Published in final edited form as:
Biol Blood Marrow Transplant. 2015 January ; 21(1): 4–7. doi:10.1016/j.bbmt.2014.09.017.

Recommendations for Donor HLA Assessment and Matching for Allogeneic Stem Cell Transplantation: Consensus Opinion of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

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Abstract

The Blood and Marrow Transplant Clinical Trials Network conducts large, multi-institutional clinical trials with the goal of improving the outcomes of hematopoietic cell transplantation (HCT) for patients with life-threatening disorders. Well designed HCT trials benefit from standardized criteria for defining diagnoses, treatment plans and graft source selection. In this perspective, we summarize evidence supporting criteria for the selection of related and unrelated adult volunteer progenitor cell donors or umbilical cord blood units. These standardized criteria for graft source selection have been adopted by the BMT CTN to enhance the interpretation of clinical findings within and among future clinical protocols.

Keywords

allogeneic transplants; cord blood donor; unrelated donor; related donor; recipient

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Introduction

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was established in 2001 to conduct large, multi-institutional clinical trials with the goal of improving the outcomes of hematopoietic cell transplantation (HCT) for patients facing life-threatening disorders. The BMT CTN allows the HCT community to conduct prospective, collaborative, clinical research within an infrastructure designed to offer participation in HCT clinical trials to patients in all regions of the United States (US). Nearly 18,000 HCTs are performed in the US annually and this increases by approximately 5% per year [1]. This growth reflects the utility of HCT in treating both malignant and non-malignant disease, higher donor availability, and treatment advances that allow HCT to be performed in older and sicker patients. While HCT is a rapidly evolving field, HCT clinical trials face unique challenges, including the relatively small number of HCTs performed at any single center, the diverse indications for HCT, the complexities of the procedure and risks for multiple post-transplant complications. The BMT CTN was established to address these challenges and execute multicenter HCT trials with broad national participation. Well designed HCT trials benefit from standardized criteria for defining diagnoses, treatment plans and graft source selection.

The development of clinical guidelines and standards founded on evidence-based research is an important aspect of directing and implementing clinical patient care. Over the past decade, there have been significant developments in HLA typing technologies and in the availability of outcome data from large multi-center studies evaluating a growing number of stem cell sources. Together, these advances provide guidance for consideration in development of clinical trial protocols to ensure generalizability of the results to standard of care treatment.

A recent review of current and completed clinical trials within the BMT CTN illustrated significant variability in the donor and recipient HLA matching criteria used in these trials*. Based upon available clinical research data, it was determined that future clinical studies would benefit from the utilization of consistent criteria regarding the most relevant HLA and non-HLA factors to consider in the selection of related and unrelated adult volunteer progenitor cell donors or umbilical cord blood units. The BMTCTN has adopted the following guidelines for HLA evaluation and donor/recipient matching.

Related Donor Stem Cell Transplants

Fully HLA Matched Sibling

An HLA identical or fully HLA matched sibling is considered the optimal and first choice graft for allogeneic HCT. The recipient, siblings and parents (where available) should be HLAA, -B typed at intermediate or higher resolution and HLA-DRB1 typed at high resolution by DNA-based methods as a minimum requirement. Where possible, familial haplotypes should be assigned to establish presumptive high resolution match identity between the donor and recipient (additional HLA loci may be considered, e.g., HLA-C and -DQB1). The recipient and selected sibling donor should be a 6/6 match at HLA-A, -B and -

*BMT CTN clinical protocols can be accessed on the public BMT CTN website https://web.emmes.com/study/bmt2/index.html.

DRB1. In the absence of family typing to establish familial haplotypes, high resolution typing by DNA based methods should be performed and the recipient and donor fully matched at HLA-A, -B, -C, and -DRB1.

HLA Mismatched Relative

Two thirds or more of all patients in the U.S. will lack an HLA matched sibling and must consider an alternative graft choice [2]. Clinical studies have shown partially HLA-mismatched related (e.g. one HLA antigen mismatched or HLA haplo-identical) hematopoietic stem cell grafts can be a suitable source of donor cells in some settings, thus extending this treatment modality to patients who lack other donors [3-5]. Mismatched related donors are assigned to categories based on the level of HLA match.

- **One Antigen Mismatched Related Donor**- The donor differs from the recipient by a single HLA antigen (e.g., sibling with a crossover). The recipient and donor should be HLA-A, -B, -C typed at intermediate or higher resolution and HLA-DRB1 typed at high resolution by DNA-based methods as a minimum requirement. The recipient and selected related donor should be a 7/8 match at HLA-A, -B, -C and -DRB1.
- **Haplo-identical Related Donor**- Parents, siblings and other relatives sharing a single HLA haplotype with the recipient are considered haplo-identical. The recipient and the selected donor should be HLA-A, -B, -C typed at intermediate or higher resolution and HLA-DRB1 typed at high resolution by DNA-based methods as a minimum requirement. Where possible, familial haplotypes should be assigned to establish haploidentity between the donor and recipient. The recipient and related donor should be ≥ 4/8 match at HLA-A, -B, -C and -DRB1, with only one mismatch per locus. A significant risk of graft failure exists in the setting of HLA-mismatched related transplantation in HLA sensitized patients [6]. Patients should be screened for the presence of antibodies and donors carrying an HLA target avoided if possible. Data on recipient desensitization to reduce titers of donor specific antibodies is now emerging, but further studies are needed to better refine this strategy.

Unrelated Donor Stem Cell Transplants

Viable alternatives to related donors are well matched unrelated donors and cord blood units. The development of large international volunteer donor registries and cord blood banks facilitate availability of a stem cell source for nearly all patients without a suitable related donor [7].

Adult Unrelated Donor

Based on the findings of numerous large, contemporary retrospective studies and comprehensive reviews, overall survival is increased and transplant-related mortality reduced when recipients of unrelated donor hematopoietic stem cell transplantations are evaluated and matched at high resolution for HLA-A, -B, -C, and HLA-DRB1 (8/8 matched) [8-10]. When 8/8 matched adult volunteer donors are not available, then a single HLA locus mismatched donor (7/8 matched) can be considered with acceptable risks of transplant-

related mortality [8]. HLA high-resolution match is defined as equivalent amino acid sequences (G group) in the antigen recognition site (ARS; exon 2 and 3 for HLA Class I and exon 2 for HLA Class II) of the molecule that binds peptide and interacts with the T cell receptor [11]. The impact of variation outside the ARS is not well characterized because of limitations of the current typing methodologies and a lack of clinical correlation studies [12-13].

When multiple equivalently matched unrelated donors are available the consideration of addition HLA loci and non-HLA factors may be used to prioritize the final donor selection. Testing of additional HLA loci (e.g., HLA-DPB1, DQB1 and DRB3/4/5) will assist in selecting donors with minimal mismatching at low expression loci [14] and T-cell epitope permissive HLA-DPB1 mismatches [15-17]. Additionally, extended HLA testing can also support the selection of appropriate donors in the context of HLAsensitized patients to avoid the potential risk of graft failure [18, 19]. In the 7/8 matched setting, donors can also be prioritized for permissive HLA-C*03:03/03:04 mismatches [20] or host versus graft only mismatches [21] to optimize outcomes. Finally, based upon the findings of a recently reported CIBMTR retrospective study [22], centers may want to consider: (1) younger unrelated donors, found to be associated with less aGVHD and better overall survival, and (2) ABO compatible donors, which were also associated with better survival.

Umbilical Cord Blood—Umbilical cord blood transplants expand access to patients unable to find a suitable unrelated adult donor due to a traditionally lower threshold of HLA match [8, 23]. The recipient and cord blood units should at minimum be typed at HLA-A, and -B at intermediate resolution (or higher) and HLA–DRB1 typed at high resolution by DNA-based methods. The recipient and selected cord blood unit or units, in the case of a multiple cord blood transplant, should be ≥ 4/6 HLA match at HLA-A, B (intermediate resolution) and -DRB1 (high resolution).

A recently published retrospective study [24] supports the consideration of high resolution matching at HLA-A, B, C and DRB1 to maximize graft success and minimize risks of non-relapse mortality. The study also found that the impacts of HLA matching were not offset by increasing cell dose beyond the minimal recommended total nucleated cell dose of ≥ 3×10^7/kg. Future clinical studies may want to consider HLA-A, -B, -C and –DRB1 typing at high resolution by DNA-based methods, with the recipient and selected cord blood unit being a ≥ 6/8 HLA allele match at HLA-A, -B, -C and -DRB1. When multiple suitably matched, adequate cell dose cord blood units are available, additional criteria may help guide the final cord blood unit selection(s). As with mismatched unrelated donors, extended HLA testing can also support the selection of appropriate cord blood units in the context of HLA-sensitized patients to avoid the potential risk of graft failure [25-26]. There is also evidence to suggest that selecting a mismatched cord blood unit where the mismatch involves a non-inherited maternal antigen may improve survival [27-28].

BMT CTN Recommendations

The minimum recommendations for donor/cord blood and recipient HLA testing and matching (Table 1) represent the consensus opinion of the BMT CTN Steering Committee,

with support and endorsement by the American Society of Histocompatibility and Immunogenetics. The recommendations have been adopted for use in future BMT CTN clinical trial development and will allow for generalization of donor/recipient compatibility across protocols.

Acknowledgments

The authors thank all the members of the BMT CTN Steering Committee for their valuable discussions that contributed to the development and application of these guidelines in both current and future clinical trial design. Finally, the authors would like to thank Alyssa Carlson of the Center for International Blood and Marrow Transplant Research for assistance in manuscript preparation.

Financial Disclosure: Support for this manuscript was provided by grant #U10HL069294 from the National Heart, Lung, and Blood Institute and the National Cancer Institute. Any views, opinions, findings, conclusions or recommendations expressed in this manuscript are those of the author(s) and do not reflect the views or the official policy or position of the above mentioned parties.

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Table 1

Recommendations for Donor HLA assessment and matching categorization for allogeneic stem cell transplantation clinical trial protocol development.

Allogeneic Transplant	Donor and Recipient HLA Matching Recommendation
Matched Sibling	**6/6 HLA match** HLA-A and -B (at intermediate or higher resolution using DNA based typing) HLA-DRB1 (at high resolution using DNA based typing)
1 Antigen Mismatched Related	**7/8 HLA match** HLA-A, -B, -C (at intermediate or higher resolution using DNA based typing) HLA-DRB1 (at high resolution using DNA based typing)
Haploidentical Related	**≥4/8 HLA match** HLA-A, -B, -C (at intermediate or higher resolution using DNA based typing) HLA-DRB1 (at high resolution using DNA based typing) [fewer than 2 mismatches per locus]
8/8 Matched Unrelated Adult	**8/8 HLA match** HLA-A, -B, -C and -DRB1 (at high resolution using DNA based typing)
7/8 Unrelated Adult	**7/8 HLA match** HLA-A, -B, -C and -DRB1 (at high resolution using DNA based typing) [7/8 donor available in most situations, do not recommend ≦6/8]
Umbilical Cord Blood	**≥4/6 HLA match** HLA-A, -B (intermediate resolution or higher using DNA based typing) and -DRB1 (at high resolution using DNA based typing)