cytogenetics, hematologic response at the time of BMT consultation and use of maintenance as these factors are known predictors of outcomes in patients undergoing transplant[24, 26, 27]. Statistical significance was considered at two-sided $p < 0.05$.

Results

Between January 1, 2010, and November 1, 2019, 79 patients ≥ 70 years old were evaluated for stem cell transplantation within 1 year after their diagnosis at the Stanford Blood and Marrow Transplantation Clinic. Thirty-eight patients (48%) proceeded to ASCT. ASCT was not pursued in 41 (52%) patients, despite most patients (80%, n=33) being deemed eligible for a transplant. Reasons for deferring ASCT in eligible patients included patient preference (52%, n=17) and physician preference (48%, n=16).

Baseline Characteristics:

There was no difference in baseline characteristics among the patients categorized by whether they received ASCT or non-ASCT therapy other than sex distribution (Table 1). Median age was 71.5 years (range 70–78) for the ASCT cohort and 71 years (range 70–77) for the non-ASCT cohort (p=0.90). High-risk cytogenetics were observed in 45% and in 34% of the two cohorts, respectively (p=0.47).

ISS stage at diagnosis was similar in both groups (p=0.16). Distribution of patients by ISS stage in this ASCT cohort was as follows: Stage I: 32% (n=9), Stage II: 21% (n=6) and Stage III: 47% (n=13). In the non-ASCT cohort, the distribution patients by the ISS was: Stage I: 34% (n=11), Stage II: 41% (n=13) and Stage III: 25% (n=8). HCT-CI comorbidity score was similar in the ASCT vs. non-ASCT groups, with low risk score (score 0) observed in 29% vs. 44% of patients and high-risk score (score >2) observed in 29% vs. 24% of patients in the two groups, respectively, p=0.38.

Treatment Regimens:

All patients received novel agent based therapy as described in Table 1.

In the transplant cohort, the induction regimen consisted of a doublet in 8 (21%) patients and a triplet in 30 (79%) patients. Doublet therapy included a proteasome inhibitor (PI) doublet in 4 (11%) patients, immunomodulatory drug (IMiD) doublet in 3 (8%) patients and daratumumab doublet in 1 (2%) patient, respectively. In the triplet group, the regimen was PI +IMiD triplet in 20 (53%) patients, PI+cyclophosphamide triplet in 9 (24%) patients and daratumumab triplet in 1 (2%) patient. The conditioning regimen before stem cell infusion was as follows: melphalan 140 mg/m^2 in 9 (24%), melphalan 200 mg/m^2 in 12 (32%) and melphalan 200 mg/m^2 + BCNU 300–350 mg/m^2 in 17 (44%) patients. Overall, the melphalan dosage in the conditioning regimen was 140 mg/m^2 in 26% and 200 mg/m^2 in 74% of patients. Twenty-one (55%) patients received maintenance therapy after ASCT for a median duration of 7 months (range 1–44) from start of maintenance at last follow-up. Maintenance included an IMiD in the majority of patients (n=14, 67%), followed by PI in 5 patients (24%) and both an IMiD and a PI in 2 patients (9%).

The treatment regimen in the non-transplant cohort included a doublet in 6 (15%) patients and a triplet regimen in 35 (85%) patients. Doublet therapy included a proteasome inhibitor (PI) doublet in 4 (10%) patients, immunomodulatory drug (IMiD) doublet in 1 (2%) patient and daratumumab doublet in 1 (2%) patient, respectively. In the triplet group, the regimen was PI+IMiD triplet in 27 (66%) patients, PI+cyclophosphamide triplet in 6 (15%) patients and daratumumab triplet in 2 (5%) patients. The median duration of initial therapy (excluding maintenance) was 8.5 months (range 1–29). Twenty (49%) patients in the non-ASCT cohort received maintenance therapy for a median duration of 22.5 months (range 3–60) from start of maintenance. Maintenance therapy was with an IMiD in 13 patients, PI in 6 patients and daratumumab in 1 patient.

There was no difference when comparing the treatment regimen category (i.e. receiving doublets vs. triplets) in the ASCT cohort to the non-ASCT cohort (p=0.56), with the majority of patients receiving triplets in both groups (79% vs. 85%). The proportion of patients receiving maintenance therapy (55% vs. 49%) was also comparable in both cohorts (p=0.65).

Transplant related toxicity: Complications in the ASCT cohort (n=38) included: arrhythmia (n=7, 18%), infection (n=5, 13%), bacteremia (n=2, 5%) and BCNU pneumonitis (n=2, 12%). One patient required intensive care unit level care. The median times to neutrophil and platelet engraftment were 11 days (range 10–22) and 17 days (range 8–91), respectively. Twenty-six (68%) patients required hospitalization with a median length of stay of 8 days (range 2–18). Between day 30 and day 90 post-transplant, 4 (11%) patients required an admission with a median length of stay of 5.5 days (range 3–12).

Survival Outcomes and TTNT:

Median follow-up of this cohort from start of treatment was 40 months [95% confidence interval (CI): 29–46], with no difference in follow-up amongst patients undergoing

transplant vs. not. Median PFS from start of treatment in patients ≥ 70 years undergoing ASCT was 41 months compared to 33 months in the non-ASCT cohort, p=0.03 (Figure 1A). Overall survival was similar in both groups, with median OS not reached in either group. Estimated 5-year OS was not significantly different with 73% in the ASCT group and 82% in the non-ASCT group, p=0.86 (Median OS not reached) (Figure 1B). TRM at D+100 was 0% in both groups. Main cause of death was progressive disease in 83% of ASCT cohort and 86% of non-ASCT cohort. No difference was noted based on the time period (2016–20 vs. 2010–15).

When comparing sub-groups of patients based on cytogenetic risk, the difference did not reach statistical significance in patients with high-risk disease (median PFS: 45 vs. 33 months, p=0.57), though sample size of the group was small (n=28).

TTNT:

The time to next treatment was significantly longer for the ASCT cohort with a median time of 44 months compared to 34 months in the non-ASCT cohort, p=0.029. There was no difference in the number of lines of therapy received within 3 years after the initial diagnosis with a median of 1.5 (range 1–5) lines in the ASCT cohort compared to 2 (1–7) in the non-ASCT cohort, p=0.67. No patient in the non-ASCT cohort received an autologous transplant at relapse.

Multivariate analysis:

On multivariate analysis using Cox proportional hazards, ASCT was associated with improved PFS in patients 70 years or older, even after adjusting for HCT-CI score, performance status (KPS), response at transplant evaluation (at least partial response vs. not), use of maintenance and cytogenetic risk. (Table 2). Hazard ratio for PFS for ASCT vs. non-ASCT treatment was: 0.30 (95% CI 0.15–0.63, p=0.002). As expected, patients in the low risk HCT-CI group (score:0) also had better PFS (HR:0.31, 95% CI 0.15–0.66, p=0.002). Maintenance was also associated with better PFS (HR:0.50, 95% CI 0.25–0.97, p=0.042).

Survival outcomes compared to patients < 70 years:

We then compared outcomes of patients ≥ 70 years undergoing ASCT to a contemporaneous cohort of patients <70 years (n=631) undergoing ASCT for myeloma our institution from 2010–19. The median PFS from transplant in patients ≥ 70 years vs. < 70 years was 36 vs. 47 months, p=0.25, respectively. (Figure 2) TRM at 3 months was at 0% and 1% in the two groups, respectively.

Discussion

Autologous stem cell transplantation is a safe and effective treatment with durable outcomes in appropriately selected older patients. Moreover, amongst older patients with MM referred for transplant, patients who ultimately underwent transplant were observed to have longer PFS compared to those who did not undergo transplant.

Several retrospective and few prospective studies have confirmed that ASCT is an effective and safe treatment for older patients with MM[5–18]. However, there is limited data comparing ASCT and non-ASCT based treatment approaches in patients with MM above the age of 70 years. Our study provides comparative data on outcomes with transplant vs. non-transplant-based therapy in older patients who were deemed fit enough to be referred for a transplant consult by their hematologist. Our findings of improved PFS in older adults are similar to those observed in the IFM 2009 clinical trial of early vs. deferred transplant, which included patients up to the age of 65 years[20]. Older adults above 70 years of age with MM were found to have a comparable magnitude of benefit with transplant vs. no transplant (PFS 41 vs. 33 months) in our study as seen in younger patients. About half of the patients in the transplant and non-transplant groups received maintenance, though duration of maintenance was only 7 months (range 1–44) in the transplant group compared to 22.5 months (range 3–60) in the non-transplant group, p=0.004. The PFS benefit of transplant persisted even after adjusting for known prognostic factors including the HCT-CI score, performance status, use of maintenance and response at the time of transplant consultation. As expected, a low HCT-CI score was also an independent favorable prognostic factor for superior PFS. HCT-CI developed by Sorror et al.[25] for the evaluation of transplantation-related mortality (TRM) in patients undergoing allogeneic transplantation has become an important tool for patient selection[28]. Subsequent studies have also validated HCT-CI in patients with multiple myeloma[24, 29–31]. Comprehensive geriatric assessment in older patients with MM has been proven helpful in predicting survival and toxicity and should be considered when evaluating older adults with myeloma in clinic[32]. Similar to the results of the IFM-2009 study, there was no difference in overall survival with transplant vs. not in our cohort of older adults with MM, with the current median follow-up of 40 months. This may be attributable to the duration of follow-up as over 75% patients were still alive at the 5-year time-point.

Multiple myeloma treatment landscape has evolved significantly over the last decade during which patients included in this study were evaluated and treated. The major practice change has been with the widespread use of triplet regimens as the standard of care over doublets, given the PFS and OS advantage seen with triplets in randomized trials[33]. There is equipoise among the different triplet regimens, with no observed PFS or OS benefit seen with one regimen over another in prospective trials. Recent data from the ENDURANCE trial reported similar PFS in patients receiving VRD (bortezomib, lenalidomide and dexamethasone) and KRD (carfilzomib, lenalidomide and dexamethasone), even though deeper responses were seen in the KRD cohort[34]. Similarly, deeper responses have been observed with VTD (bortezomib, thalidomide and dexamethasone) induction before transplant compared VCD (bortezomib, cyclophosphamide and dexamethasone) induction, though follow-up survival data has not been published[35]. Recently, daratumumab based regimens have become another attractive treatment option in the upfront setting, especially in older adults given the relatively favorable toxicity profile[36]. The role of maintenance has also been firmly established, with both PFS and OS benefit with maintenance therapy following transplant[37]. There is limited data to support maintenance in non-transplant eligible patients, though it is now frequently used in clinical practice as continuous therapy has shown to offer PFS advantage over limited duration therapy as seen in the FIRST trial[38]. The treatment options available at time of relapse have also exponentially increased, with

several new therapies being approved[39]. The ever changing treatment landscape of myeloma over the last decade resulted in a wide variety of regimens being used in our study cohort. However, it was reassuring to see a similar proportion of patients in both groups receiving triplet regimens compared to doublets and as well as similar number of patients receiving maintenance therapy, thereby minimizing any confounding of outcomes based on the heterogenous treatment landscape.

Our study also demonstrates the low toxicity of ASCT in appropriately selected patients, with day 100 TRM of 0% despite having used a more intensive regimen (Melphalan 200 mg/m^2+BCNU) in 17 patients and melphalan dose of 200 mg/m^2 used in 76% patients overall. Various retrospective studies have shown TRM between 0% and 18% with the use of the standard 200 mg/m^2 in older patients[11, 16, 40]. Melphalan 200 mg/m^2 remains the gold standard conditioning regimen for MM. Reduction of the conditioning regimen dose to 100 mg/m^2 is associated with significantly worse outcomes[41]. In patients ≥ 65–70 years old, the best melphalan conditioning dosage is still unknown. Reduction of the dose to 140 mg/m^2 is common when patients have renal impairment, heart failure or increase frailty. Retrospective studies in older patients have reported a use of different reduced melphalan doses, with 2–45% patients receiving a reduced dose in prior reports[14, 18, 42]. A recent EBMT registry study compared melphalan 200 mg/m^2 to 140 mg/m^2 and found no difference in terms of efficacy in the older patient group[43]. However, a significant number of patients (37%) received the reduced dosage primarily for renal impairment, where the total marrow exposure with a reduced dose is expected to be similar to full dose melphalan due to impaired metabolism. Our numbers are too small to compare outcomes with the two doses. Therefore, until additional data is available, melphalan 200 mg/m^2 should be the recommended conditioning regimen in fit patients, including those ≥ 70 years old. Dose reduction may be considered on a case by case basis, accounting for renal function and other patient factors.

Our study has limitations. First, there is a referral bias among our patients. Patients included in this study needed to be fit enough to be referred for consultation by their primary hematologist. However, most patients who were evaluated for transplant and did not receive ASCT were deemed fit enough to undergo transplant and the decision of not proceeding with transplant was due to physician/patient preference. Therefore, this comparison is apt in patients who are referred for transplant. Secondly, our study includes patients treated over the past decade with heterogenous induction regimens and variable use of maintenance therapy, thereby limiting the treatment homogeneity. However, all patients received novel regimens and the proportion of patients receiving triplets vs. doublets and maintenance therapy was similar between both groups. Thirdly, the retrospective design of the study is by itself a limitation. Retrospective analyses are subject to unmeasured confounding differences between groups, and it is possible that the better outcomes seen in the transplant group reflect the identification of better-risk patients for transplant. Quality of life (QoL) data remains an important aspect of transplant in that population that we were not able to evaluate. Future studies should evaluate QoL in this context. The power of the study is also a limitation, thereby limiting sub-group analyses. Despite these limitations, our study provides valuable data and is one of the only contemporary studies comparing ASCT and non-ASCT for fit older patients.

In conclusion, fit patients ≥ 70 years old with MM undergoing ASCT have a better PFS compared to patients with similar characteristics who do not undergo ASCT in this retrospective analysis. When patients are well selected, ASCT is safe in this older population and outcomes are similar when compared to younger patients with MM undergoing ASCT.

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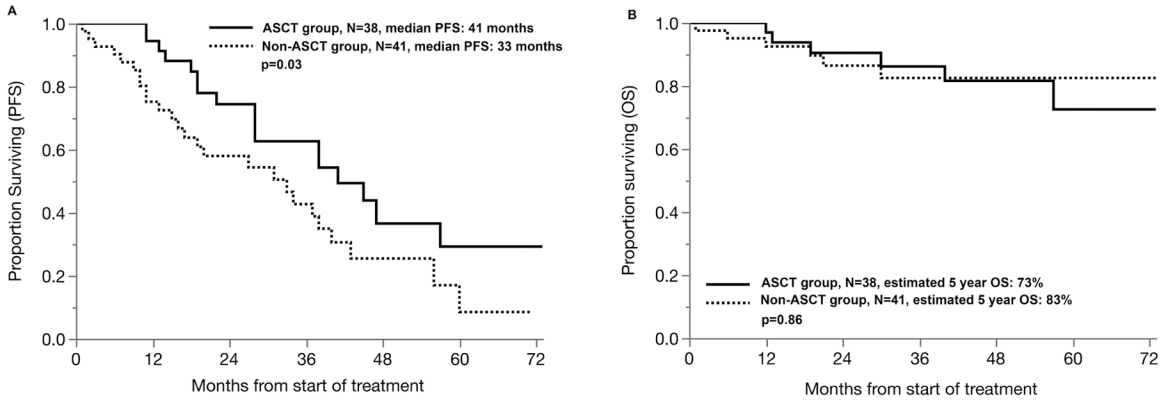

Figure 1:

Progression-free survival (A) and overall survival (B) in patients 70 years and above undergoing ASCT versus non-ASCT based treatment.

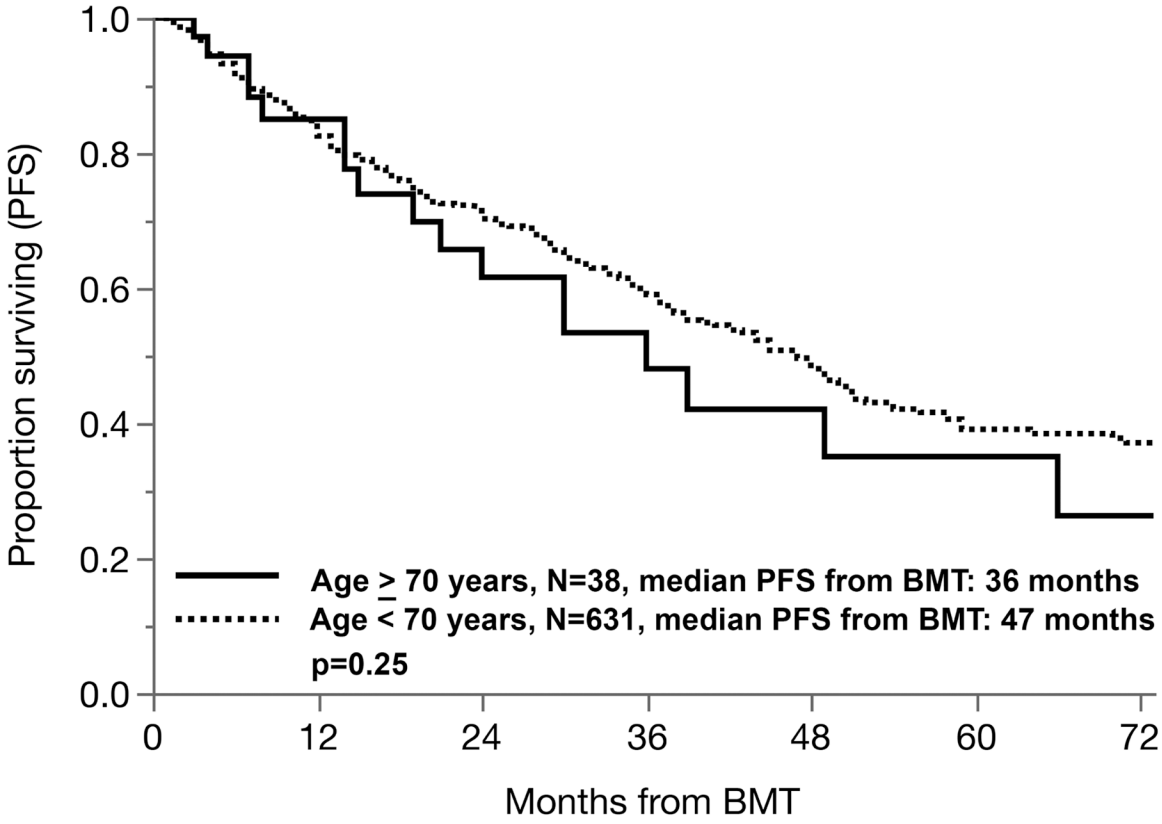

Figure 2:
Progression-free survival in patients 70 years or above undergoing ASCT compared with a younger contemporaneous cohort (< 70 years) of patients undergoing ASCT.

Table 1:

Baseline and treatment characteristics of patients aged 70 years and older evaluated for transplant within one year of diagnosis

	ASCT cohort N (%)	Non-ASCT cohort N (%)	P-value
Total number per group	**38**	**41**	
Sex			**0.02**
Male	30 (79)	21 (51)	
ISS, (n=61)	n=28	n=32	0.16
Low risk	9 (32)	11 (34)	
Intermediate risk	6 (21)	13 (41)	
High Risk	13 (47)	8 (25)	
High risk cytogenetics, (N=71)	n=33	n=38	0.47
Del 17p, gain 1q, t(14;16), t(14;20) or t(4;14)	15 (45)	13 (34)	
Median age, years (range)	71.5 (70–78)	71 (70–77)	0.90
HCT-CI			0.38
0	11 (29)	18 (44)	
1–2	16 (42)	13 (32)	
≥3	11 (29)	10 (24)	
Status at BMT consultation			0.11
On upfront therapy	30 (79)	38 (93)	
Previously treated	8 (21)	3 (7)	
KPS			0.12
90–100	22 (58)	17 (42)	
70–80	16 (42)	21 (51)	
<70	0 (0)	3 (7)	
Disease status at transplantation evaluation			0.38
Very good partial response + Complete response (VGPR+CR)	24 (63)	28 (68)	
Partial response (PR)	13 (34)	10 (24)	
Stable disease (SD)	1 (3)	1 (3)	
Progressive disease (PD)	0 (0)	2 (5)	
Treatment			0.72
Doublet IMiD	3 (8)	1 (2)	
Doublet PI	4 (11)	4 (10)	
Doublet daratumumab	1 (2)	1 (2)	
Triplet Cy + PI	9 (24)	6 (15)	
Triplet IMiD + PI	20 (53)	27 (66)	
Triplet daratumumab	1 (2)	2 (5)	
Conditioning regimen		-	
Melphalan 200 mg/m^2 + BCNU 300–350 mg/m^2	17 (44)		
Melphalan 200 mg/m^2	12 (32)		

	ASCT cohort N (%)	Non-ASCT cohort N (%)	P-value
Total number per group	**38**	**41**	
Melphalan 140 mg/m^2	9 (24)		
Maintenance received	21(55)	20(49)	0.65

BCNU: carmustine

Cy: cyclophosphamide

HCT-CI= hematopoietic cell transplantation comorbidity index

ISS= International staging system

IMiD: Immunomodulatory drugs

KPS= Karnofsky performance status

PI: Proteasome inhibitor

Table 2:

Multivariate Analysis for Progression Free Survival (PFS) amongst patients aged 70 years and older evaluated for transplant within one year of diagnosis

	Hazard ratio with 95% CI	P-value
ASCT vs not	0.30 (0.15–0.63)	**0.002**
At least a partial response vs. not at the time of transplant consultation	0.08 (0.02–0.35)	**<0.001**
HCT-CI score: 0 vs. not	0.31 (0.15–0.66)	**0.002**
High-risk cytogenetics: present vs. not	1.76 (0.84–3.70)	0.13
Use of maintenance	0.50 (0.25–0.97)	**0.042**

CI: Confidence interval

ASCT= Autologous stem cell transplant

HCT-CI= hematopoietic cell transplantation comorbidity index