Management of iron overload in myelodysplastic syndromes: combined deferasirox and deferoxamine in a patient with liver disease

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders of haematopoietic stem cells, characterised by ineffective haematopoiesis leading to peripheral cytopenias and hypercellular bone marrow, with increased propensity to progression to acute myeloid leukaemia. Anaemia is the most common symptom: it may precipitate symptoms in patients with cardiac disorders, thus affecting the patients' outcome.

Approved therapies, such as erythropoiesis-stimulating agents, azacitidine, decitabine and lenalidomide are now available for patients who are ineligible for potentially curative haematopoietic stem cell transplantation. These former options can produce haematological improvement and enhance the quality of life of patients who previously would have received only supportive care.

In this context, supportive red blood cell transfusions represent a life-saving treatment for patients with chronic anaemia, in particular for those who do not respond or have a poor response to available treatments[1]. However, transfusions lead to iron overload, with an increased risk of associated comorbidity and mortality, independently of the underlying haematological disease, in relation to iron toxicity to cardiac, hepatic and endocrine cells. The management of iron overload is problematic because humans lack effective means to excrete excess iron.

Retrospective studies revealed that transfusion-related iron toxicity is associated with reduced survival in MDS patients[2]. This is a particularly relevant problem in low-risk MDS patients, because of these patients' otherwise long-life expectancy. Adequate iron chelation therapy can, however, improve survival and may delay transformation into acute myeloid leukaemia[3-6].

Iron chelation therapy is recommended in MDS to manage iron overload when the patient has, at least, elevated serum ferritin (SF), evidence of iron-related organ dysfunction or is receiving chronic red blood cell (RBC) transfusions. Guidelines from the Italian Society of Haematology recommend iron chelation therapy with deferasirox for the treatment of MDS patients with low/intermediate-1 risk (according to the International Prognostic Scoring Scale, IPSS) after they have received at least 20 units of packed RBC[5].

It is evident from controlled clinical trials, and confirmed by real-life experience[7], that iron overload in many MDS patients is often not adequately managed[4].

Iron chelation therapy should be considered in all patients who require long-term RBC transfusions while it may not be needed in patients with MDS or other acquired refractory anaemias who have an estimated survival of less than 1 year.

Ideally, chelation therapy should be initiated prophylactically, before clinically significant iron accumulation has occurred. Treatment should begin when patients have received between 10 and 20 units of RBC. Patients who have already undergone repeated transfusions without sufficient chelation can also be successfully treated, but they may require more intensive chelating regimens. Iron chelation therapy is recommended by several treatment guidelines for patients who have a low or intermediate-1 IPSS risk and SF >1,000-2,000 ng/mL, depending on transfusion requirements.

Evaluation of the patient before the initiation or adjustment of iron chelation therapy should include a detailed characterisation of the underlying disorder, with thorough documentation of the transfusion and chelation history, determination of body iron load by measurement of hepatic iron and SF, estimation of the rate of transfusional iron loading, and assessment of cardiac iron deposition[8].

Until recently, desferoxamine and deferiprone were the only drugs available for iron chelation therapy and neither was well tolerated by patients.

Deferoxamine was developed more than 40 years ago and, due to its pharmakokinetic properties, in order to be effective, must be administered subcutaneously or intravenously, usually with a portable pump, as a slow infusion over 8-12 hours/day, 5-7 days/week, often resulting in poor compliance. Subcutaneous administration is preferred, except in patients with severe cardiac iron deposition, for whom continuous intravenous deferoxamine is recommended. This regimen is contraindicated in patients with

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thrombocytopenia and the inconvenience often results in low compliance[9-11].

Deferiprone is not approved or recommended for MDS, as it can cause neutropenia and agranulocytosis.

Deferasirox is a once-daily orally administered iron chelator, with established dose-dependent efficacy, approved for the treatment of transfusional iron overload in both adult and paediatric patients with transfusion-dependent anaemia. The initial dose of 10 mg/kg can be increased to 20-30 mg/kg based on the degree of iron load, concentration of SF and extent of iron-related organ damage[12]. The efficacy and safety of deferasirox have been evaluated in patients with β-thalassaemia and a wide range of other disorders, including MDS, sickle cell disease, aplastic anaemia, Diamond-Blackfan anaemia, and other rare anaemias[13]. *In vivo* studies in acute myeloid leukaemia and MDS cell lines showed that deferasirox is a potent nuclear factor-kB inhibitor, which may partly explain the reports regarding its ability to produce haematological improvements[14,15]. In addition to reducing key indicators of total body iron level (SF, liver iron concentration, and toxic labile plasma iron), deferasirox has also been shown to remove cardiac iron and prevent further cardiac iron accumulation. It has an acceptable safety profile: the most commonly reported side effects have been non-progressive changes in serum creatinine levels, gastrointestinal disturbances and skin rashes, with significant increases in alanine transaminase value after 12 months of treatment being possible, in direct correlation with the dose administered[7]. Because of its potential hepatotoxicity, it is usually not recommended for patients with known liver disease.

Nowadays, most patients requiring iron chelation therapy opt for deferasirox because of the convenience of its oral administration, while deferoxamine, which has been proven to reverse iron-induced heart disease and increase long-term survival[16], may be indicated if deferasirox is ineffective, and it may be favoured for severe iron overload, especially with cardiac involvement.

Deferasirox may be better in patients who are unable to tolerate subcutaneous infusions of deferoxamine and it may also be an alternative to deferoxamine after successful clearance of cardiac iron.

To our knowledge, the possibility of iron chelation therapy with a combination of deferasirox and deferoxamine has been reported only in patients with β-thalasssaemia[17-20]. There do not appear to be any data on the use of this combination in MDS patients with liver disease. We describe here the first patient affected by MDS and chronic liver disease in whom combined iron chelation therapy was successfully employed.

Case report

A 62-year old Caucasian man was first seen in our Division for anaemia. He was diagnosed as having MDS-refractory anaemia (low IPSS risk), and hepatitis C virus-correlated liver cirrhosis (Child-Pugh class B) with signs of portal hypertension (portal vein 14.6 mm, splenic vein 14 mm, normal mesenteric vein), and severe splenomegaly (longitudinal diameter 205 mm). Liver function tests at the diagnosis of MDS were: serum albumin 3.2 g/dL, normal coagulation profile, total/direct bilirubin 1.01/0.69; aspartate transaminase 38 U/L (normal values <40 U/L), alanine transaminase 60 U/L (normal values <40 U/L). The patient was initially treated with an erythropoiesis-stimulating agent (30,000 U/week), without success for 6 months, which was then withdrawn, and he continued treatment with only RBC transfusions, requiring two packs/month. Iron chelation therapy was started when he had a SF of 700 ng/mL (normal values 30-400 ng/mL): deferoxamine was given (starting dose 15 mg/kg/day, for 5 days/week, increased up to 25 mg/kg/day, for 5 days/week), in consideration of the patient's pre-existing hepatic disease. However, the patient was unable to take the drug correctly and his transfusion needs increased to two packs of RBC/week, with his SF exceeding 6,000 ng/mL (Figure 1), after 12 months of transfusion treatment. At that time,

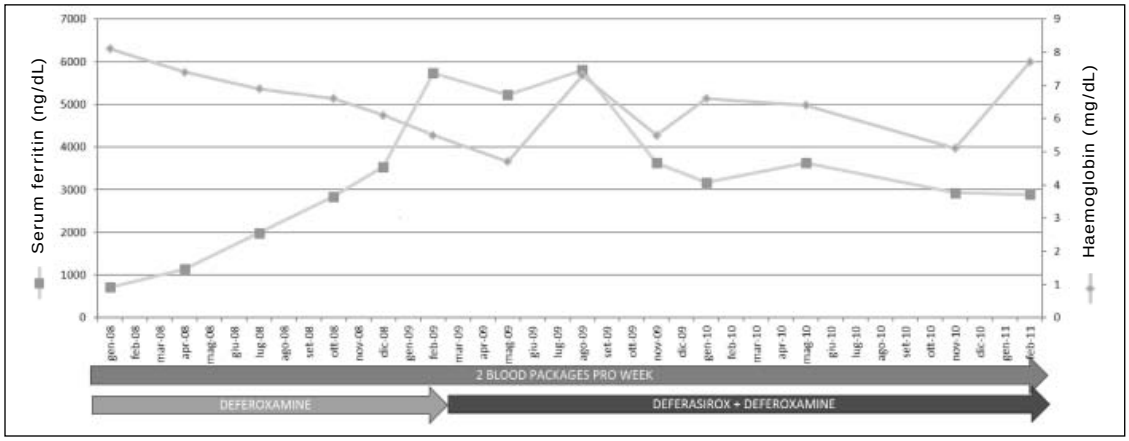

Figure 1 - Time course of serum ferritin (normal values: 30-400 ng/dL) and haemoglobin concentrations.

deferasirox was started (Table I) at the dose of 10 mg/kg/day, after a thorough investigation of the patient's hepatic, renal and cardiac function. After 3 months, neither SF nor other biochemical parameters had changed. The dose of deferasirox was then gradually increased to 30 mg/kg/die after 2 months, without evidence of liver damage. After 5 months of a full dose of deferasirox, the patient's SF concentration was 5,098 ng/mL.

Taking into consideration all risks related to secondary haemochromatosis, after informed consent, combined iron chelation therapy with deferasirox (30 mg/kg/die) and deferoxamine (25 mg/kg/day for 5 days/week) was started. After 3 months the patient's SF had decreased to 3,000 ng/mL. In the meantime, his haemoglobin concentration decreased significantly, so he had to be given two packs of RBC/week. After 2 years of combined therapy, his SF concentration was stable under 3,000 ng/mL and his transfusion requirements gradually decreased (Figure 1). No adverse events were observed and regular monitoring of hepatic (Figure 2), renal and cardiac function did not show any alterations. After 4 years of transfusions and combined iron chelation therapy, the patient died from acute respiratory distress syndrome.

Table I - Characteristics of deferoxamine and deferasirox[8].

Variable	Deferoxamine	Deferasirox
Chelator-iron complex	Hexadentate, 1:1 complex	Tridentate, 2:1 complex
Usual dose	25-50 mg/kg/day	20-40 mg/kg/day
Administration	Subcutaneous or intravenous, 8-10 h/day, 5-7 days/week	Oral, once daily
Plasma half-life	20-30 min	8-16 hr
Route of elimination	Biliary and urinary	Predominantly biliary
Regulatory approval	Approved in USA, Canada, Europe and other countries	Approved in USA, Canada, Europe and other countries
Indication	Transfusional iron overload	Transfusional iron overload
Adverse effects	Irritation at the infusion site, ocular and auditory disturbances, growth retardation and skeletal changes, allergy, respiratory distress syndrome with higher-than-recommended doses	Gastrointestinal disturbances, rash, increase in serum creatinine level; potential foetal renal and hepatic impairment or failure, gastrointestinal haemorrhage

Discussion

Supportive care of MDS patients is based on RBC transfusions, with management of iron overload being an essential, but sometimes overlooked, part of the treatment. In recent years, better understanding of the biological consequences of secondary haemosiderosis in MDS has suggested that iron chelation therapy should be started promptly to prevent serious clinical sequelae in patients with a long life-expectancy. Retrospective analyses indicated that iron overloading has an impact on the outcome of MDS patients and suggested that chelation therapy could improve patients' overall survival.

Until recently, desferoxamine and deferiprone were the only drugs available for the treatment of transfusional iron overload, but deferasirox is changing the clinical scenario of iron chelation therapy.

Deferasirox is a once-daily orally administered iron chelator, with established dose-dependent efficacy, approved for the treatment of transfusional iron overload in both adult and paediatric patients with transfusion-dependent anaemia. The drug has an acceptable safety profile, with the most common side effects reported being non-progressive changes in serum creatinine levels, gastrointestinal disturbances, and skin rash, and dose-related hepato-toxicity.

Deferasirox may allow effective iron chelation therapy in patients intolerant to subcutaneous infusions of deferoxamine.

In our case, the combination of deferasirox and deferoxamine had significant effects on iron overload,

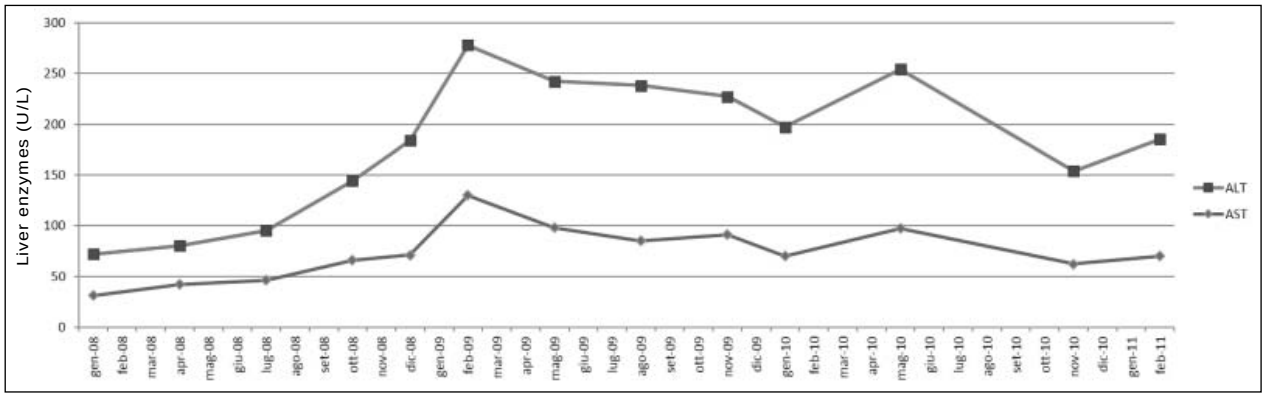

Figure 2 - Time course of liver function parameters: aspartate transaminase (AST, normal values <40 U/L) and alanine transaminase (ALT, normal values <40 U/L).

and proved to be safe in a patient with hepatitis C virus-correlated liver cirrhosis. The patient complied well with the treatment, had a good quality of life, had no side effects and did not require hospitalisation. Moreover, as reported in literature, deferasirox can also improve haematological parameters: our patient had a decrease in transfusional needs during treatment, which could have been related to the deferasirox treatment[2,6,14].

In our opinion, if deferasirox alone is not able to reduce iron overload rapidly, combined treatment with deferoxamine should be considered a safe and useful therapeutic choice, in selected patients, although our preliminary observations need to be validated by controlled clinical trials.

Authorship contributions

CC, FP and LC participated in the conception and design of the study, data analysis and interpretation, drafting the article and revising it critically for important intellectual content, and approved the final version for publication giving final approval for publication. CC also collected the data and is responsible for the overall content as guarantor.

GC, SA, RDP, NP and MP participated in the conception and design of the study, data analysis and interpretation, and approved the final version for publication.

Keywords: deferasirox, deferoxamine, iron overload, iron chelation, myelodysplastic syndromes.

The Authors declare no conflicts of interest.

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