STIMULUS REPORT

blood advances

Survival of ethnic and racial minority patients with multiple myeloma treated with newer medications

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Key Points

- Patients of minority race with myeloma have had less increase in population-level survival in the early 21st century than white patients.
- Data from clinical trials show that mortality is similar for minorities, suggesting the population-level difference is due to utilization.

Introduction

Survival for patients with multiple myeloma (MM) has increased dramatically in the early 21st century.[1,2] However, several population-level studies have suggested that there may be differences in survival based on racial or ethnic background and that these differences may be changing as new treatment options become available,[2-6] with patients of minority racial or ethnic background often having lower survival or less improvement in survival compared with non-Hispanic whites (nHws).

Several prior studies have demonstrated that patients of minority ethnic or racial background are less likely than nHws to receive autologous hematopoietic stem cell transplants (auto-HSCTs) as treatment for MM and that referral for transplantation may be delayed.[7-12] In addition, there is some evidence that minorities are less likely to receive treatment with newer agents (immunomodulatory [imid] drugs and proteasome inhibitors [PIs]) in treatment for myeloma. Several studies have demonstrated similar outcomes for minorities compared with nHws undergoing auto-HSCT when access is equal.[10,11] However, few publications have addressed the issue of differences in the efficacy of newer chemotherapeutic agents.

People of racial and ethnic minority background tend to be underrepresented in clinical trials,[13] and therefore, it is often difficult to assess whether there is differential efficacy in clinical trials. Pooling the relevant trials in a meta-analysis may provide an adequate sample size to assess potential differences in survival by race or ethnic background.

Here, we examine survival for patients with MM who participated in clinical trials involving treatment with either an imid or PI by racial and ethnic background.

Methods

Data were drawn from clinical trials submitted to the US Food and Drug Administration in support of new drug applications for either imids or PIs for patients with newly diagnosed MM (NDMM) who were not transplantation eligible. The trials had to have captured race and survival data. A total of 5 trials meeting these criteria were identified, including 4 that examined efficacy ofr imids and 1 that examined efficacy of the PI bortezomib.[14-18]

Because the case numbers for minority participants were small, patients were grouped into 3 categories: nHws, Asian and Pacific Islanders (APIs), and other races. Ethnicity (Hispanic vs non-Hispanic) was recorded as a separate variable for 3 of the 5 trials evaluated. In the 2 remaining trials, ethnicity information was coded in the race variable, and 1 patient per trial was categorized racially as Hispanic. Patients categorized ethnically as Hispanic were included in the other races category, regardless of race listed. No attempt to determine the race or ethnicity of a patient beyond that reported by the investigators of a given study was made.

The primary analysis was performed using the intent-to-treat population in each trial. A secondary analysis was performed using the safety population, defined as the population that received at least 1 dose of the study drug, to further isolate the effect of the drug on outcome. Inclusion was restricted to patients who received an imid or PI.

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Table 1. Demographics and disease characteristics by race

Characteristic	No. (%)			
	Total	nHW*	API	Other, including Hispanic
Sex				
Male	1491 (53.9)	1259 (52.5)	95 (56.9)	137 (54.8)
Female	1326 (47.1)	1141 (47.5)	72 (43.1)	113 (45.2)
Stage				
1	636 (22.6)	542 (22.6)	17 (10.2)	77 (30.8)
2	1061 (37.7)	900 (37.5)	70 (41.9)	91 (36.4)
3	997 (35.4)	844 (35.2)	75 (44.9)	78 (31.2)
Missing	123 (4.4)	114 (4.8)	5 (3.0)	4 (1.6)
Age, y				
Median	71.2	71.6	68.4	69.1
Range	35-92	36-92	43-89	35-90
Cytogenetics†				
Favorable	350 (12.4)	308 (12.8)	8 (4.8)	34 (13.6)
Adverse	675 (24.0)	570 (23.8)	47 (28.1)	58 (23.2)
Normal	637 (22.6)	548 (22.8)	50 (29.9)	39 (15.6)
Unknown	1155 (41)	974 (40.6)	62 (37.1)	119 (47.6)

*Not all studies collected data on ethnicity.
†Two studies did not collect information on cytogenetic variables, and another did not include a favorable category.

Observed mortality was examined by racial/ethnic group, and hazard ratios (HRs) for risk of death were constructed using a Cox proportional hazards analysis, stratifying for treatment arm. Data were then pooled and a meta-analysis of all trials performed. For the meta-analysis, results were stratified by trial, treatment arm, and International Staging System stage.

Analyses were performed using SAS software (SAS, Cary, NC) using standard macros for Cox proportional hazards analysis. Differences of $\leq$.05 were considered significant.

Results and discussion

Five trials meeting the inclusion criteria were identified. A total of 3407 participants were enrolled on the trials, included in the intent-to-treat population, and had race identified. One trial had little participation by minorities, with 99% of participants being white. Another had only a single participant in the API category.

Overall, there were slightly more male than female patients, and male patients were the majority in every racial/ethnic group (Table 1). The median age was slightly older for nHws compared with APIs and other races/ethnicities. API patients were less likely and other races/ethnicities more likely to have stage 1 disease compared with nHws. Cytogenetic information was missing or indeterminate for a majority of patients, but on the basis of the available data, fewer API patients had cytogenetics in the good prognostic category.

In individual studies, a trend toward higher mortality for APIs and lower mortality for other ethnic/racial groups was observed (Table 2). The HRs for mortality for API patients compared with nHws ranged from 1.15 to 3.3. However, the differences were not statistically significant. In contrast, the HRs for mortality for patients of other race/ethnicity ranged from 0.34 to 1.09 and were statistically significant for the Eastern Cooperative Oncology Group EA403 study.

The meta-analysis of all studies showed a higher HR for death for API patients vs nHws, with an HR of 1.15; however, the difference was not significant. A lower HR was observed for patients of other ethnic and racial backgrounds vs nHws, both before and after stratifying by stage, with an HR of 0.76 after stratification by stage, treatment, and study (P = .01). The results did not change significantly when studies that included few minority participants or those that did not clearly identify ethnicity were excluded. Analysis of the safety population demonstrated similar results (data not shown.)

Our results show a low participation of minorities in clinical trials of newer agents for treatment of NDMM in general. Despite this limitation, the medications under study did seem to have efficacy in minority populations similar to that in nHWs, although there was some variation between racial and ethnic groups, with mortality slightly lower in participants of other racial and ethnic groups.

Our results suggest that there could be differences in efficacy of the newer agents between different ethnic and racial groups, but the differences are small. In addition, the differences observed suggest that imid- and PI-class drugs could work, if anything, better in minorities other than APIs. Because Hispanic and African American patients have the least apparent benefit from newer agents at the population level,[2-6] this result suggests that minority patients are less likely to be appropriately treated. In addition, examination of survival in the current SEER data shows that overall 5-year survival from 2007 to 2013 increased to 52.3% for African Americans and 50.6% for whites,[19] suggesting that the earlier observed disparities were related to a temporary phenomenon (ie, differences in treatment utilization).

Several limitations should be considered when interpreting our results. First, the small percentage of minority participants limits stratification and confidence in the results. Second, participants in clinical trials are not typical of the general population, and survival in clinical trials differs from that of the average patient.[20,21] Third, it is not possible to determine whether the differences observed are due to differences in biology or differences in the social experience of people of different races. Fourth, this is a post hoc analysis, and causation cannot be determined. Finally, race has only a rough correlation with biological differences between various populations.[22,23] Finally, race is documented based on a mix of patient reporting and perception of research personnel, with the potential for error being introduced by misperceptions or incomplete information.

Low minority participation in clinical trials has been recognized as a barrier to improving health outcomes for minorities.[24] Barriers to participation include distrust of the clinical trial system because of past abuses, concern about being charged for services related to the clinical trial, and referral processes that limit trial availability to minorities, as well as higher risk of failure to meet inclusion criteria.[24-26]

In summary, our results show a minor difference in mortality by race for patients treated for NDMM on clinical trials of imids or PIs.

Table 2. Mortality by race/ethnicity stratified by treatment

Race	No. (%) of patients	Median follow-up, mo	No. (%) of deaths	HR (95% CI) ISS adjusted	*P*
FIRST					
White	1340 (83)	49	593 (44)	Ref	
Asian	129 (8)	39	50 (39)	1.15	.34
Other	154 (9)	47	54 (35)	0.81	.14
403EA403 (ECOG)					
White	377 (85)	30	93 (25)	Ref	
Asian	3 (1)	25	0 (0)	NA	NA
Other	65 (15)	32	9(14)	0.44	.03
VISTA*					
White	302 (99)	62	158 (52)	Ref	
Asian	0			NA	
Other	3 (1)	63	2 (67)	1.57	.53
S0232 (SWOG)					
White	77 (77)	33	16 (21)	Ref	
Asian	1 (1)	35	1 (100)	3.3	.25
Other	22 (22)	30	4(18)	0.80	.68
MMY3002*					
White	304 (88)	60	154 (51)	Ref	
Asian	34 (10)	56	20 (59)	1.18	.52
Other	6 (2)	62	2 (33)	1.09	.91
Meta-analysis 1†					
White	2400 (85)	49	1014 (42)	Ref	
Asian	167 (6)	40	71 (43)	1.15 (0.90-1.47)‡; 1.03 (0.81-1.32)§	.28‡; .80§
Other	250 (9)	40	71 (28)	0.76 (0.60-0.97)‡; 0.78 (0.62-0.1.00)§	.03‡; .05§
Meta-analysis 2‖					
White	2021 (84)	47	840 (42)	Ref	
Asian	166 (7)	40	70 (42)	1.14 (0.89-1.46)‡; 1.02 (0.80-1.31)§	.31‡; .87§
Other	225 (9)	42	65 (29)	0.75 (0.58-0.97)‡; 0.77 (0.59-0.99)§	.03‡; .04§
Meta-analysis 3¶					
White	1794 (83)	44	702 (39)	Ref	
Asian	133 (6)	39	51 (38)	1.14 (0.86-1.52)‡; 1.02 (0.76-1.36)§	.37‡; .90§
Other	241 (111)	40	67 (28)	0.74 (0.58-0.96)‡; 0.77 (0.60-0.99)§	.02‡; .04§

CI, confidence interval; FIRST, Frontline Investigation of Revlimid + Dexamethasone Versus Standard Thalidomide; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; NA, not available; Ref, referent; SWOG, Southwest Oncology Group; VISTA, V-domain Immunoglobulin Suppressor of T-cell Activation.

*Ethnicity was not included as a variable for these studies, although race was listed as Hispanic for 1 patient in each of these studies.

†Cox model stratified by study and treatment.

‡Stratified by study and treatment.

§Stratified by ISS stage, study, and treatment.

‖Cox model stratified by study and treatment, excluding VISTA and S0232.

¶Cox model stratified by study and treatment, excluding VISTA and MMY3002.

Greater minority participation in clinical trials is needed to provide a more definitive analysis of whether mortality varies by race.

Authorship

Contribution: All authors contributed to the interpretation of the data and critically reviewed the manuscript; E.D.P. designed the research and wrote the paper; and L.N. analyzed the data.

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