Introduction: HLA-mismatched unrelated cord blood transplantation (UCBT) is feasible and, in retrospective comparative analyses, allows survival rates similar to conventional unrelated HLA-matched adult-derived grafts. It is clear that the degree of UCB HLA mismatch in patients has a negative effect on outcomes with low-resolution HLA typing at A, B, DR. But the impact of HLA disparity on outcomes with high-resolution HLA typing HLA-A,-B,-C,-DR is unclear.

Patients and Methods: To determine the impact of HLA disparity on outcomes after UCBT, we retrospectively reviewed patients with hematologic malignancies who underwent reduced intensity CBT at Toranomon Hospital from August 2006 and December 2010 consecutively. Patients who had prior history of transplantation, were in poor performance status (ECOG PS >3), had active bacterial or fungal infections at the time of conditioning were excluded. The most frequently used conditioning regimens were fludarabine, alkylating agent (melphalan or busulfan) with total body irradiation (TBI), tacrolimus plus mycophenolate mofetil for GVHD prophylaxis. DNAs of 97 pairs were analysed for HLA-A, -B, -C, and -DRB1 based on High Resolution typing. In these cases high resolution typing was carried out retrospectively.

Results: For HLA-A, -B, -C, and -DR based on high resolution typing the following mismatch occurred: no mismatch 2(2%), one mismatch 5(5%), two mismatch 14(14%), three mismatch 32(33%), four mismatch 28(29%), five mismatch 14(14%), six mismatch 2(2%). The number of total nucleated cells and CD34+ cells were not significantly different among them.

The cumulative incidence of neutrophil recovery was 83.5% in this study population. It was higher in HLA-B matched group than in HLA-B mismatched group (94.2% vs. 78.5% up to day 60, p=0.0044), and in multivariate analysis HLA-B mismatch was independent predictor of engraftment (HR, 0.074; 95%CI, 0.0074-0.74; p=0.026). Among the HLA-A, -C, -DRB1 mismatches, the negative impact of each single HLA allele mismatch was not significant.

The cumulative incidence of grade II to IV aGVHD in this study population was 52.6%. In multivariate analysis, HLA-A mismatch (HR, 10.51; 95%CI, 1.95-56.51; p=0.0061), and HLA-B mismatch (HR, 51.59; 95%CI, 1.05-2520.0; p=0.043) were significantly associated with high incidence of grade II-IV GVHD.

There were no significant difference in the cumulative incidence of TRM, Relapse Rate and OS in this study.

Conclusion: HLA-B allele mismatch was found to have a significant negative impact on engraftment and II-IV aGVHD.
Although the impact of HLA-A, B, C and DRB1 mismatching in unrelated hematopoietic stem cell transplantation (HSCT) has been well reported, the role of HLA-DPB1 matching for transplant-related immunological events, especially chronic GVHD (c-GVHD), graft-versus-leukemia (GVL) effect and transplant-related immunological events, especially chronic GVHD, has not been well elucidated. Accumulation of large scale unrelated HSCT patient-donor pairs and retrospective 6 HLA locus allele data including HLA-DPB1 in Japan Marrow Donor Program enable us to analyze the effects of HLA-DPB1 matching.

2177 patients met the following criteria were included: HLA-A, B, C, DRB1 and DQBI allele matched unrelated donor, diagnosis of ALL (N=738), AML (N=1040) or CML (N=399), non-T cell depleted bone marrow without use of ATG, and survived more than 100 days after transplantation. 632 patients were matched for HLA-DPB1 allele, 1181 one allele mismatched, and 364 two allele mismatched in GVH direction. Tacrolimus-based regimen was employed in 1158 patients and cyclosporine-based regimen in 1019. Multivariable competing risk regression analyses were conducted to evaluate the impact of acute GVHD, chronic GVHD and leukemia relapse after transplantation. Confounders considered were combinations of patient age (linear), donor age (linear), risk of leukemia relapse (low, medi, 0.54 (0.41-0.71) respectively compared to DPB1 match (p=0.001). HR of limited type c-GVHD (n=350) and extensive type c-GVHD (n=563) were 0.55 (0.42-0.74) and 0.45 (0.36-0.58) respectively (p=0.001) compared to no c-GVHD (n=762). Retrospective analysis of HLA-A, B, C, DRB1 and DQBI complete match unrelated HSCT elucidated the biological effect of HLA-DPB1 matching without information biases at transplantation, showing that GVL effect was induced by HLA-DPB1 mismatch which was independent of c-GVHD.

A Universal Approach to Identify Permissible HLA-Mismatches in HSCT: Predicted Indirectly Recognizable HLA Epitopes

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Background: HLA mismatches in hematopoietic stem-cell transplantation (HSCT) correlate with adverse outcome due to increased alloreactivity. Identification of permissible HLA-mismatches might be beneficial for donor selection when a 10/10 matched donor cannot be found.

Methods: We developed an algorithm based upon the concept of indirect recognition of HLA mismatches to identify permissible mismatches. We subsequently analysed whether in silico prediction of the numbers of peptides derived from the recipients’ mismatched-HLA molecules that can be presented by donor-recipient shared HLA, designated as Predicted Indirectly ReCognizable HLA-Epitopes (PIRCHES), correlate with HSCT outcome.

The numbers of PIRCHES presented on HLA class-I (PIRCH-E-I) and -II (PIRCH-E-II) were calculated for 909 recipients of a single HLA mismatched unrelated donor (9/10) using the high resolution HLA-A, -B, -C, -DRBI and -DQBI typings. Recipients were subsequently divided into tertiles according to their PIRCHE score (PIRCH-E-I low: 0-1, mid: 2-4, high 5-31 and PIRCH-E-II low: 0-3, mid 4-13, high 14-79). The clinical outcome of these groups was evaluated and compared to a reference patient group transplanted with completely HLA-A, -B, -C, -DRB1 and -DQBI matched donors (10/10, n=1847).

Results: Patients in the low PIRCHE tertiles had a significantly lower risk for overall mortality, DFS, TRM, and acute and chronic GVHD, when compared to patients in the high tertiles. Moreover, these risk in the low PIRCHE tertiles were similar to those in 10/10 HLA-matched transplantations.

Conclusions: In this study, we demonstrate that PIRCHES correlate with clinical alloreactivity. In particular, patients presenting low PIRCHE-I have similar clinical outcomes as patients transplanted with a 10/10 HLA-matched donor. Our data thus suggest that indirect recognition of mismatched HLA by T cells is an important mechanism in clinical alloreactivity after HLA-mismatched HSCT. Determining the