An update on iron chelation therapy

Erika Poggiali, Elena Cassinerio, Laura Zanaboni, Maria Domenica Cappellini

IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Department of Internal Medicine, University of Milan, Milan, Italy

Introduction

Iron overload is a common clinical problem, arising from disorders of increased iron absorption such as hereditary haemochromatosis or thalassaemia intermedia syndromes or as a consequence of chronic blood transfusions for various blood disorders.

Regular red blood cell (RBC) transfusions are the principal supportive therapy for many rare anaemias involving a decrease in RBC production, an increase in cell destruction, or chronic blood loss[1]. Anaemias such as beta-thalassaemia and sickle cell disease are examples of chronic diseases that require long-term transfusion therapy to improve life expectancy.

Although transfusion requirements may vary according to the diagnosis, chronic blood transfusion therapy inevitably leads to secondary iron overload that can cause significant damage to many organs, such as the liver and heart, and to the endocrine system[2,3]. Iron overload is associated with the production of free radicals that can damage tissues, resulting in cardiac toxicity, endocrine dysfunction, and liver toxicity. The effects of iron overload are visible after damage has been done, when patients already have liver dysfunction, cirrhosis, cardiomyopathy or diabetes[1,4].

Iron is an essential element within the body and its quantity is tightly regulated physiologically; however, the body has no mechanism to excrete excess iron and it deposits iron into end organs leading to severe dysfunction. Each unit of RBC transfused contains 180 to 200 mg of iron. Chronic packed RBC transfusion therapy increases liver iron by approximately 1 mg/mL (by dry weight) for every 15 mL/kg delivered[5]. Labile plasma iron (LPI) is a toxic and chelatable form of iron that is produced continually during conditions of iron overload, and has been linked to the development of co-morbidities[6]. It is very important to remove excess iron and suppress LPI to avoid the serious clinical sequelae associated with iron overload. In this specific context phlebotomy cannot be used because patients are usually anaemic and other means must be used to mobilise the excess iron. The gold standard is iron chelation therapy.

Methods for evaluating iron overload

There are various different methods for evaluating the degree of iron overload, including serum ferritin levels, liver iron concentration determined from a biopsy, superconducting quantum interference device (SQUID) and magnetic resonance imaging (MRI). Each method has pros and cons, and often a combination of these tests is used to quantify and monitor iron burden.

The simplest way to quantify iron overload is to count the number of RBC units that a patient has been transfused over time[7]. Another simple method of evaluation is to test serum ferritin levels, which correlate with body iron stores. Although trends in serum ferritin remain an important monitoring tool, serum ferritin is a poor marker of iron balance because ferritin values can change in the presence of inflammation/infection, or ascorbate deficiency, and according to the intensity of blood transfusion therapy, making the reliability of ferritin levels questionable[8].

The gold standard for assessing the degree of iron overload is a liver biopsy, but its invasiveness limits is use for routine screening at most institutions. Liver iron concentration >15 mg/g dry weight predicts a higher risk of cardiac disease and death[9] and progression of hepatic fibrosis, which may be exacerbated by hepatitis C infection, a very common condition in patients transfused before the 1980s[10,11].

MRI is a non-invasive method which can quantify hepatic and cardiac iron, replacing liver biopsy for quantification of iron in the liver[12]. The ability of MRI to quantify extra-hepatic iron has had a great impact on patients' care and on our understanding of the pathophysiology of iron overload. In particular, cardiac iron can be investigated in asymptomatic patients by cardiac T2*, and signal changes shown by MRI could be used as pre-clinical end-points for

*Blood Transfus 2012; **10**: 411-22* DOI 10.2450/2012.0008-12

evaluating response to chelation[13]. Therefore, after at least 10 transfusions (150 mL/kg), in the absence of significant losses, chronically transfused patients merit at least an initial MRI scan. In addition, patients with a high transfusion load, an unknown transfusion burden, or with Diamond-Blackfan syndrome (in which cardiac iron loading is exhibited early[14]) may warrant cardiac examination at their initial evaluation.

Recently, MRI estimates of cardiac and liver iron have become the primary outcome measures for clinical studies on iron chelation therapy[15-17]. Cardiac complications remain the most common cause of death in transfused thalassaemia patients[8] and a central goal of iron chelation therapy is to prevent or remove cardiac iron loading. Cardiac T2* values of 10-20 ms indicate mild to moderate iron loading and values <10 ms indicate severe myocardial siderosis. In thalassaemia major, the risk of developing clinically relevant left ventricular dysfunction increases as the T2* falls below the lower limit found in healthy adults (approximately 20 ms). Patients with very low T2* values (<6 ms) have a 47% chance of developing congestive heart failure within the following year[18]. Low cardiac T2* values (<20 ms) should, therefore, trigger intensification of chelation regimes regardless of liver iron burden. The development of cardiac dysfunction or arrhythmia should also prompt intensification of chelation therapy, for example considering the combination of different iron chelators (as described below).

Iron is removed from different organs at different rates: hepatic iron burden usually improves more rapidly than cardiac iron burden with intensification of chelation. For this reason both hepatic and cardiac iron must be measured to optimise the chelation therapy. Changes in ferritin levels often parallel changes in liver iron concentration, even if a variety of factors, such as inflammation, infection and ascorbate deficiency, can decrease or increase ferritin levels. According to this evidence, serial ferritin levels may be used to assess trends in iron burden and to help to modify chelator dosing. In particular, ferritin levels above 2,500 ng/mL are associated with an increased risk of morbidity and mortality, and levels persistently above this value should trigger intensification of the chelation regimen.

Future frontiers in MRI monitoring include improved prevention of endocrine toxicities, particularly hypogonadotropic hypogonadism and diabetes.

Iron chelation therapy

The overall aim of chelation therapy is to maintain a "safe" iron status at all times. Ideally, chelation therapy should be administered to prevent iron accumulation and iron-related complications including hepatic, endocrinological and cardiac dysfunction. There is evidence showing that the age at which iron chelation is started in patients with thalassaemia major is a key factor in their survival[8,19,20], although this aspect is often not considered in retrospective analyses of survival data.

In practice, chelation therapy is often used to remove excess stored iron and to reverse related complications. Generally, chelation therapy with deferoxamine (DFO; see below) has traditionally been started only after 2 to 3 years of transfusion or when ferritin exceeds 1,000 ng/mL. Iron chelation therapy provides a viable method of treating iron overload and minimising the adverse effects associated with iron burden. The direct capture of non-transferrin bound iron and LPI with effective chelation therapy may help to prevent the adverse consequences of iron overload[6]. Several iron chelators have been developed, designed to mobilise tissue iron by forming complexes that are excreted in the faeces and/or urine (Table I).

Before the routine availability of chelation therapy, chronically transfused patients died from cardiac iron overload in their teens and twenties[21]. Since the introduction of deferoxamine (Desferal®; DFO; Novartis Pharma AG, Basel, Switzerland) in the early 1970s, the life expectancy of such patients has improved dramatically[8].

DFO was developed more than 40 years ago and the wealth of clinical experience in iron-overloaded patients has established a role for iron chelators in the improvement of patients' quality of life and overall survival[22,23]. Data indicate that DFO is effective at lowering serum ferritin levels and hepatic iron[24,25] and in preventing endocrine complications[19,26]. Long-term therapy with DFO is also associated with a reduction in cardiac complications and improved survival[8]. In addition, doses of DFO higher than 60 mg/kg/day as a continuous intravenous infusion can reverse cardiac iron burden[27] as measured by cardiac T2*[28].

Table I - Overview of iron chelators.

Property	Deferoxamine	Deferiprone	Deferasirox
Stoichiometry (chelator:iron)	Hexadentate (1:1)	Bidentate (3:1)	Tridentate (2:1)
Route	Subcutaneous, intravenous	Oral tablet or solution	Tablets for oral suspension
Usual dose	20-40 mg/kg/day over 8-24 hours, 5 days/week	75-100 mg/kg/day in 3 divided doses daily	Recommended initial dose 20 mg/kg up to a maximum of 40 mg/kg/day
Excretion	Urinary, faecal	Mainly urinary	Faecal
Half-life	20-30 min	3-4 hours	8-16 hours
Adverse effects	Local skin reactions Ophthalmological Auditory Allergic reactions Growth retardation Bone abnormalities Pulmonary at high doses Neurological at high doses	Gastrointestinal Agranulocytosis/ neutropenia Arthralgia Elevated liver enzymes	Gastrointestinal Rash Rise in creatinine Proteinuria Ophthalmological Auditory Elevated liver enzymes
Challenges	Adherence due to parenteral administration; need for yearly ophthalmology and audiometric examination	Need for weekly blood count monitoring; not commercially available in all countries; limited data in children; variable efficacy in removal of hepatic iron	Cost, especially with higher doses; gastrointestinal side effects may limit optimal dosing Need for monthly monitoring of creatinine, transaminases, bilirubin, complete blood count for potential renal or hepatic failure and/or gastrointestinal haemorrhage (more frequently in patients with advanced age and existing comorbidities)
Status	Licensed	Licensed in USA and Europe	Licensed in USA and Europe
Indications	Treatment of chronic iron overload due to transfusion-dependent anaemias (and for treatment of acute iron intoxication)	Treatment of iron overload in thalassemia major when DFO is contraindicated or inadequate.	In USA licensed for the treatment of chronic iron overload due to transfusion-dependent anaemias in individuals aged 2 years and older In Europe licensed for the treatment of transfusional iron overload in beta-thalassaemia major patients, 6 years and older, and approved for use when DFO is inadequate or contraindicated in patients with other anaemias, patients 2-5 years, and patients with non-transfusion-dependent thalassaemia
Age considerations	Not recommended for children <3 years with low transfusional burden	Limited or no data on children aged <6-10 years	Studied in children as young as 2 years old

DFO is a hexadentate chelator binding iron at a 1:1 molar ratio, thus preventing its participation in toxic reactions. In accordance with its relatively high molecular weight and highly hydrophilic properties, DFO does not readily enter most types of cells, with the exception of hepatocytes, which seem to have a facilitated uptake mechanism[29]. The iron complex of DFO is highly stable, with good iron-scavenging properties at low concentrations of iron or chelator.

The most common adverse effects of DFO are listed in Table I. Redness and induration at the infusion site are the most frequent. Ophthalmological, auditory and bone toxicity and growth retardation can be minimised by avoiding "over-chelation".

The greatest challenge with DFO is patients' adherence to therapy. Due to its poor oral bioavailability and short plasma half-life, DFO must be given by slow subcutaneous administration over 8-12 hours, 5-7 days/week, often resulting in poor compliance[30]. DFO infusions frequently have a negative impact on patients' quality of life, as the infusions can be troublesome, time-consuming and

painful. A review of published data suggests that compliance with DFO is between approximately 60% and 80%[31]. Poor compliance leads to gaps in chelation coverage, during which LPI levels can increase and cause further tissue damage. Morbidity and mortality in thalassaemia are closely linked to the adequacy of chelation. Cardiac morbidity and mortality continue to occur in patients treated with DFO, probably related to difficulties with adherence[32].

The burden of this demanding regimen and the poor compliance led to the search for more convenient oral chelators. There are currently two oral iron chelators licensed for the treatment of iron overload.

Deferiprone (Ferriprox®; DFP; Apotex Inc., Toronto, ON, Canada), first tested in clinical trials in the 1980s, is available in the European Union and Canada, and recently the U.S. Food and Drug Administration approved deferiprone for the treatment of iron overload due to blood transfusions in patients with thalassaemia, who had an inadequate response to prior chelation therapy (European Medicine Agency. http://www.ferriprox.com; U.S. Food and Drug Administration http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm275814.htm).

DFP is a small lipophilic molecule, which binds to iron in a 3:1 ratio and can enter myocytes and capture LPI in specific organelles of cardiomyocytes and macrophages. DFP facilitates transfer of iron from extracellular media into nuclei and mitochondria, from endosomes to nuclei, and from intracellular compartments to extracellular apotransferrin. Furthermore, it mobilises iron from iron-loaded cells and donates it to pre-erythroid cells for haemoglobin synthesis, both in the presence and in the absence of transferrin. These unique properties of DFP mechanistically underlie its capacity to alleviate iron accumulation in several conditions, including neurodegeneration with brain iron accumulation, such as Friedreich's ataxia[33,34], and to donate tissue-chelated iron to plasma transferrin in patients with thalassaemia intermedia[35].

DFP has a short half-life (3-4 hours) and must, therefore, be given three times daily. DFP is often used in combination with DFO; in this case, treatment can be sequential (both chelators are given in any 24-hour period) or alternating (only one chelator is administered in any 24-hour period). Adherence is likely to depend on the regimen used: a regimen that reduces the number of days of DFO therapy (e.g. alternating therapy) may improve adherence, while a regimen using the standard DFO treatment plus DFP (e.g. sequential therapy) may worsen adherence[36]. A shuttling hypothesis, according to which DFP binds iron and then redistributes it to DFO, has been proposed[37,38], and co-administration of these two chelators with an additive effect, could be an optimal strategy.

Common adverse effects of DFP are presented in Table I. The most serious adverse effects associated with DFP are agranulocytosis and neutropenia, with an incidence of 0.2 and 2.8 per 100 patient-years, respectively[39]. Weekly blood counts are strongly recommended in patients taking DFP. In particular, patients with bone marrow failure syndromes such as Diamond-Blackfan anaemia may be at higher risk of developing neutropenia with DFP[40].

Retrospective studies have demonstrated reduced cardiac morbidity and mortality[32,41-43] and lower myocardial iron deposition[13] among patients treated with DFP than among those treated with DFO. Furthermore, in a randomised clinical trial among patients with moderate cardiac siderosis and normal cardiac function, significantly greater improvements in cardiac T2* and left ventricular function were seen after treatment with DFP than after treatment with DFO[44]. In a large clinical observational study, treatment with DFP resulted in an improvement in cardiac T2* among patients with all degrees of cardiac iron loading[45].

The combination of DFO and DFP is currently the most effective means of reducing cardiac iron loading and should be started in patients with significant cardiac siderosis. The chelators can be alternated to provide continuous exposure to chelation; for example, DFO given every night and DFP during the day can provide 14-hour removal of LPI[6]. The chelators can also be given at the same time, considering the possibility of a drug interaction through a so-called shuttle mechanism in which iron is chelated rapidly by DFP at sites relatively unavailable to DFO and then donated to the more stable DFO molecules. There is experimental evidence of this effect in animal models of iron overload[37], and this shuttling was recently shown to occur in the removal of non-transferrin bound iron from the plasma compartment of patients with thalassaemia major[38].

In practice, sequential use of DFO and DFP is more commonly adopted[46-50].

The superiority of this combination compared with DFO alone was demonstrated in a randomised, placebo-controlled trial of 65 patients with mild to moderate cardiac iron loading[51]. Subjects who received combination therapy had significantly greater improvements in cardiac T2* and left ventricular ejection fraction than those receiving DFO with placebo. Furthermore, in a single-arm trial of patients with severe myocardial siderosis and myocardial dysfunction, combined treatment with DFO and DFP was effective in significantly improving cardiac T2* and left ventricular ejection fraction, as well as reducing serum ferritin and liver iron concentration after 12 months of therapy[52].

More recently, a multicentre, randomised, open-label trial was designed to assess the effectiveness of long-term alternating sequential DFP-DFO versus DFP alone in patients with beta-thalassaemia[53]. DFP 75 mg/kg for 4 days/week and DFO 50 mg/kg/day for 3 days/week was compared with DFP alone 75 mg/kg for 7 days/week during a 5-year follow-up. A total of 213 thalassaemic patients were randomised and intention-to-treat analysis was performed. The decrease of serum ferritin level was statistically significantly greater in patients treated with the alternating sequential DFP-DFO patients than in those treated with DFP alone (P=0.005). Kaplan-Meier survival analysis for the two chelation treatments did not show statistically significant differences (log-rank test, P=0.3145). Adverse events and costs were comparable between the groups. These findings were confirmed in a further 21-month follow-up. These data suggest that alternating sequential DFP-DFO treatment may be useful for some patients with beta-thalassaemia who may not be able to receive other forms of chelation treatment.

Formal safety data on combined treatments are limited. In general, alternating regimes are less likely to be an issue for toxicity compared with regimes in which chelation is simultaneous or overlapping. A meta-analysis of the incidence of agranulocytosis in patients treated with combined regimes suggested that the risk may be increased several-fold compared with that in patients treated with DFP monotherapy, although the number of evaluable patients was small[54]. The increased incidence seemed to occur mostly in regimes in which the drugs were administered simultaneously.

Deferasirox (DFX; Exjade®; Novartis Pharma AG, Basel, Switzerland) is the most recent oral iron chelator. It was developed as a once-daily oral iron chelator through a rational drug development programme and represents a new class of tridentate iron chelators[55]. DFX is currently approved in many countries worldwide for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older (EXJADE® [deferasirox]. http//www.pharma.us.novartis.com/product/pi/odf/exjade.pdf).

The efficacy and the safety of DFX have been evaluated in patients with beta-thalassaemia[24] and in a wide range of patients with other underlying anaemias including myelodysplastic syndromes (MDS), sickle cell disease, aplastic anaemia, Diamond-Blackfan anaemia and various other rare anaemias[30,47,55-61].

Iron chelation with DFX may be beneficial because of its once-daily formulation, supported by its plasma half-life of 11 to 19 hours[30,56]. There are now data on compliance with DFX which, in the Evaluation of Patients' Iron Chelation with Exjade (EPIC) study, was reported to be greater than 80%[60].

Two DFX studies in patients with beta-thalassaemia and sickle cell disease evaluated actual patients' feedback in the form of patient-reported outcomes. Most patients were more satisfied with DFX and found it more convenient than DFO therapy. A recent study by the Thalassemia Clinical Research Network examined adherence in 79 patients on DFO and 186 on DFX from 2007 to 2009. Adherence to both DFO and DFX was highest in children, followed by adolescents and older adults. Switching chelators resulted in increased adherence, regardless of the direction of the switch, although switching from DFO to DFX was more common.

The most common adverse effects of DFX are reported in Table I. DFX is typically well tolerated, with adverse events generally being mild. Transient gastrointestinal events, including abdominal pain, nausea and vomiting, diarrhoea and constipation occur in approximately 15% of patients with thalassaemia[24] and in higher numbers of patients with MDS. Gastrointestinal disturbances are, in fact, the most common side effects but can often be improved by changing the time of day of DFX administration.

Skin rashes occur early in approximately 10% of patients and are usually transient[24]. There have been rare reports of fulminant hepatic failure, leading to the suggestion that liver function should be monitored every 2 weeks for 1 month after starting therapy with DFX and then monthly thereafter. The levels of serum creatinine increase in approximately one-third of patients within a few weeks of starting or increasing therapy, but rarely reach the abnormal range[24]. Kidney function needs, therefore, to be monitored monthly. Audiometric effects and lens opacity did not differ significantly from those in patients treated with DFO[24], and no drug-related agranulocytosis was observed. Because of its poor solubility in water, DFX is administered as a suspension in fruit juice. Its metabolism is predominantly to iron-binding glucoronides in the liver; iron excretion is dose-dependent and almost entirely faecal[30,56].

The efficacy of DFX at a dose of 20-30 mg/kg/day was shown to be similar to that of DFO in reducing liver iron concentration and serum ferritin levels in a large randomised trial in patients with thalassaemia major[24]. The drug's ability to remove hepatic iron has been demonstrated in several additional studies[57,61].

Deugnier *et al.* observed an improvement in liver pathology in iron-overloaded beta-thalassaemia patients treated with DFX for at least 3 years[62]. In this study, histological data from 219 patients who had biopsy samples taken at baseline and after at least 3 years of treatment with DFX. DFX reversed or stabilised liver fibrosis in 83% of the patients and this therapeutic effect was independent of a reduction in the concentration of liver iron or previous exposure to hepatitis C virus[62].

In a trial of 101 patients with mild to severe cardiac iron loading treated with DFX, cardiac T2* improved significantly in both the groups with mild-to-moderate and severe iron loading over 2 years of treatment[63]. No significant improvement in left ventricular ejection fraction was observed, although the ejection fraction was normal at baseline[63]. In another study of 22 patients with cardiac T2* <20 ms treated with DFX for 18 months, cardiac T2* worsened in 14 patients and no change in left ventricular ejection fraction was seen over the 18 months of treatment.

The failure to respond was predicted by higher baseline liver iron concentration and ferritin levels[17].

DFX can also prevent cardiac iron accumulation, as shown by Pennell *et al.*[16]. In 78 patients with thalassaemia without evidence of cardiac iron loading, cardiac T2* did not worsen over 1 year of treatment and no subjects with normal cardiac T2* at baseline developed an abnormal value over the follow-up period. In contrast to the patients with low cardiac T2* values, a significant improvement in ejection fraction was observed in the group of patients with a normal cardiac T2* at baseline.

The combination of DFX and DFO has not been extensively studied. In a pilot study, patients with thalassaemia major and evidence of iron-related organ dysfunction were treated with DFX daily and DFO for 3-7 days/week[64]. Liver iron concentration improved significantly and no toxicity was observed. Unfortunately, the combination of DFO and DFX did not show additive or synergetic effects on iron excretion in an iron-overloaded gerbil model, suggesting that the two chelators compete for a common iron pool[65]. It is not clear whether the same happens in human beings, but sequential rather than combination therapy could be preferred if the two chelators compete for the same iron pool. Further research regarding the safety and efficacy of combined treatment with DFO and DFX is necessary before recommendations can be made for routine clinical practice. Likewise, the combination of DFX and DFP still needs to be studied.

The ability of DFX to reverse cardiac disease has not yet been investigated, because all the prior studies required normal heart function for inclusion. Reversal of heart failure with DFX was reported in one patient with beta-thalassaemia and transfusional iron overload[66]. Further studies are needed to better delineate the effect of DFX on cardiac iron overload and iron-related cardiac dysfunction.

In the last year the level of "acceptable" iron burden in chronically transfused patients has been called into question[67] and more "aggressive" chelation regimens have been advocated. Comparing the efficacy of the three chelators in suppressing LPI, it can be seen that a limitation of both DFO and DFP monotherapy is their inability to control levels of LPI constantly as a result of their short plasma half-lives[68,69]. In addition monotherapy may not be effective in all patients for a large variety of reasons. For example, adverse effects may prevent optimal dosing, while poor adherence to treatment may lead

to underdosing. Combination therapy may be more effective in these contexts.

DFO/DFP sequential therapy provides more consistent suppression of LPI than monotherapy with either chelator[70] and is accompanied by a subsequent reduction in the frequency and dose of DFO reducing the risk of chelator toxicity. Recently, the combination of high doses of DFO (20-60 mg/kg/day) and DFP (75-100 mg/kg/day) led to normalisation of total body iron load in thalassaemia patients[71]. Furthermore, cardiac and endocrine complications, including hypothyroidism, hypogonadism and non-insulin-dependent glucose intolerance, were reversed in some, but not all, patients treated with this regimen[71].

As DFX is detectable in the blood within the therapeutic range over a 24-hour period, it offers complete chelation coverage with standard dosing and can provide a sustained reduction in LPI[72]. The first prospective study to report long-term monitoring of the efficacy and safety of iron chelation with DFX in both paediatric and adult patients with beta-thalassaemia suggests that treatment is generally well tolerated and effectively reduces iron burden[73]. Many patients achieved maintenance serum ferritin levels of ~1,000 ng/mL, and treatment for ≤5 years was well tolerated. The study also provided the first data on the long-term effects on paediatric growth and adolescent sexual development for any oral iron chelation therapy. DFX did not show an adverse effect on paediatric growth or adolescent sexual development in paediatric patients who are prone to growth retardation as a result of iron overload[73]. These data confirm the results obtained in the published shorter-term clinical trials of 1-year duration[60,61].

Iron chelation therapy in clinical practice

There are substantial data demonstrating the efficacy and safety of iron chelation therapy in the treatment of iron overload in regularly transfused patients with beta-thalassaemia[8,57,60]. The blood transfusion rate influences the chelator dose and careful monitoring of transfusional iron intake is needed, especially in young children, in order to avoid exceeding the therapeutic index of the chelator and, as a consequence, increasing the risk of adverse effects.

Data supporting the use of iron chelation therapy in other transfusion-dependent anaemias such as MDS, aplastic anaemia and sickle cell disease are also accumulating[57,58,60,74,75] and suggest that the response in terms of iron balance is mainly dependent on chelator dose and transfusional iron loading rate[57,58,60,74-76].

Studies in patients affected by rare anaemias related to decreased RBC production, including Diamond-Blackfan anaemia and pure red cell aplasia, as well as those in patients with haemolytic anaemia have been limited[57], and response has not been analysed with respect to the underlying mechanism of anaemia. However, the 1-year EPIC study enrolled a large number of patients with different types of transfusion-dependent anaemia[60], thereby enabling the investigation of disease-specific factors that might affect iron chelation therapy with DFX. A subsequent study, including patients with rare transfusion-dependent anaemias from the EPIC study, examined how responses of these rare blood disorders to DFX chelation were affected by the underlying mechanism of the anaemia (decreased RBC production or haemolysis)[77]. The efficacy and safety of DFX were evaluated over 1 year, with the change in serum ferritin concentration being the primary efficacy end-point. Transfusional iron-loading rates, mean DFX dosing and baseline median serum ferritin levels were comparable in patients with anaemia due to either decreased RBC production or haemolysis. In both cohorts the responses to DFX were similar at 1 year, irrespective of the underlying pathogenic mechanism necessitating the chronic blood transfusions[77]. These data provide evidence that transfusional iron overload in patients with a variety of rare anaemias may be effectively managed using a tailored DFX dosing regimen, based on individual blood transfusion requirements, regular monitoring of serum ferritin trends and safety parameters[77].

The efficacy of iron chelation on survival in patients with MDS is still a matter of discussion because of the lack of randomised trials with a survival end-point, although evidence suggests that improvements in survival are likely[78-81]. In the EPIC study, 341 patients with MDS were treated with DFX, obtaining a significant decrease in the overall median serum ferritin levels after 1 year of treatment[82]. Recently, data from patients with MDS showed that DFX can improve haematological parameters, including haemoglobin concentration, transfusion requirements and neutrophil and platelet counts[83-86].

Survival data for patients with MDS treated with DFX are lacking; a randomised, double-blind, placebo-controlled phase III trial (TELESTO) comparing DFX to placebo is currently underway.

The benefits of reduced iron levels in bone marrow transplant patients, before and after transplantation, have been recognised and DFX could have a potential role in the treatment of iron load in this population of patients. Iron overload has been reported in adults after haematopoietic stem cell transplantation (HSCT)[87,88] and could be a significant contributor to treatment-related mortality in patients with haematological malignancies undergoing HSCT. It is well known that iron overload is an important adverse prognostic factor for patients with thalassaemia undergoing HSCT[89,90]. This may also hold true for patients who undergo transplantation for haematological malignancies[91]. Recent studies have suggested a link between iron overload and post-transplantation liver toxicity (including chronic liver disease and veno-occlusive disease)[92], susceptibility to infections[93], and veno-occlusive disease[94].

Although iron overload both before and after transplantation and its effects on end organ toxicity are legitimate concerns in high-risk MDS, many questions remain unresolved with regards to the potential role of iron chelation therapy in this context. Prospective studies incorporating T2* MRI of the heart and iron as well as alternative biomarkers of iron stores are needed to improve our understanding of the extent as well as the temporal significance of iron overload in patients undergoing allogeneic HSCT. The studies should also address the relationship between pre-transplant transfusions and iron overload within each haematological disease group. Given the absolute difference in 5 year-overall survival for patients with MDS between those with the highest and lowest ferritin quartiles[95], judicious chelation therapy could lead to a significant improvement in transplantation outcomes for these patients.

Iron chelation therapy is currently focused on the treatment of patients with transfusional iron overload; however, a wider prospective is being taken with the use of DFX being investigated in a number of other conditions including hereditary haemochromatosis, characterised by progressive iron loading through increased intestinal iron absorption[96]; porphyria cutanea tarda, a common type of porphyria which can be associated with haemochromatosis[97]; and mucormycosis[98].

Finally, studies have demonstrated that iron is a crucial element for the proliferation of tumour cells, and as a consequence, the potential role of iron chelation in the treatment of cancer must be considered in the near future[99].

Conclusion

Long-term RBC transfusion therapy is required for the treatment of several types of congenital and acquired anaemia, such as thalassaemia syndromes, sickle cell disease, MDS, Diamond-Blackfan anaemia and aplastic anaemia. Chronic blood transfusions inevitably lead to iron overload and serious clinical sequelae and patients receiving such transfusions, therefore, requires lifelong chelation therapy. Several factors, including the availability of a given chelator and its properties, drug tolerability, transfusional iron burden and the patient's compliance must be considered in the design of optimal, individualised chelation regimens, and all these factors must regularly be reviewed and the chelation modified accordingly. Adherence to DFO is generally poor and a patient's attitude to adherence can change over time. The availability of oral iron chelators, such as DFP and DFX, may contribute to improved compliance, especially among paediatric and adolescent patients in whom compliance is a particular issue. Adherence may also be improved by offering patients greater choice in chelation.

The challenging task for the future is to design a chelator that: (i) is orally active; (ii) can cross cell membranes; and (iii) is capable of scavenging iron from specific areas of the body, such as the heart, the liver, the endocrine glands and the brain, sparing the bulk of physiologically essential iron.

A number of oral iron chelators are currently under development, including an α-ketohydroxypyridine analogue of DFP, LINAII, and a novel oral once-daily iron chelator, FBS0701[100].

In a multicentre phase 2 study of the safety, tolerability and pharmacodynamics of FBS070I, 51 adult patients, stratified by transfusional iron intake, were randomised to FBS0701 at a dose of 14.5 or 29 mg/kg/day (16 and 32 mg/kg/day of the salt form)[101]. FBS0701 was generally well tolerated at both doses. Forty-nine patients (96%) completed the study. There

were no drug-related serious adverse events. No adverse events showed dose-dependency in frequency or severity. Treatment-related nausea, vomiting, abdominal pain, and diarrhea were each noted in <5% of patients. The most common treatment-related adverse event was increased transaminases (16%, N=8). Three of these eight patients acquired a hepatitis C virus infection on-study from a single blood bank; the five others had abnormal baseline alanine transaminase. Mean serum creatinine did not change significantly from baseline or differ between dose groups. The change in 24-week liver iron concentration (ΔLIC) differed according to the dose of FBS0701: the mean ΔLIC for patients treated with 14.5 mg/kg/day was +3.1 mg/g (dry weight); 29% achieved a decrease in LIC. The mean ΔLIC among the patients treated with 29 mg/kg/day was –0.3 mg/g (dry weight) and 44% achieved a decrease in LIC (P<0.03 for ΔLIC between doses). The safety and tolerability profile at therapeutic doses compare favourably with those of other oral chelators[101].

Finally, the development of more sensitive methods for quantifying iron could improve treatment and monitoring of therapeutic efficacy in iron overload disorders.

Keywords: iron overload, chelation therapy, transfusion-dependent disorders, thalassaemia, iron.

The Authors declare no conflicts of interest.

References

1) Shander A, Cappellini MD, Goodnough L. Iron overload and toxicity: the hidden risk of multiple blood transfusions. Vox Sang 2009; **97**: 185-97.
2) Kushner JP, Porter JB, Olivieri NF. Secondary iron overload. Hematology Am Soc Hematol Educ Program 2001; 47-61 http://asheducationbook.hematologylibrary.org/archive/index.dtl.
3) Takatoku M, Uchiyama T, Okamoto S, et al. Retrospective nationwide survey of Japanese patients with transfusion-dependent MDS and aplastic anemia highlights the negative impact of iron overload on morbidity/mortality. Eur J Haematol 2007; **78**: 487-94.
4) Hershko C, Abrahamov A, Konijm AM, et al. Objectives and methods of iron chelation therapy. Bioinorg Chem Apl 2003; **1**: 151-68.
5) Angelucci E, Brittenham GM, McLaren CE, et al. Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med 2000; **343**: 327-31.
6) Cabantchik ZI, Breuer W, Zanninelli G, Cianciulli P. LPI-labile plasma iron in iron overload. Best Prat Res Clin Haematol 2005; **18**: 277-87.
7) Gattermann N, Rachmilewitz EA. Iron overload in MDS-pathophysiology, diagnosis, and complications. Ann Hematol 2011; **90**: 1-10.
8) Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 2004; **89**: 1187-93.
9) Telfer PT, Prestcott E, Holden S, et al. Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassaemia major. Br J Haematol 2000; **110**: 971-7.
10) Ardalan FA, Osquei MR, Toosi MN, Irvanloo G. Synergic effect of chronic hepatitis C infection and beta thalassemia major with marked hepatic iron overload on liver fibrosis: a retrospective cross-sectional study. BMC Gastroenterol 2004; **4**: 17.
11) Angelucci E, Muretto P, Nicolucci A, et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. Blood 2002; **100**: 17-21.
12) Wood JC. Impact of iron assessment by MRI. Hematology Am Soc Hematol Educ Program 2011; **2011**: 443-50.
13) Anderson LJ, Wonke B, Prescott E, et al. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. Lancet 2002; **360**: 516-20.
14) Wood JC. Cardiac iron across different transfusion-dependent diseases. Blood Rev 2008; **22** (Suppl 2): S14-S21.
15) Pennell DJ, Berdoukas V, Karagiorga M, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood 2006; **107**: 3738-44.
16) Pennell DJ, Porter JB, Cappellini MD, et al. Efficacy of deferasirox in reducing and preventing cardiac iron overload in beta-thalassemia. Blood 2010; **115**: 2364-71.
17) Wood JC, Kang BP, Thompson A, et al. The effect of deferasirox on cardiac iron in thalassemia major: impact of total body iron stores. Blood 2010; **116**: 537-43.
18) Kirk P, Roughton M, Porter JB, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation 2009; **120**: 1961-8.
19) Brittenham GM, Griffith PM, Nienhuis AW, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. N Engl J Med 1994; **331**: 567-73.
20) Davis BA, O'Sullivan C, Jarritt PH, Porter JB. Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. Blood 2004; **104**: 263-9.
21) Engle MA, Erlandson M, Smith CH. Late cardiac complications of chronic, severe, refractory anemia with hemochromatosis. Circulation 1964; **30**: 698-705.
22) Olivieri NF, Nathan DG, MacMillan JH, et al. Survival in medically treated patients with homozygous beta-thalassemia. N Engl J Med 1994; **331**: 574-8.

23) Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood 1997; **89**: 739-61.
24) Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood 2006; **107**: 3455-62.
25) Cohen A, Martin M, Schwartz E. Depletion of excessive liver iron stores with desferrioxamine. Br J Haematol 1984; **58**: 369-73.
26) De Sanctis V, Eleftheriou A, Malaventura C. Thalassaemia International Federation Study Group on Growth and Endocrine Complications in Thalassaemia. Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). Pediatr Endocrinol Rev 2004; **2** (Suppl 2): 249-55.
27) Davis BA, Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk beta-thalassemia. Blood 2000; **95**: 1229-36.
28) Anderson LJ, Westwood MA, Holden S, et al. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. Br J Haematol 2004; **127**: 348-55.
29) Porter JB, Rafique R, Srichairatanakool S, et al. Recent insights into interactions of deferoxamine with cellular and plasma iron pools: implications for clinical use. Ann N Y Acad Sci 2005; **1054**: 155-68.
30) Nisbet-Brown E, Olivieri NF, Giardina PJ, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet 2003; **361**: 1597-602.
31) Delea TE, Edelsberg J, Sofrygin O, et al. Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: a literature review. Transfusion 2007; **47**: 1919-29.
32) Borgna-Pignatti C, Cappellini MD, De Stefano P, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Blood 2006; **107**: 3733-7.
33) Abbruzzese G, Cossu G, Balocco M, et al. A pilot trial of deferiprone for neurodegeneration with brain iron accumulation. Haematologica 2011; **96**: 1708-11.
34) Boddaert N, Le Quan Sang KH, Rötig A, et al. Selective iron chelation in Friedreich ataxia: biologic and clinical implications. Blood 2007; **110**: 401-8.
35) Sohn YS, Breuer W, Munnich A, Cabantchik ZI. Redistribution of accumulated cell iron: a modality of chelation with therapeutic implications. Blood 2008; **111**: 1690-9.
36) Porter JB, Evangeli M, El-Beshlway A. The challenges of adherence and persistence with iron chelation therapy. Int J Hematol 2011; **94**: 453-60.
37) Link G, Konijn AM, Breuer W, et al. Exploring the "iron shuttle" hypothesis in chelation therapy: effects of combined deferoxamine and deferiprone treatment in hypertransfused rats with labeled iron stores and in iron-loaded rat heart cells in culture. J Lab Clin Med 2001; **138**: 130-8.
38) Evans P, Kayyali R, Hider RC, et al. Mechanisms for the shuttling of plasma non-transferrin-bound iron (NTBI) onto deferoxamine by deferiprone. Transl Res 2010; **156**: 55-67.
39) Cohen AR, Galanello R, Piga A, et al. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone. Blood 2003; **102**: 1583-7.
40) Henter JI, Karlén J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. Blood 2007; **109**: 5157-9.
41) Addis A, Loebstein R, Koren G, Einarson TR. Meta-analytic review of the clinical effectiveness of oral deferiprone (L1). Eur J Clin Pharmacol 1999; **55**: 1-6.
42) Taher A, Sheikh-Taha M, Sharara A, et al. Safety and effectiveness of 100 mg/kg/day deferiprone in patients with thalassemia major: a two-year study. Acta Haematol 2005; **114**: 146-9.
43) Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica 2003; **88**: 489-96.
44) Smith GC, Alpendurada F, Carpenter JP, et al. Effect of deferiprone or deferoxamine on right ventricular function in thalassemia major patients with myocardial iron overload. J Cardiovasc Magn Reson 2011; **13**: 34.
45) Berdoukas V, Chouliaras G, Moraitis P, et al. The efficacy of iron chelator regimes in reducing cardiac and hepatic iron in patients with thalassaemia major: a clinical observational study. J Cardiovasc Magn Reson 2009; **11**: 20.
46) Gomber S, Saxena R, Madan N. Comparative efficacy of desferrioxamine, deferiprone and in combination on iron chelation in thalassemic children. Indian Pediatr 2004; **41**: 21-7.
47) Galanello R, Kattamis A, Piga A, et al. A prospective randomized controlled trial on the safety and efficacy of alternating deferoxamine and deferiprone in the treatment of iron overload in patients with thalassemia. Haematologica 2006; **91**: 1241-3.
48) Aydinok Y, Ulger Z, Nart D, et al. A randomized controlled 1-year study of daily deferiprone plus twice weekly desferrioxamine compared with daily deferiprone monotherapy in patients with thalassemia major. Haematologica 2007; **92**: 1599-606.
49) Daar S, Pathare AV. Combined therapy with desferrioxamine and deferiprone in beta thalassemia major patients with transfusional iron overload. Ann Hematol 2006; **85**: 315-6.
50) El-Beshlaway A, Manz C, Naja M, et al. Iron chelation in thalassemia: combined or monotherapy? The Egyptian experience. Ann Hematol 2008; **87**: 545-50.
51) Tanner MA, Galanello R, Dessi C, et al. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. Circulation 2007; **115**: 1876-84.

52) Tanner MA, Galanello R, Dessi C, et al. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. J Cardiovasc Magn Reson 2008; **10**: 12.
53) Pantalone GR, Maggio A, Vitrano A, et al. Sequential alternating deferiprone and deferoxamine treatment compared to deferiprone monotherapy: main findings and clinical follow-up of a large multicenter randomized clinical trial in beta-thalassemia major patients. Hemoglobin 2011; **35**: 206-16.
54) Macklin, Investigational New Drug submission to the U.S. Food and Drug Administration, unpublished data, 2004.
55) Piga A, Galanello R, Forni GL, et al. Randomized phase II trial of deferasirox (Exjade, ICL670), a once-daily, orally-administered iron chelator, in comparison to deferoxamine in thalassemia patients with transfusional iron overload. Haematologica 2006; **91**: 873-80.
56) Galanello R, Piga A, Alberti D, et al. Safety, tolerability, and pharmacokinetics of ICL670, a new orally active iron-chelating agent in patients with transfusion-dependent iron overload due to beta-thalassemia. J Clin Pharmacol 2003; **43**: 565-72.
57) Porter J, Galanello R, Saglio G, et al. Relative response of patients with myelodysplastic syndromes and other transfusion-dependent anaemias to deferasirox (ICL670): a 1-yr prospective study. Eur J Haematol 2008; **80**: 168-76.
58) Vichinsky E, Onyekwere O, Porter J, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Br J Haematol 2007; **136**: 501-8.
59) Cappellini MD. Efficacy and safety of deferasirox (exjade®) in pediatric patients with beta-thalassemia: update of 4.7-year efficacy and safety form extension studies [abstract]. Blood 2008; **112**: ABS3883.
60) Cappellini MD, Porter J, El-Beshlawy A, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica 2010; **95**: 557-66.
61) Taher A, El-Beshlawy A, Elalfy MS, et al. Efficacy and safety of deferasirox, an oral iron chelator, in heavily iron-overloaded patients with beta-thalassaemia: the ESCALATOR study. Eur J Haematol 2009; **82**: 458-65.
62) Deugnier Y, Turlin B, Ropert M, et al. Improvement in liver pathology of patients with β-thalassemia treated with deferasirox for at least 3 years. Gastroenterology 2011**; 141**: 1202-11, 1211.e1-3.
63) Pennell DJ, Porter JB, Cappellini MD, et al. Continued improvement in myocardial T2* over two years of deferasirox therapy in β-thalassemia major patients with cardiac iron overload. Haematologica. 2011; **96**: 48-54.
64) Lal L. Safety of combined chelation therapy with deferasirox and deferoxaminein transfusion-dependent thalassemia [Abstract]. Blood 2009; **114**: 2021.
65) Otto-Duessel M, Brewer C, Gonzalez I, Nick H, Wood JC. Safety and efficacy of combined chelation therapy with deferasirox and deferoxamine in a gerbil model of iron overload. Acta Haematol 2008; **120**: 123-8.
66) Trad O, Hamdan MA, Jamil A, et al. Reversal of iron-induced dilated cardiomyopathy during therapy with deferasirox in beta-thalassemia. Pediatr Blood Cancer 2009; **52**: 426-8.
67) Berdoukas V, Farmaki K, Wood JC, Coates T. Iron chelation in thalassemia: time to reconsider our comfort zones. Expert Rev Hematol. 2011; **4**: 17-26.
68) Porter JB. Deferoxamine pharmacokinetics. Semin Haematol 2001; **38** (1 Suppl 1): 63-8.
69) al-Refaie FN, Sheppard LN, Nortey P, et al. Pharmacokinetics of the oral iron chelator deferiprone (L1) in patients with iron overload. Br J Haematol 1995; **89**: 403-8.
70) Cabantchick ZI, Breuer W, Zanninelli G, Cianciulli P. LPI-labile plasma iron in iron overload. Best Pract Res Clin Haematol 2005; **18**: 277-87.
71) Farmaki K, Tzoumari I, Pappa C, Chouliaras G, Berdoukas V. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol 2010; **148**: 466-75.
72) Daar S, Pathare A, Nick H, et al. Reduction in labile plasma iron during treatment with deferasirox, a once-daily oral iron chelator, in heavily iron-overloaded patients with beta-thalassaemia. Eur J Haematol 2009; **82**: 454-7.
73) Cappellini MD, Bejaoui M, Agaoglu L, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood 2011; **118**: 884-93.
74) Park SJ, Han CW. Complete hematopoietic recovery after continuous iron chelation therapy in a patient with severe aplastic anemia with secondary hemochromatosis. J Korean Med Sci 2008; **23**: 320-3.
75) Gattermann N, Arisch A, Schlag R, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: results from the large 1-year EPIC study. Leuk Res 2010; **34**: 1143-50.
76) Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. Blood 2008; **111**: 583-7.
77) Porter JB, Lin KH, Beris P, et al. Response of iron overload to deferasirox in rare transfusion-dependent anaemias: equivalent effects on serum ferritin and labile plasma iron for haemolytic or production anaemias. Eur J Haematol 2011; **87**: 338-48.
78) Fox F. Matched-pair analysis of 186 MDS patients receiving iron chelation therapy or transfusion therapy only [abstract]. Blood 2009; **114** (22): ABS1747.
79) Leitch HA, Chase JM, Goodman TA, et al. Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy. Clin Leukemia 2008; **2**: 205-11.
80) Rose C, Brechignac S, Vassilief D, et al. Does iron chelation therapy improve survival in regularly transfused lower risk MDS patients? A multicenter

study by the GFM (Groupe Francophone des Myélodysplasies). Leuk Res 2010; **34**: 864-70.
81) Sanz G. Independent impact of iron overload and transfusion dependency on survival and leukemic evolution in patients with myelodysplastic syndrome [abstract]. Blood 2008; **112** (II): ABS640.
82) Gattermann N, Finelli C, Porta MD, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: results from the large 1-year EPIC study. Leuk Res 2010; **34**: 1143-50.
83) Oliva EN, Ronco F, Marino A, et al. Iron chelation therapy associated with improvement of hematopoiesis in transfusion-dependent patients. Transfusion 2010; **50**: 1568-70.
84) Breccia M, Loglisci G, Saiaroli A, et al. Deferasirox treatment interruption in a transfusion-requiring myelodysplastic patient led to loss of erythroid response. Acta Haematol 2010; **24**: 46-8.
85) Gattermann N. Hematologic responses in myelodysplastic syndrome (MDS) patients treated with deferasirox: an EPIC post-hoc analysis using International Working Group (IWG) 2006 criteria [abstract]. Blood 2010; **116** (21): ABS2912.
86) Molteni A. Independent impact of iron overload and transfusion dependency on survival and leukemic evolution in patients with myelodysplastic syndrome [abstract]. Haematologica 2010; **95** (Suppl 2): ABS640.
87) Syfuss PY, Ciupea A, Brahimi S, et al. Mild dehydrated hereditary stomatocytosis revealed by marked hepatosiderosis. Clin Lab Haematol 2006; **28**: 270-4.
88) Kamble RT, Selby GB, Mims M, et al. Iron overload manifesting as apparent exacerbation of hepatic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2006; **12**: 506-10.
89) Mckay PJ, Murphy JA, Cameron S, et al. Iron overload and liver dysfunction after allogeneic or autologous bone marrow transplantation. Bone Marrow Transplant 1996; **17**: 63-6.
90) Lucarelli G, Galimberti M, Polchi P, et al. Marrow transplantation in patients with thalassemia responsive to iron chelation therapy. N Engl J Med 1993; **329**: 840-4.
91) Kamble R, Mims M. Iron-overload in long-term survivors of hematopoietic transplantation. Bone Marrow Transplant 2006; **37**: 805-6.
92) Butt NM, Clark RE. Autografting as a risk factor for persisting iron overload in long-term survivors of acute myeloid leukaemia. Bone Marrow Transplant 2003; **32**: 909-13.
93) Miceli MH, Dong L, Grazziutti ML, et al. Iron overload is a major risk factor for severe infection after autologous stem cell transplantation: a study of 367 myeloma patients. Bone Marrow Transplant 2006; **37**: 857-64.
94) Morado M, Ojeda E, Garcia-Bustos J, et al. BMT: Serum ferritin as risk factor for veno-occlusive disease of the liver. Prospective cohort study. Hematology 2000; **4**: 505-12.
95) Wells RA, Leber B, Buckstein R, et al. Iron overload in myelodysplastic syndromes: a Canadian consensus guideline. Leukemia Res 2008; **32**: 1338-53.
96) Pietrangelo A. Iron chelation beyond transfusion iron overload. Am J Hematol 2007; **82** (12 Suppl): 1142-6.
97) Gorman N, Zaharia A, Trask HS, et al. Effect of an oral iron chelator or iron-deficient diets on uroporphyria in a murine model of porphyria cutanea tarda. Hepatology 2007; **46**: 1927-34.
98) Ibrahim AS, Gebermariam T, Fu Y, et al. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. J Clin Invest 2007; **117**: 2649-57.
99) Yamasaki T, Terai S, Sakaida I. Deferoxamine for advanced hepatocellular carcinoma. N Engl J Med 2011; **365**: 576-8.
100) Rienhoff HY Jr, Viprakasit V, Tay L, et al. A phase I dose-escalation study: safety, tolerability, and pharmacokinetics of FBS070I, a novel iron chelator for the treatment of transfusional iron overload. Haematologica 2010; **96**: 521-5.
101) Neufeld EJ, Galanello R, Viprakasit V, et al. A phase 2 study of the safety, tolerability and pharmacodynamics of FBS0701, a novel oral iron chelator, in transfusional iron overload. Blood 2012; **119**: 3263-8.

Arrived: 19 January 2012 - Revision accepted: 21 February 2012
Correspondence: Maria Domenica Cappellini
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Dipartimento di Medicina Interna
Università di Milano
Via Francesco Sforza 35
20122 Milan, Italy
e-mail: maria.cappellini@unimi.it