COMMENTARY

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TO THE EDITOR:

TP53-mutant myelodysplastic syndrome and acute myeloid leukemia: the black hole of hematology

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A recent article in *Blood Advances* by Short et al[1] entitled "Prognostic and therapeutic impacts of mutant *TP53* variant allelic frequency in newly diagnosed acute myeloid leukemia," had very interesting conclusions that we are eager to interpret alongside our own published data on a similar topic.[2] Herein, we will summarize the fundamental problem with *TP53*-mutant myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), summarize the data by Short et al[1] and our own institutional data, and postulate a call to action to help motivate groups to collaborate on the issue of *TP53*-mutant MDS and AML.

It has been well-known for several years that *TP53* aberrations are associated with exceptionally adverse outcomes for patients with MDS or AML, and there are no US Food and Drug Administration–approved targeted therapies for the subset of patients with this mutation. The field of *TP53*-mutant myeloid neoplasms is arguably the largest black hole in hematologic malignancies. In late 2020, the leading pharmacologic compound for treatment was eprenatapopt (APR-246), but this compound missed the primary end point in phase 3 data, leaving us with no precision approaches for *TP53*-aberrant myeloid neoplasms. Transplantation is a consideration for curative-intent therapy, but because data on transplantation outcomes are a mandatory reporting requirement for the Center for International Blood and Marrow Transplant Research (CIBMTR), many centers might choose not to offer transplantation to this exceptionally high-risk subset of patients. Instead, a management plan is often designed with palliative intent, and it frequently includes temporizing rather than definitive interventions. Inadequate long-term disease control is the fundamental problem of *TP53*-mutant MDS and AML, and it warrants additional investigation.

Formal assessment of the value of transplantation has not been performed in larger cohorts of patients with *TP53*-mutant MDS or AML, and the field does not have longitudinal data. Clearly, there is an unmet need for a precision medicine-based approach to care for this subset of patients who have this genomic aberrance. To date, several single-center studies (including published studies by MD Anderson Cancer Center, H. Lee Moffitt Cancer Center & Research Institute, University of Massachusetts, and Yale University) have shown overall survival (OS) benefits of transplantation for patients with *TP53*-mutant myeloid neoplasms, but collaborative prospective large-scale efforts have been scant.[1-4]

Short et al[1] reported a median OS of 4 to 7 months for patients with *TP53*-mutant MDS or AML. In our experience of 40 patients with *TP53*-aberrant MDS or AML, the median OS was 280 days.[2] This is slightly higher than the median OS range reported by Short et al. The Short et al experience involved transplantation in 20 (9.9%) of 202 patients. We have provided transplantation for 11 (27.5%) of 40 patients with *TP53*-mutant MDS or AML. Median OS for patients who received a transplant in our cohort (14.7 months) was similar to that of the patients in the Short et al[1] study (17.6 months), and clinical benefit was especially seen with the use of hypomethylating agents (HMAs) as a bridge to transplantation. We acknowledge that the perceived benefit of transplantation is subject to selection bias: patients who have favorable clinical response and performance status are more likely to be selected for transplantation.

We sought to understand the basis for improvement in OS with transplantation, so we modeled clonal dynamics by annotating copy number variation analysis against *TP53* variant allele frequency (VAF) to infer clonality.[2] The *TP53*-mutant clones persisted during morphologic remission and fueled relapse (with

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heterogeneous descendant clones), suggesting that the *TP53*-mutant clones rest at the pinnacle of the diseased hematopoietic hierarchy. This stem cell concept may explain why cytotoxic chemotherapy alone does not lead to durable remissions: transplantation is usually necessary to eliminate genomic evidence of measurable residual disease (MRD).

Short et al[1] provided important data regarding the impact of mutant *TP53* VAF on clinical outcomes. They observed that VAF >40% is independently associated with higher risk for relapse and worse relapse-free survival. Treatment with (less toxic) HMAs may be preferable. Conversely, patients with VAF ≤40% may benefit more from cytarabine-based cytotoxic chemotherapy compared with HMAs. Some technical challenges to analyzing VAF data include thorough adjustments for copy number variation. These technical concerns merit investigation in multicenter studies, and conclusions about VAF may best be made after measurement of deletion and loss of heterozygosity events (single nucleotide polymorphism arrays or low-coverage whole genome sequencing) with subsequent copy number adjustment of the VAF. For future studies, a deeper dive into biallelic vs monoallelic variants could be important when making conclusions about VAF.

Previous studies have shown that HMA therapy has high efficacy against *TP53*-mutant myeloid neoplasms.[5] One possible reason for the benefit of HMA therapy as a bridge to transplantation is that HMAs confer less physiologic stress compared with cytarabine-based chemotherapy before starting transplantation. Cytotoxic chemotherapy may worsen a patient's performance status and functional reserve, which can lead to high nonrelapse mortality in patients after transplantation. HMAs may cause less injury to the mucosal barrier, and because patients with *TP53* mutations may harbor inherent immune defects, HMAs may pose less risk for infection.[6]

The high-stake question is whether or not patients with MDS or AML who harbor *TP53* mutations should proceed with transplantation as definitive therapy. We understand that our experience is perhaps contrary to the management paradigm offered by many transplantation centers. We have shown a low durability of remission, especially for patients with high mutant *TP53* VAF, so we favor HMA-based therapy (with or without venetoclax) with the goal of achieving a first complete remission and then proceeding to transplantation as soon as feasible to avoid the risk of progressive disease or frank relapse, which is seemingly inevitable without transplantation.[2] Although our study shows that there might be a subset of patients with *TP53*-mutant neoplasms who derive benefit from transplantation, we acknowledge our limited sample size. The current deficiencies in this arena that should be addressed include insufficient power for analysis from single-institution data and limited long-term data on durability of remission and other outcomes after transplantation. Further studies are required to corroborate the benefit of transplantation such that clinicians can advocate for this curative-intent therapy in an evidence-based manner. To this end, we are currently proposing a large-scale study within the CIBMTR on this topic.

Select subsets of patients with *TP53*-mutant MDS or AML may preferentially benefit from transplantation. Earlier this year in *Blood Advances*, Hunter et al[3] showed that *TP53* mutational clearance before transplantation led to superior OS; at our institution, only 1 patient of 40 achieved it.[2] Additional prospective validation is needed. Clinical trials of first-line (before transplantation) HMA-based treatments are needed, and MRD-adapted and maintenance strategies in the post-transplantation setting are also critical, given that *TP53* clones are the major drivers of relapse.[2]

As longevity improves and the population ages, the incidence of *TP53* mutations (and/or complex karyotypes) will likely increase, because mutational burden and genomic instability in myeloid malignancies is a direct function of the aging hematopoietic compartment. The failure of APR-246 was a disappointment to us. We will await data from clinical trials regarding the nutlin analogs (MDM2 inhibitors), magrolimab (anti-CD47 antibody), and sabatolimab (TIM-3 antibody), many of which are in the pharmacologic pipeline for treating *TP53*-mutant myeloid neoplasms as of February 2022. However, these novel therapies may not eradicate the stem cell fraction: consolidative transplantation with curative intent offers the highest chance of MRD negativity. Better treatment options may not be far away for this patient group with clearly unmet need who deserve improved therapeutics. A call to action is warranted for a more robust multicenter meta-analysis and collaboration for this genetically defined high-risk patient population to better design future prospective studies.

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