[1]Institute of Clinical Transfusion
Medicine and Immunogenetics Ulm,
German Red Cross Blood Transfusion
Service, Baden Wuerttemberg –
Hessen, and University Hospital
Ulm, Ulm, Germany
[2]Institute of Transfusion Medicine,
University of Ulm, Ulm, Germany

ABBREVIATION LIST:
aGvHD: acute graft versus host disease
ARS: antigen recognition site
BM: bone marrow
CMV: cytomegalovirus
CTLp-f: cytotoxic T-lymphocyte precursor
    frequency
CIBMTR: Center for International Blood
    and Marrow Transplant Research
HLA: human leukocyte antigen
HR: hazard ratio
HSCT: hematopoietic stem cell
    transplantation
HvG: host versus graft
FD: functional distance
GvHD: graft versus host disease
GvL: graft versus leukemia
JMDP: Japan Marrow Donor Program
MAC: myeloablative conditioning
MM: mismatch
MUD: matched unrelated donor
NMDP: National Marrow Donor Program
NRM: non-relapse mortality
OS: overall survival
PBSC: peripheral blood stem cell
RIC: reduced intensity conditioning
RR: risk ratio
TCD: T-cell depletion
TCE: T-cell epitope
TNC: total nuclear count
Treg: regulatory T-cell
TRM: transplant-related mortality
UCB: umbilical cord blood
uHSCT: unrelated HSCT

Correspondence to:
Chrysanthi Tsamadou, MD
Department of Transplantation
Immunology Helmholtzstr 10,
89081 Ulm, Germany
Tel.: +497311506784
E-mail: c.tsamadou@blutspende.de

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HLA Matching in Hematopoietic Stem Cell Transplantation: Where Do We Stand?

Chrysanthi Tsamadou, MD[1,2]

ABSTRACT

Despite the undeniable progress in the development of new effective drugs against malignant and non-malignant hematological diseases, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only therapeutic option with long lasting curative potential. Continuous research for the last fifty years has repeatedly shown that human leukocyte antigen (HLA) compatibility between recipient and donor constitutes the most decisive factor for successful engraftment and higher rates of overall survival. Unfortunately, a fully HLA matched donor is in many cases precluded, therefore the identification of better tolerated HLA mismatches has always been and still remains an important research objective. In this review we recapitulate current knowledge on how HLA- (i.e. locus, resolution level, directionality, number etc.) as well as non-HLA factors (i.e. disease stage, recipient age, graft source etc.) may impact the overall effect of HLA incompatibility on HSCT outcome, with the aim to offer an overview on potentially "permissive" HLA mismatches.

INTRODUCTION

The first hematopoietic stem cell transplantation (HSCT) clinical trials date back in the middle 50's, as E. D. Thomas in the United States and G. Mathé in Europe were the first to perform allogeneic HSCT in humans.[1,2] These initial efforts had minimal success as they were compromised by the lack of knowledge on the pivotal role of histocompatibility in transplantation. The discovery of the human leukocyte antigen (HLA) System[3] in conjunction with the development of the first HLA typing methods allowed better understanding of the immunobiological processes implicated in post HSCT engraftment, graft versus host disease (GvHD) and leukemia relapse. Since then hundreds of thousands of HSCTs have been performed with the millionth being reported by the Worldwide Network for Blood and Marrow Transplantation in December 2012.[4] Tremendous progress in HLA typing,[5] conditioning regimens as well as infection control and GvHD prophylaxis treatments have rendered this initially experimental therapeutic approach into a standard-of-care treatment for a plethora of benign as well as malignant disorders.[6] The steadily growing number of volunteer donors registered in the Bone Marrow Donor Worldwide (BMDW) database, which

appears to have surpassed the threshold of 35,900,000 in August 2019 (*www.bmdw.org*), has also contributed immensely to this development.

Despite this irrefutable progress, HSCT remains a high-risk treatment associated with high mortality rates due to transplantation-related morbidity factors such as GvHD, toxicity and severe infection, with patient/donor HLA-compatibility being long established as the most decisive donor-parameter influencing HSCT outcome.[7] An HLA-identical sibling donor is still considered the gold standard. However, it is readily available for only about 30% of patients. From those remaining, only half (i.e. 35% overall) will be able to find a 10/10 HLA matched unrelated donor (MUD)(i.e. matched for HLA-A,-B,-C,-DRB1 and –DQB1), a percentage that will probably decrease in the future, as the broad implementation of whole gene HLA typing will likely stress the need to consider additional HLA regions upon donor selection, apart from those determining the antigen recognition site (ARS) (i.e. exon 2 and 3 for HLA-class I and exon 2 for HLA-class II, respectively).[8] In fact it has been recently reported that HLA-matching at max-resolution level (i.e. inclusion of non-ARS regions for allele assignment) may lower GvHD rates and overall improve HSCT outcome[9,10] although more studies are required before definitive conclusions are drawn. It should be noted, however, that despite the aforementioned findings, mismatches outside the ARS are not considered as mismatches in daily practice with the exception of course of null alleles. Furthermore, many studies have clearly shown that even mismatches in loci that are viewed as secondary in significance, like DQB1, DPB1 and DRB3/4/5 may adversely affect HSCT outcome in a cumulative fashion.[11-13] The fact that for more than half of the patients at least one major (i.e. HLA-A,-B,-C and -DRB1) or minor (i.e. HLA-DQB1,-DPB1 and -DRB3/4/5) HLA mismatch will be inevitable, explains the large number of studies aiming at identifying so-called 'permissive' HLA mismatches.[14] Moreover, the fact that non-HLA parameters such as recipient age, disease stage, conditioning regimen, cytomegalovirus (CMV)-serocompatibility etc. have been clearly shown to differentially influence HLA-mismatch impact on HSCT outcome,[12,15-19] renders consensus as to 'mismatch-permissiveness' extremely difficult and underscores the necessity for larger and more homogenous cohorts.

Aim of this review is to recapitulate current knowledge on how HLA- (i.e. locus, resolution level, directionality, number etc.) as well as non-HLA factors (i.e. disease stage, recipient age, graft source etc.) may impact the overall effect of HLA incompatibility on HSCT outcome. Certain recommendations on how assessment of multiple parameters can potentially lead to optimal, patient-tailored donor selection are outlined in the conclusions part.

HLA FACTORS THAT INFLUENCE THE IMPACT OF HLA DISPARITY ON HSCT OUTCOME

In this section we sought to shed some light on all the HLA-relevant factors that appear to affect the overall impact of distinct HLA incompatibilities on HSCT outcome. Apart from locus and number of HLA discrepancies, mismatch resolution level along with mismatch directionality are being addressed. Finally, the HLA discrepancies located in HLA-C and HLA-DPB1 are discussed separately, as incompatibilities in these two loci appear to share features that clearly distinguish them from the other HLA loci.

LOCUS

Although there is general consensus on the fact that HLA-disparities lead to poorer post-transplant outcome, there is still a lot of controversy over the differential contribution of each HLA-locus mismatch to this negative effect. According to current standards[20] applied worldwide, a donor that is fully compatible with the patient at second-field/allele (high-resolution) typing level for the loci A, B, C, DRB1 +/-DQB1 (i.e. 8/8 or 10/10 matched in the US and in Europe, respectively) is defined as fully HLA matched. In Table 1 are listed some of the most representative studies,[13,16,17,21-28] that have tried to estimate the impact of respective HLA-locus disparities on mortality. Regardless of their heterogeneity as to some basic transplantation-related parameters like graft source, transplantation time period, patient age and conditioning regimen, most of them have reported significantly higher mortality risk ratios for mismatches concerning HLA-class I antigens. There appears to be also consensus on the minimal impact of single HLA-DQB1 disparities, though the number of studies providing data on DQB1 is far more limited. In regard to the importance of HLA-DQB1 matching, certain studies have shown that DQB1 incompatibilities appear to gain significance when combined with DRB1 or other HLA mismatches.[12,13] This also seems to apply for mismatches located in HLA-DRB3/4/5 loci, although it should be noted that the number of studies addressing this is rather small.[11,29,30] When it comes to the effect of single HLA-DRB1 discrepancies, study results tend to be more uncertain. In a large NMDP/CIBMTR study[22] as well as in some other studies,[17,21,24,31] single mismatches in HLA-DRB1 were associated with significantly lower overall survival (OS) and higher transplant-related mortality (TRM). In contrast, two Japan Marrow Donor Program (JMDP) studies, the first published in 1998[32] and the second in 2015,[13] in concordance with the results from Pidala et al.[26] reported no statistically significant association between DRB1 mismatches and survival. Nonetheless, DRB1 disparities were found to confer a significantly higher risk for grade II-IV acute GvHD (aGvHD) (Risk Ratio (RR):1.24, P<0.001). Interestingly, two large

TABLE 1. Overview of large clinical studies investigating the HLA-mismatch effect on HSCT outcome

Study	Year	Cohort size	Patient Age	Graft source	Conditioning Intensity	Year of Tx	HLA-A MM	HLA-B MM	HLA-C MM	HLA-DRB1 MM	HLA-DQB1 MM	HLA-DPB1 MM
Flomenberg et al.[21]	2004	1874	median <30	Predominantly BM	MAC	1988-1996	*1.33 (1.15-1.54)*	*1.22 (1.08-1.41)*	*1.21 (1.08-1.38)*	*1.23 (1.04-1.45)*	0.98 (0.84-1.14)	1.07 (0.89-1.27)
Lee et al.[22]	2007	3857	median <35	Predominantly BM	MAC	1988-2003	*1.36 (1.17-1.58)*	1.16 (0.92-1.47)	*1.19 (1.05-1.35)*	*1.48 (1.19-1.85)*	n.s.	1.07 (0.90-1.26)
Woolfrey et al.[23]	2011	1933	median 46	PBSC	Predominantly MAC	1999-2006	1.17 (0.93-1.47)	1.22 (0.90-1.67)	*1.41 (1.16-1.70)*	1.30 (0.87-1.94)	0.97 (0.71-1.34)	n.a.
Fürst et al.[24]	2013	2646	median 51	Predominantly PBSC	Predominantly MAC	1997-2010	*1.43 (1.19-1.72)*	*1.52 (1.20-1.93)*	*1.35 (1.17-1.56)*	*1.42 (1.10-1.82)*	1.23 (1.00-1.51)	n.a.
Kanda et al.[25]	2013	3003	median 37	BM	MAC	1993-2009	1.22 (1.00-1.51)	*1.60 (1.03-2.49)*	*1.23 (1.07-1.41)*	*1.26 (1.07-1.49)*	n.a.	n.a.
Pidala et al.	2014	8003	median <39	BM/PBSC (44%, 56%)	Predominantly MAC	1999-2011	*1.30 (1.20-1.40)*	1.20 (1.00-1.40)	*1.30 (1.20-1.50)*	1.10 (0.90-1.30)	n.s.	n.a.
Eapen et al.[27]	2014	1568	median <16	CB	MAC	2000-2010	1.27 (0.88-1.83)	1.06 (0.75-1.97)	1.41 (0.86-2.31)	1.31 (0.96-1.78)	n.a.	n.a.
Morishima et al.[13]	2015	7898	median 35	BM	Predominantly MAC	1993-2010	*1.29 (1.17-1.42)*	*1.27 (1.11-1.45)*	*1.21 (1.13-1.30)*	1.09 (0.98-1.21)	1.08 (9.97-1.19)	1.03 (0.96-1.11)
Passweg et al.[28]	2015	802	median 44	Predominantly PBSC	Predominantly MAC	2000-2013	*2.20 (1.40-3.60)*	*1.90 (1.10-3.50)*	*2.12 (1.46-3.08)*	1.10 (0.70-1.90)	1.00 (0.60-1.70)	n.a.
Verneris et al.[16]	2015	2588	median 59	Predominantly PBSC	RIC	1999-2011	*1.43 (1.20-1.71)*	*1.57 (1.22-2.02)*	1.13 (0.96-1.34)	0.97 (0.71-1.31)	n.a.	n.a.
Yokoyama et al.[17]	2017	1130	median 59	BM	RIC	1994-2013	*1.64 (1.11-2.41)*		*1.41 (1.10-1.81)*	*1.16 (0.88-1.54)*	n.a.	n.a.

BM=Bone Marrow, PBSC=Peripheral Blood Stem Cells, CB=Cord Blood, MAC=Myeloablative Conditioning, RIC=Reduced Intensity Conditioning, n.a.=non-applicable, n.s.=non-significant. Statistically significant hazard ratios are marked in bold

meta-analysis studies including 13 studies (n=13,446 transplants)[33] and 36 studies (n=100,072 transplants)[34] respectively, have similarly reported divergent conclusions as to the effect of DRB1 single mismatches on overall mortality, despite the partial overlapping of data meta-analyzed (Results of the two meta-analysis studies are summarized in Table 2). According to the bigger in volume meta-analysis of Tie et al,[34] DRB1 single mismatches were clearly associated with higher (TRM) and thus lower survival rates. This was not observed in the smaller meta-analysis study from Kekre et al. Last, the findings from Kanda et al.[25] comparing the impact of single HLA-mismatches in two distinct transplantation eras (i.e. 1993-1999 and 2000-2009) revealed an intriguing correlation between DRB1 single mismatch effect and transplantation era. According to their results, DRB1 single mismatches in the late period had a much more pronounced impact on outcome compared to the early one. This may well be attributed to the fact, that DRB1 mismatches were far more often avoided in the early era on account of evidence that clearly demonstrated the deleterious effects of that mismatch. The small number of DRB1 mismatched HSCTs of that era probably precluded statistical significance as to DRB1 mismatch effect. Progress in GvHD protection treatments has allowed for more DRB1 mismatched HSCTs in the late era and hence higher statistical power. Generally, as far as HLA-class II incompatibilities are concerned,

the impact of each respective locus appears more variable, as it can be modified by a series of other parameters such as coexistence of other mismatch (MM), racial particularities, donor selection practices and (MM)-permissiveness.[1,13,22,25,32,35] Data on HLA-C and HLA-DPB1 mismatches are reviewed in more detail in a separate paragraph.

LEVEL OF HLA-MISMATCH

The study of Flonemberg et al[21] first suggested a differential impact of antigen- versus allele-level mismatches on HSCT outcome. Apart from one study by Horan et al,[36] which however included exclusively nonmalignant disease patients, all subsequent studies addressing this issue[14,22,24,26] showed that, with the exception of HLA-C,[14] allele-level discrepancies should be viewed as equally detrimental as antigen-level ones. This discordance could stem from the significantly skewed distribution of cases with allele- versus antigen-mismatches in the HLA-C and -DRB1 loci analyzed in the Flonemberg et al study.[21] In particular, most of HLA-C mismatches, whose notable deleterious effect was in fact one of the main conclusions of the study, concerned discrepancies at antigen level (86% vs 14%). In contrast, HLA-DRB1 mismatches, were predominantly mismatches at allele level (85% vs 15%). It is therefore possible, that the skewed distribution of mismatches in these two loci as to their resolution level, might have confounded the

TABLE 2. Overview of two big meta-analysis studies

Risk of overall mortality conferred by individual HLA locus mismatches				
Tie et al. Meta-analysis (N=100,072, Nt=36)				
Allele	Studies*	HR (95% CI)	P	I2
HLA-A	12	1.33 (1.27-1.40)	<0.001	0.0%
HLA-B	12	1.35 (1.21-1.50)	<0.001	46.7%
HLA-C	14	1.23 (1.17-1.29)	<0.001	0.4%
HLA-DRB1	9	1.19 (1.07-1.32)	0.001	42.0%
HLA-DQB1	7	1.07 (0.98-1.17)	0.142	28.8%
HLA-DPB1	8	1.03 (0.97-1.09)	0.460	32.3%
Kekre et al. Meta-analysis (N=13,446, Nt=13)				
Allele	Studies*	HR (95% CI)	P	I2
HLA-A	4	1.48 (1.19-1.86)	0.001	21.0%
HLA-B	5	1.45 (1.20-1.75)	<0.001	0.0%
HLA-C	6	1.58 (1.23-2.01)	<0.001	63.0%
HLA-DRB1	3	1.16 (0.84-1.59)	0.363	15.0%
HLA-DQB1	4	0.95 (0.74-1.21)	0.668	4.0%
HLA-DPB1	3	0.99 (0.89-1.10)	0.816	0.0%

Statistical significance is marked in bold. Nt refers to the number of meta-analyzed studies.
*number of studies

conclusive estimations of the study over the differential effect of allele versus antigen HLA mismatches on HSCT outcome. Currently, there is general consensus on the irrelevance of mismatch level for HLA-A,-B, and-DRB1 incompatibilities. In the case of HLA-C, which shall be discussed later, findings suggest that allele- contrary to antigen-level-mismatches have minimal impact on HSCT outcome and thus should be considered as 'permissive' mismatches.[37]

DIRECTIONALITY OF HLA-MISMATCH

Although intuitively one would expect GvH-unidirectional or bidirectional mismatches (i.e. Graft vs Host and Host vs Graft) to be associated with higher TRM and GvHD rates compared to host versus graft (HvG)-unidirectional mismatches, data thus far have been rather inconclusive. Supportive evidence for this notion can be found in a study from Hurley et al,[38] which evaluated the impact of MM directionality in 2687 NMDP transplants on HSCT outcome. According to their analyses, 7/8 HvG MM were not associated with worse outcome in any post-transplant endpoint when compared to 8/8 M cases. In contrast, GvH-unidirectional and bidirectional MM conferred significantly higher risk of TRM and overall mortality when compared to 8/8 M transplants. If results were underpowered due to the small size of the unidirectional groups is yet unknown. A more recent study from Kanda et al,[39] investigating the impact of HLA MM directionality on HSCT outcome in 3756 JMDP transplants, detected no particular correlation between directionality and mortality in unidirectional MM cases. In this study just like in the study of Hurley et al,[38] the distribution of MM cases on account of their directionality was similarly skewed, with only 83 transplants in each unidirectional group versus 1020 in the bidirectional one. The markedly low number of unidirectional MM cases overall makes it evidently hard for even large cohort studies to identify statistically significant effects. Furthermore, the low likelihood (about 14%) of encountering a 7/8 unidirectionally MM donor upon donor- selection, makes the consideration of MM directionality rather irrelevant for now.

NUMBER OF HLA-MISMATCHES

It has long been established that multiple mismatches confer exponentially higher risk of mortality and GvHD and therefore should be avoided at least in a bone marrow (BM) or peripheral blood stem cell (PBSC) setting.[32,40-43] As mostly adverse is considered the combination of HLA-class I and II MM with respect to acute GvHD risk, while accumulation of HLA-class I MM has been shown to correlate with increased risk of graft failure.[32,40-42] Moreover, according to the observations of Petersdorf et al,[12] multiple mismatches containing one DQB1 MM have been found to confer significantly higher risk of mortality as compared to other multiple MM not including DQB1. The latter was also partially supported by the findings of Morishima et al,[13] who detected an aggravating effect of HLA-DQB1 MM on overall MM impact when combined with HLA-DRB1 MM. The detrimental effect of ≥ 2MM was also clearly demonstrated in the two large meta-analysis studies mentioned before.[33,34]

THE SPECIAL CASES OF HLA-C AND HLA-DPB1 MISMATCHES

HLA-C and HLA-DPB1 constitute special cases, as they are perhaps the only HLA loci for which 'permissive' MM have been clearly identified.[37,44] Moreover, they are both lower expressed on cell surface compared to their respective HLA-class counterparts.[45,46] Another interesting analogy is the existence of two immunogenicity models, which aim at explaining the 'permissiveness' of specific MM constellations for both loci. For HLA-DPB1 the two models are:

a) The long established T-cell epitope (TCE) model first described by Zino et al,[44] which attributes the distinct immunogenicity profile of respective HLA-DPB1 alleles to the existence or not of specific shared T-cell epitopes known to stimulate alloreactive T-cells. In other words alleles carrying these epitopes are considered highly immunogenic, while those that don't, low immunogenic. Alleles carrying the shared epitopes, yet inducing a milder alloreactive T-cell response, constitute a separate intermediate group. At the moment, there are two established versions of this TCE model, which only minimally differ from one another. A further refinement of the TCE-model has been recently proposed by the novel concept of ΔFD[47] (i.e. the net difference between functional distance (FD)-scores of mismatched HLA-DPB1 alleles in patient and donor). Before practical implementation of this latest algorithm however, further research is warranted.

b) A so-called expression-model, was recently described by Petersdorf et al,[48] which considers expression-related polymorphisms in order to explain the differential immunogenicity of HLA-DPB1 alleles. Specifically, alleles in linkage with the rs9277534A were found by means of a quantitative polymerase-chain-reaction assay to be lower expressed compared to the rs9277534G alleles.[48] Petersdorf et al in the same study[48] including 1441 11/12 MUD transplants, observed that rs9277534G-linked HLA-DPB1 MM conferred higher risk of aGvHD compared to rs9277534A-linked ones, which were subsequently defined as 'permissive'. The two models are to a high extent overlapping, yet some significant discrepancies will need to be clarified (e.g. HLA-DPB1*17:01) by future studies.

In the case of HLA-C, similarly an epitope-like- and an expression-model have been described.[49,50] According to the first epitope-like model, accumulation of discrepancies between mismatched alleles in seven key amino acid (aa) residues in the ARS (i.e. 9, 97, 99, 116, 152, 156 and 163) may be proportionally associated with worse outcomes, although further research is required before definite conclusions can be drawn.[51,52] It is of interest, that the results from in vitro cytotoxic T-lymphocyte precursor frequency (CTLp-f) assay

analyses evaluating the immunogenicity profile of various HLA-C MM combinations were concordant with the aforementioned model, as MM with 0-1 differences in the seven key aa had a negative or weak CTLp-f assay (e.g. C*03:03-03:04 and C*07:01-07:02), while C MM with 5-6 key aa disparities (C*15:02-14:02 in B*51 positive patients and C*04:01-12:03 in B*35 positive patients) had a positive one.[53] Nevertheless, another similar model proposed by Joris et al[54] aiming at predicting cytotoxic T-cell alloreactivity on account of the number of aa discrepancies in the α-helices and β-sheet between the mismatched C alleles, failed to establish such a correlation in a clinical dataset of 171 9/10 and 168 10/10 MUD transplants.[55]

A second expression-model was proposed a few years ago again by Petersdorf et al.[50] In this study a proxy model, which was based on the findings of a previous study associating high HLA-C expression levels with lower HIV viral load,[56] was implemented for the estimation of HLA-C expression variation in distinct C MM combinations and its impact on HSCT outcome. According to their findings, MM expression levels were directly correlated with worse outcomes in a proportional fashion. Interestingly, MM constellations that were previously identified as permissive by cellular assays, were strongly linked to lower expression levels (e.g. C*03:03-03:04 and C*07:01-07:02).

Finally, one more intriguing coincidence is that HLA-C and HLA-DPB1 MM are the only HLA MM associated with significantly lower relapse rates.[34] For HLA-DPB1 in particular, according to the findings of Fleischhauer et al,[57] a permissive MM donor could be from an immunological standpoint preferable to a fully matched one in a high-risk malignant setting, as permissive MM were found to confer significantly lower risk of relapse without substantially increasing the risk of aGvHD. If this could also hold true in a HLA-C permissive MM context is yet to be determined. According to current data however and at least as far as HLA-C non-permissive incompatibilities are concerned, any potential benefit from lower relapse is expected to be outweighed by significantly higher TRM rates.

NON-HLA FACTORS THAT INFLUENCE THE IMPACT OF HLA DISPARITY ON HSCT OUTCOME

The objective of this section is to offer the reader an overview of non-HLA parameters that could potentially influence the overall effect of HLA disparities on HSCT outcome.

DISEASE ASSOCIATED PARAMETERS: ENTITY AND STAGE

Allogeneic HSCT has long been established as standard of care for a plethora of primarily hematological malignant as well as nonmalignant disease entities.[58,59] According to statistical data from American as well as European research

groups,[60,61] acute leukemia is the most common indication for HSCT comprising more than 50% of total allogeneic transplant cases worldwide. This development is mainly due to the curative potential of allogeneic HSCT thanks to the graft vs leukemia (GvL) component of alloreactivity.[62] It is clear, that in a nonmalignant disease setting this beneficial aspect of HSCT deriving from partial incompatibility between patient and donor is not applicable. Could this subsequently mean that HLA disparities in a nonmalignant disorder setting could be more detrimental as to survival rates compared to a malignant one? This question was addressed by Horan et al[36] in a study of 663 BM and PBSC transplants that were performed exclusively in patients with nonmalignant disorders. As expected, single as well as double MM irrespectively of resolution level were associated with higher mortality risks. Interestingly, in this nonmalignant disease dataset higher mortality as a result of HLA incompatibility was associated with significantly higher graft failure and not higher acute GvHD or TRM as one would intuitively expect, considering previous results in malignant disease cohorts.[22,23] This could be attributed to two main factors.[63] Although the prevalence of donor specific antibodies (DSA) was not investigated in the aforementioned study, considering the high transfusion burden of patients requiring HSCT due to a non-malignant hematological disorder (i.e. aplastic anemia, thalassemia, osteopetrosis etc.), it is plausible to assume that at least a significant part of antigen-MM related graft failures could have been the result of humoral alloreactivity (i.e. antibody mediated rejection). Furthermore, nonmalignant disease patients' immune system is expected to be more apt to hinder engraftment, considering that it has not been compromised by additional chemotherapy prior to pre-transplant conditioning. However, the absence of association between HLA MM and acute GvHD, non-relapse mortality (NRM) or TRM in the malignant disease cohort most likely stemmed from the extensive use of graft manipulation (i.e. receipt of lymphocyte depleting antibody or ex-vivo T-cell depleted graft) reported.[19]

Another disease relevant parameter that has been shown to correlate with the HLA MM effect is disease stage. According to the findings of Petersdorf et al,[12] the detrimental impact of HLA disparities was far more prominent in low-risk disease patients. This could be intuitively attributed to the fact that in a low-risk disease setting any potential benefit from GvL is far weaker and thus more evidently outbalanced by HLA-MM derived GvHD. It should be noted however, that in that cohort, low-risk were exclusively CML patients in chronic phase. After the broad and successful implementation of tyrosine kinase inhibitors (TKIs) for the treatment of CML,[64] allogeneic HSCT has ceased being considered standard of care for this condition, therefore new cohorts that would better reflect current practice are mandatory in order to estimate the applicability of the Seattle group results in non-CML low risk disease patients.

RECIPIENT AGE

Although it is generally accepted that younger patient age is associated with better HSCT outcome, the direct correlation between HLA MM impact on HSCT and recipient age has only recently been addressed by Fórst et al. in a retrospective multicenter cohort of 3019 uHSC transplants.[15] Interaction analysis of the two parameters revealed an unambiguous association between higher HLA-MM-conferred mortality-risk and advanced disease age, especially in double mismatched (8/10) cases. More specifically, patients aged over 55years transplanted with 8/10 matched donors showed a disproportionally higher risk of mortality when compared to 8/10 matched transplanted patients of younger age groups (HR: 1.14, 1.40 and 2.27 in patients aged 18-35, 36-55 and >55 respectively). When the HR of 8/10 elderly patient group transplants was estimated in reference to 10/10 matched patients aged 18-35 it exponentially increased to 3.48. Before definite conclusions can be drawn, these findings will have to be confirmed by other independent cohorts. Given nevertheless, the significant proportion of elderly patients in this cohort (n=1195/3019) as well as the high representation of latest era transplantations (n=1671/3019 for 2008-2011 and n=2610/3019 for 2004-2011), it seems rather reasonable to follow the author's recommendation for best possible HLA matching in patients over 55 years of age along with consideration of alternative HSCT options in case a ≥9/10 matched donor is unavailable.

GRAFT MANIPULATION

Various T-cell depletion (TCD) techniques have been developed over the years.[65] Despite the promising results of these methods with regard to GvHD and TRM dampening, the absence of proven beneficial impact on overall survival due to delayed immune reconstitution, higher incidence of graft failure as well as increased infection prevalence has contained the extensive use of TCD in allogeneic HSCT.[65] The association between HLA MM impact on HSCT outcome and graft manipulation, has been repeatedly insinuated in many studies underscoring the significantly lower relative risk of grade II-IV aGvHD in TCD transplants[19;65]. Given the established association between HLA MM and aGvHD incidence, it becomes apparent that in a mismatched HLA unrelated HSCT (uHSCT) setting, TCD can significantly mitigate the proportionally higher risk of TRM conferred by HLA MM.[19] This was also shown in the nonmalignant cohort study of Horan et al[36] previously mentioned. New focused strategies in the field of graft manipulation, which aim at improving the immune reconstitution as well as the GvL potential of TCD grafts, may prove to be an efficient antidote to the deleterious effect of HLA disparities on HSCT outcome in the near future. (Chimeric Antigen Receptor (CAR) T-cell therapy, Bi-specific T-cell engagers, checkpoint inhibitors to control relapse following allo- HSCT along with adoptive use of regulatory T-cells (Tregs) and suicide gene manipulation to improve the risk of post-transplant GVHD post-transplant are some examples of these developing treatments).[65]

CONDITIONING REGIMEN

The constantly growing use of reduced intensity conditioning (RIC) regimens in the modern transplantation era has significantly altered the patient age range and thus the composition of the late years' cohorts.[66] Given that most of the data regarding the effect of HLA MM on post-transplant outcome mostly derive from transplantations performed in earlier time periods, when RIC transplants accounted for only a small fraction of cases, it was foreseeable that the impact of HLA matching in a RIC uHSCT setting would sooner or later be addressed by researchers. Two independent groups, one in the US[16] and one in Japan[17] explored the consequences of HLA disparities in a non-myeloablative conditioning (MAC) environment. Both studies detected higher mortality risks associated with HLA MM, with the respective relative risk values lying within the range of those previously reported in MAC cohorts.[21,22,25] Despite the relatively high number of cases included in both studies (n=2588 for Verneris et al., n=1130 for Yokoyama et al.) subgroup analyses aiming at discerning the differential effect of HLA incompatibilities with reference to locus or resolution level of MM had limited power due to the broad scattering of cases. Under this prism, the finding of Verneris et al[16] regarding the non-identified 'permissiveness' of HLA-C*03:03/03:04 MM or TCE permissive DPB1 MM should be viewed with caution. In line with this, the absence of notable difference in mortality risk conferred by single and double mismatches with reference to full 8/8 match (i.e. hazard ratio [HR], 1.34; P = .0024 for 7/8 match; HR, 1.33; P = .035 for 6/8 match) found in the Japanese cohort[17] could also be attributed to cohort-size limitations in the respective subgroups. However, the direct association between MM number and risk of NRM and GvHD observed[16], adds validity to the assumption that an enhanced HLA-MM-associated GvL effect may be more pronounced in a RIC compared to a MAC HSCT setting. If this assumption, along with the finding that HLA MM impact appeared to be less significant in the later transplantation years, hold, remains to be resolved by future RIC-specific studies.

CMV SERO-STATUS MATCHING

The significance of CMV sero-status matching between recipient and donor is acknowledged and hence considered routinely upon donor selection.[7] The potential interaction however, between this parameter and HLA matching had not but only recently been reported in literature. Particularly, Shaw et al[18] in their study of 1271 malignant disease patients receiving T-cell depleted allografts reported a clear connection between CMV and HLA matching, with combined MM being identified as the most deleterious combination. Perhaps

the most interesting finding of this study was the potential of CMV-matching to partly abrogate the detrimental effect of HLA MM on outcome. Although these data are certainly intriguing with practical implications as to the prioritization of donor selection criteria, it should be underscored that these results concerned exclusively TCD transplants. If this also applies to non-manipulated grafts is something that will have to be explored by future studies.

TYPE OF TRANSPLANTATION: PBSC, BONE MARROW, UMBILICAL CORD BLOOD OR HAPLOIDENTICAL

Graft source varied among the respective studies listed in Table 1. Despite the differences observed as to the individual effect of distinct HLA disparities on survival, there were no marked discordances on HLA MM-related mortality risk between BM and PBSC allogeneic transplants. For umbilical cord blood (UCB), it appears that single HLA MM regardless of locus had no significant impact on overall mortality. However, according to the findings of Eapen et al in two retrospective studies,[27,67] HLA-matching had a notable impact on TRM/NRM with HLA mismatching exhibiting a cumulative effect. This was also confirmed in a later study by Brunstein et al[68] concerning double unit UCB transplants. Moreover, it is of note, that certain UCB studies[69] have implied an interactive connection between total nuclear count (TNC) per unit and HLA-matching, suggesting combined consideration of these two parameters for superior outcomes. As far as haploidentical transplantations are concerned, the role of better HLA matching in outcome remains unclear, as there is no supportive evidence thus far indicating better post-transplant results linked to better HLA-matched grafts in this transplantation setting,[70,71] with the exception of HLA-B matching in non-shared haplotype, which was found to be significantly relevant in just one Chinese study.[72] Considering, nevertheless that only a few and limited in size studies have addressed this question, one cannot preclude over-turning of this conception in the future.

CONCLUSION

With this review we aimed at offering the reader a comprehensive overview of current scientific knowledge on the impact of HLA-matching in different HSCT settings, evaluating separately HLA- and non-HLA-parameters that may modify it. From presented data, it becomes apparent that any kind of HLA disparity should be viewed within the context of HSCT as a whole and not independently from other transplantation-related factors, seeing that many of the latter can substantially alter HLA MM effect on post-transplant outcomes.

RECOMMENDATION TIPS FOR BETTER ASSESSMENT OF HLA DISPARITIES IN DISPARATE HSCT SETTINGS

- Single HLA MM irrespective of locus, with the exception of HLA-DQB1 and DPB1, are associated with higher risk of mortality and should therefore be avoided
- Antigen vs allele mismatch is only relevant in HLA-C disparities, with HLA-C MM at allele level being considered as 'permissive'
- Single DQB1 MM appear to be well tolerated, yet should be avoided when combined with incompatibilities in other loci
- Accumulation of HLA MM is always detrimental, hence should be avoided even in a UCB setting (i.e. <7/8 match in PBSC and BM and <4/6 match in UCB)
- Permissive HLA-DPB1 MM might confer superior outcomes in a malignant disorder setting compared to M and non-permissive MM
- Up to now there is no substantial evidence supporting any consideration of HLA-MM directionality in regard to donor selection
- Double HLA MM have been shown to be more deleterious in elderly patients and should thus be avoided
- CMV sero-status matching should be considered upon donor selection, especially in a mismatched TCD setting
- Best possible matching should be prioritized in low-risk- as well as in nonmalignant disease patients

PROSPECTS AND FUTURE CHALLENGES

The holy grail of HSCT had always been diminishing the detrimental transplantation-related alloreactivity (i.e. GvHD) without undermining its positive GvL side. With the exception of permissive HLA-DPB1 MM, current data affirm that any putative positive effect of HLA MM on relapse is outweighed by a proportionally higher increase in TRM risk.[57] New advances in the direction of identifying 'permissive' disparities similar to HLA-DPB1 in other loci through identification of shared immunogenic epitopes, is an undoubtedly promising strategy. In parallel, progress in the field of biomolecular engineering and particularly in the development of more sophisticated GvHD prophylaxis regimens as well as techniques enhancing GvL and engraftment, is expected to completely revolutionize HSCT as we know it today. A new HSCT era has already started. "Le roi est mort, vive le roi".

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