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Platelet Refractoriness Associated with Platelets Stored in Platelet Additive Solution

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CONFLICT of INTEREST: None

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The randomized prospective trial EFFIPAP (Evaluation of the Efficacy of Platelets Treated with Pathogen Reduction Process) reported a 54% rate of platelet (PLT) transfusion failures (24-hour corrected count increment [CCI] < 4.5) with pathogen-reduced (PR) PLT (PAS/PR-PLT), which was 40% higher than PLTs stored in plasma (PLS-PLT; 31%).[1] Although less dramatic, PLT stored in platelet additive solution without PR (PAS-PLT) also showed a shortened survival and higher rate of transfusion failures (40%).[1] An older randomized study also found a small but significant decrease in post-transfusion PLT response and survival with PAS-PLT compared to PLS-PLT.[2]

We present three patients with PLT refractoriness to PAS-PLT and PAS/PR-PLT, who were successfully managed with standard plasma PLT concentrates (PLS-PLT). All 3 patients underwent a formal PLT refractory consult that included a review of their medical history, medications, physical exam and radiology findings, transfusion history, PLT ABO type, and laboratory studies including 1-hour post-transfusion PLT counts and HLA antibody testing (%PRA): PLT crossmatching was performed for two patients. To compare the transfusion response by PLT type, the absolute 1-hour PLT increment and CCI for six weeks or hospital discharge were calculated for each patient and compared by student t-test.

Our first patient was a 16-year-old, atopic, group O male with Kostmann's congenital neutropenia, who was admitted for an allogeneic, hematopoietic stem cell transplant (HSCT) from an HLA-matched, ABO-incompatible (ABOi) sibling donor (group A; 10/10 HLA). He had no history of blood transfusion prior to his HSCT and was negative for HLA antibodies. He was transplanted with plasma- and RBC-depleted, cryo-preserved bone marrow and cord blood, which was complicated by an anaphylactic reaction to the HPC-cord blood infusion. Given his history of atopy and recent infusion reaction, PAS-PLT were specifically ordered from the blood supplier, who had just begun offering PAS-PLT on a limited basis. On transplant day +10, the patient received 3 prophylactic PLT transfusions. He initially received two sequential group O PAS-PLT, from two different donors, with only a 1K/μL increase in PLT count per unit (12K/μL to 14K/μL; CCI 0.45). Pre-pooled PLS-PLT were provided for his third transfusion on day +10 with an appropriate PLT increment (14K/μL to 37K/μL; CCI=13) but complicated by a mild allergic reaction. For the remainder of his admission, he was

supported with plasma-reduced, saline-suspended apheresis PLS-PLTs with no further transfusion reactions and improved CCIs (Table 1, Fig. 1A), despite the adverse impact of washing on platelet recovery.[3] Because the patient responded well to PLS-PLTS, no platelet crossmatching or repeat HLA testing was pursued.

The second patient was a 33-year-old, group A female with chronic myelogenous leukemia who was readmitted six weeks after an allogeneic, ABOi (O donor), HLA-matched unrelated donor [MUD] HSCT for new pancytopenia despite molecular evidence of engraftment (100% donor). In addition, she had new PLT refractoriness with documented PLT decrements to three PAS/PR-PLT (CCI -0.5). She had no palpable splenomegaly or non-immune etiologies for refractoriness. She was negative for HLA antibodies pre-HSCT and upon re-testing (class 1 PRA=0%, x 2). She was crossmatch-compatible with 14/14 PLT donors. Upon review, it was noted that she had responded well to PLS-PLT during her prior HSCT but had only developed refractoriness with PAS-PLT and PAS/PR-PLT during this admission. She was given a trial of apheresis PLS-PLT with an appropriate transfusion response (Table 1, Fig. 1B). She was maintained on PLS-PLT with good responses until her final admission and death from infection and recurrent leukemia.

The third patient was a 54-year-old, group B female with myelodysplastic syndrome, who was admitted for an ABOi (O donor), MUD HSCT. She had no evidence of HLA antibodies pre-HSCT (PRA=0%, x 2) and had historically responded well to PLS-PLT transfusion at an outside facility. In contrast, she was immediately refractory to PAS-PLT and PAS/PR-PLT (CCI 2.7) at HSCT admission (day-7). Repeat HLA testing was again negative (PRA=0%) and she was crossmatch-compatible with 14/14 PLT donors. She was trialed with PLS-PLT with a two-fold increase in absolute PLT increment and CCI (Table 1, Fig 1C).

In summary, we documented specific refractoriness to PAS-PLT and PAS/PR-PLT, but not PLS-PLT, in three ABOi allogeneic HSCT recipients. Interestingly, Yale recently reported an increase in PLT alloimmunization testing and PLT refractoriness after adoption of PAS/PR-PLT.[4] The EFFIPAP trial, which included PLT refractoriness and HLA alloimmunization as secondary measures, may provide further data.[1] We suspect refractoriness in our cohort reflects a combination of patient immune dysregulation, increased macrophage

activation and acquired PLT senescent/neoantigen expression.[5] A trial of PLS-PLT may be indicated in patients with inexplicable non-immune PLT refractoriness following transfusion of PAS- or PAS/PR-PLT.

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Figure 1 Legend.

The corrected count increments (CCI) for transfusions with a 1-hour post-transfusion PLT count. Results plotted over time by PLT-type infused: PLS-PLT (—•—) and PAS-PLT or PAS/PR-PLT (—o—).

TABLE 1. Transfusion Response by Platelet Product

	PAS-PLT and PAS/PR-PLT[a]				PLS-PLT[b]				PLS-PLT vs PAS-, PAS/PR-PLT	
			Transfusion Response				Transfusion Response			
Patients	**No. Units**	**ABO Type**	**Increment[c] (median)**	**CCI[d] (median)**	**No. Units**	**ABO Type**	**Increment[c] (median)**	**CCI[d] (median)**	**Increment (P)[e]**	**CCI (P)[e]**
Case 1[b]	2	O	1 ± 0 K/μL (1)	0.45 ± 0 (0.45)	5	O	15 ± 3.8 K/μL (18.5)	8 ± 1.6 (8.3)	0.024	0.00067
Case 2	3	A	-1.7 ± 2 K/μL (-1)	-1.4 ± 1.2 (-0.5)	13	A	17.4 ± 1.2 K/μL (19)	8.1 ± 0.6 (8.8)	<0.0001	<0.0001
Case 3	4	B	5 ± 0.7 K/μL (5.5)	2.5 ± 0.4 (2.7)	5	B	13.2 ± 3 K/μL (11)	6 ± 0.8 (5)	0.049	0.009
All Cases	9	A,B,O	1.9 ± 1.1 K/μL (1)	0.78 ± 0.7 (0.45)	23	A,B,O	16 ± 5.9 K/μL (18.5)	7.5 ± 0.4 (8.3)	<0.0001	<0.0001

a. PAS-C was the platelet additive solution for PAS-PLT and PAS/PR-PLT.

b. PLS-PLT included pre-pooled, whole blood derived platelets (5 units group O/pool; n=1) and single donor apheresis (case 1; n=4). Cases 2 and 3 received single donor apheresis PLT only.

c. Absolute PLT increment at 1-hour post-transfusion (post – pre PLT count; K/μL). Results reported as mean ± SE, (median).

d. CCI, corrected count increment at 1-hour post-transfusion ([post – pre PLT count] x patient size (m^2) / no. PLT transfused). Results reported as mean ± SE, (median).

e. Student t-test.

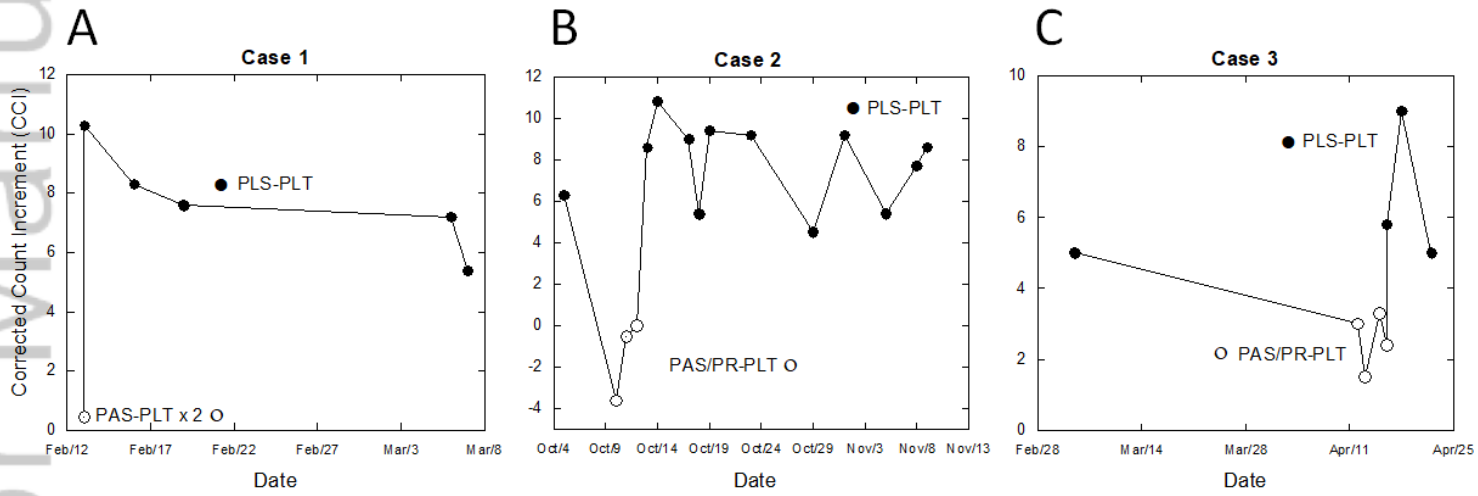

Figure 1 revised.tif