Original Article

Age no Bar: A CIBMTR Analysis of Elderly Patients Undergoing Autologous Hematopoietic Cell Transplantation for Multiple Myeloma

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BACKGROUND: Upfront autologous hematopoietic stem cell transplantation (AHCT) remains an important therapy in the management of patients with multiple myeloma (MM), a disease of older adults. **METHODS:** The authors investigated the outcomes of AHCT in patients with MM who were aged ≥70 years. The Center for International Blood and Marrow Transplant Research (CIBMTR) database registered 15,999 patients with MM in the United States within 12 months of diagnosis during 2013 through 2017; a total of 2092 patients were aged ≥70 years. Nonrecurrence mortality (NRM), disease recurrence and/or progression (relapse; REL), progression-free survival (PFS), and overall survival (OS) were modeled using Cox proportional hazards models with age at transplantation as the main effect. Because of the large sample size, a *P* value <.01 was considered to be statistically significant a priori. **RESULTS:** An increase in AHCT was noted in 2017 (28%) compared with 2013 (15%) among patients aged ≥70 years. Although approximately 82% of patients received melphalan (Mel) at a dose of 200 mg/m^2 overall, 58% of the patients aged ≥70 years received Mel at a dose of 140 mg/m^2. On multivariate analysis, patients aged ≥70 years demonstrated no difference with regard to NRM (hazard ratio [HR] 1.3; 99% confidence interval [99% CI], 1-1.7 [*P* = .06]), REL (HR, 1.03; 99% CI, 0.9-1.1 [*P* = 0.6]), PFS (HR, 1.06; 99% CI, 1-1.2 [*P* = 0.2]), and OS (HR, 1.2; 99% CI, 1-1.4 [*P* = .02]) compared with the reference group (those aged 60-69 years). In patients aged ≥70 years, Mel administered at a dose of 140 mg/m^2 was found to be associated with worse outcomes compared with Mel administered at a dose of 200 mg/m^2, including day 100 NRM (1% [95% CI, 1%-2%] vs 0% [95% CI, 0%-1%]; *P* = .003]), 2-year PFS (64% [95% CI, 60%-67%] vs 69% [95% CI, 66%-73%]; *P* = .003), and 2-year OS (85% [95% CI, 82%-87%] vs 89% [95% CI, 86%-91%]; *P* = .01]), likely representing frailty. **CONCLUSIONS:** The results of the current study demonstrated that AHCT remains an effective consolidation therapy among patients with MM across all age groups. ***Cancer* 2020;0:1-11**.

KEYWORDS: age, geriatric oncology, myeloma, transplantation.

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INTRODUCTION

Multiple recent studies have confirmed the role of early autologous hematopoietic stem cell transplantation (AHCT) in patients who are newly diagnosed with multiple myeloma (MM), even in the age of current induction therapies.[1-5] Despite these data and continued recommendations from the National Comprehensive Cancer Network that transplantation should be considered in patients with symptomatic disease, studies from the United States have suggested that the use of AHCT in patients with MM, even in recent years, is <40%.[6] Although race and ethnicity have been recognized as important barriers to the use of AHCT,[6] age also is a significant barrier.[7,8]

MM is a cancer of older adults, with a median age at diagnosis of 66 to 70 years reported in the United States.[9,10] Although the 5-year and 10-year survival rates of patients diagnosed with MM have shown significant improvements in the last 20 years, a group in whom long-term outcomes have not been encouraging includes older patients, both those aged 65 to 74 years and those aged ≥75 years.[10] Prior single-center, retrospective studies from the United States have supported the safety and benefit of AHCT in patients with MM who are aged ≥75 years,[11,12] but these studies have included patients treated in the era before novel therapies and may not reflect current clinical treatment paradigms.

The Center for International Blood and Marrow Transplant Research (CIBMTR) database has demonstrated that the number of transplantations performed in patients aged ≥70 years continues to increase annually.[13] We sought to study the outcomes of older patients with MM undergoing AHCT between 2013 and 2017 in the United States. We hypothesized that patients with MM who were aged ≥70 years would have similar nonrecurrence mortality (NRM), disease recurrence and/or progression (relapse; REL), progression-free survival (PFS), and overall survival (OS) compared with patients with MM who were aged <70 years at the time of transplantation.

MATERIALS AND METHODS

Data Source

We used the CIBMTR database, which captures and prospectively maintains the outcomes of approximately 75% to 80% of transplantations among patients with MM in the United States from 2013 through 2017.[14] The CIBMTR is a working group of >500 transplantation centers worldwide that contribute detailed data regarding HCT to a statistical center at the Medical College of Wisconsin. Participating centers are required to report all transplantations consecutively and compliance is monitored by on-site audits. Computerized checks for discrepancies, physician review of submitted data, and on-site audits of participating centers ensure data quality. Data are collected at 2 levels: transplantation essential data (TED) and comprehensive report form (CRF) data. TED forms include disease type, age, sex, pre-HCT disease stage and chemotherapy responsiveness, date of diagnosis, graft type, conditioning regimen, posttransplantation disease progression and survival, development of a new malignancy, and cause of death. All CIBMTR centers contribute to the TED set. More detailed disease information as well as pretransplantation and posttransplantation clinical information are collected for a subset of registered patients selected for CRF data using a weighted randomization scheme. TED-level and CRF-level data are collected before transplantation and 100 days and 6 months after HCT and annually thereafter or until death. Data for the current analysis were retrieved from TED report forms because the intent was to capture all patients registered with the CIBMTR.

Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The Medical College of Wisconsin institutional review board approved the current study.

Patients

Included in the current analysis were consented adult patients (those aged ≥18 years) in the United States who were diagnosed with MM and who underwent a single AHCT within 12 months of diagnosis between 2013 and 2017 with peripheral blood hematopoietic cells after melphalan (Mel) conditioning. The TED data set was used in the current study and provided data regarding patient-related (age, sex, race, Karnofsky performance score [KPS], and HCT comorbidity index [HCT-CI]), disease-related (immunoglobulin subtype, International Staging System stage, and cytogenetics), and transplantation-related (time from diagnosis to transplantation, disease status at the time of transplantation, Mel conditioning dose, and year of transplantation) covariates. Data regarding the induction therapy received were available for approximately 13% of the patients selected for the current analysis who were registered in the CRF track. Of these patients, all initially were treated with proteasome inhibitors and/or immunomodulatory drugs, thus extrapolating that patients in the current study all received novel therapy.

Definitions and Study Endpoints

The primary objective of the current study was to compare NRM in older versus younger patients with MM after AHCT, in which NRM was defined as death from any cause in the absence of REL. Secondary objectives included PFS (defined as the time from transplantation to REL or death from any cause) and OS (defined as the time from transplantation to death from any cause). The primary endpoint of the current study was to assess NRM among different age groups. The secondary endpoint was to assess PFS, OS, and REL among patients in all age groups.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics. Cumulative incidences of NRM and REL were calculated accounting for competing risks. Kaplan-Meier estimates were used to calculate the probabilities of PFS and OS. Multivariate analyses of PFS and OS were conducted using the Cox proportional hazards regression analysis to assess the main effect, age at the time of transplantation by decade, adjusting for key patient-related, disease-related, and transplantation-related covariates (sex, race, KPS, HCT-CI, stage of disease at the time of diagnosis, disease status at the time of transplantation, cytogenetics, conditioning Mel dose, time from diagnosis to transplantation, and year of transplantation). Patients aged 60 to 69 years were used as the reference group based on the maximum representation of patients. Because of the very few events noted to occur among patients aged <40 years as well as a small overall number of patients, this group was excluded from the multivariate analysis. Mel dose was studied at 2 levels: the standard 200 mg/m^2 dose and the reduced 140 mg/m^2 dose. The assumption of proportional hazards for each covariate in the Cox model was tested using time-dependent variables. A stepwise model selection approach was used to identify covariates associated with outcomes. Factors that were statistically significant at the 1% level ($P < .01$) were retained in the final model. Hazard ratios (HRs) with 99% confidence intervals (99% CIs) were shown. A lower P value was considered to be statistically significant owing to the large sample size of the population and was decided a priori. A second subset analysis was conducted in patients aged ≥70 years (2092 patients) in whom the main effect was the Mel conditioning dose. Other covariates that went into the model included sex, race, KPS, HCT-CI, stage of disease at the time of diagnosis, disease status at the time of transplantation, cytogenetics, conditioning Mel dose, time from diagnosis to transplantation, and year of transplantation. Because of the small sample size, P values <.05 were considered to be statistically significant and HRs with 95% CIs are shown. Statistical analysis was performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, North Carolina).

RESULTS

Table 1 shows the overall patient population included in the current study (15,999 patients), including 2092 patients aged ≥70 years. The median patient age was 62 years (range, 20-83 years). The majority of patients were White (78%), with a male predominance (57%). Patients aged ≥70 years were more likely to be White compared with younger patients: 85% of White patients were aged ≥70 years compared with 64% aged 20 to 39 years. All age groups were found to have similar distributions of sex, KPS, HCT-CI, and stage III disease according to the Durie-Salmon/International Staging System (DS/ISS). There was a higher percentage of high-risk cytogenetics in patients aged ≥70 years (30%) compared with those aged 40 to 49 years (24%) and 20 to 39 years (20%) in this population. Similar numbers of patients aged ≥70 years achieved a very good partial response or better prior to transplantation compared with other age groups. Although approximately 82% of the overall population received Mel at a dose of 200 mg/m^2, only 41% of patients aged ≥70 years received Mel at a dose of 200 mg/m^2. There was a higher percentage of transplantations performed among patients aged ≥70 years in 2017 (28%) compared with 2013 (15%). The median follow-up for survivors was 25 months (range, <1-72 months).

Nonrecurrence Mortality

Univariate outcomes by age group as shown in Table 2 demonstrated that the 100-day NRM was low across all age groups, including 0% in the patients aged <40 years, 0% (95% CI, 0%-1%) in the patients aged 40 to 49 years, 0% in the patients aged 50 to 59 years, 0% (95% CI, 0%-1%) in the patients aged 60 to 69 years, and 1% (95% CI, 1%-1%) in the patients aged ≥70 years ($P < .01$). Table 3 shows the multivariate analysis for NRM. Patients aged <60 years were found to have lower NRM and patients aged ≥70 years had a similar NRM compared with the patients in the reference age group aged 60 to 69 years. Other factors found to be negatively associated with NRM included a KPS <90, a HCT-CI >0, DS/ISS stage III disease, and disease status at the time of HCT of partial response or worse.

Disease Recurrence and/or Disease Progression

On univariate analysis, REL at 2 years was found to be similar across all age groups ($P = .8$) (Table 2). On

TABLE 1. Baseline Characteristics

Characteristic	Total	Patients Aged 20 to 39 Years	Patients Aged 40 to 49 Years	Patients Aged 50 to 59 Years	Patients Aged 60 to 69 Years	Patients Aged ≥70 Years
No. of patients	15,999	308	1615	4952	7032	2092
Median age (range), y	62 (20-83)	37 (20-39)	47 (40-49)	56 (50-59)	65 (60-69)	72 (70-83)
Sex						
Male	9160 (57)	186 (60)	908 (56)	2841 (57)	3960 (56)	1265 (60)
Female	6839 (43)	122 (40)	707 (44)	2111 (43)	3072 (44)	827 (40)
Self-reported race						
White	12,416 (78)	198 (64)	1088 (67)	3702 (75)	5658 (80)	1770 (85)
African American	2683 (17)	78 (25)	396 (25)	942 (19)	1024 (15)	243 (12)
Other[a]	455 (3)	18 (6)	65 (4)	158 (3)	180 (3)	34 (2)
Missing data	445 (3)	14 (5)	66 (4)	150 (3)	170 (2)	45 (2)
Karnofsky performance score						
≥90	8562 (54)	197 (64)	966 (60)	2838 (57)	3648 (52)	913 (44)
<90	7263 (45)	108 (35)	618 (38)	2066 (42)	3322 (47)	1149 (55)
Missing data	174 (1)	3 (<1)	31 (2)	48 (<1)	62 (<1)	30 (1)
HCT-CI						
0	4276 (27)	105 (34)	518 (32)	1450 (29)	1775 (25)	428 (20)
1	2144 (13)	55 (18)	240 (15)	663 (13)	928 (13)	258 (12)
2	2831 (18)	62 (20)	292 (18)	911 (18)	1213 (17)	353 (17)
3	2957 (18)	43 (14)	292 (18)	908 (18)	1320 (19)	394 (19)
4	1711 (11)	25 (8)	144 (9)	494 (10)	775 (11)	273 (13)
5	980 (6)	12 (4)	77 (5)	283 (6)	449 (6)	159 (8)
≥6	1093 (7)	6 (2)	52 (3)	240 (5)	568 (8)	227 (11)
Missing data	7 (<1)	0	0	3 (<1)	4 (<1)	0
DS/ISS stage at diagnosis						
III	8713 (54)	188 (61)	949 (59)	2697 (54)	3811 (54)	1068 (51)
I-II	6848 (43)	117 (38)	632 (39)	2112 (43)	3021 (43)	966 (46)
Missing data	438 (3)	3 (<1)	34 (2)	143 (3)	200 (3)	58 (3)
Cytogenetics						
No abnormality	3430 (21)	73 (24)	375 (23)	1101 (22)	1483 (21)	398 (19)
High risk	4398 (27)	63 (20)	380 (24)	1307 (26)	2019 (29)	629 (30)
Standard risk	4871 (30)	98 (32)	493 (31)	1513 (31)	2110 (30)	657 (31)
Test not done/unknown	3300 (21)	74 (24)	367 (23)	1031 (21)	1420 (20)	408 (20)
MEL at 140 mg/m^2	2938 (18)	32 (10)	144 (9)	475 (10)	1064 (15)	1223 (58)
MEL at 200 mg/m^2	13,047 (82)	276 (90)	1468 (91)	4473 (90)	5962 (85)	868 (41)
Unknown dose	14 (<1)	0	3 (<1)	4 (<1)	6 (<1)	1 (<1)
Disease status prior to transplantation						
sCR/CR	2520 (16)	51 (17)	269 (17)	814 (16)	1089 (15)	297 (14)
VGPR	6277 (39)	117 (38)	632 (39)	1929 (39)	2746 (39)	853 (41)
PR	6057 (38)	122 (40)	595 (37)	1842 (37)	2700 (38)	798 (38)
SD/PD/recurrence	1075 (7)	18 (6)	112 (7)	341 (7)	467 (7)	137 (7)
Missing data	70 (<1)	0	7 (<1)	26 (<1)	30 (<1)	7 (<1)
Year of transplantation						
2013	2746 (17)	70 (23)	327 (20)	859 (17)	1183 (17)	307 (15)
2014	2940 (18)	60 (19)	300 (19)	962 (19)	1272 (18)	346 (17)
2015	3034 (19)	53 (17)	312 (19)	952 (19)	1345 (19)	372 (18)
2016	3547 (22)	65 (21)	339 (21)	1100 (22)	1563 (22)	480 (23)
2017	3732 (23)	60 (19)	337 (21)	1079 (22)	1669 (24)	587 (28)
Median follow-up of survivors (range), mo	25 (<1-72)	34 (1-64)	33 (1-71)	27 (1-71)	25 (1-72)	24 (1-66)

Abbreviations: CR, complete response; DS, Durie-Salmon; HCT-CI, hematopoietic stem cell transplantation comorbidity index; ISS, International Staging System; MEL, melphalan; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.
[a]Other race: Asian (n = 323); Pacific Islander (n = 25); Native American (n = 76); more than one race (n = 31).

multivariate analysis (Table 3), age at the time of transplantation also was not found to be associated with REL; DS/ISS stage III disease, disease status at the time of HCT of very good partial response or worse, the presence of high-risk cytogenetics, and an earlier year of transplantation were associated with higher REL rates.

Progression-Free Survival

At 2 years, PFS was found to be similar across all age groups on univariate analysis ($P = .4$) (Table 2). On multivariate analysis, age at the time of transplantation was not found to be associated with worse PFS; KPS, DS/ISS stage of disease, disease status, cytogenetics, and year of

TABLE 2. Univariate Outcomes

Age Group	20 to 39 Years N = 308	40 to 49 Years N = 1615	50 to 59 Years N = 4952	60 to 69 Years N = 7032	≥70 Years N = 2092	*P*
100-d NRM	0%	0% (0%-1%)	0%	0% (0%-1%)	1% (1%-1%)	<.01
2-y REL	31% (26%-37%)	29% (27%-32%)	30% (28%-31%)	29% (28%-30%)	29% (27%-32%)	.80
2-y PFS	68% (62%-74%)	69% (67%-72%)	68% (67%-70%)	68% (67%-69%)	66% (64%-68%)	.44
2-y OS	94% (91%-97%)	91% (90%-93%)	90% (90%-91%)	89% (88%-89%)	86% (85%-88%)	<.01

Abbreviations: NRM, nonrecurrence mortality; OS, overall survival; PFS, progression-free survival; REL, disease recurrence/progression.
Probabilities with 95% confidence intervals are shown.

transplantation were found to be significant predictors of PFS (Table 3).

Overall Survival

At 2 years, OS was lower in the patients aged ≥70 years at 86% (95% CI, 85%-88%) compared with the younger age groups ($P < .01$) (Table 2). On multivariate analysis adjusted for other covariates (Table 3), age was found to be associated with OS ($P = .0003$), with patients aged 40 to 49 years found to have a lower hazards of mortality compared with patients aged 60 to 69 years (HR, 0.8; 99% CI, 0.6-0.9 [$P = .01$]) but no significant difference was noted compared with patients aged 50 to 59 years (HR, 0.9; 99% CI, 0.8-1 [$P = .05$]) or those aged ≥70 years (HR, 1.2; 99% CI, 1-1.4 [$P = .03$]). Other factors found to be associated with worse survival included KPS, HCT-CI, DS/ISS stage of disease, disease status at the time of transplantation, and cytogenetics.

Subset Analysis Studying the Effect of Mel Dose in Patients Aged ≥70 Years

The current study examined the effect of the Mel conditioning dose in patients aged ≥70 years. The majority of patients (1223 patients) received reduced Mel at a dose of 140 mg/m^2 whereas 868 patients received Mel at a dose of 200 mg/m^2. The overall NRM on univariate analysis was worse in the patients treated with Mel at a dose of 140 mg/m^2 compared with those treated with a dose of 200 mg/m^2 ($P = .003$). Both PFS and OS were found to be better among patients treated with Mel at a dose of 200 mg/m^2 compared with those receiving Mel at a dose of 140 mg/m^2. On multivariate analysis, Mel at a dose of 140 mg/m^2 was associated with a worse NRM, with an HR of 2.2 (95% CI, 1.3-3.7; $P = .003$) compared with Mel at a dose of 200 mg/m^2. Similarly, both PFS and OS were worse among the patients aged ≥70 years who were treated with Mel at a dose of 140 mg/m^2 compared with those treated at a dose of 200 mg/m^2 (Fig. 1) (Table 4). Among patients who received Mel at a dose of 200 mg/m^2, there was no difference in OS noted by age group (Fig. 2).

Cause of Death

A total of 2356 deaths were noted among the entire cohort of 15,999 patients. The cause of death was MM in approximately 72% of patients aged <40 years, 80% of patients aged 40 to 49 years, 80% of patients aged 50 to 59 years, 72% of patients aged 60 to 69 years, and 68% of patients aged ≥70 years. More patients were reported to have died of organ failure (5%) and secondary malignancy (4%) among the patients aged ≥70 years compared with younger patients.

DISCUSSION

Based on the current large database study capturing the majority of autologous transplantation activity when used as upfront therapy for patients with MM in the United States in recent years, we made the following observations. First, transplantations conducted among patients aged ≥70 years continue to increase each year, with 28% of all patients with MM undergoing AHCT in 2017 compared with 15% in 2013. Second, age ≥70 years was not found to be associated with adverse outcomes in patients with MM after HCT compared with the reference group aged 60 to 69 years. Third, the administration of Mel at a dose of 200 mg/m^2 among patients aged ≥70 years was associated with superior outcomes, most likely demonstrating that the choice of Mel at a dose of 140 mg/m^2 was based on frailty. Last, MM remains the predominant cause of death across all age groups.

The use of upfront AHCT in patients newly diagnosed with MM in the era of proteasome inhibitor and immunomodulatory agent–based induction therapies remains an important strategy to induce a deep and durable response.[5] Nevertheless, prior work by our group in which the stem cell use rate was calculated using CIBMTR data and Surveillance, Epidemiology, and End Results incidence data have shown that only a minority of patients with MM undergo AHCT in the United States.[6,7] The data from the current study indicated that with every age group, fewer non-White patients underwent transplantation in the United States.

TABLE 3. Multivariate Analysis of Outcomes

Outcome	No. of Events/No. Evaluable	HR (99% CI)	*P*
NRM			
Main effect: age			<.01
60-69 y	189/6922	1.00	
40-49 y	23/1591	0.55 (0.35-0.85)	<.01
50-59 y	86/4855	0.67 (0.52-0.87)	<.01
≥70 y	75/2063	1.30 (0.99-1.70)	.06
Karnofsky performance score ≥90	148/8236	1.00	<.01
<90	218/7028	1.52 (1.23-1.88)	<.01
Missing data	7/167	2.65 (1.24-5.66)	.01
HCT-CI 0	54/4093	1.00	<.01
1-2	109/4778	1.66 (1.20-2.30)	<.01
≥3	210/6560	2.18 (1.61-2.95)	<.01
DS/ISS I-II	131/6612	1.00	<.01
III	231/8398	1.42 (1.15-1.77)	<.01
Missing data	11/421	1.42 (0.77-2.63)	.26
Disease status at AHCT: CR	41/2460	1.00	<.01
VGPR	127/6095	1.27 (0.90-1.81)	.18
PR	158/5845	1.67 (1.18-2.35)	<.01
<PR	47/1031	2.93 (1.93-4.46)	<.01
REL			
Main effect: age			.86
60-69 y	1719/6922	1.00	
40-49 y	401/1591	1.00 (0.90-1.12)	.92
50-59 y	1243/4855	1.03 (0.95-1.10)	.43
≥70 y	498/2063	1.03 (0.93-1.13)	.56
DS/ISS I-II	1426/6612	1.00	<.01
III	2331/8398	1.36 (1.27-1.46)	<.01
Missing data	104/421	1.27 (1.04-1.56)	.02
Disease status at AHCT: CR	530/2460	1.00	<.01
VGPR	1436/6095	1.12 (1.01-1.24)	.03
PR	1561/5845	1.29 (1.17-1.42)	<.01
<PR	334/1031	1.70 (1.48-1.95)	<.01
Cytogenetics, no abnormality	66/3298	1.00	<.01
High risk	1324/4263	1.88 (1.71-2.07)	<.01
Standard risk	961/4717	1.05 (0.95-1.16)	.30
Not tested/unknown	915/3153	1.22 (1.09-1.36)	<.01
Year of transplant: 2017	454/3628	1.00	<.01
2013	829/2625	1.19 (1.04-1.36)	.01
2014	915/2819	1.18 (1.05-1.33)	<.01
2015	862/2926	1.07 (0.95-1.20)	.29
2016	801/3433	0.96 (0.86-1.09)	.54
PFS			
Main effect: age			.48
60-69 y	1908/6922	1.00	
40-49 y	424/1591	0.96 (0.86-1.06)	.45
50-59 y	1329/4855	0.99 (0.92-1.06)	.92
≥70 y	573/2063	1.05 (0.96-1.16)	.24
Karnofsky performance score ≥90	2170/8236	1.00	<.01
<90	2011/7028	1.12 (1.05-1.19)	<.01
Missing data	53/167	1.43 (1.09-1.88)	.01
DS/ISS I-II	1557/6612	1.00	<.01
III	2562/8398	1.36 (1.28-1.45)	<.01
Missing data	115/421	1.29 (1.07-1.56)	<.01
Disease status at AHCT: CR	571/2460	1.00	<.01
VGPR	1563/6095	1.13 (1.03-1.25)	.01
PR	1719/5845	1.32 (1.20-1.45)	<.01
<PR	381/1031	1.78 (1.57-2.03)	<.01
Cytogenetics, no abnormality	734/3298	1.00	<.01
High risk	1430/4263	1.82 (1.67-1.99)	<.01
Standard risk	1061/4717	1.05 (0.95-1.15)	.33
Not tested/unknown	1009/3153	1.22 (1.09-1.35)	<.01
Year of transplant: 2017	502/3628	1.00	<.01
2013	909/2625	1.20 (1.06-1.36)	<.01
2014	996/2819	1.20 (1.06-1.36)	<.01
2015	945/2926	1.09 (0.97-1.22)	.14
2016	882/3433	0.98 (0.88-1.10)	.73

TABLE 3. *Continued*

Outcome	No. of Events/No. Evaluable	HR (99% CI)	*P*
OS			
Main effect: age	659/6992		<.01
60-69 y	117/1605	1.00	
40-49 y	400/4919	0.77 (0.63-0.94)	.01
50-59 y	227/2084	0.88(0.77-0.99)	.05
≥70 y	659/6992	1.18(1.02-1.38)	.03
Karnofsky performance score ≥90	627/8323	1.33 (1.19-1.48)	<.01
<90	755/7108	1.83 (1.18-2.82)	<.01
Missing data	21/169	1.33 (1.19-1.48)	<.01
HCT-CI 0	304/4140	1.00	<.01
1-2	416/4831	1.16 (1.00-1.34)	.05
≥3	683/6629	1.33 (1.16-1.52)	<.01
DS/ISS I-II	424/6685	1.00	<.01
III	944/8488	1.77 (1.58-1.99)	<.01
Missing data	35/427	1.36 (0.96-1.92)	.08
Disease status at AHCT: CR	173/2467	1.00	<.01
VGPR	507/6148	1.21 (1.02-1.44)	.03
PR	548/5929	1.37 (1.15-1.62)	<.01
<PR	175/1056	2.55 (2.07-3.15)	<.01
Cytogenetics, no abnormality	215/3334	1.00	<.01
High risk	523/4311	2.07 (1.77-2.42)	<.01
Standard risk	262/4755	0.87 (0.73-1.04)	.13
Not tested/unknown	403/3200	1.73 (1.46-2.04)	<.01

Abbreviations: 99% CI, 99% confidence interval; AHCT, autologous hematopoietic stem cell transplantation; CR, complete response; DS, Durie-Salmon staging; HCT-CI, hematopoietic cell transplantation comorbidity index; HR, hazard ratio; ISS, International Staging System; NRM, nonrecurrence mortality; OS, overall survival; PFS, progression-free survival; PR, partial response; REL, disease recurrence/progression; VGPR, very good partial response.
A $P < .01$ was considered to be statistically significant.

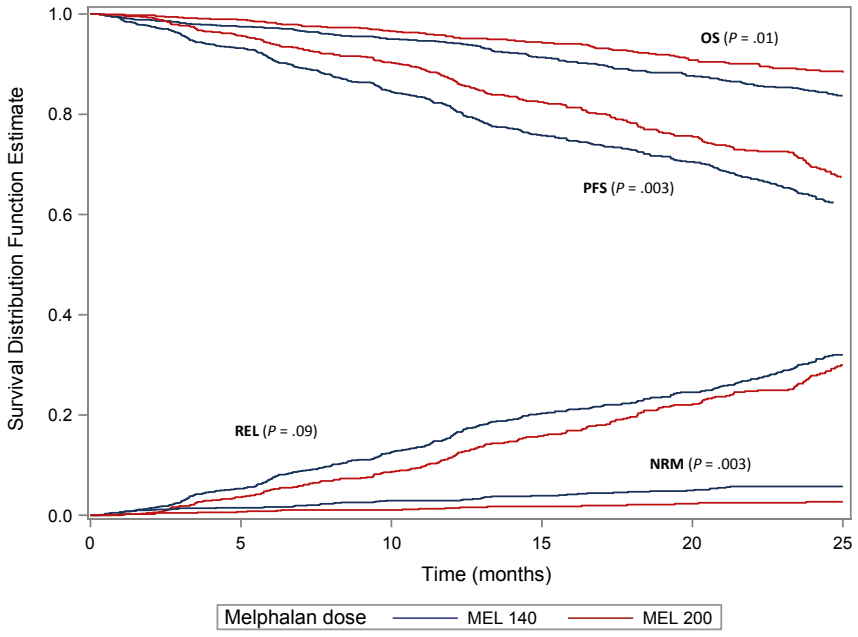

FIGURE 1. Outcomes in adults aged ≥70 years by melphalan (MEL) dose. NRM indicates nonrecurrence mortality; OS, overall survival; PFS, progression-free survival; REL, disease recurrence and/or progression (relapse).

The group of patients aged ≥70 years differed with regard to some criteria compared with younger patients. More patients in this group had a KPS <90 and an HCT-CI score >2. However, no difference was noted with regard to stage of disease or high-risk cytogenetics in older adults compared with younger adults.

TABLE 4. Multivariate Analysis of Outcomes Among Adults Aged ≥70 Years

Outcome	No of Events/No. Evaluable	HR (95% CI)	*P*
NRM			
Melphalan dose 200 mg/m^2	19/857	1.00	<.01
140 mg/m^2	56/1206	2.22 (1.31-3.73)	
REL			
Melphalan dose 200 mg/m^2	194/857	1.00	.10
140 mg/m^2	304/1206	1.17 (0.97-1.40)	
Cytogenetics, no abnormality	73/394	1.00	<.01
High-risk	190/621	1.97 (1.50-2.58)	<.01
Standard risk	129/649	1.13 (0.85-1.51)	.40
Not tested/unavailable	106/399	1.25 (0.93-1.68)	.15
PFS			
Melphalan dose 200 mg/m^2	213/857	1.00	<.01
140 mg/m^2	360/1206	1.26 (1.06-1.49)	
Cytogenetics, no abnormality	87/394	1.00	<.01
High-risk	210/621	1.80 (1.41-2.32)	<.01
Standard risk	153/649	1.12 (0.86-1.46)	.40
Not tested/unavailable	123/399	1.23 (0.93-1.61)	.15
OS			
Melphalan dose 200 mg/m^2	77/864	1.00	.02
140 mg/m^2	150/1220	1.40 (1.06-1.84)	
DS/ISS stage I-II	83/964	1.00	<.01
III	139/1063	1.57 (1.20-2.07)	<.01
Missing data	5/57	1.22 (0.49-3.01)	.67

Abbreviations: 95% CI, 95% confidence interval; DS, Durie-Salmon staging; HR, hazard ratio; ISS, International Staging System; NRM, nonrecurrence mortality; OS, overall survival; PFS, progression-free survival; REL, disease recurrence/progression.

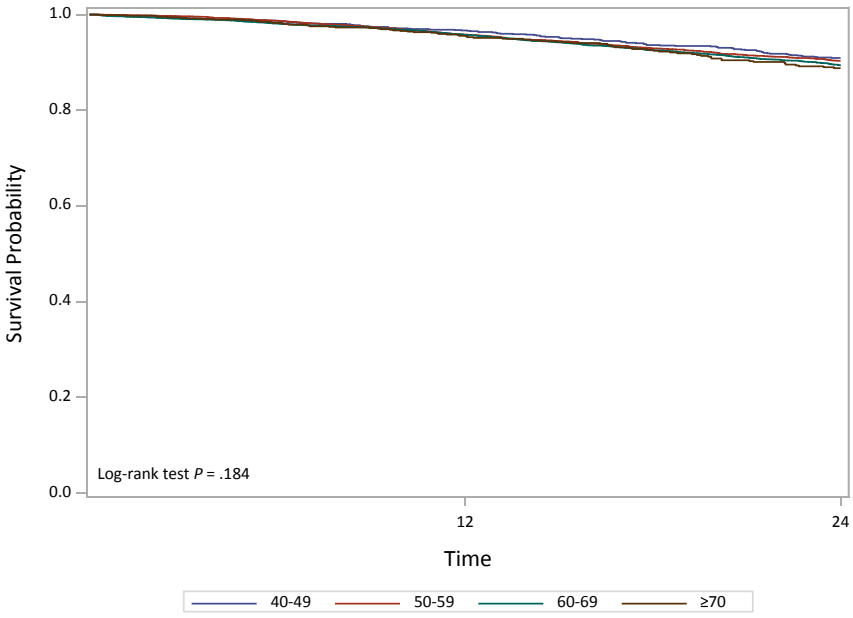

FIGURE 2. Overall survival for patients treated with melphalan at a dose of 200 mg/m^2 by age group.

As expected, more Mel conditioning dose reductions were noted among patients aged ≥70 years and 59% received reduced-dose Mel. Nevertheless, approximately 41% of patients in this group received Mel at a dose of 200 mg/m^2. Furthermore, on a separate multivariate analysis focused on the patients aged ≥70 years, the use of Mel at a dose of 200 mg/m^2 was associated with superior PFS and OS compared with reduced-dose Mel, as well as a lower rate of day 100 transplantation-related mortality. This finding suggests that perhaps patient selection based on frailty or tolerability led to dose reductions in Mel. Reasons why the dose of Mel was reduced were not

available in the current analysis, although approximately 36% of these older patients had an HCT-CI score ≥3. This further suggests that "sicker" patients are expected to have a higher NRM after AHCT, irrespective of complications related to AHCT. Notwithstanding the higher potential for toxicities when using Mel at a dose of 200 mg/m^2 compared with a dose of 140 mg/m^2 in patients aged ≥70 years and without understanding further the choice between Mel at a dose of 140 mg/m^2 versus Mel at a dose of 200 mg/m^2 beyond KPS and HCT-CI in our data set, it was not possible to recommend Mel at a dose of 200 mg/m^2 over Mel at a dose of 140 mg/m^2 in older adults based on the results of the current study, although these results provided assurance that Mel at a dose of 200 mg/m^2 can indeed be administered safely in some older adults aged ≥70 years. The data from the current study also suggested the importance of frailty assessment tools in individualizing treatment in older patients with MM.[15]

In the current analysis, patients aged ≥70 years were found to have shorter survival compared with younger patients, although using a narrower CI (99% CI with a $P < .01$ for statistical significance) demonstrated no significant difference compared with the standard reference group of patients aged 60 to 69 years. Survival was even shorter when compared with patients with MM who were aged <50 years. However, this is expected given that the life expectancy of the general US population at age 70 years is 14.4 years for males and 16.6 years for females, and is 11.2 years for males and 13 years for females at age 75 years compared with a life expectancy of 29.7 years for males and 33.3 years for females at age 50 years.[16] It is interesting to note that recent data analysis of Surveillance, Epidemiology, and End Results data demonstrated the cost-effectiveness of AHCT in the era of novel agents in elderly patients (those aged >65 years) compared with those not undergoing AHCT, with an overall survival benefit of 58 months reported in patients undergoing AHCT versus 37 months in patients not undergoing AHCT ($P < .001$).[17] We were unable to study the tolerability of maintenance therapy in this age group and how it may impact survival in older patients with MM.

Older patients often are excluded from clinical trials,[18] particularly transplantation trials, either due to ineligibility or physician decision regardless of eligibility. To the best of our knowledge, there are no randomized data examining AHCT among patients newly diagnosed with MM who are aged ≥70 years. The recent large randomized study of upfront AHCT in the United States demonstrated a median age of 56 years[19] and 59 years in a CIBMTR trends analysis.[20] Given that the median age at the time of diagnosis of myeloma is 69 years, to our knowledge clinical trials of AHCT exclude the majority of patients with MM and perhaps the overwhelming majority of non-White racial and/or ethnic groups.[21] Another important aspect of the management of MM that to our knowledge is unique to the United States compared with Europe is the management of MM predominantly in the non–transplantation-based community oncology practice. The use of transplantation thus is dependent on a referral to a transplantation center. This referral may not happen for many reasons (eg, socioeconomic, bias, distance from transplantation center, etc). The Veterans Administration has shown that providing equal care leads to the removal of disparities with no difference in transplantation use noted by race, although only approximately 10% of Veterans Administration patients underwent transplantation for myeloma.[22] Finally, the American Cancer Society estimated that approximately 30,770 new cases of MM were diagnosed in 2018,[23] with a median patient age of 69 years at diagnosis, reflecting approximately 15,000 patients aged ≥70 years. The current study averaged approximately 400 patients aged ≥70 years undergoing AHCT within 1 year, thus representing ≤3% patients in this age group.

The current study has some limitations inherent to a database study. Because our database only included patients who underwent transplantation, we were unable to make any inferences regarding those patients who did not undergo transplantation (eg, they were referred but deemed ineligible for AHCT). This is unlikely because data have demonstrated that once patients are seen and evaluated at a transplantation center, there are no apparent racial differences between patients who do or do not undergo AHCT.[24] Another potential limitation is that the current study was restricted to patients undergoing upfront AHCT. It is possible, although unlikely, that patients aged ≥70 years who delayed transplantation at the time of diagnosis would then actually undergo transplantation at the time of disease recurrence given that they would be even older and less fit. The current study had a short follow-up of only a median of 2 years and did not include details regarding maintenance therapy after AHCT. Last, there may be other important assessments focused on functional age (eg, comprehensive geriatric assessment, frailty index, etc) that would help to determine Mel dose among others, but to our knowledge these are not available.

The results of the current study, which to the best of our knowledge represents the largest study to date of older adults aged ≥70 years undergoing transplantation

for MM, indicated that although more patients aged ≥70 years are receiving AHCT for MM in the United States in recent years, these studies predominantly exclude minorities. Furthermore, the data from the current study have highlighted that transplantation remains a safe consolidation therapy across all age groups of patients with MM, and that the antimyeloma effects are not affected by patient age at the time of transplantation. Older age (≥70 years) should not be a barrier to referral for or performing AHCT among patients with MM, and where possible, full-dose Mel should be used.

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CONFLICT OF INTEREST DISCLOSURES

Pashna N. Munshi has received honoraria from Kite Pharma and Incyte for work performed outside of the current study. Mohamed A. Kharfan-Dabaja has acted as a paid consultant for Daiichi Sankyo and Pharmacyclics for work performed outside of the current study. Siddhartha Ganguly has acted as a paid member of the speakers' bureau for Seattle Genetics and Kite Pharma and as a paid member of the advisory board for Kadmon for work performed outside of the current study. Hillard M. Lazarus has acted as a member of the Data Safety Monitoring Board for Celgene for work performed outside of the current study. Ehsan Malek has received grants from MedPacto Inc and Cumberland; has acted as a paid member of the advisory board for Sanofi; has acted as a paid member of the advisory board and speakers' bureau for Takeda and Celgene; and has acted as a paid member of the speakers' bureau for Amgen and Jansen for work performed outside of the current study. Taiga Nishihori has received research support from Novartis and Karyopharm for work performed outside of the current study. Rebecca L. Olin has received grants from Daiichi Sankyo and Astellas; has received a grant from and acted as a paid consultant for Genentech; has received grants from Pfizer; and has acted as a paid consultant for Amgen and Jazz Pharmaceuticals for work performed outside of the current study. Richard F. Olsson has received personal fees from AstraZeneca for work performed outside of the current study. Gunjan Shah has received clinical trial funding from Janssen and Amgen for work performed outside of the current study. Shaji Kumar has received consulting fees and clinical trial support paid to his institution (no personal payments) from Bristol-Myers Squibb/Celgene, Takeda, AbbVie, Janssen, Adaptive, KITE, Medimmune/AstraZeneca, Merck, Novartis, Sanofi, and Roche; has received grants from Medimmune, TeneoBio, and CARsgen; and has acted as a paid consultant for Oncopeptides for work performed outside of the current study. Nina Shah has received research funding from Celgene, Janssen, bluebird bio, Sutro Biopharma, and TeneoBio; has acted in an advisory role for Genentech, Seattle Genetics, Oncopeptides, Karyopharm, Surface Oncology, Precision Biosciences, GlaxoSmithKline, Nektar, Amgen, Indapta Therapeutics, Sanofi, Bristol-Myers Squibb, and CareDx; and has stock ownership in Indapta Therapeutics. Parameswaran N. Hari has received grants and personal fees from Bristol-Myers Squibb, Takeda, Amgen, Janssen, and Pharmacyclics and personal fees from Karyopharm and Sanofi for work performed outside of the current study. Anita D'Souza has received grants from Takeda, Sanofi, and TeneoBio; grants and personal fees from Prothena; and personal fees from Pfizer and Akcea for work performed outside of the current study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Pashna N. Munshi: Study design, writing–original draft, and methodology. **David Vesole:** Study design, writing–original draft, and methodology. **Artur Jurczyszyn:** Study design, writing–original draft, and methodology. **Jan Maciej Zaucha:** Study design, writing–original draft, and methodology. **Andrew St. Martin:** Study design, methodology, and statistical analysis. **Omar Davila:** Methodology and statistical analysis. **Vaibhav Agrawal:** Study design and article editing. **Sherif M. Badawy:** Study design and article editing. **Minoo Battiwalla:** Study design and article editing. **Saurabh Chhabra:** Study design and article editing. **Edward Copelan:** Study design and article editing. **Mohamed A. Kharfan-Dabaja:** Study design and article editing. **Nosha Farhadfar:** Study design and article editing. **Siddhartha Ganguly:** Study design and article editing. **Shahrukh Hashmi:** Study design and article editing. **Maxwell M. Krem:** Study design and article editing. **Hillard M. Lazarus:** Study design and article editing. **Ehsan Malek:** Study design and article editing. **Kenneth Meehan:** Study design and article editing. **Hemant S. Murthy:** Study design and article editing. **Taiga Nishihori:** Study design and article editing. **Rebecca L. Olin:** Study design and article editing. **Richard F. Olsson:** Study design and article editing. **Jeffrey Schriber:** Study design and article editing. **Sachiko Seo:** Study design and article editing. **Gunjan Shah:** Study design and article editing. **Melhem Solh:** Study design and article editing. **Jason Tay:** Study design and article editing. **Shaji Kumar:** Study design and article editing. **Muzaffar H. Qazilbash:** Study design and article editing. **Nina Shah:** Study design and article editing. **Parameswaran N. Hari:** Study design, methodology, contributing patients, and article editing. **Anita D'Souza:** Study design, methodology and analysis, writing–original draft, and article editing.

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