Occurence and dynamics of HLA and HPA antibodies in the setting of matched related HSCT

Michelle Bräutigam,[1,2] Thomas Volken,[3] Alexandra Plattner,[1] Jakob R Passweg,[2] Jörg P Halter,[2] Andreas S Buser,[1,2] Laura Infanti,[1,2] Beatrice Drexler,[1,2] Dominik Heim,[2] and Andreas Holbro[1,2]

1 Blood Transfusion Center, Swiss Red Cross, Basel, Switzerland
2 Division of Hematology, University Hospital Basel, Switzerland
3 Zurich University of Applied Sciences, School of Health Professions, Winterthur, Switzerland

Background

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative treatment option for patients with malignant and non-malignant diseases. Matching for HLA-class I and II is currently standard practice in HSCT and improved HLA-typing through molecular techniques has eventually improved transplant outcome. HLA-antibodies are antibodies against foreign HLA antigens potentially triggering several immunological reactions with a wide range of clinical consequences, i.e. platelet transfusion refractoriness, graft rejection in solid organ transplantation and primary graft failure in HLA mismatched HSCT, mainly in cord blood and haploidentical transplantations.

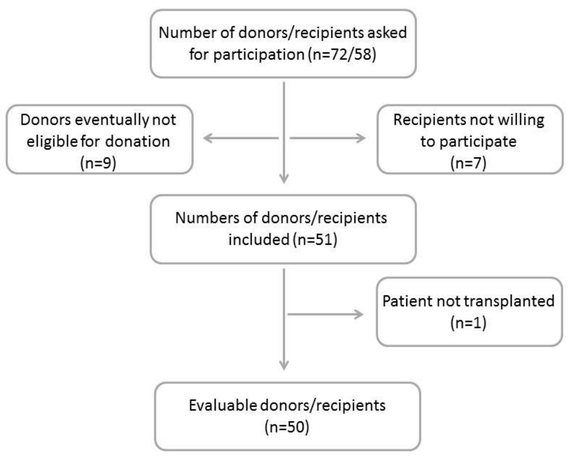
Methods

Patients and their matched related donors were prospectively included in the IRB approved study after informed consent. HLA- and HPA-antibodies were determined by Luminex® technique at predefined time points. For patients, samples were drawn at baseline (before HSCT), at HSCT and weekly thereafter until 4 weeks after HSCT and for donors at eligibility assessment and at donation. We used generalized estimating equation models of the Gaussian and negative binomial family with log links and robust standard errors in order to assess temporal trajectories of patients' average mean fluorescence intensity (MFI), highest MFI, and the number of antibodies with MFI > 500.

Results

Between November 2013 and February 2016 we prospectively included 50 patients and their corresponding 50 matched related donors in our study.

Figure 1. Consort diagram



Among those patients, 26 (51%) were female and median age at transplantation was 51 years. The majority of patients had AML (37%) and MM (15.7%), received myeloablative conditioning (58.8%) and GvHD prophylaxis consisted mainly of cyclosporine and ATG containing regimens (Table 1).

Table 1. Patient, disease and transplant characteristics

	Number	total	%
Number of patients		51	100
Females		26	51
Age at transplantation (median; range):	51.46 years; 32-65 years		
Diseases			
AML		19	37.3
ALL		5	9.8
BCL		5	9.8
TCL		3	5.9
MM		8	15.7
MDS		5	9.8
SAA		1	2
HL		2	3.9
Other		3	5.9
Disease stage[1]			
0		4	7.8
1		29	56.9
2		15	29.4
3		3	5.9
Conditioning:			
MAC		30	58.8
RIC		21	41.2
GVHD Prophylaxis:			
CYA+MTX		4	7.8
CYA+MMF		5	9.8
CYA+MTX+ATG		29	56.9
CYA+MTX+KRP		3	5.9
CYA+ATG		2	3.9
CYA+Campath		1	2
CYA+MMF+KRP		1	2
CYA+MMF+ATG		4	7.8
CYA+MTX+MMF		1	2
No GvHD-Prophylaxis (syngen)		1	2
CMV Status (D/R):			
-/-		16	31.4
+/-		5	9.8
-/+		13	25.5
+/+		17	33.3

[1]: Disease risk index according to CIBMTR;

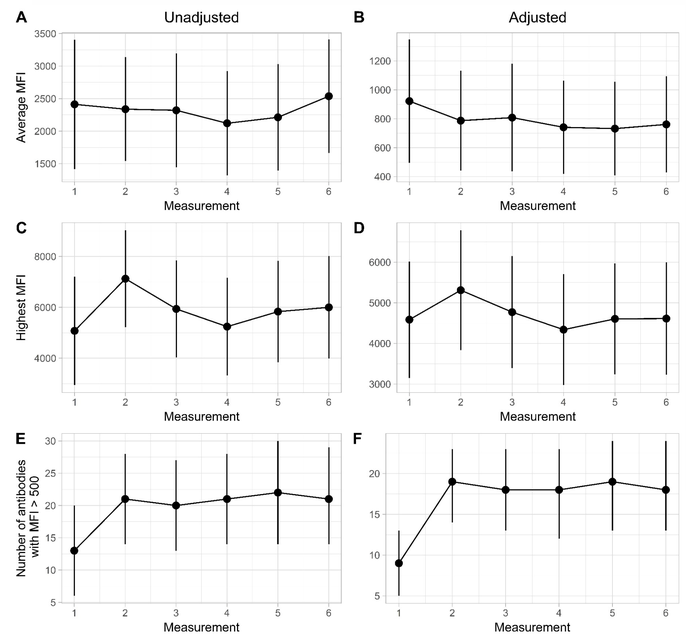
Abbreviations: AML: acute myelogenus leukemia; ALL: acute lymphatic leukemia; BCL: B-Cell-Lymphoma; TCL: T-Cell-Lymphoma, MM: Multiple Myeloma, MDS: Myelodysplastic Syndrome; SAA: Severe Aplastic Anaemia; HL: Hodgkin Lymphoma; MAC: Myeloablative Conditioning; RIC: Reduced intensity Conditioning; CYA: Cyclosporin A; MTX: Methotrexat; ATG: Antithymocyte Globuline; MMF: Mycophenolate Mofetile; KRP: Study drug.

At baseline, HLA-antibodies were detected in 49 patients (98%) (mean number of antibody specifities: 13; range 0-102) and in only 25 donors (50%) (mean number: 6; range 0-51). Of the HLA-antibody-positive donors at baseline, 13 (52%) were female and 12 (48%) were male.

Overall, both number and mean fluorescence intensity (MFI) of class I antibodies were higher compared to those of class II antibodies. At baseline, the total number was 348 for class I (mean MFI: 2330) and 310 for class II antibodies (mean MFI: 1637). The highest mean MFI for class I and class II antibodies were 4126 and 3735, respectively.

Surprisingly, a considerable increase of the number and intensity of antibodies was observed within a few days, from baseline to the day of transplantation. At HSCT the total number of antibodies was 706 for class I with a mean highest MFI of 6007 and 353 for class II antibodies with a mean highest MFI of 3482, respectively. Thereafter, the number of antibodies as well as MFI-levels - measured weekly - remained stable until the end of observation. This finding was similar after adjusting for gender, age, diagnosis, conditioning, GVHD prophylaxis, CMV status, and ABO incompatibility (Figure 2).

Figure 2. Dynamics of HLA antibodies over the period, unadjusted (A, C, and E) and adjusted (B, D, and F) for age, gender, diagnosis, conditioning, GvHD prophylaxis, CMV-status and ABO-incompatibility.



A-B Average MFI for the observed period unadjusted and adjusted (for above mentioned parameters)
C-D Highest Mean MFI for the observed period unadjusted and adjusted
E-F Number of antibodies (MFI>500) for observed periiod unadjusted and adjusted

Furthermore, 48 of the 50 patients (96%) developed new HLA antibodies over the observed time period. New class II antibodies occurred more often and at higher intensities than new class I antibodies.

In 14 of the 50 patients (28%) the molecular specifities of the emerging antibodies were the same as those found in their corresponding donors, suggesting a potential transfer of donor-derived antibodies (Table 2).

Table 2: Patients with new antibodies emerging between measurement V3 (day 7 posttransplant) and V6 (day 28 post-transplant), potentially donor derived

Age (at Tx)	Gen-der	Disease	Disease Stage (DRI-Group)	Conditioning	GvHD-Prophylaxis	Nr. of new Antibodies (MFI range)		Nr. of Transfusions	Chimerism at d+30 CD3/Whole blood
						Class I	Class II	RBC/PLT	
62	F	AML	2	MAC	CYA MTX	3 (517-1614)	0	4/6	83/76
60	M	MDS	2	MAC	CYA MTX ATG	0	24 (504-1823)	0/0	28/100
56	F	AML	1	MAC	CYA MTX ATG	6 (788-1288)	4 (545-674)	11/13	93/100
55	F	AML	2	RIC	CYA MTX ATG	10 (955-3469)	8 (527-950)	4/3	94/ 84
62	M	MM	1	RIC	CYA MTX ATG	23 (547-4558)	45 (523-6262)	8/10	100/100
58	M	MDS	2	RIC	CYA MTX ATG	3 (1250-2218)	0	6/8	100/---
49	F	AML	3	MAC	CYA ATG	1 (544)	5 (579-1757)	8/8	94/100
62	M	MM	1	RIC	CYA MTX ATG	2 (509-854)	0	4/8	100/100
45	F	AML	2	MAC	CYA MTX ATG	1 (567)	13 (509-939)	6/3	87/100
59	F	BCL	1	RIC	CYA ATG MMF	2 (2141-2236)	4 (659-2467)	12/56	78/100
49	M	MM	1	RIC	CYA MTX ATG	3 (594-894)	2 (504-640)	9/17	0/0
62	F	AML	1	MAC	CYA MTX ATG	6 (524-739)	27 (506-1457)	5/4	66/100
33	F	SAA	0	RIC	CYA Campath	2 (585-628)	0	3/4	100/100
55	M	AML	1	MAC	CYA MTX ATG	18 (501-1315)	15 (516-971)	11/15	100/100

By contrast, only one of the 50 patients had low-level HPA antibodies and HPA-antibodies were not detected in the donors.

Conclusions

Our data show that HLA antibodies are frequently present in patients undergoing HSCT and that they should be measured at the day of transplantation. Additionally, some patients develop new, including presumably donor-derived HLA-antibodies. This might have some impact regarding both transfusion strategies (platelet transfusion refractoriness) as well as transplant outcome. Since HLA-mismatched (incl. haploidentical) HSCT are increasingly performed worldwide, further studies on the significance of HLA-antibodies in these settings are warranted. On the other hand, HPA-antibodies seem to play a minor role and should be assessed only in selected patients.

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