Original Article

Impact of Human Leukocyte Antigen Loci and Haplotypes on Intestinal Acute Graft-versus-host Disease after Human Leukocyte Antigen-matched Sibling Peripheral Blood Stem Cell Transplantation

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Abstract

Background: Acute graft-versus-host disease (aGVHD) is a common and severe complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Some studies have found that the presence of certain specific human leukocyte antigen (HLA) loci could affect the occurrence of aGVHD. Meanwhile, the impact of HLA haplotypes on aGVHD has been rarely studied. This study aimed to investigate the effects of HLA loci and haplotypes on intestinal aGVHD.

Methods: Totally, 345 consecutive patients undergoing first HLA-matched sibling peripheral blood stem cell transplantation (PBSCT) from February 2004 to June 2013 at Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, were enrolled in this study. HLA loci and haplotypes of recipients with frequency over 5% were searched and their effects on intestinal aGVHD were investigated. Other important factors including donor age, recipient age, donor-recipient sex combinations, and conditioning regimens were also evaluated using logistic regression. Pure upper gastrointestinal tract aGVHD without diarrhea was excluded because the histological proof was unavailable. The follow-up end-point was 6 months after HSCT.

Results: The cumulative incidence of intestinal aGVHD was 19.4%, with 18.0% of the patients classified as classic aGVHD and 1.4% as persistent, recurrent, or late aGVHD. Multivariate analysis showed that HLA-A31 locus (odds ratio [*OR*] 2.893, 95% confidence interval [*CI*] [1.054, 7.935], $P = 0.039$), HLA B40-DR15 (*OR* 3.133, 95% *CI* [1.250, 7.857], $P = 0.015$), and HLA B46-DR9 haplotypes (*OR* 2.580, 95% *CI* [1.070, 6.220], $P = 0.035$), female donor for male recipient (*OR* 2.434, 95% *CI* [1.319, 4.493], $P = 0.004$) were risk factors for intestinal aGVHD.

Conclusion: The presence of certain HLA loci and haplotypes may influence the occurrence of intestinal aGVHD in PBSCT with HLA-identical sibling donors.

Key words: Haplotypes; Human Leukocyte Antigen; Peripheral Blood Stem Cell Transplantation

Introduction

Human leukocyte antigen (HLA) loci including HLA-A, -B, -C, -DR, -DQ, and -DP individually along with HLA haplotypes which are comprised HLA loci as a DNA string on one chromosome have been found to be associated with many diseases with autoimmune disorders, such as ankylosing spondylitis (AS),[1,2] type 1 diabetes,[3-9] inflammatory bowel disease,[10-12] with strong association between HLA-B27 and AS being the typical example. HLA loci have also been reported to have impacts on acute graft-versus-host disease (aGVHD),[13-24] which is a major complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the influences of HLA haplotypes on aGVHD have been rarely studied.

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Here, we aimed to further investigate the roles of HLA loci and haplotypes in predicting the susceptibility of patients to develop aGVHD. The factors that influence the risk of aGVHD with different grades or target organs may not be all the same even in the same study population.[13,25,26] We chose intestinal aGVHD which is significant in both prevalence and mortality as study object and investigated whether HLA loci and haplotypes played roles in its occurrence. We confined our study in a group of HLA-matched sibling peripheral blood stem cell transplantation (PBSCT) recipients without *ex vivo* T-cell depletion. In addition, we took into account other essential aGVHD-related factors such as donor age, recipient age, donor-recipient sex combinations, stem cell source, and conditioning regimen. In the study, we followed up all of the patients for 6 months after HSCT ignoring some potential late aGHVD.

Methods

Ethical approval

The research was approved by the Ethics Committee of the hospital (approval number NI2015012-EC-1) in December 2015 and was performed in accordance with the *Declaration of Helsinki*.

Patients

We retrospectively studied the clinical data of 345 consecutive patients undergoing first allo-PBSCT from HLA-matched sibling donors between February 2004 and June 2013 in Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. The patients who died or lost to follow-up without symptoms of intestinal aGVHD within 100 days after HSCT were excluded from the study. The median age of the patients at transplantation was 36 years, ranging from 4 to 55 years. Out of the 345 patients, 207 (60%) were male and 138 (40%) were female. None of the grafts underwent *ex vivo* T-cell depletion. Patients were followed up for 6 months after HSCT. Clinical characteristics of the patients are summarized in Table 1.

Table 1: Clinical characteristics of patients undergoing first allo-PBSCT from HLA-matched sibling donors (n = 345)

Characteristics	Values
Age (years), median (range)	
Recipient	36 (4–55)
Donor	36 (7–60)
Sex (male:female), *n*	
Recipient	207:138
Donor	168:177
Sex match (donor → recipient), *n* (%)	
Male → Male	97 (28.1)
Male → Female	71 (20.6)
Female → Male	110 (31.9)
Female → Female	67 (19.4)
Diseases of patients at transplantation, *n* (%)	
AML	164 (47.5)
ALL	52 (15.1)
CML	40 (11.6)
MDS	38 (11.0)
AA	35 (10.1)
Other	16 (4.6)
Conditioning regimen, *n* (%)	
TBI ± Cy ± other	74 (21.4)
Bu ± Cy ± other	245 (71.0)
Other	26 (7.5)
GVHD prophylaxis, *n* (%)	
CsA + MTX	158 (45.8)
FK506 + MTX	160 (46.4)
CsA + MTX + other	17 (5.0)
FK506 + MTX + other	9 (2.6)
CsA	1 (0.3)

AML: Acute myeloid leukemia; ALL: Acute lymphoid leukemia; CML: Chronic myeloid leukemia; MDS: Myelodysplastic syndrome; AA: Aplastic anemia; Bu: Busulfan; Cy: Cyclophosphamide; CsA: Cyclosporine; MTX: Methotrexate, FK506: Tacrolimus; allo-PBSCT: Allogeneic peripheral blood stem cell transplantation; HLA: Human leukocyte antigen; GVHD: Graft-versus-host disease; TBI: Total body irradiation.

Human leukocyte antigen typing

HLA typing was performed using polymerase chain reaction sequence specific primer method for low resolution of HLA-A, -B, and -DR loci.

Acute graft-versus-host disease definition

Diagnosis and staging of intestinal aGVHD were performed according to Seattle criteria.[26,27] Classification of aGVHD was based on NIH criteria.[28] Classic aGVHD is defined to occur within 100 days after transplantation, and persistent, recurrent, or late aGVHD is defined to occur beyond 100 days. Possible gut aGVHD with isolated upper gastrointestinal tract symptoms of nausea, vomiting, and anorexia was not included due to the lack of histological proof.

Statistical analysis

HLA loci and haplotypes with frequency over 5% (more than 18 positive cases in 345 patients) were manually searched. Other important known risk factors for aGVHD such as donor age, recipient age, donor-recipient sex combinations, and conditioning regimen (total body irradiation [TBI] or non-TBI) were also considered. Logistic regression was used to analyze the relationships between these factors and intestinal aGVHD. The factors with a $P < 0.10$ in univariate analysis were further analyzed using stepwise multivariate analysis. The factors with $P < 0.05$ in multivariate analyses were considered as statistically significant. The data were analyzed using SPSS version 18.0 (IBM Corp., Armonk, NY, USA).

Results

Frequency of human leukocyte antigen loci and haplotypes

In total, 30 HLA loci and 45 HLA haplotypes were detected in all patients, including two-locus haplotypes and three-locus haplotypes with frequency over 5%. HLA loci frequencies demonstrated Hardy–Weinberg equilibrium. HLA-A, -B,

and -DR loci and their frequency are shown in Table 2 in descending order. The frequency of HLA haplotypes (not shown in detail) varied from 18.6% (A2-DR15) to 5.2% (A24-B13).

Incidence of intestinal acute graft-versus-host disease

Intestinal aGVHD occurred in 67 recipients (19.4%). According to NIH criteria, 62 (18.0%) were classified as classic aGVHD and the rest 5 (1.4%) were classified as persistent, recurrent, or late aGVHD. The median occurrence time of intestinal aGVHD in all the recipients was 39 days after HSCT.

Relationships between all factors and intestinal acute graft-versus-host disease

Univariate analysis showed that HLA loci A31, B48, DR12, HLA haplotypes A2-DR12, B13-DR15, B40-DR15, B46-DR9, donor age, recipient age, donor-recipient sex combinations might be associated with intestinal aGVHD with $P < 0.10$, while conditioning regimen and other HLA loci or haplotypes had no significant associations with intestinal aGVHD ($P > 0.10$). Multivariate analysis confirmed that HLA-A31 locus, HLA-B40-DR15 and HLA-B46-DR9 haplotype, female donor for male recipient were risk factors for intestinal aGVHD. HLA-B13-DR15 haplotype tended to decrease the risk of intestinal aGVHD while donor age tended to increase it [Table 3]. Comparisons of intestinal aGVHD incidence among these significant loci and haplotypes positive or negative patients are shown in Table 4.

Discussion

There have been a number of studies on the association between HLA loci and aGVHD. The HLA loci such as HLA-A10, A11, A26, B18, B35, B44, B49, B50, B54, B61, Cw3, and Cw4 can increase the risk of aGVHD while HLA-Aw19, B8, Bw35, DR1, DR3, DR11, and DR15 can decrease its risk. HLA-A3 and B7 have been reported to have contrasting effects in different studies.[13,14-24] In our study, we found that HLA-A31 allele was a risk factor for intestinal aGVHD. There have been few researches about the influence of HLA haplotypes on aGVHD; we examined this issue and found that HLA-B40-DR15 and HLA-B46-DR9 haplotypes were risk factors for intestinal aGVHD.

HLA-A31 allele has been reported to induce restricted cytotoxic T-lymphocyte (CTL) effect in several kinds of malignant tumors such as melanoma,[29-31] tumors of epithelial origin such as gastric cancer,[32-37] colon cancer,[36,38] prostate cancer,[39-41] lung cancer, cervical cancer, and breast cancer,[36,41] viral infectious diseases or conditions associated with hepatitis B virus,[42] hepatitis C virus (HCV),[43] Epstein–Barr virus,[44] and HIV,[45] as well as rheumatoid arthritis,[46] Takayasu's arteritis,[47] Vogt–Koyanagi–Harada syndrome,[48] and carbamazepine-induced adverse drug reactions.[49] In addition, many of A31 restricted or presented antigens and peptides have been identified among these diseases, for example, tyrosinase-related protein in melanoma,[29,31] F4.2 and c98 (61–70) peptides in gastric cancer,[32,34,35,37] SART3 (109–118),[39] PSA (16–24), PAP (155–163), PAP (248–257), PSMA (207–215), and PSMA (431–440) in prostate cancer,[40] seven peptides (RLI 522–530, β-tublin 5154-161, β-tublin 5232-240,

Table 2: HLA-A, -B, -DR loci and their frequency

Items	Frequency (%)
HLA-A locus	
A2	55.1
A11	29.3
A24	28.1
A30	17.4
A33	9.6
A1	9.6
A3	9.6
A31	6.4
A26	5.2
HLA-B locus	
B15	29.3
B13	24.6
B40	23.8
B46	14.2
B51	12.2
B7	9.9
B35	8.4
B48	8.4
B44	8.1
B54	6.4
B58	6.4
HLA-DR locus	
DR15	32.8
DR9	26.7
DR7	22.6
DR4	22.0
DR12	20.9
DR8	12.5
DR14	12.2
DR11	11.3
DR13	9.9
DR3	5.8

HLA: Human leukocyte antigen.

Table 3: Multivariate analysis for intestinal aGVHD

Factors	*OR*	95% *CI*	*P*
HLA-B40-DR15	3.133	1.250–7.857	0.015
HLA-A31	2.893	1.054–7.935	0.039
HLA-B46-DR9	2.580	1.070–6.220	0.035
Female donor for male recipient	2.434	1.319–4.493	0.004
HLA-DR12	1.842	0.649–5.228	0.251
HLA-A2-DR12	1.088	0.326–3.636	0.891
Donor age	1.045	0.996–1.097	0.070
Recipient age	1.017	0.969–1.066	0.499
HLA-B48	0.401	0.089–1.817	0.236
HLA-B13-DR15	0.150	0.018–1.252	0.080

OR: Odds ratio; *CI*: Confidence interval; aGVHD: Acute graft-versus-host disease; HLA: Human leukocyte antigen.

Table 4: Incidence of intestinal aGVHD in valuable locus/haplotype positive and negative cases

Locus or haplotype	Present		Absent		*P*
	n	aGVHD (%)	*n*	aGVHD (%)	
HLA-A31	22	36.4	323	18.3	0.039
HLA-B40-DR15	32	31.3	313	18.2	0.015
HLA-B46-DR9	32	31.3	313	18.2	0.035

aGVHD: Acute graft-versus-host disease; HLA: Human leukocyte antigen.

β-tublin 5309-317, CGI 3772-79, KIAA 0036241-248 and KIAA 0036356-363) in a set of epithelial cancers including prostate, colon, gastric, cervical, and breast cancers,[36] IEX 47–56 and IEX 61–69 in epithelial cancers such as lung, prostate, cervical cancers,[41] the epitope between HBcAg residues 141 and 151,[42] one peptide at positions 30–39 of the core protein in HCV1b.[43] HLA-A31 also plays a role in graft-versus-leukemia (GVL), which is a special case of CTL anti-tumor reaction. The cytotoxicity of CTLs generated from the bone marrow transplantation (BMT) donor lymphocytes against the patient's leukemic cells could be induced by a minor histocompatibility antigen (mHAg) presented with HLA-A31. CTLs that detect this mHAg may play an important role in the GVL effect in HLA-A31-positive BMT patients.[44] Understanding these specific antigens or peptides would be of great value for exploring peptide-based immunotherapy against tumors or other relevant diseases. aGVHD involves a cytokine cascades where CD8+ CTLs participate at the late but essential step, with a tendency to accompanied by GVL. It is possible that in a similar way, some unknown aGVHD-specific peptides from the recipients can be presented by HLA-A31 antigen and elicit the CTL effect of aGVHD although this is just a hypothesis that needs further verification in the context of HSCT.

As to the mechanisms of how the HLA alleles affect aGVHD, two main explanations were proposed.[18,22,50] One was that HLA molecules differ in their ability to present relevant antigens or peptides to the incoming donor-derived T cells including CD8+ and CD4+ lymphocytes. The other was that the tumor necrosis factor-α (TNF-α) gene is polymorphic and the association of TNF-α haplotype with different HLA alleles leads to different TNF-α secretion level and induces hypo- or hyper-immune reactivity. Maybe, there are certain other genes such as TAP and LMP whose gene polymorphisms also have weak associations with HLA haplotypes leading to different susceptibility to aGVHD.

Despite previous reports about the impacts of HLA loci on aGVHD, there has been only one research referring to influences of HLA haplotypes on aGVHD. Morishima *et al*.[50] showed that the haplotype HLA-A*3303-Cw*1403-B*4403-DRB1*1302-DQB1*0604-DPB1*0401 reduced the risk of Grade 2 to 4 aGVHD, whereas HLA-A*2402-Cw*0702-B*0702-DRB1*0101-DQB1*0501-DPB1*0402 tended to increase the risk in allo-HSCT. We found that HLA-B40-DR15 and HLA-B46-DR9 haplotypes were risk factors for intestinal aGVHD. HLA-B46-DR9 haplotype has been found to be associated with Chinese Singaporean myasthenia gravis[51] and autoimmune thyroid disease after BMT in Chinese patients.[52] HLA-B40-DR15 haplotype has never been found to be associated with any diseases. In this study, we first demonstrated that this haplotype could increase the risk for intestinal aGVHD. As combinations of HLA alleles, various HLA haplotypes may display different susceptibility to aGVHD with similar mechanisms as the single locus described above (summarized in[50]).

There are many factors influencing aGVHD, among which HLA parity is most important, followed by donor-recipient relationship and stem cell source. Some other factors, such as donor age, recipient age, donor-recipient sex combinations, stem cell source, conditioning regimen, and T-cell depletion, may also play roles in aGVHD. In this study, we controlled these major factors by confining the analysis to HLA-matched sibling PBSCT without *ex vivo* T-cell depletion and incorporated the crucial factors into analysis.

Nevertheless, the study still has some limitations. First, it was performed in a single center with a limited group of patients. Second, we could not detect all of the late aGVHD as we are limited to a relatively short follow-up, which might give rise to a little deviation in spite of its low incidence. Third, the study did not cover all of the gut aGVHD because the patients with isolated upper gastrointestinal aGVHD were excluded due to the lack of endoscopic biopsies. However, since most of the patients of this category usually have relatively good prognosis, they require less predictive assessments just as Grade I aGVHD was likewise usually excluded in other studies.[25,26,53]

In conclusion, in this study, we further support the significance of HLA loci and haplotypes in aGVHD and found several valuable factors influencing intestinal aGVHD in our ethnic population. These findings may have some implications in donor selection and aGVHD prophylaxis and therapy. Due to the limited patients in a single center, the importance of these findings merits further investigation in a larger scale of population.

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Conflicts of interest

There are no conflicts of interest.

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