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Blacks are twice as likely to develop and die from multiple myeloma (MM), and are less likely to receive an autologous hematopoietic-cell transplant (AHCT) for MM compared to Whites. The influence of race on outcomes of AHCT for MM is not well described. We compared the probability of overall survival (OS), progression-free survival (PFS), disease progression, and nonrelapse mortality (NRM) among Black (N = 303) and White (N = 1892) recipients of AHCT for MM, who were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) from 1995 to 2005. The Black cohort was more likely to be female, and had better Karnofsky performance scores, but lower hemoglobin and albumin levels at diagnosis. Black recipients were younger and more likely to be transplanted later in their disease course. Disease stage and treatment characteristics prior to AHCT were similar between the 2 groups. Black and White recipients had similar probabilities of 5-year OS (52% versus 47%, $P = .19$) and PFS (19% versus 21%, $P = .64$) as well as cumulative incidences of disease progression (72% versus 72%, $P = .97$) and NRM (9% versus 8%, $P = .52$). In multivariate analyses, race was not associated with any of these endpoints. Black recipients of AHCT for MM have similar outcomes compared to Whites, suggesting that the reasons underlying lower rates of AHCT in Blacks need to be studied further to ensure equal access to effective therapy.

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BACKGROUND

Multiple myeloma (MM) remains an incurable disease, although prognosis has improved in the past decade [1,2]. It is the most common hematologic malignancy among Blacks, and is the only hematologic malignancy that is more frequent in this racial group compared with Whites. In the United States, MM and its precursor disease monoclonal gammopathy of undetermined significance (MGUS) are twice as common in Blacks (annual incidence of 14.4/100,000 in men and 9.8/100,000 in women compared with 6.6/100,000 in White men and 4.1/100,000 in White women) [1,3-7]. Proposed factors to explain the increased incidence among Blacks include socioeconomic factors, greater exposure to hazardous materials, genetic predisposition, greater degree of background antigenic stimulation, and a greater prevalence of obesity [8-10]. Mortality rates from MM in the United States are twice as high for Blacks compared to Whites (8.3/100,000 for men and 6.0/100,000 for women compared to 4.3/100,000 and 2.8/100,000 for White men and women, respectively) [11].

Socioeconomic factors that may have an impact on access to cancer therapy and therapeutic choices include place of residence, distance from care centers, unemployment, availability and quality of health insurance, poor nutrition, exposure to infectious agents, lower educational level, and annual income [12,13]. Prior comparisons have drawn conflicting conclusions on treatment outcomes among Blacks compared with White patients with MM. Savage et al. [13,14] found that Black patients had shorter survival times following similar therapy for MM. Presentation at later stages of disease, socioeconomic factors, or differential access to care were thought to explain this disparity. Other investigators have suggested that these disparities in outcomes are primarily because of biological characteristics [15,16].

Randomized clinical trials support the use of autologous hematopoietic-cell transplant (AHCT) as a standard therapy for MM [17,18]. We have previously shown that Blacks are less likely to receive AHCT for MM compared with their age- and sex-matched White counterparts [19]. In the current study, we compared outcomes between Black and White patients receiving AHCT for MM to determine if disparate post transplant outcomes validate lower AHCT use in Blacks.

PATIENTS AND METHODS

The Center for International Blood and Marrow Transplant Research (CIBMTR) consists of a voluntary working group of more than 450 transplant centers worldwide. Centers contribute detailed data on consecutive allogeneic and autologous transplants to a statistical center at either the Medical College of Wisconsin in Milwaukee or the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis. Subjects are followed longitudinally, with yearly follow-up. Computerized checks for errors, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are done with a waiver of informed consent and in compliance with HIPAA regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

Patients

The study included 2195 (303 Black and 1892 White) adult (aged ≥18 years) recipients of AHCT for MM who were transplanted between January 1995 and June 2005 (Table 1). Only recipients of peripheral blood (PB) AHCT were included in this study; patients who had received planned tandem AHCT (N = 582) were excluded. Centers obtained information about patient race and then reported it to the CIBMTR.

Statistical Methods

Patient-, disease-, and treatment-related factors were compared between the Black and White cohorts, using a chi-square test for categorical and a Kruskal-Wallis test for continuous variables. Outcomes analyzed included nonrelapse mortality (NRM), relapse/progression, progression-free survival (PFS), and overall survival (OS). NRM was defined as death occurring in the absence of relapse or progression of MM following AHCT. Relapse/progression was defined according to standard criteria [20]. Chemotherapy sensitivity was defined as achievement of a partial or complete response (PR, CR) to pretransplant therapy. PFS was defined as survival without disease progression or relapse. Patients alive and with no evidence of disease progression or relapse were censored at the time of last follow-up. The survival interval variable was defined as time from the date of transplant to the date of death or last contact and summarized by a survival curve. Probabilities of OS and PFS were calculated using the Kaplan-Meier estimator [21,22]. NRM and relapse/progression were calculated using cumulative incidence estimates. The log-rank test was used for univariate comparisons.

Multivariate Cox proportional hazards regression was used to examine the outcomes between Black and White patient cohorts and to identify risk factors associated with outcomes [23]. A stepwise forward selection multivariate model was built to identify covariates that influenced outcomes. Any covariate with a value of $P < .05$ was considered significant. The proportionality assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Tests indicated that all variables met the proportional hazards

Table 1. Patient Characteristics

Variable	White N (%)	Black N (%)	*P*-value
Number of patients	1892	303	
Age median (range), years	57 (27-80)	55 (27-74)	<.001
Age group at transplant, years			.002
<50	396 (21)	88 (29)	
50-64	1111 (59)	172 (57)	
≥ 65	385 (20)	43 (14)	
Male sex	1136 (60)	164 (54)	.05
Karnofsky score pretransplant			.005
≥90	1153 (61)	210 (69)	
Hypertension			<.001
Yes	471 (25)	143 (47)	
Diabetes			<.001
Yes	169 (9)	50 (17)	
Body Mass Index			.01
Underweight/normal (<25)	557 (29)	67 (22)	
Overweight (25-29.9)	741 (39)	120 (40)	
Obese/morbidly obese (≥30)	594 (31)	116 (38)	
Disease related			
Durie-Salmon stage at diagnosis			.25
I	203 (11)	25 (8)	
II	562 (30)	101 (33)	
III	1127 (60)	177 (58)	
Immunochemical subtype of myeloma			.34
IgG	1003 (53)	173 (57)	
IgA	359 (19)	45 (15)	
Light chain	329 (17)	54 (18)	
Others/unknown	125 (11)	16 (10)	
Albumin level at diagnosis			.05
>3.5 g/dL	732 (39)	101 (33)	
Hemoglobin at diagnosis <10 g/dL			<.001
<10 g/dL	552 (29)	135 (45)	
Creatinine at diagnosis			.09
>1.5 mg/dL	361 (19)	74 (24)	
B-2 microglobulin level at diagnosis			.83
≥5.5 mg/L	195 (10)	31 (10)	
Prior chemotherapy regimens			.78
MP ± others	334 (18)	50 (17)	
VAD ± others (not MP)	1104 (58)	182 (60)	
Cy ± others	300 (16)	52 (17)	
Corticosteroids ± others	154 (8)	19 (6)	
Number of lines of chemotherapy§			.29
1	1125 (59)	167 (55)	
2	536 (28)	99 (33)	
>2	231 (12)	37 (12)	
Sensitive to chemotherapy prior to transplant			.83
Sensitive	1434 (76)	228 (75)	
Disease status at time of transplant			.67
Complete remission/partial remission	1396 (74)	231 (76)	
Treatment related			
Time from diagnosis to transplant median (range), months	8 (<1-249)	9 (2-217)	<.001
Time from diagnosis to transplant			<.001
<12 months	1364 (72)	190 (63)	
≥12 months	528 (28)	113 (37)	
Conditioning regimen			.7
Melphalan only	1417 (75)	223 (74)	
Melphalan + TBI ± others	204 (11)	35 (12)	
Bu-Cy ± others (not TBI, not melphalan)	271 (15)	45 (15)	
Median follow-up of survivors, median (range)	61 (<1-145)	51 (<1-132)	

MP indicates Melphalan + Prednisone; VAD, vincristine + dexamethasone + adriamycin; Cy, cyclophosphamide; Bu, busulfan; TBI, total body irradiation; Eval, evaluable.
§ Excludes stem cell priming.

assumption. Results were expressed as relative risks (RR). Any risk factors found to be significant were adjusted in the final Cox model. The main effect tested (ie, Black versus White) was included in all models. The variables considered in multivariate analyses are summarized in Table 2. Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Table 2. Variables Tested in Multivariate Analysis

Main effect variable:
- Race/ethnicity: White* versus Black

Patient-related variables:
- Age: <50* versus 50-64 versus ≥ 65
- Sex: Male* versus Female

Karnofsky performance status at transplant: <90% versus ≥90%* versus missing

Body mass index: underweight/normal* versus overweight versus obese/morbidly obese

Hypertension anytime prior to transplant: yes* versus no

Diabetes anytime prior to transplant: yes* versus no

History of smoking prior to transplant: yes* versus no

Creatinine >1.5 mg/dL versus ≤1.5* mg/dL at diagnosis

MM subtype: IgG versus IgA versus Light chain versus others/unknown

Disease-related variables:
- Durie-Salmon stage at diagnosis: I* versus II versus III
- Number of lines of chemotherapy: 1* versus 2 versus >2
- Sensitivity to chemotherapy prior to transplant: sensitive* versus others
- Disease status prior to transplant: complete remission/partial remission* versus others (includes minimal response, no response, stable disease, relapse/progressive disease and unknown)

Prior chemotherapy regimens: MP* versus VAD versus Cy ± others versus Corticosteroids ± others

Transplant-related variables:
- Time from diagnosis to transplant: <12 months* versus others
- Conditioning regimen: melphalan only* versus melphalan + TBI ± others versus Bu-Cy ± others (not TBI, not melphalan)
- Purging: yes* versus no
- Year of transplant: 1995-2001 versus 2002-2005*

MP indicates Melphalan + Prednisone; VAD, vincristine + dexamethasone + adriamycin; Cy, cyclophosphamide; Bu, busulfan; TBI, total body irradiation.
*Reference group.

RESULTS

Patient Characteristics

Table 1 shows the characteristics of all patients evaluated. Median ages at AHCT were 55 years for Black compared to 57 years for White patients ($P < .001$). The Black cohort had a higher proportion of females and patients with Karnofsky performance status scores (KPS) >90 (69% versus 61%, $P = .005$). Blacks were more likely to have comorbidities such as hypertension (47% versus 25%, $P < .001$), diabetes mellitus (17% versus 9%, $P < .001$), and obesity (38% versus 31%, $P = .01$). No statistically significant differences in disease stage or MM subtype were identified. Blacks were also more likely to have a lower hemoglobin (Hb <10 g/dL in 45% versus 29%, $P < .001$) at diagnosis. No significant differences in the levels of serum creatinine, beta-2 microglobulin, calcium, or marrow plasmacytosis were identified. The cohorts did not differ with respect to the type and number of prior therapies or sensitivity to therapies applied before transplantation. Blacks were transplanted later in the disease course, with 37% receiving AHCT a year or more from diagnosis versus 28% in Whites ($P < .001$). There were no significant differences in conditioning regimens used or the receipt of a salvage second AHCT.

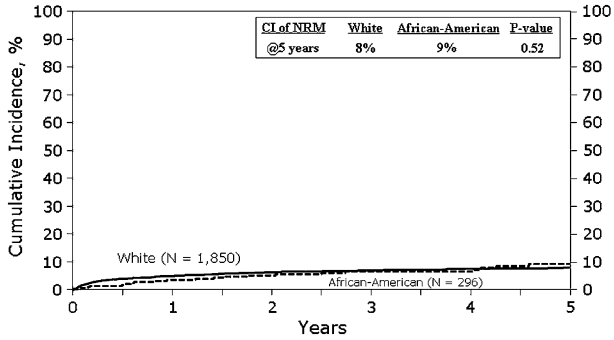

Figure 1. Cumulative incidence of nonrelapse mortality.

NRM and Relapse/Progression

Figure 1 shows the cumulative incidence of NRM. The cumulative incidence of NRM was similar in both groups. At 1 year, it was 5% (95% confidence interval [CI] 4%-6%) in Whites versus 3% (95% CI 2%-6%) in Blacks. At 5 years, it was 8% (95% CI 7%-9%) versus 9% (95% CI 6%-14%) in Whites and Blacks, respectively. In multivariate analysis (Table 3), race was not associated with NRM. Factors associated with an increased risk of NRM were age ≥65 years, KPS <90, and AHCT prior to 2002.

Figure 2 shows cumulative incidence of relapse/progression. The cumulative incidence of relapse/progression was similar in both groups. At 1 year, it was 27% (95% CI 25%-29%) in Whites versus 28% (95% CI 23%-34%) in Blacks. At 5 years it was 72% (95% CI 69%-74%) versus 72% (95% CI 65%-78%) in Whites and Blacks, respectively. In multivariate analysis (Table 3), race was not associated with disease relapse or progression. Factors associated with an increased risk of relapse included KPS score <90, Durie-Salmon stage III at diagnosis, receipt of 3 or more lines of chemotherapy before AHCT, lack of chemosensitive disease prior to AHCT, AHCT ≥12 months from diagnosis, and later year of AHCT.

PFS and OS

Figure 3 shows the probability of PFS. The 1- and 5-year probabilities of PFS were similar in both groups. At 1 year, it was 68% (95% CI 66%-70%) in Whites versus 68% (95% CI 63%-74%) in Blacks. At 5 years, it was 21% (95% CI 18%-23%) versus 19% (95% CI 14%-25%) in Whites and Blacks, respectively. In multivariate analysis (Table 4), race was not associated with PFS.

Figure 4 shows the probability of OS after AHCT. The 1- and 5-year survival rates were also similar between the 2 cohorts. At 1 year, it was 87% (95% CI 85%-88%) in Whites versus 90% (95% CI 87%-93%) in Blacks. At 5 years, it was 47% (95% CI 44%-49%) versus 52% (95% CI 45%-59%) in Whites and Blacks, respectively. In multivariate analysis (Table 4), race was not a significant predictor of survival.

Table 3. Multivariate Analysis for Relapse and Nonrelapse Mortality

Variable	Relapse			Nonrelapse mortality		
	N	RR	*P*-Value	N	RR	*P*-Value
Race						
White	1850	1.00		1850	1.00	
Black	296	0.92 (0.78-1.08)	*P* = .28	296	1.16 (0.75-1.80)	*P* = .51
Patient age, years						
<50				475	1.00	*P* < .001
50-64				1253	1.55 (1.01-2.39)	*P* = .05
≥65				418	3.50 (2.17-5.65)	*P* < .001
Karnofsky Score prior to conditioning						
<90	815	1.00		815	1.00	
≥90	1331	0.88 (0.79-0.98)	*P* = .02	1331	0.72 (0.53-0.98)	*P* = .03
Durie-Salmon stage at diagnosis						
I	222	1.00	*P* < .001	222	1.00	*P* = .004
II	652	1.23 (1.00-1.51)	*P* = .05	652	0.61 (0.35-1.06)	*P* = .08
III	1272	1.54 (1.27-1.87)	*P* < .001	1272	1.16 (0.71-1.88)	*P* = .56
Number of lines of chemotherapy‡						
1	1256	1.00	*P* = .001			
2	628	1.12 (0.99-1.27)	*P* = .07			
>2	262	1.39 (1.16-1.66)	*P* < .001			
Sensitivity to chemotherapy prior to transplant						
Other	522	1.00				
Sensitive	1624	0.76 (0.67-0.85)	*P* < .001			
Time from diagnosis to transplant						
<12 months	1519	1.00				
≥12 months	627	1.19 (1.04-1.35)	*P* = .009			
Year of transplant						
1995-2001	1331	1.00		1331	1.00	
2002-2005	815	1.17 (1.04-1.31)	*P* = .008	815	0.56 (0.39-0.81)	*P* = .002

RR indicates relative risk.
‡Excludes stem cell priming.

PFS and OS were worse in patients with older age at AHCT (>50 years), KPS score <90, higher Durie-Salmon stage, those who received 2 or more lines of therapy prior to AHCT, AHCT ≥12 months from diagnosis, and chemotherapy resistant disease (Table 4). OS was also lower in patients who underwent AHCT prior to 2002.

The major cause of mortality in both cohorts was relapse or progression of MM that accounted for 72% of all deaths.

DISCUSSION

Our analysis establishes that Black and Whites have very similar outcomes after AHCT for MM. These results concur with observations in other studies of nontransplant therapy that the disparity in outcomes for MM disappears when Blacks receive identical therapy [24].

Several investigators have shown that Blacks have outcomes similar to Whites when given the same nontransplant treatment for MM. Rohatgi et al. [25] showed that Blacks were less likely to receive chemotherapy, but they responded with similar outcomes when given similar nontransplant therapy for MM. In the pretransplant era, Modiano et al. [26] retrospectively evaluated the impact of race in the results of the SWOG 8829 study of conventional chemotherapy for MM. From 99 study sites in the United States, 116 Black and 467 White patients were shown to have

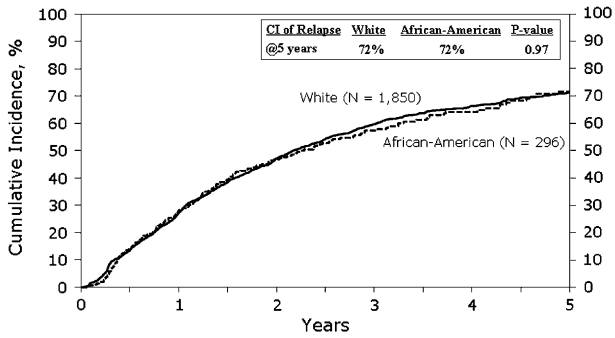

Figure 2. Cumulative incidence of disease relapse and progression.

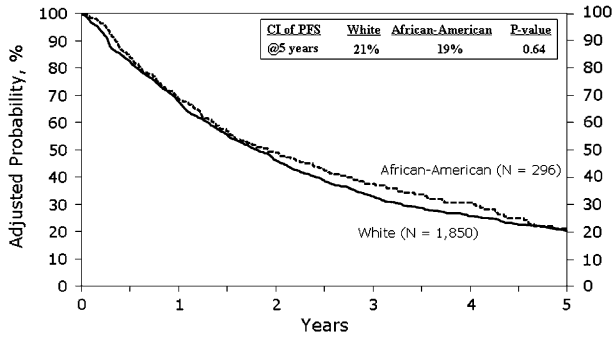

Figure 3. Probability of progression-free survival.

Table 4. Multivariate Analysis for Overall Survival and Progression-Free Survival

Variable	Overall Survival			Progression-Free Survival		
	N	RR	*P*-Value	N	RR	*P*-Value
Race						
White	1892	1.00		1850	1.00	
Black	303	0.94 (0.78-1.13)	$P = .50$	296	0.94 (0.81-1.09)	$P = .39$
Patient age, years						
<50	484	1.00	$P < .0001$	475	1.00	$P = .03$
50-64	1283	1.26 (1.09-1.46)	$P = .002$	1253	1.12 (0.99-1.27)	$P = .08$
≥65	428	1.52 (1.26-1.83)	$P < .0001$	418	1.24 (1.06-1.46)	$P = .007$
Karnofsky Score prior to conditioning						
<90	832	1.00		815	1.00	
≥90	1363	0.74 (0.66-0.83)	$P < .0001$	1331	0.87 (0.79-0.97)	$P = .009$
Durie-Salmon stage at diagnosis						
I	228	1.00	$P < .0001$	222	1.00	$P < .0001$
II	663	1.13 (0.89-1.44)	$P = .32$	652	1.12 (0.93-1.36)	$P = .23$
III	1304	1.67 (1.34-2.09)	$P < .0001$	1272	1.49 (1.25-1.79)	$P < .0001$
Number of lines of chemotherapy‡						
1	1292	1.00	$P < .0001$	1256	1.00	$P = .0002$
2	635	1.10 (0.96-1.27)	$P = .17$	628	1.13 (1.00-1.27)	$P = .04$
>2	268	1.66 (1.37-2.01)	$P < .0001$	262	1.41 (1.19-1.67)	$P < .0001$
Sensitivity to chemotherapy prior to transplant						
Other	533	1.00		522	1.00	
Sensitive	1662	0.82 (0.72-0.94)	$P = .003$	1624	0.76 (0.68-0.85)	$P < .0001$
Time from diagnosis to transplant						
<12 months	1554	1.00		1519	1.00	
≥12 months	641	1.16 (1.01-1.34)	$P = .04$	627	1.16 (1.03-1.31)	$P = .01$

RR indicates relative risk.
‡Excludes stem cell priming.

similar median survival (32 and 30 months, respectively). There were no differences by stage or MM subtype. A smaller study from the Department of Defense equal access health care system, reported on the outcomes of 36 Black and 55 White newly diagnosed patients receiving AHCT for MM and observed comparable outcomes between the 2 groups [27]. In their study, there were no differences in the stage, hemoglobin, calcium, or creatinine levels, although Blacks did have higher C-reactive protein (CRP) levels and a trend for less skeletal involvement. The authors recommended a larger retrospective study such as the current one. Other single center analyses comparing Black and White recipients of AHCT for MM have drawn conflicting conclusions. Khaled et al. [28] analyzed 101 Black patients and concluded that they were likely to relapse earlier after AHCT. Survival was not compared in this study. Saraf et al. [24] in their comparative study that included 38 Black and 32 White AHCT recipients, found that Black patients had more prolonged responses and greater event-free survival (EFS).

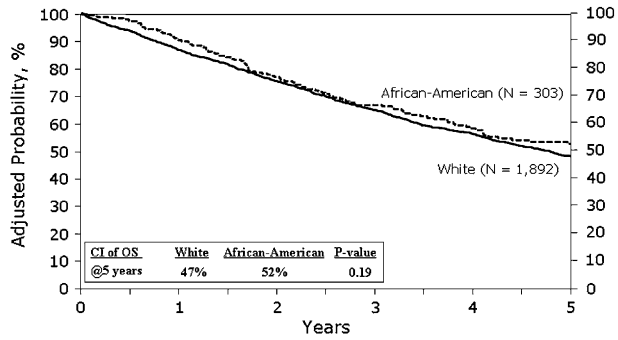

Figure 4. Probability of overall survival.

Unfortunately, there is ample evidence that Blacks are less likely to receive chemotherapy for MM as well as AHCT. Rohatgi et al. [25] reviewed patterns of chemotherapy use for patients with MM outside the clinical trial setting. From a population-based retrospective cohort of 49,021 patients aged 65 years or older with stage II or III MM, they found that only 52% received chemotherapy. Blacks were less likely to receive chemotherapy compared to Whites (47.6% versus 52.8%) despite evidence that use of chemotherapy decreased all cause mortality, myeloma specific mortality, and increased survival [25]. The reasons for the disparate access are unclear, because controlling for socioeconomic status did not eliminate the disparity in the receipt of chemotherapy.

These disparities in the receipt of therapy occur in the transplant setting as well. Joshua et al. [19], in a previous study from the CIBMTR, demonstrate that Whites are more likely to receive AHCT for newly diagnosed MM compared to an age- and sex-adjusted Black population. Using data from the SEER and CIBMTR registries, the study showed that age- and sex-adjusted odds of receiving AHCT for MM is 1.72 times greater in Whites compared to Blacks. Although our study cannot address the reasons for this underutilization of AHCT in Blacks, interesting conclusions can be drawn regarding AHCT for MM in Black patients.

It has been proposed that reduced access to treatment for MM may be related to actual or perceived worse outcomes in Black patients. Our study clearly shows that outcomes are not different between Blacks and Whites receiving AHCT for MM, suggesting this treatment modality should be offered to all patients when medically appropriate. These results are in accordance with a meta-analysis of patients treated for 14 different cancers, where survival in the majority of cancers was similar between races when comparable treatment was given [29].

The pretransplant characteristics of Black recipients of AHCT are interesting. The Black cohort was younger and had better performance status than the White cohort, despite higher rates of anemia and other comorbidities at diagnosis. These differences likely indicate a selection bias operating against older Black patients with lower KPS scores with regard to referral for consideration of AHCT. Black patients were also likely to have had a longer time between diagnosis and transplantation compared to Whites, while receiving a similar number of chemotherapy regimens and having similar responses. This suggests delayed referral for consideration of AHCT. A referral bias favoring only the healthiest Black patients for transplant may be in effect, whereas patients with less favorable clinical features may only be offered nontransplant or even nontreatment options.

The major strength of our study is the broad representation of transplant centers making it very likely that these results are applicable to the transplant community as a whole. In this analysis, we are unable to draw any conclusions about factors associated with nonreceipt of transplant in Blacks because a nontransplant population is not represented. The characteristics of the population of black MM patients not receiving AHCT need to be analyzed to identify the causes of a under utilization of AHCT. It is possible that many Blacks who are not receiving stem cell transplantation for myeloma are forgoing the transplant by choice. However, it is also possible that referral bias, unequal access to tertiary care, compliance gap, reluctance to enter clinical trials, and socioeconomic disparities account for some of the differences in utilization of AHCT for patients with MM. With the demonstration of equal outcomes for Blacks with MM, further study and definitive action to ensure better awareness and delivery of transplant options for the Black population is warranted.

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