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Optimal HLA Matching in Haematopoietic Cell Transplantation

Effie W. Petersdorf, MD

Division of Clinical Research, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D4-100, Seattle, WA 98109-1024

Effie W. Petersdorf: epetersd@fhcrc.org

Summary of Recent Advances

Only 30% of patients in need of a hematopoietic cell transplant will have an HLA identical sibling to serve as the donor. Advances in the field of immunogenetics together with the growth of donor registries and cord blood banks worldwide have provided many of these patients the opportunity for a life saving transplant. Current data demonstrate the importance of matching the unrelated donor for HLA alleles and antigens. When a matched volunteer donor is not available, use of mismatched donors may be considered. New concepts in the selection of mismatched donors include consideration for the locus, the number of mismatches, differences between alleles and antigens, the location and nature of amino acid mismatches that define class I epitopes, and the presence of haplotype mismatching. When cord blood transplantation is an option, both cell dose and HLA matching are important variables. Optimizing the overall outcome of hematopoietic cell transplantation requires an appreciation for the relative importance of HLA factors with respect to other non-genetic factors that also influence transplant outcome.

Keywords

unrelated donor hematopoietic cell transplantation (HCT); HLA epitopes; HLA haplotypes; non-inherited maternal antigens (NIMA); cord blood transplantation (CBT)

Introduction

2008 marks the 50th anniversary of the description of HLA antibodies. [1] The field of immunogenetics has witnessed many milestones during this time, beginning with the clinical application of serological typing reagents followed by the development of cellular assays. Most recently, molecular methods have provided an unprecedented view of the diversity of the HLA region. The application of DNA-based methodologies to the selection of unrelated donors (URDs) for hematopoietic cell transplantation (HCT) has contributed to the improved survival of transplant recipients and has shed light on the basis of alloreactivity in transplantation. This review highlights work in the field of immunogenetics of HLA in HCT with a focus on new studies published in 2007. Specific emphasis on the criteria for the evaluation and selection of URDs, mismatched related donors, and cord blood units is provided. The work described by these studies showcases the importance of HLA alloantigens and their haplotypes in shaping graft failure, graft-versus-host disease (GVHD)

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and relapse, and provides a platform for the use of HLA mismatched stem cell products for the treatment of hematologic disorders.

Unrelated Donor HCT

Mismatching for Different HLA Loci Confer Risks of Different Magnitude

Current criteria for the selection of URDs for hematopoietic cell transplantation (HCT) is based on high-resolution definition of the class I HLA-A, B, C, and class II DRB1, DQB1 alleles. Historically, matching for alleles at all five loci ("10/10" matched) lowers the risks of clinically severe acute graft-versus-host disease (GVHD) and mortality and is associated with superior disease free survival (DFS) compared to transplantation from mismatched donors. [2–4]

When only HLA mismatched donors are available, knowledge of locus-specific risks may aid in donor selection. [2–5] Among Caucasian transplant recipients, single locus mismatches are each associated with significantly increased risks of acute GVHD (HLA-A, B and C), transplant-related mortality (TRM) (HLA-A, C and DRB1) and mortality (HLA-A, C and DRB1). [6] Of all the classical HLA genes, HLA-DQB1 mismatching may be the most permissible. [6] These data suggest that outcome after HCT from "8/8" matched donors at HLA-A, B, C and DRB1 is associated with similarly good outcome as 10/10 HCT, and suggest that when a matched donor is not available, use of a donor with a single DQB1 mismatch may be acceptable.

Recent data suggest that HLA-DPB1 is a classical transplantation gene, mismatching of which is associated with graft failure and GVHD. [7–10] The observation that the risks of GVHD may be offset by a beneficial effect of graft-versus-leukemia (GVL) leading to lower disease recurrence, provides a potential therapeutic avenue for patients with high-risk malignancies. [8]

The Total Number of Mismatches Affects the Risks of Graft Failure, GVHD and Mortality

Risks of graft failure, acute GVHD and mortality are amplified with multi-locus mismatching. [2–4,6,7,9,11,12] Additive effects of mismatching at HLA-A, B, C and DRB1 can be measured for early, intermediate and late stage disease. The most pronounced effect of HLA disparity on survival is evident for patients with early stage disease in whom a 10 – 11% lower survival is observed with every additional HLA mismatch. [6] Although the presence of a single HLA-DQB1 mismatch was tolerable, the presence of an HLA-DQB1 disparity in addition to mismatches at HLA-A, B, C, or DRB1 was associated with worse outcome, indicating that prospective HLA-DQ typing is indicated when the choice must be made among donors with known HLA-A, B, C, or DR mismatches. [6]

The Risks of Graft Failure and GVHD are Higher with Mismatching for HLA-C Antigens Compared to Alleles

The availability of molecular methods for HLA typing in the late 1980s opened a new era of donor matching and selection; the demonstration that HLA antigens could represent a family of unique sequences or alleles, had a dramatic impact on donor matching and stimulated new research into the relative risks of alleles and antigens. Studies have suggested that antigen mismatches (disparities between two serologically different HLA determinants) are more immunogenic than allele mismatches (disparities between two unique sequences of the same HLA antigen) [4] particularly for HLA-C. [13] These data suggested that when HLA matched donors are not available, prioritization of allele mismatched over antigen mismatched donors may lower post-transplant complications. When the stage of disease is taken into account, allele mismatches may be as detrimental as antigen mismatches, [2]

suggesting that transplant outcome is defined by both the degree of donor mismatching as well as disease risk.

In the recent CIBMTR study, antigen and allele mismatches conferred similar risks with one important exception, HLA-C. [6] When compared to transplants from HLA-A, B, C, DRB1 allele matched donors ("8/8"), HLA-C allele mismatches were not associated with statistically significantly higher mortality, TRM or acute GVHD; however, transplantation from donors mismatched for HLA-C antigens conferred increased risk. These data suggest that selection of an HLA-C allele mismatched donor should be prioritized over an HLA-C antigen mismatched donor, when HLA matched donors or single DQB1 mismatched donors are not available.

Mismatching at Specific Epitopes Confer Risk

The allele and antigen-associated risks described above suggest that the immunogenicity of HLA mismatches may be influenced by the nature of nucleotide substitutions located within the peptide binding groove and/or at positions involved in contact with the T-cell receptor. Two major approaches have been taken to identify functional residues. The concept that alloreactivity arises from donor recognition of recipient sequence polymorphisms encoded in the $\alpha 1$ and $\alpha 2$ domains of class I molecules led to the use of the cytotoxic T lymphocyte precursor (CTLp) assay for measuring CD8-positive T cell mediated alloreactivity between HLA class I mismatched pairs. [14] Comparative sequence analysis has provided novel information on putative residues important in GVH allorecognition. [15,16]

Early work demonstrated a correlation between CTLp and GVHD risk; lower frequencies of patient-specific CTLs were associated with lower probability of clinical GVHD. [17] The association of clinical outcome with CTLp reactivity was informative for the number of mismatches encoded within the α helix and β -pleated sheet of single class I locus mismatches. [18] The presence of 5 α /5 β mismatches in addition to a negative CTLp was a strong predictor of favorable outcome compared to any other mismatch. These results suggest that both the number of mismatched epitopes as well as the ability of these epitopes to elicit a CTLp, provide additional information than either variable alone on the tolerability of class I mismatches.

Site-specific mutagenesis has been used to elucidate HLA-DP motifs that define alloreactive T cell epitopes. Presence of the 8LFQG11 motif encoded by the HLA-DP β chain abrogates the T cell epitope (TCE) and is indicative of permissible mismatches [10,19,20] Since the vast majority of recipients and donors selected on criteria for HLA-A, B, C, DRB1 and DQB1 are mismatched at the HLA-DP locus, the absence of this alloreactive disparity has major practical implications in the selection of donors. As many as 75% of donor-recipient pairs would not be mismatched for the TCE disparity in the host-versus-graft direction and use of such donors would be predicted to substantially lower the risk of graft failure, especially in the setting of HCT for thalassemia. [20]

Non-permissive mismatches may also be defined through a sequence comparison of each mismatched residue with clinical outcome. The putative amino acid sequence of all polymorphic positions encoded among patients and their URDs can be deduced from the high resolution typing of each HLA class I and II allele. The earliest study to correlate transplant outcome with mismatching for specific class I residues did so in a homogeneous population of HLA-B mismatched unrelated donors and recipients. [15] Mismatching at HLA-B for positions 114 and 116 was associated with increased risk of TRM; position 116 disparity was associated with increased risk of severe GVHD and likely contributed to the high TRM in these patients. A linear relationship between the number of mismatched positions and the probability that a donor-recipient would be mismatched at 116 was

observed. These data suggested that interaction of the position 116 amino acid with the P9 residue of the bound peptide plays a key role in defining immunogenicity of HLA-B molecules.

The observations from the Ferrara analysis were extended in a recent, comprehensive study of 5210 patients. [16] A total of 4 HLA-A, 1 HLA-B, 7 HLA-C, 2 HLA-DR/DQ haplotypes, and 2 HLA-DP non-permissive mismatch combinations were identified. Furthermore, risk increased as the number of non-permissive mismatches increased from 0 to 1 or 2 or more. Donor-recipient mismatching at 6 specific positions were found to define GVHD risk: Tyr9 – Phe9 of HLA-A; Tyr9 – Ser9, Asn77 – Ser77, Lys80 – Asn80, Tyr99 – Phe99, Leu116 – Ser116, and Arg156 – Leu156 of HLA-C. Interestingly, these positions also strongly correlated with the predictive models for hydrophobicity. The data provide a framework for the definition of high-risk mismatches.

Mismatching for HLA-A,B,DR Haplotypes Confers Risk

The current approach for the selection of potential URDs is based on matching each allele of each antigen defined by HLA-A, B, C, DRB1 and DQB1. Since HLA matched URDs and recipients are identical by state, they may differ for undetected variation within the HLA region; such undetected polymorphism may be functional and may account for the increased risks of GVHD compared to HLA genotypically identical sibling HCT. A haplotype-based approach for mapping novel transplantation determinants is based on the extensive linkage disequilibrium (LD) across the HLA region and the concept that the physical relationship of HLA alleles on haplotypes might serve as a surrogate marker of functionally important undefined inter-locus variation carried on those haplotypes. A novel method for physically linking markers across megabase distances has recently been applied to assess whether haplotype matching could further improve clinical outcome beyond 5-locus, 10-allele matching. [21] Although the 10/10 allele matched donor-recipient pairs encoded common HLA alleles and antigens, 20% were haplotype mismatched. The presence of haplotype mismatching was associated with a significantly increased risk of grades III – IV acute GVHD and lower risk of recurrent disease, indicating a GVL effect. These data suggest that novel transplantation determinants may be defined through evaluation of the extended HLA haplotype, and that the overall results of HLA matched URD HCT may be further optimized by haplotype matching.

Haploidentical Related HCT: The NIMA Effect

The immediate availability of family donors provides an attractive alternative to a URD, particularly when the patient's clinical status warrants expedient timing of the transplant, and/or the patient's genotypes and haplotypes strongly suggest that the search for a suitable URD may be long and difficult. Siblings may share one maternal or paternal haplotype with each other. Non-inherited maternal antigens, also known as NIMA, are those antigens of the non-shared haplotypes. Transplantation from mother to child is associated with low risk of both acute and chronic GVHD and mortality indicating that there is donor-specific suppression of T cell responses against NIMAs. In contrast, transplantation from father to child is associated with higher risk of GVHD, indicative of an immunizing effect of paternal antigens. [22–24] This clinical experience provides a means to further optimize transplant outcome through the preferential selection of family members inheriting haplotypes encoding NIMAs.

Non-genetic Factors Influence Transplant Outcome: Stage of Disease

One of the strongest risk factors for recurrence of disease after HCT is the stage of disease at the time of transplantation. [2,6] These studies indicate that disease factors as well as

availability of potential donors and their HLA match status should be taken into account when planning HCT; a balance between the risks of disease recurrence and the risks associated with HLA mismatching is imperative when the search does not yield matched donors. In addition to disease stage, recipient age, race and CMV serostatus may influence transplant outcome. [6,25] CMV positivity of the transplant recipient (regardless of the donor's serostatus), recipient age older than 31 years, and recipient African American background are each independent risk factors for mortality. [6]

The HLA Barrier in Cord Blood Transplantation

The establishment of cord blood (CB) banks has greatly facilitated cord blood transplantation (CBT) as a therapeutic modality for both pediatric and adult blood disorders. [26–35] CBT provides a unique model for understanding the HLA barrier. The current standard for the selection of CB units includes definition of HLA-A and B antigens and DRB1 alleles (6 total determinants); with this standard, the vast majority of CBTs have been performed using units with match grades of 6/6, 5/6, or 4/6 to the recipient. [36] The higher tolerance for HLA mismatching in CBT compared to bone marrow or peripheral blood stem cell transplantation has been attributed to fewer mature T cells in the cord blood graft and their diminished capacity to participate in Th1 responses. [37] Despite HLA incompatibility, acute GVHD risk may be lower after CBT than after URD HCT, and recent data suggests that chronic GVHD following CBT may be more responsive to therapy. [38] The major limitation of CBT, particularly for adults, has been the limiting cell dose per recipient body weight; low cell dose correlates not only with slower rate of engraftment and lower overall survival, but also lower probability of achieving engraftment. Several new approaches have been pioneered to surmount the limitations of cell dose, including the use of double CB units [39–41] and expansion of units to facilitate engraftment. [42] The development of reduced intensity conditioning regimens is an attractive option for patients at high risk of regimen-related toxicity. [43–45] The extensive historical background of CBT is beyond the scope of this HLA update, and the reader is invited to several outstanding recent reviews. [36,37,45–50]

Cell dose is the most important factor that consistently correlates with outcome after CBT. The complex interaction between the effects of cell dose and HLA mismatching has made the study of independent HLA effects challenging; however, HLA-associated risks can be measured when cell dose is taken into account. [26–28,30–32,35,46] Furthermore, the negative effects associated with HLA mismatching can in part be abrogated with higher cell dose. [35] An HLA dose effect is also apparent; the risks of graft failure increase as the number of HLA mismatches increases, and the combination of class I with class I mismatches correlates with risk of severe acute GVHD. [51] HLA mismatching may be especially detrimental for patients with non-malignant diseases. [35,52] Evidence for a GVL effect associated with higher degrees of HLA mismatching strongly contributes to higher disease-free survival for patients with high risk leukemia [35,48] [53]

Emerging evidence suggests that risks may be locus-specific. Disparity for class II, particularly for HLA-DRB1, may increase risk of acute GVHD and mortality. [54] If matching for HLA-A and B antigens and DRB1 alleles is associated with better outcome compared to mismatching, will matching for HLA alleles provide a means to further optimize CBT? The benefit of high resolution typing information was recently evaluated in a population of 122 recipients of CB transplants. [55] Not surprising the degree of HLA allele matching ranged from 2/10 to 8/10. No statistically significant association between the number of HLA disparities and neutrophil recovery was observed; however, mismatching at HLA-A and C were each associated with a reduced incidence of engraftment. Retrospective analysis of the role for high resolution typing and matching in CBT remains an important

question and one that will require large, well-characterized transplant populations due to the anticipated high degree of allele mismatching and the need to account for cell dose.

Conclusions

Increasing the availability of URD HCT requires information on the rules that govern permissible HLA mismatching and a better understanding of HLA-associated risks of GVHD and potential benefits of GVL. The definition of permissible mismatches according to amino acid substitutions at key residues provides a novel approach for broadening the use of mismatched donors. For patients who have HLA matched donors, haplotype matching may provide a means to achieve comprehensive matching for undetected variation linked to HLA genes. CBT is an attractive option for patients who lack a donor, and/or whose disease activity does not afford the time for an unrelated donor search. Although the limits of HLA mismatching in CBT are still coming into focus, clinical experience indicates that a higher degree of HLA disparity can be tolerated and is associated with beneficial GVL effects.

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