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Role of iron chelation in improving survival: An integral part of current therapy for myelodysplastic syndromes

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Abstract

This review article highlights the current role of iron chelation in MDS to optimize survival and quality of life. Its role in specific subtypes of MDS is also discussed.

Key words: Myelodysplastic syndromes, overload, quality of life, survival

Myelodysplastic syndromes (MDS) is a heterogenous group of malignant disorders characterized by aberrant myeloid differentiation associated with dysplastic changes, ineffective hematopoiesis and risk of progression to frank leukemia.[1] Its incidence increases with age and hence is expected to have a significant impact on the survival of geriatric patients.

Prognosis and risk stratification in MDS is based on the International Prognostic Scoring System (IPSS; published in 1997) where the features given importance are the percentage of bone marrow blasts, the number of peripheral blood cytopenias, and the cytogenetic risk-class.[1]

This scoring system was generated using a database of 806 MDS patients. It is important to remember that IPSS is intended for use only at the time of diagnosis. Also, it has several deficiencies, including no attention to the prognostic importance of red blood cell (RBC) transfusion-dependence or its consequent iron overload (IO). This led to the development of the WHO prognostic scoring system, a flexible prognostic tool that takes into consideration anemia and transfusions. As a result, we now know that an important subgroup of IPSS lower-risk (LR)-MDS patients has significantly worse outcomes than predicted by the IPSS.[2]

The majority of patients with MDS are treated with noncurative intent. For clinical decision making, patients with the IPSS risk-classes low or intermediate-1 (INT-1) are usually classified as (LR), while those with IPSS categories of INT-2 and high are classified as higher-risk. Definitive therapy will include azacitidine, decitabine or lenalidomide. In addition, supportive care required will include RBC and platelet transfusions, hematopoietic growth factors, antibiotics and use of iron chelation therapy (CT) as appropriate.[3]

With improved application of azacitidine, decitabine, and lenalidomide, survival in MDS has improved significantly. Combined with better supportive care, liberal use of hematopoietic growth factors and wider utility of allogeneic stem cell transplantation, patients are living longer and facing new challenges. IO is one of them.[4] Almost 4/5th of MDS patients present with anemia and a substantial percentage of them will become transfusion-dependent during the course of their disease.[5]

Hence, most of the MDS patients eventually require RBC transfusions, resulting in potential risks of IO. This can lead to multi organ dysfunction and even death. Iron CT has been shown to prevent and reverse such organ dysfunction, especially in thalassemia resulting in significantly better overall survival (OS).[6-8]

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Guidelines for the management of transfusional IO in MDS have been developed by several groups, including The MDS Foundation, National Comprehensive Cancer Network, Italian Society of Hematology, UK MDS Guidelines Group and Nagasaki Group – indicating some regional variations.[9]

However, they all recommend the use of IPSS and agree that RBC transfusions are clinically beneficial to treat the symptomatic anemia in MDS, and that patients with LR MDS receiving transfusions are the most likely to benefit from iron CT.

Red blood cell transfusions improve patient quality of life and remains the mainstay of treatment for MDS.[10] The hemoglobin (Hb) level at which transfusions should also be initiated considers other factors like quality of life, improved oxygenation and cardiac function, risks of infection and IO. In general, RBC transfusions are initiated when the Hb level is between 6 and 10 g/dl – a wide variation. The important consensus is that transfusions should be initiated in all patients with symptoms of anemia.

The pathophysiology of IO in MDS patients is related to that observed in thalassemia syndromes and consists of ineffective erythropoiesis and hepcidin dysregulation in some subtypes of MDS (primary IO) as well as transfusional siderosis (secondary IO). There are, however, some differences. Hepcidin is a key hormone mediating iron homeostasis. Hepcidin has a role in the down-regulation of ferroportin, the membrane transporter delivering duodenal iron from enterocytes to transferrin, thus resulting in decreased duodenal iron absorption.[11]

Iron overload really commences with the first RBC transfusions. As the supportive care progresses, it can lead to significant damage to the heart, liver and endocrine glands.[10] All guidelines include the use of iron CT to achieve a safe iron concentration in tissues and plasma – with low-risk MDS patients surviving long enough to benefit the most. Practically, speaking iron CT should be initiated when a patient's serum ferritin (SF) reaches 1000 μg/L, and/or after the patient has received two units of RBCs/month for at least 1-year. Deferoxamine (DFO, Desferal®) is the most commonly used agent for iron chelation [Table 1].[12] Audiometry and ophthalmologic examination must be done before initiating DFO therapy and repeated at least annually. Vitamin C (100–200 mg daily) is recommended 1-month after commencing DFO therapy. The availability of once-daily oral chelator (deferasirox [Exjade®]), has helped overcome many of the problems associated with administration of subcutaneous infusions of DFO and has resulted in iron CT being offered more widely to MDS patients.[11] To optimize management of individual patients, it is necessary to monitor SF levels every 3 months.[10] Target SF recommended is <1000 μg/L. Ferrioxamine renders iron unavailable to chemical reactions and hence prevents formation of reactive oxygen species. DFO promotes ferritin degradation in lysosomes by inducing autophagy.[13]

Several retrospective studies suggest a negative impact of

Table 1: Comparison of salient features of iron chelators available for the management of iron overload

Agent	Route	Schedule and dose	Clearance	Most common adverse events
Deferoxamine	SC, IV	20-40 mg/kg/days over 8-24 h 5-7 days/week	Renal hepatic	Hypersensitivity reactions, tachycardia, gastrointestinal events, increased transaminases
Deferasirox	Oral	20-40 mg/kg/days	Hepatobiliary	Gastrointestinal events involving diarrhea, nausea, constipation and abdominal pain; skin rashes and increased serum creatinine level
Deferiprone	Oral	25-33 mg/kg 3×/days for a total daily dose of 75-99 mg/kg	Renal	Gastrointestinal symptoms, granulocytosis, agranulocytosis and elevation of liver enzymes

*Contraindications to deferasirox include: Creatinine clearance <40 ml/min or serum creatinine more than twice the upper limit of normal, platelet counts <50×109/L, severe hepatic impairment (Child-Pugh Class C) and hypersensitivity to deferasirox. *Contraindications to deferoxamine include: Severe renal failure or anuria, creatinine clearance <10 ml/min and hypersensitivity to deferoxamine. SC=Subcutaneous

transfusion dependency on OS in MDS.[14] It is obvious that more severe the disease, more transfusions are required. And more the transfusions, more is the IO. Impact of IO on OS in MDS patients has been well demonstrated. In a retrospective nationwide survey of Japanese patients, Takatoku *et al*. found that in 37 of 38 patients who died of hepatic or cardiac failure had ferritin levels >1000 μg/L suggesting that IO resulted in increased mortality.[15] Cardiac risk is also increased in MDS patients, particularly in those who are transfusion-dependent.[16] In another retrospective study of 4546 MDS patients, transfusion dependency was significantly associated with risk of potential complications of IO (liver disease $P = 0.0008$ and diabetes $P = 0.0025$).[17]

Most of the data on modalities for the assessment of IO in general come from experience with transfusion-dependent thalassemia patients. These include SF, serum hepcidin hepatic iron, hepatic biopsy (contraindicated in most patients) for pathological changes, magnetic resonance imaging (noninvasive liver iron assessment).[6,18,19] Practically, the best approach is careful documentation of each transfusion in patient records. Cardiac function (by ultrasound), liver function, and glucose tolerance test are required three monthly if transfusion requirements are high.

Recently, significant improvement in survival was reported in low-risk MDS patients. Median OS in the RARS who received CT was 134.4 months versus 99 months for those who did not get iron chelation.[20] In another study of survival and causes of deaths in 97 low or INT-1 IPSS patients regularly transfused as outpatients, 44 (45%) of patients were not chelated and 53 (55%) received CT, mainly with DFO, for at least 6 months (median duration of chelation 36 months, range 6–131+). During the follow-up period, 66 of the 97 patients died, including 51% of chelated and 73% of nonchelated patients, respectively. Median OS was 53 months and 124 months in nonchelated and in chelated patients ($P < 0.0003$). Adequate chelation was the strongest independent factor associated with a better OS.[21]

Still another matched-pair analysis included 94 patients on long-term CT and 94 without it. All patients had IO, defined as SF above 1000 ng/ml or a history of multiple transfusions and SF ≥ 500 ng/ml. The difference in median survival (74 vs. 49 months, respectively; $P = 0.002$) supports the idea that iron CT is beneficial for MDS patients.[22]

A large prospective phase 3 trial (TELESTO, Clinical trials. gov: NCT00940602) is currently recruiting patients with low and INT-1 risk MDS patients to receive either deferasirox monotherapy or placebo.[23]

Specific benefits of iron CT have also been well documented. Decreases in liver iron concentration depended on the dose of deferasirox administered and transfusion requirements. Deferasirox is effective both in patients receiving CT for the 1st time as well as in patients switching from other chelation therapies. Particularly fall in SF level leads to improvement in alanine transaminase ($P < 0.00001$), an indicator of hepatocellular injury and cirrhosis.[24,25]

Hematological improvement (platelet and neutrophil counts) has also been documented with the use of iron chelation.[26] In the EPIC trial, erythroid, platelet and neutrophil responses were observed in 21.5% (53/247), 13.0% (13/100) and 22.0% (11/50) of the patients treated with deferasirox after a median of 109, 169 and 226 days, respectively. Median SF reductions were greater in hematologic responders compared with nonresponders at end of the study.[27]

In another retrospective Italian study, 42.7% of patients receiving chelation with DFO or deferasirox achieved a hematologic response. Eighteen patients became transfusion independent; 12 of which received deferasirox and the remainder DFO.[28]

In particular, eligible MDS patients for whom a hematopoietic stem cell transplantation (HSCT) is programmed should be chelated because there is growing evidence that high ferritin levels before HSCT are correlated with worst outcome in patients receiving myeloablative conditioning regimen.[29]

In conclusion, IO is most relevant for low and INT-1 risk MDS patients. For them, IO plays a critical role in exacerbating preexisting morbidity. Optimal supportive care therefore requires iron chelation to be an important component of their management.[30] Various analyses indicated an impact by IO on outcome of MDS patients and suggested that iron CT could improve OS. Deferasirox, with its manageable safety profile, confirmed efficacy and ease of administration is a preferred option for MDS patients with IO.[31]

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