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Shrinking the divide: improving myeloma CART access

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Comment on Peres et al, page 251

In this issue of *Blood Advances*, Peres et al authored the manuscript "Racial and ethnic differences in clinical outcomes among patients with multiple myeloma treated with CAR T-cell therapy."[1] Our commentary provides a broader context to the relevance of the findings and the potential implications of these results in reducing health care disparities. For any given disease, the disparities are more pronounced when the therapies for treating the disease are highly effective. Taking the example of chronic myelogenous leukemia (CML), the highly active tyrosine kinase inhibitor imatinib that revolutionized treatment of CML also showcased the widest disparities in CML (Jorge Cortes, Georgia Cancer Center, Augusta GA, personal communication, 3 October 2023).[2] In other words, in the absence of active myeloma therapies in the period between the 1970s and the 1990s (the era of chemotherapeutics), no individual group benefited more than the other. The median overall survival (OS) for patients with myeloma was close to 3 years.[3] Starting in the early 2000s (the era of molecular therapeutics), using immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), and transplant as effective antimyeloma strategies, there is visible evidence of disparities, when the median OS was beyond 10 years.[4,5] Now, in the last 5 years (the era of immunotherapeutics), in which the patients could live to or beyond their life expectancy, the divide has been expected to broaden as the clinical efficacy has improved drastically, and fewer groups of patients potentially will have better access to these coveted immunotherapeutic agents than the others.

In the recent 2 years, 5 effective immunotherapies have been approved for relapsed refractory multiple myeloma (RRMM). Not surprisingly, altogether, these are more regulatory approvals for RRMM in this short span compared with those in the previous 5 years. Not only that, but these immunotherapeutic approvals also provided a new benchmark for clinical efficacy. The chimeric antigen receptor T-cell therapies (CARTs) targeting B-cell maturation antigen (BCMA), idecabtagene vicleucel (ide-cel)[6] and ciltacabtagene autoleucel (cilta-cel);[7] the bispecific antibodies (BsABs) targeting BCMA/CD3, teclistimab-cqyv (teclistimab)[8] and elranatamab-bcmm (elranatamab);[9] and G protein–coupled receptor class C group 5 member D (GPRC5D)/CD3, talquetmab-tgvs (talquetamab)[10] reported the highest single agent response rates among patients with RRMM than ever before in the history of myeloma drug development. Clearly, ide-cel was the vanguard CART construct of this newer era of immunotherapeutic revolution. All 5 agents are currently approved for patients with RRMM who had received 4 prior lines of therapy including an IMiD, PI, and a CD38 monoclonal antibody (mAB). In this context, whether all patients with myeloma have access to these highly restricted living drugs with limited supply, and whether all patients experience similar clinical benefits from these newer immunotherapeutic agents is an unanswered question.

Peres et al presented the results of the pooled data from 11 participating institutions comprising 207 patients with RRMM who have received ide-cel as the standard-of-care therapy. Interestingly, 28% of the patients belonged to racial and ethnic minorities. The outcomes of interest in this study are the differences in the incidence of treatment related adverse events (TRAEs) as well as differences in therapeutic responses to ide-cel as measured by overall response rate (ORR), progression free survival (PFS) and OS. The authors reported ORR to be lower among Hispanic patients than among non-Hispanic White (NHW) and non-Hispanic Black (NHB) patients but report no PFS or OS differences favoring any specific group. Why are these results important? Multiple myeloma (MM) continues to be a leading disease entangled with health care disparities across the spectrum of disease care. The clinical incidence and outcomes for MM are disparate in patients belonging to certain ethnic groups such as NHB and Hispanic for reasons yet to be fully elucidated. We would address the issues in a 3-pronged approach: epidemiological, biological, and access to care.

From an epidemiological aspect, the incidence rates of MM for NHB are almost twice than that for NHW patients (15.9 vs 7.5 cases per 100 000 individuals, respectively), and the mortality rates follow similar trend (5.6 vs 2.4 deaths per 100 000 individuals, respectively).[5,11] MM tends to occur at a relatively younger age in both NHB and Hispanic individuals.[12] The Hispanic patients are significantly younger than NHB or NHW patients. Patient selection for offering ide-cel to younger patients with good organ reserve to withstand a cytokine release syndrome (CRS) while becoming acquainted with the new construct in the standard of care (SOC) setting possibly led to the inclusion of younger patients in this real-world cohort. The 11 participating institutions in the US MM immunotherapy consortium were located at regions with high Hispanic and NHB patient densities, and the treating physicians have an implicit consciousness to include minorities in their clinical trials and the SOC offerings. This experience possibly should increase the confidence for other providers that ide-cel could be safely given without increased toxicities and without any new unanticipated safety signals. As the CARTs are incorporated into earlier lines of therapy,[13,14] the question of inclusivity becomes increasingly important, and this study provides the necessary guidance.

From a biological standpoint, NHB have lower rates of genetic markers of poor prognosis, which has been reported in most prior studies. Failure to demonstrate improved outcomes despite more favorable mutational profile of myeloma in NHB with less aggressive disease is hypothesized to be driven by differences in biology, pharmacokinetics, and possible race-based differences in treatment efficacy. More importantly, in the current era of immunotherapeutics, it has been well postulated that the host immune function may play a role in tumor responses to immunotherapy. Responses to myeloma immunotherapeutics such as CD38 mABs, BCMA targeting BsABs and even CARTs potentially may be augmented in NHB patients because of their mechanisms of action involving the innate immune pathways.[8,9] There is at present no reliable comparative data that evaluates innate immunity, cytokine, and myeloma responses between NHB and NHW patients with MM. In the post hoc analysis of GRIFFIN study, we compared the efficacy of the addition of daratumumab to lenalidomide, bortezomib, and dexamethasone (D-RVd) vs RVd between NHB and NHW patients. It is interesting that the responses to RVd for both NHB and NHW patients were comparable, but the addition of daratumumab significantly benefited NHB patients more than NHW patients, supporting our hypothesis, stringent complete remission (sCR, primary end point) for D-RVd vs RVd among NHB patients was 71% vs 33%, respectively, and among NHW patients was 43% vs 34%, respectively.[15] In this study, compared with Hispanic and NHW patients, NHB patients had statistically significant higher baseline values of C-reactive protein and ferritin but lower level of serum albumin. Information about obesity or body mass index would have been helpful in this context but was not available. NHB patients were more likely to develop any grade CRS, but there were no differences in higher-grade (≥grade 3) CRS or the use of steroids or tocilizumab. This may be associated with elevated proinflammatory state among NHB patients before ide-cel infusion, because studies show that patients with a baseline proinflammatory response are more likely to develop CRS, but this did not extend to a higher-grade CRS. NHB patients were reported to have a longer median length of stay (LOS) than Hispanic or NHW patients, but all participating institutions did not have a homogenous practice of admitting CART-treated patients for a uniform LOS, confounding these results. It is interesting that Hispanic patients had a lesser ORR than NHB or NHW patients, but on the multivariable analyses, race and ethnicity were not associated with deeper response or PFS or OS. Nevertheless, no higher-grade toxicities or new safety signals were reported in this real-world study, supporting the use of ide-cel in NHB and Hispanic patients.

From an access perspective, the time from diagnosis to initiation of treatment in NHB and Hispanics is much longer compared to NHW patients. Besides, they are less likely to receive the "Triple threat therapies for myeloma" that have clearly changed the myeloma therapeutic landscape: triplets, transplant, and CART.[16] The myeloma disparities are further complicated by underrepresentation of NHB and Hispanic patients in the clinical trials leading to the approval of effective myeloma drugs in the United States. In a recent FDA publication of the 19 global MM trials including 10 157 patients between 2006 and 2019, NHB patients accounted for 4% of the study population, a significant underrepresentation compared to the 20% of NHB in the pooled myeloma population.[17] Interestingly, when included the NHB patients did better or the same as other patients.[17] This extended to the CART trials as well. The recently reported KarMMa-3 trial reported 7% as NHB, and Hispanic ethnicity was not reported.[13] The complex interplay of the described factors could possibly explain the absence of large gains in survival improvement among NHB and Hispanic patients compared with NHW patients despite major therapeutic advances. Fortunately, the advocacy efforts for policy change led by Nicole Gormley and Kenneth Anderson, which included all stakeholders including regulatory agencies Food and Drug Administration (FDA), National Cancer Institute, academic clinicians, biotech industry, pharmaceutical industry, and patient representatives have led to fruitful outcomes. Three key-take home points that emerged from the FDA–American Association of Cancer Research workshop to examine underrepresentation of NHB in MM clinical trials include (1) broad support to assure prospective plans for enrollment and achievement of accrual goals for NHB, (2) collaborative effort to reform clinical trial design, end points, and inclusion/exclusion criteria to reflect real-world experience, and (3) identify a common set of minimal data elements and harmonize line-of-treatment definitions and real-world end points to improve the utility of real-world data sources and allow for easier pooling and comparing of data.[18] As a consequence, the 2023 Consolidated Appropriations Act requires clinical trial sponsors to submit Diversity Action Plans to the FDA as part of their study protocols; it is humbling to see the new clinical trial designs concentrating on focused accrual of minorities reflecting the demographic of myeloma.[19] In the current study, the authors included 207 patients with RRMM (of 235 patients intended to treat, 215 patients received planned ide-cel, an attrition rate of <10%, a much lower number than reported from the studies that led to the approval of the CART constructs, suggesting that adequate patient selection was not affected by race or ethnicity.

In summary, the baseline characteristics did not have a significant impact on the higher-grade TRAEs in the NHB or Hispanic patients compared with NHW patients. It is encouraging the SOC cohort with real-world practices replicated the study outcomes of the clinical trials leading to their approval, highlighting the importance

of equitable distribution of the available slots to the minority population. In conclusion, it is exciting to see that the imatinib story is not repeated, and the current study proves that minorities do obtain the clinical benefit. The study also negates the hypothesis of broadening the divide of disparities with effective therapies, because access of minorities to the new life-saving myeloma immunotherapeutics will allow for leveling the playing field and shrinking of the disparities in access and patient outcome.

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References

1. Peres LC, Oswald LB, Dillard CM, et al. Racial and ethnic differences in clinical outcomes among patients with multiple myeloma treated with CAR T-cell therapy. *Blood Adv*. 2024;8(1):251-259.
2. Ailawadhi S, Yang D, Cozen W, Chanan-Khan. Ethnic disparities and their association with outcomes in chronic myeloid leukemia. *Blood*. 2013;122(21):2917.
3. Turesson I, Velez R, Kristinsson SY, Landgren. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. *J Clin Oncol*. 2010;28(5):830-834.
4. Joseph NS, Kaufman JL, Dhodapkar MV, et al. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma. *J Clin Oncol*. 2020;38(17):1928-1937.
5. Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. *Blood*. 2010;116(25):5501-5506.
6. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med*. 2021;384(8):705-716.
7. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. 2021;398(10297):314-324.
8. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med*. 2022;387(6):495-505.
9. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat Med*. 2023;29(9):2259-2267.
10. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med*. 2022;387(24):2232-2244.
11. DeSantis CE, Miller KD, Goding Sauer A, Jemal, Siegel. Cancer statistics for African Americans, 2019. *CA Cancer J Clin*. 2019;69(3):211-233.
12. Landgren O, Gridley G, Turesson I, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood*. 2006;107(3):904-906.
13. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. *N Engl J Med*. 2023;388(11):1002-1014.
14. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med*. 2023;389(4):335-347.
15. Nooka AK, Kaufman JL, Rodriguez C, et al. Daratumumab plus lenalidomide/bortezomib/dexamethasone in Black patients with transplant-eligible newly diagnosed multiple myeloma in GRIFFIN. *Blood Cancer J*. 2022;12(4):63.
16. Fiala MA, Wildes TM. Racial disparities in treatment use for multiple myeloma. *Cancer*. 2017;123(9):1590-1596.
17. Kanapuru B, Fernandes LL, Fashoyin-Aje LA, et al. Analysis of racial and ethnic disparities in multiple myeloma US FDA drug approval trials. *Blood Adv*. 2022;6(6):1684-1691.
18. Gormley N, Fashoyin-Aje L, Locke T, et al. Recommendations on eliminating racial disparities in multiple myeloma therapies: a step toward achieving equity in healthcare. *Blood Cancer Discov*. 2021;2(2):119-124.
19. Mateos M-V, Bahlis NJ, Costa LJ, et al. MajesTEC-3: randomized, phase 3 study of teclistamab plus daratumumab versus investigator's choice of daratumumab, pomalidomide, and dexamethasone or daratumumab, bortezomib, and dexamethasone in patients with relapsed/refractory multiple myeloma. *Jco*. 2022;40(suppl 16):TPS8072.

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