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Dynamic Detection of Anti–Human Leukocyte Antigen (HLA) Antibodies but not HLA-DP Loci Mismatches Can Predict Acute Graft-versus-Host Disease and Overall Survival in HLA 12/12–Matched Unrelated Donor Allogeneic Hematopoietic Stem Cell Transplantation for Hematological Malignancies

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A B S T R A C T

The National Marrow Donor Program and Center for International Blood and Marrow Transplant Research provided guidelines for the use of anti-HLA antibodies and HLA-DP–mismatched loci in unrelated donor hematopoietic stem cell transplantation (HSCT). However, a deeper understanding of other potentially useful biomarkers for predicting clinical outcomes in HLA-A, -B, -C, -DRB1, -DQB1, and -DQA1 (12/12)–matched unrelated donor HSCT is needed to further improve clinical outcomes. We tested HLA genotyping for 123 pairs of patients and donors. Anti-HLA antibodies using the Luminex method was applied to 123, 117, and 106 serum samples collected before and 1 month and 3 months after transplantation. The presences of anti-HLA antibodies at the 3 time points were 37.4% (46 of 123), 40.2% (47 of 117), and 22.6% (24 of 106). Mismatch of HLA-DPB1 and/or DPA1 allele between patient-donor pairs was 83.6% (92 of 110). Patients with anti-HLA antibodies had delayed platelet recovery. The presence of anti-HLA antibodies and their dynamic changes after transplantation were associated with increased occurrence of grades II to IV acute and chronic graft-versus-host disease (GVHD), higher treatment-related mortality, and reduced overall survival (OS) and disease-free survival, especially in acute myeloid leukemia and myelodysplastic syndrome patients. Multivariate analysis showed that presence of anti-HLA antibodies before transplantation was a risk factor for GVHD and OS. Furthermore, HLA-DP loci–matched subgroup showed a trend towards a lower rate of acute GVHD and a higher OS in the anti-HLA Abs-negative group. Our results suggest that dynamic changes of anti-HLA antibodies independently predict for a negative outcome of HSCT, independent of HLA-DP loci mismatches. Routine monitoring for anti-HLA antibody dynamics should be conducted before and after HSCT.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for patients with hematological malignancies [1]. Besides factors such as age, sex, disease stage, conditioning regimen, and degree of HLA identity that can affect the outcomes of allo-HSCT, anti-HLA antibodies, especially donor-specific anti-HLA antibodies (DSHAs), have been shown to have a negative prognostic impact on patients who undergo cord blood transplantation [2], haploidentical stem cell transplantation [3], and HLA-mismatched unrelated stem cell transplantation [4]. Possessing anti-HLA antibodies or DSHAs has a negative effect on engraftment and contributes to a lower overall survival (OS) rate and higher graft failure [5-7]. The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research provided guidelines in 2012 in which anti-HLA antibody and HLA-DP loci typing should be

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Table 1
Characteristics of Patients and Donors

	Anti-HLA Abs-Negative (n = 77)	Anti-HLA Abs- Positive (n = 46)	*P* Value
Patient age, median (range), yr	24 (9-59)	34 (8-58)	.033
Patient sex			
Male	56 (72.7)	22 (47.8)	
Female	21 (27.3)	24 (52.2)	.006
Months from Dx to Tx, median (range)	5 (3-144)	6 (3-192)	.266
Sex matching			
Matched	47 (62.3)	27 (58.7)	
Male to female	16 (20.8)	16 (34.8)	
Female to male	13 (16.9)	3 (6.5)	.100
ABO type matching			
Matched	23 (29.9)	16 (34.8)	
Mismatched	54 (70.1)	30 (65.2)	.571
Disease			
AML	30 (39.0)	25 (54.3)	
ALL	27 (35.1)	10 (21.7)	
CML	7 (9.1)	5 (10.9)	
MDS	9 (11.7)	5 (10.9)	
NHL	4 (5.2)	1 (2.2)	.430
Disease stage			
Standard risk	56 (72.7)	35 (76.1)	
High risk	21 (27.3)	11 (23.9)	.832
Conditioning regimen			
BU + CY	66 (85.7)	39 (84.8)	
TBI + CY	9 (11.7)	4 (8.7)	
FB/FC	2 (2.6)	3 (6.5)	.499
GVHD prophylaxis			
CsA + MTX + MMF	73 (100)	42 (100)	
Number of MNC, median (range), $\times 10^8$/kg	7.18 (2.5-21.74)	7.49 (3.77-15.1)	.324
Number of $CD34^+$, median (range), $\times 10^6$/kg	4.02 (1.98-11.014)	4.85 (1.3-9.99)	.915
Donor age, median (range), yr	29 (20-45)	31 (21-47)	.853
Donor sex			
Male	59 (76.6)	35 (76.1)	
Female	18 (23.4)	29 (23.9)	.946
HLA-DP*			
DPA1-M, DPB1-M	13 (19.7)	5 (11.4)	
DPA1-M, DPB1-MM	14 (21.2)	4 (9.1)	
DPA1-MM, DPB1-M	4 (6.1)	1 (2.3)	
DPA1-MM, DPB1-MM	35 (53.0)	34 (77.3)	.081

Dx indicates diagnosis; Tx, transplantation; NHL, non-Hodgkin lymphoma; Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation; FB/FC, fludarabine + busulfan/fludarabine + cyclophosphamide; CsA, Cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil; MNC, mononuclear cells.
Data presented are n (%), unless otherwise indicated.
* n = 110 evaluable, 13 samples with quality problem can not get the results of HLA-DP loci.

examined as a part of the pretransplantation work-up for unrelated adult donor and cord blood graft selection [8].

HLA typing is generally performed for 5 HLA loci (HLA-A, -B, -C, -DRB1, and -DQB1) as mismatches at HLA-DPB1 and DPA1 do not have a major effect on outcomes. Some researchers have demonstrated that matching for HLA-A, -B, -C, DRB1, -DQB1, and -DPB1 alleles between an unrelated donor and the patient presents lower risks of acute graft-versus-host disease (aGVHD) and mortality after allo-HSCT [9-13]. However, previous studies of the clinical significance of anti-HLA antibodies were based on HLA-A, -B, -C, -DRB1, and -DQB1 loci match or mismatch between the patient and donor, neglecting the effect of HLA-DP loci on outcomes. We have recently identified a higher risk of treatment-related mortality (TRM) and overall survival (OS) in patients with anti-HLA antibodies undergoing HSCT [14] and graft rejection in patients with de novo donor-specific antibodies undergoing renal transplantation [15]. This raises the concern that pre-existing anti-HLA antibodies before and after allo-HSCT may affect clinical significance. Meanwhile, it is unclear if pre-existing anti-HLA antibodies and HLA-DPB1 mismatches would correlate with each other and the interactions increase unfavorable risk on outcomes of allo-HSCT. In this study, we make a direct comparison of the risks associated with pre-existing anti-HLA antibodies and HLA-DPB1 mismatched transplantations in HLA-A, -B, -C, -DRB1, -DQB1- and -DQA1 (12/12)–matched unrelated donor HSCT for patients with hematologic malignancies.

MATERIALS AND METHODS

Patients

The 123 patients with hematologic malignancies received transplants from HLA-A, -B, -C, -DRB1, -DQB1, and -DQA1 (12/12)–matched unrelated donors from China Marrow Donor Program. Serum samples before the start of conditioning treatment and 1 month and 3 months after transplantation were included in the study. All patients gave written informed consent for HSCT between October 2011 and March 2014 in the First Affiliated Hospital of Soochow University and the study followed the ethical guidelines of the Declaration of Helsinki. The last follow-up was on May 24, 2014 and the median follow-up time was 10.7 months (range, .1 to 29.7 months).

Median patient age at transplantation was 27 years (range, 8 to 59 years). There were 78 males and 45 females in the cohort. All patients underwent HLA 12/12–matched unrelated donor HSCT for acute myeloid leukemia (AML, n = 55), myelodysplastic syndrome (MDS, n = 14), chronic myelogenous leukemia (CML, n = 12), acute lymphoblastic leukemia (ALL, n = 37), and non-Hodgkin lymphoma (n = 5). Transplantation risk was defined as follows: AML, ALL, and non-Hodgkin lymphoma in first complete remission, CML in first chronic phase, and MDS subtype refractory anemia were considered to be *standard risk*; others were considered *high risk*.

Conditioning Regimen and Graft-versus-Host Disease Prophylaxis

All patients received myeloablative conditioning. Most patients received a conditioning regimen consisting of cytarabine at 2 g/m^2 every 12 hours (on days -9 and -8), busulfan at 1 mg/kg every 6 hours (on days -7 to -5), and

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