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Review

Iron Toxicity and Chelation Therapy in Hematopoietic Stem Cell Transplant

Alessandro Isidori[1,*], Federica Loscocco[1], Giuseppe Visani[1], Martina Chiarucci[1], Pellegrino Musto[2], Anne-Sophie Kubasch[3], Uwe Platzbecker[3,†], Francesca Vinchi[4,5,**,†]

[1] Hematology and Stem Cell Transplant Center, AORMN Hospital, Pesaro, Italy
[2] Unit of Hematology and Stem Cell Transplantation, Department of Emergency and Organ Transplantation, "Aldo Moro" University School of Medicine, AOU Consorziale Policlinico, Bari, Italy
[3] Department of Hematology, Cellular Therapy and Hemostaseology, Leipzig University Hospital, Leipzig, Germany
[4] Iron Research Program, Lindsley Kimball Research Institute, New York Blood Center, New York, New York
[5] Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, New York

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A B S T R A C T

Many patients with hematologic malignancies receive RBC transfusion support, which often causes systemic and tissue iron toxicity. Because of their compromised bone marrow function, hematopoietic stem cell transplant (HSCT) recipients are especially vulnerable to excess iron levels. Iron toxicity may compromise transplant engraftment and eventually promote relapse by mediating oxidative and genotoxic stress in hematopoietic stem cells (HSCs) and further impairing the already dysfunctional bone marrow microenvironment in HSCT recipients. Iron toxicity is thought to be primarily mediated by its ability to induce reactive oxygen species and trigger inflammation. Elevated iron levels in the bone marrow can decrease the number of HSCs and progenitor cells, as well as their clonogenic potential, alter mesenchymal stem cell differentiation, and inhibit the expression of chemokines and adhesion molecules involved in hematopoiesis. In vivo, in vitro, and clinical studies support the concept that iron chelation therapy may limit iron toxicity in the bone marrow and promote hematologic improvement and engraftment in HSCT recipients. This review will provide an overview of the current knowledge of the detrimental impact of iron toxicity in the setting of HSCT in patients with hematologic malignancies and the use of iron restriction approaches to improve transplant outcome.

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Iron plays a vital role in metabolism due to its ability to readily accept and lose electrons [1]. However, this eventually translates into toxicity when excess free iron is generated [1,2]. Iron causes toxicity by generating reactive oxygen species (ROS), inducing inflammation and promoting tissue injury and organ dysfunction [3,4].

Excess iron levels can develop as a result of genetic abnormalities, which enhance intestinal iron absorption (eg, mutations in the *HFE* gene; primary hemochromatosis), or due to repeated blood transfusions (eg, transfusion-dependent β-thalassemia, myelodysplastic syndrome [MDS]; secondary hemochromatosis) [2,5,6]. In patients who receive multiple blood transfusions, excess iron is introduced through transfused RBCs, which, once senescent, undergo phagocytosis by reticuloendothelial macrophages [3,7].

Iron toxicity is relatively common in hematopoietic stem cell transplant (HSCT) recipients, especially in those with myeloid diseases, and its prevalence ranges from 30% to 60% [7]. In this patient population, iron toxicity is primarily due to repeated blood transfusions both before and after the transplant [8]. However, increased intestinal iron absorption in the gut due to chemotherapy-associated mucositis, as well as iron release from damaged tissues, may also contribute [7,8]. Iron toxicity is associated with increased morbidity and mortality in HSCT recipients [9]. Treatment for patients with iron toxicity consists of iron chelation therapy. Iron-chelating drugs available in this indication include deferasirox and deferoxamine [10].

The aim of this narrative review is to summarize the literature on the effects of iron toxicity on bone marrow function, particularly in the HSCT setting, as well as on the use of iron chelation in HSCT recipients.

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*Correspondence and reprint requests: Alessandro Isidori, Hematology and Stem Cell Transplant Center, AORMN Hospital, Via Lombroso, 61122 Pesaro, Italy.
**Francesca Vinchi, New York Blood Center, 310 East 67th Street, New York, NY 10065.
E-mail addresses: aisidori@gmail.com (A. Isidori), FVinchi@nybc.org (F. Vinchi).
† F.V. and U.P. share senior authorship.

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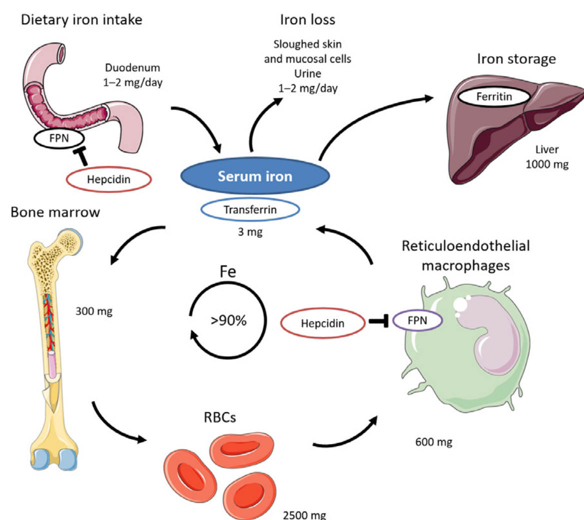

Figure 1. Iron metabolism and its regulation. FPN, ferroportin; Fe, iron.

PATHOPHYSIOLOGY OF IRON TOXICITY

The process that consumes most iron is erythropoiesis, accounting for the utilization of about 20 to 25 mg of iron per day (Figure 1). Therefore, over two thirds of iron in the human body is located in RBCs and their precursors as part of hemoglobin. While inorganic iron absorption from the diet occurs via duodenal enterocytes (approximately 1 to 2 mg/d), iron recycling from senescent RBCs is mediated by reticuloendothelial macrophages in much larger quantities (approximately 25 mg/d) [3,11,12]. Transferrin is responsible for the transport and delivery of iron to target cells that express the transferrin receptor 1, including erythroblasts [2,12]. Under physiologic conditions, extracellular iron circulates in the human body bound to transferrin, which is 20% to 40% saturated [4].

Humans lack a dedicated iron excretion mechanism, and iron loss occurs passively through sloughing of the skin and intestinal epithelium, as well as in urine [1]. Under normal circumstances, these processes are balanced as similar amounts of iron (1 to 2 mg) are absorbed and lost every day [13]. Therefore, the maintenance of this balance requires fine-tuned regulatory mechanisms to control body iron influx.

In humans, iron homeostasis is maintained through the regulation of duodenal iron absorption and macrophage iron recycling by the hepcidin/ferroportin regulatory system [13,14]. The hepatic hormone hepcidin orchestrates systemic iron fluxes by controlling the release of iron from enterocytes and reticuloendothelial macrophages through the occlusion and induction of degradation of the iron exporter ferroportin [11-13]. While elevated body iron and inflammation increase hepcidin levels, ineffective erythropoiesis and hypoxia reduce them, thus triggering ferroportin-mediated iron release from enterocytes and macrophages into the circulation. This mechanism accounts for iron toxicity, which patients with hematologic malignancies may initially develop due to the underlying hypoxia and ineffective erythropoiesis [12,14]. In these conditions, the renal production of erythropoietin is increased to stimulate erythropoiesis. This, in turn, promotes the absorption of iron from the diet, and its release from stores increases in parallel to enhance systemic iron availability for hemoglobin synthesis in newly produced RBCs [12]. This occurs due to hepcidin suppression, which is triggered by erythroferrone, a negative erythroid regulator of hepcidin. Through erythroferrone secretion, erythroblasts communicate erythron iron demand for increased systemic iron. Erythroferrone, by acting as a bone morphogenetic protein ligand trap, inhibits the activation of the bone morphogenetic protein/SMAD signaling pathway, which controls hepcidin induction in hepatocytes [15,16]. While other erythroid factors have been implicated as potential hepcidin suppressors (eg, twisted gastrulation protein homolog 1, growth/differentiation factor 15), erythroferrone appears to be the most relevant to date [11,12].

Malignancies such as MDS are often associated with ineffective erythropoiesis and anemia and characterized by reduced hepcidin levels, which increase systemic iron influx. Under these conditions, transferrin saturation may increase above 50%, eventually leading to the binding of iron to plasma proteins other than transferrin, the so-called non-transferrin-bound iron (NTBI) [2,17]. The labile plasma iron (LPI) represents the toxic fraction of NTBI that is redox active and chelatable. NTBI and LPI enter cells that express the importer ZIP14, where they accumulate bound to the iron storage protein ferritin and, eventually, contribute to the labile iron pool [17]. LPI and labile iron pool represent the target of iron chelation therapy [4]. While transferrin- and ferritin-bound iron is nontoxic, the toxicity of unbound iron lies in its ability to engage in the Fenton reaction. Through this process, iron triggers the formation of ROS, which oxidize lipids, proteins, and nucleic acids, resulting in cell and organ damage [4]. Organs that are most affected by iron toxicity include the liver, heart, pancreas, and pituitary and parathyroid glands [3].

While iron toxicity may initially develop in patients with hematologic malignancies as a result of hepcidin suppression due to ineffective erythropoiesis and hypoxia, long-term blood transfusion therapy is the main cause of iron toxicity in this patient population [14]. One unit of RBCs contains 200 to 250 mg of iron, which greatly exceeds the normal daily intake [3,14]. Chronic RBC transfusions can overwhelm the storage capacity of the reticuloendothelial system and the liver, such that the transfusion of 15 to 20 units of RBCs poses a risk of secondary hemochromatosis and iron-related toxicities [14].

IRON TOXICITY IN HSCT

For a subset of fit patients with hematologic malignancies, allogeneic HSCT is a valuable therapeutic option and the only one that is potentially curative. Despite considerable advances, HSCT-related mortality remains a major hurdle to the improvement of outcomes in HSCT recipients, particularly in elderly patients with advanced hematologic disorders.

Patients selected for HSCT frequently present with elevated transferrin saturation and serum ferritin due to a history of recurrent blood transfusions, the combined effects of which eventually lead to ineffective erythropoiesis (eg, in patients with MDS). While increased iron absorption and macrophage iron recycling from transfused RBCs enhance NTBI levels, in the HSCT setting, this effect can be amplified by additional mechanisms. NTBI formation reflects a disruption of iron homeostasis triggered by myeloablation and temporary inhibition of the main process utilizing iron (ie, erythropoiesis) and possibly predicts HSCT outcome [18-20]. It is unclear how much hepcidin production is “adequate” and how much hepcidin levels contribute to elevated NTBI levels during HSCT [21,22]. Finally, the cytotoxic action of the conditioning chemotherapy may lead to iron release from dying RBCs, promoting saturation of circulating transferrin and, therefore, NTBI formation [2,19,20,23,24]. Iron toxicity identified by the presence of NTBI can be used to establish iron toxicity during the peritransplant phase, but the effects of iron toxicity can manifest at various stages of the transplant.

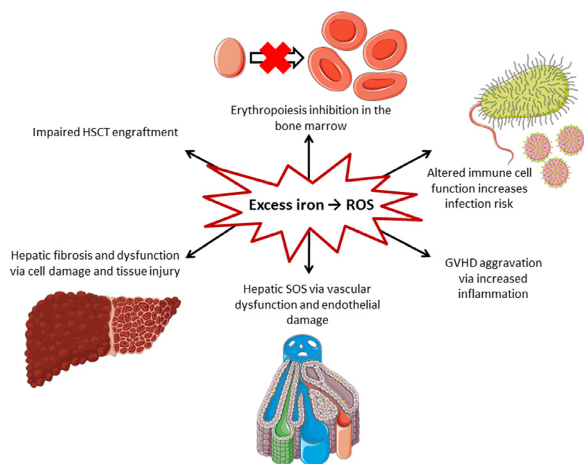

Figure 2. The effects of iron toxicity in patients who have undergone HSCT.

In HSCT recipients, iron toxicity is associated with short- and long-term complications (Fig. 2). Short-term complications include infections (both fungal, such as mucormycosis and aspergillosis, and bacterial, such as listeriosis), acute graft-versus-host disease (GVHD), and hepatic sinusoidal obstruction syndrome (SOS) [7]. Long-term complications also include infections, as well as chronic GVHD and abnormal heart and liver function [7]. Furthermore, a meta-analysis that included 4 prospective studies and 276 patients found that pretransplant ferritin levels >1000 ng/mL, but not pretransplant liver iron concentrations (LICs), were significantly associated with increased mortality (P= .036) [25].

Pretransplant Iron Toxicity

Pretransplant iron toxicity can affect the outcome of HSCT. The presence of elevated pretransplant serum ferritin is associated with an increased incidence of complications and reduced overall survival after transplant, especially in patients with MDS and acute myeloid leukemia (AML) [20,26-32].

In β-thalassemia hepatomegaly, the extent of hepatic fibrosis and adequate iron chelation are considered factors predicting HSCT outcome. These factors determine the extent of hepatic iron deposition (hepatomegaly) and toxicity (liver fibrosis), as well as effective suppression of reactive iron species NTBI and LPI (adequate chelation) [19]. Most clinical studies in patients with hematologic malignancies have explored the association of HSCT outcome and complications with markers of excess iron (eg, serum ferritin, transfusion burden), rather than toxic iron species (eg, NTBI, LPI) or the duration of exposure to these species. The first study in this direction was the ALLogeneic Iron inVEstigators (ALLIVE) trial, which evaluated the influence of biologically active iron on post-transplantation outcomes in patients with MDS and AML [20]. This study showed that NTBI levels rapidly increase during conditioning and patients with elevated pre-HSCT NTBI (0.4 μmol/L) and LIC ($\geq$125 μmol/g) have an increased incidence of nonrelapse mortality (mostly infection related) compared with patients with normal pre-HSCT NTBI and LIC [20]. Therefore, NTBI positivity predicts inferior overall survival in patients with MDS or AML who underwent transplantation. Furthermore, these findings suggest that treatment modalities that scavenge NTBI around the time of transplantation may improve survival outcomes, although clinical trials to confirm this are necessary [20]. Similarly, preliminary data from an observational study showed that patients with severe pre-HSCT iron overload (LIC >80 μmol/g) on liver magnetic resonance imaging (MRI) had significantly higher post-transplant mortality rates than those without severe pre-HSCT iron overload [33].

Early and Late Post-Transplant Iron Toxicity

Iron toxicity in the early post-HSCT period is more likely to be mediated by elevated NTBI and LPI. LPI levels substantially increase after the start of conditioning in patients with hematologic malignancies who undergo HSCT and remain elevated in the early post-transplant phase during engraftment [20]. In the late post-HSCT period, prolonged exposure of cells and tissues to NTBI/LPI and the presence of pretransplant excess iron may further compromise organ function. Excess iron in the HSCT setting may adversely affect HSCT outcome and post-transplant survival through multiple mechanisms [8,12,19]. (1) Iron excess can impair HSC engraftment early after transplant and delay anemia recovery through the detrimental effects on erythroid precursors, hematopoietic stem cells (HSCs), and the bone marrow niche (see following paragraphs). (2) In combination with a compromised immunity resulting from the conditioning regimen, cytopenias, and immunosuppressive agents, iron can further increase the risk of infections, both in the early and late post-transplant period, due to its ability to support micro-organism growth and to alter immune cell functions. As a result, infections such as aspergillosis, mucormycosis, fungal pneumonia, and candidiasis are common. (3) Iron may also aggravate acute and chronic GVHD through its proinflammatory action [34]. In addition, manifestations of excess iron can mimic exacerbated GVHD by triggering liver dysfunction and leading to unnecessary continuation/intensification of immunosuppressive therapy. (4) In the early post-HSCT period, excess iron can contribute to SOS by triggering vascular dysfunction and endothelial damage in a synergistic manner with chemotherapy [35]. (5) Finally, in the late post-transplant period, excess tissue iron can promote hepatic fibrosis and dysfunction, heart failure, diabetes, hypogonadism, and other endocrinopathies in patients who undergo transplantation [12,36].

While both experimental and clinical studies support a role for excess iron in hepatic and cardiovascular toxicity, evidence is accumulating (although clinical studies are still scarce) on iron-related toxicity in the bone marrow, with potentially detrimental consequences in the context of HSCT. In light of this consideration, below we will focus on and review the current knowledge about the cellular and molecular mechanisms underlying iron-mediated toxicities in hematopoiesis and erythropoiesis and the bone marrow.

IRON TOXICITY IN THE BONE MARROW

Iron Toxicity and Erythropoiesis

Excess reactive iron can induce dyserythropoiesis and reduce RBC production by inhibiting erythropoiesis, impairing erythroblast differentiation and maturation, and triggering dysplastic changes in erythroblasts [37]. Erythroid progenitor cells from patients with malignancies who show elevated serum ferritin display an impaired proliferation capacity when compared with patients with normal ferritin levels [38,39]. Excessive iron also promotes apoptosis of immature erythroblasts through the production of ROS. Chelating and antioxidant agents restore erythroblast differentiation by reducing ROS and cell apoptosis [40]. The enhanced sensitivity of erythropoiesis to iron toxicity is explained by the fact that both erythroblasts and RBCs can take up NTBI. Although this occurs only in pathologic conditions wherein NTBI is generated, this

form of iron cannot be utilized in heme synthesis and hemoglobin production, whereas it does contribute to ROS formation, resulting in erythroid cell cytotoxicity [41]. Iron toxicity affects the erythroid compartment; however, it may also promote the expansion of myeloid cells, with potential implications for relapse after HSCT [42].

Iron Toxicity and Hematopoietic Stem Cells

Excess iron can affect hematopoiesis by impairing hematopoietic stem and progenitor cells (HSPCs). The proliferation capacity of HSPCs from patients with excess iron is reduced and ROS levels are increased. Similarly, in vitro exposure of bone marrow mononuclear cells to iron decreases the percentage of $CD34^+$ stem cells and induces cell cycle arrest and apoptosis through ROS formation and p38 mitogen-activated protein kinase/p53 signaling pathway activation. These effects are attenuated by chelators and antioxidants [43]. Excess iron has been shown to reduce the survival and clonogenic function of HSPCs in mice [39,44]. In the bone marrow transplant setting, donor bone marrow cells from iron-loaded mice transplanted to normal recipients resulted in impaired engraftment due to iron-driven ROS production through *NOX4* induction and p38 mitogen-activated protein kinase/c-Jun N-terminal kinase signaling activation. The inhibition of these pathways by chelation and antioxidant strategies improved the long-term and multilineage engraftment of HSCs from iron-loaded donors after transplantation [37,44].

ROS critically regulate HSC stemness and control the maintenance of HSC quiescence [45]. Evidence from in vitro and in vivo studies shows that ROS impair hematopoiesis by disrupting the self-renewal, proliferation, and differentiation of HSCs [19]. In the endosteal compartment, HSCs exist in a quiescent state, which is maintained by hypoxic conditions and low ROS levels. Increased ROS activate dormant HSCs, releasing them from quiescence. Once activated, HSCs migrate to the perivascular compartment along the ROS gradient and undergo proliferation and differentiation. Therefore, high ROS levels associated with excess iron likely lead to abnormal HSC activation and exhaustion of the stem cell pool [45,46]. Importantly, ROS formation is elevated in the bone marrow of patients with MDS and is further exacerbated by iron toxicity due to repeated transfusions; however, it can be corrected by iron chelation [47]. In patients receiving HSCT, iron-driven oxidative stress may affect HSC survival and function, as well as impair engraftment, with detrimental effect on bone marrow transplant.

Iron has also been implicated in DNA damage, telomere shortening, and epigenetic abnormalities [47-50]. This suggests that iron induces genotoxic stress and likely contributes to bone marrow mutagenesis, thus acting as an additional driver of genomic instability in HSCs. The observation that conditions characterized by excess iron, such as thalassemia and hemochromatosis, are not associated with an increased incidence of malignancies indicates that iron itself does not promote leukemic transformation of HSCs. However, HSCs that already present genomic instability, as is the case in MDS, may be more sensitive to the additional genotoxic stress induced by excess iron [51,52]. This might play a role in relapse after bone marrow transplant in recipients with hematologic malignancies. However, the details of how iron affects HSCs and impairs engraftment or promotes relapse remain to be investigated.

Iron Toxicity and the Bone Marrow Microenvironment

Recently, a major role in the initiation and progression of hematologic malignancies has been attributed to the dysregulated bone marrow microenvironment [12,53-56]. The altered cytokine profile and cellular milieu in the bone marrow niche likely contributes to the loss of normal HSCs, hematopoiesis impairment, and malignant HSPC expansion.

The negative impact of excess iron on the hematopoietic microenvironment is illustrated by the observation that bone marrow transplant from non-iron-loaded donor mice to iron-loaded recipients leads to delayed hematopoietic reconstitution [37,42,57]. Iron likely exacerbates microenvironment impairment by affecting stromal, immune, and bone cell survival and function. In iron-loaded recipient mice, bone marrow stromal cells show reduced expression of key adhesion molecules, as well as altered expression profile of cytokines and growth factors that support the hematopoietic niche in iron-loaded animals [37,42,57]. Excess iron induces apoptosis and decreases the proliferation capacity of bone marrow-derived stromal mesenchymal stem cells (MSCs) and alters their osteogenic/adipogenic differentiation balance [57,58]. Finally, excess iron reduces the ability of MSCs to support colony formation by HSCs [57]. These effects have been attributed to increased ROS production due to elevated phosphatidylinositol 3 kinase expression and decreased Forkhead box protein O3 levels [57]. Moreover, ROS generation in iron-loaded MSCs is associated with depolarization of mitochondrial membrane potential and defective mitochondrial fusion/fission [59].

Excess iron, as well as iron deficiency, disrupts the delicate balance between bone destruction and production by influencing osteoclast and osteoblast differentiation and function [60,61]. Besides inducing cell death and suppressing cell proliferation, excess iron blocks the osteogenic differentiation of bone-forming osteoblasts and MSCs, suggesting an inhibitory activity of iron on osteogenic commitment and differentiation of MSCs and the matrix calcification process [58,60,62-64]. This mechanism is likely involved in osteoporosis, which is a major complication in patients with excess iron levels [60,61]. Conversely, iron chelation exerts pro-osteogenic effects on osteoblast progenitors [65]. Importantly, iron-driven impairment of MSC differentiation may interfere with the support and cross-talk of the osteo-hematopoietic niche with HSCs [66]. Overall, the dysfunctional bone marrow microenvironment produced by iron toxicity may provide defective support for hematopoiesis and erythropoiesis, as well as negatively affect recovery following HSCT.

Finally, excess iron has the potential to affect inflammation in the bone marrow microenvironment. Although specific evidence about the immunomodulatory and inflammatory action of iron in the HSCT setting is missing, iron has been shown to alter the functions and cytokine production in immune cells, including neutrophils, monocytes, and macrophages [12,67-71]. Inflammation exerts a detrimental effect on erythroid progenitors and HSPCs and thus can contribute to bone marrow failure and delayed/poor HSCT engraftment. Chronic inflammatory cytokine signaling can inhibit erythroid differentiation and alter the balance between self-renewal and differentiation in HSCs, thus aggravating anemia and leading to immune-mediated HSPC exhaustion [72-74]. Through these mechanisms, iron-driven inflammation in the bone marrow can delay or impair the recovery of hematopoiesis and erythropoiesis after HSCT. Finally, iron-activated immune cells can aggravate inflammation in organs such as the liver, potentially predisposing patients to peri- and post-transplant complications.

ASSESSMENT OF IRON TOXICITY IN HSCT PATIENTS

Direct iron measurement via liver and/or heart biopsy is an invasive procedure that is used as infrequently as possible;

therefore, estimation of total body iron stores is more often achieved indirectly via the measurement of serum ferritin and transferrin saturation, hepatic and cardiac MRI (R2 Ferriscan or T2* method), or a supraconducting quantum interface device. Serum ferritin levels are the mainstay of the clinical evaluation of excess iron [7,75]. However, because ferritin is an acute phase reactant, serum concentrations are increased by inflammatory conditions [7]. Despite the greatest accuracy, a supraconducting quantum interface device is not widely available yet due to elevated costs. Since NTBI and LPI are responsible for tissue iron accumulation, these parameters are real-time indicators of total body iron status, and their measurement in patients with hematologic malignancies likely reflects a condition of iron toxicity [19,20,76]. Specifically, NTBI/LPI may be used to assess peritransplant cell/tissue exposure to iron and define initiation and duration of iron chelation to reduce both pre- and post-transplant iron toxicity. In a study of 60 patients with various conditions associated with excess iron, transferrin saturation was found to be positively correlated with NTBI levels [77]. Suppressing the peritransplant increase in NTBI by adequate chelation likely protects organs from iron toxicity in the early post-transplant period, preventing early post-HSCT complications. However, clinical trials are needed to confirm this. Currently, numerous challenges exist with laboratory standardization and harmonization of the measurement and interpretation of NTBI and LPI. For example, in a study of patients with AML, acute lymphoblastic leukemia (ALL), or MDS undergoing HSCT, LIC estimated from MRI T2* scans was strongly correlated with serum ferritin levels and transfusion history, whereas no meaningful correlations were observed between LPI and LIC, serum ferritin, transferrin saturation, or transfusion history [78]. Improvements in methodology will help to establish reproducible and reliable techniques for NTBI and LPI quantification, as well as the adoption of these parameters as markers of iron toxicity in the clinical laboratory setting [12].

MANAGEMENT OF IRON TOXICITY IN HSCT PATIENTS

While phlebotomy is the simplest approach to removing excess iron, its use is limited to patients with venous access, platelet engraftment, and good graft function [79]. Iron chelation therapy is the main pharmacologic option for alleviating the iron burden in patients with iron toxicity [12,80]. Deferoxamine is not indicated in this setting because of its short half-life, which requires prolonged infusion, and its siderophore activity, which allows for iron release to micro-organisms. The oral chelator deferiprone has a longer half-life but is also associated with the potential for development of agranulocytosis. The latest generation chelator deferasirox has the advantage of a longer half-life and the ability to effectively scavenge NTBI/LPI. Some common adverse events (AEs) associated with deferasirox therapy may overlap with acute post-HSCT AEs. However, this aspect has been significantly improved with the latest deferasirox formulation. Importantly, the timing of intervention with chelation therapy in the HSCT setting is a key factor in minimizing iron toxicity. While patients would benefit from undergoing HSCT at the lowest possible pre-HSCT body iron burden, the formation of NTBI upon conditioning requires peritransplant chelation to limit reactive iron toxicity during the engraftment period [80]. Currently, however, there is no consensus on how to best to identify patients who would benefit from iron chelation therapy in the pre-transplant setting. Finally, effective management of late post-transplant iron toxicity may significantly improve long-term patient outcomes.

CLINICAL STUDIES ON IRON CHELATION THERAPY IN HSCT

Prospective Studies

Multiple prospective studies have evaluated the efficacy and safety of deferasirox chelation therapy in the setting of HSCT (Table 1).

A prospective, multicenter DE02 trial assessed the safety and efficacy of deferasirox, as well as its effect on iron homeostasis, in 76 allogeneic HSCT recipients [81]. Deferasirox was started a median of 168 days after HSCT, at which time, 84% of patients were on immunosuppressive therapy. Serum ferritin declined from 2045 ng/mL at baseline to 957 ng/mL at the end of the study, and a negative iron balance was observed in 84% of patients. Treatment-related AEs were reported in 54 patients (71.1%); the most common treatment-related AEs were increased blood creatinine (26.5%), nausea (9.0%), and abdominal discomfort (8.3%) [81].

The efficacy and safety of deferasirox were also evaluated in a prospective, open-label, phase IV study conducted in 30 adult patients who had undergone an allogeneic HSCT due to hematologic malignancies and had transfusion iron overload [82]. Patients received deferasirox for 52 weeks or until the serum ferritin level was below 400 ng/mL. Significant reductions in median serum ferritin (P = .002) and LIC (P = .007) were observed after 52 weeks. Patients who completed the study had a significantly greater reduction in serum ferritin than those who discontinued the study prematurely (P = .008). Treatment-related AEs occurred in 17 patients (56.7%) and were mostly mild or moderate in severity; no serious AEs were reported [82].

Iron chelation therapy with deferasirox was effective in improving overall survival and reducing the rate of relapse in a study of 83 adult patients with AML who had HSCT [83]. Immediately prior to transplantation, serum ferritin levels were 26 to 500 μg/L in 20% of patients, 500 to 2500 μg/L in 21% of patients, and over 2500 μg/L in 59% of patients. Following transplantation, 23 patients received deferasirox when their serum ferritin exceeded 1000 μg/L. After a median follow-up of 24 months, the 5-year overall survival rate was 59% for patients who were treated with deferasirox, compared with 34% for patients who were not (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.15 to 0.76; P = .008). The 5-year relapse rate was 18% compared with 41%, respectively (HR, 0.22; 95% CI, 0.07 to 0.73; P = .012). No significant AEs were noted [83].

One study investigated the possibility of using deferoxamine as pre-HSCT iron chelation therapy [84]. Patients with AML, ALL, or MDS who were scheduled for HSCT and had serum ferritin exceeding 1000 μg/L and LIC >89 μg/g received deferoxamine over 8 to 12 hours. Serum ferritin levels decreased between pre- and postchelation; however, LIC showed no change on liver MRI. Although this study closed prematurely due to slow enrollment, patient outcomes were positive, with no deaths, relapses, or cases of SOS or severe acute GVHD. This study highlights the difficulties associated with recruiting patients with pre-HSCT iron toxicity, including the short time period between the end of conditioning therapy and HSCT [84].

Retrospective Studies

Deferasirox has also been the subject of several retrospective studies (Table 1). In a retrospective analysis that included 80 patients who received allogeneic HSCT for AML, ALL, aplastic anemia, lymphoma, or MDS and had iron overload, the effectiveness of deferasirox was compared with that of phlebotomy [85]. The median duration of deferasirox treatment

Table 1
Summary of Clinical Studies Examining Iron Chelation Therapy with Deferasirox in Allo-HSCT

Author	Design and Duration	Patients	Efficacy Summary	Safety Summary
Jaekel et al. (2016) [81]	P, MC, OL 1 yr	Allogeneic HSCT recipients (n = 76) Median (range) age, 56 (19 to 70) yr	Median exposure to deferasirox was 330 d Following deferasirox treatment, serum ferritin decreased from baseline of 2045 to 957 ng/mL	Investigator-reported AEs occurred in all patients (100%); the most common were increased blood creatinine (n = 41, 54%), nausea (n = 32, 42%), and vomiting (n = 30, 40%)
Yesilipek et al. (2018) [87]	P, MC, SA, Ph2 1 yr	Patients with β-thalassemia major who underwent HSCT (n = 27) Median (range) age, 9 (3 to 16) yr	Deferasirox (10 to 20 mg/kg/d) was associated with a significant decrease in median serum ferritin level over 1 yr (from 1718.0 to 845.3 μg/L; $P < .001$)	AEs were reported by 25 patients (93%); the most common AEs were anemia (n = 7, 26%), ALT increase (n = 7, 26%), cough (n = 7, 26%), and pyrexia (n = 7, 26%)
Inati (2017) [91]	P, R, MC, 1 yr	Patients with β-thalassemia major who underwent HSCT (n = 27) Mean (SD) age, 12.4 (3.9) yr	Both deferasirox (10 to 20 mg/kg/d) and phlebotomy were associated with significant reductions in LIC and serum ferritin, among those patients with baseline serum ferritin $\geq$1000 ng/mL	AEs occurred in 2/12 patients (17%) receiving deferasirox: skin rash (n = 1, 8%) and increased liver function tests (n = 1, 8%)
Vallejo et al. (2014) [82]	P, MC, OL, Ph4 1 yr	Allo-HSCT recipients with iron overload (n = 30) Median (range) age, 47 (20 to 65) yr	Deferasirox (10 to 30 mg/kg/d) was associated with a significant reduction from baseline in median serum ferritin (1444 versus 755.5 ng/mL; $P = .002$) and median LIC (14.5 versus 4.6 mg Fe/g; $P = .007$)	AEs were reported in 29 patients (97%); 17 patients reported drug-related AEs, of which serum creatinine increase (n = 11, 37%), AST and/or ALT increase (n = 5, 17%), and diarrhea (n = 2, 6.7%) were the most common
Michallet et al. (2017) [83]	Not stated	High-risk patients with AML who received allo-HSCT (n = 80) Median (range) age, 45 (18 to 67) yr	23 patients received deferasirox (20 to 30 mg/kg/d) when serum ferritin exceeded 1000 μg/L; serum ferritin stabilized to normal values among all patients The 5-yr OS rate was significantly greater among patients who received deferasirox compared with those who did not (HR, 0.34; $P = .008$)	No significant AEs were observed in the 23 patients who received deferasirox
Sivgin et al. (2013) [85]	RT	Allo-HSCT recipients with iron overload (n = 80) Mean (SD), age 31 (10) yr	Median treatment duration was 122 d Deferasirox (20 to 30 mg/kg/d) significantly reduced serum ferritin levels ($P < .001$) Compared with deferasirox, patients receiving phlebotomy had poorer OS ($P < .001$) and DFS ($P = .023$)	AEs were reported by 14 patients (33%); the most common AEs were nausea (n = 8, 19%) and vomiting (n = 3, 7%)
Maximova et al. (2017) [86]	RT	Pediatric allo-HSCT recipients (n = 42) Median (range) age, 10 (2 to 17) yr	Mean deferasirox dose was 22.5 mg/kg/d Median duration of treatment was significantly longer in patients with trough deferasirox levels <10 μg/mL (135.7 d) than in patients with trough deferasirox levels >10 μg/mL (41.8 d, $P < .0001$) Mean tissue iron concentrations were significantly higher in the <10-μg/mL group versus the >10-μg/mL group (261.9 versus 133.4 μmol/g; $P < .001$)	Drug-related AEs occurred in 22 patients (52%); the most common drug-related AEs were fatigue (n = 14, 64%), decreased appetite (n = 14, 64%), and nausea/vomiting (n = 10, 46%)

P indicates prospective; MC, multicenter; OL, open-label; SA, single-arm; Ph, phase; ALT, alanine aminotransferase; R, randomized; AST, aspartate aminotransferase; OS, overall survival; RT, retrospective; DFS, disease-free survival.

was 122 days. Compared with phlebotomy, deferasirox was shown to significantly reduce serum ferritin levels ($P< .001$). Median (range) overall survival was 25.0 (3.0 to 72.0) months in the deferasirox group and 16.0 (1.0 to 63.0) months in the phlebotomy group; the risk of death was higher in the phlebotomy group according to the univariate (HR, 3.22; 95% CI, 1.67 to 6.23; $P = .001$) and multivariate analyses (HR, 3.51; 95% CI, 1.75 to 6.99; $P < .001$). Median (range) disease-free survival was 22.0 (8.0 to 43.0) months in the deferasirox group and 11.0 (3.0 to 24.0) months in the phlebotomy group ($P = .023$) [85].

Deferasirox treatment was evaluated in 42 pediatric patients who had undergone an allogeneic HSCT and had iron overload [86]. Patients were divided into 2 groups based on trough plasma deferasirox concentrations, with the cutoff of 10 μg/mL. The median duration of treatment was significantly longer in patients with trough deferasirox levels <10 μg/mL (135.7 days) than in patients with trough deferasirox

levels >10 μg/mL (41.8 days, $P < .0001$). Mean tissue iron concentrations were 261.9 and 133.4 μmol/g in the respective groups ($P < .001$). Most treatment-related AEs (90.5%) and all major AEs occurred in patients with trough deferasirox concentrations >10 μg/mL. Chelation therapy was interrupted in 1 patient with a trough deferasirox concentration <10 μg/mL and 16 patients (84.2%) with trough deferasirox concentrations >10 μg/mL. Close monitoring of pediatric patients on deferasirox treatment is recommended [86].

Case Reports and Case Series

In a series of 7 pediatric patients with β-thalassemia who had undergone HSCT and had poor adherence to phlebotomy or deferoxamine, deferasirox therapy was associated with a significant reduction in serum ferritin levels ($P = .018$) [87]. A significant increase in serum creatinine was also noted ($P = .034$), although it remained within the normal range in all patients.

Evidence of the effectiveness of deferasirox is provided by a case series of 8 patients who had incomplete hematologic reconstitution following allogeneic HSCT and received post-transplant transfusion of more than 20 RBC units [88]. Hemoglobin levels increased in all patients and, after a median of 23 days, all patients achieved transfusion independence. After a median of 26 days, no further platelet support or growth factor administration was required. In addition, a progressive decline in ferritin levels was observed [88].

Deferasirox reduced serum ferritin and was well tolerated in 2 pediatric patients with β-thalassemia major who underwent HSCT [89]. Deferasirox was also shown to reverse poor graft function after HSCT in a 27-year-old female patient with severe aplastic anemia [90].

FINAL CONSIDERATIONS

The effects of iron toxicity differ substantially between individuals, even in patients with the same disease and similar iron levels [13]. Iron toxicity is likely determined by the total tissue iron concentration, genetic and environmental factors, and the duration of exposure [13].

The short-term consequences of iron deposition in HSCT recipients are likely mediated by the detrimental effects of iron excess in the bone marrow as well as other organs, including the liver and heart, and the resulting ROS production [2,19]. Iron toxicity can disrupt bone marrow function and compromise hematologic improvement and transplant engraftment in HSCT recipients [2,19,42,44,57]. In addition, iron can induce infections and organ damage, as well aggravate GVHD and SOS. Encouragingly, however, iron chelation therapy was shown to reduce or prevent ROS damage in experimental studies [44,57]. The results of several prospective and retrospective studies, as well as case reports and case series, suggest that iron chelation therapy with deferasirox is effective and well tolerated in HSCT recipients with excess iron. Significantly, deferasirox also appears to promote hematologic recovery after allo-HSCT [88].

Based on the current understanding that iron excess is potentially toxic in HSCT and that iron chelation is associated with improved hematologic recovery and engraftment following HSCT, the use of chelation therapy to prevent iron toxicity may be considered. This may be achieved with short-duration deferasirox therapy, which may eventually be administered at lower doses due to tolerability issues during the post-transplant period.

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