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Allogeneic Hematopoietic Cell Transplantation for AML—A Missed Opportunity!

Margaret R. O'Donnell, MD, FRCPC

I recently received a query from the medical director of the National Marrow Donor Program (NMDP) asking what a realistic expectation was for how many patients should be candidates for allogeneic hematopoietic cell transplantation (HCT) each year. She was looking to identify ways to address the discordance between an extrapolation of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) combined with the SEER database of annual incidence of acute myeloid leukemia (AML) in patients between birth and 74 years of age and the actual numbers of patients receiving a transplant for AML as reported by the Center for International Blood and Marrow Transplant Research (CIBMTR).

Based on our recommendations that most adult patients in first remission with intermediate- and high-risk disease based on cytogenetic and molecular characteristics and patients with induction failure or relapsed disease should be referred for transplant evaluation, with a generous fudge factor to weed out “unfit” older patients (25% for age 55–64 years, and 50% for age ≥65 years), the NMDP estimated that roughly 6,500 potential candidates should be coming to transplant centers for screening. The most recent data on the CIBMTR Web site showed that only roughly 3,000 transplants for AML were performed in the United States in 2013. Why is there such a gap?

In the past, the major obstacle to transplant was donor availability. A generation ago, we felt like we had won the lotto if our adolescent and young adult (AYA) patient had a sibling donor. Over the past 3 decades, we have extended the donor pool through high-resolution human leukocyte antigen (HLA) typing to identify phenotypic HLA matches outside of families and through recruitment of an ever-expanding pool of volunteer donors worldwide. We learned that we could use less perfectly HLA-matched umbilical cord stem cell products that have a more naïve T-cell repertoire. Newer immunosuppressive agents and innovative use of older drugs have now allowed us to extend that pool to the use of haploidentical family donors. This now opens the door to anyone with a healthy parent, sibling, or child. As a last resort, cousins, nieces, nephews, and half-siblings have served as donors.

For patients at high risk in first remission, this gives the option to move quickly to transplant using a family member who is either a full or partial match rather than anxiously waiting several months for an ideal unrelated donor while enduring more consolidation chemotherapy to stave off relapse. This is particularly important for minorities, who are underrepresented in the international registries, and removes a large barrier to access. With this expanded resource, we should be able to increase the number of HCTs in younger patients (<60 years) in first complete remission from 50% to 80%, which could increase the 5-year overall survival to more than 60%. Because haploidentical HCT required greater T-cell inactivation to prevent graft-versus-host disease, the risk of graft failure and relapse is higher due to abrogation of graft-versus-leukemia effect. This makes this option less desirable for patients with active disease.

Age, however, may be the larger hurdle to overcome for referral to and acceptance for HCT. Although I agree with the NMDP assumption that salvage with a myeloablative transplant approach can be successful in patients 60 years of age or younger with active disease, NCCN Guidelines are more circumspect about HCT referral for older patients with active disease outside the context of a clinical trial. The reduced-intensity

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conditioning regimens that have opened the door for potential cure to 40% to 50% of older patients with AML in first complete remission do have a higher risk of relapse than myeloablative regimens; this is offset by lower treatment-related mortality. At best in the older population, only 50% of patients at favorable and intermediate risk and only 35% of patients at high risk treated with conventional chemotherapy are likely to experience remission and be referred for HCT. Of those who experience remission, probably 10% to 20% emerge with organ dysfunction or infections that would preclude HCT. These restrictions should leave us with a potential pool of 30% for older patients in first remission ($\approx 2,000$ people aged 60–74 years) who could be evaluated for HCT.

However, in many studies involving older patients in which HCT was a postremission consolidation strategy, it was not uncommon that fewer than half the eligible patients with donors actually received HCT. Our screening approach seems to be flawed; the tools that we have used to assess “fitness” for HCT, such as comorbidity indices or functionality scores, have not had high correlation with outcomes. “Functionality” also needs to include the social infrastructure needed to support older patients in the post-HCT setting to make this option open to more patients. As supportive care and graft-versus-host disease prophylaxis have improved, transplant-related mortality has declined significantly in the past decade, such that for most large transplant centers, 100-day mortality is less than 10% and 12-month transplant-related mortality is approximately 15% to 20%, even in these older patients.

For many patients who do not experience complete remission or who experience relapse after HCT, several types of clinical trials are available. These trials include dose-intensive radiation with total marrow/lymphoid radiation using conformational tomotherapy, the addition of anti-CD33 drug/immunoconjugates combined with either ablative or reduced-intensity conditioning, and post-HCT therapy with target inhibitors. In addition to traditional donor lymphocyte infusions for relapse, several centers are working on donor-derived CAR T cells targeting tumor-specific antigens, such as CD123.

With all of these advances, the potential population who could benefit from state-of-the-art allogeneic HCT is at least 50% higher than the numbers we are seeing, and we will need to be wise in our use of current infrastructure and resources to meet this need. Although we have made significant progress in making HCT accessible to more patients using wider donor choices and less toxic and better conditioning regimens, and these steps extend the upper age range to the mid-70s, we still struggle with the social factors that create barriers for the patients. These barriers include timely access for HCT evaluation through any form of public or private insurance, rapid access to family HLA typing so that a family donor search might begin before HCT referral, the burden of medication costs outside the hospital, and the emotional and physical toll on families and caregivers, who often lack long-term social support. Although AML induction therapy for non-acute promyelocytic leukemia seems to be stuck in the last century, the ancillary therapeutic arm of allogeneic HCT has evolved from a last-ditch effort to cutting edge therapy with potential applicability to an expanding pool of patients. Seize the opportunity!