



# Biology of Blood and Marrow Transplantation

journal homepage: [www.bbmt.org](http://www.bbmt.org)



## Opinion

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



C. Alan Howard<sup>1</sup>, Marcelo A. Fernandez-Vina<sup>2</sup>, Frederick R. Appelbaum<sup>3</sup>, Dennis L. Confer<sup>1,4</sup>, Steven M. Devine<sup>5</sup>, Mary M. Horowitz<sup>6</sup>, Adam Mendizabal<sup>7</sup>, Ginna G. Laport<sup>8</sup>, Marcelo C. Pasquini<sup>6</sup>, Stephen R. Spellman<sup>1,\*</sup>

<sup>1</sup>Immunobiology Research, Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota

<sup>2</sup>Department of Pathology, Stanford Medical School Blood Center, Stanford, California

<sup>3</sup>Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

<sup>4</sup>National Marrow Donor Program, Minneapolis, Minnesota

<sup>5</sup>Blood and Marrow Transplant Program, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio

<sup>6</sup>Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin

<sup>7</sup>The EMMES Corporation, Rockville, Maryland

<sup>8</sup>Division of Blood and Marrow Transplantation, Stanford University Medical Center, Stanford, California

## Article history:

Received 16 September 2014

Accepted 24 September 2014

## Key words:

Allogeneic transplantations  
Cord blood donor  
Unrelated donor  
Related donor  
Recipient

## ABSTRACT

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 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.

© 2015 American Society for Blood and Marrow Transplantation.

## 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. Nearly 18,000 HCTs are performed in the United States annually and this increases by approximately 5% per year [1]. This growth reflects the utility of HCT

in treating both malignant and nonmalignant disease, a higher donor availability, and treatment advances that allow HCT to be performed in older and sicker patients. Although 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-transplantation complications. The BMT CTN was established to address these challenges and execute multi-center 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 multicenter studies evaluating a growing

*Financial disclosure:* See Acknowledgments on page 6.

\* Correspondence and reprint requests: Stephen R. Spellman, Immunobiology and Observational Research, Center for International Blood and Marrow Transplant Research, 3001 Broadway Street NE, Suite 100, Minneapolis, MN 55413.

E-mail address: [sspellma@nmdp.org](mailto:sspellma@nmdp.org) (S.R. Spellman).

<http://dx.doi.org/10.1016/j.bbmt.2014.09.017>

1083-8791/© 2015 American Society for Blood and Marrow Transplantation.

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 BMT CTN has adopted the following guidelines for HLA evaluation and donor/recipient matching.

## RELATED DONOR STEM CELL TRANSPLANTATIONS

### 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 HLA-A and -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, eg, HLA-C and -DQB1). The recipient and selected sibling donor should be a 6/6 match at HLA-A, -B, and -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 United States will lack an HLA-matched sibling and must consider an alternative graft choice [2]. Clinical studies have shown partially HLA-mismatched related (eg, 1 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 (eg, 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, and -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  $\geq 4/8$  match at HLA-A, -B, -C, and -DRB1, with only 1 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 should be avoided if possible. Data on recipient desensitization to reduce titers of donor specific antibodies are now emerging, but further studies are needed to better refine this strategy.

## UNRELATED DONOR STEM CELL TRANSPLANTATION

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 transplantation-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 -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 transplantation-related mortality [8]. HLA high-resolution match is defined as equivalent amino acid sequences (G group) in the antigen recognition site (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 antigen recognition site 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 additional HLA loci and non-HLA factors may be used to prioritize the final donor selection. Testing of additional HLA loci (eg, 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 HLA-sensitized 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 Center for International Blood and Marrow Transplant Research retrospective study [22], centers may want to consider: (1) younger unrelated donors, found to be associated with less acute graft-versus-host disease and better overall survival, and (2) ABO compatible donors, which were also associated with better survival.

### Umbilical Cord Blood

Umbilical cord blood transplantations 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 a minimum, be typed at HLA-A and -B at intermediate resolution (or higher)

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

Download English Version:

<https://daneshyari.com/en/article/2101854>

Download Persian Version:

<https://daneshyari.com/article/2101854>

[Daneshyari.com](https://daneshyari.com)