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CURRENT REVIEW OF IRON OVERLOAD AND RELATED COMPLICATIONS IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Iron Overload in Hematopoietic Stem Cell Transplantation

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Abstract:

Iron overload is an adverse prognostic factor for patients undergoing hematopoietic stem cell transplantation (HSCT). In HSCT setting, pretransplant and early posttransplant ferritin and transferrin saturation were found to be highly elevated due to high transfusion requirements. In addition to that, post-HSCT iron overload had shown to be related with infections, hepatic sinusoidal obstruction syndrome (SOS), mucositis, liver dysfunction and acute GVHD. Hyperferritinemia causes decreased survival rates in both pre and post transplant setting. Serum ferritin levels, magnetic resonance imaging (MRI) or liver biopsy are diagnostic tools for iron overload. Organ dysfunction due to iron overload may cause high mortality rates and therefore a sufficient iron chelation therapy is recommended in this setting. In this review the management of iron overload in adult HSCT is discussed.

Introduction:

Hematopoietic stem cell transplantation (HSCT) is an established treatment approach in a variety of hematological disorders but is still complicated with excessive mortality and morbidity despite advances in conditioning regimens and infectious disease management (1-5). Today high dose therapy and auto-HSCT is a treatment option in selected hematopoietic and non-hematopoietic tumours (4). The common early complications include infections and mucositis (5). The allo-HSCT is recommended in congenital or acquired bone marrow failures and hematological malignancies. Sinusoidal obstruction syndrome (SOS), hemorrhagic cystitis, engraftment failure, idiopatic pneumonia syndrome, infection and graft versus host disease (GVHD) are major causes of morbidity and non-relapse mortality (6). Late complications of HSCT mainly involve skin, oral mucosa, ocular, gastrointestinal, pulmonary, endocrine and metabolic system, infectious, renal, neurological, psychosocial and cardiovascular system as well as secondary malignancies (6,7).

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Iron overload is a common condition in patients with hematological malignancies and HSCT recipients. The incidence of iron overload, in auto-HSCT is around 34%, less frequent than allo-HSCT (8). In allo-HSCT setting, the incidence of iron overload varies between 30% to 60% (9,10). Sucak et al investigated, retrospectively, 24 liver biopsies for evaluation of the cause of liver dysfunction after allo-HSCT. Iron overload was detected totally in 75% of these liver biopsy samples and as a sole histopathologic abnormality in 33% of recipients (11). The main factor of high incidence of iron overload in both transplants is exposure to red blood cell (RBC) transfusions both during initial treatment and post transplant period (10).

This review will focus on normal iron hemostasis and mechanisms of iron overload in HSCT receipents, effects and management of excess iron in the setting of HSCT.

1. Iron homeostasis and the mechanisms of iron overload

Iron is an essential element for many enzymatic functions and hemoglobin synthesis. There are four major cell types determining the iron content and distribution: duodenal enterocytes, erythroid precursors, reticuloendothelial macrophages and hepatocytes. Iron cycle in the body starts with duoedenal enterocyte absorbtion of 1 to 2 mg of iron per day. Iron binds to transferrin and is being uptaken by erythroid precursors for heme synthesis. Reticuloendothelial macrophages clear erythrocytes and release the iron from heme in order to export it to the circulation and store it in the form of ferritin. Hepotocytes are major cells for iron storage as ferritin and production of peptide hormone hepcidin. However in the state of excess of iron, reactive oxygen species (ROS) effects functions of organs such as liver, heart and endocrine glands (12). In patients receiving regular transfusions, tissue iron deposition can begin within 1-2 years, however clinically evident cardiac or hepatic dysfunction may not occur till 10 or more years (10). Excess iron is also associated with the pro-oxidant effects which contribute to DNA damage and promotion of oncogenesis.

There are many research ongoing in related to erythroid regulators of iron homeostasis. Hepcidin is the main regulator of iron absorption and tissue distribution which controls iron in plasma by absorption of dietary iron in intestine, recycling of iron by macrophages and mobilization from hepatocyte storage. Hepcidin promotes degradation of ferroportin leading to retention of iron in iron-exporting cells and decreased flow of iron into plasma (13). In inherited anemias with ineffective erythropoiesis, beta-thalassemia and congenital dyserythropoietic anemia, pathological suppression of hepcidin synthesis and hyperabsoption of dietary iron occurs (14). In thalassemia, growth differentiation factor 15 (GDF 15) and twisted-gastrulation 1 (TWSG1) were proposed as pathological suppressors of hepcidin (15,16), however, their roles were not defined. Kautz et al. defined a new erthyroid regulator essential for early suppression of hepcidin after erytropoietic stimulation and named it “erythroferrone” (ERFE). If it is confirmed in clinical studies ERFE neutralization will be a new treatment strategy in iron overload in iron-loading anemias.

Several clinical reports show that iron chelation therapy improved hematopoiesis in iron overloaded patients of MDS (17-18). Recently, for investigating the impact of iron deposition on hematopoiesis, researchers initiated studies in vivo. Okabe et al, examined iron-overloaded mice and hematopoietic parameters as well as bone marrow microenvironment. They showed that hematopoietic parameters of the peripheral blood did not change, however myeloid progenitor cells in the bone marrow were increased. The number and the function of erythroid progenitors remained the same. Bone marrow transplantation to iron-overloaded mice resulted

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with delayed hematopoietic reconstitution. The levels of erythropoietin and thrombopoietin were significantly low in iron-overloaded mice compared to normal group. The authors concluded that excess iron disrupt hematopoietic microenvironment (19). Zhang et al evaluated the effect of iron overload on the bone marrow microenvironment in mice and found that chemokine stromal cell-derived factor-1, stem cell factor-1 and vascular endothelial growth factor-1 expression were decreased. The decreased hematopoietic functions were contributed by elevated phosphatidylinositol 3 kinase (PI3K) and reduced Forkhead box protein (FOXO3) mRNA expression which could induce generation of ROS. This data showed that iron overload could impair the bone marrow microenvironment (20). Chai et al showed that iron overload markedly decreased the ratio and clonogenic function of murine hematopoietic stem and progenitor cells by elevation of ROS (21).

2. Iron overload and related complications in HSCT

Iron overload is a prominent problem in HSCT recipients. HSCT recipients receive large RBC transfusions both during the pre and peri-transplant periods. In addition to that prolonged dyserythropoiesis, increased intestinal iron absorbtion due to chemotherapy associated mucositis and release of iron from damaged tissues raise iron to undesired levels (10). Chemotherapy and radiotherapy associated hepatic damage may also contribute to the release of iron stores and diminish transferrin synthesis (22, 23). In an autologous HSCT mice model, iron overload was detected to be associated with an increased melphalan and busulfan toxicities through a pharmacodynamics interaction (24). In a recent study, the interacting effects of total body irridation and cell transplantation on the expression of iron regulatory genes had contributed to iron overload in murine recipients (25).

Armand et al retrospectively analysed the impact of elevated pre-transplant serum ferritin levels in patients undergoing myeloablative stem cell transplantation in 590 patients. In that analysis a strong relationship was detected between pre-transplant ferritin levels and survival rates. The 5-year overall survival (OS) for patients with pretransplant ferritin levels in the first quartile (0 ng/mL-231 ng/mL) was 54%; (95% confidence interval [CI], 45%-63%); in the second quartile (232 ng/mL-930 ng/mL), 50%; (95% CI, 41%-59%); in the third quartile (931 ng/mL-2034 ng/mL), 37%; 95% CI, 27%-46%); and in the fourth quartile (>2034 ng/mL), 27%; (95% CI, 18%-36%) ($P < .001$). The 5-year disease-free survival (DFS) rates, from lowest to highest quartile, were 43% (95% CI, 33%-53%), 44% (95% CI, 35%-54%), 34% (95% CI, 24%-43%), and 27% (95% CI, 19%-36%) ($P< .001$). Majority of patients diagnosed with MDS and acute leukemia had an increased risk of mortality (HR: 2.6, P=0.003; HR: 1.6, P=0.031). Authors also stated that pre-transplant ferritin levels in the top quartile were associated with a borderline increase in the risk of VOD (odds ratio=1.7, 95% Cl 1.0 to 2.9, P=0.054) (26). The effect of hyperferritinemia in allo-HSCT with reduced intensity conditioning was studied by Barba et al in 201 adult lymphoma patients. In the multivariate analysis, patients with hyperferritinemia at transplantation (>399 ng/ml) showed a lower 4-year OS (HR, 1.8 (CI,1.2 to 2.8);P=0.008) and a higher non-relapse mortality (NRM) (HR, 1.8 (CI,1.1to 3.2);P=0.03) than those without hyperferritinemia (27). Mahindra et al. studied the hyperferritinemia in autologous HSCT setting in 315 patients with Hodgkin or non-Hodgkin lymphoma. On multivariate analysis, a pretransplant ferrtitin levels of >685ng/ml was associated with significantly lower OS (P=0.002) and relapse-free survival (P=0.021) but increased risk of relapse (P=0.005) and relapse related mortality (P<0.001)(28).
In a metanalysis, pre-HSCT iron overload has been related with poor overall survival and

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higher incidence of NRM (29). Nakamae et al showed a significant relation with serum ferritin levels at day 30 and 1 year after HSCT with OS (30).

Prognostic impact of iron overload in post-transplantation period was determined by Meyer et al in 290 patients who received myeloablative unmanipulated allo-HSCT. Ferritin and transferrin saturation were elevated before and increased in the first months after transplantation as a result of high transfusion needs. Plasma iron levels were found to be variable depending on food intake and time of the day. After a peak of first 1 to 3 months post-transplantation, ferritin levels decreased gradually. Hyperferritinemia had a negative effect on survival in all periods (0 to 6 months P<.001; 6 to 12 months P<.001; 1 to 2 years P=.02; 2 to 5 years P=.002) and no relation with RBC transfusion dependency and graft-versus-host disease (31). On the other hand, Armand et al evaluated the effect of serum iron parameters as well as liver and cardiac iron deposition by MRI prospectively in 45 patients receiving myeloablative allo-HSCT. They found no significant increase in ferritin levels and liver or cardiac iron content in the 12 months following allo-HSCT. Pre-transplant ferritin (as reflected in liver iron content) was not found to be related with increased mortality, relapse, or GVHD. Authors concluded that prospective studies using direct measurement of iron overload rather than ferritin should be designed (32).

Post-HSCT iron overload had shown to be associated with infections, hepatic sinusoidal obstruction syndrome (SOS), mucositis, liver dysfunction and acute GVHD (33-37). Early and late complications of HSCT that have been associated with iron overload is summarized in Table 1. Iron accumulation may cause increased growth and virulence of *Aspergillosis* species (38). Maertens *et al*, showed an association of iron overload with mucormucosis in five allo-HSCT recipients (39). Sivgin et al suggested that higher ferritin levels generally above 1550 ng/ml were associated with invasive fungal pneumonia (IFP) in pre transplant allo-HSCT recipients. Patients with IFP had lower Karnofsky performance status ($p<0.05$) and poorer OS (39.6 vs 60.9 months, P=0.015) (40). Increased risk of hepatosplenic candidiasis was also detected in patients with higher pre-transplant ferritin levels (41). Several other bacterial infections were also detected in iron overloaded HSCT recipients (10).

Table 1. Iron overload related complications after HSCT (Adapted from 10)

Complication	**Comments**
Early (< 1 year) post transplant	
Infections	Aspergillosis, mucormucosis, invasive fungal pneumonia, candidiasis, other infections
Acute GVHD	No clear evidence
Hepatic sinusoidal obstruction syndrome	Iron overload might increase risk
Late (>1 year) post transplant	
Infections	Mucormycosis, invasive aspergillosis and other infections
Chronic GVHD	No clear evidence
Liver function abnormalities	Iron overload increases risk
Cardiac late effects	Iron overload might increase risk

Liver dysfunction was evaluated in allo-HSCT setting with a pre and post-transplant liver biopsies in 25 recipients. Fatal veno-occlusive disease occurred in 2 and biochemical abnormalities in 24 patients. Iron overload was detected to be increased in post-tranplant

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biopsies (96%, P<0.01) (42). It was suggested that Iron induced hepatotoxicity is multifactorial and consists of oxidative stress and modulation of gene expression of Kupffer cells (43). Iron-generated oxyradicals and peroxidation of lipid membranes may also cause cellular injury (44). It is well known that Sinusoidal obstruction syndrome, which is an important cause of transplant related mortality of up to 50%, characterized by the presence of at least 2 of the following features: hyperbilirubinemia, painful hepatolomegaly and weight gain (45). SOS was diagnosed in 88 patients (21%) at a median of 10 days (range, 2-29 days) in 427 HSCT recipients. Pretransplant serum ferritin levels higher than 1000 ng/dL (OR=1.78; 95% Cl, 1.02-3.08) was found to be a risk factor for SOS (46). This finding also confirmed by a prospective cohort study of 180 patients received HSCT by Morado et al (34).

The data of determining the role of iron overload in the pathogenesis of GVHD is somehow conflicting and should be confirmed by further studies. Pullakat et al evaluated the effect of pre-transplant ferritin levels on acute GVHD in 190 allo-HSCT prospective cohort. Acute GVHD was more common in patients with high ferritin levels (≥1000 ng/ml). The initiating event of pathogenesis was defined as the antigen exposition following increased ROS mediated tissue injury (35). However, Mahindra et al demonstrated the decreased incidence of chronic GVHD associated with pre-transplant ferritin level of > 1910 µg/l in 222 patients who underwent myeloablative allo-HSCT (47). In another study of 264 patients with allo-HSCT, there was no relation detected between serum ferritin levels and acute/chronic GVHD (46). In fact, elevated pre-transplant ferritin levels of > 400 µg/l was associated with lower risk of chronic GVHD (HR:0.51, 95% CI 0.33-0.79, p=0.003) in 309 allo-HSCT recipients. Authors hypothesize that ferritin might show an immunosuppressive effect and thus reduce the incidence of GVHD following the HSCT (48).

It should be keep in mind that, although advances in supportive care and techniques have improved survival of HSCT recipients (49-52); iron overload is still a challenging issue and may be associated with liver fibrosis, heart failure, hypogonadism, diabetes and endocrinopathy termed ‘bronze diabetes’ in HSCT recipients as long term complications (53).

3. Diagnosis of Iron Overload

European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research and American Society of Blood and Marrow Transplantation (ASBMT) guidelines promoted screening of serum ferritin levels at post-HSCT period for determining the risk of iron overload (54). In 2012 ASBMT guidelines, the ferritin measurement is recommended in patients who received transfusions pre-post transplant setting. Generally, the threshold for serum ferritin level is accepted as 1000 µg/L for detection of iron overload (55) It is recommended in these guidelines that patients with high liver function tests, high transfusion needs or Hepatits C infection should be monitored subsequently until ferritin levels are below 500 ng/ml (53).

Ferritin level continues to be the mainstay for the clinical evaluation of iron overload and macrophages and T cells are main sources of ferritin. Both over-transfusion and the inflammatory reactions may be accompanied to high ferritin levels. In addition to inflammation, ineffective erythropoiesis and liver disease can also be associated with high ferritin levels (13,56). Researchers hypothesized whether highly increased ferritin concentration might be related to GvHD-associated inflammation in pediatric patients. But they concluded that ferritin could not be a biomarker of chronic or acute GvHD (57). In fact, serum ferritin levels appeared to have a poor correlation with liver iron concentration (LIC) in

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pediatric patients with thalassemia and sickle cell disease (58). There was a modest correlation (P=0.47) detected by Majhail et al. between serum ferritin and LIC by MRI in allo-HSCT recipients. They indicated that ferritin can be a good screening test but a poor predictor of tissue iron overload and recommended estimation of LIC before initiating a chelation therapy (9). It was estimated that ferritin in combination with transferrin saturation has superior prognostic value in determining iron overload when compared to ferritin alone (53).

Alternative marker for determining iron overload is non-transferrin-bound iron (NTBI) which is low molecular weight form of iron. NTBI is formed when transferrin becomes saturated and unable to bind excess iron (59) There are studies conducted to show the level of NTBI has been significantly increased in iron overload and might assess the efficacy of chelation in patients with beta-thalassemia major (60). But, Goto et al. studied the prevalence of iron overload in adult allo-HCST by serum ferritin and NTBI and stated that ferritin was well correlated with NTBI but NTBI was found to be a weaker marker than ferritin in terms of iron overload outcomes. The major issue for this finding was that NTBI only refers to iron in the plasma binding to ligands other than transferrin. Ferritin was confirmed to be correlated with the number of packed RBCs received in patients without active infection, relapse or second malignancy (61).

Liver biopsy is the gold standart of evaluating of iron overload. LIC exceeding 80 mcmol/g of liver dry weight is consisted with iron overload with a hepatic index greater than 1,9 mmol/kg/year (55). Hepatic iron index is the ratio of hepatic iron concentration to the age of the patient in years. Even though liver biopsy can exclude alternative diagnosis of hepatic dysfunction such as GVHD and infections, the use is limited in HSCT patients because the procedure is invasive and patients usually have low platelet counts.

LIC measurements by magnetic resonance imaging (MRG) has gained importance since it is non-invasive, rapid and widely available. Today MRI techniques T2 and R2 are reported to have sensitivity and specifity of 89% and 80% in determination of LIC, respectively (62,63). Ferritin levels more than 1000 ng/ml was found to be correlated with LIC > 7 mg/g in HSCT survivors (10).

Superconducting quantum interference device (SQUID) can assess total body iron with a biomagnetic susceptometry by detecting paramagnetic materials ferritin and hemosiderin. Although it is the reference standart for estimation of LIC, the technique is complex, expensive and very limited (64). Busca et al showed that LIC measurement obtained by SQIUD in the presence of moderate (LIC 1000-2000 μ Fe/g wet weight) or severe iron overload (LIC>2000 μ Fe/g wet weight) was associated with high ferritin levels in 69% of patients (62). Commonly used diagnostic methods for determining iron overload are summarized in Table 2 (10).

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Table 2. Diagnostic Tecniques for determining iron stores

Diagnostic Technique	Advantages	Disadvantages
Serum ferritin and transferrin saturation	Non invasive, widely avaiable	Sensitive but not specific, may be increased in inflammation and malignancy
Liver Biopsy	Gold standart, exclusion of other reasons of liver dysfunction	Invasive, not feasible in patients with thrombocytopenia or coagulopathy
Magnetic Resonance Imaging (MRI)	Good correlation with liver biopsy, non-invasive	Variety of MRI tecniques, contraindications (ex. Metal implants)
Superconducting quantum interference device (SQUID)	Good correlation with liver biopsy, non-invasive	Very limited availability, expensive

4. Management of Iron Overload

There is no consensus in the literature when or how to treat iron overload in HSCT setting. Management of iron overload should be individualized based on the several factors such as need for ongoing RBC transfusion therapy, ability to tolerate iron-depleting therapy, cost effectiveness or urgency to reduce body iron stores. Therapy may not need in mild cases of iron overload, avoidance of alcohol and iron supplements can be recommended (65). Phelebotomy and iron chelation agents are two treatment approaches for protecting recipients from long term end organ toxicities. As a recommendation, patients with LIC>15 mg/g dry weight should be treated aggressively with both phlebotomy and chelation; when LIC is 7-15 mg/g dry weight, phlebotomy is indicated; when LIC is under 7 mg/g dry weight the treatment is only indicated if there is evidence of liver disease (53).

In adult survivors of allo-HSCT, unlike large pediatric cohorts, case series had been reported regarding the safety and feasibility of phlebotomy (63-64). In a routine phelebotomy program, approximately 250 mg of iron is removed once or twice weekly (54). Although phlebotomy has the advantage of better compliance, fever side effects and lower costs, the eficacy is limited (53). Phlebotomy did not have statistically significant effect on the reduction of pre chelator treatment ferritin levels compared with post chelator treatment ferritin levels in a small cohort of post allo-HSCT patients (66). Phlebotomies were repeated every 1-2 weeks until serum ferritin level <500ng/mL in post-HSCT patients and LIC was significantly reduced in a small cohort (median, 1419 μ Fe/g ww to 625μ Fe/g ww, P<0.001) (62). After normalization of transminases and serum ferritin levels, the maintenance phelebotomy is recommended in every 3-6 months to prevent re-accumulation (53).

Deferoxamine, is an iron-chelating agent available vials for intramuscular, subcutaneous and intravenous administration. It chelates iron from ferritin and hemosiderin but not readily from

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transferrin. The common adverse events are reported as localized irritation, pain, burning, swelling at the injection site as well as systemic allergic reaction (67). Deferoxamine has a proven efficacy and safety in HSCT recipients with a recommended schedule of at least 5 nights delivered with a subcutaneous pump for 8-12 hours (64). Neurotoxicity, ocular toxicity, oto-toxicity and growth retardation have been related with overuse (55). However parenteral administration is uncomfortable, time consuming and increases risk of infection therefore oral iron chelators have been under investigation. Deferiprone is an oral iron chelator but it has not been investigated in HSCT recipients and is not commercially available in all countries (10).

Deferasirox is an oral iron chelator which was approved by US Food and Drug Administration in 2005 and improved outcomes in iron overload. The effective dose of deferasirox is between 20 and 40 mg/kg (water soluble tablet 500 mg). Common side effects include skin rash, nausea, vomittting, diarrhea and elevation of renal function test (68). Deferasirox treatment at a dose of 20 mg/kg/day in hyperferritemia (ferritin ≥ 1,000 ng/ml) were analyzed retrospectively in 23 posttranplant patients. Iron (P=0.003), total iron binding capacity (P=0.025), ferritin (P=0.001), alanine transaminase (ALT) (P=0.019) and total bilirubin levels (P=0.001) were significantly decreased after treatment. Eight patients (34.7%) who had hemoglobin levels of >12g/dl also underwent phlebotomy. The reductions of ferritin levels were significant between deferasirox + phlebotomy group compared to deferasirox + nonphelebotomy group (P=0.025, respectively). The most common adverse effects were nausea and vomiting in 13% of patients while no renal dysfunction was observed. The authors conclude that oral deferosirox treatment was safe and effective with or without phlebotomy in post-transplant setting (66). Majhail et al included only patients whose ferritin levels of > 1000 ng/ml and LIC ≥5mg/g on liver R2 MRI in a prospective study of iron overload management in 147 adult allo-HSCT survivors, 16 out of 147 patients had significant iron overload. Based on physician and patient preference the patients divided into 3 different treatment modality groups: 5 of the patients were followed by observation only, 8 patients had phlebotomy and 3 patients were treated by deferasirox. Deferasirox decreaed the LIC after 6 months of therapy in all 3 patients. The authors concluded that phelebotomy and deferasirox appeared to be effective alternative treatments of iron overload in post allo-HSCT (69). Phase IV open-label study showed a significant reduction in serum ferritin and LIC over one year in allo-HSCT recipients treated with deferasirox (70). In a recent study of 76 non-thalassemic patients, authors reported a deferasirox induced negative iron balance in 84% of patients after intiating it at a median of 168 days after HSCT. The drug related adverse events were increased blood creatinine (26%), nausea (9%) and abdominal discomfort (8%) (71).

Deferasirox has also been tried during the administration of conditioning regimen and it was detected to be safe and reduced the appearance of labile plasma iron shortly after allo-HSCT in a preliminary study (72). The studies of deferasirox in post- HSCT survivors with iron overload is summarized in Table 3. Visani et al evaluated the effect of deferasirox on the restoration of normal hematopoiesis in 8 HSCT recipients and all patients experienced an increase in hemoglobin levels with a reduction of transfusions and followed by transfusion independence. This interesting result showed us that deferasirox might have a beneficial effect on hematopoietic recovery after allo-HCT (73).

In conclusion, iron overload is a common complication and this possibility should be considered in all HSCT recipients . Patients will benefit from careful screening and diagnostic tools such as serum ferritin and transferrin saturation levels, LIC by MRI or biopsy. The initiation of phlebotomy and/or iron chelation therapy if needed will prevent patients from

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end organ toxicities. Futher studies should be conducted in order to determine better preventive measures and to avoid iron overload as well as to improve survival in HSCT setting.

Table 3. Management of iron overload with deferasirox in HSCT recipients

Author/Year	No of patients	Comments
Sivgin, 2012	23	In posttransplant setting, median treatment duration was 94 days. Significantly reduced iron parameters. 13% of patients had side effects.
Majhail, 2010	3	Well tolerated and decreased LIC after 6 months of therapy in all patients
Vallejo, 2014	30	No drug related serious adverse events, significant reduction in ferritin and LIC
Jaekel, 2016	76	Negative iron balance in 84% of patients, serum blood creatinine increased in 26.5% of recipients with a managable safety profile even in patients receiving cyclosporine

Conflict of Interest: None

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