Commentary (Schiffer)—Thrombopoietin: Biology and Potential Clinical Applications

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As comprehensively described by Drs. Prow and Vadhan-Raj, lineage-specific preparations of thrombopoietin are now in clinical development: pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) and recombinant human thrombopoietin (rhTPO). These preparations produce marked increases in megakaryocyte mass and platelet count after SC dosing.

Early trials of thrombopoietins have shown: (1) a dose-dependent rise in platelet count beginning a few days after administration and peaking at 10 to 14 days, without changes in red blood cell or neutrophil counts; (2) the production of morphologically and functionally normal platelets; (3) mobilization of hematopoietic colony-forming units into the peripheral blood; (4) attenuation of the mild thrombocytopenia that occurs after moderately dose-intensive chemotherapy; and (5) an absence of significant side effects in recipients. Demonstrating these marked thrombopoietic effects is not the same as proving clinically meaningful benefit to support product licensing, however. Therefore, clinical trials have been initiated in selected patient populations who require repetitive platelet transfusions.

Problems Inherent in Demonstrating Clinical Benefit

It would be difficult to demonstrate a favorable impact of the use of thrombopoietin by assessments of bleeding because fatal or serious hemorrhage is uncommon even at very low platelet counts and it is difficult to quantify more minor degrees of bleeding. Thus, the benefit of a thrombopoietin must be evaluated primarily by a shorter duration of severe thrombocytopenia, a reduction in the number of platelet transfusions, and by inference, a decreased likelihood of some of the complications of transfusion.

There are wide variations in clinical practice with regard to the criteria for administering prophylactic platelet transfusions. Three recent randomized trials[1-3] in patients with acute leukemia have demonstrated the safety of a 10,000/µL "threshold" for transfusion in stable patients (compared to the older "standard" of 20,000/µL), and most physicians are now comfortable with observing clinically stable patients with lower platelet counts without administering transfusions. Wider adoption of a lower transfusion "trigger" will decrease the number of transfusions required for many patients, and this change in practice should be considered in the design and interpretation of future trials.

Methodologic Issues Related to Clinical Trials

Initial clinical trials evaluating thrombopoietin have begun in patients with acute myeloid leukemia (AML) and those who have received myeloablative therapy, because of the predictable need for platelet transfusions in these patients. The methodologic issues are similar to those addressed in randomized trials of myeloid growth factors.

These trials should be double-blind and placebo-controlled in order to objectively evaluate adverse effects of therapy, such as stimulation of leukemia cell growth with lower complete remission rates, since the mpl ligand for thrombopoietin is expressed on myeloid blasts from most patients with AML. It is also necessary to control for potential biases that could influence the decision to prescribe platelet transfusions, particularly toward the end of the aplastic period.
Preferably, there should be some standardization of the dose and type of platelets administered. Because granulocyte colony-stimulating factor (G-CSF [Neupogen]) and granulocytemacrophage colony-stimulating factor (GM-CSF [Leukine]) are used commonly in patients receiving high-dose therapy, possible interactions between the myeloid and thrombopoietic growth factors will have to be considered, although experiments in monkeys suggest that these are unlikely to be a problem.

Clinical Trials in AML

Most transfusions given during induction treatment of AML are administered during the first few weeks of treatment, either during the period of chemotherapy administration or while the marrow is aplastic and, thus, prior to any expected effect of thrombopoietin. Therefore, as was apparent in trials of myeloid growth factors in this population, there is a relatively small "window" during the last week of marrow regeneration for a thrombopoietic factor to decrease the need for transfusion. Furthermore, patients who do not achieve remission, because of death during induction therapy or persistence of drug-resistant leukemia, provide no information on platelet recovery.

One pilot trial in which patients with AML received two different doses of thrombopoietin (PEG-rHuMGDF) or a placebo after the completion of induction therapy did not show a reduction in the duration of thrombocytopenia or the number of platelet transfusions received.[4] Similarly, another small trial using PEG-rHuMGDF before and after myeloablative therapy with peripheral blood stem-cell support failed to show a reduction in the number of platelet transfusions or an acceleration in platelet count recovery.[5] As is typical of this clinical scenario, the duration of thrombocytopenia was 8 to 10 days and only two to three platelet transfusions were administered per patient. It may be impossible, therefore, to improve further on these already modest transfusion requirements. In addition, there is a marked rise in endogenous thrombopoietin production during the period of severe thrombocytopenia.[6] Therefore, the marrow may already be significantly or maximally stimulated, with little added effect to be expected from even pharmacologic doses of exogenous growth factor.

Use Following Consolidation Therapy

The situation may be somewhat more favorable following post-remission consolidation therapy. Because patients start with relatively normal marrows and mortality is low, essentially all recover normal blood counts. In addition, it has been shown that myeloid growth factors can be effective in this situation. It may be difficult to demonstrate a statistically significant reduction in the number of transfusions, however, because of the small number of transfusions required, unless the patient sample size is large.

Given the probable high cost of thrombopoietins, there is likely to be debate about the cost relative to the clinical significance of a possible "savings" of only one or two platelet transfusions. The same question arises in the stem-cell transplantation setting, as noted above.

Use in Solid Tumor and Lymphoma Patients Receiving Standard-Dose Chemotherapy

Patients receiving standard dose regimens for solid tumors and lymphomas infrequently require platelet transfusion, and when they do, it is uncommon for more than one or two transfusions to be administered per course. A small randomized clinical trial evaluating interleukin-11 (IL-11 [Neumega]) demonstrated a reduction in the use of subsequent platelet transfusions in a subset of patients treated without dose modification and identified as being "at risk" by virtue of having required transfusions during previous courses of chemotherapy.[7] However, this is an uncommon clinical situation, and it is likely that if a threshold of 10,000/µL for platelet transfusions is used, the "need" for transfusions in this circumstance will be decreased further. In addition, there is little evidence that maintenance of "dose intensity" at these levels is of benefit in patients with solid tumors or lymphomas.

Use in Other Settings

Thrombopoietin is also being evaluated in other clinical circumstances:

**Myelodysplasia or Aplastic Anemia**—In many patients with myelodysplasia or aplastic anemia, severe thrombocytopenia is a major cause of morbidity. Because of the inverse relationship between the platelet count and endogenous thrombopoietin levels, most such patients, who already have
markedly impaired marrow function and decreased ability to respond to growth factors, will perhaps already be maximally stimulated. There is also concern about accelerated transformation to acute leukemia, particularly in patients with myelodysplastic syndrome (MDS). However, a fraction of patients with MDS can have lineage-specific responses to pharmacologic doses of erythropoietin or myeloid growth factors (G-CSF or GM-CSF), with the myeloid growth factors providing at least transient benefit in terms of combating infection. It would thus be of interest to evaluate thrombopoietin, with correlation with pretreatment thrombopoietin levels. Such a study would be aimed at determining whether there are some patients, presumably those with lower endogenous production, who might benefit, particularly because of the possibility of a convenient weekly schedule of administration.

**Immune Thrombocytopenic Purpura**—Patients who have immune thrombocytopenic purpura (ITP) are thrombocytopenic because their antibody-mediated platelet destruction exceeds the rate of platelet production. Although platelet production is already expanded in most patients with ITP, it is unknown whether production can be further enhanced by pharmacologic doses of thrombopoietin, particularly in the subgroup of ITP patients in whom thrombopoietin levels are lower than predicted by the level of thrombocytopenia. Trials in the small minority of patients with severe refractory ITP and in individuals with higher counts scheduled for elective surgery would be of interest.

**Increasing Apheresis Collection Yield**—The yield of platelets obtained via apheresis is directly related to the donor’s platelet count. Although there is interest in utilizing thrombopoietin in more routine platelet collection settings, there are issues related to the cost of the drug, the necessity for the donor to come to the center twice (to receive the injection and subsequently for apheresis), with the theoretical background concern of thrombotic events in normal volunteer donors. There are selected circumstances in which higher platelet yields could be quite beneficial, however. These include collections from human leukocyte antigen (HLA)-compatible donors for alloimmunized recipients or from patients scheduled to receive intensive therapy, from whom autologous platelets can be obtained and cryopreserved for subsequent transfusion during periods of thrombocytopenia.[8] It would also be interesting to consider this maneuver in patients who are undergoing collection of stem cells. It is conceivable that platelets could be harvested either simultaneously with the stem cells or at a subsequent apheresis, with storage either in the liquid or frozen state, depending on the interval between stem-cell collection and treatment-induced thrombocytopenia.

**Conclusions**

There has been a dramatic increase in our understanding of thrombopoiesis during the past few years, due, in part, to the availability of this new "reagent" for in vitro and in vivo experiments. Somewhat ironically, it has also become apparent that proof of clinical benefit will not be straightforward, particularly when thrombopoietin is used to attenuate treatment-induced thrombocytopenia. Multiple studies patterned after the G-CSF and GM-CSF trials are in progress. It is likely that the next series of investigations will evaluate alternative scheduling, combinations of cytokines, and pretreatment with thrombopoietin to assess whether beginning chemotherapy with higher platelet counts will shorten the duration of clinically relevant thrombocytopenia.

**References:**


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