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REVIEW

Ironing out the details of iron overload in myelofibrosis: Lessons from myelodysplastic syndromes

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ABSTRACT

Myelofibrosis (MF) and myelodysplastic syndrome (MDS) are hematopoietic stem cell disorders associated with cytopenias and red blood cell (RBC) transfusion dependence. Iron overload (IO) as a consequence of RBC transfusion dependence and its effect on outcomes in MF has not been formally studied. However, IO is a demonstrated poor prognostic feature in patients with MDS and congenital or acquired chronic anemias. Evidence that iron chelation therapy (ICT) reduces the deleterious effects of IO in MDS has led to speculation of benefit in MF. However, data supporting the use of ICT in MF is lacking. Neither disease has clear consensus guidelines for the use of ICT. Moreover, JAK–STAT inhibition, the cornerstone of MF treatment, often contributes to anemia and transfusional requirements. This manuscript reviews known and potential implications of IO in MF and highlights the need for prospective clinical investigations of ICT with consideration in the setting of JAK2 inhibitor therapy.

1. Introduction

Primary and secondary (post-essential thrombocythemia/polycythemia vera (ET/PV)) myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) characterized by bone marrow myeloproliferation and reticulin fibrosis, extramedullary hematopoiesis, splenomegaly, and progressive cytopenias. Nearly 40% of MF patients are anemic (hemoglobin (Hb) <10 g/dL) at time of diagnosis [1], but more than 60% of patients develop clinically significant anemia during the course of their disease [2]. Moreover, a quarter of patients with MF are transfusion dependent at time of diagnosis [1,3]. Anemia contributes to the overall clinical burden of MF due to related symptoms, decreased quality of life, and introduction of excess iron from red blood cell (RBC) transfusions.

A number of prognostic scoring systems have been constructed in order to risk stratify patients with MF for therapeutic decision-making. The presence of anemia is a recognized adverse variable in each. The first widely utilized risk stratification tool for MF was the Lille Classification score incorporating anemia (Hb <10 g/dL) and white blood cell count (WBC; >25 or $<4 \times 10^6$/L) into a three tier risk of low, intermediate, or high [4]. The Dynamic International Prognostic Scoring System (DIPSS) is a modern prognostic scoring system developed to risk stratify patients with MF utilizing 5 clinical variables to segregate patients into four distinct risk categories (low, intermediate-1, -2, and high risk). Age > 65 years, Hb <10 g/dL, WBC $>25 \times 10^9$/L, peripheral blood blasts ≥1%, and presence of constitutional symptoms are prognostic variables used to calculate the DIPSS risk score in a dynamic fashion for an individual patient with MF [5,6] (Table 1). Anemia alone is assigned two points in the DIPSS, as it was determined to hold the most significant influence on overall outcome in this analysis. The DIPSS-plus further refines risk stratification by incorporating (RBC transfusion dependence, thrombocytopenia ($<100 \times 10^9$/L), and abnormal karyotype [7]. Thus, it is well recognized that disease related anemia and transfusion dependence are significant concerns in terms of prognostic implication in MF.

Transfusion-associated hemosiderosis has an unclear biological and clinical effect in MF, as the relative contribution of iron overload (IO) as a consequence of RBC transfusion dependence on prognosis and outcome in MF has not been formally studied. Much of what is known about the mechanisms and adverse effects of IO originate from studies of patients with myelodysplastic syndrome (MDS) and congenital or acquired chronic anemia states. For example, the estimated annual per-patient cost of care for patients with thalassemia and complications of IO is approximately $15,000–20,000 resultant from cardiac disease, liver failure, endocrinopathies, or infectious etiologies [8,9].

The clinical impact of IO and the potential relationship to the heightened inflammatory response in MF warrants consideration, as mounting evidence of impaired hematopoiesis attributed to bone marrow hemosiderosis suggests a viable therapeutic target [10,11]. In addition, potential liver dysfunction, cardiac disease, and other complications of IO likely contribute to the morbidity and mortality associated with

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Table 1
Dynamic International Prognostic Scoring System (DIPSS) plus risk stratification and prognosis for myelofibrosis [6].

Risk category	Score	Median survival (months)
Low	0	180
Intermediate-1	1	80
Intermediate-2	2–3	35
High	4–6	16

MF. Here, we review the known and potential implications of IO in MF and highlight the rationale and need for formal prospective clinical investigation.

2. Mechanisms of iron overload

Iron absorption occurs in the proximal small bowel, and is carefully regulated (Fig. 1). Transport across the luminal cell membrane occurs via divalent metal transporter type 1 (DMT-1). Once inside the gut cell, iron can be stored as ferritin or transported to the basolateral surface to plasma transferrin through ferroportin, a membrane-embedded iron exporter [12]. Hepcidin is considered the "master regulator" of iron homeostasis, as it inhibits ferroportin, and thus keeps iron contained within the cell rather than the plasma. Notably, elevated levels of hepcidin in MF contribute to dysregulated iron homeostasis [1]. Dietary iron absorption, recycling of iron from erythrocytes, and release of iron from its stores are all blocked in this state and lead to ineffective erythropoiesis and iron overload [1].

Additionally, patients with MF often have low transferrin saturation, which is associated with microcytosis [13]. Transferrin is used to transport iron in the plasma. Most of the iron bound to transferrin is delivered to the transferrin receptors on the erythroid cells of the bone marrow. Once this occurs, the iron is internalized and can be used to synthesize heme, while the transferrin receptor is recycled back to the membrane or released in circulation. The iron incorporated into hemoglobin enters circulation via the red blood cells released from the bone marrow and will not be available for utilization again until the red cell dies. Iron which is left-over from heme synthesis binds to a storage protein called apoferritin to form ferritin [12].

Excess accumulation of iron released from aging and damaged erythrocytes saturates transferrin and, once saturated, leads to the circulation of non-transferrin bound iron (NTBI) in the serum. Labile plasma iron (LPI), a form of NTBI, is redox-active, and membrane permeant [14]. LPI is readily taken up by the liver, heart, pancreas, brain, and joint parenchymal cells, contributing to oxidant-mediated cell injury [15]. Studies have shown that LPI mediated toxicity, such as lysosomal disruption in hepatocytes, collagen formation and fibrinogenesis, and lipid peroxidation in cardiac and spleen cells can contribute to the development of congestive heart failure, arrhythmias, cirrhosis, hepatocellular carcinoma, insulin resistance and diabetes, arthritis, fatigue, and sexual dysfunction (Table 2) [15,16,17,18,19]. Typically, heart failure develops more rapidly than cirrhosis, and therefore is a more common cause of death from transfusion-related IO [17]. Additionally, patients are at increased risk of developing infectious complications when in an IO state [17].

Each unit of RBC contains 200 to 250 mg of iron, for which the body lacks an effective mechanism of excretion. The reticuloendothelial

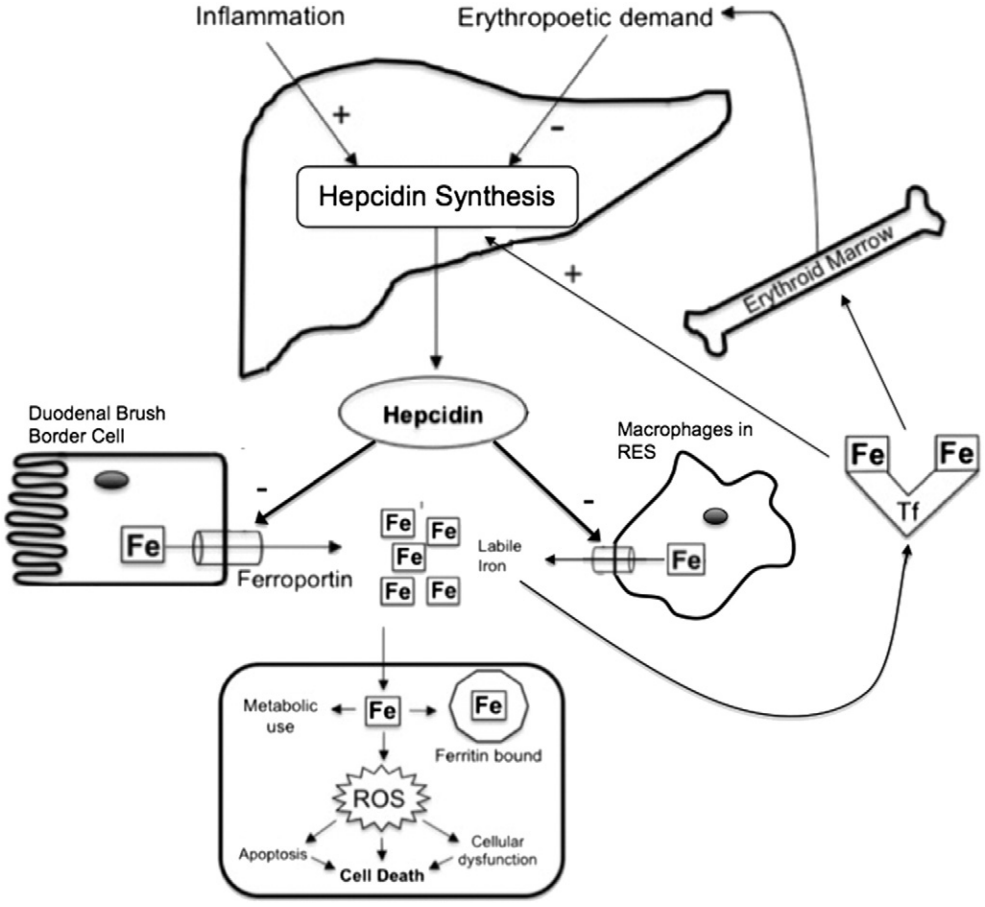

Fig. 1. Iron metabolism and regulation. Iron is absorbed in the duodenum and transported into the blood stream by ferroportin. Hepcidin, the key regulator of iron metabolism, inhibits iron transport by binding ferroportin. Hepcidin is positively regulated by transferrin levels, as well as inflammation, and is negatively influenced by erythropoietic demand. Labile iron is taken up by hepatocytes and cardiac myocytes, among other tissues, generating reactive-oxygen species (ROS) mediated dysfunction, which contributes to pathologic findings seen in iron overload states.