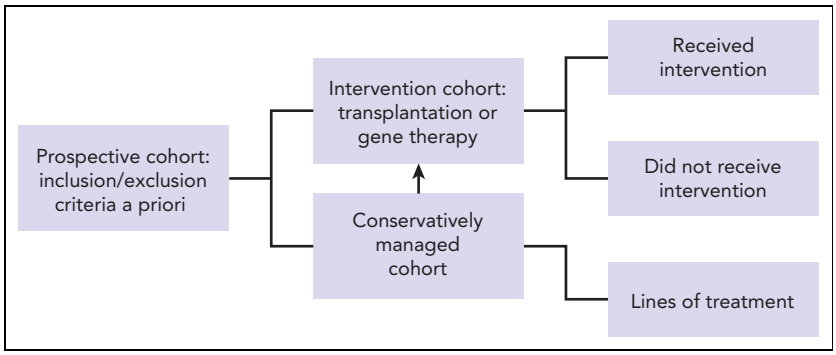

Nested prospective cohort within a disease registry.

existing registries. One option is to design a prospective observational cohort (see figure) based on eligibility criteria established a priori upon entry to a disease registry coupled with reporting of annual longitudinal follow-up data on standardized report forms to capture disease-specific information, choice of treatments, response to treatment, changes in treatment (and reasons for change) or lack thereof when clinically indicated, assessment of disease status, and survival. This would in essence capture not only those who were fit enough to receive HSCT or another intervention such as gene therapy but also those who met disease severity for an intervention but were not offered the treatment or were unable to tolerate the intervention because of multiple comorbidities or a because a suitable donor was not available. Adult patients with IEI are understudied and underrepresented in registries but are likely to offer relevant information on when the timing of a treatment strategy should be modified for the best possible outcome. Another factor that will ensure a robust nested cohort within a registry would be limiting participation to those clinical sites willing to report consecutive patients with IEI and are committed to continue longitudinal follow-up throughout a patient's life span. Supportive care measures will no doubt evolve and so will strategies for treatment intervention. A prime example is the adoption of less intense conditioning regimens for HSCT. This approach extends access to less fit patients with progressive disease and is intended to lower the burden of morbidity associated with HSCT. Striking an appropriate balance between intensity of conditioning regimen for HSCT and disease control remains a challenge.[8,9] Consequently, only through careful study of strategies among similar disease groups and/or donor types (in the case for transplantation) can we begin to make appropriate recommendations for treatments.

The proposed approach would require substantial monetary investment and participation of existing stakeholders. It is particularly important that consecutive patients with IEI be registered from each of the participating sites to minimize biases. Finally, participation in the registry and in associated research requires patients to understand the important role they play in advancing the treatments for their disease, which underscores the need for sustained longitudinal follow-up, and a recognition that registry-led studies impact future generations of patients in addition to themselves.

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MYELOID NEOPLASIA

Comment on Turcotte et al, page 90

Treatment intensity in AML: a double-edged sword

Brian D. Friend | Baylor College of Medicine

In this issue of *Blood*, Turcotte et al[1] demonstrate in the largest cohort to date of childhood acute myelogenous leukemia (AML) survivors that treatment intensification and improved supportive care measures have led to dramatically better long-term survival over time. However, they also show the unwanted effects of treatment intensification, that being a greater burden of late effects and toxicity that have persisted even in patients treated in the most recent time period.

The evolution in treatment of childhood leukemia over the past 60 years has been one of the greatest successes in the field of oncology, with 5-year overall survival rates now surpassing 90%.[2] Yet this triumph is due primarily to advances in the treatment of acute lymphoblastic leukemia (ALL), in which dose-intensive combination chemotherapy followed by a prolonged maintenance phase achieves long-term remissions for most patients. For AML, however, improving cure rates have lagged substantially behind those of ALL, requiring more intensive treatments, frequently including hematopoietic cell transplantation (HCT).

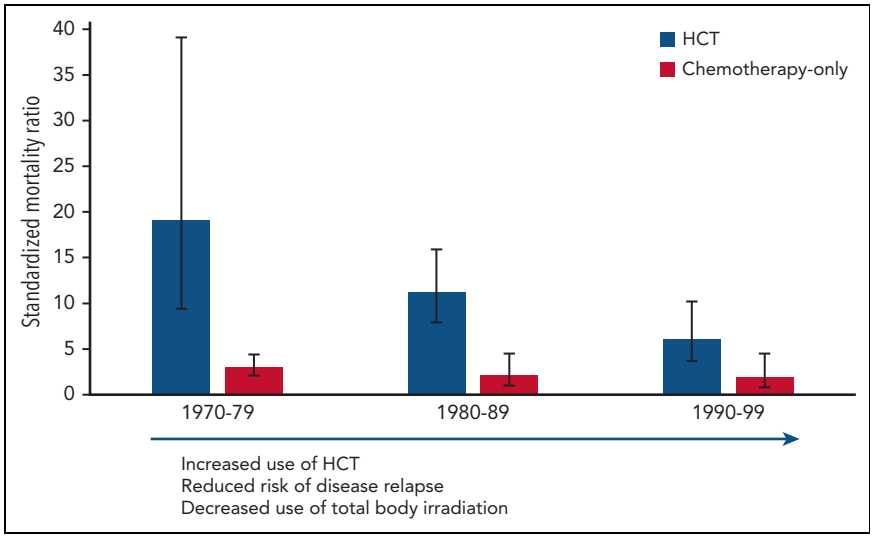
Higher rates of cure for childhood cancers have led to an estimated 500 000 cancer survivors by 2020[3] and a greater appreciation of the burden of late effects suffered by patients related to their prior treatments. Much of this understanding originated from the Childhood Cancer Survivor Study, a robust cohort of patients from 31 institutions with longitudinal data dating to 1970.[2] This recognition has resulted in earlier identification of late effects and prompt treatment, as well as the development of preventative measures to improve long-term outcomes. For example, several treatment protocols since the mid-1990s have included dexrazoxane to reduce anthracycline-related cardiotoxicity without impacting relapse mortality.[4] More notably, recent treatment protocols for several childhood cancers have shifted their focus to more nuanced systems of risk stratification, with a goal of decreasing treatment intensity to reduce the risk of developing late effects. Such efforts have maintained excellent treatment outcomes while leading to reductions in late mortality.[5]

Given that treatment plans for childhood AML have required intensification rather than deescalation to improve survival, many have suggested that these patients may also suffer an undue burden of late effects. However, data for AML survivors are limited.[6] In this report from the Childhood Cancer Survivor Study comparing outcomes of 5-year survivors of childhood AML treated between 1970 and 1999, Turcotte et al[1] illustrate the double-edged sword of this treatment approach, notably that the risk of relapse has decreased substantially over time while the chance of developing a chronic health condition is more than threefold higher in survivors than healthy siblings. The authors also conducted analyses based on selected treatment groups: (1) HCT recipients, allogeneic or autologous; (2) chemotherapy with cranial radiation; and (3) chemotherapy only. Strikingly, the incidence of late effects has decreased over time in patients who underwent HCT, yet late mortality and chronic health conditions have not changed significantly in the chemotherapy-only group among patients treated in different time periods (see figure). Still, overall most childhood survivors of AML reported good health outcomes regardless of treatment group.

These findings demonstrate that although the majority of AML survivors are living without significant perceived impairment, close monitoring and surveillance for late effects are critical during long-term follow-up, and the follow-up should be adapted on the basis of changes in treatment through the years. In addition, more preventative measures and early interventions during survivorship could be effective in reducing the burden in patients, especially those at high risk of late effects. Practical approaches, such as exercise interventions to improve cardiovascular health, could impact many childhood cancer survivors, yet to be successful and widely adopted, they will need to engage this particular patient population, likely by incorporating digital and mobile technology.

The more challenging question is how can we modify upcoming treatment protocols to reduce late toxicity in a disease where 5-year survival outcomes are still suboptimal. Development and incorporation of targeted therapies is likely the best approach to improve efficacy while minimizing toxicity. FLT3 inhibitors have shown efficacy in adult patients with this specific mutation without significant adverse effects,[7] and there are ongoing studies in pediatric AML (NCT04293562). Immune-based approaches, such as chimeric antigen receptor T-cell therapy, have demonstrated great success in ALL but have been more difficult to target in AML, though there are some promising studies in development.[8] Nevertheless, late toxicities may still be seen with targeted therapies; therefore, further studies are needed to ascertain the long-term effects for immune-based therapies.[9]

Although targeted therapies are designed primarily to reduce the risk of disease recurrence, other approaches should focus on mitigating treatment-related mortality. First, investigators should strive to identify low-risk AML patients, who do not benefit from more intensive treatment, particularly HCT. Second, advances in molecular profiling including whole exome sequencing and RNA sequencing, as well as more sensitive techniques to assess disease status such as next-generation sequencing, will



Standardized mortality ratios by decade, comparing standardized mortality ratios by decade of diagnosis and treatment group (hematopoietic cell transplantation vs chemotherapy only).

allow for more individualized and less toxic treatments in the future.[10] Third, given that a large population of patients will still require HCT for cure, novel strategies to decrease regimen related toxicity, such as the development of personalized pharmacokinetic-guided dosing algorithms, are needed.

The findings from Turcotte et al's[1] study are limited by the facts that the cohort stretches over nearly 3 decades and treatment of AML has changed substantially through the years. For example, in patients in this study who received HCT, one-third were autologous and nearly half received total body irradiation, neither of which are part of standard treatment today. Yet the long-term outcome data presented here are essential to our understanding of the late toxicity seen in AML patients and will be helpful in designing the next phase of treatment protocols. Ultimately, such protocols should optimize cure rates and long-term quality-of-life outcomes while reducing the risk of late effects.

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

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THROMBOSIS AND HEMOSTASIS

Comment on Icheva et al, page 102

Acquiring a new diagnostic approach for aVWS

Sarah O'Brien | The Research Institute at Nationwide Children's Hospital; and The Ohio State University College of Medicine

In this issue of *Blood*, Icheva et al describe a new and highly predictive approach for the laboratory diagnosis of acquired von Willebrand syndrome (aVWS) in neonates and infants undergoing surgery for congenital heart disease (CHD).[1] Although pediatric aVWS is a rare disease, it appears most commonly in the clinical setting of CHD, in which the shear stress–induced increase in von Willebrand factor (VWF) proteolysis causes the loss of high molecular weight multimers (HMWM).[2] Understanding possible risk factors of bleeding in infants with CHD is crucial for this patient population because neonates and small infants, in particular, are susceptible to the coagulopathic effects of cardiopulmonary bypass, almost invariably requiring the use of blood components and other procoagulant interventions.[3,4]

Historically, a significant barrier to the timely diagnosis of aVWS has been the lack of readily available and accurate laboratory testing. Individual and preanalytical variables affect the sensitivity of traditional laboratory testing for aVWS, particularly with ristocetin-based activity testing.[5] The gold standard for diagnosing aVWS, the VWF multimer analysis, is time consuming and unavailable on-site at many institutions. A key advancement in recent years has been in the measurement of functional assessment of VWF, with ristocetin-based activity tests gradually being supplemented or replaced by assays based on the binding of VWF to a recombinant platelet glycoprotein (GP1bM), which show greater precision and higher sensitivity.[6] In this prospective cohort study, Icheva et al take the next step of investigating how this new testing can be used in the identification of aVWS.

The investigators screened all patients with CHD aged 0 to 12 months requiring corrective or palliative cardiac surgery over a 17-month time frame and achieved a high enrollment percentage (95% of eligible infants enrolled in the study). Participants underwent detailed coagulation testing at 4 standardized time points (preoperative, intraoperative, postoperative day 1, and final testing, typically within the first 2 weeks after surgery) (figure). VWF:GP1bM testing was performed using a commercially available test, and at the authors' institution, only 1 hour elapses from blood collection to the result. In their analysis, the authors compared the predictive value of the GP1bM/VWF:antigen (Ag) ratio, the VWF:collagen binding/VWF:Ag ratio, and peak systolic echocardiographic gradients with the gold standard HMWM ratios. Among the algorithms studied, the GP1bM/VWF:Ag ratio provided the best predictive value for identifying aVWS and correlated strongly with the HMWM ratio. Another key finding from this work was that a GP1bM/VWF:Ag cutoff value of <0.83,