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HLA Association with Hematopoietic Stem Cell Transplantation Outcome: The Number of Mismatches at HLA-A, -B, -C, -DRB1, or -DQB1 Is Strongly Associated with Overall Survival

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ABSTRACT

HLA matching between the donor and recipient improves the success of unrelated hematopoietic stem cell transplantation (HSCT). Because many patients in need of an unrelated transplant have only donors with mismatch, information is needed to evaluate the limits of HLA mismatching. We examined the association of survival, acute graft-versus-host disease (aGVHD) and relapse with HLA-A, -B, -C, -DRB, -DQB1, and -DPB1 mismatching in 334 patients coming from 12 French transplant centers and who received a non-T cell-depleted bone marrow graft from an unrelated donor. All patients were prepared with the use of myeloablative conditioning regimens. Our analyses demonstrate negative effects of HLA mismatching for either HLA-A, -B, -C, -DRB1, or -DQB1 loci on survival. Multivariate Cox analyses showed that a single mismatch was associated with a significant decrement in survival (P = .046, hazard ratio [HR] = 1.41, confidence interval [CI] 95% 1.1-1.98). The presence of multiple mismatches was worse for survival (P = .003, HR = 1.91, CI 95% 1.26-2.91) and severe aGVHD (grade III-IV) (P = .002, HR = 2.51, CI95% 1.41-4.46). The cumulative incidences of aGVHD and relapse in those HLA-A, -B, -C, -DRB1, and -DQB1 identical pairs with 2, 1, or 0 DPB1 incompatibilities were 63%, 50%, and 51%, and 12%, 27%, and 20%, respectively, but these differences were not statistically significant. Similar differences of aGVHD and relapse, but not statistically significant, were observed in those HLA-A, -B, -C, -DRB1, and -DQB1 identical pairs with DPB1 disparities classified into permissive or nonpermissive mismatches according to Zino's classification based on a hierarchy of the immunogenicity of the HLA-DP molecules. "Missing killer cell immunoglobulin-like receptor (KIR) ligand" evaluated on the presence of HLA-C1, -C2, and Bw4 groups in the recipients was not associated with aGVHD, survival, and relapse in this cohort of non-T cell-depleted HSCT.

KEY WORDS

Bone marrow transplantation • HLA • KIR • GVHD • Relapse • Survival

INTRODUCTION

Graft-versus-host disease (GVHD), graft rejection, and delayed immune recovery are the major obstacles to successful allogeneic hematopoietic stem cell transplantation (HSCT), and are more severe and frequent following HSCT with an unrelated donor (UD) compared to HLA identical sibling transplant. Because identical donors are available to only about 30% of the patients, the identification of a suitable unrelated donor by a better and precise HLA matching of donor and recipient is necessary.

The level of HLA matching for an optimal HSCT outcome is still a debatable question. The debate concerns the number of authorized HLA mismatches. Some data have suggested that adverse effect on survival is observed with a single HLA-A, -B, -C, or -DRB1 mismatch [1,2]. Controversies remain as to whether mismatches at some loci have more profound clinical consequences than those at other loci. Every HLA locus has been reported to influence the outcome of unrelated donor HSCT [1-4]. However, the respective association of some of these HLA loci seems to vary with respect to different populations: for instance, HLA-A mismatches seem to be more detrimental in the Japanese population than in Caucasians [3,5].

Currently, in most transplant centers, HLA-DPB1 and HLA-DRB3/4/5 are not taken into account for the choice of unrelated donors. Only 1 study had looked at the association of DRB3 with HSCT outcome and did not observe any association. But its limited size made it difficult to reach definitive conclusions [6]. For HLA-DPB1, there is now growing body of a bulk of evidence supporting a role of its matching status in the outcome of unrelated HSCT [7-12]. However, because of the relative lack of linkage disequilibrium between HLA-DP loci and the rest of the extended MHC haplotype, it is difficult to find an unrelated donor matched for HLA-DPB1 in addition to the other "classic" HLA loci. Therefore, an algorithm for permissiveness of HLA-DPB1 in HSCT transplantation was proposed [13]. Additionally, it remains uncertain whether mismatches that can only be detected using high-resolution typing are more predictive of clinical success than those mismatches that can be detected at low-resolution typing.

In this report, we reviewed the collaborative experience of 9 French HLA laboratories and 12 transplant centers. Three hundred thirty-four patients who received an unmanipulated bone marrow graft from an unrelated donor between 1993 and 2003 were typed at high resolution for HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQB1, and -DPB1 loci. The respective association of each HLA loci, the effects of HLA mismatching, and the association of the number of mismatches between donor and recipient with GVHD, relapse, and overall survival (OS) were studied. The implications of these findings for donor selection are discussed.

MATERIALS AND METHODS

Patient, Donor, and Transplant Characteristics

Three hundred thirty-four patients who received an unmanipulated bone marrow graft from an unrelated donor between 1993 and 2003 (56% between 1999 and 2002) were included in this analysis. The grafts were performed in 12 French transplant centers for myelogenous leukemia (acute myelogenous leukemia [AML], chronic myeloid leukemia [CML] and myelodysplastic syndrome [MDS]), for lymphoid diseases (acute lymphoid leukemia [ALL] and non-Hodgkin lymphoma [NHL]), for aplastic anemia or for inborn errors. The main patient, disease, and transplant characteristics are described in Table 1.

The minimal clinical information collected for each case were acute GVHD (aGVHD) (date of onset and grade), relapse, date of last visit, and alive/dead status. All patients were prepared for transplantation

Table 1. *Patient, Disease, and Transplant Characteristics*

Characteristics	n = 334
Recipient	
Age, median (range)	23.34 (1-56)
Female	143 (43%)
Children (<17 years)	85 (25%)
Underlying diagnosis	
Chronic myelogenous leukemia	67 (20%)
Acute leukemia	175 (52%)
AML	80 (46%)
ALL	91 (52%)
Others	4 (2%)
Myelodysplastic syndrome	31 (9.3%)
Non-Hodgkin lymphoma	13 (3.9%)
Aplastic anemia	35 (10.5%)
Inborn errors	4 (1.2%)
Other diagnoses	9 (2.7%)
Donor	
Female	154 (46%)
Sex match (donor/recipient)	193 (58%)
Female to female	78 (24%)
Female to male	76 (23%)
Male to male	115 (34%)
Male to female	65 (19%)
CMV matching	
Donor pos. recipient neg.	70/304 (23%)
Donor pos. recipient pos.	48/304 (16%)
Donor neg. recipient neg	124/304 (41%)
Donor neg. recipient pos.	62/304 (20%)
Transplant	
Source of stem cells	Unmanipulated bone marrow (100%)
Conditioning regimen	myeloablative(100%)
TBI	235/277 (85%)

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CMV, cytomegalovirus; TBI, total body irradiation.