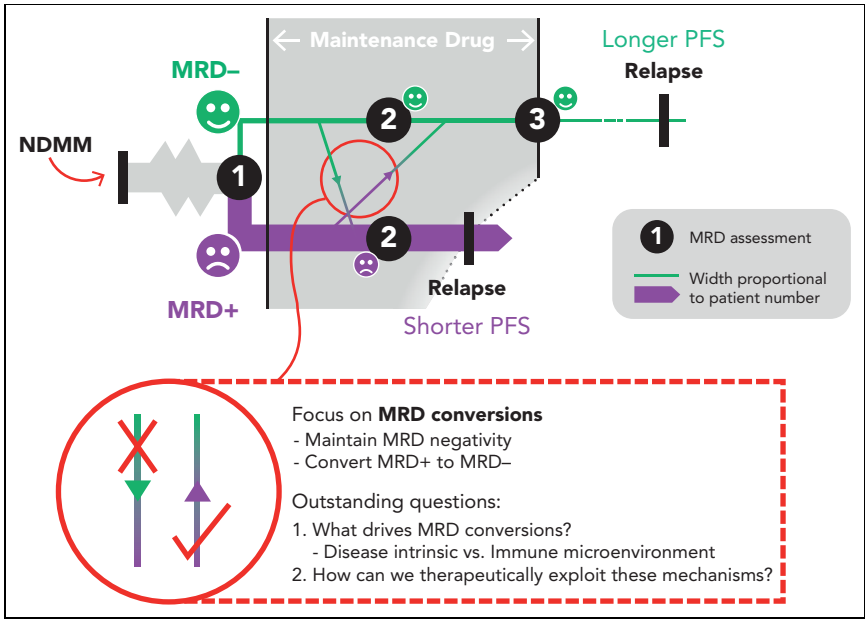

A model for MRD monitoring. MRD status is assessed following induction/consolidation. The key aim of the maintenance phase is to maximize the chance of MRD negativity to lengthen PFS. NDMM, newly-diagnosed MM.

This work from Paiva et al inspires many questions that should be addressed in prospective studies. Can we shorten maintenance duration in patients who have sustained MRD negativity, thus sparing them the burden of ongoing medication? Equally, should we escalate therapy for MRD$^+$ status to convert to MRD$^-$? Can blood-based MRD assays facilitate earlier detection of change in MRD? How do these marrow and blood MRD dynamics correlate with imaging? Can we predict which patients will convert from MRD$^-$ to MRD$^+$?

This work and other studies also raise new questions in the biology of MRD dynamics and the role of disease-intrinsic factors and MM-immune interactions in the microenvironment. With increasing treatment options made available for MM, dissecting mechanisms of MRD switch and persistent MRD positivity will inform the rational design of treatment strategies that will hopefully improve patient outcomes in MM.

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REFERENCES

1. Paiva B, Manrique I, Dimopoulos MA, et al. MRD dynamics during maintenance for improved prognostication of 1280 patients with myeloma in the TOURMALINE-MM3 and -MM4 trials. *Blood*. 2023;141(6):579-591.
2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328-e346.
3. Giles HV, Wechalekar A, Pratt G. The potential role of mass spectrometry for the identification and monitoring of patients with plasma cell disorders: where are we now and which questions remain unanswered? *Br J Haematol*. 2022;198(4):641-653.
4. Tute RMd, Pawlyn C, Cairns DA, et al. Minimal residual disease after autologous stem-cell transplant for patients with myeloma: prognostic significance and the impact of lenalidomide maintenance and molecular risk. *J Clin Oncol*. 2022;40(25):2889-2900.
5. San-Miguel J, Avet-Loiseau H, Paiva B, et al. Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE. *Blood*. 2022;139(4):492-501.
6. Munshi NC, Avet-Loiseau H, Anderson KC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv*. 2020;4(23):5988-5999.
7. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2019;393(10168):253-264.
8. Dimopoulos MA, Špička I, Quach H, et al. Ixazomib as postinduction maintenance for patients with newly diagnosed multiple myeloma not undergoing autologous stem cell transplantation: the phase III TOURMALINE-MM4 trial. *J Clin Oncol*. 2020;38(34):4030-4041.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Newman et al, page 609

Access offsets poverty in quest for CAR T cells

Rayne H. Rouce[1] **and Eneida Nemecek**[2] | [1]Baylor College of Medicine and [2]Oregon Health and Science University

In this issue of *Blood*, Newman et al[1] examined the influence of household poverty and neighborhood on access and outcomes of young patients treated with commercial (tisagenlecleucel) or investigational CD19 chimeric antigen receptor (CAR) T cells for relapsed/refractory B-acute lymphoblastic leukemia (B-ALL)/lymphoma. As a proxy for poverty, investigators used Medicaid-only insurance and the Childhood Opportunity Index, a multidimensional quality measure of US neighborhood metrics with scores across 3 domains of opportunity (education, health/environment, and social/economic).[1] On the basis of nearly a decade of data from 206 patients (aged 1-29 years) treated at Children's Hospital of Philadelphia, the authors

found that patients unexposed to household poverty were more likely to receive CAR T-cell therapy despite higher disease burden. As high disease burden is an independent prognosticator of worse outcome, it is notable that overall survival outcomes appeared the same between groups. Furthermore, despite similar rates of complete remission (CR), patients from low-opportunity neighborhoods experienced increased hazard of relapse but were less likely to proceed to salvage therapies.[1]

Five years after US Food and Drug Administration approval of the first CAR T-cell targeting B-ALL (tisagenlecleucel), research collaboratives and real-world consortia have identified predictors of toxicity, response, and remission following tisagenlecleucel beyond those detected in clinical trials.[2,3] This timely article explores the impact of social determinants of health (SDOH) on outcomes. Nevertheless, it is tricky to extrapolate the conclusions of this study to broader populations treated in the real world, given the robust resources available to the cohort of patients evaluated in this report. These patients were predominantly treated on clinical trials with closely regulated follow-up that may have protected against the adverse impact of household poverty or neighborhood resources. In addition, housing and travel support provided directly by the institution likely protected from the true impact of household or neighborhood poverty, while also protecting against the (often unconscious) referral bias that oncologists face when making clinical decisions about patients with limited resources. Despite the wide catchment area representing a broad referral base from 38 states, Black/African American patients were underrepresented, comprising only 7.28%, similar to other large studies of CAR T cells targeting hematologic malignancies.[4,5] In contrast to recent real-world reports showing worse outcomes of African Americans treated with tisagenlecleucel,[6] in this study, Black/African American and Hispanic/Latino patients had similarly high rates of CR. These findings reflect recent adult data in patients treated with axicabtagene ciloleucel,[7] highlighting the outsized contribution of delayed referral and SDOH to worse outcomes in Black/African Americans treated with CAR-T.

As the authors note, use of insurance at time of CAR T-cell infusion as a proxy for household poverty can lead to misclassification, as patients may lose private insurance or switch to public insurance during their leukemia journey. Classification of children from higher-income homes as publicly insured can lead to an unrealistically optimistic picture of how poverty and other SDOH impact patients seeking CAR-T therapy. The authors appropriately underscore the need for future multi-institutional studies that examine the impact of more granular area–based and household-level exposures and specifically explore family-reported poverty to bypass the limitations of proxied SDOH. Notably, most patients in this report had private insurance and were treated on clinical trials, raising the question of how results would differ in populations who are largely publicly insured. Delayed or denied insurance approval is another determinant of outcome, and investigating those who do and do not go on to receive this therapy, whether commercially or on a clinical trial, merits elucidation in a similar study.

Every aspect of CAR T-cell therapy challenges access for vulnerable populations: treatment must be given at a specialized center of excellence, and patients are required to remain within that vicinity for at least 1 month; there is a limited window of opportunity for referral that may exacerbate existing biases; therapy is expensive, with resource-intensive logistics; and insurance challenges remain despite existing guidelines. In the clinical trial setting, even more barriers for poverty-exposed and racial/ethnic minorities can contribute to underrepresentation, especially for complex, personalized therapies, such as CAR T cells. Obtaining insurance coverage for routine costs related to the trial can be difficult, especially for patients seeking treatment outside their coverage network, not to mention the limited referral center resources to address logistical challenges not covered by patient assistance programs.

What would Hippocrates think? Are we doing no harm by creating targeted therapeutic options intended for all, but treating patients within health care systems that unintentionally systematically exclude the most vulnerable? Perhaps this point is made most saliently by recognizing the population *not* represented within this study: patients who were not referred, excluded, or unable to travel for CAR T cells. We routinely consider these patients as we work to address the clinical obstacles that bar them from potentially life-saving therapies, while paying less attention to sociodemographic barriers. By definition, patients who "made it" to a clinical trial at a large institution despite having public insurance, living in a lower-resource neighborhood, or having household poverty are unlikely to truly represent the most vulnerable patients.

This report supports the hypothesis that predictors of response to CD19 CAR T cells may rely as much on access to treatment as on any underlying disease determinant. When patients with household poverty do receive treatment with CAR T cells, whether commercial or on a clinical trial, they have similar outcomes to patients without household poverty. As with pre-CAR T-cell disease burden and antigen load, neighborhood poverty level is not easily modifiable. However, this article highlights the importance of a robust and accessible financial infrastructure equipped to offset costs and diminish logistical burdens in providing equitable care,[8] leading to equitable outcomes regardless of socioeconomic status and neighborhood opportunity.

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REFERENCES

1. Newman H, Li Y, Liu H, et al. Impact of poverty and neighborhood opportunity on outcomes for children treated with CD19-directed CAR T-cell therapy. *Blood*. 2023;141(6):609-619.

2. Pasquini MC, Hu ZH, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma [published corrections appear in *Blood Adv*. 2021;5(4):1136 and *Blood Adv*. 2022;6(6):1731]. *Blood Adv*. 2020;4(21):5414-5424.

3. Schultz LM, Baggott C, Prabhu S, et al. Disease burden affects outcomes in pediatric and young adult B-cell lymphoblastic leukemia after commercial tisagenlecleucel: a pediatric real-world chimeric antigen receptor consortium report. *J Clin Oncol*. 2022;40(9):945-955.

4. Ahmed N, Shahzad M, Shippey E, et al. Socioeconomic and racial disparity in chimeric antigen receptor T cell therapy access. *Transplantation and Cellular Therapy*. 2022;28(7):358-364.

5. Al Hadidi S, Schinke C, Thanendrarajan S, et al. Enrollment of Black participants in pivotal clinical trials supporting US Food and Drug Administration approval of chimeric antigen receptor-T cell therapy for hematological malignant neoplasms. *JAMA Netw Open*. 2022;5(4):e228161.

6. Baggott C, Kunicki M, Prabhu S, et al. Inferior outcomes among black patients with childhood acute lymphoblastic leukemia following tisagenlecleucel. The 2021 TCT Meetings Digital Experience 2021; Abstract LBA7. 2022;27(3_suppl):S1-S488.

7. Locke F, Siddiqi T, Jacobson C, et al. Real-world outcomes of axicabtagene ciloleucel (Axi-cel) for the treatment of large B-cell lymphoma (LBCL) by race and ethnicity. *J Clin Oncol*. 2022;40(16_suppl):7571.

8. Auletta JJ, Sandmaier BM, Jensen E, et al; on behalf of Additional Contributing ACCESS Workshop Team Members. The ASTCT-NMDP ACCESS Initiative: a collaboration to address and sustain equal outcomes for all across the hematopoietic cell transplantation and cellular therapy ecosystem. *Transplant Cell Ther*. 2022;28(12):802-809.

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LYMPHOID NEOPLASIA

Comment on Ansari-Pour et al, page 620

The genome of IMiD-refractory myeloma

Alessandro Laganà | Icahn School of Medicine at Mount Sinai

In this issue of *Blood*, Ansari-Pour et al[1] present findings from their analysis on the largest whole-genome sequencing data set of relapsed and refractory multiple myeloma (rrMM), which comprised 418 tumor samples from 386 patients. The data were retrieved from 6 clinical trials that included patients refractory to lenalidomide and/or pomalidomide, which are 2 immunomodulatory imide drugs (IMiDs) that are commonly used therapeutics for newly diagnosed and relapsed patients with multiple myeloma (MM), respectively.

MM is characterized by remarkable inter- and intrapatient genomic heterogeneity.[2,3] Recent analyses of large multiomics data from newly diagnosed patients with MM revealed a complex genomic landscape and the existence of multiple genetic subtypes with distinct and well-defined sets of co-occurring genetic alterations and transcriptomic features, which could stratify patients according to their risk of progression after first-line therapy and overall survival.[4,5] Broadly, chromosomal translocations involving the immunoglobulin locus on chromosome 14 and oncogenes such as NSD2, CCND1, and MAF and hyperdiploidy, a genetic abnormality defined by the presence of 3 copies of at least 2 odd-numbered chromosomes, are often the main initiating events. Additional recurrent alterations, including both single nucleotide variants and copy number changes, can then associate with translocations and hyperdiploidy following different patterns of co-occurrence and mutual exclusivity, further contributing to increased genomic complexity. Longitudinal studies in patients with MM sequenced at diagnosis and subsequent relapses have revealed a diverse landscape of clonal and subclonal aberrations, enabling the identification of initiating driver events and alterations arising in later disease phases that drive relapse.[5-7]

Although recent studies have explored disease evolution in a small number of longitudinally profiled patients, the novel study by Ansari-Pour et al is the first to examine whole-genome data from a large population of patients refractory to a specific category of drugs (IMiDs) and compare the findings with a large data set from newly diagnosed, although unrelated, patients to identify the key features of rrMM. The high coverage breadth and uniformity of whole-genome sequencing allow the identification of broad events in MM tumors, such as whole-genome duplication and chromosomal translocations, which cannot be accurately detected using more targeted approaches, including whole-exome sequencing.

The major findings of this study include the discovery of novel candidate subclonal driver mutations in oncogenes and tumor suppressors, including the epigenetic regulator EZH2 and transcription coactivator MAML3, as well as noncoding somatic variants, such as the TP53 binding protein TP53BP1, undergoing significant clonal expansion or increased frequency in patients with rrMM than in newly diagnosed MM (ndMM). Some high-risk copy number alterations, such as 1q gain and 17p loss of heterozygosity, were not only enriched in patients with rrMM compared with patients with ndMM but were also significantly detected as co-occurring in some patients with rrMM, so called *double-hit* events, and showed an increasing trend in progressive IMiD resistance to lenalidomide and pomalidomide. Biallelic events, that is alterations affecting both alleles of a gene, were identified in driver genes at a higher prevalence in rrMM than in ndMM, with some events seemingly specific to rrMM, such as those involving CDKN2A and CREBBP, and biallelic inactivation of TP53, a high-risk abnormality associated with aggressive disease, whose frequency was almost twofold greater in the relapsed cohort than in the ndMM cohort. Furthermore, mutational signatures attributed to APOBEC (SBS2/SBS13) and defective mismatch repair (SBS12) were identified at increased activity from diagnosed to refractory stages, the latter not previously described in MM.[8] Significant elevation of mutational burden, driven by more than a twofold increase in single nucleotide variants, was observed in patients with a higher defective mismatch repair signature activity. This suggests a possible association with subclones that expand under therapeutic