How to select the best available hematopoietic stem cell transplantation donor?

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A B S T R A C T

Recognition of HLA incompatibilities by the immune system represents a major barrier to hematopoietic stem cell transplantation (HSCT). HLA genotypically matched sibling donors are, therefore, the gold standard but only 30% of patients have such a donor. For the remaining 70%, alternative donors are either a matched unrelated adult volunteer donor, a cord blood unit, or a haplo-identical donor. The definition of 'HLA matching' depends on the level of resolution and on which loci are tested. The development of HLA molecular typing technologies and the availability of more than 25 million donors in the international database has greatly facilitated unrelated donor searches. The gold standard is a high resolution level (i.e. same peptide binding region) at HLA-A, B, C, DRB1, DQB1 loci (10/10 match). Despite the extreme diversity of HLA allele and haplotypes, a 10/10 matched donor can be found for at least 50% of patients in most European populations, and an additional 20%-30% patients may have a 9/10 matched donor. The success rate drops significantly for patients of different ethnic origins. Single HLA disparities are associated with increased risk of post-transplant complications, but less so in patients with advanced disease, and in T-cell-depleted allografts. Single C or DQB1 mismatches seem to be better tolerated. Different strategies have been reported to identify unrelated donors with more permissive mismatches. Alternative sources of stem cells are mismatched cord blood units or haploidentical family donors.

Learning goals

At the conclusion of this activity, participants should know about:
- definitions of HLA compatibility;
- probabilities of identifying a suitable unrelated donor;
- the impact of HLA mismatches;
- the search for permissive mismatches.

Introduction

The continuous expansion of our knowledge of HLA gene polymorphisms represents a major barrier to hematopoietic stem cell transplantation (HSCT).[1,2] Indeed HLA differences, even at the allele level, are recognized by T lymphocytes and such allorecognition confers higher risks of acute graft-*versus*-host disease (GvHD) and mortality. Therefore HLA genotypically matched sibling donors represent the gold standard for allogeneic HSCT. Since approximately 70% of patients do not have an available HLA-identical sibling, at least in Western countries, alternative donors have to be considered, such as HLA-'matched' unrelated adult donors, cord blood units (CBU), or haplo-identical donors. Since 2007, the number of transplants with stem cells from an unrelated donor has been higher than with a matched sibling donor. As reported in the 2011 European Group for Blood and Marrow Transplantation (EBMT) survey, there were 54% unrelated and 39% matched sibling donors.[3] The developments of molecular typing technologies and the continuous increase in the number of volunteer donors in the Bone Marrow Donor Worldwide (BMDW) database have undoubtedly improved the identification of well matched unrelated donors and contributed to the impressive expansion of HSCT programs worldwide.[1,2,4] Over 25 million donors are now registered in the international database (www.bmdw.org) and an increasing fraction of these donors are typed by molecular techniques at all HLA loci. Despite these achievements, still many patients will not have a fully matched donor because of the extremely high diversity of HLA alleles and haplotypes.[1,2,4,5] In 2015, more than 12,000 HLA alleles have been assigned, accounting for more than 8,000 different HLA proteins (www.ebi.ac.uk/ipd/imgt/hla). This increasing level of complexity negatively impacts on patient/donor matching. Thus, for many patients, a challenge for the histocompatibility laboratory is to identify mismatched donors or cord blood units with the lowest potential for recognition by the immune system, in particular by the direct T-cell allorecognition mode. A better characterization of "permissive" mismatches would undoubtedly allow an increased access to HSCT for many patients.

Search for HLA compatible unrelated donors

What do we mean by 'HLA compatible'?

The compatibility status of each

patient/donor pair depends on the level of resolution HLA typing and on which loci have been tested. The different levels of resolution are:[6]

a) low resolution, or 'first field level' typing, by reference to the 2 digits preceding the first separator, or antigen level typing, e.g. A*02;

b) high resolution typing which is defined by allele(s) that share the same peptide binding site formed by the α1/α2 domains of class I alleles (encoded by exons 2+3), and by the α1 domain of class II alleles (encoded by exon 2). E.g. A*02:01:01G includes all the alleles (n=47, based on the IMGT/HLA 3.19.0 release) sharing the same exons 2+3 nucleotide sequence as A*02:01:01). This resolution is achieved by 'second and third field level' typing, referring to the 2 or more digit numbers preceding the second, respectively, third separator. Alleles with nucleotide sequences encoding the same *protein* sequence for the peptide binding domain are designated by the suffix 'P', e.g. A*02:01P;

c) allele level typing, corresponding to a unique nucleotide sequence for an HLA gene, as defined by using all digits in first, second, third and fourth fields, e.g. A*02:01:01:01. Functionally, the third and fourth fields that characterize alleles that differ respectively by silent substitutions in the coding sequence, or by substitutions in the non-coding sequence, are irrelevant, except when substitutions prevent the expression of HLA alleles (e.g. the null allele B*15:01:01:02N). Missing a null allele will lead to a mismatch that is very likely to be recognized by alloreactive T cells with deleterious clinical impact;[7,8]

d) intermediate resolution level, when only a group of alleles, irrespective of the localization of the polymorphisms, are resolved, e.g. DRB1*11:01/11:09/11:28, a string of 3 alleles that may also be depicted by the NMDP code DRB1*11:BYCC. Depending on the number and the nature of the unresolved ambiguities, the 'intermediate' level of resolution can be quite heterogeneous. It has practical relevance only when it allows discrimination between frequent alleles, as shown in the example given in Table 1 (DRB1*04:04 absent in the string of alleles assigned in the donor under the code DRB1*04:VN). Examples with these different levels of resolution and their impact on the matching status are presented in Table 1. In most European centers, the gold standard is to look for an HLA-A, B, C, DRB1, DQB1-matched donor, a so-called 10/10 match (Figure 1). An alternative matching algorithm looks for an HLA-A, B, C, DRB1-compatible donor (8/8

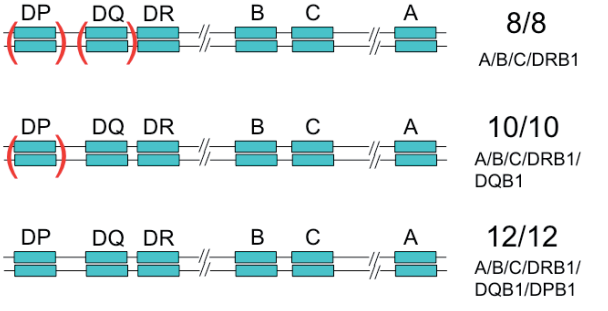

Figure 1. HLA matching criteria based on high resolution typing in unrelated donor selection. The DQA1 locus in not tested because of the strong linkage disequilibrium between the DQA1 and DQB1 loci. In some centers, compatibility at the second DRB locus (DRB3, DRB4 and DRB5) is considered. A DRB1 mismatch often occurs with a DQB1 mismatch. Similarly incompatibilities for HLA-B serotypes are often concomitant to C mismatches.

Table 1. Examples of patient/donor matching status as a function of HLA typing resolution levels.

Patient	Donor	Resolution level	Compatibility
A*02	A*02	low	potential match
A*02:01P	A*02:01P[a)]	high	match
A*02:01	A*02:06	high	mismatch
A*02:06	A*02:126[b)]	high	match
A*02:01:01G	A*02:01:01G[a)]	high	potential match
A*02:09	A*02:01:01G	high	potential match
DRB1*14:01:01	DRB1*14:54:01	high	match
DRB1*14:01:01	DRB1*14:54 :01	allele	mismatch
A*02:01:01:01	A*02:01:01:01	allele	match
A*02:01:01:01	A*02:26	allele	mismatch
A*02:01:01:01	A*02:01:01:02N	allele	mismatch
DRB1*11:BYCC (11:01/11:09/11:28)	DRB1*11:RDPB (11:01/11:95/11:97/11:100/11:117) [c)]	intermediate	potential match
DRB1*04:04	DRB1*04:VN (04:01/04:13/04:16/04:21)[d)]	intermediate	mismatch
C*07:02:01G	C*07:02	high	match
C*07:02:01G	C*07 :FEAU (07:02/07:50/07:66/07:74)[e)]	high	match

*[a)] G marks all the alleles with the same nucleotide sequence in the peptide binding site (including null alleles); P denotes a string of alleles that encode the same protein sequence in the peptide binding site (α1/α2 domains for class I and α1 for class II alleles) as the first numbered allele in the group. [b)] A*02:126 differs from A*02:06 by a residue outside the peptide binding site. [c)] The DRB1*11:01, *11:95, *11:97 and *11:100 share the same α1 domain but not DRB1 *11:117. [d)] This string of 4 alleles does not include DRB1*04:04, this donor is therefore incompatible at locus DRB1. [e)] The C*07:02, *07:50, *07:66 and *07:74 alleles share the same α1/α2 domains protein sequence, as does C*07:02:01G, these 4 alleles are included in the C*07:02:01G group of alleles.*

match). When HLA-DPB1 typing is included, 12/12 matched donors are searched. Although less polymorphic, the DRB3/B4/B5 loci may lead to additional HLA class II mismatches. There is, however, no common practice nor any international recommendation to count these mismatches in the 10/10 matching algorithm.

Probability of identifying a highly matched donor

As shown in Table 2, the average probability of identifying a matched donor vary widely depending on the ethnic origin of the patients and on the matching grade required by the transplant center (8/8 or 10/10). Still 1%-5% of the patients, depending on the ethnic origin, do not have a single potentially matched donor upon direct interrogation of the BMDW database.[4,12] Because a large majority of the donors registered in BMDW are of Western European ancestry, the ethnic origin of the patient strongly influences the probability of finding a matched donor,[16] with the lowest probability assigned to patients of African ancestry. In European countries, 45%-65% patients will eventually have a 10/10 matched donor, and a 9/10 matched donor may be identified for an additional 20%-30% of patients (Table 2).

Impact of single mismatches

There is now a general consensus that single HLA mismatches at the HLA-A, B, C and DRB1 loci are clinically relevant.[1,2,4,5,17-19] In a large scale Center for International Blood and Marrow Transplant Research (CIBMTR) study on chronic myeloid leukemia (CML) patients, no significant difference in overall survival has been noted between HLA class I and class II mismatches.[20] Concerning HLA class II disparities, several studies have reported that HLA-DQB1 disparities were not associated with mortality risk.[5,17-19] Because of the high priority given to HLA-DRB1 matching and of the strong DRB1-DQB1 linkage disequilibrium, studies may often be under-powered to disclose the clinical relevance of DQB1 disparities. Evidence for a role of HLA-DPB1 mismatches is now well documented.[21-25] In 7/8 matched transplants, additional mismatches at the DRB3/4/5, DQB1 or DPB1 loci was associated with increased mortality.[26]

As shown in the Japan Marrow Donor Program (JMDP) study, the impact of single HLA incompatibilities has also been reported to change over time, due to multiple parameters such as varying clinical protocols (GvHD prophylaxis, treatments for infections), HLA mismatches readily available in the latest period, more intensive GvHD prophylaxis in patients with DRB1 mismatches in the early time period.[27] The initial observation that HLA-B/C incompatibilities were better tolerated than A and DRB1 mismatches[17] has not been confirmed in more recent studies.[5,28] Impact of HLA mismatches on overall mortality is most apparent in patients with early disease.[29] Interestingly, in HSCT for non-malignant disorders, single HLA-A,-B,-C or DRB1 mismatches were not associated with acute or chronic GvHD but with graft failure.[19]

First field versus second field (antigen vs. allele) mismatches

A comparison of the impact on clinical outcome of single allele and single antigen mismatches did not reveal a significant difference.[5,17,29] A possible exception is locus HLA-C for which allele mismatches have been reported to be less detrimental than antigen mismatches.[18,28] This could possibly be explained by the very high frequency (68.7%) of the C*03:03 *versus* C*03:04 allele mismatch in the National Marrow Donor Program (NMDP) study.[28] This incompatibility had indeed been reported previously to be more permissive based on *in vitro* assays measuring direct cytotoxic T-lymphocyte (CTL) alloreactivity.[30,31]

Permissive mismatches

The search for so-called permissive mismatches has been a long one. As a first approach, the determination of

Table 2. Overall probabilities to identify a 7/8, 8/8, 9/10 and 10/10 matched unrelated donor.

Ethnic origin (country)[a]	Match 7/8	Match 8/8	Match 9/10	Match 10/10	Match 9-10/10	Ref.
Eur Cauc (NL)					69%[e]	9
Eur Cauc (UK)					72%	10
Eur Cauc (A)					80%[f]	11
Eur Cauc (D)			20%	61%		12
Eur Cauc (CH)			24%	58%		4
Eur Cauc (NL)			31%	48%		13
Eur Cauc (IT)			32%	43%		14
Eur Cauc (HR)			30%	65%		15
Eur Cauc (USA)	97%	75%				16
Africans (USA)	71%	18%				16
ME/ NA (USA)[b]	90%	46%				16
Asians (USA)[c]	76-88%	27-42%				16
Hispanics (USA)[d]	80%	34%				16

[a] Eur Cauc: European Caucasoids; NL: The Netherlands; UK: United Kingdom; A: Austria; D: Germany; CH: Switzerland; IT: Italy; HR: Croatia; USA: United States of America. [b] ME: Middle Eastern ; NA: North African. [c] Asians: Chinese, Korean, South Asian, Japanese, Southeast Asian, Vietnamese. [d] Hispanics: South/Central American. [e] Less than 9/10 in 13% of patients. [f] 9-10/10 match, exceptionally 8/10 matched donors.

the CTL precursor (CTLp) frequency has disclosed a number of HLA class I incompatibilities that had not been recognized and that could be considered as more permissive.[30-33] However, it was not possible to reliably predict this lack of recognition by looking at the structural differences between the mismatched alleles. It seems, however, reasonable to predict that HLA disparities characterized by substitutions in the peptide binding site that significantly alter the set of peptides presented by the HLA molecules will be more efficiently recognized by alloreactive T cells, whereas mismatches involving residues outside the peptide binding site are not expected to be recognized. Indeed, an *in vitro* semi-quantitative measurement of CD8+CD137+ alloreactive T cells in mixed lymphocyte reactions demonstrated that such a mismatch in the B44 serotype was not recognized by CTLs and could possibly be considered as permissive.[35]

Based on *in vitro* assays set up to detect anti-DP alloreactive T cells, a new algorithm has been proposed for the identification of non-permissive DPB1 disparities, as defined by the presence of T-cell epitope (TCE) mismatching.[36,37] Two groups of alleles with high (DPB1*09:01, 10:01, 17:01) and intermediate (DPB1*03:01, 14:01, 45:01, 86:01) immunogenicity have been assigned, whereas all remaining most frequent DPB1 alleles were classified in a third group. Each patient/donor pair with a DPB1 allele of the high or intermediate immunogenicity groups present in the patient or the donor only is classified as a non-permissive mismatch. Of the total donor pool, 70% consisted of either DPB1-matched donors or of donors with a permissive DPB1 mismatch. Non-permissive DPB1 mismatches were associated with increased hazards for acute GvHD (aGvHD) and transplant-related mortality (TRM), but not for relapse.[36] In the International Histocompatibility Working Group (IHWG) study,[25] DPB1 non-permissive mismatches were associated with increased risk of overall mortality both in 10/10 and in 9/10 matched transplants. In contrast to these findings, a recent study[29] reported that any DPB1 mismatch was associated with aGVHD. However, the adverse impact of non-permissive DPB1 mismatches on TRM and overall mortality was confirmed in 8/8 and in 10/10, but not in 7/8 or in 9/10 matched cases.

A few studies have reported the role of individual amino acids on clinical outcome. Thirteen amino acid substitutions accounting for the most frequent HLA mismatches were associated with early (<100 days) mortality.[38] The impact of individual HLA amino acid mismatches, such as those reported in the JMDP study,[39,40] may not be applicable in other populations which show a larger heterogeneity in HLA disparities and, therefore, fewer mismatches of a similar nature.[41] A large-scale analysis[42] evaluated the clinical impact of specific amino acid substitutions in HSCT patients with single class I mismatches. They found that patients with mismatched donors lacking amino acid substitution at position 116 of HLA-C (7%), 99 of HLA-C and 9 of HLA-B alleles, have similar outcomes as patients grafted with HSC from 8/8 matched donors. In particular, substitutions at aa116 and aa99 were both associated with increased TRM in the multivariate analysis.[42] The importance of amino acid 116 of HLA-C had been observed previously.[43]

High-dose cyclophosphamide treatment after non-myeloablative conditioning and T-cell-replete haploidentical HSCT has been shown to result in acceptable rates of graft rejection and aGvHD.[44] Thus, for adult patients with hematologic malignancies who lack a matched related or unrelated donor, this new protocol may provide a valuable alternative and drastically extends the chance of access of the patients to allogeneic transplantation.

Conclusion

When no matched sibling donor is available, an estimate of the probability to find a fully matched unrelated donor will help the transplant center to take a decision on whether to start a search for an unrelated donor, or to look for a cord blood unit (CBU) or a haploidentical donor. When no 10/10 matched unrelated donor is found, the prioritization of a 9/10 matched unrelated donor or an alternative donor (CBU, haploidentical) remains difficult in the absence of randomized trials. Nevertheless, some considerations can be made from published studies and practical recommendations for the selection of optimally matched unrelated donors can be summarized as follows:

- high resolution HLA typing is mandatory for all loci taken into consideration by the transplant protocol;
- mismatches at any of the 4 HLA-A, B, C, DRB1 loci are detrimental;
- HLA-A, B, C, DRB1 mismatches involving residues located outside the peptide binding site (e.g. A*02:01 *vs*. A*02:09), or residues that only fine tune the set of peptides bound to the HLA molecule (e.g. DRB1*11:01 *vs*. DRB1*11:04), or residues that are not seen by the T-cell receptor (e.g. C*03:03 *vs*. C*03:04) could possibly be considered as weakly or non-immunogenic;
- multiple HLA mismatches confer a higher risk;
- there is little evidence that allele mismatches should be preferred to antigen mismatches;
- impact of mismatches may vary with the kind and state of the underlying disease, with the GvHD prophylaxis used (T-cell depletion), and with the conditioning regimen;
- DQB1 and DRB3/4/5 mismatches should be preferred to other mismatches;
- whenever 2 or more 10/10 matched donors are available, the donor with a DPB1 match or with a DPB1 permissive mismatch should be given the priority.

Although it is not possible to reliably predict the impact of any single HLA mismatch, our current understanding allows us to select mismatched donors that are likely to induce a minimal alloresponse. For the moment, the choice between mismatched unrelated donor, mismatched cord blood, or haploidental seems to depend on the expertise of the transplant center and awaits randomized studies. Nevertheless, retrospective studies[45,46] show that it is possible to overcome the HLA barrier and thus to expand the number of patients who can have access to HSCT.

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