Iron Overload Update
Managing Iron Overload in Clinical Practice

Dear Colleague,

Maintaining a healthy iron balance is of critical concern in the management of transfusional-dependent anaemias and other disorders. Blood transfusions are often necessary for the patient’s survival and well-being. However, unless excess iron is removed, the treatment itself becomes a significant cause of morbidity. Although effective chelation has been available for several decades, compliance and availability have frequently limited access to this therapy. Recent advances have provided additional therapeutic options, including a once-daily oral chelator with 24-hour chelation coverage.

This newsletter presents background information and two case studies included in a symposium at the 12th Congress of the European Hematology Association (EHA), called Turning the Science of Iron Overload into Iron Chelation Practice. I present an overview of the clinical science supporting current trends in diagnosing, treating, and managing iron overload. Prof. Maria Cappellini provides detailed comparisons of the efficacy and safety of the three currently available iron chelators: desferrioxamine, deferiprone, and deferasirox.

The two case studies each highlight management considerations that arise in the treatment of iron overload in different clinical situations. Dr. Aristoteles Giagounidis describes the factors to be considered when deciding whether to chelate a high-risk patient with myelodysplastic syndrome who is a candidate for stem cell transplantation. His patient showed improvements with pretransplantation deferasirox therapy. The case presented by Dr. Ali Taher involves a patient with thalassaemia intermedia who has received infrequent transfusions, illustrating the clinical importance of chelation in patients who are not regularly transfused. We invite you to consider the clinical decision points raised in these case studies and to compare your answers to those of the EHA symposium attendees.

I hope this newsletter will provide valuable information regarding current chelation options and further your insights into whether a particular patient would benefit from chelation therapy.

Sincerely,

John B. Porter, MA, MD, FRCP, FRCPath

Chair

John B. Porter, MA, MD, FRCP, FRCPath
Professor
Department of Haematology
University College London
London, United Kingdom

Faculty Contributor

Maria D. Cappellini, MD
Professor Internal Medicine
University of Milan
Milan, Italy

Faculty Contributor

Aristoteles A.N. Giagounidis, MD
St. Johannes Hospital
Medizinische Klinik II
Duisburg, Germany

Faculty Contributor

Ali T. Taher, MD
Professor
Department of Internal Medicine
American University of Beirut Medical Center
Beirut, Lebanon

Poll Results

References

Target Audience

This activity is designed for haematologists, medical oncologists, haematology-oncology specialists, and other healthcare professionals involved in the care of adults and children with myelodysplastic syndromes and thalassaemia.

Activity Goal

The goal of this newsletter is to provide clinicians with information about recent advances in assessing, monitoring, and treating iron burden in their patients and to describe treatment strategies for iron overload in patients with myelodysplastic syndromes and occasionally transfused patients with thalassaemia intermedia.

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Learning Objectives

- Increase awareness of patients at risk for iron overload and the impact of transfusion therapy on the development of iron overload and its sequelae in patients with myelodysplastic syndromes and thalassaein in order to institute interventions that improve patients’ outcomes.
- Implement monitoring of iron levels of at-risk patients with myelodysplastic syndromes and thalassaein receiving routine/intermittent blood transfusions, utilizing a knowledge of reliable invasive/noninvasive methods.
- Assess the consequences of iron overload on organ function and organ failure and therefore the importance of intervention, based on an understanding of its pathophysiology.
- Formulate treatment strategies that include the use of iron chelators in patients with transfusion-related iron overload, assessing the efficacy and safety of iron chelator treatment options.

Disclosure Information

Maria D. Cappellini, MD, is a consultant for and has received speaker honoraria from Novartis Pharmaceuticals Corporation. Prof. Cappellini has disclosed that she will not reference any unlabeled/unapproved uses of drugs or devices.

Aristoteles A.N. Giagounidis, MD, is a consultant and is on an advisory board for Novartis Pharmaceuticals Corporation, Celgene Corporation, and Pharmion Corporation; and is a stock shareholder in Hoffmann-La Roche Inc. Dr. Giagounidis has disclosed that he will not reference any unlabeled/unapproved uses of drugs or devices.

John B. Porter, MA, MD, FRCP, FRCPath, is a consultant and has received grant/research support and speaker honoraria from Novartis Pharmaceuticals Corporation. He is also a consultant for Genzyme Corporation and Resonance Health Ltd. Prof. Porter has disclosed that he will reference the unlabeled/unapproved uses of deferiprone combined with desferrioxamine, and deferasirox.

Ali T. Taher, MD, has received speaker honoraria from and is on the advisory board for Novartis Pharmaceuticals Corporation. Dr. Taher has disclosed that he will not reference any unlabeled/unapproved uses of drugs or devices.

Iron Overload Diagnosis, Treatment, and Management Goals

John B. Porter, MA, MD, FRCP, FRCPath

Transfusional Iron Overload

In transfusion-dependent disorders, the body takes in an additional 200 mg of iron with each transfusional unit, with no mechanism for eliminating the excess iron. Eventually, the amount of iron exceeds the amount that can be bound by transferrin. This non–transferrin-bound iron (NTBI) is absorbed into some organ tissues whilst sparing others, and the distribution of this uptake accounts primarily for the toxic effects of iron overload. Excess iron deposition has been found in the pituitary gland, thyroid, parathyroid, heart, liver, pancreas, and gonads. The highest concentration of iron is found in the liver, which can lead to liver carcinoma and cirrhosis. Iron accumulation in the heart is of critical clinical importance as well; heart disease is the greatest cause of death in transfusion-dependent patients with thalassaein major (TM).

The rates of transfusional iron loading and its deleterious effects have been studied most extensively in patients with TM where transfusional rates of iron loading vary widely, with an average of 0.36 mg/kg/day. Levels of iron burden over sustained periods of time impact on clinical outcomes, and both serum ferritin (SF) levels and liver iron content (LIC) provide accurate estimates of iron burden. The rates of iron loading for other transfusional disorders vary, depending on the transfusional requirements. Patients with Diamond-Blackfan anaemia have a higher iron intake than patients with TM, averaging 0.40 mg/kg/day. Patients with myelodysplastic syndromes (MDS) and sickle cell anaemia (HbSS) on average have lower transfusional rates. Unlike patients with thalassaein, iron overloading results solely from transfusions, with no gut absorption. Transfusional requirements vary greatly among HbSS patients; some HbSS patients receive only sporadic transfusions, for intermittent complications, while others receive regular transfusions for prevention of stroke. Furthermore, iron loading is greater with top-up transfusions than with exchange transfusions. Interestingly, there is emerging evidence that HbSS patients have lower accumulations of iron in heart and endocrine organs than do TM patients, even when liver iron accumulation is comparable. Further research is needed to explore the different distribution of tissue iron in the different disease states.

Diagnosing Iron Overload and Monitoring Iron Levels

Iron burden can be estimated through a variety of different measurements. Currently, LIC is considered the gold standard for measuring iron overload, accurately reflecting body iron stores. New developments in MRI make it possible to measure LIC noninvasively. Serum ferritin is the most frequently used measure of iron overload. Over the long term, SF correlates with clinical outcomes and morbidity. Whilst there are broad correlations between SF and LIC, ferritin levels in individual patients may not accurately predict the LIC, especially in patients with HbSS and thalassaein intermedia (TI). This is partly because SF levels may fluctuate independently of iron loading, for example, rising with inflammation and falling with ascorbate deficiency.
Managing Iron Overload in Clinical Practice

Another clinically valuable tool for estimating iron burden is measuring myocardial T2: patients with increased myocardial iron (as shown by shortening of the T2*) are at increased risk of decreased left ventricular function.14

Goal of Chelation Therapy—24-Hour Coverage

Iron chelators act by removing transiently available (labile) iron pools, either in plasma or within cells, because cellular storage iron (present as ferritin and haemosiderin) are not directly accessible for chelation. Chelatable iron is derived from two main sources: (a) iron released from macrophages after the catabolism of red cells, and (b) iron released within cells after the catabolism of cellular ferritin and haemosiderin. Both of these processes are continuous: iron from (a) will be rapidly found in plasma as NTBI if it is not immediately chelated, and iron from (b) will be rapidly reincorporated into cellular ferritin if not intercepted while still in the labile state. For example, labile plasma NTBI pools re-form within minutes of removal of the chelating agent from plasma.15,16 Iron chelation must therefore provide continuous 24-hour cover to maximize chelation efficiency.

Each of the three iron chelators currently available—desferrioxamine, deferiprone, and deferasirox—have a distinct efficacy, safety, and tolerability profile, and these are discussed more fully in the following section by Prof. Cappellini. All three currently available chelators can decrease plasma levels of some NTBI species, but the duration of protection varies depending on how they are used. The clinical benefit of desferrioxamine in iron chelation has been well-established during several decades of clinical trials and clinical practice. Its major shortcomings, however, are the rigorous treatment regimen required and its short plasma half-life. Furthermore, because the half-life is so short, in the order of minutes,17 plasma concentration drops and NTBI begins to re-form almost immediately after an infusion stops.15 The fraction of plasma NTBI measured as labile plasma iron (LPI) also reappears rapidly after cessation of desferrioxamine infusion (Fig 1A).16 Thus, the standard 8- to 10-hour desferrioxamine infusion is insufficient to provide 24-hour protection and this can only be achieved with continuous infusions either subcutaneously or intravenously. The oral chelator deferiprone has a half-life of 2 to 3 hours16, and in most patients, when taken three times a day, LPI rises before the next dose is given (Fig 1B) and no protection is available at night. By combining therapy with deferiprone TID during the day and desferrioxamine infusion every night, 24-hour iron chelation is, in principle, achievable (Fig 1C). This procedure, however, is demanding for the patient, resulting in variable compliance. A simpler regimen to provide 24-hour chelation is the once-daily oral chelator deferasirox. Deferasirox has a plasma half-life of 8 to 16 hours19 and provides effective 24-hour iron chelation with a single daily dose (Fig 2, see next page).20 This has been shown to produce progressive and sustained reductions in LPI.21 The 24-hour availability of chelation with deferasirox also contributes to its high chelation efficiency (the high proportion of drug that is excreted in the iron-bound state) compared with other chelators.

Figure 1. Effects of Monotherapy and Alternating Combined Therapy on LPI

<table>
<thead>
<tr>
<th>Hour</th>
<th>DFO 40 mg/kg/day</th>
<th>Deferiprone (L1) 75 mg/kg/day</th>
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<tr>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
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<td>2</td>
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<tr>
<td>14</td>
<td>0</td>
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</tbody>
</table>

LPI = labile plasma iron.
Applying Advances in Iron Chelation: Review of Current Treatments for Clinical Practice

Maria D. Cappellini, MD

For patients with transfusional iron overload, chelation therapy reduces the risk of adverse effects on liver, heart, endocrine system, and other organs with high iron burden. In order to achieve these clinical goals, the clinician must consider specificity, efficacy, safety, tolerability, and convenience when selecting an appropriate chelation regimen.

Specificity
The ideal chelator shows specificity for iron, without removing zinc, copper, or other metals from the body. In practice, all three currently available iron chelators have high affinity for iron. However, they also bind to other metals to some degree, including copper and zinc.22-24 The affinity for copper has little clinical significance, since copper is tightly bound to proteins in vivo.22 Significant increases in urinary zinc excretion have been observed in patients receiving desferrioxamine and deferiprone, and was higher in patients with diabetes.23 Clinically significant zinc deficiencies occurred in a few patients, although they were rapidly corrected with zinc supplements.23

Efficacy
The goal of iron chelation therapy is to prevent iron accumulation in newly transfused patients, by matching iron intake with iron excretion, or to reduce the iron burden in iron-overloaded patients. All three iron chelators have demonstrated clinical efficacy in meeting this goal. For patients with TM, survival rates have continually improved since the introduction of desferrioxamine therapy in the 1970s.3 Desferrioxamine is effective in reducing LPI and NTBI, the most toxic forms of serum iron.15,16 However, these labile pools tend to re-form when the patient is not being infused. In iron overloaded patients, desferrioxamine reduces both liver and heart iron burden, although improvements in liver iron burden occur more rapidly than in the heart.25 The main limitation for the effectiveness is poor compliance, due to the difficult administration.26,27

Deferiprone was approved in the EU as a second-line treatment for iron overload in patients for whom desferrioxamine is not appropriate.18 The efficacy of deferiprone in reducing SF has been studied when deferiprone is administered either as monotherapy or in combination with desferrioxamine. When deferiprone was administered as monotherapy, it lowered SF levels in some trials but not in others. Studies of deferiprone in combination with desferrioxamine are more consistent in showing a significant reduction in SF in response to deferiprone.28

There are few published prospective, randomized trials studying the effects of deferiprone on LIC. The results of these trials have been inconsistent. One trial found a decrease in LIC during deferiprone monotherapy, relative to baseline. However, deferiprone was associated with an increase in LIC relative to baseline in a separate trial.28 Also, LIC is significantly higher following treatment with deferiprone than with desferrioxamine.29 More recently, it was claimed that deferiprone removes iron from the heart more effectively than desferrioxamine and prevents heart failure in TM patients.30 This effect is even more marked when deferiprone is used in combination with desferrioxamine.31

The efficacy of deferasirox in preventing or reversing iron overload has been established in long-term, large-scale clinical trials.7,20,32

Additionally, initial reports from the once-daily administration of deferasirox 20 mg/kg in the ESCALATOR trial showed a significant reduction in LPI over a 24-hour period. This indicates that once-daily administration of deferasirox potentially protects the heart and liver from cellular and tissue damage ensuing from iron overload.33 As illustrated in the previous section by Prof. Porter, deferasirox-induced reduction of labile iron pools is maintained over a 24-hour dosing interval (Fig 2).20,33 In a large-scale phase III trial, deferasirox 20 mg/kg/day was effective in maintaining iron balance (iron intake = iron excretion) and 30 mg/kg/day resulted in a net loss of iron.32 Patients receiving 30 mg/kg/day had a significant reduction in LIC and SF, and a negative iron balance.32

One must consider the goals of chelation therapy when selecting the starting dose; 20 mg/kg is recommended for preventing iron overload in regularly transfused patients, and 30 mg/kg is recommended for reversing iron overload that has already occurred. Iron overload causes damage to organs, including the cardiac tissue.

Therefore, by reducing the iron overload, iron chelators can produce a cardioprotective effect.
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Safety
Each of the three chelation regimens has its own safety and tolerability profile. For each patient, the clinician must weigh the risks of the drug against the risk of morbidity due to iron overload. Many side effects can be minimized by reducing the dosage or temporarily disrupting treatment, rather than discontinuing chelation therapy.

Desferrioxamine is not associated with any severe adverse effects (AEs).17,24 The most frequently reported AEs are local reactions at the injection site. These, however, can be severe enough to impact patient compliance. Additional AEs that need to be monitored for are growth delays and hearing and visual impairments.23,26 The risk of hearing loss is greatest with higher desferrioxamine doses and in patients with lower levels of SF. Porter et al (1989) have calculated a therapeutic index of 0.025 (desferrioxamine dosage mg/kg divided by SF µg/L) to be used as a guideline for safe dosage.27

The most frequently reported AEs with deferiprone are gastrointestinal symptoms and arthralgia.18 The most serious AE is agranulocytosis (neutrophils <0.5 x 10^9/L), which occurs with an incidence of 1.2%. Less-severe neutropaenia (neutrophils <1.5 x 10^9/L) occurs with an incidence of 6.5%.19 Neutropaenia and agranulocytosis resolve after therapy is discontinued. Weekly monitoring of white blood cells is required during deferiprone therapy.18

The most common AEs reported during deferasirox therapy were gastrointestinal symptoms, rash, and elevated levels of creatinine.19 Occurrences of lens opacity and hearing loss were uncommon and comparable to that observed with desferrioxamine.19 Six percent of patients experienced an increase in ALT during deferasirox treatment, with 2% considered treatment-related and two cases of drug-induced hepatitis. Interpreting the effect of a chelator on liver function is confounded by the fact that iron levels may increase during the course of treatment, especially in patients receiving insufficient dosage. Although deferasirox is generally safe and well-tolerated in both adult and paediatric patients, clinical management requires regular patient monitoring to identify potentially serious AEs (Table 1).

For severe rash or rashes that don’t resolve spontaneously, the recommendation is to temporarily discontinue treatment until the rash resolves, and then reintroduce deferasirox at a lower dose, gradually titrating up. A short period of oral steroids may be warranted for severe rash.19

In clinical trials, 36% of patients had elevated serum creatinine levels (33% above baseline for two consecutive visits).32 In addition to the year-long clinical trial, patients were followed in a 1 ½-year extension. Over the course of 2 ½ years, creatinine increases remained mild and nonprogressive. As of December 2006, more than 13,000 patients had been exposed to deferasirox. There have been cases of acute renal failure reported; however, most of these cases involved confounding medical factors. An initial dose reduction of 10 mg/kg/day is recommended for adults with creatinine levels ≥ 33% above baseline for two consecutive visits. A similar dose reduction is recommended for paediatric patients meeting the same criteria, provided the serum creatinine level is above the age-appropriate upper limit of normal.19

No cases of drug-related cytopenias were observed during deferasirox clinical trials. Cytopenias have been reported postmarketing; most of the patients had preexisting haematologic disorders that are frequently associated with bone marrow failure.

Tolerability and Convenience
According to a recent study, significantly more patients taking deferasirox (85.1%) report being very satisfied or satisfied than do those taking desferrioxamine (38.7%; P < .0001).38 Deferasirox was preferred by 96.9% of patients who had previously been treated with desferrioxamine.38 The primary reasons given for preferring deferasirox were: more convenient to take (37.4%), less soreness (25.3%), and less disruptive to their day (22.8%), their sleep (6.2%), and to their family (4.2%). In the past, compliance has been a major factor limiting the success of iron chelation therapy. The results of this study on patient attitudes suggest that compliance may improve with the availability of a once-daily oral chelator.

In summary, each of the three iron chelators has a unique efficacy, safety, and tolerability profile. When choosing a chelator, the clinician must consider the therapeutic needs, compliance issues, and co-morbidities of the individual patient. Often, dose must be adjusted to either improve efficacy or manage side effects.

Table 1. Optimizing Deferasirox Therapy: Summary of Monitoring Recommendations

<table>
<thead>
<tr>
<th>Item to monitor</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood intake</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Monthly with dose adjustment based on 3-6 month trends</td>
</tr>
<tr>
<td>Renal function tests</td>
<td>In duplicate before initiating deferasirox therapy</td>
</tr>
<tr>
<td></td>
<td>Monthly during therapy</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Monthly during therapy</td>
</tr>
<tr>
<td>Auditory and ophthalmic testing</td>
<td>Before the start of deferasirox therapy</td>
</tr>
<tr>
<td></td>
<td>Annually during therapy</td>
</tr>
<tr>
<td>Deferasirox should not be combined with other iron chelation therapies</td>
<td>Deferasirox core data sheet. Novartis data on file.</td>
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</tbody>
</table>
Myelodysplastic syndromes (MDS) are clinically heterogeneous. Consequently, even with the development of clinical guidelines, the decision to initiate iron chelation therapy must be made on a case-by-case basis. A major factor that will influence the decision to chelate is the overall prognosis of the patient. Clearly, if the anticipated survival time is short, chelation will have limited therapeutic value. The following case study describes the management of SF levels in a high-risk MDS patient who was considered to be a good candidate for iron chelation.

**Patient Description**
- 64-year-old female with transfusion-dependent MDS, RCMD-RS subtype
- Karyotype: 46, XX, del(5q), -7, add (17)(p), der(21), +mar [12]/46, XX [13]
- Neutrophils 1300/µL
- Haemoglobin 7.2 g/dL
- Platelets 73,000/µL
- Bone marrow blasts <5%
- Ferritin 3600 ng/mL in the absence of inflammation

Based on these clinical values, the patient’s International Prognostic Scoring System (IPSS) score was that of Intermediate Risk II (Int-2).

**Clinical Decision Point 1: Determining Prognosis in Newly Diagnosed MDS Patients**

**Question 1.** Factors influencing overall survival in MDS patients include:
- a) Age
- b) Bone marrow blast count
- c) Karyotype
- d) Number of cytopenias
- e) Transfusion dependence
- f) All of the above

**Discussion**

(f) All of the factors listed above are associated with survival in patients with MDS. The International Prognostic
Scoring System (IPSS) is a means of predicting survival and risk of evolution to AML based on bone marrow blast count, karyotype, and number of cytopenias. \(^{40}\) Patients are assigned to one of four risk groups: Low, Int-1, Int-2, and High. \(^{40} \) In clinical practice, those in IPSS categories Low and Int-1 are generally considered as low-risk, while Int-2 and High patients are collectively considered as high-risk. In addition to the factors included in the IPSS score, age and transfusion-dependence are also inversely related to survival in MDS patients. \(^{40,41}\)

**Case Continues**

Our patient had an IPSS classification of Int-2, placing her at high risk. The first step was to address the impact of the complex karyotype on the patient’s clinical outcome. Patients with 5q- syndrome, or a karyotype in which a 5q deletion is the only abnormality, have a relatively good prognosis, with a median survival of approximately 9 years. \(^{42}\) In contrast, patients with additional cytogenetic abnormalities, as well as the refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS) identified in this patient, have a much poorer prognosis. The median survival for patients with RCMD-RS is approximately 3 years. \(^{42}\) Prognosis in this patient depends on the ability to suppress the high-risk karyotypes.

The patient received the immunomodulatory drug lenalidomide, and was monitored with short-term bone marrow follow-ups. Shortly after the initiation of lenalidomide treatment, the patient became transfusion independent, with a normalization of the karyotype. However, the abnormal karyotype reappeared after 9 months, followed by a drop in haemoglobin after 11 months. The patient’s brother was human leukocyte antigen-compatible. Therefore, the next step was to proceed with allotransplantation.

**Clinical Decision Point 2: Is the Patient a Candidate for Iron Chelation Therapy?**

**Question 2. In MDS, I am using iron chelation:**

- a) In all transfusion-dependent patients with an elevated ferritin level
- b) Very rarely, as the expected overall survival of this patient group is low
- c) Very rarely, as I fear interactions between iron chelators and other drugs in this patient group with co-morbidities
- d) Only in low-risk MDS patients with elevated ferritin levels
- e) In both low- and high-risk MDS patients on an individual basis as long as the expected overall survival is reasonable

**Discussion**

(e) This option most closely conforms to clinical guidelines. \(^{39}\) In patients with elevated iron levels, iron chelation is an important therapeutic tool, provided the patients have a reasonable expected overall survival. One small study has found that iron chelation increases platelet and neutrophil counts and decreases transfusion requirements, suggesting that iron chelation has therapeutic effects on bone marrow function. \(^{33}\) Iron chelation is also recommended prior to allogeneic stem cell transplantation, since lower SF levels are associated with improved disease-free survival and reduced treatment-related mortality (Fig 3, see previous page). \(^{44}\) In 2005, an international conference meeting in Nagasaki developed a consensus statement for the use of iron chelation in the management of MDS. According to the Nagasaki consensus, iron chelation should be considered for patients meeting the following criteria: \(^{39}\)

- Transfusion-dependent patients
- Low-risk MDS: IPSS Low or Int-1
- WHO-type RA and RARS and 5q-
- Candidates for allografting
- MDS patients with documented stable disease
- Ferritin levels >1000–2000 ng/mL or other evidence of significant tissue iron overload
- Absence of co-morbidities severely limiting prognosis

Chelation should continue for as long as the risks of iron toxicity remain clinically relevant. For example, if the disease progresses to acute myeloid leukaemia, chelation therapy may no longer seem appropriate. \(^{39}\) The consensus guidelines for monitoring and treatment of iron overload in MDS patients are summarized in Table 2 (see next page). \(^{39}\)

**Case Continues**

Our patient was an appropriate candidate for iron chelation, meeting most of the criteria established at the Nagasaki meeting. \(^{39}\) She was transfusion-dependent, with SF >2000 ng/mL, a candidate for allotransplantation, and had no co-morbidities severely limiting prognosis. Although being in a high-risk IPSS category, the fact that this patient had a del(5q) cytogenetic abnormality and a normal bone marrow blast count made treatment with lenalidomide a possibility. Indeed, she became transfusion independent after 1 month of treatment. To reduce iron overload, treatment with deferasirox 20 mg/kg was initiated within 2 months of lenalidomide treatment and for a total of 12 months prior to the allogeneic transplantation. While
Thalassaemia intermedia has an extraordinarily wide clinical spectrum. Severe end: Presentation between age 2 and 6 years, Retarded growth and development. Mild end: Completely asymptomatic until adult life.


On deferasirox, her SF levels fell from an initial level of approximately 3500 ng/mL to approximately 1800 ng/mL at month 12, when we proceeded with the stem cell transplantation (Fig 4). During the course of coadministration with lenalidomide and deferasirox, the patient’s haemoglobin remained over 12 g/dL for several months (Fig 4). We did not, however, proceed with venesection at this point. She had a complex karyotype and it was therefore uncertain whether the haemoglobin response would be maintained. Iron chelation, however, may have provided some therapeutic advantage in maintaining improved bone marrow function, as discussed earlier.43

The patient has now been in clinical remission for 7 months following transplantation. Deferasirox was not restarted, to prevent potential interactions and cumulative toxicity with posttransplantation medications, including immunosuppressive drugs and antiviral and antibiotic prophylaxis. However, the deferasirox was effective in reducing her iron burden prior transplantation, thus reducing the risk of organ toxicity and potentially improving posttransplantation outcomes.

Table 2. Consensus Guidelines for the Monitoring and Treatment of Iron Overload in MDS Patients

<table>
<thead>
<tr>
<th>Monitoring Iron Overload</th>
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<tbody>
<tr>
<td>When should body iron stores be assessed in MDS patients?</td>
<td>At diagnosis of MDS and at regular intervals thereafter, depending on the transfusion rate</td>
</tr>
<tr>
<td>Which tools should be used to diagnose and monitor iron overload?</td>
<td>Serum ferritin, Transferrin saturation, Liver MR imaging</td>
</tr>
<tr>
<td>How frequently should iron overload be monitored?</td>
<td>At least every 3 months in patients receiving transfusions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treating Iron Overload</th>
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<tbody>
<tr>
<td>When should the initiation of chelation therapy be considered in MDS patients?</td>
<td>When serum ferritin levels reach 1000 to 2000 ng/mL, depending on the transfusion rate</td>
</tr>
<tr>
<td>How long should chelation therapy continue?</td>
<td>As long as transfusion therapy continues and as long as iron overload remains clinically relevant</td>
</tr>
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</table>


Figure 4. Clinical Outcome on Deferasirox

Courtesy of Dr. A. Giagounidis.

Thalassaemia intermedia (TI) occupies the clinical spectrum between thalassaemia minor and thalassaemia major, with a great deal of clinical variation among individual patients (Fig 5). In general, patients with TI are anaemic but typically do not require regular transfusions. TI patients are most commonly homozygous or compound heterozygous for beta-globin mutations. In beta-thalassaemia, an excess of alpha-globin chains accounts for the ineffective erythropoiesis that characterizes the disease. Three genetic factors common in TI, which reduce the clinical severity of the disease, are: 45,46:

- Inheritance of a mild or silent beta-chain mutation, rather than a complete absence of beta-chain synthesis
- Co-inheritance of an XmnI-γ polymorphism that results in production of excess γ chains, which pair with the alpha chains
- Co-inheritance of alpha thalassaemia, reducing the alpha/beta ratio.

The phenotype of TI may result from the increased production of alpha-globin chains by triplicated alpha genotype associated to beta-heterozygosity and also from the interaction of beta and delta beta thalassaemia. Thus, TI is defined by both clinical and genotypic parameters. 46

Patient Description
This patient first presented as a 3-year-old Lebanese girl of Mediterranean origin. Her chief complaints were anaemia, pallor, slightly yellow sclera, and enlarged spleen. The results of her complete blood count were:

- Low haemoglobin—7 g/dL
- Red cell (distribution) width—15 (12–18)
- Mean corpuscular volume—70 (80–95 fl)
- MCV/red blood count index—<13

Clinical Decision Point 1: Diagnosis

Question 1. What tests are needed to diagnose thalassaemia?

- a) Genotypic studies
- b) Haemoglobin electrophoresis
- c) Ferritin and iron studies
- d) Family studies
- e) a, b, and d

Discussion
(e) Genotypic studies, haemoglobin electrophoresis, and family studies are the necessary tests to rule out other possible causes of the observed anaemia. Haemoglobin electrophoresis will identify the presence of thalassaemia; genotypic and family studies are necessary to distinguish TI from TM. This patient had elevations in haemoglobin F and A2 and was homozygous for the IVSI-6 mutation, thus confirming the TI diagnosis.

Clinical Decision Point 2: Transfusions and TI

Question 2. When is transfusion indicated in thalassaemia intermedia?

- a) Growth delay
- b) Right after diagnosis of thalassaemia intermedia
- c) Definitely after the age of 1 year
- d) Never indicated
- e) None of the above

Discussion
(a) Although patients with TI are not automatic candidates for regular transfusions, transfusions are indicated in patients experiencing delayed growth, poor pubertal growth, bone deformities, increasing anaemia, thrombosis, pulmonary
hypertension, progressive splenic enlargement, and extramedullary haematopoiesis.

Case Continues
At age 7, the patient returned to the clinic due to inadequate growth. She received transfusions every 2 months for a period of 1 year. She was transfusion independent for a time, then started requiring more transfusions. At age 10, a physical exam revealed a 12-cm spleen.

Clinical Decision Point 3: Splenectomy and TI

Question 3. What are the indications for splenectomy in thalassaemia intermedia?

a) Symptomatic enlargement of the spleen
b) Growth retardation
c) Leukopaenia
d) Increased transfusion demand
e) All of the above

Discussion
(e) The main indications for splenectomy in TI patients are growth retardation or poor health, leukopaenia, thrombocytopaenia, increased transfusion demand, and symptomatic splenomegaly. Splenectomy also carries certain risks, including sepsis and thrombosis. Therefore, it is done less frequently than in the past and primarily in regularly transfused TM patients.

Case Continues
Our patient underwent a splenectomy due to her enlarged spleen and increased transfusional requirements. At age 18, she returned to our clinic with pain in the lower back and right leg and numbness of the right leg. She had not received transfusions since her splenectomy at age 10. MRI of the spine confirmed the diagnosis of extramedullary haematopoiesis, which occurs more commonly in patients with TI than TM. The patient was transfused with 2 units of red blood cells every week for 5 weeks. Her symptoms were completely relieved and no masses were observed on the follow-up MRI. She was started on hydroxyurea at a dose of 500 mg/day.

At age 26, the patient returned to the clinic with pain and warmth in her right calf. She was diagnosed with superficial venous thrombophlebitis, based on duplex ultrasound. She had several risks for thrombosis, including splenectomy, with no subsequent aspirin intake, and transfusion independence, except for the transfusions to resolve her extramedullary haematopoiesis. Smoking and family history, additional risk factors, did not apply to our patient. Her thrombosis was managed with low molecular weight heparin (LMWH) and baby aspirin for 6 months. She was also instructed to receive LMWH and transfusion before high-risk procedures.

Clinical Decision Point 4: Assessing Iron Overload

Question 4. Would you expect an occasionally transfused thalassaemia patient to be iron overloaded?

a) Yes
b) No

Discussion
(a) Although iron overload has been studied most extensively in patients with TM, a population that receives regular transfusions, it can occur in nontransfused and occasionally transfused TI patients, as well. Elevated concentrations of liver iron have been observed despite slight increase in SF in TI patients. This discrepancy between liver iron concentration and SF delays initiation of possible therapy. In TI, patients absorb 1 to 3.5 g iron per year through gut absorption. We are currently conducting a study in our clinic to establish the prevalence of iron overload in transfusion-naive patients with TI. To date, we have analyzed data from 37 TI patients; the analysis will gain more power once we enroll and analyze data from a total of 80 patients. Patients had a mean LIC of 7.76 mg Fe/g dry weight of liver and a mean SF of 957.35 µg/L. Iron chelation therapy is recommended for TI patients with LIC ≥ 7 mg Fe/g dry weight. An interesting observation from our study is that although SF is correlated to LIC in both TI and TM patients, SF more accurately reflects iron burden in patients with

Figure 6. Ferritin vs LIC in Thalassaemia Major and Thalassaemia Intermedia

LIC by MRI vs Ferritin in TM and TI

Y = 86.216x
R² = 0.034

Y = 183.76x
R² = 0.0091

TI

TM

Ferritin ng/mL

0 5 10 15 20 25 30 35 40 45 50

1000 2000 3000 4000 5000 6000 7000 8000 9000 10000

LIC mg Fe/g Dry Weight of Liver

Courtesy of Dr. A. Taher.
Managing Iron Overload in Clinical Practice

Case Study Continues
At her visit at age 26, we also found that the patient was iron overloaded. She had LIC 7.9 mg Fe/g dry weight of liver and SF 750 ng/mL. She was started on desferrioxamine 30 mg/kg/day but refused to stay on therapy. Currently, LIC is being monitored by R2MRI. We need to decide the next approach to reducing the iron burden in this occasionally transfused patient with TI.

Conclusion: Choosing the Right Therapy for the Right Patients
John B. Porter, MA, MD, FRCP, FRCPath

Excessive iron levels exert their toxic effects once they have been absorbed into the tissue of the various organs. Chelators can prevent tissue absorption by removing labile pools of iron before they are absorbed. In patients who are already iron overloaded, continual chelation will deplete the LPI and cause a reduction in body iron stores, as well. Because these labile pools can reform so rapidly, maximal therapy must provide 24-hour exposure to the chelator. As discussed in this newsletter, that can currently be provided by combined therapy with desferrioxamine, or with once-daily oral administration of deferasirox.

Which of your patients would benefit from iron chelation therapy? Appropriate patient selection is key. As discussed, a high-risk MDS patient who was in stable condition and awaiting transplantation appeared to benefit from deferasirox therapy. Patients who receive intermittent blood transfusions may also become iron overloaded and in need of chelation therapy, as demonstrated by the TI patient previously discussed. Further research is necessary to document the extent of iron overload in TI and to provide clear support for the use of chelation in patients who are infrequently transfused. Hopefully, this newsletter has provided information and insight that will help you select the right therapy for the right patients.

Poll Results

The EHA symposium attendees’ responses to each of the six Clinical Decision Point questions appearing in this newsletter are presented below.

**Case 1 (Begins on page 6)**

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