IMPACT OF HLA EPITOPE MATCH ON STEM CELL TRANSPLANTATION

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INTRODUCTION

Donor and recipient human leukocyte antigen (HLA) incompatibility is the main immunological barrier to successful organ transplantation. HLA mismatch remains one of the strongest risk factors for the risk of acute and chronic graft-versus-host disease (GVHD) and therefore trying to identify compatible donors is one of the most important parameters of pre-transplant donor evaluation. Studies have shown that HLA mismatch is associated with a higher risk of GVHD, Longer engraftment time, and leads to poor prognosis in HLA-mismatched donor-recipient pairs in unrelated donor transplantation. To understand the immunogenicity of amino acid sequences in mismatched HLA pairs, various methods have been developed to predict epitopes recognized by the immune system. Duquesnoy et al. established the HLA Matchmaker (HLAMM) algorithm, which combines in vitro antigen-antibody reactions with in silico prediction to identify B-cell epitopes presented as triplets and referred to as "eplets''. HLA alleles can be considered as a string of potential antibody epitopes. A specific HLA allele consists of a unique set of epitopes while the individual epitopes can be shared with other alleles. The consequence is that the number of foreign epitopes on an individual HLA mismatch can differ and depends on the HLA type of the potential antibody producer.

AIM

Clinically, HLA locus matching and mismatching are also strong prognostic factors and are taken into consideration. However, the underlying mechanism of the heterogeneous impact of HLA mismatch on HSCT outcomes is not yet fully understood. In our study; we investigated the relationship between the mismatch of epitopes defined by HLA antigens and the results of HSCT.

METHOD

Our study evaluated 22 patient/donor pairs who received hematopoietic stem cell transplantation from unrelated 9/10 HLA-matched donors at the Department of Hematology, Istanbul Faculty of Medicine, retrospectively between 2011-2021.

HLA tissue typing and chimerism analyses were performed at the Istanbul Faculty of Medicine Tissue Typing Laboratory which has accreditation to perform clinical typing by European Federation of Immunogenetics (EFI).

DNA isolation from peripheral blood samples was performed using the Qiagen EZ1 DNA Blood Kit with the EZ1 Advanced XL device. Sequencing-based Typing (SBT) method was used for HLA tissue typing, and STR analysis was used for chimerism analysis.

Multiplex PCR reaction was performed using Qiagen ID Plex Plus Kit and 15 different STR and Amelogenin loci for chimerism analysis. Fragment analysis-based method was used for sample run and analysis on the Applied Biosystem 3500 Dx Genetic Analyzer device.

The 'HLA Epitope Registry' www.epregistry.com.br database was used for HLA epitope matching. Epitope matches were evaluated in both directions for both recipient and donor.

RESULTS

13 patients had 1A, 4 patients had 1B, 1 patient had 1C, 3 patients had 1DR and 1 patient had 1DQ mismatched transplantation (Table:1). 'HLA Epitope Registry' database was used for epitope analysis. In contrast to 1 allelic mismatch between patient and donor, the number of epitope mismatches was highly variable. We categorized these mismatches in three different cases and compared them in terms of clinical status, chimerism status, GVHD development and survival. Of the 11 patients with 0-5 mismatched epitopes, GVHD development was observed in 4 (=0.08) and survival in 5 (>0.05). Of the 5 patients with 6-15 mismatched epitopes, 4 developed GVHD (>0.05) and 1 had survival (>0.05). Of the 6 patients with 16 or more mismatched epitopes, 5 developed GVHD (>0.05) and 4 had survival (>0.05) (Table:2). A statistically significant difference was observed in patients with 6-15 epitope mismatches in terms of relaps development. Peripheral blood chimerism analysis of all patients was determined as complete chimeric.

Eplets In Patient But Not In Donor						
	0-5 EP MM (n:11)	P value	6-15 EP MM (n:4)	P value	16 EP MM≥ (n:7)	P value
GVHD +	4	>0.05	2	>0.05	6	>0.05
GVHD -	7		2		1	
RELAPS +	0	>0.05	0	0.04	1	>0.05
RELAPS -	11		4		6	
EX	6	>0.05	3	>0.05	3	>0.05
ALIVE	5		1		4	

Table 2: Eplets in patient but not in donor and clinical status after HSCT

	Full match EP
GVHD +	2
GVHD-	4

Table 3: Full match eplet and GVHD development

Patient Num.	Diagnosis	Cell Source	Patient HLA	Donor HLA
4	AA	Bone marrow	A*02:01 A*02:05 B*35:01 B*50:01 C*04:01 C*06:02 DR*03:01 DR*07:01 DQ*02:02 DQ*05:01	A*02:01 A*02:01 B*35:01 B*50:01 C*04:01 C*06:02 DR*03:01 DR*07:01 DQ*02:02 DQ*05:01
6	AA	HSC	A*02:05 A*31:01 B*50:01 B*51:01 C*06:02 C*14:02 DR*07:01 DR*13:01 DQ*02:02 DQ*06:03	A*02:01 A*31:01 B*50:01 B*51:01 C*06:02 C*14:02 DR*07:01 DR*13:01 DQ*02:02 DQ*06:03
7	MDS	HSC	A*02:01 A*11:01 B*07:02 B*15:08 C*01:02 C*07:02 DR*09:01 DR*15:01 DQ*03:02 DQ*06:02	A*02:01 A*11:01 B*07:02 B*15:01 C*01:02 C*07:02 DR*09:01 DR*15:01 DQ*03:02 DQ*06:02
8	AML	HSC	A*01:01 A*24:02 B*35:01 B*41:01 C*04:01 C*17:01 DR*11:04 DR*11:04 DQ*03:01 DQ*03:01	A*01:01 A*24:02 B*35:02 B*41:01 C*04:01 C*17:01 DR*11:04 DR*11:04 DQ*03:01 DQ*03:01
12	SeconderAML	Bone marrow	A*01:01 A*24:02 B*07:02 B*51:01 C*07:02 C*14:02 DR*11:04 DR*15:01 DQ*06:02 DQ*03:01	A*01:01 A*24:02 B*50:01 B*07:02 C*07:02 C*06:02 DR*11:04 DR*03:01 DQ*02:01/03 DQ*03:01/04
13	AML	HSC	A*01:01 A*02:17 B*38:01 B*51:01 C*12:02 C*12:03 DR*13:01 DR*14:01 DQ*05:03 DQ*06:03	A*01:01 A*02:05 B*38:01 B*52:01 C*12:02 C*12:03 DR*14:01 DR*13:01 DQ05:03 DQ*06:03
14	CML	Bone marrow	A*03:01 A*31:01 B*35:01 B*35:03 C*04:01 C*12:03 DR*01:01 DR*07:01 DQ*02:02 DQ*05:01	A*03:01 A*31:01 B*35:01 B*35:03 C*04:01 C*12:03 DR*01:01 DR*07:01 DQ*03:03 DQ*05:01
15	CML	unknown	A*24:02 A*32:01 B*07:02 B*38:01 C*07:02 C*12:03 DR*04:01 DR*04:02 DQ*03:02 DQ*03:02	A*24:02 A*02:01 B*07:02 B*38:01 C*07:02 C*12:03 DR*04:01 DR*04:02 DQ*03:02 DQ*03:02
16	MDS	HSC	A*01:01 A*24:02 B*08:01 B*51:01 C*07:02 C*16:02 DR*03:01 DR*04:04 DQ*02:01 DQ*03:02	A*01:01 A*24:02 B*08:01 B*51:01 C*07:02 C*16:02 DR*03:01 DR*04:03 DQ*02:01 DQ*03:02
17	AML	HSC	A*03:02 A*68:01 B*07:02 B*51:01 C*07:02 C*15:02 DR*11:01 DR*16:01 DQ*03:01 DQ*05:02	A*03:01 A*68:01 B*07:02 B*51:01 C*07:02 C*15:02 DR*11:01 DR*16:01 DQ*03:01 DQ*05:02
18	AML	HSC	A*32:01 A*68:01 B*18:01 B*35:03 C*04:01 C*12:03 DR*11:01 DR*15:01 DQ*03:01 DQ*06:02	A*32:01 A*68:01 B*18:01 B*35:01 C*04:01 C*12:03 DR*11:01 DR*15:01 DQ*03:01 DQ*06:02
19	MDS	HSC	A*32:01 A*68:01 B*18:01 B*35:03 C*04:01 C*12:03 DR*11:01 DR*15:01 DQ*03:01 DQ*06:02	A*24:02 A*68:01 B*13:02 B*18:01 C*06:02 C*12:03 DR*07:01 DR*11:04 DQ*02:02 DQ*03:01
20	ALL	HSC	A*03:01 A*66:01 B*38:01 B*41:02 C*12:03 C*17:01 DR*07:01 DR*13:01 DQ*02:02 DQ*06:03	A*26:01 A*66:01 B*38:01 B*41:02 C*12:03 C*17:01 DR*07:01 DR*13:01 DQ*02:02 DQ*06:03
21	AML	HSC	A*01:01 A*24:03 B*51:01 B*51:01 C*01:02 C*15:04 DR*11:01 DR*11:01 DQ*03:01 DQ*03:01	A*01:01 A*24:02 B*51:01 B*51:01 C*01:02 C*15:04 DR*11:01 DR*11:01 DQ*03:01 DQ*03:01
23	AML	HSC	A*33:01 A*33:03 B*14:02 B*58:01 C*03:02 C*08:02 DR*01:02 DR*16:01 DQ*05:01 DQ*05:02	A*02:01 A*33:01B*14:02 B*58:01 C*03:02 C*08:02 DR*01:02 DR*16:01 DQ*05:01 DQ*05:02
24	AML	HSC	A*23:01 A*24:02 B*35:02 B*49:01 C*04:01 C*07:01 DR*01:01 DR*13:01 DQ*05:01 DQ*06:03	A*01:01 A*24:02 B*35:02 B*49:01 C*04:01 C*07:01 DR*01:01 DR*13:01 DQ*05:01 DQ*06:03
25	MDS	HSC	A*25:01 A*26:01 B*18:01 B*52:01 C*12:02 C*12:03 DR*04:03 DR*15:01 DQ*03:02 DQ*06:02	A*25:01 A*24:07 B*18:01 B*52:01 C*12:02 C*12:03 DR*04:03 DR*15:01 DQ*03:02 DQ*06:02
26	MDS	HSC	A*01:01 A*02:01 B*27:02 B*38:01 C*02:02 C*12:03 DR*03:01 DR*11:04 DQ*02:01 DQ*03:01	A*02:01 A*11:01 B*27:02 B*38:01 C*02:02 C*12:03 DR*03:01 DR*11:04 DQ*02:01 DQ*03:01
27	AA	unknown	A*02:01 A*11:01 B*18:01 B*35:01 C*04:01 C*07:01 DR*14:01 DR*15:01 DQ*05:03 DQ*06:02	A*02:01 A*11:01 B*18:01 B*35:01 C*04:01 C*07:01 DR*14:54 DR*15:01 DQ*05:03 DQ*06:02
28	MDS	Peripheral blood	A*01:01 A*02:01 B*18:01 B*27:02 C*02:02 C*07:01 DR*11:01 DR*11:04 DQ*03:01	A*01:01 A*02:01 B*18:01 B*27:05 C*02:02 C*07:01 DR*11:01 DR*11:04 DQ*03:01
29	CML, blastic phase	Peripheral blood	A*02:17 A*32:01 B*18:01 B*35:01 C*04:01 C*07:01 DR*04:03 DR*16:01 DQ*03:02 DQ*05:02	A*11:01 A*32:01 B*18:01 B*35:01 C*04:01 C*07:01 DR*04:03 DR*16:01 DQ*03:02 DQ*05:02
30	CML,accelerated phase	Peripheral blood	A*02:01 A*03:01 B*18:01 B*35:03 C*04:01 C*07:01 DRB1*04:04 DRB1*13.01 DQB1*03:02 DQB1*06:03	A*02:01 A*03:01 B*18:01 B*35:03 C*04:01 C*07:01 DRB1*04:05 DRB1*13.01 DQB1*03:02 DQB1*06:03

Table 1: Patient and donor HLA mismatches

CONCLUSIONS

In the preliminary results of our study, the development of GVHD in patients and donor pairs with an HLA allele mismatch but full matched epitope and 0-5 epitope mismatch was half as low as the rate, although it was not statistically significant (Table: 3) .

A statistically significant difference was observed in patients with 6-15 epitope mismatches in terms of relaps development (p=0.04).

These data suggest that epitope matching may provide clinicians with a prediction for the development of GVHD and relapse in alternative donor selection.

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