Platelet Transfusion Refractoriness

By Kevin Burns, MD, Medical Director, BloodSource, and Assistant Clinical Professor, UC Davis School of Medicine (UCDSM); Chris Gresens, MD, Senior Medical Director and Vice President of Global Medicine, BloodSource, and Clinical Professor, UCDSM; and the Scientific Publications Committee, America’s Blood Centers

BACKGROUND
Platelet transfusion refractoriness (PTR) is defined as the occurrence, at least twice, of a poor incremental platelet count response associated with standard-dose platelet transfusions. Its optimal diagnosis and management require prompt recognition of the problem, determination of its most likely cause(s), and application of effective therapy.

RECOGNITION AND DIAGNOSIS
Identifying a poor incremental change in platelet count that may be associated with PTR is accomplished by testing a patient sample that ideally is obtained 10-60 minutes after completion of the transfusion. Because refractoriness often develops unexpectedly, post-transfusion platelet counts should be measured following all platelet transfusions.

Two methods may be used to evaluate the post-transfusion platelet count increment: (1) the percentage platelet recovery (PPR) and (2) the corrected count increment (CCI). Each compares the incremental change in platelet count relative to the dose of platelets transfused. The PPR does this in the context of the patient’s estimated blood volume (EBV), while the CCI does this relative to the patient’s body surface area (BSA). The formulas used to calculate the PPR and CCI are found immediately below. A PPR of < 20-30% and/or a CCI of less than 5,000-10,000 µL within 10-60 minutes of transfusion is considered a poor response. Moreover, an absolute post-transfusion increment of < 5,000-10,000/µL will almost always be considered a poor response.

PPR = Actual Increment ÷ Expected Increment
(Where Actual Increment = Difference between post- and pre-transfusion platelet counts (x 10^9/L); Expected Increment = n ÷ EBV (in L); and n = total number of platelets transfused (x 10^11))

CCI = [Actual Increment x BSA] ÷ n
(Where BSA is expressed in m²; Actual Increment is expressed as platelets per µL; and n = total number of platelets transfused)

CAUSES
PTR is generally categorized as either immune- or non-immune-mediated. Immune-mediated PTR can be caused by allo- and/or autoantibodies reacting against donor antigens and is associated with the rapid removal of transfused platelets from the circulation. The most common causes of alloimmune-mediated PTR are recipient antibodies against: (1) the HLA Class I antigens HLA-A and HLA-B, (2) the human platelet antigens (HPA), and (3) the A and B red cell antigens present on platelets.
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Non-alloimmune-mediated causes for PTR are diverse. The most common include: (1) fever, (2) sepsis, (3) splenomegaly, (4) disseminated intravascular coagulation, (5) graft-versus-host-disease, (6) vasculitis, (7) immune thrombocytopenic purpura, (8) veno-occlusive disease, and (9) numerous medications (e.g., heparin, amphotericin, vancomycin, and ciprofloxacin).

**FURTHER EVALUATION AND MANAGEMENT**

Once a patient is shown to be refractory to platelets, a careful evaluation of his/her current medical condition, medications, transfusion/transplant history, and pregnancy history (since the latter two can lead to HLA/HPA alloimmunization) is important to determine the likely etiology. Appropriate management of the refractoriness will depend not only on its cause(s) but also on whether the patient is experiencing active bleeding and/or requires an urgent invasive procedure. It is important to keep in mind that PTR management strategies applicable to prophylactic platelet transfusions may be inadequate when managing more immediate/life-threatening situations.

PTR due to non-immune causes is best managed clinically by addressing the underlying condition(s). For instance, if the patient is septic, controlling the infection will often lead to improved platelet transfusion responses. By contrast, immune-mediated PTR is best managed by identifying the responsible antibodies and using this information to guide the selection of suitable units.

Patients with PTR suspected to be caused by alloantibodies should receive fresh-as-possible, ABO identical platelets (if available) while awaiting testing for: (1) their HLA-A and -B phenotypes, (2) the presence/specificity of HLA-A/B antibodies (including a "calculated percent reactive antibody" [cPRA], which in this case corresponds to the expected prevalence of incompatible platelet donors), and/or (3) their platelet crossmatch profile.\(^4,5\) When evidence exists that the patient is alloimmunized against HLA-A/B, the first two tests allow for the selection of "HLA-matched" and "HLA antigen-negative" platelet products, respectively. The platelet crossmatch, by contrast, allows for rapid selection of compatible products from available inventory for PTR patients having either HLA or HPA alloantibodies.

Experts in this field have differing opinions about which kind of special platelet product – i.e., HLA-matched, HLA antigen-negative, or crossmatch-compatible – is best and under which circumstances to use each. Suffice it to say that all have their respective advantages and disadvantages. For instance, an HLA-matched platelet product that corresponds perfectly to all four of the patient’s HLA-A/B antigens, if available, is very suitable when the PTR is suspected to be caused only by HLA class I alloantibodies (as is seen in the great majority of immune-mediated cases). The drawbacks of such a product, however, are that it: (1) sometimes can be difficult to obtain (due to the extensive heterogeneity of the HLA system), and (2) does not predict product compatibility for patients whose refractoriness is due to non-HLA antibodies. The use of antigen-negative products that lack the HLA-A/B antigens against which the patient has been sensitized can substantially expand the availability of products from the HLA – but not the HPA – perspective; while the platelet crossmatch can be used to obtain platelet products that are HLA- and HPA-compatible. Moreover, even though the platelet crossmatch is often less sensitive than commonly used HLA antibody testing methods, its employment can speed up the process by which special products are obtained (at least, when compatible products are available in the general inventory) – i.e., given that it technically can be performed on donor units within hours after receipt of a patient’s sample. This is opposed to the longer time that often is required to obtain HLA-matched and/or HLA antigen-negative products.

Figure 1 provides one schema by which special platelets can be selected for PTR patients. There are also other excellent published resources in this area.\(^4,5\)

When PTR patients, irrespective of the mechanism behind their refractoriness, present with life-threatening bleeding it may be necessary to use additional therapies. For patients with concomitant anemia, the transfusion of red blood cells (RBCs) may be beneficial, as an increased RBC mass helps to localize platelets to the endothelial lining.\(^4\) Some experts recommend that greater attention also be paid to other possible defects of hemostasis, which may be treatable via the transfusion of non-platelet blood products (e.g., plasma and/or cryoprecipitate) and/or the administration of suitable pharmacologic agents (e.g., antifibrinolytic agents\(^4\)). Other approaches that have unclear benefit but have been attempted for PTR patients with unremitting bleeding include the targeted use of: (1) large boluses of platelets (e.g., two apheresis units at a time), (2) "platelet drips" (i.e., a near-constant flow of small quantities of platelets, such as one-half apheresis unit every 4 hours), (3) intravenous immune globulin, (4) recombinant factor VIIa, and (5) thrombopoietin receptor agonists (e.g., romiplostim).\(^3,6-8\)

Lastly, all PTR patients deserve the consultative support of a suitable specialist, such as a hematologist or transfusion service medical director, as the care of these patients – especially when they are bleeding – can often be challenging.\(^4\)
Figure 1: Platelet Selection for Patients Suspected to Have Alloimmune PTR

Legend: Ab = Antibody; Ag = Antigen; ID = Identification; Plts = Platelets.
Notes: (1) The expression, "HLA-selected" units, indicates either HLA-matched or HLA-Ag-negative Plts; (2) the cPRA should be repeated periodically (e.g., monthly)^4,5 and (3) keep in mind that some experts favor earlier use of crossmatch-compatible Plts than is necessarily conveyed by this diagram.^5

References

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