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Risk assessment in haematopoietic stem cell transplantation: Histocompatibility

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Abstract

Consideration of potential donors for transplantation includes a rigorous assessment of the availability and HLA-match status of family members, and the identification of suitable unrelated donors when related donors are not available. Because HLA gene products provoke host-versus-graft and graft-versus-host alloimmune responses, HLA matching serves a critical preventive role in lowering risks of graft failure and graft-versus-host disease (GVHD). At the same time, graft-versus-leukemia effects associated with HLA mismatching may provide an immunological means to lower the recurrence of post-transplant disease in high-risk patients. The definition of a suitable allogeneic donor is ever changing, shaped not only by current typing technology for the known HLA genes but also by the specific transplant procedure. Increased safety of alternative donor hematopoietic cell transplantation (HCT) has been achieved in part through advances in the field of immunogenetics. Increased availability of HCT through the use of HLA-mismatched related and unrelated donors is feasible with a more complete understanding of permissible HLA mismatches and the role of NK-KIR genes in transplantation.

Keywords

haploidentical related donor; unrelated donor; HLA matching

The Genetics of the HLA and NK Systems

The HLA genes reside within the 7.6-Mb extended region of the major histocompatibility complex (MHC) on chromosome 6p21, residence of over 100 loci involved in immune function.¹ *HLA-A*, *-B*, *-C*, *-DR*, *-DQ* and *-DP* gene products (antigens) define histocompatibility important in allogeneic hematopoietic cell transplantation (HCT). A hallmark of HLA genes is their extensive polymorphism. HLA diversity is a reflection of their primary function to bind and present antigenic peptides for recognition by antigen-specific T-cell receptors.³ The nucleotide substitutions distinguish unique HLA alleles (Table 1). As of April 2006, 469 *HLA-A*, 794 *HLA-B*, 244 *HLA-C*, 525 *HLA-DRB*, 34 *HLA-DQA1*, 71 *HLA-DQB1*, 23 *HLA-DPA1*, and 124 *HLA-DPB1* alleles are recognized (Steven Marsh, personal communication). Approximately 150 new class-I and 50 new class-II alleles are reported to the World Health Organization yearly, with the majority of new alleles being discovered through the typing of volunteer bone-marrow-registry donors.²

If HLA alleles occurred randomly, there would be over 1×10^{23} unique *HLA-A*, *-B*, *-C*, *-DR*, and *-DQ* genotypes, and the prospects of identifying a suitable unrelated donor for transplantation would be diminishingly small. HLA genes are inherited en bloc in classical Mendelian fashion on a *haplotype* (Table 1). Certain HLA alleles are found associated with one another more frequently than would be predicted by chance alone (*linkage disequilibrium*, LD) (Table 1).⁴ For the purposes of finding an unrelated HCT donor, strong LD between two or more HLA loci can be beneficial, as matching for the antigens at two loci (for example, HLA-A1 and -B8) will often determine matching for the third (DR3). Patients who possess combinations of alleles or antigens that are less commonly observed as extended HLA haplotypes may have more difficulty finding suitably matched unrelated donors. The term *ancestral haplotype* refers to HLA-A, -B, -DR haplotypes of highly conserved sequences derived from a common ancestor. Among the best studied of ancestral haplotypes is HLA-A1, -B8, -DR3.⁵ Ancestral haplotypes are a focus of study for MHC variation.^{6,7} Their significance in outcome after allogeneic transplantation is not known.

The frequencies of HLA alleles and antigens vary greatly within a population and between ethnically diverse populations.^{8–10} For this reason, the likelihood of identifying suitable unrelated donors for HCT is highest when the patient and donor are of the same ethnic or racial background (Table 2).¹¹ Traditionally, HLA haplotypes are determined by typing as many members of a family as are available in order to establish the gametic assignment (Figure 1). In the absence of a family study, such as the case among a registry of unrelated donors, haplotype frequencies can be estimated.¹² Estimated haplotype frequencies have been used to determine the ideal size of unrelated donor registries for HCT.¹³

The family study: definition of haplotypes and identification of potential related donors

The importance of a family study at the initiation of planning for an allogeneic transplant is two-fold: to identify potential related donors, and in their absence to verify the patient's genotype for initiation of an unrelated donor search. The probability of a sibling having inherited the same parental haplotypes (HLA genotypically identical) is 25%; the probability of a sibling having inherited one identical paternal or maternal haplotype and one non-shared haplotype (haploidentical) is 50%, and the probability of having inherited neither of the same haplotypes is 25% (Figure 1). Haploidentical siblings are variably mismatched for the non-shared haplotype depending on the fortuitous sharing of maternal and paternal HLA antigens. Rarely, inheritance of a maternal or paternal recombination event will give rise to disparity between two otherwise matched siblings. Inherited maternal HLA antigens (IMA) and inherited paternal HLA antigens (IPA) define the haplo-types of a child in relation to his/her mother or father. Non-inherited maternal antigens (NIMA) and non-inherited paternal antigens (NIPA) refer to the HLA antigens expressed on the non-shared haplotypes.

HLA typing and resolution of alleles and antigens: why not all '6/6' antigen-matched donors are '10/10' allele-matched

The combination of antigens defines the HLA *phenotype* and the alleles define the *genotype* (Table 1). A nomenclature has been developed to translate serologically defined antigens and DNA-defined alleles.¹⁴ DNA-based typing methods may define the equivalent of a serologically defined antigen (e.g. HLA-A2) and are referred to as *low-resolution*. Methods that provide information beyond the serologic level but short of the unique allele are termed *intermediate-resolution* (e.g. the HLA-A2 is either the HLA-A*0201 or 0205 allele), and methods that provide unique nucleotide sequence information of an allele (e.g. HLA-A*0201) are termed *high-resolution*. Two individuals who share the same HLA antigen may encode different alleles of that antigen. In this way, HLA-A, -B, -DR serologically identical unrelated donors and recipients may harbor undetected allele mismatches at these and other HLA loci.¹⁵

Impact of HLA Disparity After Alternative Donor HCT

Haploidentical related HCT

The immediate availability of a family member to serve as a stem-cell donor makes haploidentical related HCT an attractive option for patients who lack an HLA genotypically identical sibling and for patients whose disease tempo does not afford the time required for conducting an unrelated donor search.^{16–24} HLA disparity in haploidentical related HCT increases the risks of graft failure and GVHD (often hyperacute) and delays immune reconstitution, and early on this motivated the development of T-cell depletion (TCD) strategies to lower GVHD risk.^{16,19,20,25–27} More recently, reduced-intensity and non-myeloablative regimens have provided an approach for lowering transplant-related mortality (TRM) after haploidentical related and unrelated HCT.^{28,29}

Side-by-side comparison of studies of HLA effects after HLA phenotypically matched and haploidentical mismatched related HCT is often challenging. The reasons are many-fold, but primarily relate to the difficulty in assessing the true degree of incompatibility contributed by the non-shared HLA haplotype. As described above, ‘6/6’ HLA-A, -B, -DR antigen-matched haploidentical related donors may have widely varying degrees of matching for alleles of the non-shared haplotype when DNA-based typing methods are applied; furthermore, original donor selection may have been based on matching criteria for *HLA-A*, *-B* and *-DR*, and may not reflect matching at *HLA-C* and *-DQ*.³⁰ Nevertheless, three important concepts have emerged from the haploidentical HCT experience. First, the risks of GVHD and graft failure increase with increasing numbers of HLA mismatches of the non-shared HLA haplotype^{31–34}, and are especially high in the presence of mismatching for two or more antigens from a T-replete grafting source.^{31,33}

A second concept is the clinical importance of the *vector* or direction of HLA mismatching.³⁵ The risk of graft failure correlated with the presence of donor antigens or alleles not shared by the recipient (*host-versus-graft* [HVG] vector); the risk of acute GVHD correlated with and the presence of recipient antigens or alleles not shared by the donor (*graft-versus-host* [GVH] vector) (Table 1). A third observation is a differential effect of class I and class II mismatching on GVHD risk,³⁰ in which *HLA-DR* and *-DQ* mismatches were associated with increased risk of acute GVHD, and class I mismatching (multiple class I determinants in particular) with risk of graft failure.

Comparison of clinical outcome after matched related, mismatched related, and unrelated HCT demonstrates that outcomes after transplantation from related donors with limited numbers of HLA mismatches can approach the favorable results observed after HLA-identical related HCT.^{22,23,36,37} In transplantation for thalassemia from HLA phenotypically matched related donors, haploidentical siblings or parents, there was no correlation of HLA mismatching with graft failure; however, the incidence of acute GVHD was higher after transplantation from a one- or two-antigen mismatched donor.²² A single-center analysis of genotypically matched, haploidentical and unrelated donors provides a basis for the additive effects of HLA mismatches.³⁶ In this series, overall survival after transplantation from HLA identical siblings was superior (80% overall survival). Compared to HLA-identical sibling transplants, patients transplanted from matched or single-antigen mismatched unrelated donors or 7/10, 8/10 or 9/10 *HLA-A*, *-B*, *-C*, *-DR*, *-DQ* haploidentical related donors had comparable survival. However, use of unrelated donors with two or more class I or 6/10 (or lower) haploidentical donors was associated with poor outcome. These data suggest that use of alternative donors with limited numbers of HLA mismatches may permit certain patients the opportunity for cure. Higher risks of acute and chronic GVHD after haploidentical related HCT compared to either matched or single-antigen mismatched unrelated donor HCT, and higher TRM after transplantation from a mismatched unrelated or related donor

HCT compared to matched unrelated donor HCT demonstrate a clear effect of HLA disparity.²³ Use of partially matched related donors has been associated with increased non-relapse mortality.³⁷

Unrelated donors

Transplantation from an HLA-A, -B, -C, -DRB1, -DQB1 allele-matched unrelated donor can offer disease-free survival (DFS) comparable to that with a haploidentical mismatched related donor for certain good-risk patients when an HLA-identical sibling is not available.^{23,36,38,39} The underlying disease diagnosis and stage are important prognostic features of outcome after allogeneic transplantation, and hence the timing of unrelated HCT and efficient conduct of the unrelated donor search are important. Guidelines for planning transplantation⁴⁰ and recommendations for surmounting unique challenges of the unrelated donor search^{41,42} are available as a resource for clinicians. Current data demonstrate that clinical outcome after unrelated HCT for chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL) and myelodysplastic syndrome (MDS) compare favorably with results of sibling transplantation, notably for good-risk patients when a matched unrelated donor is available.^{23,43} The early clinical experience in haploidentical related HCT provided a platform for the use of unrelated volunteer donors, beginning with HLA-matched donors and myeloablative regimens and more recently with reduced-intensity and non-myeloablative approaches.^{28,44} The criteria for the selection of unrelated donors has reflected the continuum of HLA typing technology development since the introduction of the polymerase chain reaction (PCR) in the mid-1980s. In the DNA-typing era, high-resolution methods can uncover allele disparities among phenotypically identical individuals.^{15,45,46} Because these allele disparities are functionally relevant after myeloablative⁴⁷⁻⁵¹ as well as reduced-intensity and non-myeloablative conditioning²⁸, high-resolution typing methods are now standard for donor evaluation. Although some series have not observed an association of HLA allele mismatching with transplant outcome⁴⁶, most retrospective analyses of large numbers of unrelated donor transplants performed worldwide for a broad spectrum of indications have reached similar conclusions regarding the clinical importance of donor matching at *HLA-A*, *-B*, *-C*, and *-DR*. The risks of graft failure and GVHD increase with increasing degree of donor recipient HLA class I and II incompatibility compared to matching at *HLA-A*, *-B*, *-C* and *-DR* for both early⁴⁷⁻⁵³ and late⁵⁴ complications. The risks of graft failure and GVHD may not necessarily be contributed equivalently by class-I and class-II gene products; some studies report increased GVHD associated with class-I and others with class-II mismatching.^{47,49,50,52,54} The immunogenicity of allele and antigen mismatches may be different, with fewer detrimental effects associated with mismatching between two alleles of an antigen (for example, an *HLA-A*0201* versus *-A*0205* mismatch within the A2 antigen family) compared to mismatching between two antigens (A2 versus A11).^{50,51} The pediatric experience has demonstrated the potential for more tolerability of younger patients to higher degrees of HLA disparity.^{36,55-57}

The importance of measuring independent HLA effects on transplant outcome in patients with low-, intermediate- and high-risk disease was recently described and provides a strategy for investigating permissible HLA mismatches.⁵⁸ Patients transplanted for low-risk disease did not tolerate even a single *HLA-A*, *-B*, *-C*, *-DRB1* or *-DQB1* allele mismatch compared to matched patients. When the transplant was performed for higher-risk disease, the clinical impact of a single allele or antigen mismatch did not lower overall survival.

The number and nature of *HLA-A*, *-B*, *-C*, and *-DR* mismatches are important in defining risks of graft failure and GVHD; however, the data for *HLA-DQ*^{47,50,58} and *-DP*^{47,48,50,59-62} have been heterogeneous. In a recent single-center study that compared outcomes of patients undergoing transplantation from donors with multiple HLA

mismatches, those who were *HLA-DQ*-mismatched had an increased hazard of death compared to matched patients, suggesting a trend for an additive *HLA-DQ* effect when there is additional HLA mismatching at other loci.⁵⁸ Recent analyses demonstrate that *HLA-DP* gene products function as classical transplantation determinants that participate in graft-versus-leukemia.⁶³

Permissible HLA mismatches: the NIMA-IPA effect in haploidentical related HCT

Haploidentical siblings are mismatched for NIMA or NIPA (Figure 1). In-utero exposure to NIMA may be tolerizing, and exposure to IPA may be immunizing. Donor-specific suppression of T-cell responses against the non-inherited maternal HLA antigens provides a basis for the use of NIMA-mismatched haploidentical donors.^{64–66} In the largest analysis of NIMA and NIPA effects after T-replete marrow transplantation from haploidentical mismatched related donors⁶⁴, clinical outcome of NIMA-mismatched transplants was compared to that of NIPA-mismatched transplants; lower risks of acute and chronic GVHD and TRM were observed after transplantation between mother and offspring compared to father and offspring. Separate studies from Japan have confirmed the tolerizing effect of NIMAs after myeloablative^{65,66} and reduced-intensity^{67,68} conditioning. Although no differences in risk of clinically significant acute GVHD were noted in one study⁶⁵, 5-year overall survival was significantly higher and TRM lower among recipients of maternal grafts compared to paternal grafts. In other studies, significantly lower risks of GVHD were observed among NIMA-mismatched transplant recipients.⁶⁶ The use of NIMA-mismatched donors provides an especially attractive strategy for patients who would not tolerate GVHD and prolonged immunosuppression.

Permissible HLA mismatches after unrelated HCT

The likelihood of identifying a matched unrelated donor depends on the patient's genotype, his or her racial background, and the composition and size of the donor registries. For these reasons, 20–80% of patients who initiate a search ultimately identify a suitable unrelated donor. The need to broaden availability of unrelated HCT for patients who lack a matched donor has provided the rationale to define permissible HLA mismatches. In recent analyses, single mismatches at *HLA-DQB1* or *-DRB3* are well tolerated, whereas mismatching for *HLA-C*, or for multiple *HLA-A/B/C* alleles is associated with significantly increased risk of TRM.⁵² Several loci have served as a model for understanding the rules that govern permissible mismatching. In an analysis of class I mismatches, an increased risk of acute GVHD and mortality was associated with donor mismatching for residue 116 of class I.⁶⁹ Using *HLA-DP* as a model locus, permissive combinations can be discerned and provide a means to select appropriate *HLA-DPB1*-mismatched donors bearing low-risk allele mismatches.⁷⁰ Ancillary laboratory tools – including the cytotoxic T-lymphocyte precursor (CTLp) response as a measure of alloreactivity of CD8 T cells – have also been used as a tool to select potential donors among a pool of mismatched donors.⁷¹ HLA-C mismatches involving more than five substitutions in the α -helix and in the β -sheet were not always associated with high CTLp, indicating a potential strategy for identifying permissible HLA class I mismatches.

A powerful model for examining permissible HLA mismatches compares HLA disparities across ethnically diverse transplant populations.⁷² An increased hazard of mortality depended on disease risk at the time of transplantation; a single HLA mismatch among low-risk patients was poorly tolerated, but did not lower survival among higher-risk patients. Furthermore, risks were not contributed equivalently by all HLA loci; *HLA-B* and *-C* mismatches conferred significantly increased risk among low-risk patients compared to mismatching at other loci. Most interesting is the finding that specific combinations of sequence mismatches may provide clues to permissible combinations of HLA mismatching.

A side-by-side analysis of Japanese and Caucasian unrelated donor transplants provides a unique opportunity to examine the properties of tolerable mismatches.⁷³ Using *HLA-A2* as a model, this study evaluated 3365 *HLA-A2*-positive transplants and found a statistically significantly higher hazard of mortality associated with A2 mismatching among Japanese but not Caucasian patients. Interestingly, the most common A2 mismatch among the Japanese patients involved the *HLA-A*0201/0206* combination whereas the *A*0201/0205* combination was the most frequently observed A2 mismatch among Caucasian patients. Whether the risk associated with these A2 mismatches is a direct consequence of the A2 disparity, or additional *HLA-A2* haplotype-associated mismatches, remains to be defined in a larger transplant experience. Interestingly, genetic factors associated with GVHD are hypothesized to be different in the Japanese population.⁷⁴

Graft-Versus-Leukemia Effects: The Role of HLA and NK-Mediated Alloreactivity

Graft-versus-leukemia effects in patients with clinical GVHD have provided an important anti-leukemia mechanism after allogeneic HCT^{75–80} and provide the rationale for the use of therapeutic strategies for lowering post-transplant disease recurrence with donor lymphocyte infusion. Beneficial effects of *HLA-DPB1* mismatching on lower post-transplant relapse are evident in patients transplanted for lymphoid malignancies.⁶³ GVL effects are observed after reduced-intensity and non-myeloablative conditioning.⁴⁴ The stronger GVL effects after non-myeloablative unrelated-donor compared to related-donor HCT likely reflect the influence of greater genetic disparity between unrelated individuals.⁴⁴

NK genetics

HLA-B and *-C* gene products provide the ligands for natural killer (NK) cell immunoglobulin-like receptors (KIRs) that have inhibitory or activating potential.⁸¹ The KIR family of genes displays allelic and haplotypic polymorphism.^{81–88} The specificity of the inhibitory KIR receptor for its ligand is governed by residues 77 and 80 of *HLA-C* and by the *HLA-Bw4* epitope present on some *HLA-B* and *-A* molecules (Table 3). The *KIR2DL1* receptor recognizes Asn at position 77 and Lys at position 80 of the following alleles or allele families: *HLA-Cw2*; *Cw*0307*; *Cw*0315*; *Cw4*; *Cw5*; *Cw6*; *Cw*0707*, *Cw*0709*; *Cw*1205* *Cw*12041/2*; *Cw15* (except *Cw*1507*); *Cw*1602*; *Cw17* and *Cw18*. These alleles are collectively referred to as the 'group 2' (C2) ligands (Table 3).

Inhibitory *KIR2DL2* and *2DL3* receptors recognize Ser77 and Asn80 present in the following alleles or allele families: *HLA-Cw1*; *Cw3* (except *Cw*0307*, *0310*, *0315*); *Cw7* (except *Cw*0707*, *0709*); *Cw8*; *Cw12* (except *Cw*1205*, *12041/2*); *Cw13*; *Cw14* (except *Cw*1404*); *Cw*1507*, and *Cw16* (except *Cw*1602*). These alleles are collectively termed the 'group 1' (C1) ligands. The *HLA-Bw4* epitope serves as a ligand for the inhibitory *KIR3DL1* receptor. The following *HLA-B* antigens and alleles are *Bw4*-positive: *B5*, *B13*, *B17*, *B27*, *B37*, *B38*, *B44*, *B47*, *B49*, *B51*, *B52*, *B53*, *B58*, *B59*, *B63*, *B77*, *B*1513*, *B*1516*, *B*1517*, *B*1523*, *B*1524*. High-resolution typing of *HLA* class I alleles of the recipient provides the necessary information to determine whether a patient is *Bw4*-positive or -negative, and whether the recipient is heterozygous for C1, C2 or homozygous C1, C1 or C2, C2.

GVL may be facilitated by NK cells after allogeneic transplantation.⁸⁹ Inhibitory KIRs are inhibited from killing target cells when they are engaged with their *HLA-B* and/or *C* cognate ligand.⁹⁰ Lowered post-transplant relapse may come about through different mechanisms for donor NK-mediated killing of host target cells depending on the *HLA* match status of the donor and the recipient. In haploidentical mismatched related HCT, donor-derived NK cells

that express an inhibitory KIR receptor that does not recognize the patient's *HLA-C* and/or -*B* allele leads to release of NK inhibition and subsequent killing of host cells, including residual leukemic cells (lowered relapse) and antigen-presenting cells (lowered GVHD).^{16,90} In the setting of HLA-identical transplantation, although there is no source of HLA disparity, the recipient may be homozygous for C1 or C2, and/or Bw4; the recipient therefore is missing an HLA ligand for which the donor NK cells may be expressing the inhibitory KIR receptor. Lack of the appropriate ligand may release inhibition and lead to killing of the target cell. This mechanism may be operational in both the HLA-matched as well as the HLA-mismatched transplant setting.

KIR effects in haploidentical related HCT

The ramifications of donor NK-mediated killing of host target cells with respect to enhanced anti-leukemic effects provides a tremendous clinical tool for the treatment of patients with high-risk leukemias, and may be particularly vigorous in myeloid leukemias.^{16,90,91} Adoptive immunotherapy using NK cells is now an emerging strategy for inducing anti-leukemic effects especially in high-risk patients.⁹² The transplantation of megadose ex-vivo T-cell-depleted stem cells from NK-alloreactive donors following myeloablative conditioning¹⁶ is associated with durable engraftment, low risks of GVHD, and low post-transplant disease recurrence in patients with AML, leading to superior overall outcome.⁹⁰ Although beneficial effects of KIR ligand mismatching have been observed^{93,94}, the use of different conditioning regimens, with or without TCD, may account for heterogeneous results^{95–100} and points to the need for further study under different transplant procedures and conditions.

KIR effects in unrelated HCT

GVL mediated by donor anti-host NK allorecognition may play a favorable role in unrelated HCT. Clinical experience thus far suggests that the effect of KIR ligand incompatibility on outcome after unrelated HCT may be different with different transplant procedures.^{94,95,97,99,101–103} The GVL effects may be a consequence not only of ligand incompatibility but also when the recipient is missing ligand for a donor with a complete repertoire of inhibitory KIR receptors. Although most individuals encode KIR2DL2, 2DL3, 2DL1 and 3DL1, the distribution of HLA-C and -B alleles that define group 1, group 2, and HLA-Bw4 varies significantly from population to population, indicating that missing ligand can occur among HLA-matched individuals.⁹⁸

A side-by-side comparison of the mismatched-ligand and missing-ligand models has recently been performed in a population of patients transplanted with T-replete marrow or peripheral-blood stem cells after myeloablative conditioning from *HLA-A*, -*B*, -*C*, -*DRB1*, -*DQB1*-matched or -mismatched unrelated donors.^{102,104} A decreased hazard of disease recurrence was observed in HLA-mismatched recipients homozygous for HLA-Bw6 and -C group 1 or 2 (missing KIR ligand); the lowered risk was contributed by absence of group 2 HLA-C epitopes or HLA-Bw4 ligands. Notably, the effect was observed in patients with AML, CML and ALL, and was not observed among HLA-matched transplants. A subset of the *HLA-B*- and/or *HLA-C*-mismatched transplants were analyzed to better define the role of KIR ligand mismatching on transplant outcome. Among mismatched pairs, no statistically significant differences in relapse between the KIR-ligand-mismatched and KIR-ligand-matched cases was observed; a trend towards lower hazard of relapse (which was not statistically significant) was observed among patients missing a KIR ligand compared to patient with ligands present. These data suggest that KIR ligand absence in the recipient may be a useful pre-transplant indicator for lowered disease recurrence after T-replete myeloablative conditioning, and could provide clinicians with a strategy to plan specific transplant treatment for patients at highest risk of relapse.

Finally, information on specific donor KIR–recipient HLA ligand combinations may predict transplant outcome.^{103,105,106} In a model based on the presence or absence of specific inhibitory and activating KIR genes, risk of acute GVHD (but not graft failure, relapse or survival) correlated with KIR genotype and not with mismatching or missing HLA ligand.¹⁰³ The effects arising from specific KIR–HLA combinations, interactions between KIR-mediated and T-cell-mediated signals, and the strength of KIR inhibition remain important questions that will shed light on the role of the innate immune system in HCT.

Summary

Haploidentical related and unrelated donors provide an opportunity for patients to benefit from HCT when an HLA genotypically matched sibling is not available. The HLA factors responsible for graft failure and GVHD risk have been defined for the class I *HLA-A*, *-B* and *-C* and the class II *HLA-DRB1*, *-DQB1* and *-DPB1* genes. HLA mismatching is associated with increased risks of graft failure, GVHD and delayed immune reconstitution, but also with lower risk of disease recurrence. The definition of an ideal alternative donor and the selection between a haploidentical related and unrelated donor is difficult and is shaped by the urgency of the transplant as well as by HLA risk factors. Outcome after haploidentical related and unrelated donor transplantation can be optimized through more complete and precise HLA matching of the donor and recipient, and through NK-mediated KIR effects.

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Practice points

Related HCT

- risks of graft failure and GVHD are associated with degree of donor—recipient HLA mismatching; the least mismatched donor should be selected
- risk of graft failure is associated with recipient homozygosity at the mismatched locus; mismatching at the locus for which recipient is homozygous should be avoided
- risk of graft failure is associated with anti-HLA antibodies; pre-transplant cytotoxic cross-matching should be performed
- fetal—maternal chimerism is associated with hyporesponsiveness to non-inherited maternal antigens; a haploidentical microchimeric NIMA/NIPA-mismatched family member should be considered as donor
- donor anti-host NK alloreactivity is associated with durable engraftment, lower GVHD, and lower relapse after transplantation of megadose TCD haploidentical related stem cells for the treatment of AML; consider related donor with KIR ligand incompatibility

Unrelated HCT

- risk of graft failure and GVHD is higher with antigen mismatch than allele mismatch; when no HLA-matched donor is available, the priority should be allele-mismatched over antigen-mismatched donors
- donor anti-host NK alloreactivity is associated with lower GVHD and relapse after transplantation using specific conditioning and immunosuppression regimens; KIR ligand incompatibility is useful for risk assessment and planning HCT strategies
- missing KIR ligand in the recipient is associated with lower relapse after HLA-identical transplantation; if the patient is homozygous C1, C2 $\pm$ Bw6, information useful for risk assessment and planning HCT strategies

Research agenda

- define permissible HLA mismatches under a variety of transplantation procedures and conditions, in order to increase availability of unrelated donor transplantation to patients in need of this modality
- define the HLA contributions to graft-versus-leukemia effects
- define the interactions between HLA, inhibitory and activating KIR on graft-versus-leukemia and utility in risk assessment and donor selection

Figure 1.

Family study. The paternal haplotypes are designated *a/b* and the maternal haplotypes *c/d*. Sibling 1 is the proband. Siblings have inherited *a/c* (HLA genotypically identical); *a/d* (haploidentical); *b/c* (haploidentical); *b/d* (complete mismatch) and *a/c-d* (maternal *c-d* recombinant) haplotypes. At the *HLA-A* locus, sibling 1 is mismatched with siblings 3, 4 and 6 for host-versus-graft only, due to fortuitous sharing of the HLA-A1 antigen by the parents. At the *HLA-DR* locus, sibling 1 is mismatched with sibling 4 for graft-versus-host only, due to fortuitous sharing of the HLA-DR7 antigen by the parents. Due to a maternal *c-d* recombination event located between *HLA-A* and *HLA-B* inherited by sibling 6, sibling 1 is mismatched with sibling 6 from *HLA-A* up to *HLA-B*, and is matched from *HLA-B* to *HLA-DR*.

Table 1

Dictionary of HLA terms.

Term	Definition	Example
Phenotype	The expressed protein product of the gene	HLA-A1, -B8, -DR3
Genotype	An individual's DNA sequence of the HLA gene	HLA-A*0101, B*0801, DRB1*0301
Antigen	The expressed HLA protein that can elicit a humoral response (alloantisera known)	HLA-B44
Allele	An alternative form of a gene; a unique sequence variant	HLA-B*4402
Epitope	One or more amino acid residues of an HLA protein defined by alloantisera	Bw4 and Bw6
Typing resolution	Low: equivalent to antigen; may be defined either by serology or with DNA methods Intermediate: equivalent to antigen; may define one or more related HLA phenotypes High: DNA sequence is defined	HLA-DR2 HLA-DR15 or -DR16(splits of DR2) HLA-DRB1*1501
Haplotype	Alleles that are inherited together on the same chromosome	HLA-A1, -B8, -DR3
Haploidentical	Two related individuals who share one chromosome 6 and are variably matched for the non-shared HLA haplotype	<i>Sibling 1</i> : paternal HLA-A1,B8,DR3 haplotype; maternal A3,B7,DR2 haplotype <i>Sibling 2</i> : paternal HLA-A1,B8,DR3 haplotype; maternal A29,B44,DR7 haplotype
Linkage disequilibrium(LD)	The non-random association of alleles	Strong LD between HLA-B and -C, and between HLA-DR and -DQ
Vector of incompatibility	Host-versus-graft: donor alleles not present in the recipient Graft-versus-host: recipient alleles not present in the donor	<i>Recipient</i> : HLA-A1,1 <i>Donor</i> : HLA-A1,2 <i>Recipient</i> : HLA-A1,2 <i>Donor</i> : HLA-A2,2

Table 2

HLA haplotypes.

Ethnicity/race	HLA-A,B,DR haplotype frequency ^a			
	A1-B8-DR3	A33-B58-DR3	A30-B42-DR3	A29-B44-DR7
Caucasian	0.062	0.0002	0.00009	0.016
Asian	0.003	0.019	0.00005	0.0007
African	0.012	0.0004	0.0143	0.004
Hispanic	0.017	0.0002	0.002	0.018

^aEstimated haplotype frequencies in an unrelated donor pool. From www.nmdpresearch.org. Numbers in bold indicate the frequency of most common haplotype observed in the ethnic/racial group.

Table 3

HLA–KIR interactions in allogeneic transplantation.

HLA–NK allorecognition	Recipient epitope/genotype	Donor epitope/genotype
Recipient lacks the HLA epitope present in the donor	C1, C1 homozygous(e.g. HLA-Cw*0701, 0701)	C1, C2 heterozygous(e.g. HLA-Cw*0701, 1602)
Recipient is missing the HLA epitope for donor inhibitory KIR	C1, C1 (e.g. HLA-Cw*0701, 0701)	KIR2DL1 (receptor for C2 ligand)