blood® commentary

CLINICAL TRIALS AND OBSERVATIONS

Comment on Marsh et al, page 310

Matching epitopes in platelet refractoriness

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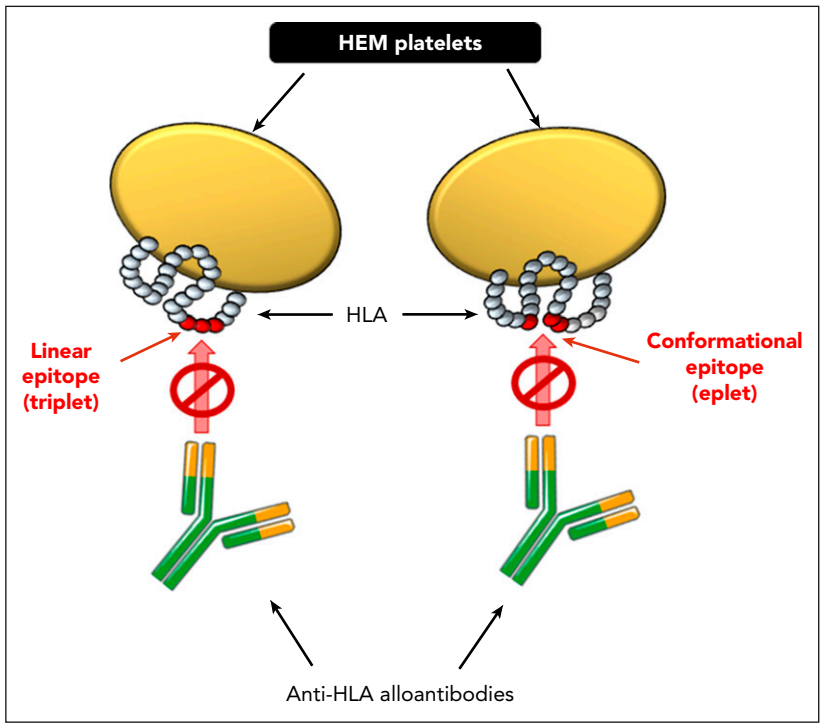
In this issue of *Blood*, Marsh et al report that, in a prospective, randomized, noninferiority trial, HLA epitope-matched (HEM) platelet transfusions are not worse than HLA standard antigen–matched (HSM) platelet transfusions for HLA alloimmunized patients with platelet refractoriness.[1]

Platelet refractoriness is a major clinical problem that remains challenging and very costly to manage. HEM platelet transfusions are less expensive and require fewer resources. The authors suggest that this very practical approach should be considered a promising alternative approach for managing platelet refractoriness.

It wasn't until around 1970 that platelet transfusions were routinely administered in clinical practice for treating patients with thrombocytopenia. This was soon followed by the emergence of alloimmunization to platelet antigens and resulted in platelet refractoriness. Platelet refractoriness is defined as a lack of adequate posttransfusion platelet count increments (PCIs) after multiple transfusions and is associated with increased bleeding risk and reduced survival. The biological mechanisms underlying platelet refractoriness are still incompletely understood, but both immune and nonimmune factors have been implicated.[2] To date, research has predominantly centered around immunologic platelet refractoriness, which occurs in about 4% to 8% of platelet transfusion recipients. In these patients, alloantibodies to platelet antigens (HLA, and to a lesser extent, human platelet antigen 1) have been associated with the destruction of transfused platelets.[3] Platelet opsonization by these alloantibodies subsequently results in platelet clearance by splenic macrophages. Recently, it was demonstrated that a proportion of anti-HLA antibodies from patients with refractory thrombocytopenia could induce FcγRIIa-dependent platelet activation, which may enhance platelet phagocytosis by macrophages.[4] Conversely, genetic variation in FcγRs was recently shown to have no influence on the chance of developing platelet refractoriness.[5] The complement cascade may also play an important role in the clearance of platelets, because anti-HLA antibodies can activate the classical complement pathway on platelets.[6] Adding to the complexity, immunologic platelet refractoriness can also be induced by $CD8^+$ T cells in the absence of antiplatelet alloantibodies.[7]



HEM platelet transfusions in HLA alloimmunized patients with platelet refractoriness. Matching at the epitope level occurs by characterizing short sequences of amino acids from linearly consecutive (left; triplet) or discontinuous and spatially close (right; eplet) amino acid residues of the HLA molecules. HEM platelets are expected to not be targeted by pathogenic donor-specific anti-HLA alloantibodies and consequently to not undergo antibody-mediated phagocytic internalization, allowing platelet counts to increase posttransfusion.

Although more research is needed to further clarify the biological mechanisms, clinical management of platelet refractoriness due to HLA alloimmunization remains very challenging. The main tactics include selection of HLA-identical platelet donors for transfusions that are negative for the HLA antigen(s) that correspond to the detected pathogenic anti-HLA antibodies, or of platelets for transfusion that are crossmatch negative.[3]

These strategies require a large HLA-typed donor pool (~10 000 typed donors), and even then, there is no guarantee that full matching for patients with broad immunization or with rare haplotypes will be achieved. In addition, these approaches are time-consuming and expensive. Other strategies that have been suggested but which require further validation include the use of acid-treated platelets[8] or the use of platelets with consistently low expression of specific HLA class I antigens such as HLA-B8, -B12, or -B35 despite HLA mismatches.[9] Instead of matching at the antigen level (HSM platelets), it has been hypothesized that it may be more feasible to match at the epitope level (HEM platelets), which takes the characterization of short sequences of amino acids from linear or discontinuous regions of the HLA molecule into account (see figure). This approach may be more efficient because it would circumvent the need to maintain a large HLA-typed donor pool and reduce the costs. Indeed, HEM platelet transfusions have previously been described to improve PCIs. However, all of these studies have been retrospective and they lacked clinical outcomes (Marsh et al, supplemental Table 1). Therefore, Marsh et al undertook the first prospective, randomized, double-blind, noninferiority, crossover trial directly comparing HEM vs HSM platelet transfusions in 49 alloimmunized thrombocytopenic patients (acute myeloid leukemia, n = 26; aplastic anemia, n = 14; myelodysplastic syndrome, n = 9). Platelet refractoriness was defined as failure to achieve a 10-minute to 1-hour posttransfusion PCI of $>5 \times 10^9$/L on 2 successive occasions, using ABO-compatible fresh platelets <72 hours old. The patients received up to 8 prophylactic HEM and HSM platelet transfusions that were randomly administered. In the study, 219 adequate platelet transfusions were evaluated (HEM, n = 107; HSM, n = 112). The primary outcome of the trial was 1-hour posttransfusion PCI. Importantly, no significant differences were observed in the 1-hour PCI posttransfusion between the 2 groups. HEM platelet transfusions were concluded to be noninferior to HSM platelet transfusions. Furthermore, there were no differences in the secondary outcomes of bleeding events, platelet counts, and transfusion requirements. It was also found that for every additional 1-epitope mismatch, the probability of an adequate PCI decreased by 15%. One limitation of the study, however, is the relatively small number of patients who received at least 8 evaluable transfusions of 4 HSM and 4 HEM platelet transfusions (n = 14 of 49 randomly assigned patients).

In conclusion, Marsh et al address an important issue and significantly push the field forward by conducting the first prospective randomized controlled study of HEM platelet transfusions. They find HEM platelet transfusions to be no worse than HSM platelet transfusions in increasing posttransfusion platelet counts. Because HEM platelet transfusions are also associated with reduced costs and resource requirements, they should be considered as a potential alternative tool for managing HLA alloimmunized patients with platelet refractoriness. Larger prospective randomized studies are now warranted to further validate these promising results.

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

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DOI 10.1182/blood.2020009283

GENE THERAPY

Comment on Gauthier et al, page 323

A second CD19 CAR T-cell infusion: yes or no?

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In this issue of *Blood*, Gauthier et al retrospectively analyzed the outcome of a second infusion of CD19 chimeric antigen receptor (CAR) T cells in patients with B-cell malignancies who relapsed or were refractory to the first infusion. The authors reported durable responses in a significant proportion of patients, with a low incidence of severe toxicity. They also identified actionable pretreatment factors associated with positive outcomes.[1]

CD19 CAR T-cell therapy has considerably changed the landscape of treatment options for B-cell malignancies. This therapy was developed as a single infusion of CAR T cells for individuals with relapsed/refractory diseases. However, the frequency of patients who fail to respond or eventually relapse after a partial or complete response is still high. The efficacy of a second infusion in patients unable to achieve durable remissions is still controversial,[2,3] and systematic analysis addressing specific clinical and biological factors in this unique setting has been missing.