

Iron overload: causes, assessment methods, significance in transplantation setting and therapeutical approaches

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Summary

Posttransfusional iron overload is a relatively common complication related to long-term treatment of various haematological diseases. Haematopoietic stem cell transplant recipients — both allogenic and autologous — often present with iron overload because of exposure to red blood cell (RBC) transfusions during the initial treatment and in the post transplant period. Despite these there are also some conditions which contribute to increased risk for iron overload.

A variety of early post transplant complications including infections, liver function abnormalities, and hepatic sinusoidal obstruction syndrome have been connected with iron overload. The late morbidity of iron overload is primarily due to involvement of heart and liver. Iron overload has been reported to increase the risk of infections late after transplantation. It has been suggested that all candidates for and all survivors of haematopoietic stem cell transplantation HSCT should be screened for iron overload at various time points before and after transplantation. Serum ferritin is sensitive but not specific for iron overload and is a poor predictor of body iron burden. It can be used for iron overload assessment, but it is recommended to use it together with some other parameters.

Adequate chelation therapy can reduce iron burden and complications and should be administered as soon as there are signs of iron overload.

More studies are needed to better define the natural history of iron overload and its impact on late morbidity and mortality in transplant recipients.

Keywords: iron metabolism, iron overload, bone marrow transplantation, complications, chelating therapy

Introduction

Iron is an essential microelement in human body [17]. It is quite important co-factor of enzymes active in mitochondrial respiratory chain, citrate cycle, DNA synthesis, and plays a central role in oxygen binding to hemoglobin and myoglobin; iron-containing proteins are indispensable for collagen, tyrosine and catecholamine metabolism. But free, non-chelated iron, due to its catalytic action in a redox-reaction may form dangerous hydroxyl radicals that may cause cell death resulting from peroxidative damage of cell membranes. In the course of evolutionary development, this was resolved by formation of specialized molecules adapted to its intestinal absorption from food, its transport and deposition in soluble, non-toxic form.

Three crucial mechanisms are important for iron homeostasis, as follows:

- Iron absorption from food products in small intestine which, generally, compensates for physiological losses;
- IRE/IRP (Iron Responsive Element/Iron Regulatory Protein) system means intracellular iron uptake or its deposition in complex with ferritin. These processes provide cellular demands of iron and, at the same time, preventing toxic effect of iron overload;
- Erythrophagocytosis and recirculation of erythrocyte-derived iron, thus ensuring main requirements for iron during erythropoiesis.

These three mechanisms provide stabilization of iron stores in the organism, as well as its intracellular metabolism and bioavailability [17,34].

The key point of intestinal iron absorption is hepcidin-mediated regulation system. Hepcidin, a peptide hormone made in the liver, is the principal regulator of systemic iron homeostasis. Hepcidin controls plasma iron concentration and tissue distribution of iron by inhibiting intestinal iron absorption, iron recycling by macrophages, and iron mobilization from hepatic stores. Hepcidin acts by inhibiting cellular iron efflux through binding to and inducing the degradation of ferroportin, the sole known cellular iron exporter. Synthesis of hepcidin is homeostatically increased by iron loading and decreased by anemia and hypoxia. Hepcidin is also elevated during infections and inflammation, causing a decrease in serum iron levels and contributing to the development of anemia of inflammation, probably as a host defense mechanism to limit the availability of iron to invading microorganisms [58].

Disorders associated with altered iron metabolism may be arbitrarily classified in two large groups: iron-deficient and iron overload states.

Iron deficiencies may be caused by alimentary factors (low amount of iron in food), increased iron losses (e.g., due to bleedings) and disturbed iron absorption (Crohn's or celiac disease, surgical removal of part of intestine, the use of some medications etc).

The most common reasons for conditions, associated with iron overload, are as follows [60,74]:

1. Genetic alterations of iron metabolism

- Hereditary haemochromatosis types 1-4

HFE-associated HH (type 1)
C282Y homozygosity
C282Y/H63D compound heterozygosity
Non-HFE-associated HH
Type 2A HJV variants
Type 2B hepcidin variants
Type 3 TfR variants
Type 4 ferroportin variants

- Acoeruloplasminaemia
- Atransferrinaemia

2. Genetic disturbances of erythropoiesis, and/or life cycle of red blood cells (hereditary dyserythropoietic, haemolytic anaemias, including thalassemias, sickle cell anaemia (SCA), Blakmond-Diamond anaemia)

3. Acquired conditions requiring long-term, repeated haemotransfusions (myelodysplastic syndrome (MDS), acute leukaemias, myelofibrosis, multiple myeloma etc)

4. Chronic liver diseases (hepatitis, alcohol abuse, nonalcoholic steatohepatitis etc)

Transfusion-associated iron overload

Iron overload due to RBC transfusions is a relatively common complication related to long-term treatment of various haematological diseases. Each unit of blood contains 200 mg of haeme iron, more than 100-fold than a daily amount of iron normally absorbed from the diet. Transfused red blood cells, upon their senescence, are degraded and their iron is re-utilized by resident macrophages. These fractions of bioavailable iron, after binding to transferrin, are released into the circulation, and dissipate to body tissues. Iron overload is an inevitable consequence of regular transfusion therapy [37]. After receiving 20 lifetime units of packed red blood cells, patients can become iron overloaded. No matter how many years pass between transfusions, the dangers are the same, because the body has no way actively excrete excess iron. Iron overload is proportional to transfusion burden [67,57].

When iron overload is evident, transferrin becomes saturated, thus leading to increased non-transferrin bound iron (NTBI) in blood plasma. Whereas tissue uptake of transferrin-bound iron is regulated by expression of membrane-bound transferrin receptor (responsible for transport of transferrin into cells [4]), excess of NTBI is often absorbed by susceptible tissues. This leads to pools of unbound iron within cells, which mediate toxicity by the formation of reactive oxygen species (ROS) [30]; Figure 1.

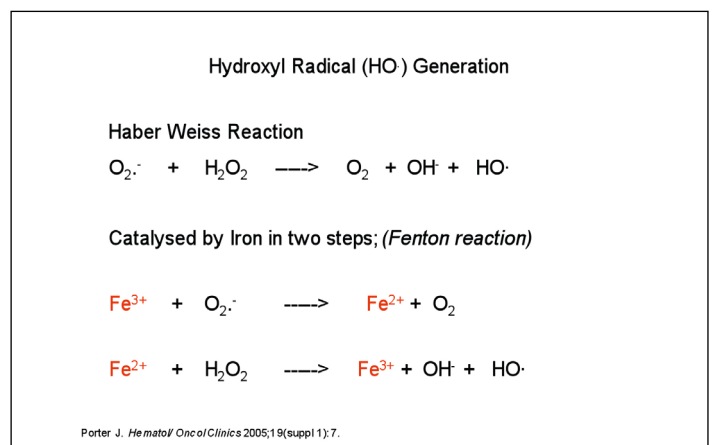


Figure 1.

ROS react with cellular components such as the plasma membrane, lysosomes, and organelle membranes, leading to cellular leakage, dysfunction, and, ultimately, cell death [33].

The organ damage that occurs with transfusional iron overload is similar to that seen in hereditary haemochromatosis, although iron accumulation occurs more rapidly, and deposition of iron in resident tissue macrophages is proportionally greater [43,74,77]. Hereditary haemochromatosis is characterized by iron accumulation primarily in the liver, heart, and pancreas. However, whereas chronic anaemias are related to errors in erythropoiesis, the main cause of haemochromatosis is a reduction or absence in expression of hepcidin (in particular, due to the haemochromatosis gene (HFE) mutations) [43,74,77].

Under steady-state conditions, hepcidin prevents excessive intestinal absorption of iron and its release from macrophages. Therefore it minimizes the amount of iron that enters into plasma. However, in conditions of chronic iron overload, blood transfusion

leads to an increase in erythrocytes, which are broken down by macrophages. This initially results in an increase in iron levels in resident tissue macrophages. Hpcidin expression also downregulates iron release from this system, leading to a “build-up” in the reticuloendothelial system and its possible saturation (a stage that is reduced or absent in patients with haemochromatosis). Subsequently, iron is deposited in various tissues, thus leading to tissue damage [43,46,63].

It is well established that, prior to advent of iron-chelating therapy, cardiomyopathy and liver fibrosis associated with iron overload were among the leading causes of death among children with thalassaemia [15,61]. The role of iron overload in MDS patients is also well established. There are different data concerning overall survival and progression free survival in MDS patients according to transfusion dependency and serum ferritin level [49,50,51,75,78]. Studies have indicated that iron overload following RBC transfusions was an independent, adverse prognostic factor for overall survival (OS) and leukemia-free survival (LFS): OS and LFS were significantly shorter in transfusion-dependent patients with MDS than in those who were not transfusion dependent.

Accurate assessment of body iron burden is necessary to diagnose iron overload and also to effectively manage therapy.

Assessment of body iron stores

There are numerous methods available for the detection and assessment of iron levels, both as total body and specific tissue levels. Because transfusions may lead to rapid iron accumulation, monitoring a patient’s number of transfused blood units, serum ferritin levels, and/or liver iron concentrations can play an essential role in the management of iron overload. Each method is associated with advantages and disadvantages [19,52].

Diagnosis of postransfusional iron overload:

- Established
 - Ferritin
 - Liver iron concentration (biopsy)
- Investigational
 - Biomagnetic liver susceptometry (SQUID)
 - Magnetic resonance imaging (MRI)

Ferritin is inexpensive, noninvasive, and widely available method, which provides reliable estimates of iron burden when performed on a serial basis. Serum ferritin levels consistently >1000 mcg/L are suggestive of iron overload [62,70], and in the absence of appropriate therapy are associated with adverse clinical outcomes in iron overload [50,62,75]. Ferritin is the simplest method for assessment of iron overload, but it has limitations of the value [13]. The advantages and disadvantages of the ferritin measure are summarized in table 1.

Liver biopsy provides direct information about the structure, function, and extent of iron deposition within the liver, and may also have prognostic value.

Liver iron concentration (LIC) predicts total body storage iron [5,13], but measuring LIC by Liver Biopsy has its limitations, too (Table 2).

Advantages	Disadvantages
• Easy to assess	• Indirect measurement of iron burden
• Inexpensive	• Fluctuates in response to inflammation, abnormal liver function, metabolic deficiencies
• Repeat measures are useful for monitoring chelation therapy	• Serial measurement required
• Positive correlation with morbidity and mortality	

Table 1. Ferritin as a marker of iron overload

Advantages	Disadvantages
• Direct measurement of LIC	• Invasive, painful procedure associated with potentially serious complications
• Validated reference standard	• Risk of sampling error, especially in patients with cirrhosis
• Quantitative, specific, and sensitive	• Requires skilled physicians and standardized laboratory techniques
• Allows for measurement of non-haeme storage iron	• Poorly correlated with cardiac iron
• Provides information on liver histology/pathology	• Difficult follow-up
• Positive correlation with morbidity and mortality	

Table 2. LIC as a marker of iron overload

Magnetic resonance imaging (MRI) provides a noninvasive, quantitative method of estimating parenchymal iron levels. In principle, MRI can be used to quantify iron stores wherever they exist in the body. In practice, MRI has been investigated in the assessment of hepatic, cardiac, and anterior pituitary iron stores. MRI measures tissue iron concentration indirectly via the detection of the paramagnetic influences of storage iron (ferritin and haemosiderin) on the proton resonance behavior of tissue water [39]. The longitudinal (R1) and transverse (R2) nuclear magnetic relaxation rates of nearby solvent water protons can then be calculated. Both R1 and R2 rates are increased when interacting with paramagnetic particles such as iron. R2 (or spin-echo imaging) is preferable to R1 for determining LIC, since ferritin enhances the relaxation of both R1 and R2, while haemosiderin only has a strong R2 relaxation accelerating effect. Gradient echo imaging produces images for calculating T2* and R2*, where $R2^* = 1000/T2^*$. A T2* of 20 ms is equivalent to an R2* of 50 Hz. MRI provides a non-invasive alternative to liver biopsy, and may actually be more accurate in patients with heterogeneous liver iron deposition (such as those with cirrhosis) since it measures iron in the whole organ. In addition, the pathologic status of the liver can also be assessed using MRI [3,25,27]. MRI remains the only noninvasive modality in clinical use with the ability to detect cardiac iron deposition. T2* MRI is rapidly becoming the new standard for measuring cardiac iron levels. One study found that below a myocardial T2* of 20 ms, there was a progressive and significant decline in left ventricular ejection fraction (LVEF). In general, the lower the T2*, the higher the risk of cardiac dysfunction, with a T2* <8 ms suggestive of severe iron overload [3].

SQUID stands for Superconducting Quantum Interference Device. This imaging modality uses a very low-power magnetic field with sensitive detectors that measure the interference of iron within the field. The sensor requires a cryogenic environment, since it must be superconducting to operate. Although SQUID is still considered investigational, linear correlations have been demonstrated between SQUID measurements and liver biopsy LIC levels [14,16,59,66].

Although SQUID directly measures the magnetic susceptibility of ferritin and haemosiderin, at present it does not have sufficient spatial or temporal resolution to evaluate myocardial iron. In a large clinical trial, LIC data obtained by SQUID were shown to underestimate LIC values obtained from biopsy by a factor of 0.46 [64].

Both SQUID and MRI have linear correlations with LIC assessed by biopsy, but they provide indirect measurement of LIC, have high cost and as highly specialized equipment requires dedicated technician [3,7]. Limitations of these methods are summarized in Table 3.

Method	Advantages	Disadvantages
MRI	<ul style="list-style-type: none"> • Non-invasive • Able to analyze whole organ • Pathologic status of the liver can be assessed in parallel • Allows longitudinal follow-up of patients 	<ul style="list-style-type: none"> • Requires imager with a dedicated imaging method • Indirect measurement of LIC
SQUID	<ul style="list-style-type: none"> • Non-invasive • Measurement may be repeated frequently • Linear correlation with LIC assessed by biopsy 	<ul style="list-style-type: none"> • Limited availability • High cost • Indirect measurement of LIC • Complex procedure requiring trained personnel • Underestimates LIC versus biopsy

Table 3. SQUID and MRI as a markers of iron overload

Various additional laboratory tests have been developed to assess iron overload. While not widely available, they may hold promise of providing additional clinical information.

- Serum ferritin iron may be less susceptible than serum ferritin to confounding factors such as inflammation [36].
- Serum transferrin receptor concentration has been used to detect both iron deficiency and excess iron. In the presence of iron overload, cells downregulate transferrin receptor expression, and therefore serum transferrin receptor concentration would be expected to be reduced [41].
- Non-transferrin-bound iron (NTBI) - which is normally not found in plasma, increased rapidly during conditioning therapy and contribute to oxidative stress after high-dose radiochemotherapy [24].
- Labile plasma iron (LPI) quantifies the oxidative activity of the patient's plasma-borne NTBI. In theory, this test can be used as a direct measure of iron overload. One approach to measuring LPI is to measure the reactive radicals generated in the subject's blood

by exposure to ascorbate, compared to those generated after the addition of a chelating agent (which blocks the oxidative activity of the NTBI) [26].

- Directly chelatable iron (DCI) is not a test for iron overload per se, but rather an experimental assay for assaying the plasma pool of non-transferrin-bound iron (NTBI).

If to speak about recommendations three guidelines concerning MDS, SCD and thalassemia should be mentioned.

Consensus recommendations developed by leading MDS researchers and clinicians recommend baseline assessment of body iron stores at diagnosis of MDS and at regular intervals — at least every 3 months — thereafter [28]. They recommend that monitoring be performed with a combination of serum ferritin, serum transferrin, and liver MRI [28].

U.S. National Heart, Lung, and Blood Institute (NHLBI) guidelines for the management of sickle cell disease state that, even in patients who receive intermittent transfusions, „a comprehensive program to monitor and treat iron overload is necessary“ [56]. NHLBI guidelines state that [56]:

- Screening for iron overload with serum ferritin testing is recommended at the onset of transfusions.
- Iron overload is likely to be detected after 20 transfusions.
- Liver biopsy is the most accurate test for confirming iron overload in SCD.

According to the Thalassaemia International Federation (TIF) Guidelines for Clinical Management, iron overload constitutes „the most important complication in β -thalassemia and the major focus of clinical management“ [21].

TIF guidelines recommend screening for iron overload at the onset of transfusions. Iron overload is likely to be detected after the first 10-20 transfusions (near age 3 years) [22]:

- Monitor serum ferritin at least every 3 months
- Do not rely on serum ferritin alone
- Liver iron concentration — determined by biopsy or noninvasively by MRI or SQUID — is the reference standard for estimating iron loading

Thus, summarized these guidelines, it can be recommended for all haematological conditions to accurately evaluate and record the iron input, start screening for iron overload at the time of beginning the initial treatment then after each 10-20 transfusions and every three months. Serum ferritin can be used as the basic parameter, but though it is not highly specific marker, it shouldn't be used alone. LIC measurement by biopsy (if indicated) or by MRI or SQUID (if available) is desirable. Assessment of the heart iron by MRI T2* (cardiac risk), at least once is also recommended, If positive, it should be used as the main result to set treatment [16].

Iron overload in transplantation setting

Iron overload commonly accompanies bone marrow transplantation [73]. Haematopoietic cell transplant recipients - both allogeneic and autologous - often present with iron overload because of exposure to RBC transfusions, both during the initial treatment of their disease and in the post transplant period [48]. Despite these there are some conditions which contribute to increased risk for iron overload: the genetic background (heterozygous C282Y mutations can be identified in ~30% of patients with MDS); chemo/radiotherapy (total body irradiation (TBI)/alkylator-induced alterations which increase NTBI and decrease total radical-trapping antioxidant activity in plasma); chronic infections and inflammation; haemolytic disorders induced by immunosuppressive agents (cyclosporine and tacrolimus) [60]. Even in patients without a history of transfusions, a predictable increase in serum iron, transferrin saturation, ferritin and non-transferrin bound iron has been observed in the early post transplant period [11,20,31,71].

There are several studies concerning importance of iron overload in transplantation setting [9,20,35,47,53,60,69,73,76]. The majority of data are devoted to thalassemia and MDS patients. Concerning thalassemia patients hepatomegaly, hepatic fibrosis due to iron overload and poor compliance with iron chelation were identified as being independent prognostic factors, and a classification system according to these factors was developed and adopted by most centers [71]. Age is also an important factor when predicting outcome, with adult patients usually having a poorer outcome when compared to children [44]. In MDS the recently defined WHO classification-based Prognostic Scoring System (WPSS) (which include the transfusion dependency as a prognostic factor) was able to identify five risk groups of untreated MDS patients with different survival and risk of leukaemic progression, compared with the four groups defined by IPSS [32]. It was observed in addition that WPSS has an independent prognostic significance on both overall survival (OS) and probability of relapse in MDS patients undergoing allo-HSCT. This score appeared to improve post transplantation prognostic stratification with respect to the International prognosis scoring system (IPSS). Considering MDS patients without excess of blasts, the WPSS identified two groups of patients (low vs. intermediate risk) with a significant difference in OS and treatment related mortality (TRM), whereas in the same group of patients IPSS failed to stratify the prognosis [49]. Interestingly, both WHO classification and WPSS maintained their prognostic effect on post transplantation outcome also in specific subsets of patients, such as patients older than 50 years as well as patients receiving reduce intensity chemotherapy (RIC). This observation might be relevant in the light of the increased number of RIC performed in MDS in most recent years, after the demonstration of their efficacy in allowing engraftment and in decreasing TRM in patients ineligible for standard conditioning allo-HSCT [49]. In particular, WHO classification and WPSS show a relevant prognostic value in post transplantation outcome of MDS patients and might help decision making in transplantation.

Armand et al. estimated that iron overload could be a significant contributor to TRM for patients with haematologic malignancies undergoing HSCT. They studied 590 patients who underwent myeloablative allogeneic HSCT at their institution, and on whom pre-transplantation serum ferritin was available. An elevated pre-transplantation serum ferritin level was strongly associated with

lower OS and DFS. Subgroup multivariable analyses demonstrated that this association was restricted to patients with acute leukemia or MDS [9].

Altes et al. concluded that very high level (VHL) of ferritin and transferrin saturation (TS) $\geq 100\%$ at the time of conditioning are associated with an increase in toxic deaths after transplant [2].

Several other studies also confirm that iron overload can increase morbidity and mortality in transplanted patients [9,20,35,47,53,60,71,73,76].

Early and late complications of HCT that have been associated with iron overload are summarized in Table 4.

Complication	Comments
Early (<1 year) post transplant	
Infections	Mucormycosis, invasive aspergillosis, <i>Listeria monocytogenes</i> and other infections
Acute GVHD	No clear evidence available, elevated ferritin might increase risk
Hepatic sinusoidal obstruction syndrome	Iron overload might increase risk
Nonrelapse mortality	Elevated ferritin associated with increased risk in allogeneic and autologous recipients
Late (>1 year) post transplant	
Infections	Mucormycosis, invasive aspergillosis, and other infections
Chronic GVHD	No clear evidence available, elevated ferritin might decrease risk
Liver function abnormalities	Iron overload might increase risk
Cardiac late effects	Iron overload might increase risk
Nonrelapse mortality	No clear evidence available

Table 4. Iron overload-related complications after HSCT [43]

A variety of early post transplant complications including infections, liver function abnormalities, and the hepatic sinusoidal obstruction syndrome have been connected with iron overload [35,38,47,53,54,76].

The late morbidity of iron overload is primarily due to involvement of heart and liver. Although iron-related liver function abnormalities have been reported, there are no studies describing the role of iron overload in late onset of cardiomyopathy and hepatic fibrosis in patients transplanted for diseases other than thalassemia [1,8,15,42,61,80]. Iron overload has been reported to increase the risk of infections late after transplantation. The impact of iron overload on long-term nonrelapse mortality has not been studied. Iron overload can mimic liver GVHD. Whether it can increase the

risk of GVHD is an open question and more investigations are required to confirm this idea [48].

Iron chelation therapy

The principal goal of chelation therapy is to decrease tissue iron concentrations to lower levels without risk of iron-mediated toxicity. Guidelines for iron overload treatment in MDS patients (IPSS low or intermediate-I, stable disease, candidates for allograft) recommend starting chelation therapy after receiving 20 units of red blood cell transfusions and clinical evidence of chronic iron overload (serum ferritin levels > 1000 µg/L or liver ferritin < 2 mg/g dry weight) [28]. TIF guidelines also recommend managing iron overload when serum ferritin is >1000 mcg/L [21,22]. NIH recommends start iron chelation in SCD patients when liver iron stores rise to 7 mg/g dry weight; cumulative transfusion of 120 cc of pure red cells/kg body weight and serum ferritin level in steady-state is >1000 ng/mL [57].

There are no clear-cut guidelines for when to start screen and initiate therapy for iron overload in transplanted patients. End-organ damage related to iron overload is dependent on the rate of iron accumulation and the period of overload state. HSCT recipients frequently get RBC transfusions during their treatment and in the early post transplant period. Decisions regarding management of iron overload should be individualized and be based on several factors including the need of transfusion therapy, time since transplantation, and urgency to reduce body iron stores which is dependent on the presence of liver tests abnormalities or cardiac dysfunction. According to those studies which estimated the role of iron overload on complications and mortality after transplantation, screening and treatment of iron overload might have to be considered in the pre-transplant and early post transplant period. Many patients become transfusion independent with time and if having mild iron overload without signs of organ damage, can be observed without any treatment. There are published recommendations for screening and prevention of late effects of iron overload in HSCT which suggest to monitor the ferritin level at one year post transplant [69].

The treatment modalities for iron overload are summarized in Table 5.

Treatment modality	Administration
Phlebotomy	7 ml/kg body weight weekly
Desferrioxamine (Desferal)	8–12 hours subcutaneous infusion 5–7 days per week; dose, infusion duration, and number of administrations to be decided according to patient age and severity of iron overload
Deferasirox (Exjade)	Once-daily oral dosing; initial daily dose of 20 mg/kg (10–30 mg/kg)
Deferiprone (Ferriprox)	Twice-daily oral dosing; total daily dose of 75 mg/kg

Table 5. Treatment modalities for iron overload

Phlebotomy is a feasible and effective method of iron overload treatment. Its efficacy was demonstrated in many studies [5,6,40,53], but patients with persisting anemia are not able to undergo phlebotomy. Although the use of erythropoiesis stimulating agents to enable phlebotomy has been reported following HSCT,

caution should be performed in their use because of recent reports of an increased risk of thromboembolism [10,68]. Patients not being eligible for phlebotomy can be treated with iron chelators. Deferoxamine (Desferal, Novartis Pharmaceuticals Corporation, USA) has a proven efficacy and safety with decades of experience and has been studied in HCT recipients [29,30]. The main disadvantages are side effects such as ototoxicity, growth retardation and the inconvenient administration (prolonged daily subcutaneous infusion for 5-7 days) which often leads to poor compliance. Deferiprone is an oral iron chelator, but is not available in all countries, including the Russian Federation, and has not been investigated in HSCT recipients. Deferasirox (Exjad, Novartis Pharmaceuticals Corporation) is a recently introduced oral iron chelator with efficacy similar to deferoxamine [18,65,79]. Commonly reported side effects include skin rash, nausea, vomiting and elevation in serum creatinine level. Most of them are mild to moderate and dose-dependent. More experience with its use in HSCT recipients is also needed.

Two iron chelators are currently in earlier stages of clinical trials. Attaching deferoxamine to hydroxyethyl starch creates a high molecular weight compound with a longer circulation time. Studies are underway to seek a dose that would allow acceptable intervals between intravenous infusions while still promoting an effective level of iron excretion. Deferittrin is an orally active tridentate compound from the ferrithiocin class of chelators. Phase I and II studies have not shown evidence of renal toxicity that had been noted in animal studies with some ferrithiocin analogues, and a current dose-escalation study is designed to identify the appropriate strategy for a pivotal trial [23].

Conclusions

1. Disturbed iron balance is a common condition in the patients undergoing intensive chemotherapy, HSCT and multiple RBC transfusions.
2. Iron overload is a subject to iron-chelating therapy because of its negative influence on early posttransplant complications and even mortality.
3. Although there are no clear guidelines for iron overload screening in HSCT recipients it can be recommended to monitor at least the ferritin level before the transplantation and at one year post transplant.
4. Decision on when to treat must be individualized and depends on transfusion history, ferritin levels, and signs of organ iron toxicity.
5. More studies are needed to better define the natural history of iron overload and its impact on late morbidity and mortality in transplant recipient.

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Перегрузка железом: причины, методы оценки, значимость при трансплантации и подходы к терапии

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Резюме

Посттрансфузионная перегрузка железом (ПЖ) является относительно частым осложнением, возникающим при длительном лечении различных гематологических заболеваний. У реципиентов гемопоэтических стволовых клеток (ГСК), как аллогенных, так и аутологичных, часто отмечается ПЖ из-за проведения трансфузий эритроцитов в период первичного лечения и в посттрансплантационном периоде. Кроме того, есть и некоторые состояния, которые приводят к повышенному риску ПЖ.

Целый ряд ранних посттрансплантационных осложнений, включая инфекции, нарушения функций печени и синдром обструкции синусоидов печени, связаны с ПЖ. Позднее развитие этого заболевания исходно связано с поражением сердца и печени. Сообщалось о том, что ПЖ повышает риск инфекций в поздние сроки после трансплантации. Предлагается скрининг всех кандидатов на трансплантацию ГСК и всех больных после трансплантации на наличие ПЖ до трансплантации и в различные сроки после нее. Ферритин сыворотки неспецифичен для ПЖ и является плохим прогностическим маркером нагрузки организма железом. Он может быть использован для оценки ПЖ, но его рекомендуется применять вместе с рядом других параметров.

Адекватная терапия хелатами может ослабить нагрузку железом и ее осложнения и должна назначаться по мере появления признаков ПЖ. Необходимы дальнейшие исследования для уточнения естественной истории ПЖ и ее вклада в позднюю заболеваемость и смертность у реципиентов после трансплантации.

Ключевые слова: метаболизм железа, перегрузка железом, трансплантация костного мозга, осложнения, хелатная терапия