High prevalence of pre-transplant HLA antibody in female patients with primary myelofibrosis or aplastic anemia

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Introduction

Donor-specific antibody (DSA), defined as HLA antibody reactive to donor HLA antigen(s), is known to increase the risk of engraftment failure in allogenic stem cell transplant (SCT) (Dehn 2019, Ciurea, 2020). Donor compatibility must be assessed when a patient has HLA antibody.

Initially, development of HLA antibody requires allo-immunization (pregnancy, transfusion, or transplant). Long-term HLA antibody status is influenced by antigen re-exposure (ex. transfusion) or inflammation (ex. infection). Thus, HLA antibody positive rates among pre-SCT patients may vary depending on gender and disease diagnosis.

Methods

Included in this study are the patients who received allogenic SCT n 2016-2024 at the Penn State Hershey Med Center for hematological malignancy [primary myelofibrosis (PMF), aplastic anemia (AA), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), acute lymphocytic leukemia (ALL), lymphoma, chronic myeloid leukemia (CML), and chronic myelomonocytic leukemia (CMML)].

HLA antibody was tested at the time of donor selection and one month before SCT. Detecting >0% PRA I or PRA II by Labscreen PRA with a cutoff of 1000 MFI (Thermofisher, CA) was considered HLA antibody positive. The rate of positive patient (%) was compared by gender, diagnosis, and HLA class. Fisher Exact Test ($p<0.05$) was used.

Results

In the total 485 patients, 93 patients had HLA antibody (19.2%). The rates were higher in class I than in class II (18.1% s. 9.3%, p=0.0001) and in female patients than in male patients [30.4% vs.10.8% (class I/II), 29.5% vs. 9.7% (class I), 16.4% vs. 4.0% (class II), all p<0.00001, **Table 1**].

Table 1. HLA antibody positive rates by gender and HLA class

	Female	Male	Total
class I antibody	61/207 (29.5%)	27/278 (9.7%)	88/485 (18.1%)
class II antibody	34/207 (16.4%)	11/278 (4.0%)	45/485 (9.3%)
class I/II antibody	63/207 (30.4%)	30/278 (10.8%)	93/485 (19.2%)

P<0.00001 (class I antibody vs class II antibody)
P<0.00001 (class I/II antibody)

The HLA class II antibody positive rate was higher in the patients with class I antibody than in patients without (p<0.00001 in female, male, and total, **Table 2**)

Table 2. HLA class II antibody rate by Class I antibody status

	Class I antibody status	% patient with class II antibody
Female	pos	32/61 (52.5%)
	neg	2/146 (1.4%)
Male	pos	8/26(30.8%)
	neg	3/252 (1.1%)
Total	pos	40/87 (46.0%)
	neg	5/398 (1.3%)

P<0.00001 (Female)
P<0.00001 (Male)
P<0.00001 (Total)

Disease-specific HLA antibody rates (%) compared to the gender and HLA class-specific mean (%) (**Table 3)** were

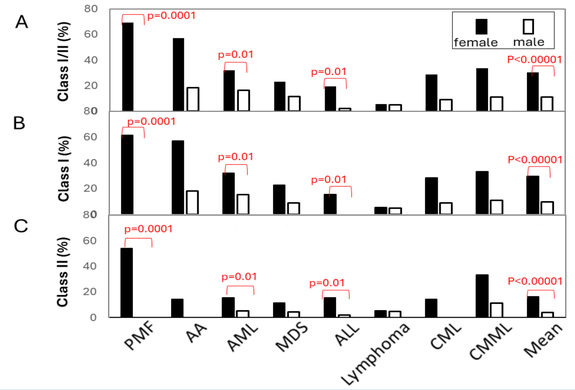
- Higher in the female PMF patients [61.5% vs.29.5% (class I), p=0.03; 53.8% vs. 16.4% (class II), p=0.0035; 69.2% vs. 30.4% (class I/II), p=0.011] and in the female AA patients [57.1% vs. 29.5% (class I), p=0.0392].
- Higher in female patients than male patients in PMF, AML, and ALL (class I, II, and I/II, **Figure**).
- Lower in the female lymphoma patients [5.6% vs. 29.5% (class I), p=0.0283] and in the male ALL patients [0% vs. 4.0% (class I), p=0.0209].

Table 3. HLA antibody prevalence in patient, N (%)

		PMF	AA	AML	MDS	ALL	Lymphoma	CML	CMML	Mean
All	**class I/II**	9/28 (32.1%)	10/25 (40.0%)	48/208 (23.1%)	13/79 (16.5%)	6/76 (7.9%)	2/39 (5.1%)	3/18 (16.7%)	2/12 (16.7%)	93/485 (19.2%)
Female	**class I**	8/13 (61.5%)*	8/14 (57.1%)*	29/91 (31.9%)	8/35 (22.9%)	4/26 (15.4%)	1/18 (5.6%)*	2/7 (28.6%)	1/3 (33.3%)	61/207 (29.5%)
	class II	7/13 (53.8%)*	2/14 (14.3%)	14/91 (15.4%)	4/35 (11.4%)	4/26 (15.4%)	1/18 (5.6%)	1/7 (14.3%)	1/3 (33.3%)	34/207 (16.4%)
	class I/II	9/13 (69.2%)*	8/14 (57.1%)	29/91 (31.9%)	8/35 (22.9%)	5/26 (19.2%)	1/18 (5.6%)*	2/7 (28.6%)	1/3 (33.3%)	63/207 (30.4%)
Male	**class I**	0/15 (0%)	2/11(18.2%)	18/117 (15.4%)	4/44 (9.1%)	0/50 (0%)*	1/21 (4.8%)	1/11 (9.1%)	1/9 (11.1%)	27/278 (9.7%)
	class II	0/15 (0%)	0/11 (0%)	6/117 (5.1%)	2/44 (4.5%)	1/50 (2.0%)	1/21 (4.8%)	0/11 (0%)	1/9 (11.1%)	11/278 (4.0%)
	class I/II	0/15 (0.0%)	2/11 (18.2%)	19/117 (16.2%)	5/44 (11.4%)	1/50 (2.0%)	1/21 (4.8%)	1/11 (9.1%)	1/9 (11.1%)	30/278 (10.8%)

The rates was higher (*) or lower (*) when compared to the gender/HLA class-specific mean.

Figure. HLA antibody prevalence (%)



Discussion

HLA antibody positive rates were higher in female patients, especially with PMF and AA. This can be explained by the sensitization during pregnancy and stimulation through long-term transfusion-dependency. However, in male patients, the rates with PMF or AA was not significantly higher compared to other diagnosis. This suggests that in absence of prior allo-immunization, transfusion is ineffective in establishing new sensitization or stimulating preformed antibody. Additionally, in FPM, inflammation is considered critical in the evolution of mutated clones (*JAK2, CALR,* or *MPL)* into myeloproliferative neoplasms (MPNs) (Ref: Luque, 2023, 3-4). The same inflammation may have stimulated HLA antibody production in female PMF/AA patients.

The lower rate of HLA antibody in the female lymphoma patients and male ALL patients may be attributed to the lymphotoxic chemotherapy effects.

Conclusions

Female patients with MF and AA have higher rates of positive HLA antibody, which may limit the acceptability of haploidentical or unrelated donors. Such variability may be considered in the pre-SCT HLA antibody testing protocol (timing and frequency).

References

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