Biol Blood Marrow Transplant 25 (2019) e303–e304

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Is Haploidentical HCT Better Than. . .? A Wrong Question for Future Studies

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Article history:
Received 12 July 2019
Accepted 15 July 2019

The Northside Group, one of the first institutions to perform haploidentical hematopoietic cell transplantation (HCT) in the United States, has published a well-written retrospective analysis addressing the optimal donor type for patients with a hematologic malignancy undergoing first allogeneic HCT performed between 2005 and 2016 [1]. The donor types compared in the study were haploidentical family members age <35 years, matched sibling donors (MRDs), and matched unrelated donors (MUDs) age >35 years. There were some expected discrepancies across the 3 groups. In addition to the selected donor age for this study, the patients who underwent haploidentical HCT were younger and received more myeloablative total body irradiation (TBI) and more bone marrow. Haploidentical transplantations were also performed more frequently in recent years and in minority patients.

Most of the major outcomes investigated, including nonrelapse mortality (NRM), disease-free survival, and overall survival, were similar among the 3 groups. Most of the superior outcomes observed after haploidentical HCT compared with MUD or MRD HCT resulted from decreased transplantation-related mortality and chronic graft-versus-host-disease (cGVHD) and increased GVHD-free, relapse-free survival. These results are not surprising, given that some other large registry retrospective comparisons have found similar outcomes after haploidentical HCT and MUD HCT in patients with acute myelogenous leukemia (AML) [2], patients with lymphoma [2], and older patients with AML [3,4]. Moreover, a recent CIBMTR study found similar outcomes in haploidentical HCT and MRD HCT in patients with AML in first complete remission [5]. However, a European Society for Blood and Marrow Transplantation comparison [6] and meta-analysis [7] showed better leukemia-free survival and transplantation-related mortality in MRD HCT.

It is fair to mention that controversies regarding relapse remain. Although in this study, MUD HCT had a higher relapse rate than seen with haploidentical HCT and MRD HCT, higher relapse rates have been reported after haploidentical HCT compared with MUD HCT in older patients with AML or myelodysplastic syndrome [8], as well as in patients with AML receiving a reduced-intensity conditioning regimen [2]. The variations in relapse after haploidentical HCT among studies could be related to differences in patient populations (ie, some patients had lymphoid disease in the study, which might result in better relapse rate in the haploidentical group given haploidentical HCT might be associated with improved relapse in lymphoid malignancies in prior studies [9–11]), disease state at transplantation (ie, less advanced disease or minimal residual disease [12]), conditioning (ie, greater use of myeloablative conditioning regimens), and donor source (ie, greater use of peripheral blood stem cell grafts). Moreover, haploidentical HCT has some drawbacks, including treatment of and survival after relapse, due to in part to unknown factors surrounding donor lymphocyte infusion [13].

These studies, although not prospective studies, consistently demonstrate that haploidentical family members are legitimate donor sources, as are MUDs and umbilical cord blood [14]. Furthermore, haploidentical HCT has clear advantages, including a cost-effective donor search, rapid movement to HCT, and expansion of HCT to more groups of patients, including minorities. Therefore, we HCT providers are now more equipped with these beneficial options. To me, the very general question of what donor type should be replaced by haploidentical donors is not the correct question to ask. Instead, future studies should aim to identify the best donor type at a much more granular level to personalize HCT. (We should move forward the next stage from the studies that showed MUD, MRD, umbilical cord blood, and haploidentical

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https://doi.org/10.1016/j.bbmt.2019.07.020

HCTs have grossly similar outcomes in highly diverse populations. Although these studies have effectively proven that these are all legitimate, good donor sources, these do not help to choose a donor type over another for a specific patient.). In this regard, the most important risks and priorities for each individual patient should be defined (eg, risk of relapse versus risk of poor quality of life due to severe cGVHD) by taking into account the specific disease characteristics (eg, myeloid versus lymphoid, highly proliferative versus slowly progressing), the age of the patient (eg, adolescent versus >70 years), and disease status (eg, active disease versus first complete remission without minimal residual disease). The donor type, donor source, and conditioning intensity should be an essential part of personalized medicine. We need to consider the strengths and concerns of each donor option; for example, haploidentical HCT: strengths, less NRM and cGVHD; concern: graft-versus-tumor (GVT) effect in myeloid disease; umbilical cord blood: strengths, strong GVT effect and less cGVHD; concern, greater NRM (especially in early phase after HCT); MUD: strengths, better engraftment, GVT effect in myeloid disease; concerns, more acute GVHD and cGVHD. In conclusion, haploidentical donors represent a viable donor type to expand our options while moving into personalized medicine in HCT.

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