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CORRESPONDENCE

Effect of HLA mismatch on post-transplant infections in allogeneic hematopoietic stem cell transplantation with PTCy-based GvHD prophylaxis

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TO THE EDITOR:

Post-transplant cyclophosphamide (PTCy) has increased the use of haploidentical (HAPLO) donors [1] Early data associated HAPLO transplants with increased infections, though only HAPLO patients received PTCy [2]. In a registry-based study comparing HAPLO vs. MATCHED grafts with PTCy [3], there were increased bacterial infections and fungal infections in HAPLO transplants with myeloablative and reduced-intensity conditioning, respectively [3].

In the present study, we compared post-transplant infections in a cohort of patients with HAPLO or MATCHED donor and uniform PTCy-based immunosuppression.

PATIENTS AND METHODS

This cohort includes all patients treated at our center from 2016–2020 with HAPLO or MATCHED donor and PTCy as previously described (Table 1). HAPLO grafts were performed using BM and MATCHED with PB. G-CSF was used from day +6 until neutrophil engraftment in HAPLO grafts.

Per our institutional protocol, antibacterial prophylaxis is not used in neutropenia, and prophylactic posaconazole is used in patients with GvHD. For CMV-seropositive patients, prophylaxis with letermovir was started in 2019 for HAPLO transplants and 2020 for MATCHED transplants.

Infections

Follow-up for infections set at 100 days post-transplant.

In scoring BSI, common contaminants were excluded unless isolated from consecutive cultures. Positive cultures from central line paired with negative cultures from peripheral vein were considered CVC colonization and excluded.

IFI was classified as proven, probable, or possible based on international guidelines [5]. CMV or EBV infection/reactivation was defined as DNA copies >1000 ml^{-1} or >5000 ml^{-1}, respectively.

Statistical analysis

We performed competing risk analysis to compare risk of infections in MATCHED vs. HAPLO grafts [6] with non-infection mortality as the competing risk.

A confirmatory analysis with propensity matching was performed, limited to 68 MATCHED and 68 HAPLO transplants. Criteria for matching included donor and recipient age, disease status, and conditioning.

Categorical data were compared using chi-square test.

RESULTS

Patient characteristics

MATCHED and HAPLO transplant patients were similar in age, sex, diagnosis, conditioning, and disease status (Table 1). The groups differed in transplant date, with PTCy for MATCHED grafts from 2019.

Engraftment

Average time to leukocyte and neutrophil engraftment was 20 days, both in HAPLO and MATCHED transplants. Average WBC on day +20 was similar in HAPLO vs. MATCHED transplants (1581/mm^3 vs. 1742/mm^3; $p = 0.47$). On day +50, neutrophil count was similar between the two groups (3690/mm^3 vs. 3390/mm^3), while HAPLO patients had a trend for decreased lymphocyte count (870/mm^3 vs. 1080/mm^3).

Infections

Bloodstream infections. The risk of BSI was increased in HAPLO grafts, compared with MATCHED grafts (HR 2.54; 95% CI 1.39–4.62; $p = 0.002$) (Table 1). Results were confirmed in propensity-matched analysis (data not shown).

During the first 20 days, there were 75 BSI events, of which 8/75 were CVC-related. The most frequent pathogens were gram-negative bacteria. During days +21 to +100, BSI were less frequent, and the most frequent were gram-positives.

To account for GvHD and steroid therapy on BSI, we characterized patients according to GvHD. Of 56 HAPLO patients with BSI, 2/56 developed GvHD prior to BSI, compared with 0/14 MATCHED patients. To test for an effect of conditioning, we stratified patients according to days of busulfan: BSI occurred in 45%, 63%, and 41% of HAPLO grafts with TBF1, TBF2, and TBF3, respectively, compared with 20%, 19%, and 12% of MATCHED grafts.

Among MATCHED grafts, no difference was observed in patients with matched sibling donors vs. matched unrelated donors (data not shown).

Viral reactivation. CMV infection/reactivation occurred in 52/116 (48%) of HAPLO grafts and 10/68 (15%) of MATCHED grafts. In competing risk analysis, CMV reactivation was significantly increased in HAPLO transplants (HR 3.51; 95% CI 1.79–6.87; $p < 0.001$), which was confirmed in propensity-matched analysis.

Among the 151 patients pre-letermovir, there was increased CMV infection/reactivation in HAPLO grafts (HR 3.55; 95% CI 1.77–7.12; $p < 0.001$), which was not influenced by intensity of conditioning. Of 33 patients given letermovir, only 1/33 (3%) developed CMV reactivation.

EBV reactivation occurred in 8/116 (7%) of HAPLO transplants vs. 1/68 (2%) of MATCHED transplants (HR 2.17; 95% CI 0.46–10.2; $p = 0.3$).

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Table 1. Patient and transplant characteristics, incidence of infections, and causative pathogens.

	HAPLO ($n = 116$)	MATCHED ($n = 68$)	p
Patient and transplant characteristics			
Diagnosis			0.50[a]
Acute leukemia	69 (60%)	37 (54%)	
Acute myeloid leukemia	53 (46%)	23 (34%)	
Acute lymphoblastic leukemia	16 (14%)	14 (21%)	
Other	47 (40%)	31 (46%)	
Myelofibrosis	21 (18%)	13 (19%)	
Myelodysplastic syndrome	13 (11%)	4 (6%)	
Hodgkin lymphoma	9 (8%)	4 (6%)	
Non-Hodgkin lymphoma	3 (3%)	5 (7%)	
Multiple myeloma	0	3 (4%)	
Chronic myelocytic leukemia	0	1 (1%)	
Chronic myelomonocytic leukemia	0	1 (1%)	
Chronic lymphocytic leukemia	1 (1%)	0	
Disease status			0.31[a]
Complete remission	67 (58%)	34 (50%)	
Relapse or Stable/ progressive disease	49 (42%)	34 (50%)	
Conditioning regimen			0.17[a]
TBF1	11 (9%)	5 (7%)	
TBF2	35 (30%)	24 (35%)	
TBF3	37 (32%)	17 (25%)	
Cy-Flu-TBI	15 (13%)	8 (12%)	
Cy-Flu-Mel	6 (5%)	1 (1%)	
Flu-TBI	7 (6%)	11 (16%)	
Other	6 (5%)	1 (1%)	
Donor type			
Matched unrelated donor, 8/8 (MUD)	0	39 (57%)	
Matched related donor, 8/8 (MRD)	0	29 (43%)	
Haploidentical (HAPLO)	116 (100%)	0	
Donor source			
Peripheral blood (PB)	0	68 (100%)	
Bone marrow (BM)	116 (100%)	0	
Donor age (years)			0.11[b]
Median	37	33	
Mean	37	34	
Standard deviation	11	13	
Recipient age (years)			0.06[b]
Median	57	48	
Mean	53	49	
Standard deviation	15	13	
Incidence of infections			
Bloodstream infections (BSI)			
Days 0 to +100	56 (48%)	14 (21%)	0.002[c]
Days 0 to +20	50 (43%)	14 (21%)	
Days +21 to +100	13 (11%)	1 (1%)	
Viral infections			
CMV infection/reactivation	52 (45%)	10 (15%)	<0.001[c]
EBV infection/reactivation	8 (7%)	2 (3%)	0.30[c]
Invasive fungal infections (IFI)			
Proven, probable, or possible IFI	34 (29%)	11 (16%)	0.10[c]
Proven IFI	4 (3%)	0	
Probable IFI	14 (12%)	4 (6%)	
Possible IFI	16 (14%)	7 (10%)	
Infection-related mortality			
Infection-related mortality	11 (9%)	1 (1%)	0.03[a]
Causative pathogens			
Days 0 to +20			
Gram-positive bacteria			
Staphylococcus aureus	2	1	
Coagulase-negative BSI (CoNS)	14	1	
Streptococcus spp.	7	0	
Enterococcus spp.	3	1	
Gram-negative bacteria			
Escherichia coli	13	6	
Klebsiella spp.	10	3	
Citrobacter spp.	1	0	
Enterobacter kobei	1	0	
Proteus mirabilis	1	0	
Serratia marcescens	0	1	
Stenotrophomonas maltophilia	0	1	
Acinetobacter spp.	1	0	
Haemophilus parainfluenzae	1	0	
Pseudomonas aeruginosa	3	2	
Fungi			
Candida parapsilosis	1	0	
Candida tropicalis	1	0	
Days +21 to +100			
Gram-positive bacteria			
Coagulase-negative BSI (CoNS)	7	0	
Enterococcus spp.	6	1	
Gram-negative bacteria			
Escherichia coli	1	0	
Raoultella ornitholyca	1	0	
Fungi			
Aspergillus terreus	1	0	
Candida albicans	1	0	
Candida parapsilosis	1	0	

[a]p values based on chi-square test.
[b]t-test.
[c]competing risk analysis.

Invasive fungal infections. IFI occurred in 34/116 (29%) of HAPLO grafts and 11/68 (16%) of MATCHED grafts. In the competing risk analysis, there was a trend for increased IFI in HAPLO grafts (HR 1.80; 95% CI 0.90–3.57; $p = 0.10$).

Since prophylactic antifungal in the post-transplant period was limited to patients treated with steroid for GvHD, we stratified patients with IFI according to whether they were receiving steroid and antifungal at the time of IFI. Of 34 HAPLO patients with IFI, 7/34 (20%) were receiving steroid and posaconazole for acute GvHD (aGvHD) (1 grade 1 and 6 grade 2–4), compared with 2/11 (18%) of MATCHED patients with IFI who were receiving for steroid and posaconazole for aGvHD (1 grade 1 and 1 grade 2).

Infection-related mortality. Deaths from infections in the first 100 days occurred in 11/116 (9%) of HAPLO and 1/68 (1%) of MATCHED grafts ($p = 0.03$).

IRM in HAPLO grafts included 6 gram-negative BSI, 2 gram-positive BSI, 3 IFI, and 1 pulmonary infection. The only IRM in MATCHED grafts was a gram-negative CVC-BSI.

DISCUSSION

In patients receiving PTCy, HAPLO grafts had increased post-transplant infections and IRM, compared with MATCHED transplants. Increased BSI in HAPLO patients included increased gram-positive and fungal BSI. While gram-positives are generally less lethal than gram-negatives, 2/9 (22%) of IRM in HAPLO grafts were gram-positive BSI; notably, neither patient developed GvHD. While gram-negative BSI occurred with similar frequency in HAPLO vs. MATCHED grafts, gram-negative BSI were more lethal in HAPLO patients: 6/30 (20%) vs. 1/12 (8%) in MATCHED.

Our data suggest more marked impairment in immune function conferred by HLA mismatch given a uniform PTCy-based immunosuppression. This model would be consistent with data on immune reconstitution showing impaired reconstitution of NK cells and T cells in HAPLO transplants [7]. While our data indicate similar time to leukocyte engraftment, others have shown differences, including $CD4^+$ T cells in HAPLO patients skewed in favor of Tregs and NK cells represented by immature subsets ($CD16^-$, $CD56^{bright}$) [7].

Our group previously found an association between HAPLO grafts and increased grade 2–4 acute GvHD and moderate-severe chronic GvHD [4]. While steroids for GvHD contributes to immunosuppression in HAPLO grafts, it does not account for increased infections in the present study. Surprisingly, majority of IFI occurred in the absence of GvHD, with increased GvHD and a trend for increased IFI in HAPLO grafts.

Compared with other reports, we observed a relatively high frequency of early BSI in HAPLO grafts (43%), though early BSI in MATCHED grafts were relatively infrequent (21%) [8, 9]. Others have reported similar rates of pre-engraftment BSI between HAPLO and MATCHED grafts [8, 9]. A relatively high rate of pre-engraftment BSI in non-HAPLO grafts seen in one study may reflect inclusion of single-antigen-mismatched grafts in the non-HAPLO group [9]. It was also hypothesized that threosulfan-based conditioning lessened the mucosal injury predisposing to BSI [9], of which HAPLO patients are more susceptible [2]; that said, we did not observe an effect of conditioning. Additionally, there are differences in infection protocols, with patients at other centers routinely receiving prophylactic fluoroquinolone and azole [9, 10].

Limitations of our study are the retrospective nature and that MATCHED grafts were performed with PB, vs. BM for HAPLO transplants. PB transplants are associated with earlier engraftment. A study on HAPLO BM vs. HAPLO PB grafts, however, showed no difference in neutrophil engraftment or graft failure [11].

In conclusion, patients with HAPLO donors have increased risk of post-transplant infections and IRM, compared with patients with MATCHED donors. Our findings call for diligent monitoring in patients undergoing a HAPLO transplant.

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DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

JDM and AB designed the study and drafted the paper. EG, SG, PC, EM, FS, LL, II, FA, MAL, AF, AB, and SS provided clinical data. EG, PC, and SS critically reviewed the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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