To the editor:

Alloimmunization to red blood cell antigens by transfusion

In their impressive report in a previous issue of Blood, Higgins and Sloan examined large patient databases and developed a model of alloimmunization to red blood cell antigens as a stochastic process.1 They identified a subgroup of recipients that had a substantially increased risk of alloimmunization that was independent of common disease states, age, or number of alloantibodies previously formed. Their model suggests that approximately 13% of the transfusion recipient population are responders and at risk of forming red blood cell alloantibodies.

The authors mention that there are reports that have identified a higher proportion of red blood cell alloantibodies in patients with sickle cell disease (SCD). They also state that they have excluded “any antibodies for these patients” from their report. Indeed, there are numerous studies that have found rates of alloimmunization in patients with SCD between 18% and 36%.2-10 For example, Rosse et al reported an alloimmunization rate of 18.6% in 1814 patients with SCD who had been transfused. (Unlike Higgins and Sloan, they also noted a strong correlation between the prevalence of alloimmunization and the number of transfusions received.)9 Garratty summarized 12 reports, encompassing 2818 transfused SCD patients, that collectively found a mean and median alloimmunization rate of 25%.5

It would be interesting for Higgins and Sloan to comment on how their stochastic modeling aligns with the widely reported higher rate of alloimmunization in patients with SCD. Do they feel that the well-known disparities in antigen frequencies between SCD patients and the blood donor population, as well as the immunocompetence of SCD patients, fully account for the difference between these reports and their findings?

Response

Other factors may contribute to differences between sickle cell and non–sickle cell patients

We appreciate the comments by Dr Mintz concerning the differences in alloimmunization rates reported for sickle cell patients and our findings based on data that excluded sickle cell patients.1 In planning our analysis, we did not expect sickle cell patients to differ from the general population. However, we excluded sickle cell patients because our study hospitals prospectively matched for the C, E, and K antigens for sickle cell patients and no other patients. Because we did not analyze sickle cell patients, we do not have direct evidence to explain the apparent

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differences we saw in the non-sickle cell patient population and those reported by others in sickle cell patients.

While differences in antigen frequencies between racial groups might explain such a difference, our preliminary analysis does not find a significant difference in the alloimmunization rates of African-American patients who do not have sickle cell disease and that of the general patient population at our adult study hospital. Hence, we suspect other factors contribute to apparent differences between sickle cell disease patients and other patients but we have no evidence to support or refute any such factor.

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To the editor:

Thrombotic microangiopathy after GVHD prophylaxis with tacrolimus/sirolimus: a call for use of consensus definition in reporting

We read with great interest the manuscript published by Rodriguez et al describing outcomes of a phase II pilot study of a tacrolimus/sirolimus regimen for graft-versus-host disease (GVHD) prophylaxis in 85 recipients of matched-sibling donor hematopoietic cell transplantation (HCT) using 3 different regimens (fludarabine-melphalan [Flu-Mel] = 46, total body irradiation [TBI] plus etoposide = 28, and busulfan-cyclophosphamide [Bu/Cy] = 11). The authors describe an overall incidence of posttransplantation thrombotic microangiopathy (TMA) of 19% occurring at a significantly higher rate (55%, $P = .005$) in patients who received conditioning with Bu/Cy.

The reported high incidence of TMA in 19% of cases is particularly noteworthy and certainly higher than previously reported (10.8%) with the concurrent use of tacrolimus and sirolimus in the transplant setting. There are several limitations, however, to this finding. First, the definition of posttransplantation TMA used by Rodriguez et al “consisting of simultaneous occurrence of schistocytosis, increased lactate dehydrogenase (LDH), and persistent thrombocytopenia (below 50,000/uL)” is particularly nonspecific. In contrast, the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) operational definition of TMA requires the following: microangiopathic hemolysis (red blood cell fragmentation and $\geq 2$ schistocytes per high-power field on a peripheral blood smear), concurrent increased serum LDH above institutional baseline, concurrent renal (defined as doubling of serum creatinine from baseline or 50% decrease in creatinine clearance from baseline) and/or neurologic dysfunction without other explanations, and negative direct and indirect Coombs tests results. The BMT-CTN consensus definition of TMA, as well as the proposed adaptation of the CTC criteria $^4$ (Version 3.0) for TMA severity, requires renal or neurologic compromise. Importantly, these are not included in the criteria used by Rodriguez et al, which may have resulted in overestimating the true incidence of TMA. Therefore, comparisons to the incidence of TMA previously reported with the concurrent use of tacrolimus and sirolimus are limited. We believe that it would be of more value to the transplant community if the authors report the incidence of TMA by grade according to proposed BMT-CTN consensus definition. Second, while the association between TMA and myeloablative conditioning (with Bu/Cy or TBI-etoposide) is intriguing, one should also consider the impact of elevated tacrolimus levels in the Bu/Cy group: the median and the interquartile range (IQR) for serum tacrolimus levels (nanograms per milliliter) were significantly higher ($P = .003$) in patients conditioned with Bu/Cy compared with those receiving TBI-etoposide or Flu-Mel. As well, univariate analysis demonstrated a non-significantly increased hazard for TMA with advancing quartile of median tacrolimus level. The authors acknowledge the limitations imposed by relatively small number of patients and TMA events in this analysis. This may in part explain the higher incidence of TMA in this group and suggests that a narrower therapeutic range for tacrolimus be considered when used in combination with sirolimus in the setting of Bu/Cy.

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