**Comment on Kelly et al, page 214**

**Bruised platelet transfusions work**

Thomas S. Kickler  
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

In this issue of *Blood*, Kelly et al report on a clinical trial that addressed the question of whether genetic differences in donor platelet reactivity affect the clinical outcome from transfusion, and they report no effect of hyperreactivity.1

Practitioners of transfusion medicine have not addressed the importance of platelet functional reactivity despite our increasing knowledge that there are phenotypic differences determined by the genotype of the blood donor. The general philosophy of platelet preparation has been to minimize the amount of platelet activation so that transfused platelets reflect their resting state.2 Otherwise, transfusion function and survival would be impaired.

We have personalized red cell transfusions on the basis of genotype matching for patients with sickle cell anemia. Why not consider choosing platelet donors on the basis of genetic attributes? Genetically selected farming practices have helped reduce bruised tomatoes in the supermarket, so who knows? Bruised (activated) platelets may become a thing of the past in the blood bank.

Kelly et al previously showed an association between in vitro tests of platelet activation and a variety of genes so that platelets can be categorized as having a persistently higher degree of reactivity or a lower degree.3,4 They hypothesized that platelets derived from high-responder donors (ie, donors with highly reactive platelets) might be more rapidly cleared after transfusion without exerting a therapeutic benefit. This was a reasonable assumption because the fundamental goal of preparing platelets is to do as little as possible to activate them; platelets that seem to have intrinsic hyperreactivity might be the type most affected by the steps required for collection, preparation, and storage. Categorization of platelets as having low or high reactivity was based on a scoring system in which the degree of responsiveness of 2 activation markers (P-selectin expression or fibrinogen binding) was measured after stimulation with collagen or adenosine 5′-diphosphate. Donors with the most reproducible responses in the upper and lower 10% distributions were selected to be the platelet donors. Although the logic of this approach seems sound, there were no quantitative data regarding percentage of platelet activation, which is typically provided. The study by Kelly et al seems to refute earlier smaller studies on platelet activation and platelet transfusion outcome, but it is important to know whether the degree of activation in their current study was comparable to that previously reported.5

Results of the study show no significant differences between patients who received platelets from high-responder donors and those who received platelets from low-responder donors in either 1-hour recovery or 24-hour survival. Furthermore, hemostasis seemed to be well maintained on the basis of bleeding scores determined by clinicians, and time to next transfusion and number of transfusions were similar.

The strengths of the study include a high level of adherence to the protocol and little loss to follow-up. In addition, the contributions of the donors should not be underestimated. Performing clinical trials in platelet transfusion therapy is not easy, given the complexities of the patients and the difficulty of providing the blood product when needed, which is totally dependent upon a cooperative donor population. As the authors note, the data are applicable to prophylactic platelet transfusions in patients with chemotherapy-induced thrombocytopenia rather than to patients with active bleeding. It is well known that platelets have a nursing effect on the endothelium, which may be sufficient in that patient group instead of providing primary hemostasis as would be needed for patients with active bleeding.6 One point of concern is the issue of transfusing activated platelets, which presumes that a substantial number of platelet microparticles are present.7 Platelet microparticles can activate thrombin, which raises the question of whether some vulnerable platelet recipients, such as a fetus or newborn or an adult with a tendency toward a prothrombotic state, can tolerate this microparticle load as well as the population studied.

A list of factors that influence the development of platelet activation during storage, collection, and supplemental treatments is provided (see table).2 Addressing the effects of these processes on platelet activation has laid the foundation for the safety and efficacy of platelet transfusion over the last several decades. On the basis of the results of the study by Kelly et al, it seems that there will be no selection step (donor recruitment) in which platelets are preselected on the basis of their genetic makeup with the presumption that intrinsic hyperactivity of the platelet will not be more susceptible to these factors. The history of improved platelet transfusion safety and efficacy has been one in which in vivo studies have played a major role in assessing the changes in the production, treatment, and preparation of platelets.8 Transfusion medicine specialists have known for the last several decades that laboratory measures of platelet responsiveness do not translate to differences in clinical outcome. This is well demonstrated in the article by Kelly et al through their conduct of a well-designed clinical trial. Advancements in platelet transfusion will continue to require an in vivo transfusion trial, ideally designed to cover a specific patient population.
approach is neither easy nor inexpensive. Although no single in vitro test has proved to be the gold standard, we recognize that the following variety of measurements of platelet metabolism, morphology, and function provide an approximation of platelet transfusion outcome: visual inspection and swirling phenomena, phase-contrast microscopy scoring system, mean platelet volume, hypotonic shock response, platelet activation markers by flow cytometry or supernatant plasma analysis and, recently, markers of metabolism and proteomics.

In summary, as we look ahead toward improving platelet transfusion therapy, the article by Kelly et al does not support the selection of platelet donors with different genetic composition based on in vitro function testing of donors. Of particular importance is our reliance upon apheresis donors; in this case, only one phenotype is used to transfuse a patient. This could potentially lead to a complete failure of the transfusion if the platelets were hyperactive instead of reducing the risk of failure which could be accomplished by using pooled platelet concentrates from several donors. As we look down the road toward platelets being produced in vitro from human stem cells and ponder the need for a particular genetic makeup, we may find it unnecessary to consider a particular genetic makeup. Of course if we ever reach this goal, a well-planned clinical trial will still be needed to provide the final answer.

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REFERENCES


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Checking up on checkpoint inhibitors

Richard F. Little and Howard Streicher NATIONAL INSTITUTES OF HEALTH

In this issue of Blood, Haverkos et al present timely and compelling data revealing both the opportunity and serious hazards incurred with the use of programmed death 1 (PD-1) pathway blockade after allogeneic hematopoietic cell transplant (allo-HCT) in relapsed lymphoma patients.1

The enthusiasm for cancer immunotherapy is fueled by studies showing meaningful responses in several refractory solid tumors and lymphomas. In rapid succession over the last 4 years, objective responses and survival benefit have been demonstrated in many settings, including melanoma, lung, renal, and bladder cancers. Among lymphoid tumors, classical Hodgkin lymphoma (cHL) has stood out as remarkably responsive to PD-1 blockade. Initial studies show activity with 85% response rates and 86% 2-year progression-free survival in relapsed and refractory disease.2

The authors, assisted by the Center for International Blood and Marrow Transplant Research, which records basic data for every patient undergoing HCT, identified 15 high-volume centers that had used PD-1 monoclonal antibodies (mAbs) after allo-HCT. Although not eliminating selection bias, this approach provided a reasonably representative sample for estimating the response rates and incidence of adverse events in the absence of a prospective study. Chart reviews provided data on response and on acute or chronic graft-versus-host disease (GVHD) that emerged after initiation of anti–PD-1 therapy. Twenty-nine cHL patients, 1 with follicular lymphoma (FL) and 1 with composite FL and cHL, were included in the analysis. Consistent with the anti–PD-1 cHL literature, they found a high response rate of 77%. The median follow-up of only 428 days is too short to allow firm conclusions on clinical benefit, but median overall survival was not yet reached. However, the rapid onset (after 1 or 2 doses of PD-1 mAb) of severe GVHD in 55% of patients, with only 2 of these 17 patients having a complete response to GVHD therapy, is troubling.

The relatively benign toxicity signal seen in most settings, including cHL, has fostered the perception that the risk/benefit of single-agent anti–PD-1 mAb therapy favors increased off-label use of these agents in settings where good standard options are limited. However, the widespread acceptance of immune-based therapy continues to require critical evaluation.

Case reports and an earlier smaller retrospective report by Hebaux et al3 suggested that the use of nivolumab after allo-HCT for cHL had an extraordinary response rate with a low rate of GVHD, providing cautious optimism for PD-1 in this setting. So why not combine PD-1 checkpoint inhibition with allo-HCT? The current report in Blood by Haverkos et al heralds a portentous check in cHL is more complex and less certain.4 Any effect that creates additional treatment-related risk is likely to adversely affect overall survival in cHL patients undergoing allo-HCT with PD-1 blockade. However, the efficacy signal,
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