Safety and efficacy of deferasirox in the management of transfusion-dependent patients with myelodysplastic syndrome and aplastic anaemia: a perspective review

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Abstract: Deferasirox is an orally administered, once-daily iron chelator with a generally good safety and efficacy profile. Reported adverse events in the older myelodysplastic population are somewhat different to the more intensively investigated and younger thalassaemic population. Renal impairment is the most concerning adverse event, but this is reversible if identified and the drug is withdrawn early. Gastrointestinal effects, particularly diarrhoea, can be troublesome for older patients, but can be minimized with tailored therapy. Negative iron balance can be achieved in most patients with a median dose of 20 mg/kg/day, and doses up to 40 mg/kg are possible in patients with severe iron overload, who are at risk of cardiac decompensation.

Keywords: aplastic anaemia, deferasirox, efficacy, iron chelation, myelodysplastic syndrome, safety

Introduction

Disorders characterized by chronic anaemia, such as myelodysplastic syndrome (MDS) and aplastic anaemia (AA), rely on supportive red blood cell (RBC) transfusions for the treatment of symptomatic anaemia. Several guidelines have been published, recommending the institution of iron chelation therapy to counteract the effects of transfusional iron overload [Bennett, 2008; Bird *et al.* 2012; Greenberg *et al.* 2011]. This paper will discuss the development of iron overload in these patients, considerations in the monitoring of iron status, the factors involved in the decision to institute chelation therapy and the therapeutic options available for iron chelation, and will focus on the safety and efficacy of deferasirox as the most convenient and commonly used agent for this purpose.

Iron overload

Iron homeostasis is tightly controlled by regulation of iron absorption at the enterocyte level. This precise control is essential to balance the role of iron as a necessary element for survival, against its potentially toxic effects. The essential role of iron in oxygen transport, cellular respiration, metabolic reactions, production of oxygen radicals, anti-oxidation, DNA synthesis and repair, and also inflammation is balanced against the potential harmful effects of iron, including tissue deposition, oxidative stress, production of reactive oxygen species (ROS) and cellular damage. In conditions characterized by ineffective erythropoiesis, such as MDS, there is an inappropriate increase in iron absorption mediated by decreased hepcidin levels in response to increased, although ineffective, erythropoiesis. MDS patients are therefore prone to iron loading, even in the absence of RBC transfusion. As there is no physiological mechanism for the excretion of iron, additional iron in the form of RBC transfusions can result in loss of equilibrium, with resultant iron overload. Each unit of red cell concentrate contains approximately 250 mg of iron, with the reticuloendothelial system having a storage capacity of about 10–15 g [Leitch, 2011], meaning that after about 50 units of RBC, the storage capacity

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is saturated, and parenchymal deposition and tissue damage may occur. Not only is the inert storage form of ferritin increased, but saturation of the carrier protein transferrin results in the formation of the potentially more destructive non-transferrin-bound iron (NTBI) and labile plasma iron (LPI) fraction [Hershko *et al.* 1978], which have been associated with increased formation of ROS, linked to oxidative DNA damage [Kikuchi *et al.* 2012], lipid peroxidation, oxidation of amino acid side chains, formation of protein–protein crosslinks and protein fragmentation [Hershko, 2010], all of which mediate tissue damage. The effects of transfusional iron overload have been well described in the thalassaemic population, with hepatic, cardiac and endocrine dysfunction prominent, as well as an increased risk of infection, and premature death [Hershko, 2010]. In a large, retrospective analysis of 467 MDS patients, it was demonstrated that transfusional iron overload was an independent adverse prognostic risk factor for survival [Malcovati, 2007], and transfusion dependence is recognized as an independent adverse prognostic factor in the World Health Organization classification-based prognostic scoring system for MDS.

Monitoring iron status

The ability to monitor iron status is essential for determining the appropriate timing of institution of chelation, and also in ensuring therapeutic efficacy. Several methods for estimating iron status are available with differing precision, availability and cost.

The most widely available and affordable option is serum ferritin. This accurately reflects reticuloendothelial iron stores [Olivieri *et al.* 1995], but may not be predictive of parenchymal tissue iron. Ferritin is an acute phase protein, so is raised in response to inflammatory stimuli, and elevated in tissue injury. Most authors recommend its main utility is in the serial assessment of iron status.

Assessment of tissue iron by liver or cardiac biopsy is considered the gold standard in thalassaemic patients, however in the MDS and AA populations, utility is limited by concomitant thrombocytopenia and neutropenia, predisposing to haemorrhage and infection. There is also a concern that heterogeneous distribution of tissue iron deposits may predispose this modality to sampling error [Barosi *et al.* 1989; Mahesh *et al.* 2008].

Magnetic resonance imaging has been validated as an alternative noninvasive technique for assessment of organ iron loading, which correlates well with iron load as assessed by liver biopsy in the thalassaemia population [Virtanen *et al.* 2012]. Simultaneous assessment of liver and cardiac iron load is possible using this technique. As cardiac disease is a major cause of death in transfusion-dependent patients with iron overload, direct measurement of myocardial iron is important in the assessment of prognosis.

The superconducting quantum interference device is a modality that is available in only a few centres worldwide and provides a noninvasive direct assessment of liver iron deposits, and is mentioned for completeness.

NTBI can be measured by fairly straightforward methods, but is not yet widely available, and remains investigational. Recently, kits have been developed that are likely to enable more widespread use of NTBI assay in routine service laboratories [Aferrix Ltd, 2012], and have been used to assess LPI in the clinical trial setting [Giagounidis *et al.* 2012], but clinical algorithms based on NTBI measurement will need to be developed.

Factors influencing the decision to chelate

Although several groups have published guidelines recommending chelation in chronically transfused patients with MDS and AA, it should be recognized that the basis for these recommendations is mainly in the form of retrospective case-control studies in these populations, and prospective randomized supportive data have been extrapolated from the thalassaemic and haemochromatosis populations. There are no level one randomized prospective data on which to base recommendations in MDS and AA, although this is awaited in the Food and Drug Administration-mandated Myelodysplastic Syndromes Event-free Survival with Iron Chelation Therapy Study (TELESTO) trial [ClinicalTrials.gov identifier: NCT00940602].

Currently, the main factors in deciding appropriateness to chelate focus on the degree of iron loading (transfusion burden), evidence of iron excess (elevated ferritin), the underlying disease and life-expectancy measures. Recommendations are that patients diagnosed with low or intermediate-1 International Prognostic Scoring

Table 1. Factors affecting information communication technology decision.

Transfusion burden
> 2 units PRBC per month for > 1 year
Cumulative > 20–40 units PRBC transfused
Iron excess
Serum ferritin > 1000 µg/l
Disease (life expectancy > 1 year)
MDS (IPSS low, Int-1, responding to DMT)
AA (transfusion dependent)
Allogeneic stem-cell transplantation
Patient factors
Absence of life-shortening comorbidities
Allogeneic transplant candidate
Organ function threatened by iron overload

AA, aplastic anaemia; DMT, disease-modifying therapy; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; PRBC, packed red blood cells.

System (IPSS) score MDS, transfusion-dependent AA, those who respond to disease-modifying therapy, or who are eligible for haematopoietic stem-cell transplantation (HSCT) should be considered for iron chelation (see Table 1).

Iron chelators

Iron chelators are agents that promote negative iron balance by binding and allowing excretion of iron in a nontoxic form. Desferrioxamine is the chelator that has been in use for the longest time, but its poor oral bioavailability and short half-life require administration by continuous parenteral infusion. Deferiprone is orally administered three times daily, but due to its potential to produce agranulocytosis requires close monitoring, and is generally avoided in the MDS and AA population, where neutropenia due to the underlying disease is common.

Deferasirox is an orally administered once-daily agent, with an accumulating body of evidence relating to tolerability and efficacy in patients with MDS and AA, in addition to the well-studied thalassaemic population.

Mechanism and pharmacodynamics

Deferasirox shows selectivity for iron in its trivalent form (Fe^{3+}), with a low affinity for zinc and copper. It shows a dose-dependent response, with increasing dosage resulting in greater iron elimination [Novartis Pharmaceuticals Australia Pty Ltd, 2012], and the usual starting dose of 20 mg/kg/day resulting in mean net losses of 0.329 mg Fe/kg/day in an adult thalassaemic population.

Pharmacokinetics

Rapid absorption following ingestion results in a median time to maximum plasma concentration (C_{max}) of about 1–4 h, with an approximately linear dose response. Once-daily dosing is possible by virtue of the plasma half-life of 8–16 h. The absolute bioavailability of deferasirox from dispersible tablets is about 70% compared with an intravenous dose, and due to variation in total drug exposure (area under the curve) with different meal compositions, it has been recommended to be taken on an empty stomach at least 30 min prior to ingestion of food [Novartis Pharmaceuticals Australia Pty Ltd, 2012], based on pharmacokinetics trials [Galanello *et al.* 2008; Sechaud *et al.* 2008]. A small trial has investigated the tolerability and comparative effectiveness of dispersion of tablets in food or taken with food, in comparison with the manufacturers' recommended mode of administration. It reported that patients tolerated a variety of food and liquid options for dispersion, and that although not statistically significant, showed a trend towards better tolerability, with no definite conclusions able to be made regarding pharmacokinetic data or efficacy in iron reduction [Giardina *et al.* 2011]. Deferasirox promotes faecal excretion of iron by virtue of its metabolism through primarily hepatic glucuronidation and subsequent biliary excretion. Renal excretion is minimal (about 8%), however, renal failure is a consideration, and will be discussed further below.

Safety aspects

Deferasirox has a well-described safety profile in the MDS and AA population, with discontinuation due to adverse events reportedly around 25–40%, and those due to laboratory abnormalities around 13–15% [Gattermann *et al.* 2010; List *et al.* 2009, 2012; Porter *et al.* 2008]. Although the majority of patients experience adverse events, they are commonly of mild to moderate severity, and can be managed supportively or through dose reduction.

The most common adverse events related to deferasirox administration seen in clinical trials were gastrointestinal, skin rash and increases in serum creatinine. These were mainly of mild to moderate severity, and rarely required discontinuation, either resolving spontaneously or responding to dose reduction.

Postmarketing surveillance, in addition, has noted several cases of renal or hepatic toxicity, and cases of gastrointestinal haemorrhage, which in some cases proved fatal. This prompted a boxed warning in the package insert to ensure that adequate monitoring of patients with serial creatinine, liver function tests (LFTs) and appropriate clinical surveillance was maintained during therapy.

In clinical trials, elderly patients, who tended to represent the MDS population, experienced a higher frequency of adverse events than younger patients, and therefore more intensive monitoring is recommended in this population. A more detailed discussion of the various safety aspects follows.

Gastrointestinal

The most common adverse events of nausea, vomiting and diarrhoea are reported in around 15% across all populations, and appear to be dose related. In addition, gastrointestinal adverse events are more commonly reported in the elderly MDS population than in the younger thalassaemic population. Elderly patients were also found to be at greater risk of potentially fatal gastrointestinal haemorrhage with comorbidities, such as advanced haematological malignancy with concomitant thrombocytopenia, associated with this event [Novartis Pharmaceuticals Australia Pty Ltd, 2012].

Although dosing prior to food ingestion is recommended in the manufacturers' product information, the authors' experience is that gastrointestinal tolerability is improved by drug administration with food, and in the MDS and AA population, dose titration at initiation of therapy up to target dose over 2–3 weeks, improves patient compliance [Giagounidis *et al.* 2012], without compromising the goal of negative iron balance in the longer term. However, the bioavailability of deferasirox depends on many variables, including whether drug is taken in the fed or fasting state, and also depending on the caloric and fat content of the meal with which it is ingested [Galanello *et al.* 2008]. The resultant variability in drug levels associated with a single dose (up to 50% higher plasma levels after ingestion with a fatty meal) remains a significant limitation of this approach. Another approach often used is evening administration to minimize abdominal discomfort or nausea. As yet, there is no published evidence to support these approaches in minimizing gastrointestinal intolerance. Studies are warranted to validate the effect of these approaches on drug pharmacokinetics and efficacy.

Upper gastrointestinal effects, such as ulceration, irritation and haemorrhage, are reported in patients of all ages following administration of deferasirox. Caution should be exercised in patients with preexisting risk factors for gastrointestinal haemorrhage, including concurrent administration of other drugs associated with gastrointestinal irritation (nonsteroidal anti-inflammatories, glucocorticoids, bisphosphonates) and in situations of impaired haemostasis (thrombocytopaenia, platelet dysfunction and coagulopathy, including anticoagulant therapy). Early and proactive evaluation of symptoms suggestive of gastrointestinal haemorrhage is indicated.

A detailed approach to the evaluation and management of gastrointestinal side effects has been compiled by an expert panel [Nolte *et al.* 2011], and provides an algorithmic and practical approach, with severity-specific recommendations for the management of commonly described gastrointestinal side effects.

Dermatological

Skin rash is reported in around 10% of patients, and often described as maculopapular, can be pruritic, is commonly of mild to moderate severity and, in many cases, resolves spontaneously without dose reduction. However, in more severe cases, dose reduction or temporary cessation with reintroduction at lower doses and in association

with topical or oral steroid has been effective [Vichinsky, 2008]. Rare cases of erythema multiforme have been reported in association with deferasirox administration [Novartis Pharmaceuticals Australia Pty Ltd, 2012].

Renal

Since reports of acute renal failure associated with deferasirox, some fatal and some leading to long-term dialysis, there has been an increased emphasis on ensuring appropriate patient selection based on pre-existing renal function as assessed by creatinine concentration and creatinine clearance (Cockcroft–Gault or similar formula), and vigilance in co-administration with nephrotoxic drugs. For example, co-administration of cyclosporine in AA was a statistically significant factor in predicting renal impairment in this population [Lee *et al.* 2010]. Care should be taken to ensure adequate hydration in situations in which renal function may be compromised, for example, dehydration, sepsis or reduced renal blood flow. Commencement of deferasirox therapy is contraindicated in patients with creatinine clearance < 40 ml/min or serum creatinine more than twice the upper limit of normal, and so serum creatinine/creatinine clearance are assessed in duplicate prior to initiation of therapy, and at regular intervals after therapy has commenced. Monthly monitoring is recommended in patients with previously normal renal function, and in those with pre-existing renal impairment or other risk factors for renal impairment; weekly monitoring in the first month of treatment is recommended [Vichinsky, 2008].

Renal adverse events are associated with rapid deironing, as evidenced by a brisk fall in serum ferritin [Ponticelli *et al.* 2010]. For this reason, dose reduction in deferasirox is recommended when the serum ferritin falls below 1000 µg/l, and drug withdrawal when the ferritin falls below 500 µg/l [Novartis Pharmaceuticals Australia Pty Ltd, 2012; Vichinsky, 2008].

Fatalities in patients who developed renal failure were observed predominantly in patients with multiple medical comorbidities and with advanced stage haematological disorders.

In patients who develop a rise in serum creatinine > 33% of pretreatment levels or creatinine clearance decreases below the lower limit of the normal range (< 90 ml/min) on two consecutive visits with no other obvious cause, a decrease in dose by 10 mg/kg can be trialled, and if the renal impairment does not improve, dose interruption should follow [Novartis Pharmaceuticals Australia Pty Ltd, 2012].

Proteinuria, which may be intermittent, has been reported in about 18% of patients, and may be more common in children with Fanconi anaemia, with a single small study of this population reporting an unexpectedly high proportion of these children developing proteinuria [Tunc *et al.* 2012]. It is recommended that urinary protein be monitored in patients who develop renal impairment.

Hepatic

Abnormalities in LFTs showing elevation in liver enzymes have been reported in conjunction with deferasirox therapy, some of which have resulted in hepatic failure and fatalities. These have been seen most commonly in older patients (> 55 years of age), with comorbidities including pre-existing significant hepatic impairment (cirrhosis) and multi-organ failure [Novartis Pharmaceuticals Australia Pty Ltd, 2012]. Assessment of serum transaminases, bilirubin and alkaline phosphatase is recommended prior to initiation of therapy, fortnightly in the first month of therapy and monthly thereafter. In the case of progressive increase in transaminase levels, interruption of therapy is recommended. If the cause of LFT derangement is subsequently clarified, or if levels return to normal, reinstitution of therapy at a lower dose may be considered. In patients with moderate hepatic impairment, initiation of therapy at a 50% dose reduction may be trialled, with regular monitoring of hepatic function [Novartis Pharmaceuticals Corporation, 2012].

Haematological

Cytopenias, including agranulocytosis, neutropenia, thrombocytopenia and pancytopenia, have been reported rarely, mainly in patients with pre-existing haematological disorders associated with bone-marrow failure. As is standard practice in such patients, regular monitoring should be instituted, and in patients in whom cytopenias are unexplained by other causes, or in whom deferasirox is strongly implicated, treatment interruption should be instituted [Novartis Pharmaceuticals Australia Pty Ltd, 2012]. An important consideration in the MDS and AA populations is whether these cytopenias represent a manifestation of

disease progression or relapse, especially in view of the rarity of deferasirox-associated cytopenias.

Hypersensitivity

Anaphylaxis and angioedema hypersensitivity reactions have been reported, most usually in the first month of therapy [Novartis Pharmaceuticals Australia Pty Ltd, 2012].

Special senses

Auditory and ocular disturbances have been reported in fewer than 1% patients in clinical trials [Novartis Pharmaceuticals Australia Pty Ltd, 2012], however, considering the serious consequences of such impairment, auditory and ophthalmic examination are recommended prior to initiation of therapy and if disturbances are noted.

Infections

Iron overload is associated with an increased susceptibility to infection with a variety of microorganisms, as a result of the increased availability of iron, which is essential for their proliferation [Kontoghiorghes *et al.* 2010]. An increased incidence of infections with ferrophilic organisms has been reported in patients on desferrioxamine [Ibrahim *et al.* 2008; Robins-Browne and Prpic, 1983; Zurlo *et al.* 1989], and is thought to be related to desferrioxamine's biologically derived structure [Ma *et al.* 2012], a component of which can be paradoxically acquired by some microorganisms, enhancing iron acquisition and facilitating growth [Chan *et al.* 2009]. However, this observation does not appear to be a class effect, and no increased incidence of infections has been noted in patients treated with deferasirox [Ibrahim *et al.* 2008]. Although there are some data that deferasirox may have potential as an adjunct therapy in patients with mucormycosis [Ibrahim *et al.* 2007], a recent prospective trial failed to show benefit for deferasirox in combination with standard treatment as upfront therapy [Spellberg *et al.* 2012].

Medications

Limited data suggest that concomitant administration of deferasirox with newer therapies such as azacitidine and lenalidomide is not associated with an increased rate of adverse events [Breccia *et al.* 2012]. Caution should be exercised with the co-administration of nephrotoxic drugs.

Clinical efficacy

Multiple studies in patients with transfusional iron overload (the majority comprising patients with B-thalassaemia major) have shown that the effects of iron overload can be reversed with effective chelation. Deferasirox has been shown to be an effective iron chelation agent in all populations studied, including the MDS and AA population, with its efficacy as a chelating agent first detailed by Cappellini and colleagues [Cappellini *et al.* 2006].

Iron overload

The Evaluation of Patients' Iron Chelation with Exjade® (EPIC) study remains the largest study of efficacy in the populations of MDS and AA patients as separately analysed subsets of total patients treated with deferasirox. It demonstrated a statistically significant decrease in iron burden as assessed by serum ferritin at the completion of the 1-year study in these groups (in addition to the overall study population composed of primarily thalassaemic patients) [Gattermann *et al.* 2010]. The eXtend noninterventional observational study demonstrated that in chelation-naïve patients with MDS and in those with other transfusion-dependent anaemias, a statistically significant decrease in serum ferritin was achieved over the 1-year study period [Gattermann *et al.* 2012b]. Two further studies prospectively assessed heavily transfused patients with IPSS low and intermediate-1 MDS, and showed not only decreases in serum ferritin over the course of a year, but also LPI and liver iron concentration in these patients, despite ongoing RBC transfusion during this time [Greenberg *et al.* 2010; List *et al.* 2012]. Negative iron balance can be achieved in most patients with a median dose of 20 mg/kg/day [Greenberg *et al.* 2010], and doses up to 40 mg/kg possible in patients with severe iron overload [Taher *et al.* 2009], which might result in cardiac decompensation.

Monitoring of serum ferritin is recommended monthly, in order to establish the effectiveness of therapy and guide dose adjustments [Novartis Pharmeceuticals Australia Pty Ltd, 2012].

Hepatic improvement

Improvements in transaminases, most commonly assessed by alanine transaminase, have been reported in association with reductions in serum ferritin, and are thought to represent improvement in liver function as a result of reduction in tissue iron deposition with consequent physical

and ROS effects of increased liver iron concentration being remediated [Gattermann *et al.* 2011; Lee *et al.* 2010; List *et al.* 2012].

Haematological response

Reduction in transfusion requirement has been reported after successful iron chelation therapy with deferasirox, in the absence of other treatment for ineffective erythropoiesis, in both MDS and AA patients [Breccia *et al.* 2012; Gattermann *et al.* 2012a; Lee *et al.* 2011; Nishiuchi *et al.* 2010]. Although the mechanism is unknown, hypotheses include improvement of marrow function with reduced tissue iron, reduced formation of oxygen free radicals as a result of effective iron reduction in the bone marrow, or a novel theory which postulates that as a result of deferasirox-specific inhibition of nuclear factor-kappa B, a transcription factor that is upregulated in MDS blasts, and that this effect is seen particularly in the malignant clone [Messa *et al.* 2010]. However, as haematological improvement has been reported with the use of all of the currently available chelators, a class effect seems likely. In addition to improvement in erythropoiesis, improvements in both granulopoiesis and megakaryopoiesis have been reported [Gattermann *et al.* 2012a; Guariglia *et al.* 2011; Messa *et al.* 2008], presumably related to the same factors.

There is some evidence that reduction in iron loading is associated with a trend towards improvement in leukaemia-free survival in MDS cohorts [Pullarkat, 2009], however this effect has not been observed in all cohorts [Neukirchen *et al.* 2012], and although various biological mechanisms have been postulated, including decreased oxidative DNA damage [Kikuchi *et al.* 2012], and induction of differentiation of MDS blasts by iron deprivation [Callens *et al.* 2010], this requires further assessment in a prospective study.

Overall survival

Overall survival has been demonstrated to improve after chelation with deferasirox [Neukirchen *et al.* 2012; Rose *et al.* 2010], however due to the design of these studies (case control, matched-pair analysis) interpretation requires a degree of circumspection. The underlying mechanism for improved survival is unclear, but contributions of improvement in cytopenias, reduction in or freedom from transfusion requirements, and possible reduction in leukaemia transformation could be factors. Whilst it would appear biologically plausible that the well-reported effects of improved overall survival in thalassaemic patients could be replicated in this population, the older age and comorbidities, as well as the relatively reduced prognosis for long-term survival, mean that prospective studies are required to better address this question.

Haematologic Stem Cell Transplant (HSCT)

In the haematologic stem cell transplant (HSCT) setting, iron overload is associated with inferior outcomes, including decreased overall survival, increased rate of relapse, liver disease, graft *versus* host disease, infections and delayed engraftment [Armand *et al.* 2007; Mahindra *et al.* 2009; Pullarkat, 2010; Pullarkat *et al.* 2008], providing a strong impetus for chelation in patients who could potentially undergo this therapy. There is also mounting evidence as to the safety and efficacy of deferasirox in the postallogeneic HSCT setting for reducing iron overload, when phlebotomy is inappropriate or contraindicated [Majhail *et al.* 2010; Sivgin *et al.* 2012], and studies are ongoing in this area.

Quality-of-life indicators

Quality-of-life (QoL) studies in MDS patients are heterogeneous in design and assessment tools, and there are few studies that specifically address the question of QoL indicators associated with initiation of chelation therapy in this population. Inferior QoL has been associated with transfusion dependence, age and haemoglobin < 100 g/l in MDS patients [Buckstein *et al.* 2009, 2011], and in an analysis of results from the EPIC trial, there were improvements in QoL when deferasirox was compared with desferrioxamine, with greater improvement in QoL in thalassaemia patients than MDS patients [Porter *et al.* 2012]. Although a subjective and intangible measure, more studies into QoL are warranted in this population to assess the effects of iron chelation therapy on this aspect of patient care.

Deferasirox treatment is a dynamic process, requiring continuous monitoring of therapeutic efficacy in relation to treatment goals.

Conclusion

The mounting evidence, albeit predominantly retrospective and from small series, is that iron chelation with deferasirox is beneficial in patients

with MDS and AA, with lowering of ferritin levels and improvements in overall survival shown in several studies. Appropriate patient selection remains a critical component of successful therapy, combined with careful monitoring for both adverse effects and clinical efficacy, in order to derive the most benefit from a carefully implemented chelation strategy. Further studies incorporating prospective, randomized assessment of patient outcomes following chelation therapy are awaited, although in many jurisdictions, the availability of subsidized deferasirox for MDS and AA patients with transfusional iron overload has already lead to the widespread adoption of chelation in this group.

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Conflict of interest statement

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