blood commentary

TRANSFUSION MEDICINE

A rose is a rose is a rose, or not

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In this issue of *Blood*, Roubinian et al provide important evidence to confirm, and refute, a long-standing maxim in clinical medicine that a 1-unit transfusion of red blood cells (RBCs) should yield a posttransfusion hemoglobin increment of 1 g/dL.[1] Although true, in general, this rule was not always accurate, and deviations could be misleading. They evaluated many single-unit transfusion outcomes in stable adult patients by mining electronic health records (EHRs) and linked blood donor data. This approach was not only pragmatic, but it also points the way to future studies.

This work fits with recent efforts to improve the quality, safety, and efficacy of blood transfusions. These efforts are significantly supported by the National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI), which sponsored symposia and workshops on this topic.[2-4] These meetings encouraged the study of questions such as "What's in the bag?" "How can we make better products?" "How can we build better donors?" "How do we know if it works?" These issues are also being studied in the NHLBI-supported Recipient Epidemiology and Donor Evaluation Study III (REDS-III)[5] and REDS-IV-P[6] programs.

To provide context for these efforts, one can think of blood products metaphorically as pharmaceuticals. This analogy is straightforward regarding hemophilia A, in which patients were historically treated with plasma or cryoprecipitate (ie, blood products), whereas current treatment uses recombinant factor VIII, which is considered a drug. Although this metaphor may be less concrete in the context of RBC transfusions, it may become relevant in the not too distant future. Indeed, with the advent of patient blood management, multiple drugs (eg, iron, tranexamic acid, erythropoietin) can

supplement transfusions or render them unnecessary altogether.

If one accepts the pharmaceutical metaphor, then some pharmacology concepts become heuristically useful, including active ingredients, purity, stability, dosage, volume of distribution, pharmacokinetics/pharmacodynamics, indications, effectiveness, and adverse outcomes. These are relevant to the current contribution, particularly quality and efficacy. But RBC quality is not easy to define. Thus, US Food and Drug Administration criteria for licensing purposes include quantifying spontaneous hemolysis in vitro and posttransfusion recovery of radiolabeled RBCs in vivo, both at the end of storage[7]; however, neither readily correlates with desirable outcomes in transfused patients. More clinically relevant criteria could include improving tissue perfusion and/or oxygenation[4] or preventing or ameliorating end-organ damage, but these are not widely accepted or applied. Finally, as in the article by Roubinian et al, posttransfusion hemoglobin increment is clearly relevant in ameliorating anemia and/or increasing reserve (eg, for ongoing or anticipated bleeding). Indeed, although hemoglobin increment can be a surrogate

for overall RBC transfusion quality, in some settings (eg, chronic transfusion for hemoglobinopathies), one can argue that hemoglobin increment actually is quality.

Using the pharmaceutical metaphor, some of the current findings are not unexpected, and they fit with pharmacologic concepts. For example, an increased dose (eg, RBC units from male donors) yields an increased response in the recipient. Similarly, a decreased dose (eg, irradiated donor units) yields a decreased response in the recipient; the latter is also expected when washed or frozen/thawed RBCs are used. In addition, a smaller volume of distribution (eg, in female recipients) yields an increased response, and the opposite is seen with increasing body mass index; similar results were found in a REDS-III–supported study.[8] In contrast, some results in the Roubinian et al study were somewhat surprising or potentially controversial. For example, although a univariate analysis did not identify a correlation between hemoglobin increment and storage age, the authors did find smaller increments at 24 and 48 hours posttransfusion when storage age was >35 days; these results are similar to those in a prospective, randomized clinical trial[9] and a large epidemiologic study.[10] The article by Roubinian et al also identified novel and, as yet, unanswered questions. For example, hemoglobin increments were lower in RhD-negative individuals, whether they were donors or recipients. It is unknown whether this relates to the function of RhD, inventory control issues, or some other cause.

The validity of the Roubinian et al results is supported by the strengths of their approach. These include studying large numbers of transfusions, evaluating single-unit transfusions in otherwise stable patients with appropriately timed pre- and posttransfusion hemoglobin determinations (including both inpatients and outpatients), and linking donor databases with recipient EHRs. Indeed, the latter pragmatic approach, which does

not require consent, will be exploited further in observational studies in REDS-IV-P. In addition, their results will help inform the design of future prospective clinical trials. The authors also acknowledged several weaknesses in their study, including using only stable adult patients, using blood products from only one supplier, and providing relatively little insight regarding variations induced by different manufacturing methods.

Finally, the Roubinian et al study results may prompt a reevaluation of hemoglobin dose. The current standard of care for routine RBC transfusions in adults uses a standard dose (eg, 1 or 2 units) for all adult patients without modification based on donor or recipient characteristics. This differs from the approach used in pediatrics, in which transfusions are based on mL/kg calculations. It also differs from treating adult or pediatric patients with sickle cell disease by exchange transfusion, for which we calculate the number of units required to achieve specific final total hematocrit and hemoglobin S levels. Because the hemoglobin dose is knowable for every RBC unit (ie, what's in the bag), should this information routinely be provided to the ordering physician? If so, would it be useful? For example, that information could be used to dose adults more appropriately. It could also help in decision-making regarding what hemoglobin increment to expect, allowing one to judge transfusion efficacy. For example, when the increment does not meet expectations, that would suggest an underlying pathology (eg, ongoing or new bleeding, a hemolytic transfusion reaction). Although these ideas may seem far-fetched at the moment, misinterpreting an expected hemoglobin increment currently leads to unnecessary clinical investigations and potential patient harm. Indeed, given that Roubinian et al found the different modifiers of hemoglobin increments to be additive, the potential for misinterpretation was evocatively emphasized in Table 6 of their article, in which the expected posttransfusion hemoglobin increment per unit ranged between 0.59 and 1.65 g/dL. Thus, it is hoped that future studies based upon their results will continue to help optimize transfusion therapy.

Conflict-of-interest disclosure: S.L.S. is a member of the Scientific Advisory Board of Hemanext, Inc. ∎

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CLINICAL TRIALS AND OBSERVATIONS

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Ibrutinib and lenalidomide: when 1+1 = >2

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In this issue of *Blood*, Goy et al report on the promising activity of a phase 1b trial of the targeted therapy triplet rituximab, ibrutinib, and lenalidomide in patients with relapsed nongerminal center diffuse large B-cell lymphoma (DLBCL).[1]

Approximately 2 of 3 patients with DLBCL, the most common lymphoid cancer, are cured with a chemotherapy combination originally created in 1976 (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]), which was last successfully modified in 1999 (by adding rituximab [R-CHOP]).[2] For patients with DLBCL who are not cured by R-CHOP, a second chance for curative therapy is high-dose chemotherapy and autologous stem cell transplantation (ASCT). Patients who are not able to tolerate, do not respond to, or cannot access aggressive approaches such as ASCT or chimeric antigen receptor T-cell therapy have few therapeutic options with the potential for long-term disease control and are often considered palliative.[3]

DLBCL is a heterogeneous disease, most commonly classified on the basis of the putative cell of origin. The activated B-cell (ABC) subtype of DLBCL is characterized by chronic active B-cell receptor (BCR) signaling and requires NF-κB signaling for survival.[4]

The use of novel therapies that specifically target aberrant DLBCL biology has great promise, but it has yielded frustratingly few advances relevant to daily