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Real World Predictors, Timing, and Outcomes of Autologous Stem Cell Transplantation in Patients with Multiple Myeloma

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Abstract: Background—Autologous stem cell transplant (ASCT) is integral to the treatment of multiple myeloma (MM), although its absolute necessity in first remission has been recently questioned. We report real-world factors that influence clinical decision-making and outcomes from ASCT in 733 patients with MM. Results—Similar to recent prospective data, we found a significant progression-free survival (PFS) benefit with early versus deferred ASCT (median PFS of 5.1 years versus 2.6 years, $p < 0.001$); however, there was no significant difference in overall survival (median OS of 8.3 years and 8.6 years, $p = 0.21$). Patient preference, age, marital status, body mass index, and comorbidities influence ASCT timing. Conclusion—These findings highlight the emerging role of an individualized, shared decision-making model regarding the timing of ASCT between patients and physicians with the myriad of treatment options available in the contemporary era.

Keywords: myeloma; early transplant; deferred transplant; outcomes; decision-making

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1. Introduction

Patients with newly diagnosed multiple myeloma (MM) have traditionally been treated with induction therapy followed immediately by autologous stem cell transplantation (ASCT) if eligible. This practice has been supported by data from randomized clinical trials (RCTs) demonstrating progression-free survival (PFS) and potentially overall survival (OS) benefits among those who received ASCT after an initial remission versus chemotherapy alone [1–3].

However, the universality of this practice paradigm has been called into question recently with the array of novel treatments available to patients with MM as well as the results of recent randomized clinical trials evaluating the role of ASCT in first-line therapy [4]. In the IFM 2009 study, newly diagnosed MM patients received induction therapy with lenalidomide, bortezomib, and dexamethasone (RVD) [5]. The results demonstrated a PFS benefit for ASCT versus an additional four cycles of RVD, but no difference in OS [5]. Similarly, the DETERMINATION study comparing early versus deferred transplant after RVD induction also showed improved PFS with early ASCT but no OS difference [6].

These results have fostered an interest in whether carefully selected patients may defer ASCT in the first remission, necessitating the increased importance of a shared decision-making model between patients and physicians regarding the timing of ASCT. ASCT in the first remission exposes patients to increased early toxicity and may negatively impact the quality of life (QoL). Alternatively, patients who choose to defer ASCT may have a shorter first remission, more intensive ongoing treatment, more chronic side effects, and QoL

burden. In the IFM 2009 study, patients receiving RVD alone and those receiving RVD and ASCT both experienced sustained, similar improvements in global health-related quality of life, physical functioning, and role functioning scores, although the patients receiving ASCT reported transient worsening in QoL immediately after ASCT [7]. Individualizing the risks and benefits of such a decision lends itself to a shared decision-making model between physicians and patients [8,9], as patient preferences and individual attitudes toward treatment risks, benefits, and outcomes vary and may directly impact treatment decisions [10,11]. To inform how shared decision-making may be better incorporated into the care of MM patients, we sought to understand the disease-, physician-, and patient-related factors that have influenced early versus deferred ASCT at our institution and how these decisions are associated with survival outcomes. We report our institutional experience with progression-free survival (PFS) and overall survival (OS) as a function of transplant timing and assess the physician-related factors that influence practice regarding transplant timing.

2. Methods

2.1. Study Population

Patients newly diagnosed with MM between January 2015 and February 2021 and who underwent stem cell mobilization at our institution were included in this retrospective study. Patients who were prisoners, received a second ASCT, or were positive for human immunodeficiency virus testing were excluded from the study. For this study, early transplant was defined as a planned ASCT during the first line of therapy. Deferred transplant was defined as patients who did not proceed directly to ASCT following stem cell collection. This study was approved by the Institutional Review Board at The Ohio State University.

2.2. Data Collection

Clinical data included the date of diagnosis, initial treatment, induction regimen, induction outcome, date of autologous stem cell collection, stem cell mobilization regimen, number of stem cells collected, number of collections required, date of ASCT (if applicable), subsequent treatment after achieving remission, treatment-free intervals, date of first progression/relapse, date of death (if applicable), date of last contact, and primary physician. Patient-specific variables included age, race, sex, marital status, zip code (converted to distance from treatment center in miles), school district (correlate of personal income), Eastern Cooperative Oncology Group (ECOG) performance status, Revised International Staging System (RISS) stage, Charlson comorbidity index (CCI), and body mass index (BMI). Disease-specific variables collected from the medical records included disease type (IgG, IgA, IgM, or light chain) and features of initial presentation (presence of renal disease, bone involvement, plasmacytoma, hypercalcemia, anemia).

Physician data were collected via RedCap and included a self-assessment rating of the most important indicators that each physician used to recommend early versus delayed ASCT from the following list: income, ethnicity, race, age, gender, marital status, disease subtype, Revised International Staging System (RISS) stage, initial presentation, response to initial treatment, ECOG performance status, BMI, number of stem cells collected, CCI, albumin, toxicity from first-line therapy, and patient preference.

2.3. Statistical Considerations

Based on published prospective data, the goal was to detect a difference in PFS (median PFS of 50 months in early ASCT versus 36 months in deferred ASCT, corresponding to the PFS rate at 7 years of 31% in early ASCT versus 20% in deferred ASCT). Our sample size was calculated a priori to achieve 80% power at a 0.10 significance level to detect such a difference using a one-sided log rank test. The power calculation predicted at least 495 patients (with 348 PFS events) would be required in the early ASCT group and 55 patients (with 38 PFS events) in the deferred ASCT group.

Descriptive analyses were performed for all covariates, including mean, standard deviation, median, and range, or frequency and percent depending on the data type and distribution. MM patient characteristics who underwent early ASCT versus those who deferred ASCT were compared using t tests, Wilcoxon–Mann–Whitney tests, chi-square tests, or Fisher's exact tests where appropriate for the data type.

To identify factors influencing a decision to delay ASCT, logistic regression analyses were performed to assess associations between pre-specified variables of interest and the decision to proceed with ASCT or delay. For survival outcomes, PFS was calculated from the date of diagnosis to the date of progression or date of death, censoring those without progression or death at the last clinical assessment date; OS was calculated from the date of diagnosis to the date of death, censoring alive patients at the last contact date. PFS and OS probability were estimated using the Kaplan–Meier method, and Cox proportional hazard regression models were conducted to evaluate the associations between pre-specified variables of interest and survival outcomes. Significant risk factors from univariable analyses were included in the multivariable regression model to further evaluate its independent effect. Analyses were performed using standard Stata 16 (StataCorp LLC, College Station, TX, USA), and the statistical tests were two-sided with statistical significance defined as $p < 0.05$.

3. Results

3.1. Patient, Disease, and Induction Therapy Characteristics

A total of seven hundred and thirty-three patients underwent autologous stem cell mobilization, among which 85.8% (n = 629) received early ASCT while 14.2% (n = 104) stored stem cells and opted to defer ASCT (however, only 42% (n = 44) of patients who opted to defer ASCT subsequently underwent transplant at the time of this analysis). The majority of patients (84%) received triplet induction regimens: 66% received RVD; 14% received cyclophosphamide, bortezomib, and dexamethasone; and 4% received carfilzomib, lenalidomide, and dexamethasone. Thirteen percent received doublet induction therapy with either bortezomib and dexamethasone or lenalidomide and dexamethasone. The remainder of the patients (3%) received other induction regimens such as bortezomib, thalidomide, and dexamethasone, or bortezomib, lenalidomide, dexamethasone, and daratumumab. The median follow-up at the time of data analysis was 1320 days (3.61 years, mean 3.97 years; range 141 days to 10,596 days).

Table 1 summarizes patient and disease characteristics by ASCT timing. With respect to patient factors, no differences between early or deferred ASCT were seen regarding patient gender, race, ethnicity, body mass index, performance status, income, or distance from the treatment center. There were no differences regarding the ISS stage or cytogenetic risk, with high risk defined as 17p13 deletion, t(4; 14), t(14; 16), t(14; 20), and gain, or amplification of 1q. Patients receiving early ASCT tended to be slightly older (61.4 years versus 59.6 years, $p = 0.045$), were more likely to be married (72.7% versus 59.6%, $p < 0.01$), and had fewer comorbidities ($p < 0.001$). Of note, six patients in the early ASCT group and five patients in the deferred ASCT group experienced delays in care associated with the coronavirus pandemic.

Table 1. Baseline characteristics of patients receiving early vs. deferred transplant.

Characteristic	Early Transplant (n = 629)	Deferred Transplant (n = 104)	*p*-Value
		patients (%)	
Ethnicity			0.99
Hispanic	8 (1.3)	1 (1.0)	
Non-Hispanic	609 (98.7)	102 (99.0)	
Race			0.51
Asian	5 (0.8)	1 (1.0)	
Black	69 (11.1)	16 (15.5)	

Table 1. *Cont.*

Characteristic	Early Transplant (n = 629)	Deferred Transplant (n = 104)	*p*-Value
White	544 (87.6)	86 (83.5)	
Race > 1	3 (0.5)	0 (0.0)	
Age			0.045
Age (mean ± SD)	61.4 ± 8.6	59.6 ± 8.2	
Age range (years)	28–78	35–76	
Gender			0.16
Female	250 (39.7)	49 (47.1)	
Male	379 (60.3)	55 (52.9)	
Marital status			<0.01
Married	457 (72.7)	62 (59.6)	
Unmarried	172 (27.3)	42 (40.4)	
Body Mass Index			0.14
<25	118 (18.8)	24 (23.1)	
25–30	210 (33.4)	41 (39.4)	
≥30	301 (47.9)	39 (37.5)	
Income			0.66
Income (mean ± SD)	$61,073 ± 34,462	$62,647 ± 32,742	
Income range	$11,598–393,918	$21,418–203,409	
Distance from treatment center			0.98
Distance (miles, mean ± SD)	85.7 ± 148.1	85.4 ± 146.2	
Distance (miles, range)	0–2372	0–1275	
CMI category			<0.001
1	132 (21.0)	14 (13.5)	
2–3	210 (33.4)	13 (12.5)	
4–5	216 (34.3)	17 (16.3)	
6+	71 (11.3)	60 (57.7)	
ECOG performance status			0.26
1	268 (42.7)	37 (35.6)	
2	340 (54.2)	62 (59.6)	
3	19 (3.0)	5 (4.8)	
Revised ISS stage			0.39
1	106 (25)	10 (16.9)	
2	236 (55.7)	37 (62.7)	
3	82 (19.3)	12 (20.3)	
Cytogenetics risk			
High-risk	233 (42.4)	30 (34.1)	0.14
Standard risk	316 (57.6)	58 (65.9)	

3.2. Progression-Free and Overall Survival Outcomes

The comparison of PFS between the early and deferred ASCT groups is shown by Kaplan–Meier analysis in Figure 1. Early ASCT was associated with significantly longer PFS ($p < 0.001$). The median PFS for the early ASCT group was 5.1 years (95% confidence interval (CI): 4.7–5.5 years) while the PFS for the deferred ASCT group was 2.6 years (95% CI: 1.7–4.1 years). In the early transplant group, 86% of patients received post-ASCT maintenance therapy, most commonly with single-agent lenalidomide, while 43% of patients in the deferred transplant group who underwent ASCT at the time of the analysis also received post-ASCT maintenance therapy, with single-agent lenalidomide being the most common.

No significant difference in OS (Figure 2) was found between the two groups, with a median OS of 8.3 years and 8.6 years, $p = 0.21$. We also evaluated OS at five years in each group. The 5-year OS rate for patients receiving early transplant was 75.1% (95% CI 70.2–79.2), whereas the 5-year OS for patients in the deferred transplant group was 73.6% (95% CI 62.7–81.8%, $p = 0.21$).

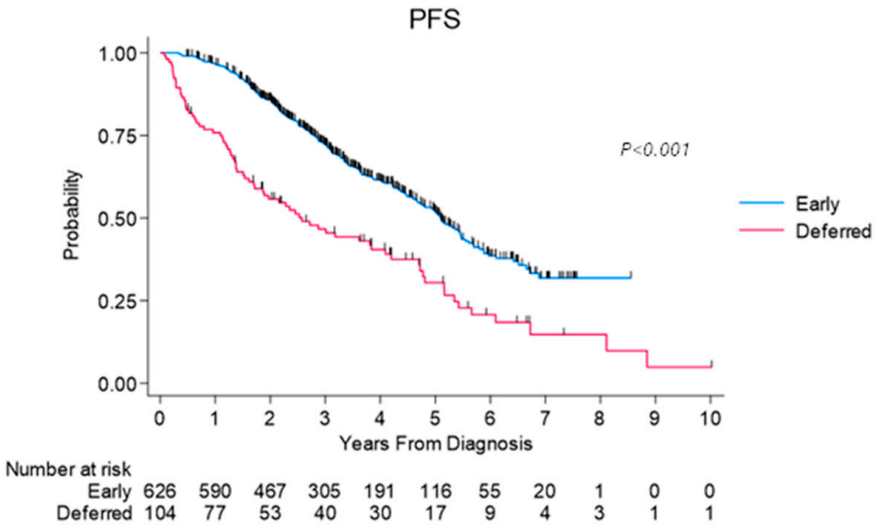

Figure 1. Progression-free survival as a function of transplant timing.

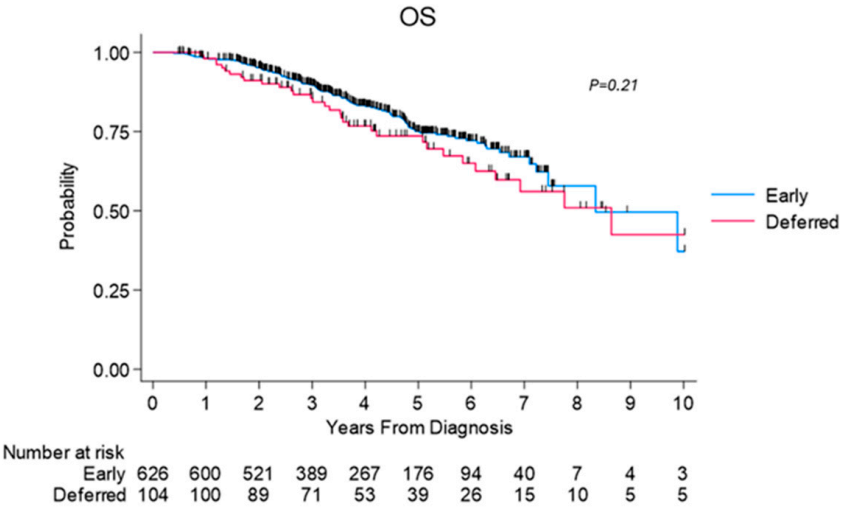

Figure 2. Overall survival as a function of transplant timing.

3.3. Predictors of Transplant Timing and Survival Outcomes

Multivariable logistic regression (Table 2) on the odds ratio related to ASCT timing showed that older patients (OR = 0.96, 95% CI: 0.93–0.99, $p = 0.024$) (for 1 year increase in age) and obese patients (OR = 0.30, 95% CI: 0.14–0.66, $p = 0.003$) were less likely to defer ASCT, while unmarried patients (OR = 2.01, 95% CI: 1.14–3.53, $p = 0.016$) and patients with higher CMI (six or more comorbidities, OR = 10.83, 95% CI 4.99–23.52, $p < 0.001$) were more likely to defer ASCT.

We sought to assess potential variables that impact PFS and OS outcomes as a function of transplant timing. In order to understand the potential impact of various factors influencing care, we conducted extensive univariate and multivariate modeling on available candidate predictor variables for both PFS and OS endpoints. Statistically significant predictors of superior PFS in the univariable analysis included early transplant, R-ISS stage, response to induction therapy, ECOG performance status, cytogenetic risk, and serum albumin (Table 3). In a multivariable model, the predictors of PFS included early transplant, R-ISS stage, response to induction therapy, ECOG performance status, cytogenetic risk, and serum albumin (Table 4).

Table 2. Logistic regression on the odds of deferred ASCT.

Variable	Odds Ratio	Confidence Interval	*p*-Value
Age	0.96	0.93–1.00	0.024
Gender			
Male			
Female	1.26	0.72–2.18	0.416
Marital Status			
Married			
Unmarried	2.01	1.14–3.53	0.016
CMI category			
1			
2–3	0.37	0.14–0.94	0.037
4–5	0.6	0.25–1.39	0.232
6+	10.83	4.99–23.52	<0.001
Body Mass Index			
<25			
25–30	1.2	0.58–2.50	0.62
≥30	0.3	0.14–0.66	0.003
High-risk cytogenetics			
No			
Yes	0.8	0.45–1.41	0.434
Albumin	0.41	0.18–0.90	0.027
Response to initial therapy			
sCR/CR/VGPR			
PR	1.11	1.11–2.14	0.761
MR	0.52	0.0.8–3.26	0.488
SD	3.22	1.43–7.24	0.005
PD	6.86	2.13–22.03	0.001

Table 3. Univariable predictors of progression-free survival.

Variable	Hazard Ratio	Confidence Interval	*p*-Value
Timing of ASCT			
Early			
Deferred	2.17	1.67–2.83	<0.001
Age	1.00	0.98–1.01	0.659
Race			
White			
Black	1.05	0.75–1.45	0.789
Others	0.84	0.37–1.89	0.674
Gender			
Male			
Female	0.89	0.71–1.12	0.323
Marital status			
Married			
Unmarried	0.95	0.74–1.21	0.68
Revised ISS stage			
1			
2	1.07	0.74–1.56	0.71
3	1.99	1.31–3.03	0.001
Response to initial therapy			
sCR/CR/VGPR			
PR	1.45	1.13–1.87	0.004
MR	1.61	0.95–2.75	0.077
SD	1.52	1.06–2.17	0.024
PD	1.53	0.81–2.91	0.191

Table 3. *Cont.*

Variable	Hazard Ratio	Confidence Interval	*p*-Value
ECOG			
1			
2	1.42	1.13–1.79	0.002
3	1.03	0.53–2.04	0.923
Body Mass Index			
<25			
25–30	1.28	0.93–1.77	0.132
>30	1.12	0.82–1.53	0.47
CMI category			
1			
2–3	0.95	0.69–1.31	0.746
4–5	1.07	0.78–1.48	0.665
6+	1.27	0.90–1.80	0.174
High-risk cytogenetics			
No			
Yes	1.51	1.19–1.91	0.001
Albumin	0.66	0.49–0.88	0.005

Table 4. Multivariable predictors of progression-free survival.

Variable	Hazard Ratio	Confidence Interval	*p*-Value
Timing of ASCT			
Early			
Deferred	1.97	1.47–2.65	0.001
Age	0.99	0.98–1.01	0.32
Revised ISS stage			
1			
2	0.98	0.66–1.46	0.928
3	1.68	1.08–2.61	0.02
Response to initial therapy			
sCR/CR/VGPR			
PR	1.47	1.11–1.93	0.006
MR	1.79	0.99–3.26	0.056
SD	1.49	1.01–2.19	0.043
PD	1.24	0.63–2.47	0.531
ECOG			
1			
2	1.39	1.09–1.78	0.009
3	1.13	0.55–2.34	0.74
High-risk cytogenetics			
No			
Yes	1.55	1.21–1.98	<0.001
Albumin	0.63	0.45–0.87	0.006

Statistically significant predictors of OS in the univariable analysis included the R-ISS stage, ECOG performance status, comorbidity index (CMI), cytogenetic risk, and serum albumin (Table 5). In a multivariable model, the predictors of superior OS included the R-ISS stage, ECOG performance status, cytogenetics risk, and serum albumin (Table 6). CMI was highly correlated with the timing of ASCT and thus was not included in the multivariable model.

In the deferred ASCT group, at the time of the analysis, 40% of patients experienced progressive disease and underwent ASCT, 32% of patients did not experience progressive disease and did not yet undergo ASCT, 26% of patients experienced progressive disease but did not yet undergo ASCT and received additional conventional regimens, and 2% of patients underwent ASCT more than a year after diagnosis having not experienced objective disease progression. Of patients who deferred transplant, 58% remained

on lenalidomide maintenance after induction, 14% received subsequent treatment with lenalidomide and dexamethasone, 14% received pomalidomide-based combinations, 6% went onto carfilzomib-based combinations, 5% received daratumumab-based combinations, and 3% received ixazomib-based combinations.

Table 5. Univariable predictors of overall survival.

Variable	Hazard Ratio	Confidence Interval	*p*-Value
Timing of ASCT			
Early			
Deferred	1.29	0.87–1.92	0.211
Age	1	0.98–1.02	0.871
Race			
White			
Black	0.93	0.57–1.50	0.752
Others	0.94	0.30–2.96	0.915
Gender			
Male			
Female	0.74	0.53–1.04	0.082
Marital status			
Married			
Unmarried	0.84	0.58–1.21	0.355
Revised ISS stage			
1			
2	1.59	0.82–3.08	0.167
3	3.81	1.93–7.55	<0.001
Response to initial therapy			
sCR/CR/VGPR			
PR	1.32	0.92–1.91	0.134
MR	0.93	0.38–2.30	0.877
SD	1.51	0.92–2.48	0.1
PD	0.51	0.12–2.06	0.342
ECOG			
1			
2	1.47	1.04–2.08	0.028
3	2.28	1.08–4.82	0.031
Body Mass Index			
<25			
25–30	1.31	0.82–2.08	0.26
>30	1	0.64–1.58	0.987
CMI category			
1			
2–3	1.1	0.66–1.82	0.718
4–5	1.35	0.83–2.22	0.228
6+	1.75	1.05–2.93	0.032
High-risk cytogenetics			
No			
Yes	1.84	1.31–2.59	0.001

Table 6. Multivariable predictors of overall survival.

Variable	Hazard Ratio	Confidence Interval	*p*-Value
Timing of ASCT			
Early			
Deferred	1.12	0.71–1.75	0.631
Age	0.99	0.97–1.01	0.463
Revised ISS stage			
1			
2	1.15	0.58–2.27	0.694
3	2.84	1.41–5.71	0.003

Table 6. *Cont.*

Variable	Hazard Ratio	Confidence Interval	*p*-Value
Response to initial therapy			
sCR/CR/VGPR			
PR	1.28	0.86–1.92	0.226
MR	0.8	0.29–2.25	0.672
SD	1.75	1.04–2.94	0.035
PD	0.45	0.11–1.86	0.27
ECOG			
1			
2	1.28	0.88–1.85	0.199
3	2.48	1.13–5.44	0.023
High-risk cytogenetics			
No			
Yes	1.79	1.25–2.55	0.001
Albumin	0.39	0.24–0.63	<0.001

3.4. Physician-Reported Factors Affecting ASCT Timing

To further understand the physicians' approach towards ASCT timing, we surveyed current MM physicians with a "Physicians Transplant Decision Making Self-Assessment" tool. Physicians were asked to rate the importance of twenty-one different indicators in planning the timing of ASCT with patients with MM. Each indicator was rated on a five-point Likert scale, with 1 being extremely unimportant to the physician and 5 being extremely important. The average rating of the seven most important indicators of early versus deferred ASCT is shown in Figure 3; supplementary, with the most important factor being the patient preference followed by cytogenetics, outcome from previous treatment, ECOG performance status, toxicity from previous treatment, geriatric assessment, and CMI. We then collected patient data from the nine MM physicians at our center. Of interest, while the majority of patients of all nine physicians received early ASCT, heterogeneity in practice was evident, and these differences in physician practice are reflected in Figure 4.

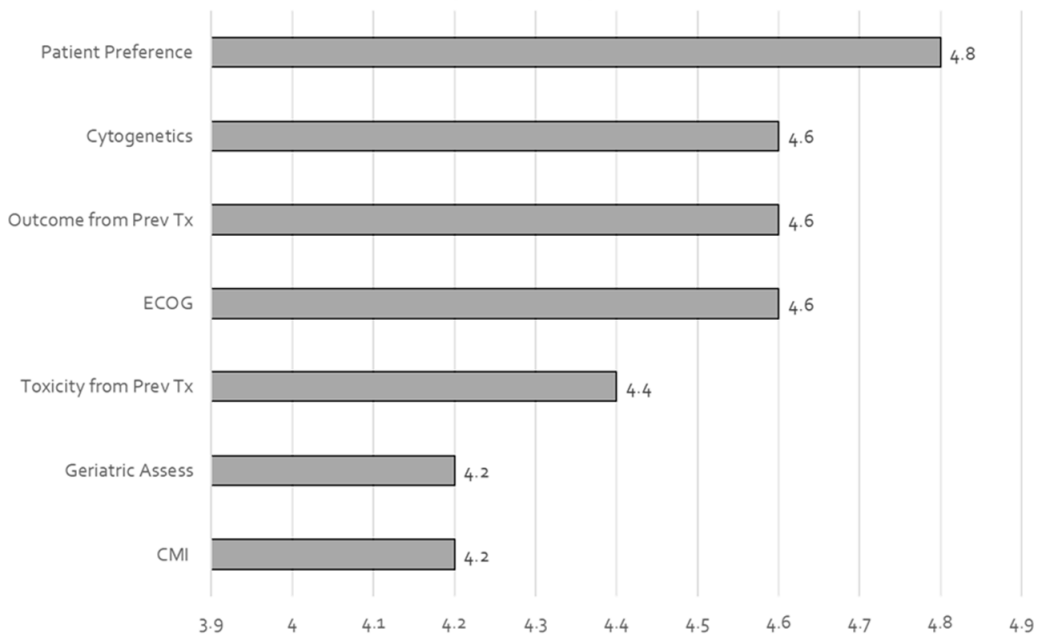

Figure 3. Important factors considered by physicians in transplant timing.

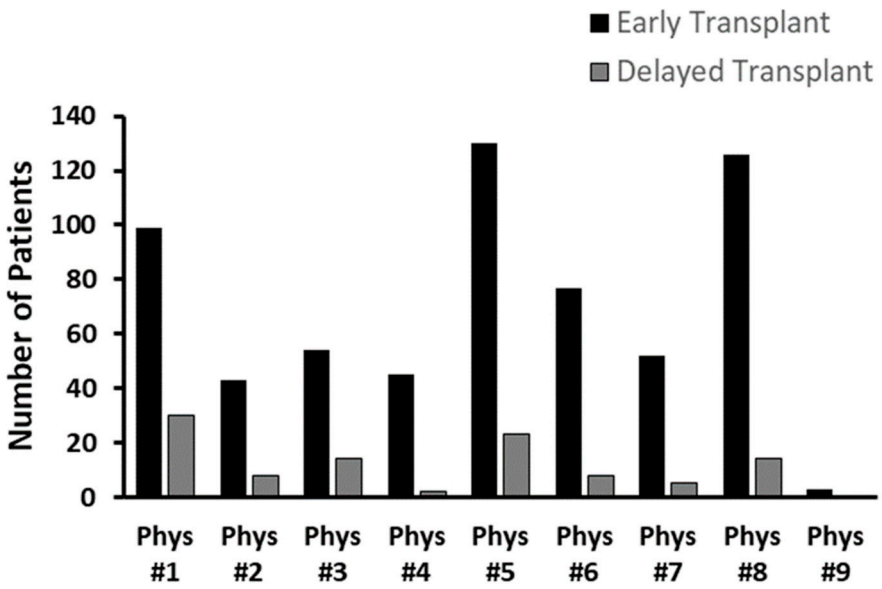

Figure 4. Physician utilization of early versus delayed transplant.

4. Discussion

ASCT remains critical to the treatment of eligible patients with MM as an integrated part of the initial line of therapy (early ASCT). However, the results from recent randomized trials have introduced the question of whether deferring ASCT could be an option for selected patients without compromising OS. Our study provides new, real-world data regarding the predictors associated with the timing of ASCT as well as associated outcomes.

The DETERMINATION study was a large, randomized phase 3 trial in which patients with newly diagnosed MM received uniform induction (RVD) followed by stem cell collection and randomization to early versus deferred ASCT [6]. The study demonstrated a PFS benefit (67.5 months for early transplant versus 46.2 months for deferred ASCT) but no difference in OS. In the IFM 2009 trial, patients with MM received either three cycles of RVD followed by ASCT or eight cycles of RVD [5]. A PFS benefit in favor of the ASCT arm (50 months versus 36 months) was observed, but, again, no difference in OS was evident, even with long-term follow-up [12]. In our present study, despite differences in induction regimens and other factors, our PFS and OS outcomes closely approximate the survival outcomes from the DETERMINATION and IFM 2009 studies.

A recent survey of oncologists in the United States suggested that OS was viewed as the most significant factor in first-line treatment decisions, and only 42% of responding physicians indicated that the PFS benefit found in DETERMINATION persuaded them to increase their use of early ASCT [13]. Indeed, other studies have also shown that MM physicians prioritize perceived treatment efficacy and likelihood to prolong life (OS) as principal priorities when making recommendations about treatment options to patients [14]. On the other hand, patients with MM are reported to more commonly express a preference for treatments associated with superior quality of life even ahead of treatments that may prolong life [11]. Decision-making in contemporary practice is further complicated by the myriads of available, effective therapies for MM, each with its own potential risks and benefits. Moreover, although the role of ASCT has long been established in the care of eligible patients with MM, a recent randomized, prospective study of patients with MM aged 60–75 years comparing continuous lenalidomide/dexamethasone with lenalidomide/dexamethasone induction followed by ASCT (using a preparative regimen of melphalan dosed at 140 mg/m^2) followed by lenalidomide maintenance found no differences in either PFS or OS, although this study utilized less intensive treatments and a lower dose of melphalan than those incorporated in other trials [15]. Moreover, the recent PERSUES trial [16] demonstrated a significant improvement in PFS with the addition of

daratumumab in induction and maintenance after early transplant. However, no data are available presently on the effect of quadruplet induction and delayed transplant.

While the preferred approach to treatment for patients with newly diagnosed, high-risk MM is early ASCT irrespective of depth of response to initial induction therapy [17], multivariate analyses of the DETERMINATION dataset suggest possible subgroups of patients with MM who may achieve both superior PFS and OS without ASCT [18]. For example, for patients in whom minimal residual disease was not detected after RVD induction, 59.2% achieved a 5-year PFS with deferred transplant and 53.5% achieved a 5-year PFS with early transplant (p = n/s) [6].

The CCI is the most commonly used tool to predict the outcome of transplant and has been shown to predict the risk of non-relapse mortality and survival after transplantation [19]. Nutritional assessments, including BMI, while not found to be associated with OS post-transplant, are associated with length of hospital stay and platelet and neutrophil engraftment post-transplant [19]. In our study, we found that patients with a higher CCI category tended to defer ASCT, suggesting that for these patients, while deemed "eligible" for ASCT (in that they underwent stem cell collection), the interpretation of the risk/benefit of early ASCT placed heavier weight on the short-term toxicities and discounted the associated, potential PFS benefit. Indeed, in one study, fear of side effects was reported as the most common reason for patients with MM to decline ASCT at all [20]. Abnormal, high-risk bone marrow cytogenetics have been found to predict poorer survival outcomes after ASCT for MM [13]. Interestingly, in our study, even though deemed an important variable by MM-treating physicians, the presence of high-risk cytogenetics was not statistically different between our early and deferred ASCT groups.

The possible reasons why more married patients were represented in the early ASCT group than the deferred ASCT group are unclear. It may simply be, in part, that marital status is a correlate of having the immediate availability of a post-ASCT caregiver for the patient. Alternatively, this may reflect possible differences in terms of assessing the risks and benefits of early ASCT between married and unmarried patients and highlight the influence of marital status on patient preference/decision-making.

This present study has several limitations. First, it is a single-center study and retrospective in nature, and, thus, is descriptive, hypothesis-generating, and necessarily limited in the conclusions that may be drawn from the data. In addition, the retrospective nature introduces limitations in interpreting the decision-making process of patients and physicians in each particular instance. Second, caution is advised whenever comparing outcomes from distinct studies and in drawing any conclusions from comparing the reported PFS and OS endpoints from our study with others such as DETERMINATION and IFM 2009, as the patient populations may not have been similar.

There are potential confounders influencing the PFS and OS outcomes reported in our research. First, in the time period studied, there were numerous new treatments approved, adding novel, effective treatment options and combinations to patients in both the early and deferred transplant groups. Second, the median follow-up for our study was relatively short; a 10-year median follow-up is increasingly necessary for the evaluation of serial therapies and outcomes in MM. Most importantly, while our study informs "real world" perceptions on the timing of ASCT from physicians and patients with MM, the potential, underlying motivations, incentives, values, and behavioral economics at work in these decision-making processes are not able to be well characterized in this present study and are the subject of ongoing research.

The myriad of advances in the treatment of MM has led to dramatic improvements in patient outcomes. Ongoing prospective studies continue to define the optimal role of ASCT in the context of the increasing number of novel treatment options. In parallel, prospective studies characterizing patient-specific preferences, goals, and values are needed, as well, in order to develop truly personalized therapies to maximize outcomes for unique individuals diagnosed with MM.

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