Efficacy of HLA virtual cross-matched platelet transfusions for platelet transfusion refractoriness in hematopoietic stem cell transplantation

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Conflict of interest

The authors have disclosed no conflicts of interest.

Short running title

HLA-matched PLT for PTR after HSCT

Word count: 1940words

Abstract

BACKGROUND: Cross-matched platelet (cross-matched PLT) transfusion is effective for immune-mediated platelet transfusion refractoriness (PTR), but is more costly and time-consuming for physical cross-match than using standard PLT units. Recent studies have reported the utility of human leucocyte antigens (HLA) virtual cross-matched PLT (HLA-matched PLT) that is defined as HLA-A/B matched or no antibody against donor-specific antigen. Here, we evaluated the effect of HLA-matched PLT for PTR in post hematopoietic stem cell transplant (HSCT) recipients.

STUDY DESIGN AND METHODS: Our study included a total of 241 PLTs in 16 patients who underwent HSCT at Okayama University Hospital between 2010 and 2017, receiving either HLA-matched or cross-matched PLT. We calculated the 24-hour corrected count increments (CCI-24) to evaluate the effect of PLTs. A CCI-24 ≧4500 was considered to be a successful transfusion.

RESULTS: We analyzed 139 cross-matched PLTs and 102 HLA-matched PLTs. In the immune-mediated PTR, the rate of successful transfusion was 60.5% for cross-matched PLT and 63.4% for HLA-matched PLT ($p = 0.825$). On the other hand, the median CCI-

24 for cross-matched PLT transfusions and HLA-matched PLT transfusions were 1856 and 5824 ($p < 0.001$), with a success rate of 28.1% and 54.1% in cases with non-immune-mediated PTR, respectively ($p = 0.001$).

CONCLUSION: The effectiveness of HLA-matched PLT is not inferior to cross-matched PLT. This result indicates that physical cross-match can be omitted in post HSCT PTR.

Key words: hematopoietic stem cell transplantation, platelet transfusion refractoriness, HLA virtual cross-matched platelet transfusion,

Abbreviations: PLT= platelet transfusion; HLA-matched PLT= HLA virtual cross-matched PLT; HSCT = hematopoietic stem cell transplantation; PTR= platelet transfusion refractoriness; BM = bone marrow; CR= complete response; PBSCT= peripheral blood stem cell transplantation; UCBT= umbilical cord blood transplantation; CB = cord blood; MAC = myeloablative conditioning; RIC = reduced-intensity conditioning; CsA = cyclosporine A; FK = tacrolimus; MTX = methotrexate; SEM= standard error of the mean; VOD= veno-occlusive disease

INTRODUCTION

Transfusion-dependent patients often display platelet transfusion refractoriness (PTR). With PTR, if the platelet count is not restored, the risk of bleeding may cause fatal complications.[1] The causes of PTR fall into two broad categories: non-immune-mediated and immune-mediated. Non-immune factors, including fever, infection, hypersplenism, disseminated intravascular coagulation (DIC), bleeding, and medications, are the major causes (60%–80%) of platelet-refractory cases.[2,3] Included in immune-mediated factors are ABO, human leukocyte antigen (HLA) Class I (mostly HLA-A and HLA-B), and human platelet antigen (HPA) antibodies, causing a minority (10%–25%) of all PTR cases.[2] Cross-matched PLTs are effective for immune-mediated PTR.[4] However, a cross-matched PLT is more expensive and requires greater effort than standard PLT for physical cross-match. A recent report attests to the utility of virtual HLA cross-matched PLT (HLA-matched PLT) that is defined as HLA-A/B matched or excludes cross-reactive groups.[5]

Before undergoing hematopoietic stem cell transplantation (HSCT), patients frequently receive multiple transfusions. As a result, the HLA antibody detected among 10%–15% of cases causes PTR.[6,7] After HSCT, many complications, including infection, bleeding,

and thrombotic microangiopathy (TMA), can cause PTR.[7] Inadequate post-transfusion platelet increment occurs in over 50% of PLTs in patients undergoing HSCT. PTR after HSCT is also associated with early non-relapse mortality and the effect of PLT is critical for prognosis.[8,9] When HSCT recipients with HLA antibody have post PTR, we order cross-matched PLT units consistent with HLA Class I and also confirmed by physical lymphocyte cross-matching. It is difficult, especially after HSCT, to predict the extent of thrombocytopenia; therefore, it is often necessary to order PLT units on the day of PLT transfusion.

While the efficacy of HLA-matched PLT has been reported and used in hematological malignancies[10], the effect of HLA-matched PLT in only HSCT recipients having complex factors, remains fully elucidated. Here, for PTR in post HSCT recipients, we evaluated the effect of HLA-matched PLT.

PATIENTS AND METHODS

We reviewed the records of all patients who underwent HSCT at Okayama University Hospital between 2010 and 2017 to identify 16 patients who received either cross-matched PLT or HLA-matched PLT products after HSCT for hematologic malignancy. All patients had the HLA Class I antibody. There were no patients with the HPA

antibody, and they had all had at least one episode of PTR immediately prior to using cross-matched or HLA-matched PLT products. We recorded the following data for each patient: disease, age, sex, body surface area, HSCT donor source, HLA typing (Class I), HLA Class I antibody screen, WHO Grade 3 to 4 bleeding episodes, complications, death, and platelet-corrected count increment (CCI). We defined non-immune-mediated causes as an episode of fever (≧38 ℃), bleeding (Grade 3 to 4), DIC, infection, TMA, and splenomegaly.

HLA typing test

We performed high resolution typing for PLT donors using PCR-rSSO method with the Luminex system and used the obtained data as "Low resolution data" when we selected the HLA matched donors .[11] For example, we handled A*02:01 and A*02:06 as A2 together.

Physical cross-matching test

Immunocomplex capture fluorescence analysis (ICFA) method with patient's serum and donor lymphocytes is used as a cross-matching test. This is a rapid, simple, and reliable method adopted by Japan Red Cross Blood Centers in Japan .[12]

PLT products supply

We acquired PLT products (cross-matched and HLA-matched units) from the Japanese Red Cross Society. It is required to reserve cross-matched PLT a week before the day of using the product because the registered candidate donor are requested to undergo apheresis. The policy of donor selection is as follows. First, we determine the HLA type and the specificity of the HLA antibody of the patient suffering from PTR with HLA antibody. Next, we determine cross-reactive antigens and permissible antigens for selection of HLA-matched donors, extracting candidates from the registered donor list.

We have a donor pool of 20,000 people with HLA typing data in order to supply cross-matched PLT or HLA-matched PLT for an approximately 100% of patients in our area of Japan. Finally, we select suitable donors from the list based on the convenience of the place of residence, ABO blood type, or current history of blood donation, rather than necessarily selecting in the order of higher HLA compatibility. The donor who accepts the request visits the blood center on the designated day and undergoes apheresis. The collected product is supplied after it is confirmed negative for physical cross-match test. For HLA-matched PLT, we select the product from the post-apheresis inventory or from the pre-apheresis donor list for the day by virtual cross-match using information about

recipient's HLA antibody and HLA typing data of PLT product and supply it without physical cross-match. The definition of HLA-matched PLT in our study is no antibody against donor-specific antigen and as many HLA-A, B matched as possible.

CCI calculation

We performed CCI calculations for all PLT transfusions according to a previous report. [4] We obtained the exact PLT content of each unit from the Japanese Red Cross Society. We calculated the 24-hour corrected count increments (CCI-24) to evaluate the effect of PLTs.

Statistical analysis

We used computer software R (version 3.4.1) to perform the statistical analysis. We present descriptive statistics for variables. We compared categorical variables by means of the Chi-square test or the Fisher exact test. We used the Mann–Whitney U test for continuous variables to compare the groups, when applicable. We determined the relative importance of clinical factors independently influencing the efficacy of platelet

157 transfusion with multivariate linear regression analysis, having previously performed
158 factor selection using stepwise linear regression analysis.
159
160 **RESULTS**
161 Patient characteristics are shown in Table 1. Most patients in our study were female
162 (93.8%). Most cases involved myeloid malignancy and had a non-CR status (75% and
163 68.8%), respectively. Sixteen patients received a total of 241 PLTs, of which 139 PLTs
164 were cross-matched, and 102 PLTs were HLA-matched. We analyzed 84 PLTs in the
165 absence of causes for non-immune-mediated PTR. Under such conditions, the
166 percentage of successful transfusions and the median CCI-24 (60.5% and 6684) for
167 cross-matched PLT were comparable with those for HLA-matched PLT (63.4% and
168 7108) ($p = 0.825$, Figure1, Table 2).
169 Of the 241 transfusions, we analyzed 157 (65.1%) transfusions under situations with
170 non-immune-mediated PTR. When patients had non-immune-mediated PTR, only
171 28.1% for cross-matched PLTs and 54.1% for HLA-matched PLTs were successful
172 transfusions ($p = 0.001$, Figure1, Table 3). The median CCI-24 was 1856 and 5824 for
173 cross-matched PLT and for HLA-matched PLT, respectively ($p < 0.001$, Figure1, Table
174 3). Although neither PLT transfusion was sufficiently efficacious, the HLA-matched

PLT proved to be superior for non-immune-mediated PLT. In the analysis of all transfusions, the median CCI-24 for cross-matched PLT transfusions and HLA-matched transfusions was 2626 and 6137, respectively ($p < 0.001$, Figure1, Table 4). The transfusion success rate was 38.1% for cross-matched PLT and 57.8% for HLA-matched PLT, respectively ($p < 0.001$, Table 4).

We also evaluated factors that influenced the efficacy of PLTs for non-immune-mediated PTR by univariate analysis and multiple linear regression analysis. In univariate analysis, we found disease status, conditioning, splenomegaly, and ABO match to be factors influencing the efficacy of PLT (Table 5). We observed a higher response in HLA-matched PLT, and a lowered incidence of bleeding and splenomegaly episodes by multiple linear regression analysis (Table 6).

DISCUSSION

In our study, we observed a similar response in both cross-matched PLT and HLA-matched PLT for immune-mediated PTR, indicating that cross-matching might be omitted. While, as expected, splenomegaly and bleeding were risk factors for low CCI, HLA-matched PLT was superior to cross-matched PLT in situations with non-immune-mediated PTR.

193 The incidence of PTR in hematology/oncology patients has been reported as being
194 between 7% and 34%.[3,6,13] In previous reports, PTR in HSCT was associated with
195 increased 100-day non-relapse mortality, post-transplant length of hospital stay, the
196 need for intensive care unit admission, and the number of organs affected by severe
197 toxicity.[8] Especially in the case of HSCT, a low platelet count may lead to fatal
198 outcomes and immediate treatment for PTR is required. Once a patient is
199 alloimmunized, both HLA-matched PLT and cross-matched PLT improve platelet count
200 increments.[5,10,14,15]
201 The gold standard in transfusions for PTR remains cross-matched PLT in Japan,
202 although previous reports suggest that HLA and cross-matched platelets are
203 equivalent .[16] Heal et.al. previously reported the percentage of poor CCIs following
204 transfusion of platelets with a positive cross-match ranges between 70% and 100%, and
205 the percentage of adequate CCIs following a negative cross-match ranges from 80% and
206 92% in selected patients without non-immune causes of platelet refractoriness.[17] They
207 also reported the improved CCI found with better HLA compatibility among cross-
208 matched PLTs. [17]
209 Several articles have reported the effectiveness of HLA-matched PLT.[5,18-26]
210 Currently, the sensitivity and specificity of virtual cross-match analysis has undergone

211 remarkable progression. Bub et.al. reported that the new EpHLA/EpVix method of
212 virtual cross-matching has proved to be effective, feasible, fast, and capable of
213 minimizing efforts on donor identification.[19] For patients who received chemotherapy or
214 HSCT, the use of HLA-matched PLT provided equivalent CCI compared to that of
215 cross-matched PLT.[10] These results indicate the effectiveness of HLA-matched PLT to
216 be on par with that of cross-matched PLT in situations involving immune-mediated
217 PTR.
218 The superior CCI of HLA-matched PLT in our current study was difficult to explain.
219 First, we suspected the cause to lie in the effect of differences in HLA compatibility
220 between the two groups. Undeniably, no patient received a platelet unit with specific
221 antigen against which the patient had an antibody. Furthermore, we observed that HLA
222 compatibility of PLT unit and the max MFI of HLA antibody had no influence on
223 transfusion effectiveness in our study (data not shown). Previously, Karlström et al. also
224 reported that both a complete HLA match and an acceptable HLA mismatch based on
225 genomic typing and donor-specific antibody information predicted 86% successful PLT
226 transfusion responses.[18] Second, because previous studies reported the effect of ABO
227 compatibility on platelet transfusion efficacy,[17,27,28] we assessed the influence of ABO
228 compatibility in the two groups. Because platelets express ABH blood group antigens

229 on their surfaces, transfused platelets may be directly affected by ABO antibodies,
230 leading to premature destruction of the transfused incompatible platelets after ABO
231 major-mismatched transfusions. Julmy et.al. reported that, in children, ABO major-
232 mismatched platelets were inferior to those of ABO-identical platelets.[27] In our study,
233 ABO compatibility was an influential factor in univariate analysis; however, in in
234 multivariate analysis it was not significant, although the number of ABO matched or
235 minor mismatched units in HLA-matched PLT units was slightly more than that in
236 cross-matched PLT units. Third, we analyzed the effect of the age of the unit and found
237 no significant difference between cross-matched PLT and HLA-matched PLT.

238 A difference has been reported in CCI depending on the type of stem cell source.
239 There was a higher rate of PTR in patients who received umbilical cord blood
240 transplantation as compared to patients who received peripheral blood stem cell
241 transplantation.[29] Here, we could not assess the effect of stem cell source because the
242 number of patients given cells from each stem cell source was limited, and the variance
243 of CCI-24 between each patient was large.

244 The other limitation of our study was that PLT units were cross-matched PLT units or
245 HLA-matched PLT units, precluding comparison with random PLT units.

In summary, HLA-matched PLT is at least equally useful compared with cross-matched PLT for post HSCT in immune-mediated PTR. These results suggest that we may be able to omit physical cross-matching. HLA-matched PLT may also have superior efficacy for non-immune-mediated PLT. Future research analyzing more cases under non-immune-mediated PTR is required.

Acknowledgments

The authors would like to express their appreciation for the contributions of all the doctors and nurses at Okayama University Hospital.

The authors would like to thank Enago (www.enago.jp) for the English language review.

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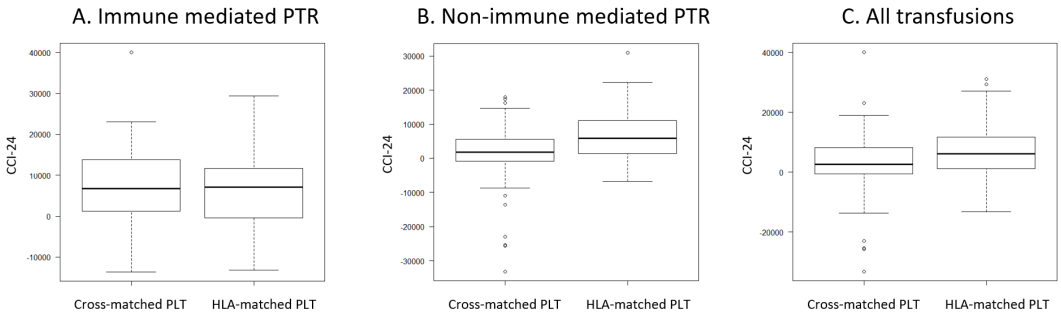
Figure 1. Results of CCI-24 in each situation



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351 Figure 1

352 Comparisons of CCI-24 between cross-matched PLT and HLA-matched PLT in each

353 situation. (A) Under the situations without non-immune mediated PTR (B) Under the

354 situations with non-immune mediated PTR (C) ALL PLT transfusions

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TABLE 1. Patients characteristics

Characteristics	Number of patients
Gender	
Male	1 (6.2)
Female	15 (93.8)
Age, Median [range]	51 [42, 67]
Diagnosis	
Acute lymphocytic leukemia	1 (6.2)
Acute Myeloid Leukemia	6 (37.5)
Myelodysplastic syndromes	6 (37.5)
Myelofibrosis	2 (12.5)
Non-Hodgkin lymphoma	1 (6.2)
Disease status	
Complete response	5 (31.2)
Non Complete response	11 (68.8)
Stem cell source	
Unreated BM	6 (37.5)
Related PBSC	6 (37.5)
Unreated PBSC	2 (12.5)
CB	2 (12.5)
Sex compatibility between donor and recipient	
Match	9 (56.3)
Unmatch	7 (43.7)
Conditioning	
MAC	6 (37.5)
RIC	10 (62.5)
GVHD prophylacxis	
CyA/short-term MTX	5 (31.2)
FK/short-term MTX	11 (68.8)

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TABLE 2. Corrected count increment and the rate of successful transfusion of platelet transfusions used in the absence of causes for non-immune-mediated PTR

Factor	Cross-matched PLT, n=43	HLA-matched PLT, n=41	P-value
CCI-24, median [range]	6684 [-13680, 40081]	7108 [-13155, 29348]	0.717
CCI-24≧4500, n(%)	26 (60.5)	26 (63.4)	0.825

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TABLE 3. Corrected count increment and the rate of successful transfusion of platelet transfusions used under situations caused by non-immune-mediated PTR

Factor	Cross-matched PLT, n=96	HLA-matched PLT, n=61	P-value
CCI-24, median [range]	1856 [-33255, 17910]	5824 [-6726, 31034]	<0.001
CCI-24≧4500, n(%)	27 (28.1)	33 (54.1)	0.001

TABLE 4. Corrected count increment and the rate of successful transfusion of all platelet transfusions

Factor	Cross-matched PLT, n=139	HLA-matched PLT, n=102	P-value
CCI-24, median [range]	2626 [-33255, 40081]	6137 [-13155, 31034]	<0.001
CCI-24≧4500, n(%)	53 (38.1)	59 (57.8)	<0.001

TABLE 5. Únivariate analysis for the search of correlations between each factor and CCI-24

	CCI-24, median[range]	P-value
Disease status		
CR	6595 [-13535, 17489]	<0.001
Non CR	1837 [-33255, 31034]	
Conditioning		
RIC	2359 [-33255, 31034]	0.047
MAC	8140 [-3759, 14581]	
Bleeding		
No bleeding	3203[-25352, 31034]	0.063
Active bleeding	0 [-33255, 22271]	
Splenomegaly		
No splenomegaly	6510[-33255, 31034]	<0.001
Splenomegaly	1238 [-7860, 7911]	
ABO match		
ABO match or minor mismatch	4887 [-13535, 17319]	0.003
Major and Major/minor	1215 [-33255, 31034]	

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TABLE 6. Multiple linear regression analysis of factors influencing CCI of platelet transfusions used under the situation with causes of non-immune mediated PTR

Factor	Coefficients	SEM	P-value
HLA-matched PLT	2,561	1,099	<0.05
Bleeding	-3,514	1,743	<0.05
Splenomegaly	-3,490	1,310	<0.01
Fever(38℃)	-2,150	1,571	0.17
VOD	-1,990	3,202	0.54
Non CR	-1,382	2,231	0.54