Treating anemia: It's not just the EPO

We are aerobic organisms. The ultimate component in our complex physiologic oxygen delivery system is the metabolically active, membrane-bound hemoglobin valet, the erythrocyte. So it is natural that we focus clinically on the readily measured hemoglobin and laboratory test derivatives of the red blood cell (RBC) count. A "normal" red cell count and hemoglobin are sufficient to support adequate physiologic function under even greater than routine demands, and there are multiple homeostatic controls that fine-tune the efficiency of oxygen delivery. The redundancy of these controls directed at RBC mass and hemoglobin concentration and function indicate that these values matter, and pharmacologic manipulation should have significant clinical effect.

In patients without advanced kidney disease, erythropoietin (EPO) levels begin to rise proportionately to restore the RBC mass as the hemoglobin falls below 12 to 13 g/dL. Erythrocyte 2,3-diphosphoglycerate levels rise with hypoxia or anemia, enabling more efficient release of oxygen from hemoglobin to peripheral tissue. Persistent exposure to a decreased external partial pressure of oxygen at elevated altitudes, or even intermittent exposure to relative hypoxia, as in patients with untreated sleep apnea, elicits an increased EPO with resultant elevated hemoglobin and hematocrit.

With all of these controls (and more) in place to maintain a normal capacity for oxygen delivery, it would seem clinically advantageous to therapeutically assist critically acute and chronically ill patients in maintaining close-to-normal RBC mass when their intrinsic controls are overwhelmed. And yet multiple studies, done in various settings, have demonstrated limited outcome benefits in utilizing a liberal RBC transfusion policy to reverse anemia and maintain a close-to-normal hemoglobin and hematocrit.

With knowledge of the transfusion experience, recognizing that the transfusion studies relate more to acute scenarios, perhaps it should not be a major surprise that pharmacologic efforts to normalize the anemia in patients with chronic inflammatory diseases, heart failure, and chronic kidney disease directly with EPO (or its derivatives) have had only modest outcome benefits. And these pharmacologic interventions are indirect and physiologically more complex than simple transfusion. As noted by Souaid et al[1] in this issue in their discussion of anemia of chronic kidney disease, normalizing the hemoglobin with EPO in clinical trials of patients with chronic kidney disease and heart failure has yielded only modest outcome benefits and has been fraught with complications including an increase in cardiovascular events.

Yet we have all had patients who have been extremely dependent on the maintenance of a higher hemoglobin and hematocrit in order to maintain their energy and a reasonable quality of life. So efforts to normalize anemia, as with most aspects of managing patients with chronic disease, must be individualized in the clinic.

Taking a step back and reviewing the biology and pathophysiology of the control of erythropoiesis and iron utilization, as Souaid et al do so clearly, I am struck by the interplay between inflammation, iron metabolism, and the renal production and bioefficacy of EPO. At the core of this complex molecular dance is the liver-derived

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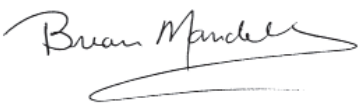
peptide hepcidin, which increases as part of the acute-phase inflammatory response and decreases in response to anemia and hypoxia. By decreasing the functionality of the major transmembrane iron transporter, hepcidin decreases both absorption of iron from the gut and release of macrophage iron stores. The biologic survival rationale for this may be to prevent iron overload and limit the availability of iron to invading microorganisms in the setting of sepsis—the ultimate inflammatory scenario. Elevated hepcidin levels in the setting of chronic inflammation result in a relative resistance to the desired marrow-stimulating effects of exogenously provided EPO. This may explain the limited benefits observed with EPO treatment in patients with chronic kidney disease, congestive heart failure, and inflammatory disease, and the higher EPO levels may cause off-target adverse effects. A challenge in translating the results of these clinical trials to clinical practice is our limited ability to accurately and routinely assess and interpret hepcidin levels and the adequacy of usable iron stores in individual patients. The routinely utilized iron, total iron-binding capacity, and ferritin tests have accuracy limitations. Furthermore, the unrecognized presence of functional iron deficiency, likely mediated in many patients by their elevated hepcidin levels, significantly reduces the marrow response to EPO. Provision of parenteral iron may benefit some of these patients.

The 2019 Nobel Prize in medicine and physiology was awarded to 3 investigators for their work in describing how intracellular oxygen levels are sensed and translated into cellular responses via hypoxia-inducible factor (HIF) transcription-mediated events. When oxygen levels decrease, intracellular HIF increases in many tissues, resulting in the induction and control of more than 50 genes, including EPO and others active in angiogenesis and cell growth. HIFs increase EPO production in the kidney and liver, enhance iron utilization, and promote effective erythropoiesis. Therapeutically increasing the HIF level demonstrably decreases the hepcidin level, which should augment iron availability and thus enhance the RBC response to the increased EPO,[2] especially in patients with elevated hepcidin levels due to chronic inflammation.

Souaid et al[1] summarize ongoing studies of a novel approach to increase HIF levels by stabilizing the HIF molecule by decreasing its prolyl hydroxylation, thus slowing its normally rapid proteasomal catabolism. But the long-term effects of treatment with these new oral inhibitors of prolyl hydroxylase will need to be carefully monitored, as prolyl hydroxylase is a key structural component of diverse proteins including collagens and mannose-binding lectin. The latter is an integral component of the protective innate immune response, and diminution of its function may have adverse infectious complications.

So while it is the erythrocyte-bearing hemoglobin that ultimately gets oxygen to our tissues, the mechanism by which we attempt to increase RBC mass may affect both efficacy and safety.



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