How I Treat...

Iron Overload in MDS —and Why

Heather A. Leitch, MD, PhD, FRCPC

Heather A. Leitch, MD, PhD, FRCPC
Hematologist, Division of Hematology
St. Paul's Hospital
University of British Columbia
Vancouver, British Columbia

Case 1

A previously well and fit 60-year-old man with a 10-year history of refractory anemia with ring sideroblasts (RARS; International Prognostic Scoring System [IPSS] low risk) and red blood cell (RBC) transfusion dependence for four years was referred for treatment of iron overload (IOL). Early in his daily workout, he developed shortness of breath and was found to be in atrial flutter with a rapid ventricular response. An echocardiogram showed dilated cardiomyopathy with a left ventricular ejection fraction of 20%. He received 79 units of RBCs, and his serum ferritin (SF) level was 5,500 ng/mL with a transferrin saturation of 100%. T2 magnetic resonance imaging (MRI) showed a liver iron concentration (LIC) of 5-10 mg/g dry weight, indicating moderate to severe hepatic IOL, and the myocardial value was 10-15 milliseconds, indicating significant cardiac IOL.*

Case 2

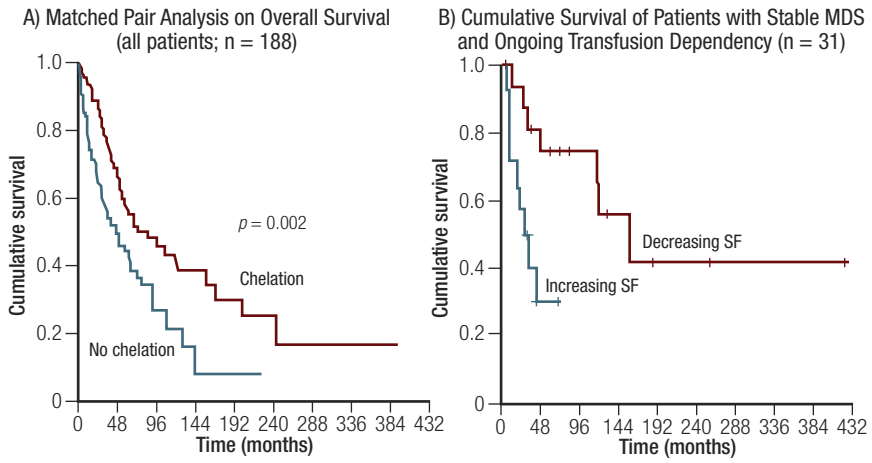
A 76-year-old man with a seven-year history of refractory anemia (RA) was referred when he became RBC transfusion dependent. Cytopenias had been discovered incidentally, and a diagnostic marrow showed no increase in blasts with a +8 on karyotype analysis (IPSS intermediate-1 risk). This was unchanged at the onset of RBC transfusion dependence. He received 3 units of RBCs up to this point; his SF level was 1,300 ng/mL. Following 20 units of RBCs, he was offered chelation with deferoxamine (DFO) but declined. He received, in total, 80 units of RBCs over two years, and his SF rose to 5,300 ng/mL. He started deferasirox (DFX) when it became available. Within six weeks, the transfusion requirement ceased and his hemoglobin (Hb) normalized over the following weeks. His Hb remained normal until he died of unrelated causes at age 84, more than six years after starting chelation.

Introduction

In congenital anemias such as beta-thalassemia major (BTM), IOL impairs organ function (cardiac, hepatic, endocrine) and limits survival.[1] The introduction of iron chelation therapy (ICT) with DFO improved the lifespan of patients with BTM from the teens to normal life expectancy, with benefit directly related to compliance with chelation.[2] However, because life expectancy in patients with myelodysplastic syndromes (MDS) is limited by marrow failure and progression to acute myelogenous leukemia (AML), examination of the benefits of chelation in these patients has lagged behind BTM.

Ineffective erythropoiesis in MDS may lead to increased iron absorption through the gastrointestinal (GI) tract via the hepcidin pathway, and myelosuppressive therapy may decrease erythropoiesis and iron utilization. However, the main pathway of IOL is RBC transfusions, which leads to increased transferrin saturation, the appearance of non-transferrin bound iron (NTBI), and clinical endpoints.[3] The Pavia group demonstrated that MDS patients with an RBC transfusion requirement

FIGURE 1
Overall Survival (OS) of MDS Patients in a Matched Pair Analysis



	Median cumulative survival
Chelation therapy	75 months
No chelation	49 months

A) In the whole group, patients receiving chelation had significantly superior OS compared to non-chelated patients. B) Survival was significantly longer in well-chelated patients with decreasing SF level compared with patients with increasing SF.
Adapted from Neukirchen J, et al. Leuk Res 2012; 36(8):1067-70. With permission from Elsevier Ltd., Philadelphia, USA.

have inferior overall survival (OS) and leukemia-free survival compared to transfusion-independent patients.[4,5] Survival was inversely associated with both the degree of transfusion dependence and the degree of IOL, as measured by SF level, with a stepwise decrease in survival for each increase in SF of 500 ng/mL above 1,000 ng/mL. In an analysis of the European LeukemiaNet (ELN) MDS registry, the outcomes of transfusion-independent and dependent MDS patients with and without MDS progression were compared. In both cases, transfusion-dependent patients fared worse.[6] Several analyses have suggested that MDS patients receiving ICT have improved survival compared to those not receiving chelation.[7-14] Moreover, the degree of benefit is associated with the duration[12] and intensity[8,9] of chelation (see Figure 1). However, as no data from randomized controlled trials (RCT) are available, some hematologists remain skeptical of the benefits of reducing IOL in MDS.[15] Despite the lack of RCT data, the balance of existing and emerging clinical and preclinical evidence supports active management of IOL in MDS.[16]

TABLE 1
Assessment of Iron Overload and Common Adverse Events of Chelators. Ideal assessments are listed and mandatory assessments bolded.

Observation	Frequency	IOL assessment	AE monitoring
Iron intake rate	Each transfusion	√	
Chelation dose and frequency	3 monthly	√	√
Renal function[a]	As frequently as required		√
Liver function	3 monthly	√	√
Sequential serum ferritin, transferrin saturation[b]	3 monthly	√	
GTT, thyroid, calcium metabolism (BMD)[c]	Yearly in adults	√	
Liver iron (T2* MRI)[d]	At baseline, where feasible; and, subsequently, as clinically indicated		√
Cardiac function (echo, MRI, ECG)	At baseline, then as clinically indicated	√	
Cardiac iron (T2* MRI)	For patients receiving > 50 units RBC prior to ICT, or with CHF or arrythmias	√	
Slit lamp examination, audiometry	Yearly		√

[a]Creatinine should be measured at least every two weeks with each dose increase until stable. [b]Transferrin saturation > 80% may indicate the presence of oxidative stress.[48] [c]Based on early/suggestive data in transfusion-dependent hemoglobinopathies.[49] [d]Hepatic IOL is underestimated in up to 25% of patients.[18]

IOL: iron overload; AE: adverse event; GTT: glucose tolerance test; BMD: bone mineral density; MRI: magnetic resonance imaging; echo: echocardiogram; ECG: electrocardiogram; RBC: red blood cells; ICT: iron chelation therapy; CHF: congestive heart failure.

TABLE 2
Proposed Classification System for Severity of Iron Overload in MDS

Serum ferritin level (ng/mL)	Organ function*	
	Normal (A)	Abnormal (B)
501–1,000	1A	1B
1,001–2,500	2A	2B
2,501–5,000	3A	3B
> 5,000	4A	4B

*Cardiac, liver and pancreatic endocrine related to iron overload; organ dysfunction progresses as ferritin or transfusion burden increases.

Criteria for organ dysfunction: Cardiac, left ventricular ejection fraction < 50%; hepatic, abnormal transaminase levels, hepatic fibrosis or cirrhosis; pancreatic endocrine, impaired glucose tolerance.

Adapted from Suzuki T, et al. Int J Hematol 2008; 88(1):30-5. With permission from the *International Journal of Hematology*, Springer Press.

TABLE 3
Iron Chelation Agents Currently Available for Clinical Use; Properties and Indications

Property	Deferoxamine	Deferiprone	Deferasirox
Usual dose	20–60 mg/kg/day	75–100 mg/kg/day	20–30 mg/kg/day
Route	s.c., i.v. ≥ 8–12 h, ≥ 5 days/week	p.o. 3 times daily	p.o. once daily
Half-life	20–30 min	3–4 h	8–16 h
Excretion	Urinary, fecal	Urinary	Fecal
Side effects[a]	Injection site reaction Potential ocular and/or otic toxicity[b]	(Rare) agranulocytosis	Renal insufficiency in up to one-third[c] GI disturbance
Indications	Acute iron intoxication Chronic IOL from TD anemias	IOL in BTM when DFO contraindicated or inadequate	BTM ≥ 6 years with IOL from frequent RBC transfusion IOL when DFO contraindicated or inadequate in: – Other anemias – Age 2-5 years – BTM with IOL from infrequent RBC transfusion

[a]Monitoring as per product monograph for all agents; [b]yearly monitoring recommended for all; [c]usually reversible or non-progressive.

GI: gastrointestinal; IOL: iron overload; TD: transfusion dependent; BTM: beta-thalassemia major; DFO: deferoxamine; RBC: red blood cell.
Reprinted from Leitch HA and Vickars. Hematology Am Soc Hematol Educ Program 2009; 664-72. With permission from the American Society of Hematology.

Diagnosis and Staging

IOL is most frequently measured by SF; SF levels over 1,000 ng/mL are considered significant in most guidelines. SF levels may be affected by other factors such as inflammation, thus it is important to monitor trends rather than individual values and to interpret SF measurements in the context of transfusion history and transferrin saturation. Assessment of organ function (cardiac, hepatic, endocrine) should be done at baseline assessment of IOL and as clinically indicated. Since LIC may be underestimated by SF level in up to 25% of MDS patients, LIC should be measured where available by imaging such as T2* MRI at baseline, with follow-up measurements as clinically indicated to ensure that it is decreasing appropriately with chelation.[17] Table 1 shows a summary of mandatory and desirable assessments and monitoring for IOL. A proposed classification scheme for severity of IOL is presented in Table 2.

Clinical Benefits of Iron Reduction/ Goals of Chelation

Characteristics of the currently available chelators are shown in Table 3. DFO is given subcutaneously, ideally by continuous subcutaneous infusion (see below). Deferiprone (DFP) is an oral agent taken three times daily; however, it is rarely used in MDS due to concern for an increased risk of agranulocytosis in patients who may already be neutropenic. DFX is an oral agent taken once daily.

ICT is effective at reducing SF, LIC and elevated transaminases.[16,18] Cardiac events are a leading cause of non-leukemic deaths in MDS[5,14,19]; however, detectable cardiac iron is found in only a minority of patients,[20] and the mechanism of cardiac complications from IOL is not well understood. Where obtaining LIC by T2* MRI is indicated, cardiac function may also be measured during the same scan, as would (rarely) be done to measure cardiac iron deposition.

There is evidence that oxidative stress may be important in iron toxicity. Iron results in the formation of labile plasma iron (LPI), labile cellular iron (LCI) and reactive oxygen species (ROS)—measures of oxidative stress—by virtue of its Fenton chemistry. In BTM, decreased cardiac disease-free survival (DFS) is associated with an SF over 2,500 ng/mL. Cardiac function improves with chelation before changes in cardiac iron are seen, consistent with removal of a toxic labile iron pool within cardiomyocytes.[21] In MDS, reductions in LPI[16,22] and cellular ROS[23] with chelation have been demonstrated. Oxidative stress, however, has not yet been tied to clinical endpoints, possibly because LPI is suppressed so quickly by chelation.[16,22]

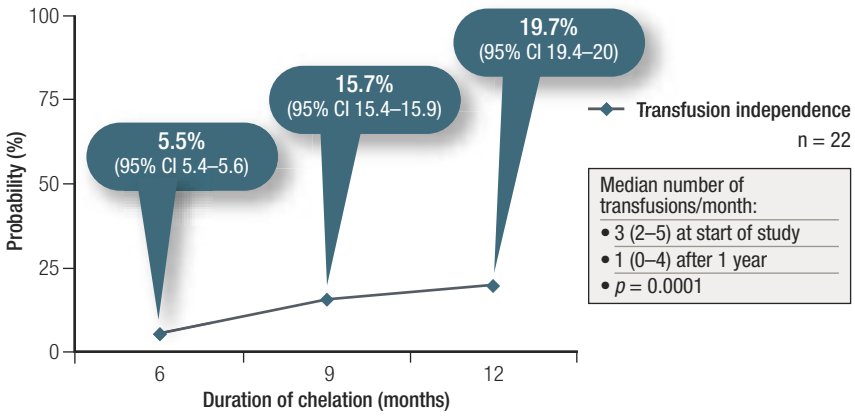
TABLE 4
Hematologic Improvement in MDS with Chelation

Reference	N	IPSS Risk	RBC Response	Neutrophil Response	Platelet Response
Cilloni D *et al* 2011*[25]	57	Low/Int-1	45.6%	NR	NR
List A *et al* 2012*[22]	173 52 77	Low/Int-1	15%	15%	22%
Gattermann N *et al*, 2012*[28]	247 50 100	Low/Int-1	21.5%	22%	13%
Nolte F *et al*, 2012[26]	50	Low/Int-1	11%	NR	NR
Angelucci E *et al*, 2012[27]	152	Low/Int-1	Transfusion independence in 12%	NR	NR

IPSS: International Prognostic Scoring System; RBC: red blood cell; NR: not reported; IWG: International Working Group.

*RBC, platelet, and neutrophil responses are assessed according to IWG 2006 criteria (Cheson et al[50]).

FIGURE 2
Probability of Acquiring Transfusion Independence



The probability of acquiring transfusion independence over the period of chelation with deferasirox increased from 5.5% at 6 months to 19.7% at 12 months.
Adapted from Angelucci E, et al. Eur J Haematol 2014; 92(6):527-36. With permission from John Wiley & Sons Ltd., Hoboken, USA.

Hematologic improvement (HI), including RBC transfusion independence, has been reported in multiple cases (reviewed in *Advances in Hematology*[24]). This phenomenon has been reported with all three chelators, suggesting that HI is related to iron reduction rather than a fortuitous off-target effect. In recent analyses, erythroid responses were seen in 11–46% of patients (see Table 4),[22,25-28] with the probability of transfusion independence increasing with the duration of chelation[27] (see Figure 2). Transfusion independence has been maintained long term in some cases after stopping chelation.[29,30] The mechanism of HI is an area of active investigation; however, these data suggest that iron reduction is in some way favourably altering bone marrow failure in some MDS patients.

Preclinical data indicate that IOL may promote progression to AML. IOL is associated with DNA damage.[31,32] Mice receiving sublethal irradiation (to induce genomic instability) and iron progressed to AML, while control mice that received irradiation alone did not.[31] Epigenetic changes induced by IOL and which promote AML progression have been reported.[33] Clinical data in this regard are scant, with some indicating an increased propensity to AML progression in MDS patients with IOL,[14] while another shows no impact of effective ICT on AML progression.[8] A study in progress is evaluating the utility of chelation in higher-risk MDS.[34] Accumulating data indicate that transfusion dependence and IOL negatively impact on endpoints (OS, non-relapse mortality) surrounding hematopoietic stem cell transplantation (HSCT),[35,36] and that chelation pre-[37] and post-HSCT[38,39] impacts favourably on these outcomes and on relapse incidence.[39] In many cases, SCT must be undertaken before it is practical to address IOL, in which case IOL reduction should be undertaken following SCT.

To summarize, the goals of chelation are to prevent organ damage, induce hematologic improvement where possible, minimize the risk of AML progression, and optimize outcomes around HSCT. In patients such as the one presented in Case 1, chelation must be intensified (if possible) in an attempt to rescue damaged tissue, which may be constrained by dose-limiting side effects.

Guidelines and Treatment

Guidelines for chelation are largely based on the experience with DFO in BTM, and are likely to evolve. A consensus statement by Bennett and colleagues suggests that patients be considered for chelation if they have lower IPSS-risk MDS, SF greater than 1,000 ng/mL, and a life expectancy of at least one year.[40,41] Candidates for HSCT should also be considered for chelation. According to more recent guidelines, patients with higher-risk MDS who are eligible for potentially disease-modifying therapies such as azacitidine, should also be considered.[42] In practical terms, chelation is available according to provincial criteria for reimbursement, which, in British Columbia, are largely based on current guidelines. Criteria for access to chelators by Canadian region are listed in Table 5.

Chelators available in Canada include

TABLE 5
Criteria for Access to Deferasirox or Deferoxamine by Province or Group

Province or Group	Deferasirox Access Criteria[a]	Deferoxamine Access Criteria[b]
British Columbia	Acquired anemia: aplastic anemia, myelofibrosis, low-IPSS-risk MDS Transfusion-dependent Life expectancy > 2 years Prescribed by a hematologist Cannot be adequately treated with deferoxamine Required information: • Number of RBC units • BMBx and cytogenetics report • Ferritin, creatinine, AST, ALT • Initial request requires a serum ferritin level > 1,000 ng/mL	Administered through the Provincial Home Hemosiderosis Program based at St. Paul's Hospital
Alberta	Require iron chelation Inadequate response to deferoxamine (minimum 6 months) or deferoxamine is contraindicated	Limited by access to pumps
Saskatchewan	Transfusion-dependent anemia Chronic iron overload Contraindication to deferoxamine	Covered
Manitoba	Not listed, under review May be available on an individual basis by Pharmacy and Therapeutics committee review	No restriction
Ontario	Management of chronic iron overload Transfusion-dependent anemia Low-risk MDS or other rare anemia Contraindication or severe intolerance to deferoxamine: • Hypersensitivity to deferoxamine • Recurrent infusion-site reactions • Bleeding disorder • Documented risk of significant infections with parenteral administration	Covered
Québec	« *Patient d'exception* » list: • Special & exceptional need • Individualized to the patient • Appropriate scientific literature specific to the therapeutic indication • Different therapeutic use • Condition is chronic and serious • Treatment of last resort	No restriction
Nova Scotia	Require iron chelation Deferoxamine is contraindicated	Covered
New Brunswick	Require iron chelation Deferoxamine is contraindicated	Covered
Newfoundland	Require iron chelation Deferoxamine is contraindicated	Covered
Prince Edward Island	Require iron chelation Deferoxamine is contraindicated	Possibly available on an individual basis through the hospital pharmacy
Nunavut	Not covered	Considered on a case-by-case basis
Northwest Territories	Not covered	Covered
Yukon	Not covered	Covered
National Defence	Require iron chelation Deferoxamine is contraindicated	May be covered[c]
Veterans	Not covered	May be covered depending on the individual's (assigned) class of coverage
First Nations NIHB Program	Not covered	Considered on a case-by-case basis

NIHB: non-insured health benefits.

[a]Information supplied by Novartis Corporation; [b]information supplied by colleagues from across Canada; [c]listed medication. May be on a case-by-case basis.

FIGURE 3
Guidelines for the Management of Deferasirox Side Effects

Diarrhea	Abdominal pain	Nausea and vomiting
• Hydration	• Switch to pre-prandial dosing	• Use antemetics
• Loperamide	• For upper abdominal pain, use antacids	• Switch to preprandial dosing
• Lactaid®, if indicated	• Consider spasmolytic drugs	• Reduce dose or interrupt treatment
• Dose at night	• Reduce dose or interrupt treatment	
• Use water to disperse tablets		
• Reduce dose or interrupt treatment		

Adapted from Nolte F, et al. Leuk Res 2011; 35(9):1131-5. With permission from Elsevier Ltd., Philadelphia, USA.

FIGURE 4
Dispersal of Deferasirox Microparticles with the Battery-operated Disperser to Reduce GI Side Effects

DFX and DFO. DFO, because of its short half-life, must be administered by continuous subcutaneous infusion. This medication should be managed by a hematologist who has experience with its administration, monitoring, and side-effect management. Twenty-four-hour chelation can be considered for patients requiring intensification, such as patients with cardiac IOL or severe hepatic IOL. Combination with DFP—an oral chelator not generally available in Canada—has been used.

More recently, DFO has been safely and successfully combined with DFX.[43] DFX is an oral medication that is administered once daily, dispersed in liquid, and is often preferred by patients. It is usually started at a dose of 20 mg/kg/day and escalated to 30 mg/kg/day, or even higher, to achieve a negative iron balance. Although it may be started at doses as low as 5 mg/kg/day and gradually escalated to minimize side effects, this dose is usually insufficient to achieve effective reduction of established IOL. Because of provincial guidelines requiring that patients receive more than a few RBC units and have SF levels greater than 1,000 ng/mL to be eligible for coverage, this medication is usually started at 20 mg/kg/day and escalated as tolerated in order to achieve effective reduction of IOL. Dose-limiting side effects of DFX include GI disturbances (nausea, vomiting, diarrhea, constipation, abdominal pain) and renal insufficiency, which occur in up to one-third of patients.

There are published guidelines for the management of GI side effects (Figure 3).[44] Renal insufficiency is best addressed by managing GI side effects and volume status, although dose reductions and interruptions may be needed. Good responses of GI side effects with the battery-operated disperser have been noted (Figure 4). Although manually the medication appears dispersed to the naked eye, microparticles that may irritate the GI tract are completely dispersed using this device. It is important to monitor patients and side effects according to recommendations in the product monographs; a simplified monitoring scheme is presented in Table 1. More detailed and readily accessible information on dosing, safety and efficacy, adverse event management and provincial reimbursement may be found at *www.MDSClearPath.org*. Proposed response criteria for IOL therapy are shown in Table 6; however, given the decrease in cardiac DFS noted at an SF level over 2,500 ng/mL, it may be desirable to decrease the SF further than suggested in this table.

To summarize, the usual first choice for chelation (where accessible) is DFX, given at a dose of 20 mg/kg/day for patients with an SF level over 1,000 ng/mL and dose-adjusted to GI and/or renal side effects. Where DFX is not tolerated or is insufficient to effectively offfload excess iron, DFO or combinations may be used. This approach should be supervised by a hematologist who is experienced with the use of DFO or combinations of agents.

Future Directions

Areas of future investigation include: clarification of the mechanism of cardiac complications in MDS with IOL; clarification of the extent and impact of endocrine complications; identification of which MDS subtypes benefit most from iron reduction[45]; examination of chelation for higher-risk MDS; examination of initiating chelation at a lower ferritin threshold/iron burden in order to prevent complications rather than attempting to rescue tissue once damage has occurred; reducing SF to lower than 1,000 ng/mL with current chelators (the toxicity of DFO is increased at an SF level less than 1,000 ng/mL); reducing IOL with medications other than chelators[46]; and examination of the results of oxidative stress (products of oxidative DNA damage, lipid peroxidation products, depletion of antioxidants such as glutathione and N-acetyl-cysteine) in relation to clinical endpoints. The Kallisto trial[47] not only examines chelating at a lower SF threshold (300–1,000 ng/mL), but also aims to identify whether the hematologic improvement seen with chelation is additive or synergistic with that of erythropoietin. This trial is currently open and enrolling in Vancouver, Toronto and Hamilton.

Conclusions

The goals of chelation in MDS are to pre-

TABLE 6
Proposed Response Criteria for the Therapy of Iron Overload

Response	Criteria
Complete (CR)	Decrease in SF to < 2,000 ng/mL AND Decrease in SF by > 500 ng/mL
Minor (MiR)	Decrease in SF to < 2,000 ng/mL BUT Decrease in SF by < 500 ng/mL
Stable iron load (SIL)	SF constantly elevated BUT < 4,000 ng/mL
No response (NR)	Increase in SF of > 500 ng/mL OR SF constantly > 4,000 ng/mL

SF: serum ferritin.
Adapted from Valent P, et al. Eur J Clin Invest 2008; 38(3):143-9. With permission from Wiley-Blackwell.

vent organ damage, induce hematologic improvement in a substantial minority of patients, minimize the risk of AML progression, and optimize outcomes around HSCT. In some patients, chelation must be intensified in an attempt to rescue damaged tissue. Future studies will examine endpoints in the context of prospective controlled trials, determine the mechanisms by which chelation is conferring benefit, and determine whether different starting/stopping thresholds should be considered in regard to those used in congenital anemias with historical chelators. The significant rate of hematologic improvement seen with chelation in MDS suggests that this intervention may be considered active treatment rather than supportive care.

References:
1. Olivieri NF, Nathan DG, MacMillan JH, et al. Survival in medically treated patients with homozygous beta-thalassemia. N Engl J Med 1994; 331(9):574-8.
2. Gabutti V, Piga A. Results of long-term iron-chelating therapy. Acta Haematol 1996; 95(1):26-36.
3. Pullarkat V. Objectives of iron chelation therapy in myelodysplastic syndromes: more than meets the eye? Blood 2009; 114(26):5251-5.
4. Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. Haematologica 2006; 91(12):1588-90.
5. Malcovati L, Della Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol 2005; 23(30):7594-603.
6. de Swart L, Smith A, Fenaux P, et al. Early mortality in 1000 newly diagnosed MDS patients with low- and intermediate-1 risk MDS in the European Leukemianet MDS (EUMDS) Registry. ASH Annual Meeting 2012. Abstract 3830.
7. Leitch HA, Leger CS, Goodman TA, et al. Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy. Clinical Leukemia 2008; 2(3):205-11.
8. Neukirchen J, Fox F, Kundgen A, et al. Improved survival in MDS patients receiving iron chelation therapy – a matched pair analysis of 188 patients from the Düsseldorf MDS registry. Leuk Res 2012; 36(8):1067-70.
9. Rose C, Brechignac S, Vassilief D, et al. Does iron chelation therapy improve suvival in regularly transfused lower risk MDS patients? A multicenter study by the GFM (Groupe Francophone des Myélodysplasies). Leuk Res 2010; 34(7):864-70.
10. Delforge M, Selleslag D, Triffet A, et al. Retrospective analysis on the impact of iron chelation therapy on survival and leukemia progression in transfusion dependent MDS patients in Belgium. EHA Annual Meeting 2012. Abstract 898.
11. Komrokji RS, Al Ali NH, Corrales-Yepez M, et al. Impact of iron overload in higher risk myelodysplastic syndromes. ASH Annual Meeting 2011. Abstract 2777.
12. Zeidan AM, Hendrick F, Friedmann E, et al. Deferasirox is associated with reduced mortality risk in a medicare population with myelodysplastic syndromes. ASH Annual Meeting 2012. Abstract 426.
13. Remacha A, Arrizabalaga B, Villegas A, et al. The IRON 2 Study: a retrospective observational study to describe the evolution of iron overload in patients with low-risk myelodysplastic syndrome. ASH Annual Meeting 2012. Abstract 1723.
14. Lyons RM, Marek BJ, Paley CS, et al. 48-Month update on survival and AML transformation in a 600-patient registry of lower-risk MDS patients. ASH Annual Meeting 2013. Abstract 2775.
15. Steensma DP. Myelodysplasia paranoia: iron as the new radon. Leuk Res 2009; 33(9):1158-63.
16. Gattermann N, Finelli C, Porta MD, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: results from the large 1-year EPIC study. Leuk Res 2010; 34(9):1143-50.
17. Gattermann N, Greenberg P, Urabo A, et al. Estimation of the relationship between serum ferritin and liver iron concentration in patients with myelodysplastic syndromes. EHA Annual Meeting 2013. Poster 419.
18. Gattermann N, Greenberg P, Urabe A, et al. Chronically transfused myelodysplastic syndromes (MDS) patients have severe iron burden: deferasirox treatment reduces iron overload and improves liver function. EHA Annual Meeting 2012. Abstract 344.
19. Goldberg SL, Mody-Patel N, Warnock N. Prevalence of cardiac disease among a US medicare population with myelodysplastic syndromes. Leuk Res 2007; 31(Supplement 1):S103.
20. Pascal L, Beyne-Rauzy O, Brechignac S, et al. Cardiac iron overload assessed by T2* magnetic resonance imaging and cardiac function in regularly transfused myelodysplastic syndrome patients. Br J Haematol 2013; 162(3):413-5.
21. Porter JB, Rafique R, Srichairatanakool S, et al. Recent insights into interactions of deferoxamine with cellular and plasma iron pools: implications for clinical use. Ann N Y Acad Sci 2005; 1054:155-68.
22. List AF, Baer MR, Steensma DP, et al. Deferasirox reduces serum ferritin and labile plasma iron in RBC transfusion-dependent patients with myelodysplastic syndrome. J Clin Oncol 2012; 30(17):2134-9.
23. Ghoti H, Amer J, Winder A, et al. Oxidative stress in red blood cells, platelets and polymorphonuclear leukocytes from patients with myelodysplastic syndrome. Eur J Haematol 2007; 79(6):463-7.
24. Badawi MA, Vickars LM, Chase JM, et al. Red blood cell transfusion independence following the initiation of iron chelation therapy in myelodysplastic syndrome. Adv Hematol 2010; 2010:164045.
25. Cilloni D, Messa E, Biale L, et al. High rate of erythroid response during iron chelation therapy in a cohort of 105 patients affected by hematologic malignancies with transfusional iron overload: an Italian multicenter retrospective study. ASH Annual Meeting 2011. Abstract 611.
26. Nolte F, Hochsmann B, Giagounidis A, et al. Results from a 1-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral Deferasirox in patients diagnosed with low and int-1 risk myelodysplastic syndrome (MDS) and transfusion-dependent iron overload. Ann Hematol 2013; 92(2):191-8.
27. Angelucci E, Santini V, di Tucci AA, et al. Deferasirox chelation therapy in transfusion dependent MDS patients. Final report from the Gimema MDS0306 Prospective Trial. ASH Annual Meeting 2012. Abstract 425.
28. Gattermann N, Finelli C, Della Porta MG, et al. Hematologic responses in myelodysplastic syndromes (MDS) patients treated with deferasirox: an EPIC post-hoc analysis using international working group (IWG) 2006 criteria. ASH Annual Meeting 2011. Abstract 2912.
29. Di Tucci AA, Murru R, Alberti D, et al. Correction of anemia in a transfusion-dependent patient with primary myelofibrosis receiving iron chelation therapy with deferasirox (Exjade, ICL670). Eur J Haematol 2007; 78(6):540-2.
30. Jensen PD, Heickendorff L, Pedersen B, et al. The effect of iron chelation on haemopoiesis in MDS patients with transfusional iron overload. Br J Haematol 1996; 94(2):288-99.
31. Chan LSA, Gu LC, Rauh JJ, et al. Iron overload accelerates development of leukaemia: evidence from a mouse model. ASH Annual Meeting 2011. Abstract 122.
32. Kobune M, Kikuchi S, Iyama S, et al. Iron chelation therapy could rapidly reduce oxidative DNA damage in CD34+ hematopoietic cells before decrease of serum ferritin level. ASH Annual Meeting 2013. Abstract 959.
33. Yamamoto M, Tanaka H, Toki Y, et al. Iron-induced epigenetic abnormality of mouse bone marrow through aberrant activation of aconitase and isocitrate dehydrogenase without gene mutation: analysis by high throughput sequencer and GC-MS. EHA Annual Meeting. 2014. Abstract LB-6206.
34. Musto P, Maurillo L, Simeon V, et al. Iron-chelating therapy with deferasirox in higher risk myelodysplastic syndromes: a retrospective, multicenter, Italian study. Haematologica. EHA Annual Meeting 2014. Abstract 4061.
35. Alessandrino EP, Della Porta MG, Bacigalupo A, et al. Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a GITMO study. Haematologica 2010; 95(3):476-84.
36. Wermke M, Schmidt A, Middeke JM, et al. MRI-based liver iron content predicts for nonrelapse mortality in MDS and AML patients undergoing allogeneic stem cell transplantation. Clin Cancer Res 2012; 18(23):6460-8.
37. Lee JW, Kang HJ, Kim EK, et al. Effect of iron overload and iron-chelating therapy on allogeneic hematopoietic SCT in children. Bone Marrow Transplant 2009; 44(12):793-7.
38. Sivgin S, Baldane S, Akyol G, et al. The oral iron chelator deferasirox might improve survival in allogeneic hematopoietic cell transplant (alloHSCT) recipients with transfusional iron overload. Transfus Apher Sci 2013; 49(2):295-301.
39. Michallet M, Sobh M, Morisset S, et al. Significant impact of iron chelation after allogeneic hematopoietic stem cell transplantation on disease recurrence: potential anti-leukemic activity. ASH Annual Meeting 2013. Abstract 180.
40. Bennett JM. Consensus statement on iron overload in myelodysplastic syndromes. Am J Hematol 2008; 83(11):858-61.
41. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997; 89(6):2079-88.
42. Santini V, Alessandrino PE, Angelucci E, et al. Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines. Leuk Res 2010; 34(12):1576-88.
43. Cassinerio E, Orofino N, Roghi A, et al. Combination of deferasirox and deferoxamine in clinical practice: An alternative scheme of chelation in thalassemia major patients. Blood Cells Mol Dis 2014 May 17.
44. Nolte F, Angelucci E, Beris P, et al. Clinical management of gastrointestinal disturbances in patients with myelodysplastic syndromes receiving iron chelation treatment with deferasirox. Leuk Res 2011; 35(9):1131-5.
45. Leitch HA, Chan C, Leger CS, et al. Improved survival with iron chelation therapy for red blood cell transfusion dependent lower IPSS risk MDS may be more significant in patients with a non-RARS diagnosis. Leuk Res 2012; 36(11):1380-6.
46. Tsang E, Leitch HA. Pre and post-treatment serum ferritin levels in patients with lower risk myelodysplastic syndromes receiving erythropoiesis stimulating agents. Haematologica. EHA Annual Meeting 2014. Abstract 3456.
47. Combination study of deferasirox and erythropoietin in patients with low- and int-1-risk myelodysplastic syndrome. ClinicalTrials.gov. Verified July 2014 by Novartis. NCT01868477. https://clinicaltrials.gov/ct2/show/NCT01868477?term=A2421&rank=1
48. Sahlstedt L, Ebeling F, von Bonsdorff L,et al. Non-transferrin-bound iron during allogeneic stem cell transplantation. Br J Haematol 2001; 113(3):836-8.
49. Ezzat H, Wu JK, McCartney H, et al. Association between increased liver iron concentration and vitamin D deficiency in patients with transfusion dependent hemoglobinopathies in British Columbia. ASH Annual Meeting 2012. Abstract 3203.
50. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006; 108(2):419-25.