

Oral Iron Chelation in MDS

INDICATION

Iron chelation should be considered for patients on a regular red cell transfusion programme who have a prognosis of greater than 2 years (IPSS-R score of 3.0 or less). Typically, this includes patients with red cell predominant MDS (i.e. RA, RARS or del 5(q)) after they have received ~ 25 units of red cells and whose serum ferritin is greater than 1000 mcg/L. Consider chelation therapy in patients with higher risk forms of MDS who are transplant eligible

The mainstay of iron chelation has been subcutaneous desferrioxamine (DFO) infusions (see DFO protocol [\[Link\]](#)). The most recent BCSH guidelines continue to recommend this as first line treatment. However, subcutaneous infusion with DFO is frequently not tolerated or advisable in patients with MDS. Deferasirox is an oral iron chelator that is safe and effective in transfusion dependent patients with MDS. An alternative iron chelator, deferiprone, can be considered in patients who have a normal neutrophil count.

Investigation of MDS patients on regular transfusions to document extent of iron overload.

1. FBC.
2. Serum ferritin.
3. End organ toxicity - Cardiac: ECG and echocardiogram documenting left ventricular ejection fraction. Liver: serum albumin, fasting blood glucose, prothrombin time and serum transaminases and, if indicated, test adrenal function.
4. T2* MRI scans should be considered in those patients considered to be appropriate iron chelation candidates. This has replaced the tests in (3) for a number of reasons. Firstly, it directly measures tissue iron. Secondly, it is quantitative. Thirdly, it measures iron in the heart and liver in one investigation (and could look at other organs such as the pancreas). Fourthly, serial scans allow one to measure iron loading over time.

The scan takes approximately 30 minutes and is performed at the John Radcliffe Hospital. To request a scan from OUH, email OCMR.department@ouh.nhs.uk with a copy of the patient's latest clinic letter. The service is also available to the region- contact the email above to request a referral form.

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Deferasirox protocol:

Deferasirox is currently available as both dispersible and film coated tablets. The older dispersible tablets are being phased out in June 2017 in favour of film coated tablets which are thought to be better tolerated. The dose of film coated tablets is 40% lower than for dispersible.

The starting dose of Deferasirox depends on transfusion intensity. During treatment, the dose should be adjusted every 3-6 months either upwards or downwards according to response. The aim is to achieve a target ferritin of 500-1000mcg/l. It is important to adjust doses downwards when there has been a good response as, anecdotally, side effects are more likely to occur as the ferritin falls. Not all patients can tolerate their maximum dose. In these cases, the highest possible dose before intolerable side effects occur should be given.

Baseline investigations prior to starting Deferasirox

1. Assessment of R-IPSS score and transfusion intensity
2. Serum ferritin
3. T2*MRI of whole body
4. ECG
5. Serum creatinine and eGFR
6. Liver function tests
7. Urine dip for proteinuria
8. Ophthalmic and audiology assessments

Toxicity monitoring of patients after starting Deferasirox

1. Serum creatinine and eGFR (weekly for first month and during first month after dose modification; monthly thereafter)
2. Urine dip for proteinuria – monthly
3. Liver function tests – monthly
4. Ophthalmic and auditory testing - annually
5. If renal tubular dysfunction suspected at any point – check for glycosuria, low serum potassium, urate, phosphate, magnesium, phosphaturia, aminoaciduria

Efficacy monitoring

1. Serum ferritin every 3-6 months
2. FBC and assessment of transfusion intensity every 6 months (15% show haematologic improvement)
3. T2* MRI – annually
4. ECG – annually

The following table outlines the recommended dosing for both film coated and dispersible tablets

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	Deferasirox Preparations		Indications		
	Film-coated tablets	Dispersible tablets	Transfusions		Serum ferritin
Starting dose	14 mg/kg/day	20 mg/kg/day	After 25 units (about 100 ml/kg) of PRBC	or	>1,000 µg/l
Alternative starting doses	21 mg/kg/day	30 mg/kg/day	>14 ml/kg/month of PRBC (approx. >4 units/month for an adult)		
	7 mg/kg/day	10 mg/kg/day	<7 ml/kg/month of PRBC (approx. <2 units/month for an adult)		
For patients well managed on deferoxamine	One third of deferoxamine dose	Half of deferoxamine dose			
Maximum dose	28 mg/kg/day	40 mg/kg/day			
Monitoring					
	Serum ferritin				
Target range	500-1,000 mcg/L	Maintain Dose			
Adjustment steps (every 3-6 months)	>2,500 mcg/L	Increase Dose			
		3.5 - 7 mg/kg/day Up to 28 mg/kg/day	5-10 mg/kg/day Up to 40 mg/kg/day		
	<2,500 mcg/L	Decrease Dose			
		3.5 - 7 mg/kg/day In patients treated with doses >21 mg/kg/day	5-10 mg/kg/day In patients treated with doses >30 mg/kg/day		
<500 mcg/L	Consider interruption				

Table 1 Deferasirox dosing for dispersible and film-coated tablets

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Toxicities of Deferasirox

Renal impairment (including renal tubular acidosis)
Liver impairment
Upper GI ulceration and haemorrhage
Diarrhoea
Sensorineural deafness
Cataracts

Toxicity management

Renal:

Deferasirox is contra-indicated if GFR <60ml/min

If serum creatinine >33% above pre-treatment average at two consecutive visits and the GFR is below 90ml/min, the dose should be reduced by 10mg/kg/day (dispersible tablets) or 7mg/kg/day (film-coated tablets). After dose reduction, if the serum creatinine remains >33% pre-treatment value and GFR<90ml/min, interrupt treatment.

Dose reduction should also be considered in patients with worsening proteinuria or who have features suggestive of renal tubular dysfunction.

Liver:

Deferasirox is contra-indicated in patients with a Child-Pugh C liver disease i.e. severe liver disease

Rising serum transaminases are common. If there is a persistent and progressive increase in transaminase to greater than 3xULN that cannot be attributed to other causes, Deferasirox should be stopped. Once the LFTs have returned to normal levels, cautious re-introduction of Deferasirox at a lower dose should be attempted and gradual dose escalation considered.

Diarrhoea:

The following applies to dispersible tablets only:

Mild (<4 episodes/day)	Hydrate and Loperamide
Moderate (4-6 episodes/day)	As per mild plus reduce Deferasirox to 10mg/kg/day
Severe (>6 episodes/day)	As per mild but stop Deferasirox. Re-introduce when diarrhoea resolved at 10mg/kg/day and increase by 5mg/kg/week until target dose reached. Discontinue if unmanageable diarrhea returns

Deferiprone protocol

Deferiprone is most effective at removing cardiac iron. It is renally excreted and gives the urine a characteristic rusty colour.

Dose Range

25mg/kg three times daily, to a total of 75-100mg/kg/day. The dose should be rounded down to the nearest half tablet (i.e. to the nearest 250mg)

Deferiprone oral solution (100mg/mL) has similar bioavailability as the film-coated tablets

Relative contraindications

- History of unexplained neutropenia
- Pre-existing arthropathy
- End-stage renal failure

Baseline investigations

- FBC, LFT, renal, urine dip
- Ferritin
- Whole body T2*MRI

Initial Dose

- 75-100mg/kg/day in three divided doses
- Increase monthly to maximum dose of 100mg/kg/day

Monitoring

- Weekly FBC for first month
- LFT, renal, protein dip – monthly
- Zinc – 6 monthly
- Ferritin-3 monthly (stop and monitor if Ferritin < 500mcg/l)
- T2*MRI- annually

Dose modifications for adverse events

Agranulocytosis (1-2%) i.e. neutrophils < 0.2 x 10⁹/L

- Stop the drug immediately and give G-CSF
- Monitor neutrophils weekly until recovery
- **Do not re-challenge**

Neutropenia (4%) i.e. neutrophils < 1.0 x 10⁹/L

- Usually reversible
- Temporary withdrawal of drug until resolves
- Monitor FBC weekly

Arthropathy

- Provide analgesia (NSAIDs), consider dose reduction
- Consider Rheumatology referral

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Name	Revision	Date	Version	Review date
Dr Alex Sternberg	Previous protocol has been re-drafted	March 2017	2.0	March 2019
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Update contact details for MRI scan request	July 2017	2.1	March 2019

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