Deciphering racial disparities in multiple myeloma outcomes

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Comment on Shah et al, page 236

In this issue of *Blood Advances,* Shah et al report a retrospective clinical study evaluating the impact of diabetes and obesity on survival among patients with multiple myeloma from 2 academic medical centers.[1] This study is among the first to evaluate the association separately in Black and White patients. Over a median follow-up of 4.6 years, the data showed that patients with multiple myeloma and preexisting diabetes had worse overall survival compared to patients with nondiabetic conditions, whereas patients with elevated body mass index (BMI $\geq$25 kg/m^2) had improved overall survival compared to those with BMI <25 kg/m^2. However, discordant results were observed in White and Black patients. Intriguingly, the negative impact of diabetes was driven entirely by results for White patients, even after adjustment for treatment; Black patients with diabetes had no worse survival than those without diabetes. Furthermore, when analyzed by race, the inverse association noted for elevated BMI was stronger in Black patients than in White patients.

Multiple myeloma is the second most frequent hematologic malignancy in the United States. Compared to non-Hispanic White individuals, Black men and women have a >2-fold higher incidence of multiple myeloma (14.4 vs 6.4 cases per 100 000).[2] In addition, Black patients present at younger ages and more advanced disease with higher rates of anemia, hypercalcemia, and renal failure requiring hemodialysis than non-Hispanic White patients. Although overall 5-year relative survival has improved in recent years owing to advances in treatment, prognosis remains poor (5-year relative survival <60%) and stark racial disparities persist (5.9 vs 2.9 deaths per 100 000 in Black vs non-Hispanic White individuals).[2] Hispanic and Latinx individuals, the most rapidly growing racial and ethnic group in the United States, also experience higher incidence rates, earlier ages of diagnosis, underutilization of standard and novel therapies, and delays in treatment compared to non-Hispanic White individuals. It is clear that not all patients have benefited from therapeutic advances. To advance equity in multiple myeloma outcomes, the drivers of persistent racial disparities in outcomes require comprehensive evaluation.

The prevalence of diabetes based on race in the study by Shah et al largely reflects patterns in the general population: 25% of Black patients presented with diabetes compared to 12% of non-Hispanic White patients. It is reasonable to ask whether the presence of diabetes may explain the differential mortality rates between Black and White patients. The results from the study by Shah et al, however, suggest that diabetes, although a significant driver of mortality in non-Hispanic White patients, does not appear to explain the higher mortality rates among Black patients. Indeed, Black patients with or without diabetes had similar outcomes. Information on diabetes management was not available in this study. Whether there were differences in diabetes control or use of antidiabetic medications by race is unknown but could be informative given observations of better and worse survival associated with metformin and insulin, respectively.[3] To complement their epidemiologic findings, Shah et al also present results from a mechanistic study showing increased number and rate of growth of tumors (MM1.S xenografts) in a diabetic mouse model vs control. These data support a possible role for diabetes in multiple myeloma progression but do not provide insight into the observed differences by race.

Obesity is the only established modifiable risk factor for multiple myeloma[4] and has been associated with increased incidence in both White and Black individuals;[5] however, the impact of obesity on survival is less clear. Shah et al report an inverse association of BMI with all-cause mortality, which was stronger among Black patients, who had higher prevalence of overweight and obesity than among White patients. This finding was somewhat unexpected; elevated BMI has previously been associated with worse survival in patients with multiple myeloma, albeit inconsistently.[6] "Reverse causation" owing to myeloma-associated weight loss is a possible explanation; however, weight histories were not available in this study. Alternatively, this finding could implicate a role for obesity and metabolic disease

in treatment response. Further evaluation of cause-specific vs all-cause mortality may help to provide more insight. In addition, an "obesity paradox" has been reported in relapsed/refractory myeloma, such that patients with higher prevalence of overweight and obesity had better survival than those with healthy BMI.[7,8] In the study by Shah et al, the proportion of patients who developed relapsed or refractory myeloma or whether there were differences by race was unknown.

Importantly, the data from Shah et al suggest that even after accounting for the impact of diabetes and obesity, White patients fare better in terms of overall survival than Black patients, although this result was not statistically significant (hazard ratio, 0.88; 95% confidence interval, 0.77-1.01). Although these results require confirmation, these findings suggest that factors other than diabetes and obesity must be considered to explain disparities in outcomes by race and ethnicity.

While comorbidities and access to treatment are critical issues, mortality disparities in multiple myeloma largely reflect disparities in incidence across different racial and ethnic groups. Currently, there are no known prevention measures for multiple myeloma. Understanding the factors, especially potentially modifiable factors, that lead to development of multiple myeloma offers the best opportunity to reduce death from this disease by preventing it in the first place. Critical gaps exist in the understanding of etiologic factors that increase risk of multiple myeloma and its precursor conditions, particularly for underrepresented populations, who experience the highest burden of these diseases. To date, few risk factors, most of which show only modest associations, have been established.

As noted, obesity is considered an established risk factor for multiple myeloma.[4] Whether diabetes is independently associated with incidence of multiple myeloma is still an unanswered question, though some epidemiologic studies have suggested a possible association.[9] Whether or not diabetes is established to be a significant contributor to disease development and progression, future research should consider novel risk factors, such as social and neighborhood stressors, including interpersonal and systemic racism, which are disproportionately experienced by marginalized individuals.

The new era of advances in treatment with the advent of cellular therapies has already transformed the landscape of multiple myeloma as we know it. Survival has improved substantially in the past decade. Continued efforts to innovate are expected to boost survival even more; however, it is critical that all patients derive benefit. In addition, efforts to understand the pathogenesis of multiple myeloma and its precursor conditions are urgently needed to identify additional opportunities to reduce the clinical impact of these diseases, particularly in high-risk populations. Research efforts to include patients from underrepresented minority groups are critical to ensure that racial disparities in outcomes are not exacerbated and that no patient is left behind.

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