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As more transplants are performed yearly and outcomes continue to improve, long-term survivorship has become increasingly important. This is particularly true in pediatric patients.

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for multiple malignant and nonmalignant hematologic disorders. Overall survival has improved substantially. More than 40,000 HSCTs are performed yearly worldwide. Therefore, the number of long-term, disease-free survivors is continuously increasing. Unfortunately, these long-term survivors may also face late transplantation-associated morbidity and mortality. These include a variety of malignant and nonmalignant complications that may affect physical and psychological performance, normal integration into family and social life, and quality of life (reviewed in Tichelli et al). The choice of conditioning regimen and the development of chronic graft-versus-host disease (GVHD) are key risk factors in the development of late transplantation-related complications. Unfortunately, new late toxicities are still being identified; notably, very late cardiovascular complications (reviewed in Tichelli et al). Awareness of long-term effects after HSCT is thus crucial to provide adapted pretransplantation counseling and recommendations for posttransplantation care including screening, prevention, and early treatment of these late complications, if they are found. In this issue of Blood, 2 articles describe long-term survivorship of patients who underwent transplantation during childhood.

In the first article, Sanders et al describe late effects among pediatric patients followed for nearly 4 decades after HSCT for severe aplastic anemia (SAA) at the Fred Hutchinson Cancer Research Center. The authors decided to focus their study on patients who survived more than 1 year after transplantation. They included 154 patients (137 patients with acquired SAA and 15 with Fanconi anemia). Survival was negatively affected by chronic GVHD and by the diagnosis of Fanconi anemia. Sanders et al also describe a number of late complications including thyroid abnormalities (increased in patients who received irradiation) and solid cancers (in particular in patients with Fanconi anemia and/or in those having developed chronic GVHD). Sanders and colleagues have to be congratulated for this life-long surveillance of patients with this rare disease. Mainly because of the efforts of Drs Sanders and Storb to improve outcomes, the conditioning regimen in SAA they developed many years ago (high-dose cyclophosphamide and ATG) has became the gold standard worldwide, leading to sustained engraftment in most patients with few late effects, notably often preserving fertility. However, even if the survival rate in acquired SAA is excellent, it still does not reach what would be expected in the general population. This decreased survival in acquired SAA is

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mainly due to chronic GVHD. Fanconi anemia patients, unfortunately, still harbor the genetic defect in other somatic tissues (including epithelial cells) and have a high propensity to develop secondary solid cancers (in particular of the head and neck) even if cured of their aplastic anemia by the transplant. Lamentably, transplantation for Fanconi anemia, probably through chronic GVHD, increases the risk of head and neck cancers; thus, these patients need life-long surveillance.

In the second paper in this issue, by Armenian et al, the Bone Marrow Transplant Survivor Study (BMTSS) and the Childhood Cancer Survivor Study (CCSS) groups report a seminal study on the long-term health-related outcomes in survivors of childhood cancer. These authors compared the risk of chronic health conditions and adverse health among children with cancer treated with HSCT with survivors treated conventionally, as well as with sibling controls. Nearly 150 HSCT survivors were drawn from BMTSS and more than 7000 conventionally treated survivors and 4000 siblings were drawn from CCSS. All chronic conditions were self-reported. Nearly 60% of HSCT survivors reported 2 or more conditions, and one-quarter reported severe/life-threatening conditions. HSCT survivors were more likely than sibling controls to have severe/life-threatening conditions and multiple conditions, as well as functional impairment. Compared with CCSS survivors, BMTSS survivors demonstrated significantly elevated risks of severe/life-threatening conditions, multiple conditions, and functional impairment, thus providing evidence for close monitoring of this high-risk population. This a seminal study in many aspects because of the large number of patients studied, a comparison with more advanced disease (data not shown). Readers should look carefully at the date of diagnosis: patients treated in the CCSS cohort were treated from the 1970s to the late 1980s while the BMTSS patients underwent transplantation mostly in the late 1980s to the mid-1990s. Given the time period, it is highly likely that a substantial proportion of the patients in the BMTSS group received single-dose total body irradiation and that most patients with ALL were given 24-Gy irradiation to the CNS. It is all but impossible to dissect these factors. How can we estimate the health-related outcome of a patient with ALL (or lymphoma) who was treated by standard protocol at the time (including CNS irradiation), who then relapsed early and was successfully reinduced in remission and underwent HSCT after single-dose, 10-Gy total body irradiation? What is the appropriate comparison group? Are there enough patients at risk for meaningful analysis?

There have been major changes in our practice of transplantation in childhood. Thanks to major advances in chemotherapy, only very high-risk patients with ALL in CR1 and selected patients in CR2 are candidates for transplantation; progress has been made using less-toxic conditioning regimen and, more importantly, we are aware of complications and the community is educated about prophylaxis and early intervention of late effects after HSCT. But we are still faced with the same quest: What is the most efficacious treatment leading to the fewest complications?

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Survivors after blood wars

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