blood *commentary*

HEMATOPOIESIS AND STEM CELLS

Using patient-reported outcomes to improve survivorship care

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In this issue of *Blood*, Yen and colleagues report that adult survivors of pediatric hematologic malignancies have high symptom prevalence and poor patient-reported outcomes (PROs), whether treated with conventional therapy or hematopoietic stem cell transplantation (HSCT), and that the poor PROs correlated with the presence of chronic health conditions.[1]

PROs are increasingly used to paint a clearer picture of patients' short- and long-term health-related quality of life (HRQOL), including physical, mental, and social functioning. Results from the cross-sectional analysis presented by Yen and colleagues bring into focus the substantial burdens carried by adult survivors of pediatric hematologic malignancy. Utilizing data from the St. Jude Lifetime Cohort Study, the report compared PROs across 10 symptom domains and Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) HRQOL summary scores among 112 survivors who received HSCT, 1106 conventionally treated survivors (without HSCT), and 242 noncancer community controls. They report that survivors who received HSCT faced a significantly increased burden compared with noncancer controls across a wide range of symptom domains, including sensation, motor/movement, pulmonary, cardiac, fatigue, memory, and anxiety. However, this burden was largely comparable to that experienced by conventionally treated survivors, except for a higher frequency of sensation symptoms primarily related to vision, particularly among survivors with a history of graft-versus-host disease. Notably, symptom occurrence was correlated with the diagnosis of clinically confirmed comorbid health conditions, many of which were more common among HSCT-treated survivors, including cardiovascular, gastrointestinal, ocular, pulmonary, and reproductive conditions.

How do we improve survivorship care to reduce symptom burden and enhance longer-term quality of life? Results from Yen and colleagues and prior studies emphasize the importance of PROs as an invaluable tool for achieving these goals. Although the current report uses PROs to reveal the substantial impact of chronic health conditions on symptom burden and quality of life,[1] previous studies have demonstrated that PROs also are responsive and sensitive to changes in disease severity and activity[2] and are predictive of survival outcomes.[3] Beyond these standard clinical metrics, PROs and HRQOL are also being actively investigated in relation to biological outcome measures. One example is gene expression profiling, such as the Conserved Transcriptional Response to Adversity (CTRA) score, which measures expression of 53 inflammation- and immune function-related genes and is related to stress-associated illness.[4] In HSCT recipients, CTRA profiles have been associated with socioeconomic status and survival,[5] but β-adrenergic antagonism can modify CTRA gene expression, thereby inhibiting cellular and molecular pathways associated with adverse outcomes after HSCT.[6] In sum, the current body of evidence surrounding PROs suggests their promise as a critical tool for the early identification of newly developing health problems and assessment of patients most likely to benefit from interventions.

Several key challenges must be overcome, however, before PROs are adopted widely into research trials and standard clinical practice. First, PRO and HRQOL measures must be standardized and harmonized. Yen and colleagues assessed symptoms with a 37-item questionnaire, as recommended by the Children's Oncology Group Long-Term Follow-Up Guidelines, and measured HRQOL using the SF-36. They also highlight the PRO version of the Common Terminology Criteria for Adverse Events as an important tool to consider given its relevance and correlation to clinical events measured in cancer clinical trials. Within the HSCT community, the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) has been proposed as a primary metric for PROs because of certain advantages compared with other instruments. Most importantly, PROMIS covers a number of physical, emotional, and social domains, which can be combined in various lengths, offering flexibility to specific areas of study. PROMIS also has been evaluated in a variety of conditions, has been subject to rigorous development and validation, and has key features that facilitate widespread adoption. PROMIS is free, has been made available in multiple languages, can be administered in multiple ways including computerized adaptive testing to maximize precision while minimizing patient burden, and is available for both adults and children, as well as for proxy reporting. Recent studies have demonstrated PROMIS as a sensitive and well-performing tool in

HSCT long-term survivors,[7] among many other patient populations. Although PROMIS fulfills many PRO metrics, it is important to note that it, as well as many HRQOL measures, does not assess specific sociobehavioral and environmental domains such as occupational, financial, and health behavior concerns. Although PROs do exist to address these domains, there are no uniform validated measures within the HSCT and cancer survivorship populations. Because of the availability of numerous tools to assess PROs and HRQOL, harmonization of metrics from various tools is essential for interpreting results across studies in order to identify optimal survivorship care practices.

Second, challenges related to the feasibility of standard longitudinal collection of PROs must be addressed, as there remains significant heterogeneity in the use and timing of symptom assessments. All patients with cancer face challenging transitions in care as they complete initial therapy and shift to long-term follow-up, a situation only accentuated among HSCT recipients, who may be followed by their transplant center, primary oncologist, or primary cancer physician. Although it is important to account for the survey burden that patients may face in participating in potentially frequent PRO measurement, the Center for International Blood and Marrow Transplant Research (CIBMTR) has established feasibility of routine longitudinal PRO assessment, with initial recruitment by the transplant center and then centralized posttransplant PRO collection through the CIBMTR.[8] Further work is ongoing to implement the standard collection of longitudinal PROs through the CIBMTR to be able to correlate PROs with clinical outcomes data. However, the optimal timing of PRO collection may depend on the specific patient population.

Despite the challenges in adopting PROs into research trials and standard clinical practice, the results from Yen and colleagues demonstrate the importance of PROs for illuminating the substantial burdens carried by adult survivors of pediatric hematologic malignancy. Particularly for patient populations with substantial long-term morbidity, such as HSCT recipients and pediatric cancer survivors, the widespread and consistent use of longitudinal PROs will be an essential tool for further understanding and improving survivorship care.

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A predictive tool for early-stage CLL

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In this issue of *Blood*, Condoluci et al report that, using a large international cohort of 4933 patients from 11 groups, they have developed an international prognostic score (IPS-E) for predicting time to first treatment (TTFT) in patients with asymptomatic, early-stage CLL.[1] Although there have been multiple past publications on prognostication in CLL, previous models have predominantly addressed overall survival as the end point of interest.[2] Although survival is obviously of interest for both physicians and patients, the long survival duration of patients with early-stage CLL[3] means that a more immediately relevant and often asked question is: "Doctor, how long do I have before I have to put my life on hold and accept treatment for my leukemia?"

To answer this question, Condoluci et al examined features associated with TTFT in a training set of 333 consecutive patients followed over a median of 7.2 years at the University of Eastern Piedmont.[1] This cohort was remarkably complete in terms of biological information, with immunoglobulin HV (IgHV) mutation, fluorescence in situ hybridization, and *TP53* mutational status known in all patients. Using a multivariable model, 3 factors of equal weighting (1 point each) were identified to be independently predictive of TTFT: unmutated IgHV status, lymphocyte count higher than 15×10^9/L, and palpable nodes. Successful validation of these factors in 10 other European and US cohorts led to establishment of the IPS-E, which divided patients into approximately thirds: patients with score 0 (30%) have a low risk of requiring treatment (2.0 per 100 person-years), score 1 (36%) yields an intermediate risk of requiring treatment (6.1 per 100 person-years), and score 2 to 3 (34%) indicates a high risk of requiring treatment (16.1 per 100 person-years). Importantly, although *TP53* deletions/mutations are key determinants of treatment response and overall survival after commencement of therapy, in this study, *TP53* aberrations are not found to be independently predictive of TTFT