REFERENCES

1. Garg S, Reyes-Palomares A, He L, et al. Hepatic leukemia factor is a novel leukemic stem cell regulator in DNMT3A, NPM1, and FLT3-ITD triple-mutated AML. *Blood*. 2019;134(3):263-276.
2. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
3. Ley TJ, Miller C, et al; Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med*. 2013;368(22):2059-2074.
4. Pabst C, Bergeron A, Lavallée VP, et al. GPR56 identifies primary human acute myeloid leukemia cells with high repopulating potential in vivo. *Blood*. 2016;127(16):2018-2027.
5. Hunger SP, Ohyashiki K, Toyama K, Cleary ML. Hlf, a novel hepatic bZIP protein, shows altered DNA-binding properties following fusion to E2A in t(17;19) acute lymphoblastic leukemia. *Genes Dev*. 1992;6(9):1608-1620.
6. Komorowska K, Doyle A, Wahlestedt M, et al. Hepatic leukemia factor maintains quiescence of hematopoietic stem cells and protects the stem cell pool during regeneration. *Cell Reports*. 2017;21(12):3514-3523.
7. Wahlestedt M, Ladopoulos V, Hidalgo I, et al. Critical modulation of hematopoietic lineage fate by hepatic leukemia factor. *Cell Reports*. 2017;21(8):2251-2263.

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TRANSPLANTATION

Comment on Cuvelier et al, page 304

Joint effort to target the orphan of the orphan

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In this issue of *Blood*, Cuvelier and colleagues from the Applied Biomarkers of Late Effects of Childhood Cancer (ABLE) Consortium evaluate, for the first time, the performance of the National Institutes of Health Consensus Criteria (NIH-CC) for diagnosing chronic graft-versus-host disease (cGVHD) in pediatric patients in a prospective multicenter trial. They demonstrate the utility and limitations of the criteria and provide a benchmark for incidence and severity distribution of late-acute GVHD (L-aGVHD) and cGVHD in a large pediatric population.[1]

Clinical research in cGVHD after allogeneic hematopoietic stem cell transplantation (alloHSCT) is increasingly focused on new drug development fostered by the NIH consensus conferences in 2005[2] and 2014.[3] Until now, pediatric cGVHD has been largely ignored for several reasons. First, the average number of pediatric alloHSCTs per center is significantly lower than adult alloHSCTs and represents only 20% of the total transplantations. Second, the indications for pediatric alloHSCT are more heterogeneous with up to 40% to 50% of patients receiving transplants for nonmalignant diseases. Finally, the frequency of cGVHD is lower in children compared with adults for reasons that are not well understood. As a consequence, until recently, pediatric cohorts for evaluating cGVHD were either small or did not use the NIH-CC, which prevented any reliable conclusion on the current incidence of cGVHD and performance of NIH-CC in pediatric cGVHD.[4] To overcome these issues, the ABLE Consortium, consisting of 27 pediatric transplant centers, performed a multicenter trial to validate the performance of NIH-CC for diagnosis of L-aGVHD and cGVHD and to develop biomarkers to diagnose and predict the course of cGVHD. Even with 27 centers, it took almost 4 years to recruit 302 patients, indicating that large international multicenter activities are a crucial prerequisite for success because single centers or even national cohorts would fail to recruit sufficient numbers of pediatric patients with cGVHD.

The ABLE trial provides several valuable results. First, it confirms the low (21%) incidence of cGVHD in pediatric cohorts, which is basically half the incidence in adult patients.[5] Second, in this study population, the significance of aGVHD is noticeable because of a low rate of de novo cGVHD and a higher incidence of L-aGVHD (24%, mostly persistent or recurrent) than of cGVHD, late acute being the major reason for re-classification, which implicates the relevance of aGVHD as the dominant risk factor for pediatric cGVHD. The specific role of aGVHD in the pediatric population is highlighted by the effect of age older than 12 years as a risk factor for cGVHD but not for L-aGVHD. Moreover, the results emphasize the importance of applying NIH criteria to prevent incorrect classification. Even within the trial, a review committee re-classified a significant proportion (25%) of patients. This also indicates that physicians continue to diagnose cGVHD by day posttransplant (ie, after day 100), most likely for its simplicity, even if diagnostic or distinctive symptoms of cGVHD are lacking. This emphasizes the need for rigorously monitoring the classification of all GVHD cases within clinical trials.

Third, the ABLE trial (for the first time) validated the 2014 NIH-CC in bronchiolitis obliterans syndrome (BOS)[3] in pediatric patients; this demonstrates a significant failure rate in diagnosing BOS, mostly because of the age limitations of lung function testing, nonspecific changes in the computed tomography chest scan, and inconclusive histopathology. Because these obstacles are unlikely to be easily resolved, the development of diagnostic biomarkers to identify patients with BOS is an area of great medical need.[6,7]

Fourth, the authors also captured immunologically driven events such as immune thrombocytopenia or nephrotic syndrome that do not meet the NIH-CC but require immunosuppression, which have been recently labeled as "undefined other cGVHD."[8] The latter has typically been ignored in previous prospective trials, although events such as these often require immunosuppressive treatment.

Last but not least, the trial provides important evidence regarding the incidence of cGVHD during the first year after alloHSCT. However, some patients with L-aGVHD may develop the quiescent onset of cGVHD after the 1-year assessment. Finally, the long-term outcome after diagnosis of cGVHD in pediatric patients, including crucial information on

the rehabilitation of these patients, still needs to be determined.

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REFERENCES

1. Cuvelier GDE, Nemecek ER, Wahlstrom JT, et al. Benefits and challenges with diagnosing chronic and late-acute GVHD in children using the NIH consensus criteria. *Blood*. 2019;134(3):304-316.
2. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11(12):945-956.
3. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21(3):389-401.e381.
4. Eapen M, Horowitz MM, Klein JP, et al. Higher mortality after allogeneic peripheral-blood transplantation compared with bone marrow in children and adolescents: the Histocompatibility and Alternate Stem Cell Source Working Committee of the International Bone Marrow Transplant Registry. *J Clin Oncol*. 2004;22(24):4872-4880.
5. Arai S, Arora M, Wang T, et al; Graft-vs-Host Disease Working Committee of the CIBMTR. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant*. 2015;21(2):266-274.
6. Wolff D, Greinix H, Lee SJ, et al. Biomarkers in chronic graft-versus-host disease: quo vadis? *Bone Marrow Transplant*. 2018;53(7):832-837.
7. Paczesny S. Biomarkers for posttransplantation outcomes. *Blood*. 2018;131(20):2193-2204.
8. Schoemans HM, Lee SJ, Ferrara JL, et al; EBMT (European Society for Blood and Marrow Transplantation) Transplant Complications Working Party and the "EBMT−NIH (National Institutes of Health)−CIBMTR (Center for International Blood and Marrow Transplant Research) GvHD Task Force". EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transplant*. 2018;53(11):1401-1415.

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