this French cohort is particularly well cared for and carefully monitored by a very experienced clinical research team, the current report was not in the context of a rigorous randomized clinical trial and thus represents early “effectiveness” data to indicate that there are safe alternatives to lifelong chronic transfusion therapy.

While certainly encouraging, these findings are not yet a “slam dunk” to suggest that hydroxyurea is a universal replacement for chronic transfusions to prevent neurologic complications for children with SCA. Thirteen of the 36 patients transitioned to hydroxyurea demonstrated reversion to abnormal TCD velocities, although 4 occurred within the first 6 months of hydroxyurea therapy before maximum tolerated dose had been reached. Once an abnormal TCD was identified, the patients were again placed on chronic transfusions, and, ultimately, 6 of 13 were transplanted and 4 of 13 were able to be successfully transitioned a second time back to hydroxyurea therapy with normalization of TCD velocities. These carefully documented observations provide important data to suggest that a combination of therapies with careful surveillance may be a safe and effective alternative to indefinite chronic transfusions alone. The figure provides a potential clinical algorithm for the short- and long-term management of children with abnormal TCD velocities.

With easily available TCD and MRI/MRA studies and multimodal disease-modifying therapy starting early in life, we continue to see changes with the natural history of SCA and are moving toward the goal of a stroke-free childhood for patients with SCA. The early initiation of hydroxyurea therapy for infants with SCA is likely to reduce the number of children who develop abnormal TCD velocities in the first place, and a careful treatment and follow-up strategy for children with abnormal velocities will further reduce the frequency and severity of neurologic complications for children with SCA. It will be critical to further validate these results to determine whether it truly is safe to “flip the switch” from chronic transfusions to hydroxyurea, particularly in the context of the real-world clinical challenges around medication adherence, appropriate dose escalation, and timely monitoring and follow-up.

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Transfusion Medicine

Platelet refractoriness: it’s not the B-all and end-all

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In this issue of Blood, Arthur et al uncover that HLA alloantibodies cannot solely account for the immune mechanism in platelet refractoriness.1

The explosion of blood transfusion therapy about 60 years ago was accompanied by the frequent complication of alloimmunization to the cellular components of blood, mainly toward leukocytes, red cells, or platelets. Correspondingly, leukoreduction of transfused blood products decreased the prevalence of alloantibodies in heavily transfused patients; nevertheless, sensitization remains a serious clinical problem. Platelets harbor antigens that could potentially be mismatched between donor and recipient, including HLA class I, ABO blood group antigens, and human platelet antigen 1. Alloantibodies to all three groups of platelet antigens have been demonstrated in platelet-refractory patients, and have also been associated with increased clearance and destruction of transfused platelets.2

Laboratory investigation of platelet refractory patients has focused on HLA matching or crossmatching of platelets, which in turn has led to increased health care costs and significant delays in treatment.

Antibodies to platelets have been described since the late 1960s with much focus centered on anti-HLA antibodies.3 By the early 1990s, characterization of donor and recipient HLA antigens led to some clinical improvement in a small fraction of platelet-refractory patients, yet large numbers of patients remain at risk, with estimates as high as half of all patients treated for hematologic malignancies.

Although anti-platelet alloantibodies have received most of the attention, several clinical observations have prompted intense investigation to uncover other causative factors. First, most patients who are highly sensitized to HLA antigens do not exhibit platelet refractoriness. Second, many cases of platelet refractoriness do not appear to have any anti-platelet antibodies detectable by standard laboratory assays. Third, interventions to alter antibody production or suppress B cells have not resulted in improved outcomes.2

The concomitant diseases and therapies in patients inherently confound studies of platelet refractoriness. Mouse models to study platelet refractoriness were pioneered 20 years ago, and elegantly demonstrated that T cells play a major role in the immune response toward transfused platelets.3,4 In these initial studies, both anti-major histocompatibility complex (MHC) antibodies and CD8 T-cell–mediated cytoxic T-lymphocyte (CTL) responses were found to be active in the disease.5,6 Further work also implicated natural killer (NK) cells in driving an anti-platelet antibody response. Moreover,

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Immune mechanisms in platelet clearance induced by prior transfusion. Anti-CD8 T cells in green. These findings support a direct role for T cells in platelet clearance induced by prior blood transfusion. Professional illustration by Somersault18:24.

antigen-processing pathways indicated that macrophages, among other cells, could serve as antigen-presenting cells (APCs) to induce alloimmunity. More recent studies have shown the importance of CD4 T cells, the CTL-associated protein 4 axis, the splenic microenvironment, and complement receptors in inducing transfusion-associated platelet refractoriness.7-9

These reports set the stage for the current study where Arthur et al immunize recipient mice with donor blood cells from a strain of mice that differ in MHC antigens. They find that mice with an intact immune system clear only the platelets from the MHC-mismatched mice, and not their own platelets. They then tested whether μMT mice (ie, B-cell deficient mice) were able to mediate increased clearance of mismatched donor platelets. They found that platelet clearance at 24 hours was indistinguishable between mice with an intact immune system and the B-cell defective mice. These studies indicate that immune-mediated clearance of platelets can occur independently of anti-MHC antibodies. Furthermore, depletion of CD8 T cells in vivo in μMT mice improved survival of transfused MHC-mismatched platelets. The depletion of NK cells did not prevent the immune-mediated clearance of donor platelets.

Although these findings strongly implicate the direct role of T cells in altered platelet clearance after alloimmunization, more work remains to be done to understand the interplay between anti-MHC antibodies, B cells, and T cells. Genetically defined mouse models deficient for specific immune cells or completely lacking antibodies can help elucidate the role of factors such as the timing of the immune response after transfusion, the role of the underlying disease and of chemotherapy, or other treatment-related immune modifications that may further affect platelet recovery. These findings of course must also be tested in patients refractory to platelet transfusion. This is highly relevant because much focus still remains on testing for and treating the antibody component, eg, plasma exchange and rituximab. The effect of T cells has been reported for chronic immune thrombocytopenia, where a direct interaction between T cells and platelets was demonstrated.10 These findings may be extended and tested in other diseases, including neonatal alloimmune thrombocytopenia or posttransfusion purpura, where antibodies do not fully explain the pathogenesis of increased platelet clearance. We now recognize the role of several arms of the immune system in this disease and can potentially test therapeutic targets that do not solely rely on removing anti-HLA antibodies or simply impairing B-cell activity (see figure). Although anti-HLA antibodies play a role in this disease, a more comprehensive therapeutic approach should include other components of the immune system.

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