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Older Patients with Myeloma Derive Similar Benefit from Autologous Transplantation

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A B S T R A C T

Autologous hematopoietic cell transplantation (AHCT) for plasma cell myeloma is performed less often in people >70 years old than in people ≤70 years old. We analyzed 11,430 AHCT recipients for plasma cell myeloma prospectively reported to the Center for International Blood and Marrow Transplant Research between 2008 and 2011, representing the majority of US AHCT activity during this period. Survival (OS) was compared in 3 cohorts: ages 18 to 59 years (n = 5818), 60 to 69 years (n = 4666), and >70 years (n = 946). Median OS was not reached for any cohort. In multivariate analysis, increasing age was associated with mortality (P = .0006). Myeloma-specific mortality was similar among cohorts at 12%, indicating an age-related effect on nonmyeloma mortality. Analyses were performed in a representative subgroup comparing relapse rate, progression-free survival (PFS), and nonrelapse mortality (NRM). One-year NRM was 0% for age >70 years and 2% for other ages (P = not significant). The three-year relapse rate was 56% in age 18 to 59 years, 61% in age 60 to 69 years, and 63% age >70 (P = not significant). Three-year PFS was similar at 42% in age 18 to 59 years, 38% in age 60 to 69 years, and 33% in age >70 years (P = not significant). Postrelapse survival was significantly worse for the older cohort (P = .03). Older subjects selected for AHCT derived similar antimyeloma benefit without worse NRM, relapse rate, or PFS.

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INTRODUCTION

Plasma cell myeloma is the most common indication for autologous hematopoietic cell transplantation (AHCT); however, a large number of eligible subjects are not offered a transplantation because of advanced age [1-3]. Randomized studies confirm the benefit of autologous transplantation in subjects ≤65 years of age, but these studies typically excluded older subjects [4,5]. The median age at diagnosis of patients with myeloma is 69 years and prospective transplantation studies in these older subjects are limited or use lower doses of conditioning [6]. Single-institution retrospective studies suggest that older persons with myeloma may receive an autologous transplantation with low risk of nonrelapse mortality (NRM) [7-18]. It is also well established that the recent dramatic improvements in survival have accrued disproportionately to younger patients, with relatively minor improvement in survival of those above age 60 [19].

We analyzed the effects of age on outcomes in persons with myeloma receiving upfront autologous transplantation.

SUBJECTS AND METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a voluntary group of more than 450 transplantation centers worldwide that contribute data on allogeneic and autologous transplantations to a statistical center at the Medical College of Wisconsin in Milwaukee or the National Marrow Donor Program Coordinating Center in Minneapolis, Minnesota. Participating centers are required to register all transplantations done consecutively in a prospective fashion. Subjects are followed longitudinally, with yearly data update. Computerized checks for errors, physicians' review of submitted data, and on-site audits of participating centers are used to ensure data quality and compliance. Studies conducted by the CIBMTR are performed with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act regulations as determined by the institutional review board and the privacy officer of the Medical College of Wisconsin. All CIBMTR centers contribute to the registration or transplant essential data. Detailed data are collected on the comprehensive report form (CRF) level on a subset of registered subjects and include detailed disease and pretransplantation and post-transplantation clinical information. Statistical methods (weighted randomization schema) are used to ensure that the CRF subset are representative of the transplant essential data cohort.

Study Population

Outcomes of 11,430 AHCT recipients with plasma cell myeloma between 2008 and 2011 (n = 11,430) reported from 148 transplantation centers in the United States and Canada were analyzed. During this period, the CIBMTR collected 60% of AHCT activity performed in the United States [20]. The study population included only those receiving a single AHCT within 24 months of diagnosis and receiving high-dose melphalan alone as conditioning.

Statistical Plan

The objective of this study was to analyze the effect of age on survival, NRM, relapse rates, and progression-free survival (PFS) after transplantation. Survival after AHCT was compared and subject to multivariate analyses in 3 age-dependent cohorts: ages 18 to 59 years (cohort 1, n = 5818), 60 to 69 years (cohort 2, n = 4666), and ≥70 years (cohort 3, n = 946).
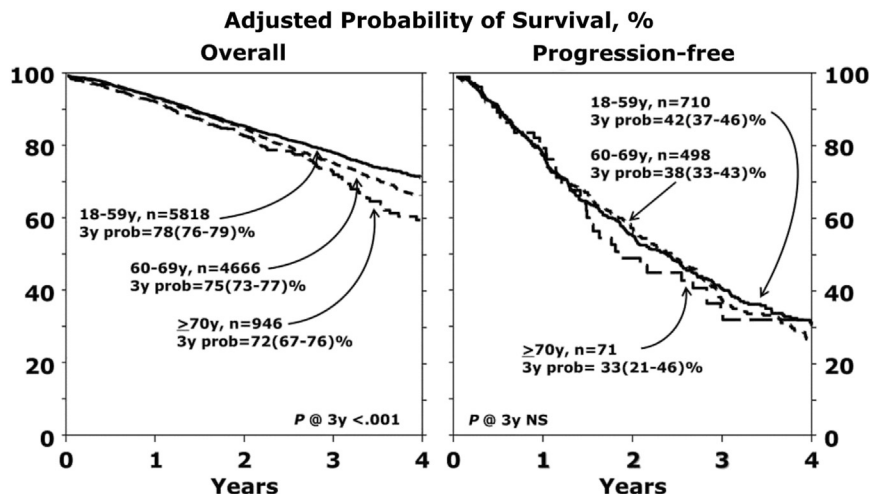

Figure 1. Adjusted probability of survival. (Left) Shows OS and (Right) shows PFS.

Table 1
Characteristics of Subjects who Underwent First PBSC AHCT within Two Years of Diagnosis for Plasma Cell Myeloma in the United States and Canada, Registered to CIBMTR between 2008 and 2011 (Transplant Essential Data)

Characteristics of Subjects	Cohort 1 (ages 18-59 yr)	Cohort 2 (ages 60-69 yr)	Cohort 3 (70+ yr)	P Value
No. of patients	5818	4666	946	
Age at transplantation, median (range), yr	53 (18-59)	64 (60-69)	72 (70-89)	
Age at transplantation, yr				
18-49 yr	1728 (30)	—	—	<.0001
50-59 yr	4090 (70)	—	—	
60-64 yr	—	2617 (56)	—	
65-69 yr	—	2049 (44)	—	
70-74 yr	—	—	794 (83)	
75-79 yr	—	—	146 (15)	
80+	—	—	6 (<1)	
Male sex	3278 (56)	2689 (58)	608 (64)	<.0001
Region				
United States	5488 (94)	4424 (95)	938 (99)	<.0001
Canada	330 (6)	242 (5)	8 (<1)	
KPS before transplantation				
>90	766 (13)	500 (11)	88 (9)	<.0001
80-90	4213 (72)	3444 (74)	716 (76)	
<80	515 (9)	515 (11)	106 (11)	
Missing	324 (6)	207 (4)	8 (<1)	
HCTCI score				
0-1	3277 (56)	2373 (51)	454 (48)	<.0001
2-3	1551 (27)	1295 (28)	307 (32)	
≥4	725 (12)	795 (17)	117 (19)	
Missing	265 (5)	203 (4)	8 (<1)	
Serum creatinine ≥ 1.5 at diagnosis	164 (23)	121 (24)	17 (24)	
Immunochemical subtype of plasma cell myeloma				
IgG	3312 (57)	2690 (58)	535 (57)	<.0001
IgA	1127 (19)	1028 (22)	234 (25)	
Light chain	1170 (20)	807 (17)	152 (16)	
Others (Ig M, D, or E)	82 (1)	45 (1)	11 (1)	
Nonsecretory	127 (2)	96 (2)	14 (1)	
Disease status at transplantation				
CR	839 (14)	662 (14)	117 (12)	.1209
VGPR	1628 (28)	1384 (30)	278 (29)	
PR	2798 (48)	2186 (47)	462 (49)	
SD	341 (6)	248 (5)	57 (6)	
REL/PROG	180 (3)	170 (4)	31 (3)	
Missing	32 (<1)	16 (<1)	1 (<1)	
MEL	200 (100-220)	200 (100-220)	200 (100-200)	
<140	140 (2)	132 (3)	44 (5)	<.0001
140-180	336 (6)	552 (12)	354 (37)	
≥180	4982 (86)	3715 (80)	480 (51)	
Missing	330 (6)	267 (6)	68 (7)	
Time from diagnosis to transplantation, median (range), mo	7 (<1-24)	8 (<1-24)	8 (<1-24)	
<12 mo	4739 (81)	3632 (78)	745 (79)	<.0001
12-18 mo	760 (13)	698 (15)	136 (14)	
18-24 mo	319 (6)	336 (7)	65 (7)	
Yr of transplantation				
2008	1177 (20)	877 (19)	149 (16)	
2009	1392 (24)	1077 (23)	195 (21)	
2010	1566 (27)	1273 (27)	286 (30)	
2011	1683 (29)	1439 (31)	316 (33)	

VGPR indicates very good partial response; PR, partial response; SD, stable disease; REL, relapse; PROG, progression.

Relapse, PFS, and NRM were compared in a representative subset of 1279 subjects with CRF data after ensuring that survival was identical to the larger sample (Supplemental Figure 1). NRM was defined as mortality after AHCT in the absence of disease relapse or progression. Cumulative incidence probabilities for NRM were calculated accounting for relapse/progression as a competing risk. Point-wise comparison and log-rank analysis were used to analyze the NRM and survival of different groups.

Subject characteristics in study cohorts were compared using the Mann-Whitney-Wilcoxon test for continuous variables and chi-square test for discrete variables. Survival probabilities (overall survival [OS] and PFS) were calculated by using the Kaplan-Meier estimator with the variance estimated by Greenwood's formula. Multivariate analysis was performed using Cox proportional hazard regression model to adjust for potentially confounding effects of other risk factors. The variables considered in multivariate analysis for survival included age, HCT-specific comorbidity index (HCTCI) [21,22], Karnofsky performance score (KPS), time from diagnosis to transplantation, year of transplantation, disease status at the time of transplantation, and the dose of melphalan conditioning regimen (in mg/m^2). The variables considered in multivariate analyses for NRM, progression/relapse, and PFS included age, gender, KPS, HCTCI, disease status at the time of transplantation, melphalan dose (mg/m^2), time from diagnosis to transplantation, and the year of transplantation. Stepwise variable selection at a .05 significance level was used to identify significant covariates. In the model, the assumption of proportional hazards was tested for each variable using a time-dependent covariate and graphical methods. All variables considered in the multivariate analysis satisfied the proportionality assumption. All computations were made using the statistical package SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS
Subject Characteristics

Subject characteristics are summarized in Table 1, which compares 3 cohorts: patients from 18 to 59 years old (cohort 1, n = 5818), 60 to 69 years old (cohort 2, n = 4666), and ≥70 years

Table 2
Characteristics of Subjects with High-Level Data Reporting

Characteristics of Subjects	Cohort 1 (18-59 yr)	Cohort 2 (60-69 yr)	Cohort 3 (70+ yr)	P Value
No. of subjects	710	498	71	
Age at transplantation, median (range), yr	53 (22-59)	64 (60-69)	71 (70-78)	
Age at transplantation, yr				
18-49 yr	222 (31)	−		<.0001
50-59 yr	488 (69)	−	−	
60-64 yr	−	303 (61)	−	
65-69 yr	−	195 (39)	−	
70-74 yr	−	−	64 (90)	
75-79 yr	−	−	7 (10)	
Male sex	408 (57)	275 (55)	49 (69)	.0878
Region				
United States	693 (98)	484 (97)	70 (99)	.7494
KPS before transplantation				
≥80	394 (55)	248 (50)	35 (49)	.3293
<80	281 (40)	219 (44)	31 (44)	
Missing	35 (5)	31 (6)	5 (7)	
HCTCI score				
0-1	423 (60)	280 (56)	36 (51)	.6178
2-3	195 (27)	138 (28)	23 (32)	
≥3	79 (11)	69 (14)	11 (15)	
Missing	13 (2)	11 (2)	1 (1)	
Immunochemical subtype of plasma cell myeloma				
IgG	410 (58)	297 (60)	40 (56)	.7742
IgA	138 (19)	114 (23)	15 (21)	
Light chain	135 (19)	71 (14)	14 (20)	
Others (Ig D/M/E)	12 (2)	5 (1)	1 (1)	
Nonsecretory	15 (2)	11 (2)	1 (1)	
Serum creatinine at transplantation ≥1.5	70 (10)	71 (14)	13 (18)	.0245
Lines of chemotherapy before transplantation				
1	551 (78)	375 (75)	55 (77)	.6394
2	159 (22)	123 (25)	16 (23)	
Induction chemotherapy				
Thalidomide + bortezomib	58 (8)	43 (9)	6 (8)	.1158
Lenalidomide + bortezomib	160 (23)	79 (16)	12 (17)	
Thalidomide-based	116 (16)	103 (21)	20 (28)	
Lenalidomide-based	175 (25)	134 (27)	16 (23)	
Bortezomib-based	161 (23)	116 (23)	14 (20)	
Steroids/cytoxan	40 (6)	23 (5)	3 (4)	
Disease status before AHCT				
CR	114 (16)	85 (17)	12 (17)	.8670
VGPR	199 (28)	143 (29)	22 (31)	
PR	326 (46)	230 (46)	30 (42)	
SD	56 (8)	32 (6)	4 (6)	
REL/PROG	15 (2)	8 (2)	3 (4)	
Sensitivity to chemotherapy before transplantation	639 (90)	458 (92)	64 (90)	.4992
MEL, median (range), mg/m^2	200 (116-214)	200 (137-220)	200 (108-200)	
<140 mg/m^2	5 (<1)	2 (3)	6 (8)	<.0001
140-180 mg/m^2	68 (10)	86 (17)	22 (31)	
180- ≥200 mg/m^2	631 (89)	406 (82)	43 (61)	
Unknown	6 (<1)	4 (<1)	0 (0)	
Cytogenetic before transplantation				
Abnormal	311 (44)	220 (43)	33 (46)	.2932
Normal	294 (41)	191 (38)	32 (45)	
Untested/unknown	105 (15)	87 (17)	6 (8)	
Time from diagnosis to transplantation, median (range), mo	7 (2-23)	8 (3-24)	8 (4-23)	
<12 mo	605 (85)	411 (83)	61 (86)	.5835
12-18 mo	77 (11)	66 (13)	6 (8)	
19-24 mo	28 (4)	21 (4)	4 (6)	
Type of transplantation				
Single	632 (89)	454 (91)	70 (99)	.0249
Tandem	78 (11)	44 (9)	1 (1)	
Year of transplantation				
2008	364 (51)	252 (51)	35 (49)	.0068
2009	92 (13)	98 (20)	16 (23)	
2010	102 (14)	53 (11)	12 (17)	
2011	152 (21)	95 (19)	8 (11)	
In-hospital days, median (range)	14 (0-71)	14 (0-60)	14 (0-42)	.0012
Evaluable	597 (84)	442 (89)	64 (90)	
Median follow-up of survivors, mo	35 (3-61)	37 (3-60)	36 (5-52)	

Follow-up completeness index: at 1 year (99%), at 3 years (90%), and at 5 years (82%).

old (cohort 3, n = 946). Median age at transplantation in cohorts 1, 2, and 3 was 53, 64, and 72 years, respectively. Subjects in cohort 3 were more likely to be male, have their transplantation in the United States, have a lower Karnofsky score (KPS <90), a worse comorbidity score (HCTCI >2), and have IgA myeloma as compared with those in cohorts 1 and 2. Older subjects in

Table 3
Univariate Results

Outcome	At Risk, n	Cohort 1 (18-59 yr)		Cohort 2 (60-69 yr)		Cohort 3 (70+ yr)	P Value Cohort Comparison		
		Prob. % (95% CI)	At Risk, n	Prob. % (95% CI)	At Risk, n	Prob. % (95% CI)	1 versus 2	1 versus 3	2 versus 3
OS (n = 11430)									
At 1 yr	4430	94 (93-94)	3511	94 (93-94)	693	93 (91-94)	.7490	.2123	.2874
At 2 yr	2505	86 (84-87)	1927	85 (83-86)	362	83 (80-85)	.3003	.0737	.2272
At 3 yr	1168	78 (76-79)	904	75 (73-77)	133	72 (67-76)	.0136	.0071	.1603
PFS (n = 1279)									
At 1 yr	492	77 (74-80)	340	77 (73-81)	52	80 (69-88)	.8655	.5626	.5160
At 2 yr	267	56 (52-60)	198	57 (52-62)	25	50 (37-62)	.7581	.3805	.3173
At 3 yr	136	42 (37-46)	101	38 (33-43)	12	33 (21-46)	.2829	.2178	.4934
NRM (n = 1279)									
At 1 yr	492	2 (1-3)	340	2 (1-3)	52	0	.6264	.0003	.0048
At 2 yr	267	3 (2-5)	198	2 (1-3)	25	0	.1980	.0001	.0027
At 3 yr	136	3 (2-5)	101	2 (1-4)	12	6 (1-16)	.3898	.4663	.3406
Progression (n = 1279)									
At 1 yr	492	21 (18-24)	340	21 (18-25)	52	20 (11-30)	.7525	.8481	.7359
At 2 yr	267	41 (37-45)	198	42 (37-46)	25	50 (37-62)	.9546	.2075	.2264
At 3 yr	136	56 (51-60)	101	61 (55-66)	12	63 (48-74)	.1827	.3570	.7900

Prob indicates probability.

cohorts 2 and 3 were less likely to receive transplantation within the first year of diagnosis and more likely to have melphalan dose (MEL) reduction (MEL <180 mg/m^2 in 42%).

Table 2 summarizes data in subset of subjects (n = 1279) analyzed for relapse and NRM, specifically. Survival curves for this subset were identical to those of the larger set (P = .41, Supplemental Figure 1). There were 710 subjects in cohort 1, 498 in cohort 2, and 71 in cohort 3 (Table 2). Age distribution in the subset was similar to the total cohort of 11,430 subjects. Gender, KPS, HCTCI, immunochemical subtype, and time from diagnosis to AHCT showed similar distribution trends but did not reach statistical significance, primarily because of smaller cohort size. Higher international staging system stage, serum creatinine at diagnosis, and increased frequency of MEL reduction was noted in subjects ≥70 years of age. The median time in the hospital was 14 days for all cohorts. Median follow-up of survivors was 3 years.

OS (n = 11430)

Median OS is not yet reached for any cohort. Survival data at 1, 2, and 3 years are summarized in Table 3 and Figure 1. In multivariate analysis, increasing age was associated with worse survival (P = .0006) (Table 4). Hazard ratios for death were 1.12 (95% confidence interval [CI], 1.02 to 1.24) for cohort 1 versus cohort 2, 1.35 (95% CI, 1.15 to 1.59) for cohort 1 versus cohort 3, and 1.2 (95% CI, 1.02 to 1.42) for cohort 2 versus cohort 3. The primary cause of death was myeloma in all 3 cohorts, with a similar myeloma-specific mortality rate (Table 5). In multivariate analysis, significant predictors of worse survival were higher HCTCI score, lower KPS, longer interval from diagnosis to transplantation, and inferior disease status (not in complete remission [CR]) at transplantation.

Relapse (n = 1279)

The 3-year rate of relapse was 56% (95% CI, 51% to 60%), 61% (95% CI, 55% to 66%), and 63% (95% CI, 48% to 74%) in cohorts 1, 2, and 3, respectively, which was not statistically significant (Table 3, Figure 2). On multivariate analysis, a lower KPS (<80), longer interval from diagnosis to AHCT (>12 months), and inferior disease status before AHCT (not

in CR) were predictive factors for relapse. Increasing age was not associated with greater incidence of relapse.

PFS (n = 1279)

The 3-year PFS in cohorts 1, 2, and 3 was similar at 42% (95% CI, 37% to 46%), 38% (95% CI, 33% to 43%), and 33% (95% CI, 21% to 46%), respectively, which was not statistically significant (Figure 1). Age was not a significant risk factor for PFS in multivariate analysis; however, KPS, longer interval from diagnosis to transplantation, and more advanced disease (not in CR) at transplantation were significant predictors of treatment failure (and worse PFS).

NRM (n = 1279)

One-year NRM was 0% for cohort 3 and 2% (95% CI, 1% to 3%) for cohorts 1 and 2, respectively (Figure 2). Age was not significantly associated with NRM in multivariate analysis but KPS <80% was predictive in multivariate analysis.

Postrelapse Survival

Survival after myeloma relapse was significantly worse for cohort 3 (P = .03, Figure 3). The 2-year postrelapse survivals were 63% (95% CI, 56% to 69%), 50% (95% CI, 42% to 57%), and 54% (95% CI, 32% to 71%) for cohorts 1, 2, and 3, respectively.

Causes of Death

The primary cause of death was myeloma in all 3 cohorts (Table 5). Incidence of second malignancy was similar and low at <1%. A higher proportion of deaths in the older cohort were attributed to vascular and unknown causes.

Outcomes in Those >75 Years Old

There were 146 patients 75 to 79 years old and 8 who were ≥ 80 years old. The use of reduced MEL (<180 mg/m^2) was 57% among those 75 to 79 years old and 67% in those ≥80 years old. Two-year survival in the 75 to 79–year-old cohort and ≥80-years-old cohort was 91% (83% to 95%) and 100%, respectively.

DISCUSSION

Our data indicate that freedom from progression of myeloma is similar regardless of age in persons who receive

Table 4
Multivariate Analyses

Risk Factors	Hazard Ratio (95% CI)	P Value
For mortality:		
Age group (main effect)	Overall test	.0006*
Reference group : 18-59 yr	1	NA
60-69 versus 18-59 yr	1.123 (1.018-1.239)	.0204*
70+ versus 18-59 yr	1.353 (1.150-1.593)	.0003*
70+ versus 60-69 yr	1.205 (1.022-1.420)	.0261*
HCTCI	Overall test	<.0001*
≥ 2 versus <2	1.279 (1.163-1.407)	<.0001*
KPS	Overall test	<.0001*
80-90 versus 100	1.242 (1.058-1.407)	.0082*
<80 versus 100	1.640 (1.344-2.002)	<.0001*
Time from diagnosis to transplantation		
12-24 versus 0-12 mo	1.321 (1.188-1.469)	<.0001*
Disease status at transplantation	Overall test	<.0001*
VGPR/PR versus CR	1.313 (1.127-1.530)	.0005*
SD versus CR	1.693 (1.353-2.119)	<.0001*
REL/PROG versus CR	3.301 (2.647-4.116)	<.0001*
For treatment failure/PFS:		
Age group (main effect)	Overall test	.7014
60-69 versus 18-59 yr	1.046 (.892-1.226)	.5832
70+ versus 18-59 yr	1.131 (.816-1.567)	.4598
70+ versus 60-69 yr	1.082 (.776-1.507)	.6433
KPS	Overall test	.0029*
80-90 versus 100	1.069 (.817-1.398)	.6279
<80 versus 100	1.594 (1.128-2.253)	.0082*
Time from diagnosis to transplantation		
12-24 versus 0-12 mo	1.294 (1.066-1.571)	.0092*
Disease status at transplantation	Overall test	<.0001*
VGPR/PR versus CR	1.327 (1.062-1.658)	.0129*
SD versus CR	1.963 (1.423-2.708)	<.0001*
REL/PROG versus CR	3.076 (1.882-5.028)	<.0001*
For NRM:		
Age group (main effect)	Overall test	.9734
60-69 versus 18-59 yr	.921 (.450-1.884)	.8214
70+ versus 18-59 yr	1.006 (.232-4.365)	.9941
70+ versus 60-69 yr	1.092 (.245-4.866)	.9082
KPS	Overall test	
80-90 versus 100	2.890 (.389-21.485)	.2998
<80 versus 100	9.554 (1.170-78.039)	.0352*
Time from diagnosis to transplantation		
12-24 versus 0-12 mo	2.158 (.997- 4.668)	.0508
For progression:		
Age group (main effect)	Overall test	.6811
60-69 versus 18-59 yr	1.052 (.893-1.238)	.5465
70+ versus 18-59 yr	1.136 (.813-1.587)	.4548
70+ versus 60-69 yr	1.080 (.769-1.518)	.6561
KPS	Overall test	.0209*
80-90 versus 100	1.039 (.792-1.363)	.7847
<80 versus 100	1.456 (1.020-2.079)	.0385*
Time from diagnosis to transplantation		
12-24 versus 0-12 mo	1.259 (1.031-1.539)	.0241*
Disease status at transplantation	Overall test	<.0001*
VGPR/PR versus CR	1.299 (1.036-1.630)	.0237*
SD versus CR	1.935 (1.939-2.688)	<.0001*
REL/PROG versus CR	3.074 (1.858-5.085)	<.0001*

  * Significant at level of .05.

Table 5
Causes of Death

Characteristics of Patients	Cohort 1 (18-59 yr)	Cohort 2 (60-69 yr)	Cohort 3 (70+ yr)
No. of patients	5818	4666	946
No. of deaths	843	770	176
Myeloma	655 (11)	552 (12)	118 (12)
Infection	23 (<1)	18 (<1)	3 (<1)
Pulmonary	3 (<1)	3 (<1)	1 (<1)
Organ failure	14 (<1)	20 (<1)	6 (<1)
Secondary malignancy	11 (<1)	16 (<1)	5 (<1)
Hemorrhage	1 (<1)	0 (0)	0 (0)
Vascular/thrombotic/other	136 (3)	161 (3)	43 (5)

Data presented are n (%) unless otherwise indicated.

the time of transplantation, and longitudinally thereafter, in 60% of all AHCT for multiple myeloma (MM) in the United States. The characteristics of the elderly population receiving AHCT and the practice of AHCT are, thus, indicative of actual practice. In the older cohort, we observed significant MEL reductions (MEL <180 mg/m^2 in 42%), worse HCTCI and KPS, and approximately 40% in > very good partial response (VGPR) disease state before AHCT. Multivariate analysis revealed that the risk factors for earlier relapse and shorter PFS included a lower KPS, longer time from diagnosis to transplantation, and a less than very good partial response before transplantation. NRM was 0% in subjects >70 years old, which indicates that careful subject selection and dose adjustment of melphalan were highly successful at controlling treatment toxicity without compromising benefit.

The perception of advanced age being an indicator of inferior outcomes after an autologous transplantation is a barrier to using high-dose melphalan as a therapeutic modality. Although autologous transplantation is now being offered more often to older patients, there still remains a large population of eligible patients who can benefit from this treatment modality [24]. The inclusion of older patients eligible for an autologous transplantation has been, in part, due to the improvement in supportive care and improved understanding of patient selection, as well as several studies showing that biologic fitness, rather than chronological age, is crucial in patient selection for transplantation in general [25,26]. The alternatives to autologous transplantation for older subjects include the continuation of the induction antimyeloma regimen or oral melphalan and prednisone (MP)–based induction regimens. Until recently, MP in combination with thalidomide, lenalidomide, or bortezomib was believed to be the optimal treatment strategy for
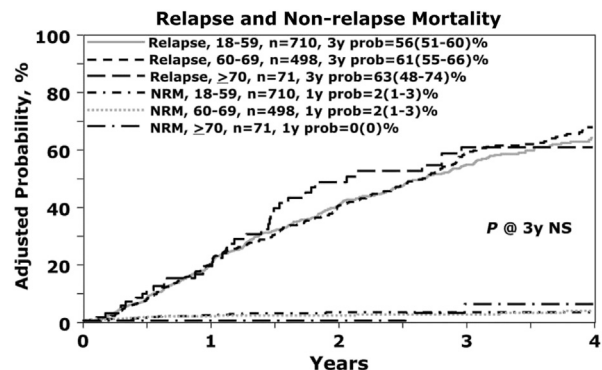
autologous transplantations. Expectedly, survival was worse in older persons. Interestingly, the increased mortality was not correlated with NRM or early progression but rather with worse postrelapse survival. The cause of death in these older subjects was mainly myeloma (as it was in younger cohorts) and not from transplantation-related causes, as might be speculated. Lack of clinical studies specifically applicable to this subject population may contribute to limited options after relapse and postrelapse survival [23]. The role of post-AHCT maintenance therapy was not analyzed in this study and, as such, we are unable to determine if differential use of maintenance therapy contributed to the results.

The survival analysis presented involves >11,000 subjects and represents approximately prospectively collected data at

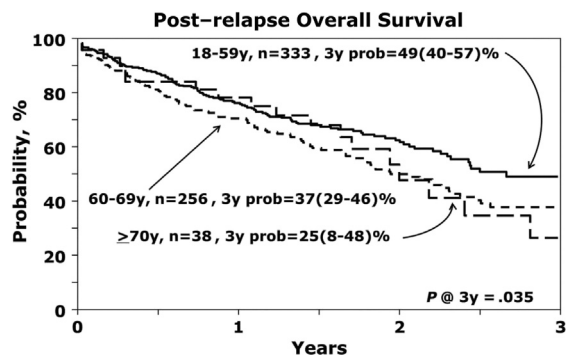

Figure 2. Relapse and NRM.

Figure 3. Postrelapse OS.

transplantation-ineligible subjects. In a recent study, ongoing lenalidomide plus dexamethasone was shown to be superior to oral melphalan, prednisone, and thalidomide in a phase III randomized study [27].

MP has been studied in combination with thalidomide (MPT) [28-33], lenalidomide [34], and bortezomib [35-38] in randomized, phase III trials in Europe. The NRM using these regimens is 5% to 7% in patients selected for clinical trials, and OS has been shown to be higher in patients receiving either MPT or MP with bortezomib, compared with MP. Facon et al. compared the outcomes in older subjects randomized to either MP, MPT, or to an autologous transplantation using lower intensity conditioning with melphalan 100 mg/m^2 [30]. The incidence of death in the first 3 months of therapy in the MP, MPT, and transplantation group was 7%, 2%, and 9%, respectively. The MPT arm was associated with a longer PFS and OS, compared with transplantation or MP, which had similar outcomes.

Palumbo et al. compared MP versus 2 courses of melphalan 100 mg/m^2 followed by stem cell transplantation and were able to show an improvement in event-free survival and OS in patients receiving stem cell transplantation [39]. Whether a single melphalan 140 mg/m^2 is equivalent to a single melphalan 200 mg/m^2 is currently unknown. In our study, melphalan dose reduction did not impact myeloma-related outcomes, although the majority of >70-year-old patients still received melphalan 200 mg/m^2. However, it seems that the optimal manner in which to administer melphalan is at higher doses with autologous stem cell support, rather than as a part of MP-based regimens, as NRM is lower in the transplantation strategy in the modern era. Notably, our subjects underwent transplantation more recently compared with the studies mentioned above, and 97% received a novel agent (lenalidomide or bortezomib)–based induction regimen.

In conclusion, advanced subject age was not associated with a worse NRM, relapse rate, or PFS after AHCT for MM. Post-relapse survival and OS of older subjects were inferior compared with younger subjects, which is likely multifactorial. Subjects with MM and an adequate performance status or acceptable HCTCI scores should not be considered for AHCT on the basis of age alone. Strategies offered to younger patients, such as post-AHCT maintenance, aggressive therapy at relapse, and clinical trial enrollment, may improve overall and post-relapse outcomes further for older persons with myeloma.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2014.07.013

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