Pakistan Thalassaemia Welfare Society
Technical Instructions

1. Iron Chelation Therapy

One unit of blood (420 ml) contains about 200 mg of iron. Repeated blood transfusions in thalassaemia are a major cause of iron overload. Another less well recognized cause of iron overload in thalassaemia is the excessive absorption of iron from the intestine. Normal intestinal iron absorption is about 1-2 mg/day. This increases several folds in the patients of thalassaemia major who are not on regular blood transfusions. The transfusion regimen that keeps the pre-transfusion haemoglobin above 9.0 g/dl increases the iron overload but prevents excessive absorption of iron from the intestine.

1. **Iron toxicity**

The iron absorbed from the intestine is carried by transferrin to the tissues. In conditions of iron overload when transferrin is fully saturated the non-transferrin bound iron (NTBI) becomes available in plasma. The NTBI is preferentially taken up by tissues like myocardium, endocrine glands, and liver where it is deposited as ferritin and haemosiderin. During transition of iron from ferric to ferrous and vice versa free radicals are generated that cause cell death and fibrosis by damaging cell membranes and nuclei.

2. **Objectives of iron chelation**

A child with thalassaemia on regular blood transfusions needs some alternate means to eliminate extra iron from the body. The objective of iron chelation is to maintain safe levels of body iron at all times. A small proportion of the newly entered iron remains in a labile pool while the bulk of the excess iron enters storage sites and becomes stable. The iron chelators effectively remove iron only when it is in the labile pool. Therefore chelation should be started early in life to prevent accumulation of iron in the body stores. The free iron is very toxic and it is best managed by continuous chelation rather than by bolus doses of the chelator. It may take several months of treatment before the extra iron is removed to a safe level.

3. **When to start iron chelation?**

The iron chelation therapy should be started after the first 10-15 blood transfusions or when the serum ferritin has reached 1000 µg/L. In the Non Transfusion Dependent Thalassaemia (NTDT), iron chelation should be started when the patient has received 20 or more blood transfusions or when the serum ferritin is >800 µg/L.

4. **Desferrioxamine**

Desferrioxamine (Desferal) is a time tested iron chelator. When given in adequate doses and at regular intervals it has an established impact on the complications of iron overload and the overall survival of thalassaemia patients. The main limitations of desferal include a high cost and the parenteral route of administration.

<u>Subcutaneous infusion</u>

The standard dose of desferal for children is 20-40 mg/kg body weight and for adults the dose is up to 50-60 mg/kg body weight. It is given by subcutaneous infusions lasting 8-12 hours for 5-6 nights a week. The daily dose of desferal is usually calculated by the serum ferritin level (Table 2). Because of the short half-life desferal is not effective through intramuscular injections. Vitamin C (2-3 mg/kg/day) enhances iron chelation by increasing its labile pool. In left ventricular failure secondary to iron overload continuous intra-venous infusion of desferal at 50-60 mg/kg is beneficial.

Side effects

Local allergy to desferal causing redness pain and itching is not uncommon. A dose related effect of desferal on hearing and vision has been reported. Desferal may cause some growth retardation in children less than 3 years of age. The patients on desferal have an increased risk of developing blood transfusion related infection with *Yersinia enterocolitica*. Desferal should be discontinued if the infection is suspected.

Table 2. The recommended daily dose of desferal at various serum ferritin levels.

Serum ferritin	**Desferal**
<2000 µg/L	20 mg/kg/day
2000-3000 µg/L	30 mg/kg/day
>3000 µg/L	40 mg/kg/day

5. **Deferiprone**

Deferiprone (L1, Feriprox®, Kelfer®) is an orally absorbed iron chelator. A pooled data analysis shows statistically significant decrease in the serum ferritin at six months in patients receiving Deferiprone at 75 mg/kg/day in three divided doses. The effect on serum ferritin at this dose appears greater at baseline ferritin values >2,500 µg/L but not at values <2,500 µg/L. Deferiprone has an edge over desferal in chelating iron from heart and thus improving its function. Deferiprone is available as 500 mg tablets or as suspension for paediatric use. It should be used with caution in children less than 5 years of age.

The side effects of Deferiprone include neutropenia, agranulocytosis and thrombocytopenia. The onset of agranulocytosis is variable, starting from a few months to nine years after taking drug. The patients receiving Deferiprone should be monitored by weekly blood counts. If severe neutropenia or agranulocytosis develops, the drug should be stopped. Haematopoietic growth factors like GM-CSF should be considered in case of agranulocytosis.

A loss or gain of appetite and nausea occurs in 3-24% of the patients taking Deferiprone. Variable fluctuation in liver enzymes (ALT) has been reported in about a quarter of the

patients. Arthropathy may also be seen in some patients. Deferiprone is teratogenic in animals and must be avoided in patients attempting to conceive.

Deferiprone can be used as a second line drug in patients who are unable to use desferal or when desferal therapy has proven ineffective.

6. **Deferasirox**

Deferasirox (Exjade®, Asunra®, Oderox®) is an orally active iron chelator. Due to a long half-life Deferasirox is taken once daily as suspension in water preferably before meal. A starting dose of 20 mg/kg is recommended for thalassaemia major patients who have received 10-20 transfusions. In patients with high levels of iron loading 30 mg/kg/day is recommended.

The criteria for starting treatment (ferritin level, age, number of transfusions) are the same as for desferal. The side effects like agranulocytosis, arthropathy, or growth failure are not reported with Deferasirox. Neurosensory deafness or hypoacusis have been reported in similar number of patients as with desferal. Deferasirox is contra-indicated in patients having impaired renal function. It should be used with caution in patients with liver disease.

The recommended initial daily dose of Deferasirox is 20 mg/kg body weight. An initial daily dose of 30 mg/kg may be considered for patients receiving more than 14 ml/kg/month of packed red blood cells (>4 units/month for adult). An initial dose of 10 mg/kg may be considered for patients receiving less than 7 ml/kg/month of packed red blood cells (<2 units/month for adult).

The patients who are well managed on desferal, Deferasirox at half the dose of desferal may be considered (e.g. patient receiving 40 mg/kg/day of desferal for 5 days a week may be given 20/mg/kg/day of Deferasirox.

7. **Combination therapy for iron chelation**

A combination of different iron chelators is used when mono-therapy alone is unable to control the iron overload. In the combination therapy the two drugs are mostly given sequentially (alternating). For example desferal may be given at night and Deferiprone during the day time. Serum ferritin can be controlled with desferal given twice or thrice a week combined with Deferiprone at the standard doses of 75 mg/kg/day. The safety data on the combined therapy of iron chelators is limited.

8. **Monitoring of iron status**

Serum ferritin is the most commonly used parameter for assessing body iron stores. The test is widely available and its results generally correlate well with the body iron stores in thalassaemia major. However, the results of ferritin become less reliable at very high iron overload (ferritin >3000 µg/L). Ferritin is an acute phase protein that is synthesized in liver. Therefore, any inflammatory condition or liver disease may cause false high levels of ferritin. In vitamin C deficiency ferritin may appear lower than the actual. In patients showing sudden

increase in ferritin a possibility of hepatitis or other inflammatory diseases should be considered. Ferritin is also reported to underestimate the degree of iron overload in thalassaemia intermedia.

In a patient of thalassaemia major it is recommended to keep the serum ferritin level below 1000 µg/L. In the poorly managed patients of thalassaemia major ferritin often rises to >3000 µg/L. At such high levels there is poor correlation between the ferritin and the actual body iron content. The measurement of ferritin at very high levels is technically difficult and such samples should be adequately diluted to get an accurate result. Therefore, the lab requests for ferritin in patients of thalassaemia major should include a note to dilute the sample before estimation.