blood® commentary

TRANSPLANTATION

Comment on Haddad et al, page 1737

Predicting the future with TRECs

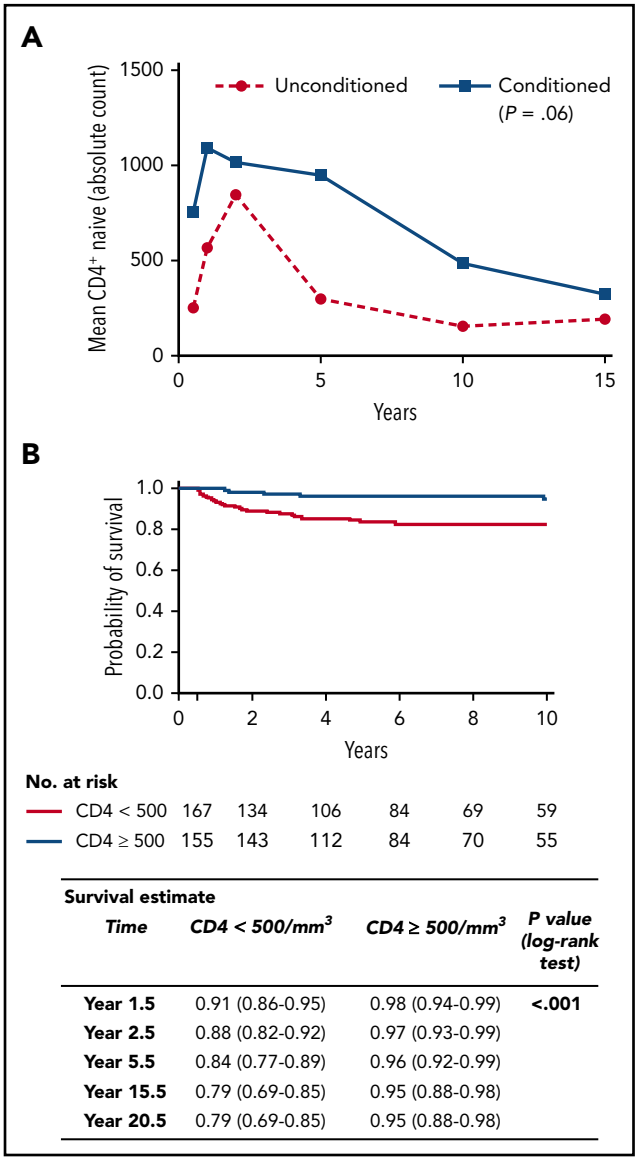
Andrew R. Gennery | University of Newcastle upon Tyne

In this issue of *Blood*, Haddad and colleagues on behalf of the Primary Immune Deficiency Treatment Consortium report retrospective outcome data on hematopoietic stem cell transplantation (HSCT) for 662 patients with severe combined immunodeficiency (SCID) treated between 1982 and 2012 in 33 North American institutions.[1]

Inborn errors of immunity are genetic diseases predisposing affected individuals to an increased risk of infection, autoimmunity, or malignancy. The most severe of these disorders, SCID, characterized by absent or dysfunctional T lymphocytes affecting cellular and humoral adaptive immunity, is life threatening when recognized too late. Contingent on the genetic defect, B lymphocytes and natural killer cells may be present or absent. Since the first HSCT for SCID was performed 50 years ago, discussion among specialists caring for these patients has continued over the best approach to treatment. Following that first report, much has been learned about different SCID genotypes, clinical and immunophenotypes, and natural history. In parallel, transplant techniques and approaches have evolved so that today, survival in this group of infants approaches 90% in recent series.[2,3] However, debate around the best alternative donor, use of conditioning, and optimum early biomarkers indicating requirement for a further transplant procedure continues. Problems in resolving the issues include rarity of the disease, and limited experience of any 1 center in treating these patients. Furthermore, historic series have analyzed SCID on phenotypic presentation, whereas genotype, rather than phenotype, may be more important.[4,5] In this issue, Haddad and colleagues analyze outcome of 662 SCID patients treated between 1982 and 2012 in 33 North American institutions. This is one of the largest multicenter studies to date, and for the first time in such a cohort, outcome has been documented according to genotype. As with any such study, a number of limitations are apparent: over the timescale of 30 years, there have been tremendous improvements in approach to diagnosis of SCID and all aspects of HSCT. The multicenter approach means it is inevitable that data are missing, and not all patients will be adequately accounted for. Centers may use different transplant techniques and specialize in treating specific genetic defects. Furthermore, genetic information was incomplete and only available in 58% of patients. Nevertheless, given the rigorous eligibility criteria for the study, important information can be gleaned.

First, the superiority of matched sibling donors corroborates results from previous studies. However, there were no significant differences in survival when comparing other donor types, which confirms observations from the European Inborn Errors Working Party in their most recent epoch analysis, and others.[3,6] This information will be useful for resource-limited centers for which use of unrelated donors may be precluded. Fine detail about differences in T-lymphocyte depletion methods was not available, and in the modern era, nuances in technique may improve survival further. Second, the importance of transplantation before infection is present is now well established,[2] but the current study noted outcome differences in age at transplant in those with infection, with patients >3.5 months of age at transplant having a worse outcome than those transplanted <3.5 months of age. The reasons for this are not clear and may include more advanced end-organ damage in the older group, but emphasize that SCID is a medical emergency, and early diagnosis through newborn screening and early transplant lead to best outcomes.[7]

Third, this study found no difference in transplant outcome between patients with "classical" or atypical/leaky SCID, in contradistinction to the results reported by the European group.[3] The reasons for this difference in outcome are not obvious, and detailed analysis of the 2 groups may be required to explain this difference. Fourth, similar to the European group, this study found no survival difference between those receiving chemotherapy conditioning and those receiving only immunosuppression or no preparative regimen. Although at first reading this might argue that either approach is valid, the present study also confirmed observations that a pretransplant preparative regimen is associated with durable engraftment,[8] the primary goal of treatment of these patients. Thus, this study adds to the growing body of evidence that suggests best outcomes in terms of graft durability and immune reconstitution occur when a chemotherapy-based preparative regimen is administered before allograft infusion. However, the importance of detailed analysis based on genotype is clearly demonstrated by the finding that survival of patients with radiosensitive SCID (Artemis deficiency) was worse than those of *RAG*-deficient SCID, despite similar immunotypes, and not demonstrated in a previous report.[9] Importantly, the increased mortality in the radiosensitive SCID group was not due to infectious causes, suggesting that the interplay of chemotherapy and the systemic nature of the radiosensitive defect may play an



Survival estimate

Time	CD4 < 500/mm³	CD4 ≥ 500/mm³	P value (log-rank test)
Year 1.5	0.91 (0.86-0.95)	0.98 (0.94-0.99)	**<.001**
Year 2.5	0.88 (0.82-0.92)	0.97 (0.93-0.99)	
Year 5.5	0.84 (0.77-0.89)	0.96 (0.92-0.99)	
Year 15.5	0.79 (0.69-0.85)	0.95 (0.88-0.98)	
Year 20.5	0.79 (0.69-0.85)	0.95 (0.88-0.98)	

(A) Longitudinal increased numbers of naive T lymphocytes are associated with chemotherapy conditioning. Adapted from Abd Hamid et al.[4] (B) Overall longterm survival is associated with increased numbers of naive T lymphocytes. Panel (B) has been adapted from Figure 3A in the article by Haddad et al that begins on page 1737.

important role in outcome, so although conditioning may be required to achieve enduring immunity, safer, less toxic methods of achieving robust stem cell engraftment are required.[10]

Finally and importantly, this study leads us closer to identifying failing grafts, to enable early and effective intervention. It is difficult to identify in which patients immune reconstitution is likely to be suboptimal, and therefore, in whom an early decision to boost or retransplant should be taken, important because early intervention is more likely to be successful. However, additional procedures should be avoided in those patients who do not require them. This large cohort study confirms and connects observations from a number of previous small studies, namely that durable T-lymphocyte reconstitution associates with better survival; good T-lymphocyte reconstitution at 1 to 2 years post-HSCT associates with better T-lymphocyte long-term immune reconstitution, and high T-lymphocyte receptor excision (TREC) circle counts, markers of thymopoiesis, at 6 months associate with robust long-term T-lymphocyte reconstitution (see figure).

This study and other large cohort studies of SCID patients strongly emphasize the critical importance of multicenter collaboration and long-term follow-up of these rare patients in experienced centers collecting good-quality data; without careful analysis of the minutiae of immune reconstitution according to preparative conditioning regimen and genotype over 30 years, this study would have no added value over previous studies. Over the years, small pieces of the jigsaw puzzle have been pieced together, so we now have a much clearer picture of how our treatments impact our patients in the short and long term. The next steps will be to gather good-quality data on the impact of our treatment on life quality, and on very long-term outcomes. This study helps lay the foundation for those future analyses.

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

REFERENCES

1. Haddad E, Logan BR, Griffith LM, et al. SCID genotype and 6-month posttransplant CD4 count predict survival and immune recovery: a PIDTC retrospective study. *Blood*. 2018;132(17):1737-1749.
2. Pai S-Y, Logan BR, Griffith LM, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. *N Engl J Med*. 2014;371(5):434-446.
3. Gennery AR, Slatter MA, Grandin L, et al; European Society for Immunodeficiency. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? *J Allergy Clin Immunol*. 2010;126(3):602-10. e1-11.
4. Abd Hamid IJ, Slatter MA, McKendrick F, Pearce MS, Gennery AR. Long-term outcome of hematopoietic stem cell transplantation for IL2RG/JAK3 SCID: a cohort report. *Blood*. 2017;129(15): 2198-2201.
5. Abd Hamid IJ, Slatter MA, McKendrick F, Pearce MS, Gennery AR. Long-term health outcome and quality of life post-HSCT for IL7Rα-, Artemis-, RAG1- and RAG2-deficient severe combined Immunodeficiency: a single center report. *J Clin Immunol*. 2018;38(6): 727-732.
6. Cavazzana-Calvo M, Carlier F, Le Deist F, et al. Long-term T-cell reconstitution after hematopoietic stem-cell transplantation in primary T-cell-immunodeficient patients is associated with myeloid chimerism and possibly the primary disease phenotype. *Blood*. 2007; 109(10):4575-4581.
7. Dvorak CC, Puck JM, Wahlstrom JT, Dorsey M, Melton A, Cowan MJ. Neurologic event-free survival demonstrates a benefit for SCID patients diagnosed by newborn screening. *Blood Adv*. 2017;1(20): 1694-1698.

8. Hassan A, Lee P, Maggina P, et al. Host natural killer immunity is a key indicator of permissiveness for donor cell engraftment in patients with severe combined immunodeficiency [published correction appears in J Allergy Clin Immunol. 2016;137(4):1286]. *J Allergy Clin Immunol*. 2014;133(6):1660-1666.

9. Schuetz C, Neven B, Dvorak CC, et al. SCID patients with ARTEMIS vs RAG deficiencies following HCT: increased risk of late toxicity in ARTEMIS-deficient SCID. *Blood*. 2014;123(2):281-289.

10. Derderian SC, Togarrati PP, King C, et al. In utero depletion of fetal hematopoietic stem cells improves engraftment after neonatal transplantation in mice. *Blood*. 2014;124(6):973-980.

DOI 10.1182/blood-2018-09-873638

IMMUNOBIOLOGY AND IMMUNOTHERAPY

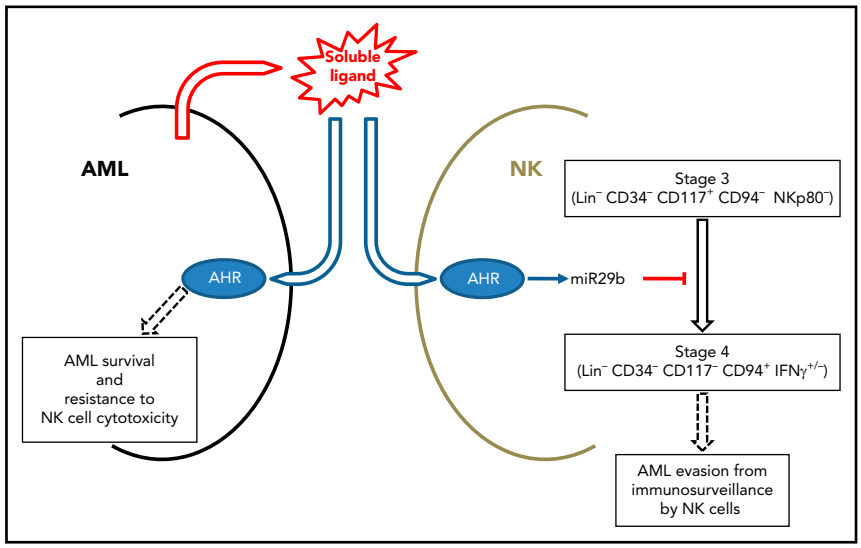
Comment on Scoville et al, page 1792

AHR: leukemic countermeasure against NK cells

Nicolas Dulphy | Université Paris Diderot

In this issue of *Blood*, Scoville et al report an original mechanism by which the aryl hydrocarbon receptor (AHR) allows acute myeloid leukemia (AML) to escape the natural killer (NK) cell–mediated antitumor immunosurveillance by increasing expression of microRNA (miR)–29b, thereby inhibiting NK-cell maturation and function.[1]

The seminal work by Ruggeri et al demonstrated that NK cells are critical effector cells in graft-versus-leukemia in AML after hematopoietic stem cell transplantation.[2] AML patients at diagnosis show deeply impaired NK-cell function against leukemia, with decreased capacity to release cytokines, such as interferon γ, and reduced cytotoxicity with low expression of intracellular cytolytic enzymes (perforin, granzymes). In that context, NK-cell defects are often associated with a specific AML transcription program,[3] emphasizing the intimate relationship taking place between both cell types during leukemogenesis. Mechanisms by which AML induces such profound and sustained NK cell defects are still largely unknown.[4]



AML can escape NK-cell antitumor responses by stimulating the AHR pathway both in NK and AML cells, which will inhibit NK cell maturation and function and promote AML cell survival.

Consequently, there is a quest to develop strategies to reactivate antitumor NK-cell function in support of patients' treatment at diagnosis or after complete remission.

Scoville et al identified AHR as a key factor in the NK cell/leukemia cross talk resulting in the inhibition of the NK-cell maturation and function, and in inducing resistance of AML blasts to NK-cell-mediated killing (see figure). Soluble ligands secreted by AML cells, which remain unidentified, trigger the AHR pathway in NK cells, which in turn increases the transcription of miR-29b and thereby inhibits NK-cell maturation, with a blockade at an immature and poorly functional differentiation stage. The importance of miR-29b in regulating NK-cell maturation and function in the context of AML, previously described in mouse models by the authors,[5] was herein confirmed in humans. AHR appears to be a direct regulator of miR-29b transcription through its binding onto the miR-29a/b1 promoter, suggesting the AHR pathway is a major mechanism by which AML dampens antitumor immunity. Treatment with an AHR antagonist of NK cells cocultured with AML could abrogate increased miR-29b expression and restore NK-cell maturation and function. Interestingly, AHR was also involved in AML survival and its resistance to NK-cell cytotoxicity.

There is growing interest in the role of AHR in the emergence and progression of cancer. Notably, AHR has been associated with the regulation of numerous biological processes important in tumorigenesis, including proliferation, migration, and inflammatory signaling.[6] In addition, AHR expression is increased in tumors relative to healthy surrounding tissues. However, AHR function varies according to the cell where it is expressed. Together with the wide diversity of endogenous and exogenous AHR ligands, it explains the difficulty in addressing the role of this transcription factor in cancer. Scoville et al showed that the AHR pathway could not only promote intrinsic capacities of resistance and survival of tumor cells, but also generate an inhibiting microenvironment preventing the antitumor immune response. Importantly, the AHR/miR-29b pathway did not directly inhibit NK-cell function when AHR was triggered in mature NK cells but impaired the upstream development of the NK-cell precursors. This observation is reminiscent of previous data by Roeven et al