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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Parrow et al, page 1553

Less (Fe) is more (Hb) in SCA

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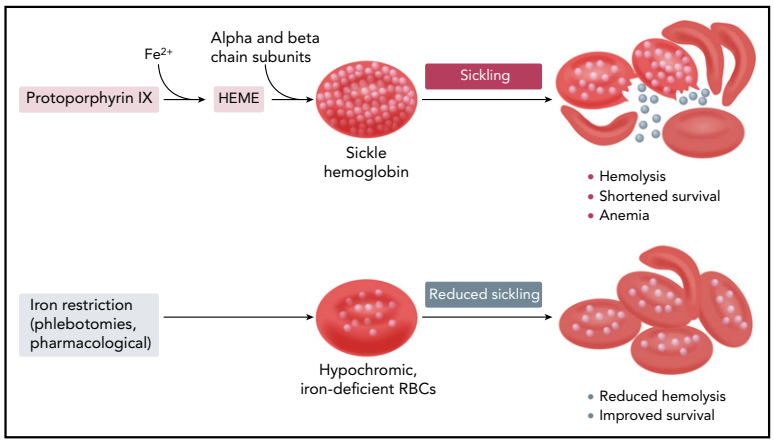
In this issue of *Blood*, Parrow et al describe their findings in a murine model of sickle cell anemia (SCA) in which mice were exposed to an iron (Fe)-restricted diet.[1] This intervention resulted in improved hematocrit, with an increased number of red blood cells (RBCs) and a decreased mean corpuscular hemoglobin concentration (MCHC) and serum bilirubin. The tendency of the cells to sickle in vitro was reduced, and an improvement was also detected in the serum concentration of VCAM-1, a biomarker of endothelial activation.

Although these effects were mild and did not significantly affect total hemoglobin (Hb) and reticulocyte count, this study in a well-established mouse model of the disease provides further support to the notion that, within certain limits, iron restriction may be beneficial for patients with sickle cell disease (SCD). The "iron hypothesis" was first put forward by Lincoln et al in 1973[2] and finds its pathophysiological basis on the kinetics of Hb polymerization and its unique dependence on Hb concentration. Hypochromic cells have a reduced Hb concentration, and thus in SCD, their Hb polymerization is delayed and they are less likely to sickle. It has also been known for a long time that coinheritance of diseases that ultimately reduce both Hb content (MCH) and concentration (MCHC) is a powerful modifier of SCD (see figure): Hb S/β thalassemia is recognized as a generally less-severe (but not complication-free) form of sickle cell anemia, whereas homozygous sickle cell anemia with associated α thalassemia. Hb S/β thalassemia has been known to exhibit less hemolysis, and possibly because of the higher Hb values, more frequent vaso-occlusive complications such as bone disease and painful crises.

The iron-restriction hypothesis was championed for many years by Oswaldo Castro at Howard University and has found many followers in France, especially for the treatment of patients heterozygous for both Hb S and Hb C (Hb SC disease). Hb SC disease is characterized by a milder clinical phenotype, but it still has significant complications related to higher cellular Hb concentration, higher Hb values (>10 g/dL in most patients) resulting in increased blood viscosity, and symptoms related to vaso-occlusion (painful crises, retinopathy, sensorineural otological disease, avascular necrosis, and nephropathy).[3]



Hb synthesis and sickling in sickle erythrocytes with normal and reduced Hb content and concentration.

In several case reports of patients affected by SCA, Castro et al showed that iron deficiency decreased hemolysis (lower serum bilirubin and lactate dehydrogenase and lower reticulocyte counts), reduced the fraction of dense cells, and improved RBC survival.[4-6] Clinical improvement was also described with iron deficiency and worsening of symptoms with iron replacement therapy. Rombos et al[7] showed similar hematologic and clinical improvements in 13 Greek patients, most of them affected by Hb S/β thalassemia. In a large retrospective study in patients with Hb SC disease, Lionnet et al[8] showed measurable, but uncontrolled, clinical improvements in 71% of patients treated with regular phlebotomies. More recent studies have also highlighted a connection between nocturnal hypoxia and higher iron availability (estimated from transferrin saturation), again suggesting the deleterious effect of iron on SCD, although the investigators of this study did not invoke the mechanisms described above.[9]

The iron hypothesis has been in existence for at least 4 decades, but no controlled, properly designed studies have been carrier out to test it. Patients affected by SCD have an iron metabolism poised toward increased absorption, which ultimately leads to iron overload. Thus, an iron-deficient state can be induced only with repeated phlebotomies; until recently, no other pharmacologic therapy could have been considered to modify the iron balance in SCA. With the expanding repertoire of novel therapies that target iron regulatory molecules, new potential therapeutic modalities that do not rely on repeated phlebotomies may finally be tested. Although it is based on a different pathophysiology, a similar therapeutic approach is also being considered for β thalassemia.

Because iron replacement therapy is not totally risk free (see potential increase for malaria infection associated with oral iron supplements), so is the induction of an iron-deficient state. This approach is contra-indicated for young children and

pregnant women. Poor adherence to serial phlebotomies has been reported, as well as decreasing fetal HB (Hb F) values with iron restriction. An increased platelet count is a well-known accompanying feature of iron-deficient states, and its pathophysiology is now better understood. Recently, the increased platelet count of iron deficiency anemia has been associated with increased thrombotic risk in a large retrospective survey.[10] This potential complication should be carefully considered, given the prothrombotic, procoagulant state of SCD. However, the convergence of multiple case reports, small case series, and the report of Parrow et al in a validated murine model of the disease all seem to indicate that iron restriction should now be seriously considered for both SCA and Hb SC disease, either as repeated phlebotomies or novel therapies, or both.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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TRANSPLANTATION

Comment on Greco et al, page 1556

Acute GVHD: do we trust our gut?

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In this issue of *Blood*, Greco and colleagues analyzed fecal microbiome diversity by 16S next-generation-sequencing techniques at 3 early time points in 100 consecutive hematopoietic stem cell transplantation (HSCT) recipients at a single center, suggesting that changes in microbiome diversity during the peri-HSCT period can identify recipients at higher risk of developing acute graft-versus-host disease (GVHD).[1] In recent years, there have been multiple analyses suggesting associations between restricted intestinal microbiome diversity (dysbiosis) and adverse outcomes after HSCT. As more data accumulate, those of us who treat patients are left wondering if any of these associations have any practical clinical value.

A 65-year-old man with complex karyotype acute myeloid leukemia in first complete remission is referred for evaluation for allogeneic HSCT. He was initially treated with conventional induction chemotherapy. His course was complicated by extended-spectrum β-lactamase–resistant *Escherichia coli* and vancomycin-resistant enterococcus bacteremia followed by *Clostridium difficile* colitis. A fully matched unrelated donor was identified. Normally, given the patient's age, disease, and donor, my recommendation would be a reduced-intensity conditioning HSCT employing standard tacrolimus/methotrexate GVHD prophylaxis. However, the recent infectious complications would indicate that this patient likely has significant dysbiosis. Should this alter my approach to GVHD prevention, perhaps adding anti-thymocyte globulin or employing a posttransplant cyclophosphamide-based approach? Should I defer HSCT after 1 to 2 cycles of consolidation chemotherapy in hopes that his microbiome can recover? Should I add measures designed to reconstitute microbiome diversity before, during, or after HSCT?

The multiple analyses suggesting the association of dysbiosis with outcomes such as acute GVHD, relapse, and mortality have been well summarized in a recent review in *Blood*.[2] In a landmark international study from 4 large centers involving 1362 patients, Peled and colleagues observed a pattern of loss of microbiome diversity through the HSCT process with domination by single taxa. Greater microbiome diversity during HSCT was associated with improved overall survival with subset analyses, suggesting this was driven by acute GVHD-related mortality.[3] Greco et al have built on this observation with samples collected at baseline, during nadir, and at engraftment, even finding that certain single-taxa predominance of *Enterococcus* or *Staphylococcus* species appeared to be associated with specific organ manifestations of acute GVHD. The limitations of this study reside in the relatively small sample size, homogenous conditioning/GVHD prophylaxis regimens, and lack of presented data on any association with nonrelapse mortality or survival.[1] Larger and more comprehensive analyses are needed to prove if such single-center analyses suggesting specific taxa associations with specific outcomes, as has been shown by other centers for GVHD[4] and relapse,[5] are valid, as these associations likely also reflect significant influences of local practices, antibiotic choices, hospital flora, and diet. Importantly, the BMT CTN 1801 collaboration is an ongoing prospective multicenter observational trial investigating if fecal microbiome diversity around the time of engraftment predicts 1-year nonrelapse mortality after reduced-intensity conditioning HSCT