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Disparities in Utilization of Autologous Stem Cell Transplantation as Consolidative Therapy for Multiple Myeloma: A Single Institution Retrospective Review

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Original Study

Disparities in Utilization of Autologous Stem Cell Transplantation as Consolidative Therapy for Multiple Myeloma: A Single Institution Retrospective Review

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Abstract

Background: Most guidelines recommend induction therapy followed by autologous hematopoietic cell transplantation. A Surveillance, Epidemiology, and End Results–Medicare database analysis from 2000 to 2011 noted a lower use of HCT and bortezomib among Black patients, despite adjusting for care barriers, and this practice was associated with a poorer outcome. The goal of this study was to evaluate patterns of acceptance of HCT as consolidative therapy for MM. **Methods:** Cox proportional hazards model was used to investigate the association between the survival time of the patients (overall survival) and age of the diagnosis, race, socioeconomic status, disease cytogenetic, and initial induction regimens. A total of 194 patients with a confirmed diagnosis of MM who were referred for HCT between January 1, 2009, and June 30, 2019, were included in this study. Patients who received autologous stem cell transplant for relapsed MM were excluded. **Results:** We found that income category was not significantly associated with overall survival, time to transplant or transplant-/relapse-related mortality. High-risk cytogenetic was significantly associated with shorter overall survival, higher transplant-related mortality and relapse-related mortality ($P < .002$). The use of aggressive induction choices was associated with poorer transplant outcomes ($P = .02$). Time to transplant tended to be shorter in African American compared with other ethnic groups ($P = .07$). **Conclusion:** There was no significant difference in the use rate of the HCT between Caucasians and AA patients with MM. Further comparative studies of MM induction therapy and access to clinical trials in African Americans and other racial minorities are warranted.

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Introduction

Multiple myeloma (MM) accounts for about 17% of hematologic malignancies in the United States. It is a disease of older adults, with a median age at diagnosis of 66 years. The incidence in African Americans is 2 to 3 times greater that in Caucasian Americans, and this disparity has been found to be greater among patients less than 50 years old.[2] MM had traditionally been treated with cytotoxic agents such as alkylating agents, anthracyclines, and steroids. In the last 1 to 2 decades, several other novel therapies have become available, including proteasome inhibitors, immunomodulatory drugs, and antibodies. Hematopoietic cell transplantation (HCT) is an important part of the treatment algorithm for MM. Although the exact timing of the HCT remains debatable and the overall survival rate is similar whether the transplant is done upfront or delayed, most experts recommend upfront HCT (done after the initial induction therapy) because it is associated with the improved depth of the response and progression-free survival.[5,6]

There are multiple barriers to the use of HCT, including referral bias, cultural barriers, lack of care coordination, barriers to access to care, refractory or progressive disease, conscious or unconscious bias among physicians, and ineligibility based on pretransplant evaluation.[3,4] Personal choice of the patient also plays an important role and may be influenced by inherent mistrust of the medical

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system, religious beliefs, literacy level, nonadherence, loss to follow-up, performance status, or financial challenges.[7] The goal of this study was to evaluate the patterns of acceptance of autologous stem cell transplant as consolidative therapy of MM. Because the receipt of upfront autologous stem cell transplant depends on response to induction therapy, our study also investigated disparity in transplant outcomes and time to transplant, which are areas that previous studies had not looked at.

Methods

This retrospective review used electronic medical records to identify patients diagnosed with MM and were referred for bone marrow transplant team (BMT) consultation between January 2009 and June 2019 at our academic health system. The *International Classification of Diseases*, Tenth Revision, Clinical Modification, code C90 was used to identify patients with MM and code Z94.81 for patients who underwent autologous bone marrow transplantation. Of 294 patients identified with MM who were treated with autologous steam cell transplantation, 194 entered the final statistical analysis. Demographic data were collected using electronic medical records. Area-based median household income was obtained by geocoding patients' addresses and linking with census data. The median household income by zip code was downloaded from the website https://factfinder.census.gov. The Charlson comorbidity index for all subjects was calculated. Institutional review board approval was obtained before the study initiation.

Statistical Analysis

Continuous variables were summarized with means and standard deviation or median and interquartile range and compared using the 2-sample *t* test or Wilcoxon rank-sum test. Categorical variables were summarized with frequencies and proportions and compared using the χ^2 test or Fisher exact test. Survival curves were estimated using the Kaplan-Meier method. Multivariable analyses were assessed by Cox proportional hazard models. A *P* value of less than .05 was considered significant for all statistical methods used. The statistical analyses were completed using R (version 3.6.2; The R Foundation, Vienna, Austria).

Results

Table 1 summarizes the demographic and clinical characteristics for the study participants. The age at diagnosis for the deceased group (median, 65 years) was significantly higher compared with the alive group (median, 60 years), with 70% of the deceased group having high-risk cytogenetics, which was statistically significantly higher than the alive group (33.1% for high-risk cytogenetics). Gender, race, induction groups, and income categories were not significantly different between the 2 groups.

The Cox proportional hazards model for overall survival (Table 3) indicated that high-risk cytogenetics was significantly associated with higher hazard (i.e., shorter survival). The hazard ratio (HR) was 3.14 ($P < .001$) for high-risk cytogenetics compared with low-risk cytogenetics. Induction with the aggressive regimens such as dose-adjusted EPOCH, Hyper-CVAD, DT-PACE (group 3) was associated with shorter survival (HR, 6.49; $P = .02$) compared with the reference group (group 1), which represents the standard of care most commonly used lenalidomide/bortezomib-based induction regimens.

Table 1 Demographic Characteristics

Group	All ($n = 194$)
Age at dx, median (IQR)	61.5 (55, 68)
Gender, n (%)	
Female	81 (41.8)
Male	113 (58.2)
Race, n (%)	
Non-Hispanic White	76 (39.2)
Black	82 (42.3)
Others/unknown	36 (18.6)
Cytogenetic, n (%)	
High risk[a]	102 (56.4)
Standard risk	79 (43.6)
Charlson, comorbidity index (%)	
≥2	150 (78.1)
0	14 (7.3)
1	28 (14.6)
Induction chemotherapy, n (%)	
Bortezomib/lenalidomide–based regimens	130 (71)
Cyclophosphamide-based regimens	23 (12.6)
Aggressive regimens[b]	5 (2.7)
Others	17 (9.3)
More than 1 induction regimen	8 (4.4)
Income categories, n (%)	
[0-42 K]	71 (36.6)
[42-65 K]	60 (30.9)
[65-Inf]	63 (32.5)

[a] High-risk cytogenetics: 17p13 deletion, t(4;14), t(14;16), t(14;20), Gain 1q.
[b] Aggressive regimens: DA-EPOCH, HYPECVAD, DT-PACE, Melphalan.

The Cox proportional hazards model (Table 4, Figure 1) indicated that none of the clinical characteristics was significant for time to transplant. The Cox proportional hazards model in Table 5 shows that, for transplant-related mortality, high-risk cytogenetics was significantly associated with a greater hazard (HR, 3.31; $P = .002$) compared with low-risk cytogenetics. The Cox proportional hazards model for relapse-related mortality indicated high-risk cytogenetics was significantly associated with shorter survival (HR, 3.18; $P = .02$) compared with low-risk cytogenetics (Table 6).

Discussion

Historically, racial and ethnic minorities have been found to be less likely to undergo stem cell transplantation. Our study aimed to explore disparities in the use of HCT in these minority populations at our institution, which serves a predominantly African American population. We found no statistically significant differences in the HCT use in MM management between Black, non-Hispanic White, and other race patients. In fact, interestingly, time to transplant for Black patient population tended to be shorter (HR, 1.40; 95% confidence interval, 0.97-2.02; $P = .08$) (Table 4, Figure 1).

Figure 1 Time to transplant. Time to transplant tends to be shorter in Black population.

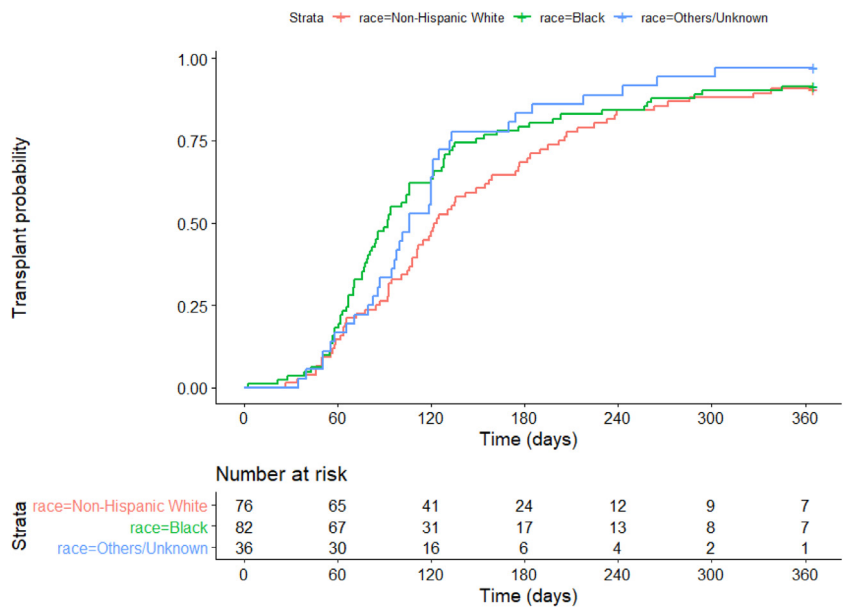

Table 2 Demographic Variables

Group	All ($n = 194$)	Alive ($n = 137$)	Deceased ($n = 57$)	*P* Value
Age at diagnosis, median (IQR)	61.5 (55-68)	60 (54-67)	64 (59-70)	.005
Gender, n (%)				
Female	81 (41.8)	55 (40.1)	26 (45.6)	.587
Male	113 (58.2)	82 (59.9)	31 (54.4)	
Race, n (%)				
Non-Hispanic White	76 (39.2)	55 (40.1)	21 (36.8)	.831
Black	82 (42.3)	56 (40.9)	26 (45.6)	
Others/unknown	36 (18.6)	26 (19)	10 (17.5)	
Cytogenetic, n (%)				
Standard risk	102 (56.4)	87 (66.9)	15 (29.4)	<.001
High risk	79 (43.6)	43 (33.1)	36 (70.6)	
Charlson Comorbidity Index, n (%)				
≥2	150 (78.1)	99 (73.3)	51 (89.5)	.028
0	14 (7.3)	11 (8.1)	3 (5.3)	
1	28 (14.6)	25 (18.5)	3 (5.3)	
Induction groups, n (%)				
Bortezomib/lenalidomide based	130 (71)	92 (71.3)	38 (70.4)	.111
Cyclophosphamide based	23 (12.6)	19 (14.7)	4 (7.4)	
Aggressive regimen	5 (2.7)	2 (1.6)	3 (5.6)	
Others	17 (9.3)	9 (7)	8 (14.8)	
More than 1 induction regimen	8 (4.4)	7 (5.4)	1 (1.9)	
Income categories				
<42 K	71 (36.6)	45 (32.8)	26 (45.6)	.129
≥42 K	123 (63.4)	92 (67.2)	31 (54.4)	

Abbreviation: IQR = interquartile range.

Previous studies reported a significantly longer time from diagnosis of MM to HCT referral for Black patients compared with White patients (1.3 ± 1.5 years vs 0.9 ± 1.0; $P = .003$).[8] In a literature search, we have not found other studies showing a shorter time to transplant for Black patients.

Our findings suggest that the barrier to HCT among Black patients may lie within the external factors such as the proximity to health care, primary care providers availability, or transportation issues, rather than the ability to receive an HCT for MM management. The difference in our findings might be due to our institution having a transplant center on site in Detroit, where we serve a predominantly Black community. Increased accessibility to minority populations could have prevented delay of care. As an academic nonprofit organization, we strive to provide equal level of care regardless of socioeconomic factors. We also offer financial assistance to the underserved population (our Game-on-Cancer program is well-equipped and funded to offer financial assistance to patients undergoing cancer therapy or stem cell transplant in the form of money, bill payments). Additional studies looking at the socioeconomic factors in referral patterns and time to an autologous HCT are needed to further validate those findings.

Although it is true that an earlier Surveillance, Epidemiology, and End Results–Medicare analysis (including predominantly Black urban centers) showed a longer time to transplant, more recent studies point toward a decreasing gap in racial disparities in terms of auto HCT use in patients with MM. Data from the Surveillance, Epidemiology, and End Results–Medicare database (2007-2014 from Medicare) showed no significant difference in the likelihood for the African American and White cohorts to receive HCT (4.9% vs 6.9%).[14] Additionally, an increasing trend in the rate of HCT use within 1 year of index diagnosis date was observed among whites (2007-2009, 3.6%; 2012-2013, 9.7%; $P < .05$) and African Americans (2007-2009, 2.5%; 2012-2013, 9.3%; $P < .05$).[14] Although pooled Surveillance, Epidemiology, and End Results–Medicare analysis studies did not show time to transplant to be shorter in Black population, their limitations include retrospective data collection from multiple centers with the introduction of many confounders.

The current study did not demonstrate significant differences in gender, race, induction regimens, or income categories with regard to the time to transplant, transplant-related mortality, or relapse-related mortality (Table 4, Table 5, and Table 6). As mentioned elsewhere in this article, time to transplant (defined as a time from the initial BMT consultation to HCT procedure) was trending toward a shorter period in Black patients (HR, 1.40; 95% confidence interval, 0.97-2.02; $P = .08$.

Concordant with prior research, high risk cytogenetics in our study was significantly associated with shorter overall survival (HR, 3.14; 95% confidence interval, 1.62-6.09; $P < .001$) (Table 3). More patients in the deceased group had high risk cytogenetics (70%) compared with the alive group (33.1%) (Tables 1 and 2). In addition, high-risk cytogenetics was associated with transplant-related mortality (HR, 3.32; 95% confidence interval, 1.55-7.11; $P = .002$) as well as for relapse-related mortality (HR, 3.18; $P = .02$) (Table 5 and Table 6). Those findings are similar to prior studies regarding the effect of cytogenetics effect on treatment outcome.[9]

Table 3 Overall Survival (Time to Death or Last Follow-up Date from the Procedure Date)

	HR (95% CI)	*P* Value
Cytogenetic (high-risk cytogenetic)	3.14 (1.62-6.09)	<.001
Age at diagnosis	1.04 (0.99-1.09)	.13
Race		
Non-Hispanic White (ref)	–	–
Black	0.66 (0.32-1.39)	.28
Others/unknown	0.87 (0.36-2.13)	.76
Charlson comorbidity index		
≥2 (ref)	–	–
0	1.44 (0.30-6.82)	.65
1	0.64 (0.17-2.41)	.51
Induction groups		
Bortezomib/lenalidomide based (ref)	–	–
Cyclophosphamide based	0.81 (0.28-2.35)	.70
Aggressive treatment	6.49 (1.34-31.34)	.02
Others	0.53 (0.19-1.45)	.21
More than 1 induction regimen	1.21 (0.15-9.56)	.85
Income categories		
<42 K(ref)	–	–
≥42 K	0.73 (0.36-1.46)	.37

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference.
High-risk cytogenetics associated with a decreased overall survival: a HR of 3.14 and a *P* value of <.001. Induction with the aggressive regimens such as dose-adjusted EPOCH, Hyper-CVAD, DT-PACE (group 3) was associated with shorter survival (HR, 6.49; $P = .02$).

Regarding demographic variants, we found that the age at diagnosis of MM for the deceased group (median, 65 years) was significantly higher compared with the alive group (median, 60 years) (Table 1 and Table 2). This finding is supported by previous studies that showed increased risk of mortality in myeloma patients older than 60 years of age.[1] Age as a prognostic factor in autologous bone marrow transplant for MM is not as apparent. A study comparing older (>65 years old) and younger (60-65 years old) patients undergoing autologous bone marrow transplant for MM did not find significant difference in terms of overall survival and transplant-related mortality.[5] However, patients who were older than 60 years of age at the time of autologous bone marrow transplant for MM were found to have a 2.2-fold higher risk of developing grade 3 and 4 chronic health conditions compared with younger patients in a retrospective analysis.[4] Because more autologous bone marrow transplants are being performed in older patients, more studies are needed to elucidate the prognostic value of patient age.

Induction with aggressive regimens such as dose-adjusted EPOCH, Hyper-CVAD, DT-PACE (Table 3) was associated with shorter survival (HR, 6.49; $P = .02$) compared with the reference bortezomib/lenalidomide group. EPOCH has been studied as salvage therapy before reduced-intensity allogeneic hematopoietic SCT in MM.[10] Hyper-CVAD has been evaluated in refractory and heavily pretreated patients with relapsed MM.[11,12] Patients with extramedullary/blastoid myeloma have a poor clinical outcome, even when treated with the intensive regimen DT-PACE; however, a subgroup can do well if DT-PACE is consolidated by autologous stem cell transplant.[13] The difference in survival between the

Table 4 Time to Transplant (Time to Transplant from the First Bone Marrow Transplant Team Visit)

	HR (95% CI)	*P* Value
Cytogenetics (high risk)	0.86 (0.62-1.18)	.35
Age at the diagnosis	1.01 (0.99-1.03)	.35
Race		
Non-Hispanic White (ref)	–	–
Black	1.40 (0.97-2.02)	.08
Others/unknown	1.28 (0.82-2.00)	.27
Charlson comorbidity index		
≥2 (ref)	–	–
0	0.98 (0.48-2.00)	.95
1	1.18 (0.71-1.98)	.52
Induction regimens		
Bortezomib/lenalidomide based (ref)	–	–
Cyclophosphamide based	0.67 (0.42-1.07)	.10
Aggressive treatment	1.30 (0.39-4.28)	.67
Others	0.71 (0.42-1.22)	.22
More than 1 induction regimen	0.85 (0.39-1.85)	.67
Income categories		
<42 K (ref)	–	–
≥42 K	1.16 (0.82-1.64)	.39

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference.
None of the clinical characteristics was significant for time to transplant; time to transplant tends to be shorter in Black population (HR, 1.40; 95% CI, 0.97-2.02; and $P = .08$).

Table 5 Transplant-related Mortality

	HR (95% CI)	*P* Value
Cytogenetics (high-risk cytogenetics)	3.32 (1.55-7.11)	.002
Age at the diagnosis	1.03 (0.98-1.08)	.30
Race		
Non-Hispanic White (ref)	–	–
Black	0.60 (0.24-1.51)	.28
Others/unknown	0.56 (0.17-1.88)	.35
Charlson comorbidity index		
≥2 (ref)	–	–
0	0.75 (0.08-7.45)	.81
1	0.25 (0.03-2.10)	.20
Induction groups		
Bortezomib/lenalidomide based (ref)	–	–
Cyclophosphamide based	0.97 (0.33-2.85)	.95
		NA
		.94
		NA
Income categories		
<42 K (ref)	–	–
≥42 K	0.69 (0.28-1.70)	.42

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference.
Transplant-related mortality associated with the high-risk cytogenetics with HR 3.31, *P* value 0.002.

Table 6 Relapse-related Mortality

	HR (95% CI)	*P* Value
Cytogenetic	3.18 (1.25-8.12)	.02
Age at the diagnosis	1.08 (1.00-1.16)	.04
Race		
Non-Hispanic White (ref)	–	–
Black	0.80 (0.28-2.29)	.68
Others/unknown	1.38 (0.42-4.50)	.59
Charlson comorbidity index		
≥2 (ref)	–	–
0	6.43 (0.76-54.22)	.09
1	2.20 (0.43-11.27)	.34
Induction groups		
Bortezomib/lenalidomide based (ref)	–	–
Cyclophosphamide-based	0.47 (0.06-3.77)	.48
Aggressive regimen	19.92 (3.22-123.24)	.001
Others	0.41 (0.08-2.04)	.28
More than 1 induction regimen	3.02 (0.33-28.04)	.33
Income categories		
<42 K (ref)	–	–
≥42 K	0.73 (0.28-1.89)	.52

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference.
Relapse-related mortality significantly associated with high-risk cytogenetics (HR, 3.18; $P = .02$), older age at the time of the diagnosis (HR, 1.08; $P = .04$), and aggressive treatment regimens (HR, 19.9; $P = .001$).

standard regiment and aggressive regimens for induction is at least in part owing to difference in disease biology.

The limitations of this study include its small sample size and the retrospective nature of the study, with the potential for unmeasured confounders that might bias the study outcome. A single-center patient population may not be a true representation of the overall national population. Our study can serve as a platform for further national collaboration to explore racial disparities in MM treatment. It is hoped that the results of this study will better guide interventions to improve access to and use of HCT as consolidative therapy for MM, especially in patients with high-risk cytogenetics.

Clinical practice points

There was no significant difference in the use rate of the HCT between Caucasians and AA patients with MM. Our findings suggest that the barrier to HCT among Black patients may lie within the external factors such as the proximity to health care, primary care providers availability, or transportation issues, rather than the ability to receive an HCT for MM management.

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Disclosure

The authors have stated that they have no conflicts of interest.

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