A novel strategy for the screening for platelet refractoriness: prospects and limitations

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Over the last decades the progressive increase in platelet use has coincided with increasingly aggressive myelosuppressive therapy for malignancies or allogeneic hematopoietic stem cell transplantation. The US National Marrow Donor Program predicts a doubling in allogeneic transplants between 2010 and 2015[1]. More than three million Brazilian donors were registered in the Bone Marrow Donors Worldwide program by 2010[2]. Together, it is anticipated that there will be a continuing growth in the number of allogeneic transfusions. Although platelets were identified over 100 year ago, data accumulated from the last ten years has provided a boost of novel information on platelet biology, and hope for the development of therapy to improve platelet production and survival[3,4].

Current data suggest that platelets emerge from the tips of the proplatelet extension of mature megakaryocytes, and individual platelets may be capable of dividing in the circulation[3]. The identification of thrombopoietin, the primary cytokine required for normal numbers of marrow megakaryocytes and circulating platelets, resulted in the generation of its recombinant derivatives, now used to minimize the duration of thrombocytopenia. Interleukin-11 the only US Federal Food and Drug Agency (FDA) approved drug to treat thrombocytopenia has a limited effect on platelet numbers after intensive myelosuppression. Other cell-based therapies, such as the generation of megakaryocytes and the use of human embryonic/mature pluripotent hematopoietic precursors, raise the possibility of a future supply of platelets[1]. To date, the platelet products available for transfusion are based on platelet concentrates from whole blood or platelet apheresis. The main complication in the use of platelets is the development of alloantibodies that precludes the improvement of severe thrombocytopenia, which is associated with increased morbidity and mortality[5,6].

Platelet transfusion refractoriness (PTR) is characterized by the lack of adequate post-transfusional platelet increments, with the underlying mechanisms being due to immune and non-immune pathologies[4,6]. The latter comprises the large majority (~70-80%) of PTR cases. Platelet alloimmunization is the result of both the donor product transfused and the immune status of the recipient. Platelets express a number of antigens that have been shown to influence post-transfusion counts and platelet survival; these include ABO, human leukocyte antigens (HLA) and human platelet antigens (HPA). Primary immunization against HLA-antigens, which are also expressed in other cells, is caused mostly by contaminating leukocytes in platelet products; HPA-specific immunization is less frequent.

The management of alloimmune PTR is clinically challenging and without consensus on the ideal therapeutic approach[6]. Thus, it is highly attractive to develop preventive strategies to minimize the risk of PTR and to develop diagnostic and screening tests to assess the risk of platelet alloimmunization and to guide the most appropriate therapy. Currently, clinically suspected PRT is confirmed by using a series of laboratory tests such as those listed in Table 1[4,6]. There is no clear gold standard, and the goal is to determine a panel-reactive antibody (PRA) score in terms of the percentage of positive tests in the panel and their specificity towards the antigen. The agreement of different tests in detecting HLA antibodies varies considerably depending on the antigen source and purity, specific technical design and laboratory experience.

In this issue of the Revista Brasileira de Hematologia e Hemoterapia, Bub et al. sought to determine whether screening for PTR using a simplified method based on the flow cytometry immunofluorescence test (FC-PIFT) could be advantageous compared to standard tests using anti-HLA antibody assays[7]. The results showed an overall accuracy of the FC-PIFT of 80%, with sensitivity of 86% and specificity of 75%, and with a negative predictive rate of 86%. These results were comparable, yet not identical, with the data using anti-HLA antibody tests. The main concern is the relative discrepancy of FC-PIFT positive/anti-HLA negative results that will require further tests to determine whether these findings represent the relative rare HPA-restricted or non-clinically relevant antibodies. The limited number of patients tested also imposes limitations on the overall impact of these findings. Nevertheless, this initial study has the potential to provide an alternative screening detection method for clinically relevant

Conflict-of-interest disclosure:
The author declares no competing financial interest

Submitted: 6/24/2013
Accepted: 6/28/2013

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DOI: 10.5581/1516-8484.20130065

Table 1 - Tests for the diagnosis of anti-HLA or anti-HPA antibodies related to platelet transfusion refractoriness

Assay	Target	Comments
Lymphocytotoxicity test (LCT)	HLA	Only detects cytotoxic antibodies, technically complex
Platelet immunofluorescence test (PIFT)*	HLA and HPA	
Lymphocyte immunofluorescence test	HLA	Detection by flow cytometry is preferable
Antigen capture ELISA*	HLA	
Monoclonal antibody specific immobilization of platelet antigen (MAIPA)	HPA or HPA-HLA	The most sensitive for HLA alloantibodies
Solid-phase red cell agglutination test	HLA-HPA	
Multiple flow cytometric bead assays*	HLA	

HLA: human leukocyte antigens; HPA: human platelet antigens; ELISA: enzyme-linked immunosorbent assay

* Methods used in some or in all samples in the report by Bud et al. as standard for anti-HLA alloantibodies.

platelet alloantibodies. It is possible that selecting a high-risk population for PTR using a simplified and fast methodology may be an attractive strategy. Notably, studies in the Brazilian pediatric and adolescent population are desired to define the best approach to recognize PTR[8].

Finally, the cost assessment of an intermediary test also needs to be taken into account. Although the total cost of a platelet transfusion procedure is unclear, it is estimated that a standard clinical situation (i.e. no anticipated platelet refractoriness) in the US could range from ~470 to 760 dollars[9]. The cost in the Brazilian public health systems is unknown. Thus, in patients with a high risk of PR, the costs of suboptimal transfusions (not properly tested) and the delay in restoring hemostasis all may favor the use of additional tests to improve the most beneficial platelet product to a specific patient population.

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