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The Bottom Line

Consider Allogeneic Bone Marrow Transplantation for Older, Fit Patients with Aplastic Anemia

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Effective treatment for severe aplastic anemia (SAA) is either allogeneic bone marrow transplantation (BMT) [1,2] or nontransplant immunosuppressive therapy (IST) containing antithymocyte globulin (ATG) [3,4]. Both treatment approaches have advanced over the recent decades to achieve significantly improved outcomes. Considering that allogeneic BMT is a more durable treatment with a reduced risk of long-term complications and improved overall survival compared with IST, there is widespread consensus that BMT is the preferred first-line therapy for younger patients with SAA who have an HLA-matched sibling donor [1]. *Younger* has been generally defined as patients <40 years of age. There is also recent evidence that if an HLA-matched unrelated donor can be rapidly identified (with an urgent, fast-track search), younger patients with SAA also have improved long-term survival if unrelated donor BMT is used as first-line therapy [5]. Based on previous registry data and clinical trials, older patients (generally >40 or 50 years of age) with SAA had poor survival outcomes with allogeneic BMT, and IST was recommended as first-line therapy for older patients [6]. Twenty years ago, the question of whether allogeneic BMT should even be offered to older patients who had failed IST (with relapse of SAA) was considered controversial [7]. However, over the past decade, less toxic conditioning regimens, improved selection of patients and donors, and improved control of both acute and chronic graft-versus-host disease (GVHD) have significantly decreased treatment-related mortality for older patients with SAA undergoing allogeneic BMT [8,9]. Despite this progress, there was a dearth of recent registry data that focused on the outcome of allogeneic BMT for older patients with SAA.

In this issue, Rice et al. [10] provide a comprehensive analysis on the outcome of 499 SAA patients ≥50 years old (median age, 57.8; range, 50 to 77) who underwent hematopoietic cell transplantation between 2005 and 2016 from an HLA-matched sibling or unrelated donor at a median of 10 months (range, <1 to 29.7 years) since diagnosis. This was a retrospective combined European Group for Blood and Marrow Transplantation/Center for International Blood and Marrow Transplant Research registry study. Multivariate analysis indicted higher mortality risk for patients with performance scores <90 and recipients of unrelated donor grafts. The 3-year probability of overall survival for patients with performance scores of 90 to 100 and after HLA-matched sibling and unrelated donor transplant was 66% and 57%, respectively. For patients with performance scores <90 and after HLA-matched sibling and unrelated donor transplant, the 3-year overall survival was 57% and 48%, respectively. These data support the rationale for performing allogeneic BMT in older patients with SAA, especially after failure of first-line therapy with IST.

Although there are several shortcomings with a retrospective combined registry analysis, the overall conclusions and observations are important and highly relevant for clinical practice. First, based on the favorable survival data for older patients with SAA, all patients who experience failure of first-line IST must be considered for allogeneic BMT as second-line therapy. Compared with published results for a second course of IST for refractory SAA [11,12], and the risk of progression to myelodysplastic syndrome or acute myeloid leukemia [13,14], the outcome for allogeneic BMT is superior. Even for select patients with performance status <90, an unrelated donor BMT may be more appropriate than a second attempt at IST. The unanswered question is whether an older patient with excellent performance status (90 to 100) and an HLA-matched donor should proceed to allogeneic BMT as first-line treatment for SAA. The case can be made that for the appropriately informed older patient, allogeneic BMT should be considered as first-line therapy [15].

A weakness of the current study is the lack of adequate recognition that either ATG or alemtuzumab in the conditioning regimen reduces the incidence of both graft failure and GVHD (acute and chronic), and that the inclusion of ATG/alemtuzumab in the conditioning regimen may be a more important predictor of GVHD than some of the alternate versions of post-transplant

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GVHD prophylaxis regimens. Based on the well-documented superiority of conditioning regimens that contain ATG for SAA [16,17], it was somewhat surprising that for some categories of GVHD prophylaxis (calcineurin inhibitor + mycophenolate mofetil and calcineurin inhibitor + methotrexate), >50% of patients received regimens that did not contain ATG or alemtuzumab. In this study, several patient outcomes were analyzed based on the category of a specific chemotherapy/radiation regimen ± ATG, meaning that recipients of non-ATG-containing regimens were not analyzed separately. Limitations such as these suggest that interpretation of the optimal GVHD prophylaxis regimen and the analysis of graft source (peripheral blood stem cells versus bone marrow) may be incomplete. In addition, definitive conclusions cannot be drawn regarding the risk factor analysis for acute or chronic GVHD.

For older patients with SAA, the use of a more effective conditioning regimen will very likely lead to superior overall survival when compared with the registry outcomes. For example, an optimal conditioning regimen consists of cyclophosphamide, fludarabine, ATG (or alemtuzumab), and, for unrelated donor transplants, 2 Gray total body irradiation [9,18,19]. Additionally, the use of bone marrow for the hematopoietic cell source [20,21] and 2-drug post-transplant GVHD prophylaxis (e.g., calcineurin inhibitor + methotrexate) are important factors contributing to an optimal transplant outcome [22,23].

The bottom line is that despite any of the potential shortcomings of this retrospective registry analysis, this study is an important contribution to the field. The report by Rice et al. [10] confirms the efficacy of allogeneic BMT for the treatment of older patients with SAA. Despite the recent progress in IST with combined ATG, cyclosporine, and eltrombopag [4], this report demonstrates the long-term value of allogeneic BMT for SAA.

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