ASBMT
American Society for Blood and Marrow Transplantation

Minor ABO-Mismatches are Risk Factors for Acute Graft-versus-Host Disease in Hematopoietic Stem Cell Transplant Patients

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We investigated the impact of ABO and Rhesus (Rh) blood group matching on the outcome of hematopoietic stem cell transplantation (HSCT) of 154 patients matched at 10/10 HLA loci with unrelated donors. ABO and Rh, as potential risk factors, were modeled with the clinical outcome—acute and chronic graft-versus-host disease (aGVHD, cGVHD), relapse, treatment-related mortality (TRM), and overall survival (OS)—by simple, multiple, and competing risk analyses. We found that minor ABO-mismatches represent a significant risk factor for aGVHD (II-IV) with an estimated risk increase of almost 3-fold (hazard ratio [HR] = 2.92, 95% confidence interval [CI]: 1.43-5.95, $P = .003$), and even 4-fold for aGVHD (III-IV) (HR = 4.24, 95% CI: 1.70-10.56, $P = .002$), but not for other transplant endpoints. No significant association of the Rh matching status with any of the HSCT endpoints was seen. These results suggest that ABO minor mismatches may play a role in aGvHD pathophysiology, possibly by providing the setting for T cell activation and antibody mediated damage. To decrease the risk of aGVHD, ABO matching should be considered in HSCT.

Biol Blood Marrow Transplant 15: 1400-1406 (2009) © *2009 American Society for Blood and Marrow Transplantation*

KEY WORDS: Minor ABO-mismatch, Rh antigen, aGVHD, unrelated HSCT

INTRODUCTION

Graft versus host disease (GVHD) is one of the major causes of morbidity and mortality after hematopoietic stem cell transplantation (HSCT). The occurrence of acute GVHD (aGVHD) in a substantial number of patients given 10/10 HLA matched unrelated or sibling donor grafts [1,2] indicates that antigens other than major HLA may be relevant for the disease development.

Minor histocompatibility antigens (mHags) are polymorphic allopeptides capable of eliciting an allogeneic T cell response in HLA-matched individuals [3], and they have been associated with the occurrence and control of GVHD [4,5]. In addition, cytokine gene polymorphisms and killer immunoglobuline-like receptor (KIR) genotypes of patients and donors have been suggested to play a role in the aGVHD, albeit via different mechanisms [6-8].

ABO antigens are carbohydrates expressed on red blood cells and various epithelial and endothelial cells [9]. Their synthesis depends on ABO glycosyltransferases, coded by more than 160 different alleles described until now [10]. Regarding this polymorphism, Eiz-Vesper and colleagues [11] have recently shown in vitro that different synthetic glycosyltransferase peptides can induce peptide-specific T cell responses. This finding indicates potential mHag properties of glycosyltransferases and supports previous clinical reports, showing a significant association of minor ABO-mismatches with increased risk of aGVHD [12-14] and shorter overall survival (OS) in transplant patients [14-16]. A recent large, multicenter study of 3103 patients given sibling grafts showed only an association of bidirectional ABO-mismatches with a higher risk of severe aGVHD (III-IV), but not with aGVHD (II-IV) or overall aGVHD [13]. There are, however, several reports that showed no impact of ABO matching status on HSCT outcome [17-19]. Rhesus (Rh) mismatches were also either associated with the shorter

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Financial disclosure: See Acknowledgments on page 1405.

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Received December 12, 2008; accepted July 6, 2009

1083-8791/09/1511-0007$36.00/0
doi:10.1016/j.bbmt.2009.07.002

Table 1. Patient and Donor Characteristics by ABO Matching Status

Characteristic	ABO Matching Status				Total	Fischer's Test *P*-Value
	Matched	Major mm	Minor mm	Bidirectional mm		
Number of patient/donor pairs (%)	58 (38)	30 (19)	44 (29)	22 (14)	154	na
Age patients, years, mean [range]	42 [19-62]	41 [18-61]	44 [19-63]	39 [21-55]	42 [18-63]	na
Age donors, years, mean [range]*	36 [23-57]	35 [22-52]	37 [18-52]	36 [21-51]	36 [18-57]	na
Sex (patient/donor), no.† (%)						
F/F	10 (18)	6 (22)	12 (27)	2 (9)	30 (20)	.17
F/M	15 (26)	7 (25)	9 (20)	7 (32)	38 (25)	
M/F	11 (19)	4 (14)	3 (7)	8 (36)	26 (17)	
M/M	21 (37)	11 (39)	20 (46)	5 (23)	57 (38)	
CMV status (patient/donor), no. (%)						
Pos/Pos	17 (29)	5 (16)	20 (45)	7 (32)	49 (32)	.48
Pos/Neg	19 (33)	11 (37)	12 (27)	7(32)	49(32)	
Neg/Pos	7 (12)	6 (20)	6 (14)	3 (13)	22 (14)	
Neg/Neg	15 (26)	8 (27)	6 (14)	5 (23)	34 (22)	
Disease, no. (%)						
AL	26 (45)	17 (57)	13 (30)	8 (36)	64 (42)	.17
CML	13 (22)	3 (10)	16 (36)	7 (32)	39 (25)	
"Other"	19 (33)	10 (33)	15 (34)	7(32)	51 (33)	
Disease stage, no. (%)						
Standard risk	35 (60)	15 (50)	21 (48)	12 (55)	83 (54)	.61
High risk	23 (40)	15 (50)	23 (52)	10 (45)	71 (46)	
Conditioning regime, no. (%)						
Myeloablative	41 (71)	22 (73)	29 (66)	17 (77)	109 (71)	.81
Reduced intensity	17 (29)	8 (27)	15 (34)	5 (23)	45 (29)	
T cell depletion, no. (%)						
T cell depleted	21 (36)	10 (33)	19 (43)	6 (27)	56 (36)	.64
Non-T cell depleted	37 (64)	20 (67)	25 (57)	16 (73)	98 (64)	
HSC source, no. (%)						
BM	27 (47)	8 (27)	22 (50)	9 (41)	66 (43)	.21
PBSCs	31 (53)	22 (73)	22 (50)	13 (59)	88 (57)	
Cell dose infused: $CD34^+$ cells $\times 10^{-6}$/kg median [range]‡	5.46 [1.24-14.30]	6.88 [0.99-19.40]	5.04[1.65-12.00]	3.68 [1.16-10.90]	5.4 [0.99-19.4]	na
GVHD prophylaxis, no. (%)						
CsA + MTX	34 (59)	19 (63)	24 (54)	12 (55)	89 (58)	.42
CsA + MMF	16 (27)	11 (37)	14 (32)	8 (36)	49 (32)	
CsA	8 (14)	0 (0)	6 (14)	2 (9)	16 (10)	

CMV indicates cytomegalovirus; CML, chronic myelogenous leukemia; GVHD, graft-versus-host disease; HSC, hematopoietic stem cell; BM, bone marrow; PBSCs, peripheral blood stem cells; CsA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; y, year; no, number; mm, mismatches; na, not applicable; F, female; M, male; AL, acute leukemia.

*Age of 4 donors are missing.

†Sex of 3 donors are missing.

‡Thirty-three data points are missing.

OS after HSCT [20], or it lacked this association [21]. However, to our knowledge, the effect of blood group mismatches on the HSCT outcome has not been studied in unrelated, HLA-matched pairs.

We therefore examined the impact of ABO and Rh patient-donor incompatibilities on the HSCT outcome of 154 adult patients receiving 10/10 HLA-matched grafts from unrelated donors at 2 transplant centers in Vienna and Prague. Our aim was to investigate if ABO and Rh matching status could be used for risk estimations of HSCT endpoints in patients with HLA class I and class II matched HSCT donors.

MATERIALS AND METHODS

Study Population

The study population consisted of 154 consecutive patients from Vienna (n = 122) and Prague (n = 32), who had undergone HSCT with unrelated donors. Transplantations took place between September 1995 and December 2005. Data were analyzed as of September 20, 2008. Median follow-up time of the patients alive was 74 months (range: 35-158 months). All patients and donors were matched for HLA class I (HLA-A, -B, -C) and class II (HLA-DRB1, -DQB1) alleles, and patients transplanted in the Vienna center were additionally matched for HLA-DRB3/4/5 alleles. Retrospective typing showed that 14% of all pairs were also matched for HLA-DPB1 alleles. HLA typing was performed as previously described [22,23]; ABO and Rh typing was performed by standard blood banking methods [24]. Neither ABO nor Rh matching was paid regard to in the donor selection process.

Patient and donor characteristics are shown in Table 1. The "acute leukemias" (AL) group consisted of 43 patients with acute myelogenous leukemia (AML) and 21 patients with acute lymphoblastic