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Original article

HLA-DP mismatch and CMV reactivation increase risk of aGVHD independently in recipients of allogeneic stem cell transplant

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ABSTRACT

HLA-DP mismatched allogeneic hematopoietic stem cell transplantation (allo-HCT) is associated with increased risk of aGVHD and decreased risk of relapse with no effects on overall survival (OS). It has been proposed that CMV-reactivation induces expression of HLA-DP molecules on GVHD target tissues by releasing inflammatory cytokines. We hypothesized that the increased GVHD incidence in HLA-DP mismatched allo-SCTs correlates with recipient CMV serostatus or CMV reactivation. In addition, CMV reactivation is associated with increased risk of GVHD with an unknown mechanism. Here, we analyzed the association between HLA-DPB1 and CMV reactivation on cumulative incidence of aGVHD and relapse as well as OS in 613 patients with AML and MDS who underwent matched related or unrelated allo-HCT at MD Anderson Cancer Center from 2005 to 2011. In multivariable analysis, HLA-DPB1 mismatching was associated with increased risk of aGVHD (hazard ratio (HR): 1.53, $P < 0.001$) independent of CMV serostatus and CMV reactivation. Additionally, HLA-DPB1 mismatching was associated with decreased risk of relapse and no effect on OS. CMV reactivation increased risks of aGVHD (HR: 5.82, $P < 0.001$) independent of HLA-DP mismatching with no effect on relapse or OS. In conclusion, our data suggests that HLA-DPB1 mismatching and CMV reactivation increase risk of aGVHD independently.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a potentially curative treatment for a broad spectrum of hematological malignancies. The current standard for a fully matched allo-HCT is transplant from a donor matched at HLA-A, HLA-B, HLA-C, and HLA-DRB1. HLA-DP mismatching is associated with higher rate of grade II-IV acute graft versus host disease (aGVHD) and lower relapse rate resulting in no impact on overall survival (OS) [1,2]. For this reason, many centers do not take matching for HLA-DP into consideration when selecting an unrelated donor. HLA-DP antigens are αβ heterodimers encoded by the genes of two loci: (1) DPA1 locus, which has limited polymorphism, and (2) DPB1 locus which is highly polymorphic, with 520 alleles coding for 424 different proteins [3]. HLA-DPB1 is a low expression locus (LEL) with both constitutive and inducible expression. Its constitutive expression is restricted to only thymic epithelial cells, antigen-presenting cells such as dendritic cells and mononuclear phagocytes as well as activated T cells and B cells. HLA-DPB1 expression can be induced in other tissues after exposure to interferon gamma and other cytokines [4,5].

Stevanovič et al. have previously demonstrated a link between CMV reactivation and HLA-DPB1 directed aGVHD. Their study suggested that CMV reactivation induces HLA-DPB1 expression resulting in HLA-DPB1 directed GVHD after HLA-DPB1-mismatched $CD4^+$ donor lymphocyte infusion (DLI) [4,6]. No study has so far tested whether the increased aGVHD risk in HLA-DPB1 mismatched allo-HCTs correlates with recipient CMV serostatus, or more importantly, CMV reactivation. In addition, CMV reactivation is associated with increased risk of aGVHD with an unknown mechanism [6–8]. No study has analyzed whether the increased risk of aGVHD in patients with CMV reactivations is restricted to

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HLA-DPB1 mismatched allo-HCTs. Here in this retrospective study, we demonstrate that increased risk of aGVHD in HLA-DPB1 mismatched allo-HCT is independent of CMV reactivation. We also demonstrate that CMV reactivation increases risk of aGVHD independently of HLA-DPB1 matching status.

Materials and methods

We retrospectively evaluated all adult patients with AML or MDS who received matched related or unrelated allo-HCT at MD Anderson Cancer Center (MDACC) from January 2005 to December 2011 (total: 613 patients; HLA-DPB1 matched: 363 [59%], and HLA-DPB1 mismatched: 250 [41%]). All patients were matched at HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 (HLA level matching of 10/10). HLA typing was based on allelic typing. Patients receiving umbilical cord or haploidentical stem cell transplants, patients who died within 30 days of allo-HCT, and those less than 18 years of age were excluded from the analysis. All patients underwent weekly surveillance by CMV pp65 antigen testing from the time of engraftment and at least until day 100 post allo-HCT. CMV reactivation was defined as presence of > 1pp65 Ag cells/million WBC's. Preemptive therapy was initiated for patients with > 3 pp65 Ag cells/million WBC's. Clinical outcomes of interest included OS as well as cumulative incidences (CI) of GVHD, non-relapse mortality (NRM) and relapse. Severity of aGVHD was defined according to Glucksberg criteria [9]. OS was estimated using the Kaplan-Meier method and the association between OS and HLA-DPB1 mismatching was determined using a Cox proportional hazards model. The CI of GVHD, NRM, and relapse were determined using the competing risks method (i.e., competing risks for GVHD: relapse and death; NRM: relapse and death) and associations with HLA-DPB1 mismatching were evaluated by proportional subdistribution hazards models [10]. Additional factors considered were age in years (>50 vs. ≤ 50), race (others vs. Caucasian), gender (male vs. female), HLA-DPB1 mismatching direction (host versus graft vs. graft versus host), CMV donor (D)/recipient (R) group (D+/R−, D-/R+, D+/R + vs. D−/R−), transplantation year (2005–2008 vs. 2009–2011), conditioning regimens (myeloablative vs. non-myeloablative), ATG use (yes vs. no), and disease status at transplant (no CR vs. CR). Since CMV reactivation (yes vs. no) occurred after transplantation, it was included in the hazards models as a time-dependent covariate. Statistically significant factors in univariate analyses that were associated with the outcome at $P \leq 0.05$ were included in the final multivariable models. The effect of HLA-DPB1 mismatching on transplant outcomes was evaluated in the whole cohort. To analyze the effect of recipient CMV serostatus on HLA-DPB1 related aGVHD, we compared the CI of aGVHD in HLA-DPB1 mismatch/CMV seropositive recipient with HLA-DPB1 mismatch/CMV seronegative recipients. Additionally to analyze the effect of CMV reactivation on HLA-DPB1 mismatch related aGVHD, we compared the CI of aGVHD in HLA-DPB1 mismatch/CMV reactivated recipients with HLA-DPB1 mismatch/no CMV reactivated recipients. For all analysis CMV reactivation was defined as presence of > 1pp65 Ag cells/million WBC's except for a single analysis testing if CMV reactivation increases the chance of aGVHD in which CMV reactivation was defined as positive when the first day of CMV antigenemia occurred before or up to 7 days after the first day of aGVHD. For the purpose of this analysis, of the 270 with CMV reactivation, 178 (66%) were considered not CMV reactivated because it was discovered more than 7 days after the first day of aGVHD. Lastly, a landmark analysis was produced at day 100 to compare differences in OS, relapse, and NRM between patients who experienced CMV reactivation before 100 days and those who did not. For OS, differences between groups were assessed using the log-rank test while differences between groups for relapse and NRM were assessed using Gray's test [11]. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and StataCorp 2013 (College Station, TX: StataCorp LP).

Results

Characteristics of the patients and transplantation

Total of 613 patients with AML and MDS who underwent allo-HCT at MDACC from 2005 to 2011 were included. Table 1 shows patient and clinical characteristics. From the whole group 529 patients were CMV seropositive and 84 patients were CMV seronegative. Among CMV seropositive recipients 220 patients (42%) were mismatched at HLA-DPB1 loci and in CMV seronegative recipients 30 patients (36%) were found to be mismatched at HLA-DPB1 loci. The rates of CMV seropositivity among HLA-DPB1 mismatched and HLA-DPB1 matched recipients were 88%, and 86%, respectively.

CMV. reactivation

The rates of CMV reactivation in CMV seropositive and CMV seronegative recipients were 49% and 12%, respectively. Fig. 1A shows CI of any CMV antigenemia, CMV antigenemia >10 positive cells of any duration and CMV antigenemia >10 positive cells more than 2 weeks. Sixteen out of 613 patients developed CMV disease (3%).

HLA-DPB1 and transplant outcomes

In multivariable analysis (Table 2) of the whole cohort, HLA-DPB1 mismatching was associated with increased risk of aGVHD (hazard ratio [95% confidence interval]) (1.53 [1.24, 1.90]; $P < 0.001$), decreased risk of relapse (0.73 [0.55, 0.98]; $P = 0.034$), and no effect on OS (1.01 [0.81, 1.26]; $P = 0.91$). This multivariable analysis was adjusted for baseline covariates that were significant in the univariate models in addition to CMV reactivation and HLA-DPB1 mismatching direction (host versus graft vs. graft versus host). These results suggest that increased rate of aGVHD in HLA-DPB1 mismatch group was independent of CMV reactivation. Interaction analysis including CMV reactivation (yes/no) and HLA-DPB1 mismatching (yes/no) showed no statistically significant ($p = 0.68$) differences in CI of aGVHD in four groups, confirming no apparent interaction between HLA-DPB1 and CMV reactivation. Among HLA-DPB1 mismatched group, the CI of grade II—IV aGVHD was 41% in CMV seropositive and 40% in CMV seronegative recipients ($P = 0.95$) suggesting that CMV seropositivity of recipients had no additional effect on the risk of grade II—IV aGVHD in HLA-DPB1 mismatch transplant.

CMV. reactivation effects on transplant outcomes

In multivariable analysis including ATG use and HLA-DPB1 matching status in the model, CMV reactivation was associated with increased risk of all grade aGVHD (5.88 [4.62, 7.49]; $P < 0.001$] and grade II—IV aGVHD (4.25 [3.04, 5.93]; $P < 0.001$) but had no statistically significant effects on chronic GVHD, relapse, NRM, and OS (Table 2). In the day 100 landmark analysis, CMV reactivation had no statistically significant effects on relapse, NRM, and OS (Fig. 1B–D). Additionally, CMV reactivation was associated with increased incidence of grade II—IV aGVHD in both HLA-DPB1 matched (3.33 [1.91, 5.80]; $P < 0.001$) and HLA-DPB1 mismatched (4.38 [2.90, 6.63]; $P < 0.001$) group suggesting that increased risk of aGVHD in CMV reactivated patients was independent of HLA-DPB1 matching status.

Table 1
Patient and Clinical Characteristics – All Patients and by Recipient CMV Serostatus.

Measure	All (N = 613)	R+ (N = 529)	R− (N = 84)
Diagnosis			
AML	464 (76)	413 (78)	51 (61)
MDS	149 (24)	116 (22)	33 (39)
HLA DPB1 matching status, n (%)			
Yes	363 (59)	309 (58)	54 (64)
No	250 (41)	220 (42)	30 (36)
HLA DPB1 mismatching direction, n (%)			
GvH	37 (15)	29 (13)	8 (27)
HvG	17 (7)	13 (6)	4 (13)
Both	196 (78)	178 (81)	18 (60)
Gender, n (%)			
Male	346 (56)	293 (55)	53 (63)
Female	267 (44)	236 (45)	31 (37)
Age at allo-SCT (years)			
Mean	53.0	52.6	55.4
Standard deviation	12.4	12.4	11.8
Median	55.6	55.2	57.2
Minimum, Maximum	19.6, 77.0	19.6, 74.4	20.5, 77.0
Race/Ethnicity, n (%)			
White	495 (81)	415 (78)	80 (95)
Hispanic	69 (11)	67 (13)	2 (2)
Black	21 (3)	20 (4)	1 (1)
Asian	12 (2)	12 (2)	0
Other	1 (0.2)	1 (0.2)	0
Unknown	15 (2)	14 (3)	1 (1)
Transplant type, n (%)			
MRD	297 (48)	255 (48)	42 (50)
MUD	316 (52)	274 (52)	42 (50)
Conditioning regimen, n (%)			
Myeloablative	497 (81)	430 (81)	67 (80)
Non myeloablative	116 (19)	99 (19)	17 (20)
Conditioning regimen type, n (%)			
Fludarabine + Busulfan+/-ATG	376 (61)	321 (61)	55 (65)
Fludarabine + Melphalan+/-ATG	83 (14)	71 (13)	12 (14)
Other	154 (25)	137 (26)	17 (20)
In vivo T-cell depletion (ATG)	313 (51)	273 (52)	40 (48)
Yes	300 (49)	256 (48)	44 (52)
No			
CMV risk groups, n (%)			
D+/R+	269 (44)	269 (51)	0
D-/R-	50 (8)	0	50 (60)
D+/R-	34 (6)	0	34 (40)
D-/R+	260 (42)	260 (49)	0
Transplant cell source, n (%)			
PBMC	432 (70)	369 (70)	63 (75)
Marrow	181 (30)	160 (30)	21 (25)
Transplant year, n (%)			
2005-2008	285 (46)	242 (46)	43 (51)
2009-2011	328 (54)	287 (54)	41 (49)
Disease risk, n (%)			
Low	34 (6)	29 (6)	5 (6)
Int	175 (29)	155 (29)	20 (24)
Int-1	45 (7)	33 (6)	12 (14)
Int-2	52 (9)	41 (8)	11 (13)
High	304 (50)	268 (51)	36 (43)
Disease status at transplant, n (%)			
Complete response	333 (54)	294 (56)	39 (46)
Refractory	205 (33)	178 (34)	27 (32)
Untreated	73 (12)	56 (11)	17 (20)
Not evaluated	1 (0.2)	0	1 (1)
Unknown	1 (0.2)	1 (0.2)	0
GVHD prophylaxis, n (%)			
Methotrexate + Tacrolimus	562 (92)	490 (93)	72 (86)
Methotrexate + Tacrolimus + Others	0	0	0
MMF + Tacrolimus	3 (0.5)	2 (0.4)	1 (1)
Other	47 (8)	37 (7)	10 (12)
None	1 (0.2)	0	1 (1)

Abbreviations: R+CMV seropositive Recipient; R-CMV seronegative Recipient; AMLAcute Myelogenous Leukemia; MDSMyelodysplastic Syndrome; GvHGraft vs. Host; HvGHost vs. Graft; MRDMatched Related Donor; MUDMatched Unrelated Donor; DDonor; RRecipient; PBMCPeripheral Blood Mononuclear Cells.

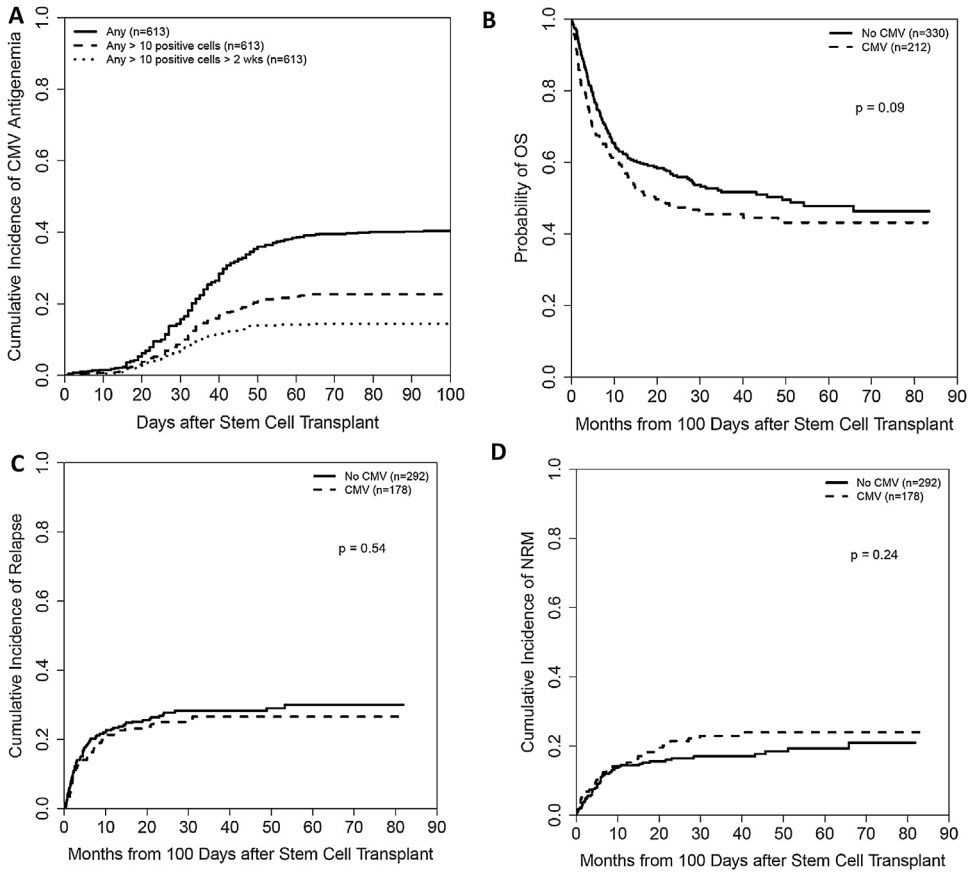

Fig. 1. (A) Cumulative incidence of CMV Antigenemia. (B–D) Landmark analysis at day 100 comparing differences in OS, CI of relapse and NRM between patients who experienced CMV reactivation before day 100 and those who did not.

Discussion

This study assesses impacts of HLA-DPB1 and CMV reactivation on GVHD, relapse, and OS after allo-HSCT. Here we demonstrate that HLA-DPB1 and CMV reactivation both increase aGVHD risk independently. Consistent with reported data, we show that HLA-DPB1 mismatching is associated with increased risk of aGVHD and lower relapse resulting in no effects on OS. In contrast to recently published data [12,13], our study showed that CMV reactivation has no impact on relapse or OS after allo-HSCT.

Stevanovic et al. had suggested that CMV reactivation induces HLA-DPB1 expression in GVHD targets as a result of inflammatory conditions created by immune response to CMV [4,6]. Our data suggest that increased risk of aGVHD in HLA-DPB1 mismatched allo-HCT cohorts is independent of CMV serostatus or CMV reactivation. One explanation for this discrepancy is that CMV infection is not the only factor that can provide an inflammatory milieu after allo-HCT. Inflammation post allo-HCT can be created by myeloablative conditioning, sepsis, and many types of viral infections [14]. It is well known that HLA-DPB1 mismatching is one but by far not the only potential target of alloreactivity causing GVHD. It is thus likely that up-regulation of these targets themselves, and/or of the relevant HLA restriction elements presenting them, could be at the basis of increased GVHD risk in the HLA-DPB1 matched setting. Additionally, Petersdorf et al recently reported that rs9277534G and rs9277534A alleles are associated with high and low expression of HLA-DPB1 respectively [15]. One limitation of our study is that we did not assess the frequency of these alleles nor evaluate permissive versus non permissive status of HLA-DPB1 mismatching. The clinical association between HLA-DPB1 mismatches and transplant outcomes has been shown to be different in the T cell epitope group permissive vs non-permissive setting [16–19]. Another limitation of our study is that we included both matched related and unrelated allo-allo-HCTs. There are significant immunogenetic differences other than HLA-DPB1 matching status between a genotypically HLA-identical sibling transplant and a phenotypically HLA-identical matched unrelated donor transplant. In our study, matched related donor

Table 2
Multivariable analysis of associations between Outcomes and HLA-DPB1 matching status (mismatched vs. matched) and CMV reactivation (yes vs. no).

Whole cohort (613 patients)	HR (95% CI)	p-value
HLA-DPB1 matching status (mismatched vs. matched)		
aGVHD	1.53 (1.24, 1.90)	<0.001
Grade II-IV aGVHD	1.74 (1.32, 2.31)	<0.001
cGVHD	0.65 (0.50, 0.86)	0.002
NRM	1.25 (0.90, 1.74)	0.19
CIR	0.73 (0.55, 0.98)	0.034
OS	1.01 (0.81, 1.26)	0.91
OS	1.05 (0.83, 1.33)	0.68
CMV reactivation (yes vs. no)		
aGVHD	5.88 (4.62, 7.49)	<0.001
Grade II-IV aGVHD	4.25 (3.04, 5.93)	<0.001
cGVHD	1.17 (0.81, 1.69)	0.40
NRM	0.82 (0.50, 1.34)	0.43
CIR	1.26 (0.87, 1.81)	0.22
OS	1.06 (0.79, 1.43)	0.69

Abbreviations: HR = hazard ratio; aGVHD = acute graft versus host disease; cGVHD = chronic graft versus host disease.
NRM = non-relapse mortality; CIR = cumulative incidence of relapse; OS = overall survival.

allo-HCT comprised 79% and 4% of HLA-DPB1 matched and HLA-DPB1 mismatched groups. In the other word majority of HLA-DPB1 matched group were matched related allo-HCTs while majority of HLA-DPB1 mismatched groups were matched unrelated allo-HCTs. These two measures were highly correlated (Pearson correlation = 0.7), and as such, were not included together in the multivariable analysis. Surprisingly in our study patients with HLA-DP mismatch group had lower risk of chronic GVHD (Table 2). To our knowledge this has not been reported in previous studies [1,2,20].

There has been a notion of "CMV vs. leukemia effect" since the 1980s and recent studies by Elmaagacli et al and Green et al suggested a beneficial effect of CMV reactivation on leukemia relapse in patients with AML [12,13]. In our study, CMV reactivation had no effect on relapse after allo-HSCT. This is consistent with a recent CIBMTR study by Teira et al showing no CMV versus leukemia effect in a large multi-institutional study [21]. We assessed CMV reactivation by CMV pp65 antigen assay that is less sensitive and reproducible than CMV PCR assay [22] and may have resulted in underestimation of CMV reactivation in this study. CMV disease was rare in our study (3%) that is similar to other studies reporting CMV disease in patients receiving preemptive CMV treatment [23].

In conclusion, our study suggests that excess aGVHD risks noted in HLA-DPB1 mismatched transplants is independent of recipient's CMV serostatus or CMV reactivation. These results need to be further evaluated in a larger multi-institutional study preferably including only matched unrelated donor transplants.

Conflict of interest

The authors declare no conflict of interest.

Authorship

A.G., R.C., D.M., R.C., E.S., A.A., and Q.B. designed the study. G.R., A.G., A.H., L.G., and A.A. performed data collection. D.M. performed the statistical analysis. A.G. wrote the manuscript. All authors discussed the results and commented on the paper.

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