patients with refractory normoblastic anemia that Bowman described and named 60 years ago.[4] It represents a prototype of the functional studies that should be conducted in splicing factor mutant-neoplasms to understand how abnormal splicing results in abnormal cell differentiation and maturation. Ideally, these studies should be aimed not only at deciphering disease pathogenesis but also at developing novel effective treatments.

SF3B1-mutant MDS is a distinct disease subtype, mainly characterized by ineffective erythropoiesis and a relatively indolent clinical course.[10] The major factor in the pathogenesis of anemia in *SF3B1*-mutant MDS is represented by the apoptosis of late-stage erythroblasts, that is, polychromatic and orthochromatic erythroblasts. As these erythroid precursors are also characterized by ring sideroblast formation, a causal relationship between mitochondrial iron overload and increased propensity to apoptosis is likely. However, this relationship needs to be verified experimentally, and this might be the next task of the Doulatov laboratory in Seattle. Patients with MDS-RS may respond to luspatercept with the abolition of their transfusion requirement, but how this compound targets ineffective erythropoiesis in this MDS subtype has never been definitely documented. Verifying how luspatercept improves red cell production in MDS-RS is therefore important. However, the approach described by Clough et al might also lead to the identification of new targets and the discovery of novel drugs.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Clough CA, Pangallo J, Sarchi M, et al. Coordinated missplicing of TMEM14C and ABCB7 causes ring sideroblast formation in SF3B1-mutant myelodysplastic syndrome. *Blood.* 2022;139(13):2038-2049.
2. Kaplan E, Zuelzer WW, Mouriquand C. Sideroblasts: a study of stainable nonhemoglobin iron in marrow normoblasts. *Blood.* 1954;9(3):203-213.
3. Bessis MC, Breton-Gorius J. Iron metabolism in the bone marrow as seen by electron microscopy: a critical review. *Blood.* 1962;19(6):635-663.
4. Bowman WD Jr. Abnormal ("ringed") sideroblasts in various hematologic and non-hematologic disorders. *Blood.* 1961; 18(6):662-671.
5. Cazzola M, Invernizzi R, Bergamaschi G, et al. Mitochondrial ferritin expression in erythroid cells from patients with sideroblastic anemia. *Blood.* 2003;101(5): 1996-2000.
6. Papaemmanuil E, Cazzola M, Boultwood J, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N Engl J Med.* 2011;365(15):1384-1395.
7. Malcovati L, Papaemmanuil E, Bowen DT, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium and of the Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. *Blood.* 2011;118(24):6239-6246.
8. Shiozawa Y, Malcovati L, Gallì A, et al. Aberrant splicing and defective mRNA production induced by somatic spliceosome mutations in myelodysplasia. *Nat Commun.* 2018;9(1):3649.
9. Cazzola M. Myelodysplastic syndromes. *N Engl J Med.* 2020;383(14):1358-1374.
10. Malcovati L, Stevenson K, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS [published correction appears in *Blood.* 2021;137(21):3003]. *Blood.* 2020;136(2):157-170.

DOI 10.1182/blood.2021014923

TRANSPLANTATION

Comment on Albert et al, page 2066

Towards a standard of care in transplant for WAS

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In this issue of *Blood*, Albert et al[1] continue the tradition established in 1968 of punctuating the timeline of hematopoietic transplant with important advances in the treatment of this rare nonmalignant disorder. In their article, they demonstrate that, even in the absence of prospective trials, uniform adoption of a limited number of regimens combined with the use of novel composite end points allows a meaningful analysis that establishes a standard of care for these boys.

Wiskott-Aldrich syndrome (WAS) was first identified in 1936 and affects just 1 in ~100 000 males born worldwide, causing bleeding, immune deficiency, and eczema, in addition to a predisposition to autoimmunity and malignancy. The identification of the *WAS* gene in 1994 quickly led to the realization that a range of disease severity was related to mutations in the *WAS* gene and that disease severity could be predicted by protein expression.[2] For some boys with WAS, prognosis based on phenotype can be made at the time of diagnosis. Although advances in diagnosis and supportive care have improved the outcome for boys not undergoing definitive therapy, especially those with less severe disease, patients with severe disease continue to have a poor chance of surviving into the third decade.[2] Stem cell transplantation has long been studied as a definitive therapy for WAS. One of the first allogeneic hematopoietic stem cell transplants (HSCTs) was performed in 1968 in a boy with WAS.[3] This child had only partial correction of disease. Subsequent studies showed that myeloablation, initially with total body irradiation[4] and shortly thereafter with busulfan,[5] was associated with durable and complete chimerism and improved outcomes. Correction of the WAS phenotype was one of the first targets of ex vivo gene therapy; however, unfortunately, it was also one of the first examples of the potential genotoxicity of γ-retroviral vector therapies.[6]

Cooperative groups have performed retrospective analyses for this rare genetic disorder, documenting serial improvements in transplant outcomes, especially those using alternative

donors. These groups have demonstrated the power of cooperation and pooling of results in identifying modifiable variables associated with superior results in boys transplanted at a younger age[7] who achieve complete donor chimerism.[8] These findings have led to practice changes in the age at which boys are transplanted and heightened attention to complete donor chimerism as an outcome of interest associated with myeloablative or busulfan containing regimens.[9] The study of Albert et al demonstrates several important principles in a contemporary cohort.

In 2005, the European Bone Marrow Transplant Inborn Errors Working Party made recommendations for the use of a limited number of transplant regimens. For transplant for WAS, they recommended 2 regimens: busulfan and fludarabine or treosulfan and fludarabine. Depending on the specifics of the patient, donor, and center, allowance was made for the addition of thiotepa and/or serotherapy to these regimens. As a result, 197 of 347 boys received one or the other of these conditioning regimens and have complete data available for analysis such that this group is now in the position to analyze a large group of boys transplanted between 2006 and 2017. As the largest retrospective study of HSCT outcomes for patients with WAS, this study shows excellent overall survival (OS) and event-free survival (EFS), regardless of conditioning regimen, donor type, and stem cell source. Older age at HSCT remains a significant risk factor for decreased OS and EFS, as found in previous studies.

In addition, the authors have extended their analysis beyond simple OS and EFS to include analyses of end points including chronic graft-versus-host disease (GVHD)-free, relapse-free survival and a modified GVHD-free, relapse-free survival (GRFS) that captures events including graft failure, death, grade III to IV acute GVHD, extensive/moderate/severe chronic GVHD, or any secondary procedure (conditioned or unconditioned second HSCT, donor lymphocyte infusion, or splenectomy). Composite end points have relatively recently been introduced and have limitations[10] but are especially critical when evaluating outcomes for nonmalignant disease where it can be difficult to capture/define "relapse." Underlining the importance of this analysis is the finding that the modified GFRS at 3 years with treosulfan/fludarabine was 59.4% compared with 78.7% with busulfan/fludarabine ($P = .007$). It can be difficult to identify a single variable driving differences in composite end points, but in this instance, the difference was largely because of the cumulative incidence of secondary procedures, which was significantly higher in the treosulfan/fludarabine group (26.6% vs 6.2%). These findings support the concept that full myeloablation may be advantageous in WAS, especially in young patients without additional risk factors for organ toxicity. This finding is partially confounded by the treosulfan cohort more frequently having received serotherapy (exposure of which was also not consistently dosed based on measured or predicted exposure); it is still reasonable to conclude that treosulfan/fludarabine, with or without serotherapy, at currently used doses, and without pharmacodynamic and pharmacokinetic monitoring of exposure, may not be as myeloablative as busulfan/fludarabine. Missing from the analysis performed thus far is full assessment of milestones of immune reconstitution.

Importantly, one of the clear ways in which outcomes for transplant for WAS have improved is that donor type and age did not significantly influence GRFS. One of the findings in this study, like the recently published study by the Primary Immunodeficiency Treatment Consortium,[9] was an improvement in the outcomes for all patients, including those transplanted from alternative donors. As the authors state, HSCT from matched sibling donor/matched family donor remains the gold standard, but the outcomes demonstrated in transplant for this rare disorder with the implementation of standardized regimens and analysis using appropriate composite end points move the field toward an improved standard of care and sets the stage for the next advancements in transplant for WAS. These next advancements will likely include more uniform monitoring of exposure to the agents used in cytoreduction with the goal of improving outcomes by attainment of full donor chimerism and meaningful milestones of immune reconstitution.

Conflict-of-interest disclosure: S.E.P. receives support for the conduct of sponsored trials through Atara Biotherapeutics, Jasper Therapeutics, and AlloVir and is an inventor of IP licensed to Atara Biotherapeutics with all rights assigned to Memorial Sloan-Kettering Cancer Center. ■

REFERENCES

1. Albert MH, Slatter MA, Gennery AR, et al. Hematopoietic stem cell transplantation for Wiskott-Aldrich syndrome: an EBMT Inborn Errors Working Party analysis. *Blood*. 2022; 139(13):2066-2079.
2. Imai K, Morio T, Zhu Y, et al. Clinical course of patients with WASP gene mutations. *Blood*. 2004;103(2):456-464.
3. Bach FH, Albertini RJ, Joo P, Anderson JL, Bortin MM. Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome. *Lancet*. 1968;2(7583):1364-1366.
4. Parkman R, Rappeport J, Geha R, et al. Complete correction of the Wiskott-Aldrich syndrome by allogeneic bone-marrow transplantation. *N Engl J Med*. 1978; 298(17):921-927.
5. Kapoor N, Kirkpatrick D, Blaese RM, et al. Reconstitution of normal megakaryocytopoiesis and immunologic functions in Wiskott-Aldrich syndrome by marrow transplantation following myeloablation and immunosuppression with busulfan and cyclophosphamide. *Blood*. 1981;57(4): 692-696.
6. Braun CJ, Boztug K, Paruzynski A, et al. Gene therapy for Wiskott-Aldrich syndrome: long-term efficacy and genotoxicity. *Sci Transl Med*. 2014;6(227):227ra33.
7. Filipovich AH, Stone JV, Tomany SC, et al. Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. *Blood*. 2001;97(6):1598-1603.
8. Moratto D, Giliani S, Bonfim C, et al. Long-term outcome and lineage-specific chimerism in 194 patients with Wiskott-Aldrich syndrome treated by hematopoietic cell transplantation in the period 1980-2009: an international collaborative study. *Blood*. 2011;118(6):1675-1684.
9. Burroughs LM, Petrovic A, Brazauskas R, et al. Excellent outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome: a PIDTC report. *Blood*. 2020;135(23):2094-2105.
10. Kim HT, Logan B, Weisdorf DJ. Novel composite endpoints after allogeneic hematopoietic cell transplantation. *Transplant Cell Ther*. 2021;27(8):650-657.

DOI 10.1182/blood.2022015612