Based on the available data, alemtuzumab, 300 cGy TBI, and sirolimus may be one such regimen, or it is certainly an excellent candidate for matched sibling donors.

There is renewed interest in allo-HSCT for SCD and steady progress has been made. For adults or those with high comorbidity, patients and transplantation physicians alike now have options with reasonable expectation for great outcome. Thus, I believe we have arrived: allo-HSCT from matched sibling donors can be considered part of the standard of care in adults with SCD. Additionally, we have a regimen—alemtuzumab, 300 cGy TBI, and sirolimus—with excellent clinical outcomes to be used alone or as a backbone for further modification. I am very hopeful that the same success with low toxicity can be extended to other institutions to offer this curative option to more adults.

ACKNOWLEDGMENTS

This work is supported by the intramural research program of the National Heart, Lung, and Blood Institute.

Financial disclosure: The author has nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to declare.

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To Match or Not to Match in Cord Blood Transplantation: A Modern Look at a Recurring Question

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Article history:
Received 11 January 2016
Accepted 11 January 2016

The question of the importance of HLA matching in hematopoietic stem cell transplantation (HSCT) with umbilical cord blood (CBT) has been debated without resolution for almost 2 decades. Every few years, the pendulum swings, with publication of reports favoring greater or lesser degrees of matching [1]. The report by Brunstein et al [2] in this issue swings the pendulum back to mismatching once again. The report shows, in a well-characterized cohort of 342 patients treated at a single institution, that greater allele-level HLA mismatching between donor and recipient cord blood grafts in patients with hematologic malignancy undergoing double cord blood transplantation (dCBT) did not negatively impact the incidence of engraftment, acute and chronic graft-versus-host disease (GVHD), or nonrelapse mortality. Furthermore, greater HLA mismatching protected against leukemic relapse in a subset of 174 patients who underwent dCBT for acute leukemia.

Financial disclosure: See Acknowledgments on page 399.

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http://dx.doi.org/10.1016/j.bbmt.2016.01.020

There is clearly something different about cord blood compared with more mature sources of hematopoietic stem cells, such as bone marrow (BM) and mobilized peripheral blood stem cells. From the earliest days of CBT, it was known that GVHD was dramatically decreased when using HLA-matched cord blood from a sibling compared with HLA-matched BM from a sibling [3]. This effect was hypothesized to be due to increased tolerance of cord blood lymphocytes induced by the state of pregnancy, in which the infant and the mother tolerate one another despite an HLA mismatch between them. Support for this theory was provided by the observation of successful haploidentical CBT when the mismatch involved the noninherited maternal haplotype (NIMA). John Van Rood and Pablo Rubinstein subsequently demonstrated that cord blood units mismatched at NIMA performed as well as fully matched units as donor grafts for unrelated donor CBT (UCBT) [4].

Recent reports of the feasibility of and encouraging short-term results of haploidentical CBT using post-transplantation cyclophosphamide have reduced the enthusiasm for the use of cord blood donors. After all, experienced transplantation centers and oncologists are equipped to administer high-dose cyclophosphamide, and the cost of a BM harvest for a related haploidentical donor is less than the cost of 2 publically banked cord blood units. However, although engraftment, GVHD, and early survival may be equivalent in these 2 graft sources, in the limited available reports, relapse rates are higher with haploidentical grafts.

If relapse-free survival is the endgame, and if donor selection can decrease the chance of relapse as observed with dCBT, then strong consideration of the donor source should be undertaken by the transplantation team. Although best demonstrated in the current report, suggestions that increasing mismatching with unrelated cord blood donors has equivalent outcomes and prevents leukemic relapse also have been suggested in the Cord Blood Transplantation (COBLT) Study [5] and the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) study 0501 [6]. In the COBLT study, no relationship between HLA mismatching at the allelic level was seen, even though units were demoted from 5/6 and 4/6 matches to as low as 3/6 and 2/6 matches. In the BMT-CTN 0501 study, the relapse rate was lower in older children with acute lymphoblastic leukemia undergoing transplantation with dCBT compared with those undergoing single-unit CBT.

These observations are critically important to help define the role of unrelated donor banked cord blood as an alternative graft source for patients lacking fully HLA-matched related donors or unrelated adult donors in national and international registries. With the current inventory of >700,000 units worldwide, appropriately dosed mismatched units can be identified for more than 95% of patients. If the results of Brunstein et al. are confirmed in larger multi-institutional studies, then mismatched cord blood should become the graft source of choice for patients with high-risk, refractory, relapsed leukemia undergoing HSCT. For patients with acute leukemia, even if early costs of UCBT may be greater than those with other graft sources, the overall cost of preventing a post-transplantation relapse will be realized in studies that follow patients out to 2 to 3 years, not to mention the fact that a life saved cannot really be measured in dollars. Mismatched cord blood is a promising weapon in the arsenal against relapsed leukemia, and Brunstein et al. have brought us another step closer to understanding the best way to mobilize this asset to increase the likelihood that HSCT can cure patients with leukemia.

ACKNOWLEDGMENTS

Financial disclosure statement: The author has nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to declare.

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