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Blood 142 (2023) 2183–2185

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Effect of Immunopeptidome Gap Caused By Recipient-Donor HLA Mismatch in Umbilical Cord Blood Transplantation and HLA-Haploidentical Hematopoietic Stem Cell Transplantation

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Introduction

The immune response by alloreactive T cells plays a crucial role in allogeneic hematopoietic stem cell transplantation (allo-HCT), causing not only graft-versus-leukemia but also harmful graft-versus-host disease (GVHD). Human leukocyte antigens (HLA), which are highly polymorphic and differ widely among individuals, are the key molecules that present antigens to T cells. This individual variation in antigen-presenting capacity, the immunopeptidome, is thought to be assessable as HLA evolutionary divergence (HED) between alleles. Several autoimmune diseases are explained by HED, and HED is reported to be associated with outcome in HLA-matched allo-HCT. Thus, HED can be a useful indicator of potential immune reactivity.
HLA-mismatched allo-HCT, including umbilical cord blood transplantation and HLA-haploidentical allo-HCT (Haplo-HCT), has been increasing in recent years. The combination of HLA mismatch alleles varies from case to case, thus speculating that it causes individual differences in immune responses is easy. HLA mismatches have long been known to be associated with recurrence and GVHD, but a few risk assessment studies have focused on the immunopeptidome gap due to each HLA mismatch in individual cases.

Aim

This study aimed to examine the prognostic impact of the gap of immunopeptidome in mismatched HLA between recipient and donor in HLA-mismatched allo-HCT.

Methods

Allo-HCT was performed on 317 patients at our institution from 2006 to 2022. Of the 272 patients with evaluable allele data, 123 patients who underwent more than 3 alleles HLA-mismatched allo-HCT were retrospectively analyzed. Graft sources included cord blood (n=69, 56.1%) and haploidentical stem cells derived from peripheral blood (n=54, 43.9%). The median age at allo-HCT was 44 (range: 16-67) years and the median observation period was 545 [8-5551] days. Diagnoses include acute myeloid leukemia (n=61, 49.6%), acute lymphoblastic leukemia (n=24, 19.5%), malignant lymphoma (n=24, 19.5%), myelodysplastic syndrome (n=10, 8.1%), and others (n=4, 3.2%). The conditioning regimens was non-myeloablative (n=89, 72.4%). GVHD prophylaxis for 54 Haplo-HCT was anti-thymocyte globulin in 27 (50%) and post-transplant cyclophosphamide in 27 (50%) patients. The immunopeptidome gap of HLA mismatch (HED-mis) was evaluated between each mismatched allele. Grantham distance, which predicts amino acids from HLA allelic information and attempts to measure evolutionary distance based on the chemistry of the two amino acids, was used to calculate HED-mis. HLA allele data were drawn from clinical records. Tobias Lenz et al. produced the calculator program (https://hladiv.net/). HED-mis for each HLA class I: HLA-A (HED-mis A), HLA-B (HED-mis B), and HLA-C (HED-mis C) were calculated to evaluate acute and chronic GVHD (aGVHD and cGVHD), cumulative relapse rate (CIR), and overall survival (OS).

Result

The median [range] of HED-mis for 123 patients was 0.13 [0.00-13.70] for HED-mis A, 7.15 [0.00-11.25] for HED-mis B, and 4.19 [0.00-7.58] for HED-mis C. Patients were divided into 4 groups at each HED-miss value quartile: Q1, Q2, Q3, and Q4. Non-Q4 (Q1, Q2 and Q3 with the lower gaps) and Q4 with the highest gap of HED-mis A, B, and C were compared to confirm the effect of gap size. Univariate analysis revealed that non-Q4 of HED-mis B was associated with increased aGVHD 2-4 up to 100 days after all-HCT, compared to Q4 (non-Q4 49.8% vs. Q4 25.0%, p=0.017), but was unrelated to the incidence of severe aGVHD 3-4 (p=0.58). Q4 of HED-mis A demonstrated no difference in aGVHD 2-4 compared to non-Q4 (p=0.20) but was associated

with increased severe aGVHD 3-4 (non-Q4 of 0.06% vs. Q4 of 20.7%, p=0.019, Table and Figure). Similarly, multivariate analysis adjusted for each HED-mis, graft, and conditioning revealed that Q4 of HED-mis A was a risk factor for severe aGVHD 3-4 (hazard ratio [HR]: 3.85, p=0.015), and non-Q4 of HED-mis B was a risk factor for developing aGVHD 2-4 (HR: 3.64, p=0.017). HED-mis C was unrelated to any grade aGVHD, but Q4 of HED-mis C may have a better 2-year CIR in univariate (20.3%, vs. in non-Q4, 46.2%, p=0.055) and multivariate analyses (HR: 0.34, p=0.051). No association was found with each HED gap and each quartile for cGVHD and OS.

Conclusion

Gaps in the immunopeptidome of HLA-mismatched alleles, especially in HLA-A, should be considered in severe aGVHD development during donor selection.

Disclosures No relevant conflicts of interest to declare.

Figure.

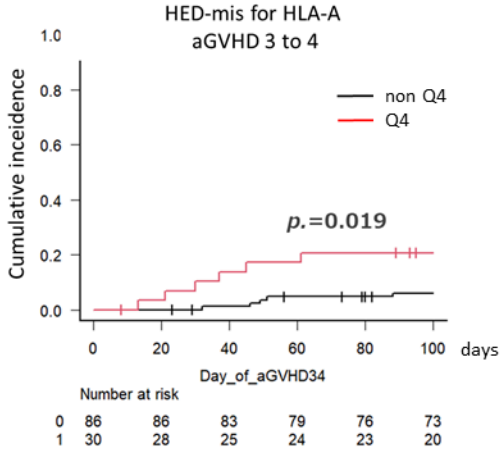

Table. Multivariate analysis

aGVHD234	Factor	Hazard.ratio	p.value
	conditioning.RIC	1.00 (0.53-1.91)	1
	graft.PBSCT	0.52 (0.28-0.96)	0.037
	HED-miss A_Q4	1.90 (0.98-3.71)	0.059
	HED-miss B_non-Q4	2.82 (1.2-6.63)	0.017
	HED-miss C_Q4	1.01 (0.51- 2)	0.97
aGVHD34			
	conditioning.RIC	1.18 (0.3- 4.71)	0.81
	graft.PBSCT	0.88 (0.28- 2.77)	0.82
	HED-miss A_Q4	3.85 (1.3-11.41)	0.015
	HED-miss B_non-Q4	1.61 (0.33- 7.82)	0.55
	HED-miss C_Q4	1.21 (0.32- 4.59)	0.78
cGVHD			
	conditioning.RIC	0.75 (0.27-2.06)	0.58
	graft.PBSCT	0.79 (0.3-2.09)	0.63
	HED-miss A_Q4	0.78 (0.19-3.19)	0.73
	HED-miss B_non-Q4	1.96 (0.7-5.51)	0.2
	HED-miss C_Q4	1.30 (0.54-3.11)	0.56
relapse			
	conditioning.RIC	1.30 (0.6-2.83)	0.51
	graft.PBSCT	0.70 (0.31-1.56)	0.38
	HED-miss A_Q4	0.97 (0.38-2.48)	0.95
	HED-miss B_non-Q4	0.98 (0.41-2.32)	0.97
	HED-miss C_Q4	0.34 (0.12- 1)	0.051
OS			
	conditioning.RIC	1.59 (0.87-2.92)	0.14
	graft.PBSCT	0.66 (0.38-1.16)	0.15
	HED-miss A_Q4	1.26 (0.66-2.43)	0.48
	HED-miss B_non-Q4	0.84 (0.45-1.55)	0.57
	HED-miss C_Q4	0.78 (0.42-1.45)	0.43

Figure 1

https://doi.org/10.1182/blood-2023-184381