Published in final edited form as:
Lancet Oncol. 2012 April ; 13(4): . doi:10.1016/S1470-2045(12)70004-9.

Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study

Katharina Fleischhauer[*], **Bronwen E Shaw**[*], **Theodore Gooley**, **Mari Malkki**, **Peter Bardy**, **Jean-Denis Bignon**, **Valérie Dubois**, **Mary M Horowitz**, **J Alejandro Madrigal**, **Yasuo Morishima**, **Machteld Oudshoorn**, **Olle Ringden**, **Stephen Spellman**, **Andrea Velardi**, **Elisabetta Zino**, and **Effie W Petersdorf on behalf of the International Histocompatibility Working Group in Hematopoietic Cell Transplantation**

Unit of Molecular and Functional Immunogenetics, Division of Regenerative Medicine, Stem Cells and Gene Therapy, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) H San Raffaele, Milan, Italy (K Fleischhauer MD, E Zino BSc); Haemato-Oncology Research Unit, Division of Molecular Pathology, The Institute of Cancer Research, London, UK (B E Shaw MD); Anthony Nolan Research Institute, Royal Free Hospital, London, UK (B E Shaw, Prof J A Madrigal MD); Fred Hutchinson Cancer Research Center, Seattle, WA, USA (Prof T Gooley PhD, M Malkki PhD, Prof E W Petersdorf MD); Transplant Services Laboratory, Australian Red Cross Blood Service, Melboune, Victoria, Australia (P Bardy MD); Cancer Services Central Adelaide Local Health Network, Royal Adelaide Hospital, Adelaide, SA, Australia (P Bardy); HLA Laboratory, Établissement Français du Sang, Nantes, France (J-D Bignon MD); HLA Laboratory, Établissement Français du Sang, Lyon, France (V Dubois BSc); Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI, USA (Prof M M Horowitz MD); Center for International Blood and Marrow Transplant Research, Minneapolis, MN, USA (S Spellman MBS)**; Aichi Cancer Center, Nagoya, Japan** (Prof Y Morishima MD)**; Japan Marrow Donor Program, Tokyo, Japan** (Prof Y Morishima); Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, Netherlands (M Oudshoorn PhD) **Europdonor Foundation, Leiden, Netherlands** (M Oudshoorn PhD); Division of Clinical Immunology and Centre for Allogeneic Stem Cell Transplantation, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden (Prof O Ringden MD); and Division of Haematology and Clinical Immunology, University of Perugia, Perugia, Italy (Prof A Velardi MD)

Summary

Background The risks after unrelated-donor haemopoietic-cell transplantation with matched HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1 alleles between donor and recipient (10/10 matched) can be decreased by selection of unrelated donors who also match for HLA-DPB1; however, such donors are difficult to find. Classification of HLA-DPB1 mismatches based on T-

Correspondence to: Bronwen E Shaw.

Correspondence to: Dr Bronwen Shaw, Anthony Nolan Research Institute, Royal Free Hospital, Pond Street, Hampstead, London, NW3 2QG, UK **bshaw@doctors.org.uk**.

[*]These authors contributed equally to this work

Contributors

KF, BES, TG, MM, and EPW contributed to the design, set up, data collection and collation, writing, and review of the report. TG did the statistical analysis. PB, J-DB, VD, MMH, JAM, YM, MO, OR, SS, AV, and EZ contributed to data collection, oversight of the study, and review of the report. All authors have approved the final version of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

cell-epitope groups could identify mismatches that might be tolerated (permissive) and those that would increase risks (non-permissive) after transplantation. We did a retrospective study to compare outcomes between permissive and non-permissive HLA-DPB1 mismatches in unrelated-donor haemopoietic-cell transplantation.

Methods HLA and clinical data for unrelated-donor transplantations submitted to the International Histocompatibility Working Group in haemopoietic-cell transplantation were analysed retrospectively. HLA-DPB1 T-cell-epitope groups were assigned according to a functional algorithm based on alloreactive T-cell crossreactivity patterns. Recipients and unrelated donors matching status were classified as HLA-DPB1 match, non-permissive HLA-DPB1 mismatch (those with mismatched T-cell-epitope groups), or permissive HLA-DPB1 mismatch (those with matched T-cell-epitope groups). The clinical outcomes assessed were overall mortality, non-relapse mortality, relapse, and severe (grade 3–4) acute graft-versus-host disease (aGvHD).

Findings Of 8539 transplantations, 5428 (64%) were matched for ten of ten HLA alleles (HLA 10/10 matched) and 3111 (36%) for nine of ten alleles (HLA 9/10 matched). Of the group overall, 1719 (20%) were HLA-DPB1 matches, 2670 (31%) non-permissive HLA-DPB1 mismatches, and 4150 (49%) permissive HLA-DPB1 mismatches. In HLA 10/10-matched transplantations, non-permissive mismatches were associated with a significantly increased risk of overall mortality (hazard ratio [HR] 1·15, 95% CI 1·05–1·25; p=0·002), non-relapse mortality (1·28, 1·14–1·42; p<0·0001), and severe aGvHD (odds ratio [OR] 1·31, 95% CI 1·11–1·54; p=0·001), but not relapse (HR 0·89, 95% CI 0·77–1·02; p=0·10), compared with permissive mismatches. There were significant differences between permissive HLA-DPB1 mismatches and HLA-DPB1 matches in terms of non-relapse mortality (0·86, 0·75–0·98; p=0·03) and relapse (1·34, 1·17–1·54; p<0·0001), but not for overall mortality (0·96, 0·87–1·06; p=0·40) or aGvHD (OR 0·84, 95% CI 0·69–1·03; p=0·09). In the HLA 9/10 matched population, non-permissive HLA-DPB1 mismatches also increased the risk of overall mortality (HR 1·10, 95% CI 1·00–1·22; p=0·06), non-relapse mortality (1·19, 1·05–1·36; p=0·007), and severe aGvHD (OR 1·37, 95% CI 1·13–1·66; p=0·002) compared with permissive mismatches, but the risk of relapse was the same in both groups (HR 0·93, 95% CI 0·78–1·11; p=0·44). Outcomes for HLA 10/10-matched transplantations with non-permissive HLA-DPB1 mismatches did not differ substantially from those for HLA 9/10-matched transplantations with permissive HLA-DPB1 mismatches or HLA-DPB1 matches.

Interpretation T-cell-epitope matching defines permissive and non-permissive HLA-DPB1 mismatches. Avoidance of an unrelated donor with a non-permissive T-cell-epitope mismatch at HLA-DPB1 might provide a practical clinical strategy for lowering the risks of mortality after unrelated-donor haemopoietic-cell transplantation.

Funding National Institutes of Health; Associazione Italiana per la Ricerca sul Cancro; Telethon Foundation; Italian Ministry of Health; Cariplo Foundation; National Cancer Institute; National Heart, Lung and Blood Institute; National Institute of Allergy and Infectious Diseases; Office of Naval Research; IRGHET Paris; Swedish Cancer Society; Children's Cancer Foundation; Swedish Research Council; Cancer Society in Stockholm; Karolinska Institutet; and Leukemia and Lymphoma Society.

Introduction

Matching for human leucocyte antigen (HLA)-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 (“10/10”) alleles between an unrelated donor and patient is undertaken to lower risks of acute graft-versus-host disease (aGvHD) and mortality after haemopoietic-cell transplantation.1-9 Another allele mismatch, at HLA-DPB1, increases the risk of aGvHD, the effect of which may be counterbalanced by a reduced risk of leukaemia relapse.7-9 Although matching for HLA-DPB1 lowers overall risks after haemopoietic-cell transplantation, HLA-DPB1-matched unrelated donors are difficult to find.6,7 Therefore, an

unmet clinical need is to identify HLA-DPB1 mismatches that do not increase risks (permissive mismatches) and avoid the use of unrelated donors with HLA-DPB1 mismatches that are associated with increased risk (non-permissive mismatches).

HLA-DPB1 mismatches can induce alloreactive T-cell responses.10-18 On the basis of crossreactivity patterns, our group has proposed and investigated a model for identification of non-permissive HLA-DPB1 mismatches as defined by the presence of T-cell-epitope (TCE) mismatching.19-21 Alleles were classified into three T-cell-epitope groups predicted to have high, intermediate, and low immunogenic potential. On the basis of this classification, HLA-DPB1-allele mismatches are defined as permissive if the mismatched alleles belong to the same group, or as non-permissive if they belong to different groups. Later, a four-group model was put forward based on the fact that in the original experimental system both the patient and the donor shared the DPB1*02:01 allele.21 Thus, a separate group containing only DPB1*02 of intermediate immunogenicity was added. Using both models, results from the Italian Bone Marrow Donor Registry (IBMDR) showed that non-permissive HLA-DPB1 T-cell epitope group mismatches were associated with a significantly higher risk of adverse outcome than permissive mismatches in the setting of HLA 10/10-matched unrelated-donor haemopoietic-cell transplantation.19,21 Other retrospective studies have reported similar associations, although they did not always reach significance.22,23 Because of limitations in sample size, a direct comparison of the risks associated with HLA-DPB1 matched transplantations and permissive or non-permissive HLA-DPB1-mismatched transplantations (ie, three groups) has not yet been possible.

Within the International Histocompatibility Working Group (IHWG), we had the unique opportunity to address this question in 8539 international transplant recipients. In this cohort, the risks associated with non-permissive HLA-DPB1 T-cell epitope group mismatches could be assessed in comparison with permissive mismatches and with HLA-DPB1 matches in the setting of HLA 10/10-matched unrelated donors, and in comparison with single mismatches at either HLA-A, HLA-B, HLA-C, HLA-DRB1, or HLA-DQB1 (HLA 9/10-matched unrelated donors).

Methods

Patients and data collection

This study included patients who received a transplant from an unrelated donor for the treatment of a blood disorder between 1993 and 2007. Data were contributed by transplantation centres, transplantation registries, and donor registries (full listing of contributors provided in appendix). All pairs had complete demographic, clinical, and HLA tissue typing data for HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, and HLA-DPB1.

Research samples and data were collected according to guidelines approved by institutional review board-approved guidelines and protocols of every participating institution. For samples contributed by the US National Marrow Donor Program (NMDP), all surviving recipients included in the analysis were contacted retrospectively and provided informed consent for participation in the research programme. To address potential bias introduced by inclusion of only a proportion of surviving patients (those who consented) but all deceased recipients, a sample of deceased patients was selected using a weighted randomised scheme that adjusts for over-representation of deceased patients in the consented cohort.

Procedures and definitions

The methods used for tissue typing in the study cohort have been previously described.7,24 Briefly, HLA typing was done with the following methods: sequencing-based typing (82·6%), sequence specific priming (8·5%), reference strand conformation analysis (6·8%),

sequence specific oligonucleotide probing (1·9%), reverse dot blot (0·2%). Participating laboratories and registries chose the typing methods.

A HLA 10/10 match refers to donor-recipient pairs matched for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 at the allele level. A HLA 9/10 match refers to pairs with a single allele or antigen mismatch at either HLA-A, HLA-B, HLA-C, HLA-DRB1, or HLA-DQB1. A HLA-DPB1 match refers to donor-recipient pairs matched for HLA-DPB1 alleles in both the graft-versus-host and the host-versus-graft direction.

A graft-versus-host direction mismatch means that the patient possesses one or more alleles not present in the donor and thus an alloreactive response mounted by the donor T-cells (graft) towards the patient (host) tissue may be expected. By contrast, a host-versus-graft direction mismatch means that the donor possesses one or more alleles not present in the patient, such that an alloreactive response mounted by the patient T-cells (host) towards the donor (graft) cells may be expected.

HLA-DPB1 mismatch refers to either a single or a double HLA-DPB1 allele mismatch in the graft-versus-host or the host-versus-graft direction, or both.

HLA-DPB1 permissive or non-permissive mismatches (T-cell-epitope group matching or T-cell-epitope group mismatching) were defined in HLA-DPB1 allele mismatched pairs according to the previously published three-group model19 as follows: both HLA-DPB1 alleles carried by the patient and by the donor were assigned to three different T-cell-epitope groups containing the alleles HLA-DPB1*09:01, 10:01, and 17:01 (group 1); HLA-DPB1*03:01,14:01, 45:01, and 86:01 (group 2); and most other frequent HLA-DPB1 alleles (group 3). Precise grouping of the different alleles can be found in the appendix. Subsequently, pairs were defined as HLA-DPB1 permissively mismatched (T-cell-epitope group matched) in the three following circumstances (appendix): (1) if all alleles in the patient and donor are from the same group (all group 1, all group 2 or all group 3); (2) if both the patient and the donor had at least one allele from group 1; or (3) where neither the patient nor donor had a group 1 allele, but both the patient and donor had at least one group 2 allele. According to this definition, HLA-DPB1 permissive mismatches do not have a graft-versus-host or host-versus-graft direction, because they are T-cell-epitope group matches.

All other groupings of alleles were defined as HLA-DPB1 non-permissive mismatches (T-cell-epitope group mismatched). Such mismatches were in the graft-versus-host direction if the patient type contained an allele from a higher group than the donor, and in the host-versus-graft direction if the donor type contained an allele from a higher group than the patient (appendix).

Statistical analysis

We assessed the association of the various match categories with the cause-specific hazard of failure with Cox regression for the time-to-event outcomes of overall mortality, non-relapse mortality, and relapse. We examined the association of the probability of the binary outcome of aGvHD using logistic regression. We adjusted each regression model for major clinical variables which have been shown to be associated with outcome (patient's age, patient's and donor's sex, patient's serological status for cytomegalovirus, year of transplantation, donor registry (Japanese Marrow Donor Programme, JMDP *vs* non-JMDP), source of stem cells, conditioning regimen, T-cell depletion, disease severity at transplantation). We did statistical tests of the interaction for T-cell-epitope match status (permissive *vs* non-permissive) and donor registry (JMDP *vs* non-JMDP) and disease severity at transplant (low *vs* intermediate *vs* high) by including appropriate terms in the

regression models. We obtained estimates of overall mortality with the Kaplan-Meier method, and used cumulative incidence estimates to summarise the probability of non-relapse mortality and relapse. Death without relapse was regarded as a competing risk for relapse, and relapse a competing risk for non-relapse mortality. All reported p values were two-sided and were estimated using the Wald test. No adjustments were made for multiple comparisons. The software used was SAS, version 9.1.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. EWP, TG, MM, BES and KF had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The characteristics of the study population are shown in table 1. Most transplantations were done with myeloablative regimens in the absence of T-cell depletion, with bone marrow as stem-cell source (table 1). 3634 (77%) of 4749 of patients contributed by registries and centres outside the JMDP self-described as white. 5428 (64%) of 8539 patients and their unrelated donor were matched for ten of the ten HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 alleles (HLA 10/10 matched), and 3111 (36%) of 8539 were matched for nine of these ten alleles (HLA 9/10 matched), as determined by allele level typing (table 1). Of the 5965 transplantations matched for HLA-A, HLA-B, HLA-C, and HLA-DRB1, 537 (9%) were mismatched for HLA-DQB1 (HLA 8/8 matched).

Only 49 (33%) of the 150 known HLA-DPB1 alleles25 were recorded in the study population, with a similar allelic distribution in patients and unrelated donors (appendix), in line with previously described allele frequencies for this locus.26 In line with previous reports,6,7,19 20% (1719 of 8539 pairs) were HLA-DPB1-matched, 31% (2670 of 8539 pairs) were non-permissive HLA-DPB1 mismatched, and 49% (4150 of 8539 pairs) were permissive HLA-DPB1 mismatched (table 1, appendix). HLA-DPB1 matching status was similar in HLA 10/10-matched and 9/10-matched pairs (table 1).

5-year estimates for the entire cohort were 57% (95% CI 56–58) for overall mortality, 36% (35–37) for non-relapse mortality, and 24% (23–25) for relapse. Among 8272 patients who had an aGvHD grade available, 1613 (19·5%, 95% CI 18·7–20·4) had grade 3–4 aGvHD.

For the HLA 10/10 matched group, the adjusted hazard of overall mortality in the HLA-DPB1 matched subgroup did not significantly differ from that of the permissive HLA-DPB1-mismatched subgroup (figure 1, table 2). The hazard of relapse, however, was significantly higher in the HLA-DPB1-matched subgroup than in the permissive HLA-DPB1-mismatched subgroup (figure 1, table 2), which was counterbalanced by a reduced risk of non-relapse mortality (figure 1, table 2). No significant difference in the odds of grades 3–4 severe aGvHD was noted between groups (figure 1, table 2). However, when grade 2 aGvHD was included, there was a significant reduction in the odds of GvHD recorded in the HLA-DPB1 matched group compared with the permissive mismatched group (odds ratio [OR] 0·74, 95% CI 0·64–0·86; p<0·0001).

By contrast, in the same HLA 10/10 matched group, the risks of overall mortality, non-relapse mortality, and grade 3–4 aGvHD were significantly higher in the non-permissive HLA-DPB1-mismatched subgroup than in the permissive HLA-DPB1 mismatched subgroup (figure 1, table 2). When grade 2 aGvHD was also included, the increase in odds was less pronounced than when only grade 3–4 aGvHD was taken into account (OR 1·17, 95% CI

1·03–1·33; p=0·02). There was no significant difference in risk of relapse between non-permissive and permissive HLA-DPB1 mismatches (figure 1, table 2). The risk of relapse was significant, however, when only the non-permissive HLA-DPB1 mismatches in the graft-versus-host direction were considered, compared with HLA 10/10-matched permissive HLA-DPB1 mismatches (HR 0·80, 95% CI 0·66–0·97; p=0·02; appendix).

For all endpoints except relapse, separate analysis of non-permissive HLA-DPB1 mismatches in the host-versus-graft or graft-versus-host directions yielded similar results (appendix). The magnitude of the difference between permissive and non-permissive HLA-DPB1 mismatches in the HLA 10/10-matched group was similar across categories of disease severity (low *vs* intermediate *vs* high), donor registry (JMDP *vs* non-JMDP), and number of mismatched HLA-DPB1 alleles in the non-permissive group (one *vs* two; data not shown). A separate analysis of HLA 8/8-matched transplantations yielded the same qualitative conclusions with respect to differences between permissive and non-permissive mismatches as those obtained for HLA 10/10-matched transplantations (appendix). Additionally, analysis of HLA 10/10-matched or 9/10-matched transplantations coded according to the four-group model we previously described,21 yielded similar results to the three-group model for all clinical endpoints (data not shown).

In the HLA 9/10-matched group, the difference between permissive and non-permissive HLA-DPB1 mismatches for the four outcomes studied was also present, although less marked than for HLA 10/10-matched group, except for aGvHD (table 2).

For the HLA 10/10-matched population, the effect of HLA-DPB1 T-cell epitope-group matching status on outcome without adjustment for non-T-cell-epitope factors is summarised in the appendix, as is the effect of the non-T-cell-epitope factors on outcome. The appendix shows multivariable regression models with results for all factors, including the non-T-cell-epitope variables.

In line with previous observations,2,4,23 overall mortality was significantly higher after unrelated donor haemopoietic-cell transplantation that was HLA 9/10 matched than after transplantation that was 10/10 matched (HR 1·19; 95% CI 1·12–1·26; p<0·0001). The risks of overall mortality, non-relapse mortality, and grade 3–4 aGvHD in the permissive HLA-DPB1-mismatched and HLA-DPB1-matched groups of the HLA 9/10-matched population were much the same as those in the non-permissive HLA-DPB1-mismatched group of the HLA 10/10-matched population (figure 2; table 3). These risks were more pronounced in those with non-permissive HLA-DPB1 mismatches for the HLA 9/10 matched population.

Discussion

In this study, we have shown that non-permissive HLA-DPB1 disparities between donor and patient, defined according to an easily applied functional algorithm for T-cell-epitope group matching, are associated with a significantly increased risk of mortality after haemopoietic-cell transplantation from an unrelated donor in a HLA 10/10-matched population compared with permissive HLA-DPB1 disparities.

These findings represent an important step forward in the understanding of the risks after unrelated haemopoietic-cell transplantation. The present state of the art regards matching for HLA-A, HLA-B, HLA-B, HLA-DRB1, and HLA-DQB1 alleles between donor and recipient as the major immunogenetic variables associated with patient survival.2-5,23 Our results show the added value of avoiding non-permissive HLA-DPB1 mismatches in this setting. Moreover, permissive HLA-DPB1 mismatches are associated with similar mortality as allele matches, suggesting that the recommendable donor pool can be expanded to include both categories. The net result of increased non-relapse mortality in the permissive

mismatches but decreased relapse compared with the allele matches results in similar mortality outcome between the two groups (table 2).

This approach is highly feasible since donors who are HLA-DPB1 matched, or permissively mismatched, with recipients make up 70% of the donor pool for a given patient. Moreover, non-permissive HLA-DPB1 mismatches can be easily identified by targeted typing, with minimum time and cost constraints.26 This policy would have the additional advantage of making it possible to validate prospectively the findings from this retrospective study. It is important to point out that due to the large sample size of this study, there was ample power to detect even modest true differences between groups; nonetheless, we feel that the increase in the risk of mortality of 15% noted with non-permissive DPB1 is also clinically significant. It is also worthwhile to point out that the increased risk of mortality associated with non-permissive mismatches relative to permissive mismatches in the HLA 10/10-matched population was present in all categories of disease severity, and a statistical test of interaction showed no evidence that this effect differed across the three risk groups.

The standard approach to donor selection for unrelated haemopoietic-cell transplantation relies on nucleotide per nucleotide matching for polymorphic exons, attributing the same relative importance to any aminoacid variation(s) in the peptide binding region of the HLA molecule.2-5,23 The present study provides proof of principle for a new concept of unrelated-donor selection based on biological observations that could not have been predicted on the basis of structural data. Investigations have attempted to classify clinically non-permissive HLA mismatches in unrelated-donor-haemopoietic-cell transplantation by systematic structural comparison of aminoacid similarities or differences between mismatched HLA molecules. But these attempts have been hampered by the absence of a proven biological rationale to guide the selection of potentially important regions, resulting in a high degree of complexity in the conduct of these investigations, with often heterogeneous results.22,27-30 It should be noted that the T-cell-epitope group classification for HLA-DPB1 used in the present study builds on the principles of thymic selection31 and therefore takes into account both HLA-DPB1 alleles in patient and donor, regardless of whether only one or both of them are mismatched. This point should be taken into account when comparing the clinical associations of HLA-DPB1 T-cell epitope matching from this study with those of acceptable mismatch combinations reported previously.27,28 Moreover, Moreover, the present study shows a significant effect of non-permissive HLA-DPB1 mismatches in 10/10 HLA-matched transplantations overall, and this effect could vary when subgroups of patients with defined HLA-DPB1 allele mismatch combinations are analysed, as has been done in the past.27-29,32

It is well established that the risk of adverse clinical events after unrelated-donor haemopoietic-cell transplantation increases with every mismatch at HLA-A, HLA-B, HLA-C, or HLA–DRB1 between recipient and unrelated donor, whereas the risk associated with HLA-DQB1 mismatching is lower.2-5,23 This difference has led many centres to adopt matching for HLA-A, HLA-B, HLA-C, and HLA-DRB1 (8/8) as the gold standard for selection of unrelated donors. The purpose of the present study was not to compare the relative effect of single or combined mismatches at different HLA loci on clinical outcome, but to retrospectively assess the predictive value of our innovative functional algorithm for T-cell epitope-group matching of HLA-DPB1. The most informative group for this analysis was the HLA 10/10-matched transplantations because no allogenicity resulting from mismatches at the other major polymorphic loci exists in this setting, allowing us to isolate the DPB1 effects. However, the relative difference in outcome between permissive and non-permissive DPB1 mismatches was almost the same in the 8/8-matched population as it was in the 10/10-matched population (appendix), suggesting that our functional matching

algorithm is predictive in both settings and that HLA-DPB1 typing should also be recommended for unrelated donor in centres where 8/8 matching is accepted.

We previously provided evidence that an overlapping algorithm foreseeing four rather than three T-cell-epitope groups by regarding HLA-DPB1*02 alleles as an independent group, could enhance predictions of clinical outcome after unrelated-donor haemopoietic-cell transplantation.21 Here, we showed similar associations with all clinical endpoints with the four-group algorithm to those noted with the three-group algorithm (data not shown). A difference between the previous21 and the present study is the use of anti-thymocyte globulin for GvHD prophylaxis: more than 90% of the transplantations in the previous study used such prophylaxis,21 compared with less than 20% in the present study. The specific drugs used for prophylaxis, as well as differences in patient characteristics, could account for these partly differing results, and call for more detailed comparative investigation of the two algorithms in different cohorts.

Previous studies compared outcomes between non-permissive and permissive HLA-DPB1-mismatched transplantations without HLA-DPB1-matched controls, prompting the conclusion that permissive mismatches are not potential targets of aGvHD.16-18 However, this conclusion contrasts with previous clinical and experimental evidence. 6-8,10-15,19,28,33 In the present study, we showed that the odds of aGvHD are decreased (although not significantly) in HLA-DPB1-matched transplants compared with permissive HLA-DPB1-mismatched transplants (table 2). It is interesting to note that the odds of aGvHD associated with non-permissive HLA-DPB1 mismatches relative to permissive HLA-DPB1 mis matches were similarly increased in the graft-versus-host and the host-versus-graft directions (appendix). This is in line with our previous reports19,21 and could indicate an "allocrine loop" analogous to the well known "autocrine loop of human malignancies" of GvHD-associated cytokine production by donor antigen-presenting or effector cells, after triggering through non-permissive host-versus-graft disparities.34

We and others have previously shown that HLA-DPB1 mismatches are associated with a significantly lower rate of leukaemia relapse after unrelated-donor haemopoietic-cell transplantation,7,28 suggesting that mismatched HLA-DP antigens are targets of graft-versus-leukaemia activity.35 Interestingly, in this study, we noted that permissive and non-permissive mismatches were each associated with a decrease in the risk of disease relapse when compared with the HLA-DPB1-matched cohort (table 2, figure 1C). This effect was stronger in the non-permissive HLA-DPB1 mismatches in the graft-versus-host direction than it was in the host-versus-graft direction compared with permissive mismatches (appendix), an observation in line with the underlying biological model of T-cell alloreactivity.

Panel: **Research in context**

Systematic review

We searched PubMed with the search terms "HLA-DP", "TCE", "T cell epitope matching", and "haematopoietic cell transplantation". The existing evidence in this area consists of primary laboratory findings by our group,19 combined with a clinical model investigating the effect of HLA-DPB1 allele level matching, also published by this group7.

Interpretation

Our results suggest that consideration of HLA-DPB1 T-cell epitopes might benefit some patients when selecting a donor for a transplantation, to lower the morbidity and mortality of GvHD and improve outcomes.

In conclusion, we showed that non-permissive HLADPB1 mismatches can be defined by T-cell-epitope mismatching (panel). Our results suggest that overall outcome after HLA-matched or HLA-mismatched unrelated-donor haemopoietic-cell transplantation could be improved through prospective assessment of unrelated donors for HLA-DPB1 and the selection of T-cell-epitope-matched unrelated donors when HLA-DPB1-matched unrelated donors are not available.

Acknowledgments

The members of the IHWG haemopoietic-cell transplantation component who contributed data to this publication are listed in the appendix. We acknowledge support from the following funding agencies: grants AI069197, CA18029 from National Institutes of Health, USA (EWP, TG, and MM); Associazione Italiana per la Ricerca sul Cancro (AIRC), GGP08201 Telethon Foundation, Ricerca Finalizzata RF2007 Italian Ministry of Health, Cariplo Foundation (KF); Public Health Service grant or cooperative agreement U24-CA76518 from National Cancer Institute (NCI), National Heart, Lung and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases (MMH); contract HHSH234200637015C with Health Resources and Services Administration (HRSA/DHHS), grant N00014-10-1-0204 and N00014-1-1-0339 from the Office of Naval Research, and other grants (MMH and SS); IRGHET-Paris (JDB); Swedish Cancer Society (CAN 2008/562, 10 0333), Children's Cancer Foundation (PROJ09/093), Swedish Research Council (K2008-64X-05971-28-3), Cancer Society in Stockholm, and Karolinska Institutet (OR); Leukemia and Lymphoma Society Grant number 6260-11 (AV). The views expressed in this article are those of the authors and do not reflect the offcial policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, or any other agency of the US government.

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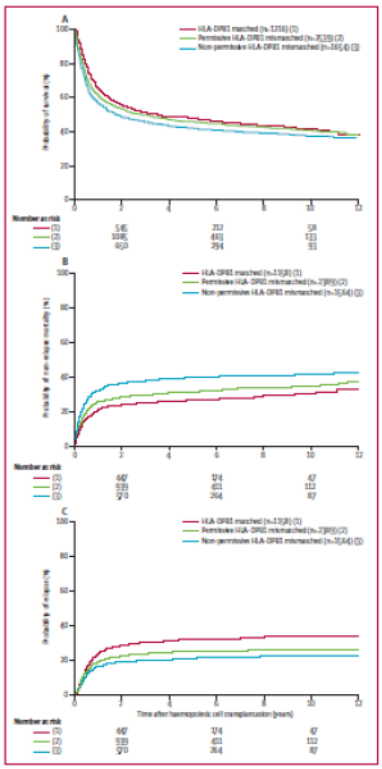

Figure 1.

Association of HLA-DPB1 T-cell-epitope match status with clinical endpoints in HLA 10/10-matched unrelated donor haemopoietic-cell transplantation

Shown are Kaplan-Meier estimates of overall survival (A), non-relapse mortality (B), and relapse (C) for HLA 10/10-matched HLA-DPB1-matched, permissive HLA-DPB1-mismatched or non-permissive HLA-DPB1-mismatched transplants.

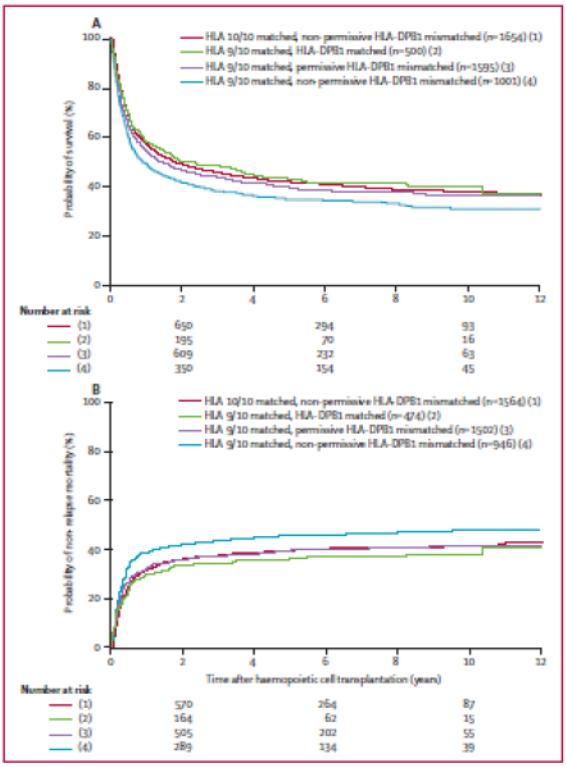

Figure 2.

Effect of HLA-DPB1 T-cell-epitope match status on mortality in HLA 9/10-matched compared with HLA 10/10-matched non-permissive DPB1 mismatched unrelated-donor haemopoietic-cell transplantation

Kaplan-Meier estimates of overall survival (A) and non-relapse mortality (B) for HLA-DPB1 matched, permissive HLA-DPB1 mismatched, or non-permissive HLA-DPB1 mismatched transplantations.

Table 1

Demographics of the study population

	HLA 10/10 matched (n=5428)	HLA 9/10 matched (n=3111)
Median recipient age (years) *	34·0 (0·38-71·9)	33·0 (0·35-75·0)
Recipient–donor sex *		
Male–male	2260 (42%)	1167 (38%)
Male–female	930 (17%)	594 (19%)
Female–male	1170 (22%)	702 (23%)
Female–female	1008 (19%)	610 (20%)
Missing	60 (1%)	38 (1%)
Recipient serological status for cytomegalovirus *		
Positive	2874 (53%)	1648 (53%)
Negative	1864 (34%)	1117 (36%)
Unknown	690 (13%)	346 (11%)
Year of transplantation *		
1993–97	1413 (26%)	833 (27%)
1998–2002	2818 (52%)	1585 (51%)
2003–07	1197 (22%)	693 (22%)
Donor registry *†		
Japan Marrow Donor Program	2553 (47%)	1237 (40%)
Non-Japan Marrow Donor Program	2875 (53%)	1874 (60%)
Source of cells *		
Bone marrow	4861 (90%)	2724 (88%)
Peripheral blood stem cells	548 (10%)	378 (12%)
Missing	19 (<1%)	9 (<1%)
Conditioning regimen *		
Ablative/no TBI	992 (18%)	577 (19%)
Ablative/TBI	3693 (68%)	2051 (66%)
Non-ablative/reduced intensity	602 (11%)	375 (12%)
Unknown	141 (3%)	108 (3%)
GvHD prophylaxis *		
Any single drug alone	165 (3%)	95 (3%)
Two or more drugs‡	4249 (78%)	2164 (70%)
T-cell depletion with or without other drugs *§	891 (16%)	759 (24%)
Other	5 (<1%)	5 (<1%)
Missing	118 (2%)	88 (3%)
Disease		
Acute myeloid leukaemia	1505 (28%)	878 (28%)
Acute lymphoblastic leukaemia	1219 (22%)	714 (23%)
Chronic myeloid leukaemia	1339 (25%)	758 (24%)
Myelodysplastic syndrome	687 (13%)	359 (12%)

	HLA 10/10 matched (n=5428)	HLA 9/10 matched (n=3111)
Other[¶]	678 (12%)	402 (13%)
Disease stage at transplantation[*†]		
High[/]	1278 (24%)	774 (25%)
Intermediate[/]	1204 (22%)	771 (25%)
Low[/]	2127 (39%)	1110 (36%)
Not applicable[/]	224 (4%)	149 (5%)
Unknown	595 (11%)	307 (10%)
HLA-DPB1 matching		
Matched	1218 (22%)	501 (16%)
Mismatched	4210 (78%)	2610 (84%)
TCE groups[**]		
Permissive (TCE group matched)	2550 (47%)	1600 (51%)
Non-permissive (TCE group mismatched)	1660 (31%)	1010 (32%)

Data are number (%) or median (range). HLA=human leucocyte antigen. TBI=total body irradiation. GvHD=graft-versus-host disease. TCE=T-cell-epitope.

[*] Clinical variable used for adjustment in the multivariable models.

[†] Statistical tests of interaction showed that TCE effect (comparison of permissive *vs* non-permissive) did not differ significantly across the categories of these factors.

[‡] 6382 (99·6%) of 6413 patients in this category were treated by calcineurin inhibitor plus any other drug.

[§] T-cell depletion was done with a variety of methods, including the addition of anti-thymocyte globulin (ATG) or alemtuzumab to the conditioning regimen. Because of the small numbers of patients receiving each methodology, this was grouped into the category of T-cell depletion.

[¶] Aplastic anaemia, acute leukaemia undifferentiated, chronic lymphocytic leukaemia, Fanconi anaemia, haemoglobinopathy, Hodgkin lymphoma, other malignancies, multiple myeloma, myeloproliferative syndrome, non-Hodgkin lymphoma, other non-malignancies, other leukaemias, plasma cell disorder, paroxysmal nocturnal haemoglobinuria, severe combined immunodeficiency, and other immune system disorders.

[/] High corresponds to any relapse of acute or chronic leukaemia, lymphoma, myeloma, or myelodysplastic syndrome more advanced than refractory anaemia or refractory anaemia with ringed sideroblasts. Intermediate corresponds to acute leukaemia in second or higher complete remission; chronic myeloid leukaemia in second or higher chronic phase; or lymphoma in second or higher complete remission. Low corresponds to acute leukaemia in first complete remission, chronic myeloid leukaemia in first chronic phase; lymphoma in remission, myelodysplastic syndrome, refractory anaemia or refractory anaemia with ringed sideroblasts, or multiple myeloma in remission. Not applicable corresponds to aplastic anaemia, Fanconi anaemia, haemoglobinopathy, severe-combined immunodeficiency, or other malignancies.

[**] TCE groups according to the three-group model previously described.19

Table 2

Multivariable regression models assessing the effect of HLA-DPB1 T-cell epitope match status on clinical outcome

	HLA 10/10 match					HLA 9/10 match				
	Permissive HLA-DPB1 mismatch	HLA-DPB1 match		Non-permissive HLA-DPB1 mismatch		Permissive HLA-DPB1 mismatch	HLA-DPB1 match		Non-permissive HLA-DPB1 mismatch	
		HR or OR	p value	HR or OR	p value		HR or OR	p value	HR or OR	p value
Overall mortality	1 (ref)	0·96 (0·87–1·06)	0·40	1·15 (1·05–1·25)	0·002	1(ref)	0·98 (0·85–1·13)	0·80	1·10 (1·00–1·22)	0·06
Non-relapse mortality	1 (ref)	0·86 (0·75–0·98)	0·03	1·28 (1·14–1·42)	<0·0001	1 (ref)	0·98 (0·82–1·17)	0·81	1·19 (1·05-1·36)	0·007
Relapse *	1 (ref)	1·34 (1·17-1·54)	<0·0001	0·89 (0·77–1·02)	0·10	1 (ref)	1·05 (0·84–1·31)	0·68	0·93 (0·78–1·11)	0·44
Grade 3-4 aGvHD	1 (ref)	0·84 (0·69–1·03)	0·09	1·31 (1·11–1·54)	0·001	1(ref)	0·93 (0.71–1·21)	0·58	1·37 (1·13–1·66)	0·002

Data are HR (95% CI) for overall mortality, non-relapse mortality, and relapse, and OR (95% CI) for aGvHD. Models were done separately among HLA 10/10-matched and 9/10-matched pairs, with the permissive pairs of each group as reference. HLA=human leucocyte antigen. HR=hazard ratio. OR=odds ratio. ref=reference. aGvHD=acute graft-versus-host disease.

* Transplantations done for non-malignant disease were excluded from the analysis.

Table 3

Multivariable regression models assessing the effect of HLA-DPB1 T-cell epitope match status on clinical outcome

	HLA 10/10 match, non-permissive DPB1 mismatch (n=1654)	HLA 9/10 match, permissive DPB1 mismatch (n=1595)		HLA 9/10 match, DPB1 match (n=500)		HLA 9/10 match, non-permissive DPB1 mismatch (n=1001)	
		HR or OR	p value	HR or OR	p value	HR or OR	p value
Overall mortality	1 (ref)	1·04 (0·94–1·14)	0·39	1·02 (0·89–1·18)	0·70	1·13 (1·02–1·26)	0·01
Non-relapse mortality	1 (ref)	1·01 (0·90–1·13)	0·81	1·00 (0·84–1·19)	0·98	1·19 (1·05–1·35)	0·006
Relapse *	1 (ref)	1·12 (0·96–1·31)	0·14	1·16 (0·92–1·45)	0·19	1·04 (0·87–1·24)	0·64
Grade 3-4 aGvHD	1 (ref)	1·00 (0·84–1·19)	0·97	0·93 (0·72–1·21)	0·62	1·36 (1·13–1·65)	0·001

Data are HR (95% CI) for overall mortality, non-relapse mortality, and relapse, and OR (95% CI) for grade 3-4 aGvHD. Models are shown for HLA 9/10-matched pairs, using the HLA 10/10-matched non-permissive DPB1-mismatched pairs as reference.

* Transplantations done for non-malignant disease were excluded from the analysis.

Lancet Oncol. Author manuscript; available in PMC 2013 October 30.