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Case Report Open Access

Epitope Matched Platelets: An Effective Way to Provide Platelet Transfusion Support in Platelet Refractory Patients in a Tertiary Care Oncology Centre

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Abstract

Platelet transfusion refractoriness is failure to achieve desired level of platelet counts in patients following platelet transfusions. Immune platelet refractoriness remains a challenging problem in platelet transfusion therapy. Patients who are refractory as a result of HLA alloimmunization are given HLA-matched or cross matched platelets. But the HLA matched donors can be potential candidates for stem cell harvest in future and patients can develop antibodies to minor antigens causing graft rejection. Another alternative is to provide platelets from donors matched at HLA-epitope level. This is based on the concept that, HLA antibodies are produced for epitopes that can be structurally defined as eplets, which are present on different HLA alleles. We report here three patients who responded to HLA-epitope matched platelet transfusions from unrelated healthy donors. Duquesnoy antigen match grade for the three patients were B1X, D and D respectively. Corrected count increment (CCI) within 10-60 minutes of unmatched platelet transfusion were 1600 and 2667 in first patient; 4800 and 3200 in second patient and 1200 and 3200 in third patient on two consecutive occasions. CCI within 10-60 minutes of epitope matched platelet transfusion were 12,750; 21,000 and 12,000 respectively. Therefore, HLA epitope matching is expected to benefit platelet transfusion outcome and increase the number of compatible donors for refractory patients.

Introduction

Platelet refractoriness is defined as the repeated failure to achieve satisfactory responses to platelet transfusions. [1]. Two consecutive platelet transfusions with corrected count increment (CCI) below 7,500 within 10-60 minutes after transfusion is an evidence of refractoriness [2]. The causes of platelet refractoriness can be subdivided into immune and non-immune. Non-immune platelet consumption is associated with fever, sepsis, disseminated intravascular coagulation (DIC), splenomegaly and intravenous antibiotics (especially antifungal drugs such as amphotericin B) etc. Alloimmunization against HLA Class I antigens has remained the major immune cause of refractoriness of thrombocytopenic patients to platelet (PLT) transfusions. As the alloimmunization-induced refractoriness is caused by HLA or human platelet antigens (HPA), different platelet cross-matching methods have been applied to select compatible platelets from the platelet inventory [3-5]. The best approach for an HLA-based platelet transfusion support of refractory patients is matching for compatible antigens determined by screening for HLA antibodies [6]. But the HLA matched donors can be potential candidates for stem cell harvest in future and patients can develop antibodies to minor antigens causing graft rejection. Rooney et al. suggests benefits of triplet matched platelet transfusion in efficient use of limited donor pool. Even though the triplet version of HLA Matchmaker has proven to be clinically useful, it does not provide a complete description of the structural HLA epitope collection. An important consideration is that HLA antigens have multiple epitopes which can be recognized by specific antibodies. Recently, the development of a structurally defined HLA epitope collection is based on stereochemical modelling of crystallized complexes of antibodies with different protein antigens [7]. Many eplets represent short linear sequences identical to triplets but others have residues in discontinuous sequence positions that congregate on the molecular surface. Eplets are polymorphic amino acid residues on human leukocyte antigen (HLA) molecules and are considered as essential components of HLA epitopes recognized by antibodies. Therefore, the eplet version of HLA Matchmaker represents a more complete collection of HLA epitopes and provides an elaborate assessment of HLA compatibility.

Case Details

We hereby present 3 patients of haematological malignancies with immune cause of platelet refractoriness showing positive response to epitope matched platelets. Non-immune causes of platelet refractoriness like fever, sepsis, disseminated intravascular coagulation (DIC), splenomegaly and intravenous antibiotics (especially antifungal drugs such as amphotericin B) were ruled out by checking the electronic medical records.

Case 1

A 22-year-old male, diagnosed with Acute Myeloid Leukemia (AML) developed immune cause of platelet refractoriness after Induction chemotherapy in July, 2016. He was transfused with 14 SDP (Single donor platelet), 12 RDP (Random donor platelet) at an interval of 7-15 days. CCI within 10-60 minutes of platelet transfusion was 1,600 and 2,667 on two consecutive occasions. Epitope based HLA matching of the patient from an unrelated platelet donor inventory led to identification of a donor with HLA class I mismatch eplet 12. The eplet matched platelet transfusion resulted in CCI of 12,750 (Table 1).

Case 2

A 33-year-old female, diagnosed with AML, M2 developed

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immune cause of platelet refractoriness after 1st HIDAC (high dose chemotherapy) in July, 2016. She was transfused with 11 SDP, 8 RDP at an interval of 7-15 days. CCI was 4,800 and 3,200 within 1 hour of platelet transfusion on two consecutive occasions. Patient showed no improvement even after multiple platelet transfusions at frequent intervals. Epitope based HLA matching of patient with unrelated donor showed HLA class I mismatch eplets 8 which resulted in CCI of 21,000 (Table 2).

Case 3

A 41-year-old, female diagnosed with AML developed immune cause of platelet refractoriness after induction chemotherapy. She was transfused with 14 SDP, 12 RDP at an interval of 7-15 days. CCI was 1,200 and 3,200 within 1 hour of platelet transfusion on two consecutive platelet transfusions. Epitope based HLA matching of patient done with unrelated donor showed HLA class I mismatch eplets 9 which resulted in CCIof 12,000 (Table 3).

Discussion

Human leukocyte antigen (HLA) mismatches are important risk factors for HLA alloimmunization and thus cause an increase in frequency of platelet transfusions. It is known that HLA antibodies recognize epitopes rather than antigens. Therefore, it has become imperativethat donor-recipient compatibility should be assessed at the epitope level [8]. A computer algorithm called HLA Matchmaker considers each HLA antigen as a series of small configurations of polymorphic residues namely eplets. By quantifying the total number of antibody-accessible eplet mismatches (EMMs) between patient and donor, the likely success of the donor-recipient mismatch can be estimated [9].

The triplet algorithm has helped to define the relative immunogenicity of mismatched triplets by analysis of serologic reactivity patterns of highly allosensitized patients. The program can identify the subset of highly immunogenic mismatches (HIMMs) [10]. Validation of this algorithm previously has been done for the prediction

Donor alleles	Patient alleles	Grading system of Duquesnoy [12]	Matched eplets	Mismatched eplets	CCI within 10-60 minutes
A*01:01	A*01:01	**B1X**	All	None	12750
A*11:01	A*11:01		All	None	
B*40:01	B*27:01		9	12	
B*57:01	B*57:01		All	None	
Matched eplets with B*40:01: 9Y, 11 AMR, 62RE, 82LRG, 142TI, 151RV, 163E, 184P, 193PI					
Mismatched eplets (eplets present in donor while absent in patient) with B*40:01: 147I, 41T, 44RKE, 65QIT, 70TNT, 73TN, 76ERN, 113HN, 116S, 144SQR, 177DT, 180E					
B1X: 4 antigens detected; 3 HLA antigens identical and 1 cross reactive					
PRA: 23%					
Antibody specificity: A*02:01, A*02:02, A*02:05, A*69:01, A*02:03, A*68:02,A*68:01, B*56:01, B*15:01, B*50:01, B*15:16, B49:0, B*35:08, B*15:03, B*15:18, B*35:01, B*67:01, B78:01					

Table 1: Mismatch eplets between Patient and donor alleles and correlation with CCI.

Donor alleles	Patient alleles	Grading system of Duquesnoy	Matched eplets	Mismatched eplets	CCI within 10-60 minutes
A*33:01	A*11:01	**D**	All	None	21000
A*33:01	A*33:01		All	None	
B*27:01	B*35:01		8	8	
B*58:01	B*41:01		14	5	
Matched eplets with B*27:01: 9H, 62RE, 116D, 142TI, 144TQR, 151RV, 184P, 193PI					
Mismatched eplets with B*27:01: 44REE, 65QIA, 70AKA, 73TN, 76ERT,82ALR, 113YH					
Matched eplets with B*58:01: 9Y, 11AMR, 44RTE, 65RNA, 94I, 113HD,116S, 131S,142TI, 144TQR,151RV, 163L, 184P, 193PV					
Mismatched eplets with B*58:01: 62GE, 70ASA, 73TN, 76ERI, 82ALR					
D: All other ≥ 2 antigen mismatches					
PRA: 8% **Antibody specificity:** A*66:01, B*08:01, B*46:01, B*48:01, B*37:01, B07:03, B*51:01, C*08:02					

Table 2: Mismatch eplets between Patient 2 and donor alleles and correlation with CCI.

Donor alleles	Patient alleles	Grading system of Duquesnoy.	Matched eplets	Mismatched eplets	CCI within 10-60 minutes
A*11:01	A*01:01	**D**	All	None	12000
A*11:01	A*03:01		All	None	
B*13:01	B*57:01		9	9	
B*15:01	B*58:01		12	6	
Matched eplets with B*13:01: 9Y, 44RMA, 73TN, 82ALR, 131S, 142TI, 151RV, 184P, 193PI					
Mismatched eplets with B*13:01: 41T, 62RE, 65QIT, 70TNT, 76ERT, 113HN, 116L, 144TQL, 163E					
Matched eplets with B*15:01: 9Y, 11AMR, 44RMA, 82LRG, 113HD, 116S, 131S, 142TI, 144TQR, 163L, 184P, 193PI					
Mismatched eplets with B*15:01: 62RE, 65QIT, 70TNT, 73TS, 76ERN, 151RE. **D:** All other ≥ 2 antigen mismatches					
PRA: 85%					

Table 3: Mismatch eplets between Patient 3 and donor alleles and correlation with CCI.

Patient Number	Occasions	Pre transfusion platelet count before eplet matched platelet transfusion	Post transfusion platelet count before eplet matched platelet transfusion	No of platelets transfused (Yield of platelet transfused) ($\times 10^{11}$)	CCI after unmatched SDP transfusion and (PPR *)	Pre transfusion platelet count after eplet matched platelet transfusion	Post transfusion platelet count after eplet matched platelet transfusion	No of platelets transfused ($\times 10^{11}$) (Yield of the platelet bag)	CCI after eplet matched SDP transfusion and (PPR*)
Patient 1	Occasion 1	2000	6000	4	1600 (4%)	4000	19000	2	12750 (30%)
	Occasion 2	4000	9000	3	2667 (6.7%)				
Patient 2	Occasion 1	4000	13000	3	4800 (11.7 %)	3000	29000	2	21000 (50%)
	Occasion 2	3000	11000	4	3200 (7.7%)				
Patient 3	Occasion 1	3000	6000	4	1200 (2.6%)	4000	19000	2	12000 (26%)
	Occasion 2	5000	11000	3	3200 (7%)				

Corrected count increment (CCI)= $\frac{\text{(Post transfusion platelet count- Pre transfusion platelet count) (/uL)} \times \text{BSA (body surface area) } (m^2)}{\text{No of the platelets transfused } (\times 10^{11})}$

Body surface of these patients were between 1.6 m^2 to 1.7 m^2

Percent Platelet recovery (PPR)= $\frac{\text{Estimated body volume (ml)} \times \text{Platelet count increment} \times 100}{\text{No of the platelets transfused } (\times 10^{11})}$

* : PPR mentioned in the brackets () in column 6 and column 10

Table 4: Corrected count increment (CCI) and percent platelet recovery (PPR) before and after eplet matched platelet transfusions.

of kidney transplant survival [11,12]. It is hypothesized that platelet donors matched at the epitope level must be considered compatible, even if donor HLA antigens appear mismatched by conventional criteria. The number of mismatched eplets (EMMs) has been shown to correlate with the CCIs of PLT-refractory patients; with lesser the mismatch more is the CCI [9]. It was observed in the above three cases, that epitope matched platelet transfusions showed a significant increase in CCI (Table 4).

Conclusion

HLA epitope matching approach in immune refractory patients can have very impressive 1 hour CCI results. It can be expected to benefit platelet transfusion outcome and increase the number of compatible donors for refractory patients. Because the HLAMM algorithm provides a quantitative method to measure donor-recipient mismatches, using this method for donor selection could expand the available donor pool while improving PLT transfusion outcomes.

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