

Clinical Guidelines on the Use of Iron Chelation in Children Receiving Regular Blood Transfusions

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Clinical Guidelines on the Use of Iron Chelation in Children Receiving Regular Blood Transfusions

This guideline covers the monitoring and management of children (receiving transfusions on Philip Isaacs ward) with transfusion-related iron overload, and is aimed at the paediatric and haematology members of the multi-disciplinary team. These guidelines are based on the UK Forum on Haemoglobin Disorders 2007 document 'Consensus view on choice of iron chelation therapy in transfusional iron overload for inherited anaemias'.

Background

Regular blood transfusion results in the gradual accumulation of iron, initially in the liver, and then throughout the body including the heart and endocrine organs. If iron is allowed to accumulate it causes tissue damage, with hepatic, endocrine and cardiac failure, the latter resulting in death if untreated. Cardiac iron overload is rare in children with sickle cell disease, but an important complication in thalassaemia. Iron chelators remove iron and prevent this tissue damage. Any child who is receiving regular blood transfusion over a six month period or more should be considered for iron chelation. Indications for iron chelation in children at KCH are

- Sickle cell disease requiring long-term transfusions
- Transfusion dependent thalassaemia
- Other rare haemolytic anaemias
- Diamond-Blackfan anaemia, aplastic anaemia (rare)

Children requiring frequent blood transfusions due to chemotherapy do not usually require chelation due to the temporary nature of the erythropoietic failure.

Indications for Starting Iron Chelation

- The need for iron chelation should be discussed from an early stage when it is clear that a child is going to need long-term regular transfusion. This should be included in any discussions with the parents concerning the risks and benefits of transfusion.
- Iron chelation should be started when:
 - 10 or more blood transfusions have been given
 - The serum ferritin is consistently more than 1000 μ g/l
 - The child has been receiving regular transfusions for more than one year
 - It is planned to continue the transfusions for at least a further 12 months
- Ideally chelation should not be started before the age of 2 years

Choice of Iron Chelation Regime

- Desferrioxamine (DFO)
 - Licensed for all ages. Generally not started before the age of 2.
 - Dose for children is 20-40 mg/kg/day (not above 30mg/kg/day in children age <5)
 - Infusions are usually started 2-3 times per week, before increasing to 5-6 infusions over 10-12 hours per week using an infusor pump.

- Deferasirox (DFX) (Exjade)
 - Licensed as second line agent for children age 2-5, and as first line agent in children age >5.
 - Initial dose 20mg/kg/day, adjusted up to 40mg/kg depending on assessments of iron overload.
 - Serum creatinine should be checked one week after starting and monthly thereafter.
 - Urine albumin:creatinine ratio should be measured at each transfusion
- Deferiprone (DFP)
 - Not recommended for children age <6 years of age
 - Only licensed for use in thalassaemia
 - Initial dose 25/mg/kg tds (better tolerated if started od and then built up over 4 weeks).
 - Dose may be increased up to 100mg/kg/day.
 - Agranulocytosis risk 1-2%. Monitor FBC weekly. Patients need to be continually educated about this risk, know that they must stop DFP if they have a fever or infection, and get a FBC done urgently. They should carry some written information explaining this.

Initiating Treatment Iron Chelation Treatment

- Iron chelation should be discussed regularly with children and parents when they attend for blood transfusion.
- After about 10 transfusions the clinical nurse specialist will give the information leaflets on desferrioxamine and deferasirox to parents and discuss the advantages and disadvantages.
- Desferrioxamine is the first choice iron chelator and should be started initially unless
 - The family/child are very strongly against or refuse to use desferrioxamine as opposed to oral iron chelation; this may be influenced by social circumstances, previous family experiences and any parental disability
 - In practice, most children and parents are strongly in favour of oral iron chelation
- If the child and parents decide that they could not use subcutaneous chelation, deferasirox should be started at a dose of about 20mg/kg.
- Deferiprone is not offered as a first choice iron chelator.

Monitoring of Children Receiving Iron Chelation

- All patients on iron chelation require careful monitoring
- Prior to each transfusion, the following laboratory tests will be performed
 - Full blood count and reticulocyte count
 - Renal and hepatic function, including ALT
 - Corrected calcium
 - Random glucose
 - Serum ferritin
 - Haemoglobin HbS (and C) percentage – (SCD only)

- Urine albumin:creatinine ratio (patients on deferasirox only)
- Clinical assessment at each transfusion
 - If the child has any symptoms, she/he will be assessed by the paediatric haematology specialist registrar
 - Children will be formally examined every 2-3 months by a paediatric haematology consultant
 - Weight will be recorded at each transfusion and used to calculate the volume of blood transfused.

Annual Review of Patients Receiving Iron Chelation

- Annual review will be initiated by the paediatric haemoglobinopathy clinical nurse specialist
- Review blood tests will be performed annually on all regularly transfused patients (order set on EPR).
 - Routine monthly blood tests as listed above
 - Thyroid function tests
 - Parathyroid hormone levels
 - Cystatin C
 - Serum magnesium, zinc, selenium, copper
 - Insulin-like growth factor 1
 - CMV IgG (if previously negative)
 - Hepatitis A, B and C serology
 - Urine for microscopy and culture
 - Urine albumin:creatinine ratio
- Other investigations at annual review
 - Audiometry and ophthalmology review for patients on iron chelation
 - Height
 - ECG
- The results of Annual Review blood tests will be discussed at the MDT meeting.
- The child will be reviewed by a paediatric haematology consultant with the results on Philip Isaac's ward, according to the timetable organized by the clinical nurse specialist. This will include:
 - Full examination
 - Discussion of iron chelation, including adherence, treatment options
 - Discussion of venous access, and assessment of Portacath, if in use
 - Review and update of immunizations
 - Assessment of growth and development
 - Pubertal Tanner staging if appropriate
 - Assessment of school attendance and performance
 - The need for continuing blood transfusions
 - Social, housing and financial status
 - Birth of siblings or other family changes which might make HLA typing possible
 - Discussion of bone marrow transplantation
 - Discussion of transition to adult services if appropriate

Additional Review of Sickle Cell Disease patients receiving Iron Chelation

- The majority of these have cerebrovascular disease and the following investigations should be performed regularly, typically every 12 months
 - Neurocognitive assessment – normally organized by Sarah Mellor but may need specific referral if a new patient.
 - Brain MRI/MRA – after the age of seven this is typically performed annually, but in younger children general anaesthesia is required and this will be requested only if there are new neurological symptoms or evidence of progressive vasculopathy.
 - Transcranial Doppler imaging – typically this will be performed every 6-12 months, although it may not be informative or necessary if there are assessable vessels due to vasculopathy or inadequate ultrasound window.
 - Review in the paediatric joint sickle/neurology clinic with Dr Keith Pohl.
- Indications for transfusions in non-neurological patients should be reviewed regularly as most will not be transfused indefinitely.
- If the child is older than 7 years, and the ferritin is consistently greater than 2500µg/l, T2* cardiac MRI should be requested by writing to Professor Dudley Pennell at the Royal Brompton Hospital. Consideration should also be given to organizing an R2 MRI of the liver at KCH.

Additional Review of Children with Transfusion-Dependent Thalassaemia

- Bone densitometry should be requested annually from the age of 10 years.
- T2* cardiac MRI should be requested at the age of 7-8 years. This should be repeated approximately annually depending on the initial result and the chelation history of the patient. This is currently requested by referring to Professor Dudley Pennell at the Royal Brompton Hospital.
- If the ferritin is persistently > 2000µg/l or the T2* MRI suggests significant hepatic iron overload, an R2 liver MRI scan should be organized (at KCH/Maudsley).

Management of Chelation Side-Effects

- If a child is thought to be allergic to an iron chelator, it should be stopped and an alternative used.
 - Referral to the paediatric allergy team may be helpful at a later stage to establish the degree and nature of any sensitivity
- Desferrioxamine
 - The main problem is pain and inflammation at the site of the infusion
 - Children and parents should be taught to rotate the site of infusion
 - Other factors which may help include changing the type of needle used, altering the volume/concentration of the desferrioxamine

- Any infection should be treated appropriately with systemic antibiotics
- Deferasirox
 - The main side-effects are gastrointestinal disturbances and mild skin rashes
 - Gastrointestinal side-effects may be helped by
 - Altering the time of day when it is taken, typically from the morning to the evening
 - Eating natural yoghurt or lactase supplements a few hours before deferasirox
 - Taking the drug in divided doses
 - Mild rashes may fade whilst continuing the drug at the same dose
 - If severe rashes occur, the deferasirox should be stopped and reintroduced at a low dose once the rash has faded

Management of Chelation Toxicity

- Desferrioxamine
 - Main toxicities include retinopathy, hearing loss and growth restriction, particularly of the spine
 - If these are detected the dose of desferrioxamine should be reviewed and reduced, depending on the urgency of iron chelation
 - In most cases patients will switch to an alternative iron chelator
- Deferasirox
 - If serum creatinine more than doubles, the dose of deferasirox should be reduced, and gradually increased once the renal function has returned to normal.
 - If ALT increases above the upper limit of normal, or doubles if elevated before starting deferasirox, reduce dose of drug and monitor. The dose can be gradually increased once ALT returns to base-line levels.
 - If reintroduction causes the creatinine or ALT to increase significantly again, the patient should be switched to desferrioxamine.
- Deferiprone
 - Neutropenia is the main toxicity and weekly full blood counts should be performed.
 - If neutropenia ($<1 \times 10^9/l$) occurs deferi-prone should be stopped and alternative chelation used.

Monitoring and Encouraging Adherence to Chelation Treatment

- Infrequent use of iron chelation is the major reason for iron chelation to fail and iron toxicity to occur. This is a particular problem with teenagers.
- Problems with adherence should be discussed at each attendance for transfusion
- Children and parents should be informed of the trends in their serum ferritin and shown the results of any T2* or R2 MRI scans
- If iron chelation use is inadequate with evidence of iron accumulation, the following measures should be taken:
 - Review dose to ensure that it is in the therapeutic range

- Review the volume of blood transfused (ml/kg/year), available in the MDT record (should be less than 220ml/kg/year)
 - Examine for splenomegaly
- Discuss any reasons for infrequent use
- Consider changing to alternative regime or chelator
- Consider referring to paediatric haemoglobinopathy psychologist

Management of Patients with Cardiac Iron Overload

- Patients at increased risk of cardiac disease
 - LV impairment (low ejection fraction MRI)
 - Changing ECG patterns, in particular development of RV strain
 - Cardiac loading on T2* MRI (T2* < 15ms)
- Chelation should incorporate deferiprone either alone or with desferrioxamine or continuous iv desferrioxamine (requires insertion of Portacath or equivalent)
- The choice of chelator should be reviewed when cardiac function and T2* return to normal and will depend on hepatic iron stores, patient tolerance and ferritin levels.
- Acute cardiac decompensation
 - These patients require intensive chelation: treat with continuous i.v DFO over 24 hr at 50 mg/kg/day via Portacath. After 1-2 weeks, deferiprone may be introduced.

Referral of Patients with Iron-Related Tissue Damage

- Cardiac disease: paediatric cardiologists at Evelina Children's Hospital
- Endocrine disease: paediatric endocrinologists at KCH
- Liver disease: paediatric hepatologists at KCH

References

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