Hematopoietic stem cell transplantation (HSCT) is an aggressive and expensive therapy formulated, in part, to achieve cure in patients with very high-risk or relapsed hematologic malignancies thought to be incurable with standard therapy.[1] Mortality rates have continued to improve with methodologic and supportive care advances, but these remain significant, particularly in the older adult. The procedure requires considerable pretransplant planning, multidisciplinary expertise, personal and cancer center resources, and intense follow-up care.

The Ballester/Tirona/Ballester article provides a systematic review of the data in elderly patients in an attempt to help us manage our older patients. The authors point out immediately, however, that data are generally insufficient to make firm clinical recommendations in an evidenced-based manner for HSCT in the elderly, adding an appropriate plea for increased trials to provide data that will improve our clinical decision-making.

**Assessing Fitness for Therapy**

Historically, patients selected for clinical trials based on established data-derived indications and protocols for the application of HSCT for hematologic malignancies have been restricted to patients less than 50 years old for allogeneic transplant and under 65 for autologous transplant. Use of a single chronologic age as a precise cutoff to indicate clinical fitness for therapies that produce a wide range of organ toxicities from chemotherapy, radiation, graft-vs-host disease, and other insults is well recognized to be problematic. When allogeneic transplant was first implemented, an age over 35 was too old. The development of nonmyeloablative and reduced-intensity conditioning allogeneic HSCT has expanded the age limit.

Since HSCT can be considered one of our most aggressive treatments, with significant morbidity and mortality, this is a clinical situation in need of accurate predictive methodologies for fitness rather than age. Approaches in general oncology practice are under development including applications such as the comprehensive geriatric assessment of fitness for older patients with cancer.[2-4] For HSCT, the authors review a general transplant fitness assessment tool that includes an analysis of comorbidities,[5] which recently has been applied to acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).[6] Overall, as reviewed by the authors and discussed below, such fitness measures in elderly adults need further development and application in the transplant arena.

**Mobilizing Stem Cells**

In the first part of their review, Ballester, Tirona, and Ballester consider three critical questions that are particularly relevant for the older patient. First, can the older individual mobilize sufficient numbers of hematopoietic stem cells that functionally restore stable and long-term hematopoiesis in the recipient? Anyone who has practiced hematology and evaluated bone marrow specimens from individuals of different ages is familiar with the predictable decreased cellularity seen with increasing age (10% per decade, on average). The reported decline in hematopoietic reserve, therefore, is not surprising.

The authors review interesting murine data showing that we have much to learn. Older mice are more anemic but can mobilize more hematopoietic stem cells and progenitor cells.[7,8] Additionally, myeloid/lymphoid ratios and stromal functions are abnormal, potentially of great significance in graft
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biology and the development of graft-vs-host disease. In healthy older humans, CD34+ peripheral blood stem cells are decreased, and again, myeloid/lymphoid ratios are altered, but not necessarily in the same direction as in mice.[9]

Interestingly, the response of hematopoietic stem cells to hematopoietic growth factors may differ in older individuals as well.[10] Although progress awaits the development of biologic measures of bone marrow reserve, advances in improved peripheral blood stem cell mobilization and expansion, and alternative graft sources including double cord transplants and embryonic stem cells, Ballester and coauthors identify studies that support the idea that older individuals—including those over 70—can mobilize sufficient numbers of hematopoietic stem cells to functionally restore stable and long-term hematopoiesis.

**Tolerating High-Dose Therapy**

The second critical question considered by the authors is: Can the older patient tolerate high-dose therapy with reasonable safety? In a large Stanford study of 500 autograft cases, transplant-related mortality (TRM) was 12.7% for those over 50 compared to 7.4% for those over 50,[11] but the oldest patient in the series was 65. The authors conclude that the upper age limit of high-dose therapy with autologous progenitor-cell and/or bone marrow support remains to be defined. Studies of autologous transplants for multiple myeloma have been particularly informative, as reviewed by Ballester and coauthors, and again suggest that for brave, motivated older individuals, appropriately selected, high-dose therapy can be tolerated.

**Clinical Benefit**

The authors’ third critical question relates to whether the older patient can expect clinical benefits similar to those demonstrated for younger individuals. This answer very likely depends, in part, on whether the same hematologic diagnosis is in fact the same biologic entity in older and younger patients. Acute myelogenous leukemia is a case in point. A decreased sensitivity to chemotherapy in many elderly patients is well established, involving factors such as the increased expression of multidrug resistance–related proteins.[12]

Unfavorable cytogenetic profiles correlated with poor outcomes in many studies are also increased in this cohort. We can expect progress with the advent of more sensitive genomic assays, which are revolutionizing our insight into the genetic abnormalities that accompany myelodysplastic syndrome and provide new potential predictors of survival.[13,14] A better ability to identify biologic differences in individual patients in genetic, epigenetic, and underlying oncogene, tumor-suppressor gene, and signaling pathways will presumably improve our ability to select appropriate patients for appropriate therapies.

In the here and now, the reviewers report that older patients with multiple myeloma and chemotherapy-sensitive diffuse large B-cell lymphoma derive benefits from autologous HSCT similar to those seen in younger patients. Small studies suggest that patients with high-risk MDS, AML, and possibly acute lymphocytic leukemia may benefit from nonmyeloablative/reduced-intensity conditioning allogeneic HSCT. This requires additional study.

At Johns Hopkins, protocols are being tested for advanced hematologic malignancies utilizing haploidentical donors in older and younger patients for whom more suitable grafts are unavailable.[15] Subset analysis of these and other ongoing trials at other institutions may provide future feasibility and outcomes data. It will be critical to assess quality-of-life measures with long-term follow-up in these trials, to help answer these questions for individual patients.

**What Does the Future Hold?**

One way to assess potential future progress is to review trials registered with the National Cancer Institute (NCI) Clinical Trials Network (http://www.cancer.gov/clinicaltrials) and proposals supported by the Blood and Marrow Transplant Clinical Trials Network (BMTCTN).[16] The NCI Clinical Trials Network lists only one HSCT trial specifically designed for elderly adults (protocol 3831495) out of 113 registered transplant trials. This is a phase I/II investigation of allogeneic transplantation from related haploidentical donors in older patients with indolent hematologic malignancies, being conducted at Stanford.

The BMTCTN also reports one current investigation, #0502, a phase II study of nonmyeloablative allogeneic HSCT for older patients with AML in complete remission.[16] Review of the BMTCTN evaluation on the current state of the science for this field identifies many potential research questions relating to the application of HSCT in older adults, including identification of genetic predictors for risk of regimen-related organ toxicities after HSCT, exploration of alternative sources of hematopoietic stem cells, graft-vs-host disease prevention and treatment, and standardization of outcomes-collecting measures, including quality-of-life endpoints. Unfortunately, for many reasons, only a few of these concepts will likely be studied in network clinical trials by this important group.
In the AML section of the BMTCTN, one trial that did receive enthusiastic feedback for development was a proposal to investigate allogeneic transplantation compared to chemotherapy for adults over 60 with AML in first complete remission. The rationale for this study relates to poor results with conventional chemotherapy applied as consolidation in this group, with a median disease-free survival of 7 to 9 months and fewer than 15% alive and disease-free at 3 years.[12] A reduced-intensity conditioning regimen administered to individuals in this age group showed encouraging results, producing a 3-year disease-free survival rate of 44% for recipients with matched-related donors, and 63% for those with matched-unrelated donors.[17] The network has identified the proposed study as a high-priority trial needed to confirm these results prospectively. Among potential proposals related to MDS, the BMTCTN recognized the possible utility of treatment with DNA methyltransferase inhibitor prior to proceeding to an allogeneic transplant for patients with intermediate-2/high-risk disease. This modality to improve outcomes (possibly by changing the biologic response to the transplant) was considered to be of interest, but not of the highest priority.

In Summary
Ballester, Tirona, and Ballester have written an admirably thorough review of hematopoietic stem cell transplantation in the elderly, and current results provide optimism for tolerability and efficacy. It is clear that new advances must be explored, developed, and studied in clinical trials involving older adults with cancer. As the population ages, representation of older patients in clinical trials must be increased to translate findings into meaningful applications of HSCT in this challenging group of patients.

—Michael A. McDevitt, MD, PhD

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