inactive. The study shows that transgenic mice with enhanced expression of TM in embryonic tissue did not develop the extracellular vesicle–induced phenotype of preeclampsia. Does the TM expressed on the embryonic tissue of the transgenic mice resist shedding or slow the kinetics of shedding? The answers to these questions could help identify the role of TM in the placental development and pathogenesis of pregnancy-associated vascular disorders.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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DOI 10.1182/blood.2020008659

TRANSPLANTATION

Comment on Qayed et al, page 983

Harmonization, biomarkers, disease risk index

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In this issue of *Blood*, Qayed et al[1] describe the development and validation of a disease risk index (DRI) to better predict (leukemia-free) survival and to stratify pediatric acute leukemia patients undergoing allogeneic hematopoietic cell transplantation (HCT). This desperately needed risk stratification is based on disease status (including minimal residual disease), age, and cytogenetics prior to HCT.

The outcome of allogeneic HCT is influenced by multiple variables, including patient-, donor-, and transplantation (platform)–specific ones. The large number of variables makes data analyses complicated. Pediatric HCT outcome analyses is further complicated by limited numbers, more indications, and pediatric-specific features. Validated risk scores, such as a DRI, can help to identify patients at highest risk for HCT failure, as well as to stratify patients undergoing HCT. Clinical trials aimed at improving results of HCT, which are limited by small numbers of pediatric patients, need to rely on a larger number of pediatric HCT centers to participate in trials. This further underscores the immense need for validated risk scores, like the pediatric DRI described by Qayed et al. In addition, harmonization of (disease-specific) clinical trial design, using harmonized transplant platforms and monitoring thereafter, are important steps toward better, predictable, and improved outcomes after HCT.

The HCT-Comorbidity Index (HCT-CI) was developed and validated more than a decade ago[2] and is currently used in all registry studies, as well as in clinical trials. After publishing the HCT-CI, it took almost a decade until the Adult DRI was developed and published in 2014.[3] In pediatrics, such a DRI was lacking until now. The consortium, led by Muna Qayed, obtained data from the Center for International Blood and Marrow Transplant Research to perform the analyses. Patients who underwent their first transplantation for acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) between 2008 and 2017 were included. This validated pediatric DRI, which includes age, cytogenetics, and residual disease status, can be used to facilitate prognostication and stratification of children with AML and ALL for allogeneic HCT. A limitation is that modest patient numbers for myelodysplastic syndrome, juvenile myelomonocytic leukemia, chronic myeloid leukemia, and Hodgkin and non-Hodgkin lymphoma prohibited the investigators from developing a training and validation set for these groups. Also, most patients came from centers in the United States, and the number of patients older than 12 years was relatively limited. However, by just starting to use this DRI, these limitations can eventually be overcome. With larger numbers and more details about disease status, the DRI may be fine-tuned in the upcoming years. It is important to note that we need to be cognizant that different (and more precise) methods to detect minimal residual disease may have an impact on the outcomes and predictions.

In addition to the now available and desperately needed pediatric DRI, we as a (pediatric) HCT community need to agree on harmonizing clinical trial design and trying to identify, validate, and use early biomarkers for outcome.[4] In particular, the relatively limited number of pediatric patients and existing medical need to improve the outcomes should encourage us to take these important steps. Interventions, including immune-based ones, in the context of HCT are being developed for a variety of indications to improve outcomes for diseases/disorders with a clear medical need. All of

these interventions have the overarching goal of achieving better disease control, reducing toxicity, and improving quality of life. It was recently demonstrated in a study by Soiffer et al[5] that harmonizing the transplant platform (standard chemotherapy, serotherapy [eg, anti-thymocyte globulin], and/or total-body irradiation [TBI] combinations, considering the pharmacokinetics, timing, and sequence of the various modalities) is crucial. In that study, 3 conditioning regimens were allowed in a randomized controlled clinical trial to study the impact of anti–T-lymphocyte globulin (ATLG) on outcomes. The primary outcome, chronic graft-versus-host disease (GvHD)-free disease-free survival (DFS), showed inverse outcomes among the conditioning regimens allowed: adding ATLG to the allowed TBI-containing regimen resulted in inferior chronic GvHD-free DFS compared with no ATLG, whereas adding ATLG to the fludarabine + busulfan regimen showed superior chronic GvHD-free DFS compared with no ATLG. In the combined data set, this resulted in overlapping curves for the entire cohort.[5] Furthermore, identifying early biomarkers for outcomes is important. Examples are the recently described GvHD biomarker score (ST2, REG3), from the MAGIC consortium,[6,7] in predicting acute GvHD and related nonrelapse mortality (NRM). Also, the more recently described early (<100 days) $CD4^+$ immune reconstitution (defined as 2 consecutive measures above 50/μL) was found to be a predictor of viral reactivations and NRM.[8,9] This $CD4^+$ marker, as a predictor for NRM, was described in various cohorts (pediatrics, adults, and various transplantation platforms), including in the context of acute GvHD.[10]

The investigators did an essential job by developing and validating a pediatric DRI for allogeneic HCT. This is an important tool that could be used in predicting leukemia-free survival and stratifying patients for HCT. Further development of this pediatric DRI, as well as harmonization of clinical trial design and identifying, validating, and implementing early biomarkers for outcome, are fundamental next steps to make (pediatric) transplant safer and more effective. This will eventually result in higher survival chances with a better quality of life.

Conflict-of-interest disclosure: J.J.B. has acted as a consultant for Race Oncology, Takeda, BlueRock Therapeutics, AVROBIO, Omeros, and Advanced Clinical. ■

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DOI 10.1182/blood.2020009862