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HLA-matched platelet transfusions are effective only in refractory patients with positive HLA antibody screening

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BACKGROUND: Recipients of platelet transfusions with 1-hour corrected count increments (1hCCIs) of 7.5 or less on two subsequent platelet transfusions with random platelets may benefit from human leukocyte antigen (HLA)-matched platelet concentrates. We aimed to quantify the efficacy of HLA-matched platelets concentrates expressed in 1hCCIs.

METHODS: We performed a cohort study among consecutive refractory patients who received HLA-matched platelet concentrates in the Netherlands between 1994 and 2017. We performed mixed-model linear regression comparing 1hCCIs after HLA split-antigen–matched transfusions with 1hCCIs after HLA-mismatched transfusions, adjusted for within-patient correlations. A donor-to-patient match was categorized as a split-match if all donor HLA-A and -B antigens were present in the patient as well; that is, donor and patient were HLA identical or compatible. Subgroup analyses were performed for patients with positive or negative HLA antibody screens. Finally, the additional effect of ABO mismatches on 1hCCIs was investigated.

RESULTS: The 1hCCI after an HLA-matched transfusion was 14.09 (95% reference interval, 1.13-29.89). This was 1.94 (95% confidence interval [CI], 0.74-3.15) higher than 1hCCI after HLA-mismatched transfusions. In patients with negative HLA antibody screening tests, HLA matching did not affect 1hCCIs. Conditional on HLA matching, 1hCCIs decreased by 3.70 (95% CI, -5.22 to −2.18) with major ABO mismatches.

CONCLUSION: Matched platelet concentrates yielded maximal 1hCCIs, whereas mismatched transfusions still resulted in adequate increments. There is no indication for HLA-matched platelets in patients with negative antibody screens.

Recipients of platelet transfusions may develop refractoriness, which is defined as 1-hour corrected count increments (1hCCIs) of 7.5 or less on two subsequent ABO-compatible platelet transfusions.[1] On average, the corrected count increment (CCI) after platelet transfusion in the general Dutch patient population is 17.1.[2] Although in general practice absolute count increments are mostly used to evaluate transfusion successes, CCIs are more accurate to evaluate a transfusion, as the body surface area is taken into account. In 80% to 90% of patients, refractoriness is caused by non–immune-mediated factors like fever, infection, splenomegaly, bleeding, and medication use. In the case of immune-mediated clearance of transfused platelets, this is predominantly caused by alloantibodies directed against human leukocyte antigen (HLA) class I expressed on platelets.[3,4] If these antibodies are directed against high-frequency HLA antigens, it is likely that these antigens are expressed on the majority of platelets present in a random five-donor pooled platelet concentrate, resulting in rapid clearance of the transfused platelets.[3] This does not necessarily imply that it will be difficult to find a suitable donor, but it explains why the vast majority of random platelet concentrates result in insufficient increments.

HLA class I matched, ABO-compatible, platelet transfusions can improve 1hCCI in these patients.[3,5] Matching is performed on HLA-A and -B antigens.[6,7] In the Netherlands, a panel of approximately 20,000 HLA-typed donors are available to donate apheresis platelets upon request for specific HLA-matched refractory patients.

In the current study, we aimed to investigate the effect of HLA–split-antigen–matched platelet transfusions to patients refractory to random pooled platelet transfusions. We compared 1hCCIs after HLA-matched transfusions with increments after transfusions containing an acceptable HLA antigen mismatch.

METHODS

We performed a cohort study using the nationwide registry of consecutive refractory patients for whom an HLA-matched platelet product was ordered at Sanquin, the national Dutch Blood Supply organization. An HLA-matched product can be requested for patients with 1hCCIs of 7.5 or less on at least two platelet transfusions with HLA antibody-mediated clearance as the suspected cause, regardless of whether HLA antibodies have been detected yet. For HLA matching, single-donor apheresis products are used, in contrast to our standard buffy coat–derived five-donor concentrates.[3]

Since the start of the registry in 1994, HLA typing techniques have improved significantly. Nowadays, DNA-based typing has replaced serologic typing. In the current study, we included only patients who were minimally DNA typed at low resolution (two digits). Neonates were excluded from all analyses due to differences in pathophysiological mechanisms underlying refractoriness, as immune-mediated thrombocytopenia in neonates is predominantly caused by transferred maternal antibodies.[8,9]

Matching is performed on HLA-A and -B antigens. In our matching strategy, we consider grade A, BU, and B2U matches according to the Duquesnoy criteria as equivalent. This means that all antigens expressed by the donor are identical to the patient, but not all patient antigens have to be expressed by the donor (i.e., the donor may be homozygous).[10] In case of insufficient split-matched donors, partially matched products containing one or more HLA antigen mismatches are being used. An HLA mismatch is considered acceptable when the donor antigen is absent in the patient, but acceptable according to either antibody specificity, epitope matching, cross-reactive groups, the effect of previous transfusions, or any combination of these strategies. A 1hCCI greater than 7.5 was deemed satisfactory, as in this case there is by definition no platelet refractoriness. In the current study, we did not take matching on human platelet antigens into account, as not all patients nor donors were human platelet antigen typed.

We compared 1hCCIs after HLA-matched transfusions with 1hCCIs after transfusions containing at least one HLA antigen mismatch. Knowledge about patient-specific responses to previous transfusions with the same HLA could influence the selection of the next donor. An adequate 1hCCI after a mismatched transfusion increases the likelihood that this combination of HLA antigens is used in the next transfusion, whereas in case of low increments this mismatched HLA antigen will be excluded

Characteristics	Total cohort	HLA-matched transfusion	Mismatched transfusion
Patients, n	581	427	290
Female sex, n (%)	385 (66.3)	285 (66.7)	194 (66.9)
Age at first transfusion (y), mean (SD)	54.1 (16.2)	55.2 (15.1)	51.8 (17.6)
Diagnosis			
Acute leukemia	278 (47.9)	214 (50.1)	137 (47.2)
Chronic leukemia	29 (5.0)	25 (5.9)	13 (4.5)
Lymphoma	26 (4.5)	17 (4.0)	12 (4.1)
Multiple myeloma	16 (2.8)	7 (1.6)	9 (3.1)
Myelodysplastic syndrome	47 (8.1)	36 (8.4)	22 (7.6)
Myelofibrosis or aplastic anemia	50 (8.6)	37 (8.7)	33 (11.4)
Benign hematologic diseases*	12 (2.1)	6 (1.4)	10 (3.5)
Solid tumor	14 (2.4)	11 (2.6)	4 (1.4)
Solid organ transplantation	5 (0.9)	2 (0.5)	4 (1.4)
Other or unknown	104 (17.9)	72 (16.9)	46 (15.9)
Number of transfusions per patient, median (IQR)	1 (1-2)	1 (1-1)	1 (1-3)
Number of transfusions	1068	427	641
Year of transfusion			
1994-2000, n (%)	113 (10.6)	36 (8.4)	77 (12.0)
2001-2006, n (%)	210 (19.7)	68 (15.9)	142 (22.2)
2007-2011, n (%)	263 (24.6)	109 (25.5)	154 (24.0)
2012-2017, n (%)	482 (45.1)	214 (50.1)	268 (41.8)

TABLE 1. Demographics of the study population

The total registry contains all patients in the registry. The final cohort includes only patients and transfusions for whom the first transfusion at which a patient was exposed to a new antigen could be identified.

* Including Glanzmann thrombasthenia, Bernard Soulier syndrome, Castelman disease, gray platelet syndrome, thalassemia, polycythemia vera, autoimmune thrombocytopenia, and immune thrombocytopenia.

IQR = interquartile range.

TABLE 2. Corrected count increments according to different matching strategies

Matching	Number (%)	Difference 1hCCI (95% CI)	Adjusted AB0 incompatibility (95% CI)
HLA matched	427 (40.0)	*Ref*	*Ref*
HLA mismatched	641 (60.0)	−1.94 (−3.15 to −0.74)	−1.99 (−3.28 to −0.71)
Minor ABO incompatibility*	187 (23.3)	N/A	−1.06 (−2.65 to 0.52)
Major ABO incompatibility†	177 (22.0)	N/A	−3.70 (−5.22 to −2.18)
Patients with positive alloantibody screen			
HLA matched	215 (34.9)	*Ref*	*Ref*
HLA mismatched	401 (65.1)	−3.09 (−4.68 to −1.50)	−3.28 (−4.97 to −1.59)
Minor ABO incompatibility*	125	N/A	−1.55 (−3.60 to 0.49)
Major ABO incompatibility†	119	N/A	−4.00 (−5.93 to −2.09)
Patients with negative antibody screen			
HLA matched	83 (53.9)	*Ref*	*Ref*
HLA mismatched	71 (46.1)	−0.26 (−2.75 to 2.21)	0.28 (−2.14 to 2.71)
Minor ABO incompatibility*	24 (19.1)	N/A	−0.27 (−3.48 to 2.92)
Major ABO incompatibilit†	27 (24.4)	N/A	−2.87 (−5.82 to 0.08)
Matching incorporating the results of the Luminex (LSA) single-antigen test			
HLA split-matched	215 (77.6)	*Ref*	N/A
Acceptable mismatch	38 (13.7)	−3.08 (−6.32 to 0.15)	N/A
Mismatch against LSA	24 (8.7)	−3.11 (−6.94 to 0.73)	N/A

We excluded patients from the stratified analyses if antibody screening was not performed or if results were missing.
* Defined as the presence of anti-A and/or anti-B alloantibodies in the product directed against patients' blood group antigens.
† Defined as the presence of anti-A or anti-B alloantibodies in patient plasma directed against donor blood group antigens.
1hCCI = 1-hour corrected count increment; CCI = corrected count increment; CI, confidence interval; N/A = not applicable.

from the selection for future transfusions. To prevent bias due to this knowledge, we selected only the first HLA-matched transfusion per patient and, if applicable, the first transfusion at which that patient was exposed to a specific new acceptable HLA mismatched antigen. As multiple transfusions per patient could be included, a mixed-model linear regression with a random intercept per patient was used to adjust for within-patient correlations.

We performed three additional analyses. First, we aimed to evaluate the efficacy in subgroups of patients with and without demonstrated HLA antibodies. HLA-matched products can be requested precautionary for patients pending HLA antibody testing results and the screening turns out negative in a subset of patients.

Second, we aimed to assess the contribution of antibody specificity obtained from the Luminex single-antigen (LSA) test. In this analysis, we excluded patients for whom the HLA antibody specificity had not been tested.

Finally, we examined the effect of ABO mismatching conditional on HLA matching, as major ABO-incompatible platelet concentrates could lower 1hCCIs by 10% to 35%.[1,11,12] We perform ABO matching only if feasible given the availability of HLA-matched donors.[13]

RESULTS

The final analyses comprised 1068 transfusions issued to 581 patients, receiving a median number of one (interquartile range, 1-2) transfusion per patient. Patients were on average aged 54.1 years; the majority were female (66.7%) and suffered from hematologic malignancies (76.9%), predominantly acute leukemias (47.9%) (Table 1). A total of 427 transfusions (40%) were completely HLA matched, resulting in an average 1hCCI

of 14.09 (95% reference interval, 1.13-29.89), whereas HLA-mismatched transfusions were associated with 14% lower 1hCCI (−1.94; 95% confidence interval [CI], -3.15 to −0.74); Table 2).

A total of 295 patients demonstrated HLA antibodies and received in total 616 transfusions. HLA-mismatched products resulted in lower 1hCCIs (−3.09; 95% CI, −4.68 to −1.50), a reduction of 22% as compared to an HLA-matched transfusion. In contrast, in patients without antibodies (110 patients, 154 transfusions), HLA-matched and HLA-mismatched transfusions were equally effective (difference − 0.26; 95% CI, −2.75 to 2.21). The HLA antibody specificity was taken into account in the matching of 62 transfusions, comprising 38.0% of HLA-mismatched transfusions. A mismatch with acceptable HLA antigens according to the LSA might lower 1hCCIs (−3.08; 95% CI, −6.32 to 0.15). This reduction is −3.11 (95% CI, −6.94 to 0.73) for mismatches with HLA antigens against which the patient has antibodies (Table 2).

Minor ABO incompatibility was associated with lower 1hCCIs (−1.06; 95% CI, −2.65 to 0.52). Major ABO incompatibility decreased the 1hCCIs with 3.70 (95% CI, −5.22 to −2.18; Table 2).

CONCLUSION AND DISCUSSION

For refractory patients with proven HLA antibodies, a completely HLA-matched donor is preferred, as this yielded statistically significant higher CCIs. However, HLA-mismatched transfusions still result in adequate increments. By definition, refractory patients have 1hCCI less than 7.5 after transfusion of random platelet concentrates.[1,6] Transfusion of completely HLA-matched platelet concentrates yielded a 1hCCI of approximately 14. This seems somewhat lower than in the general

Dutch transfusion population, where the mean 1hCCI on random plasma-stored platelet concentrates was 17.1.[2] Although the reference intervals are broad, this suggests that refractoriness is a multifactorial condition with additive effects from several underlying mechanisms that cannot be corrected only by administration of HLA-matched platelets alone. Moreover, refractory patients in whom antibody screening turns out negative, that is, patient without antibodies, HLA-matched products do not improve 1hCCIs. This supports the recommendation to treat these patients with random platelet concentrates.[4,6]

In general, a minimum of five donors is mandatory to guarantee platelet support for a prolonged period of time, for example, during the course of chemotherapy. Due to limited availability of donors with rare HLA antigens, it is often not feasible to provide completely HLA-matched products for all patients. In patients with proven antibodies, antibody specificity is used to determine acceptable antigens for HLA-mismatched transfusions. In our analyses, matching based on this information had no additional benefit. This counterintuitive finding should be interpreted with caution, as LSA results were only available for a minority of patients and were only used in the minority of patients for whom an HLA-mismatched transfusion was necessary to ensure sufficient platelet support. This is predominantly explained by the large time span of this nationwide registry (from 1994) and the relative recent introduction of the LSA test (October 2013). Future research should focus on optimizing matching strategy. The widespread use of the LSA enables performing such a study in the near future, which might demonstrate an added value of the LSA to improve matching strategies.

In all patients, major ABO mismatches lead to significantly reduced 1hCCIs, confirming that ABO-identical platelets should be pursued, especially when no HLA-matched donor is available. However, even major ABO-mismatched, HLA-matched products still result in an estimated 1hCCI of 10.4, which is well above the 7.5 that is considered to be adequate, but considerably lower than the 14.1 after an HLA-matched, ABO-identical transfusion. This is in line with the results of a systematic review of 19 studies among hematologic and oncologic patients, which showed consistently higher increments for ABO-identical platelet transfusions.[11]

To the best of our knowledge, this study is the first to evaluate the current practice for platelet-refractory patients in a large population of patients. A strength of this study is that we were able to adjust for within-patient correlations, as patient characteristics largely influence the effect of platelet transfusions and multiple transfusions per patient could be included. In addition, we selected only the first transfusion at which a patient was exposed to a new foreign antigen because, in most cases, the 1hCCI of a mismatched transfusion determines whether this specific antigen remains acceptable for the next transfusions. We do not expect any bias due to the retrospective nature of this study, as the registry is nationwide and comprises all patients who received an HLA-matched product. The major limitation of this study is that 1hCCIs have not been routinely measured in

all hospitals and were missing in 48% of platelet transfusions. Therefore, the results of this study could be biased. On the other hand, treatment of hematologic disorders follows strict, nationwide protocols, and Sanquin is the only supplier of HLA-matched platelets in the Netherlands. This minimizes the inter-hospital variation to a level that is, in our opinion, unlikely to introduce bias. In many cases of missing 1hCCIs there are some data available on CCIs somewhat longer after transfusion, providing useful information when these CCIs are 7.5 or above. A second reason for bias due to missing 1hCCIs is the degree to which this information is considered to be crucial for selecting donors for subsequent transfusions. In a small proportion of patients, we specifically request careful monitoring of 1hCCIs due to persisting low increments on HLA-matched products. In our experience, this concerns only a small minority of patients with limited influence on the overall effect estimates. Moreover, bias resulting from overrepresentation of this group in the analyses, if any, will underestimate the 1hCCIs observed in patients receiving either HLA-matched or HLA-mismatched products. We are therefore assured that our estimates represent the true effect in the study population to draw valid conclusions from these data.

In conclusion, in the current study we evaluated the HLA matching strategy as used in the Netherlands for HLA-matched platelet support. HLA matching by selecting donors with identical or compatible HLA antigens on a two-digit level results in adequate CCIs. Refractory patients with demonstrated HLA antibodies benefit most from HLA-matched, ABO-identical platelet transfusions, and these should be provided if feasible. In case of insufficient donors, we demonstrated satisfactory 1hCCIs when applying less stringent selection criteria by allowing for HLA mismatches and/or ABO incompatibility. Our study shows that all these matching strategies lead to satisfactory 1hCCIs, even when applied in combination. On the other hand, refractory patients without HLA antibodies do not show any additional benefit from HLA-matched transfusions and should therefore not receive HLA-matched products.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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