

THALASSAEMIA

Introduction

β -Thalassaemia major is an inherited blood disorder presenting with anaemia at 4 - 6 months of age. Common presenting symptoms are lethargy, failure to thrive and hepatosplenomegaly.

In Malaysia, the β -thalassaemia carrier rate is estimated at 3-5%, most of whom are unaware of their carrier / thalassaemia minor status.

Baseline investigations to be done for all new patients: -

- full blood count, peripheral blood film (In typical cases, the Hb is about 7g/dl)
- haemoglobin analysis by electrophoresis / HPLC:
 - typical finding: HbA decreased or absent, HbF increased, HbA2 variable
- serum ferritin
- red cell phenotyping (ideal) before first transfusion.
- DNA analysis (optional)
 - for confirmation of difficult cases, used in prenatal diagnosis and detection of α - carrier (limited availability upon request at IMR, HUKM, UMMC and USM)
- liver function test
- infection screen – HIV, Hepatitis B & C, VDRL screen (before first transfusion)
- HLA typing (for all patient with unaffected siblings)
 - *all nuclear family members must be investigated by Hb Analysis for genetic counseling.*
 - *1st degree and 2nd degree relatives should also be encouraged to be screened & counseled (cascade screening).*

Management

Regular maintenance blood transfusion and iron chelation therapy is the mainstay of treatment in patients with transfusion dependent thalassaemia.

Maintenance Blood Transfusion

Beta thalassaemia major

- when to start blood transfusion?
 - after completing blood investigations for confirmation of diagnosis.
 - Hb < 7g/dl on 2 occasions > 2 weeks apart (in absence other factors e.g. infection)
 - Hb > 7g/dl if impaired growth, bone changes, enlarging liver and spleen.
- transfusion targets?
 - maintain pre transfusion Hb level at 9 -10 g/dl
 - keep mean post-transfusion Hb at 13.5-15.5g/dl (not advisable > 15.5 g/dl)
 - current recommendation: keep mean Hb 12 - 12.5g/dl
 - This allows for normal physical activity and growth, abolishes chronic hypoxaemia and reduce compensatory marrow hyperplasia which causes irreversible facial bone changes*
- transfusion interval?
 - usually 4 weekly interval (usual rate of Hb decline is at 1g/dl/week). Interval varies from individual patients (range: 2 - 6 weekly)
 - volume: 15 - 20mls/kg (maximum) packed red cells over 4 hours
 - round-up to the nearest pint of cross-matched blood provided.
 - i.e. if calculated volume is just > 1 pint of blood, give 1 pint, or if calculated volume is just < 2 pints, give 2 pints. This strategy would minimize the number of exposure to immunologically different units of blood product and avoid wastage of donated blood.*

Note:

- In the presence of cardiac failure or Hb < 5g/dl, use low volume red packed cells (< 5ml/kg) at slow infusion rate over > 4 hours with frusemide 1 mg/kg (20 mg maximum dose).
- It is recommended for patients to use leucodepleted (pre-storage, post storage or bedside leucocyte filters) packed cells < 2 weeks old. Leucodepletion would minimize non-haemolytic febrile reactions and alloimmunization by removing the white cells.
- **Aim for a pre transfusion Hb of 9 g/dl**

Beta thalassaemia intermedia

Late onset and milder form of β -thalassaemia, usually presenting > 2 years age with Hb 8g/dl or more. Severity of patients is heterogeneous from being symptomatic at presentation to being asymptomatic until later adult life. If they require regular transfusion, then follow a β -thalassaemia major transfusion regime

Alpha thalassaemia (Hb H disease)

Transfuse only if Hb persistently < 7g/dl and/or symptomatic.

Iron Chelation Therapy

This is essential to prevent iron overload. Current effective medication readily available throughout the country and approved for use in all children is

Desferrioxamine (Desferral®). Compliance to treatment is directly related to superior survival outcome.

- when to start?
 - usually when the child is > 2 years old and when the serum ferritin reaches 1000ng/ml. This usually occurs after 10-20 blood transfusions.
- dosage and route
 - average daily dose is 20 – 60mg/kg/day by subcutaneous (s.c.) continuous infusion using a portable pump over 8-10 hours daily, 5 - 7 nights a week.
 - aim to maintain serum ferritin level below 1000 ng/ml.
 - vitamin C augments iron excretion with Desferral®.
 - severely iron loaded patients require longer or continuous s.c. or i.v. (via portacath) infusion of Desferral®.

Complications of Desferral®

- local skin reactions usually due to inadequately diluted Desferral®.
- Yersinia infection: presents with fever, abdominal pain & diarrhoea.
Stop Desferral® and treat with cotrimoxazole, aminoglycoside or 3rd generation cephalosporin.
- severe allergy (rare)
- Desferral® toxicity (high doses > 50mg/kg/day in presence of low serum ferritin)
- ocular toxicity: reduced vision, visual fields, night blindness; reversible
- auditory toxicity: high tone deafness. Not usually reversible
- growth retardation
- skeletal lesions: pseudo rickets, metaphyseal changes, vertebral growth retardation

Complications of chronic iron overload in thalassaemics over 10 years

- endocrine: growth retardation, pubertal delay, hypothyroidism, hypoparathyroidism & diabetes mellitus
- cardiac: arrhythmias, pericarditis, cardiac failure
- hepatic: liver cirrhosis

Oral iron chelator

Deferiprone / L1 (Kelfer® / Ferriprox®) is an alternative if iron chelation is ineffective or inadequate despite optimal Desferal® use, or if Desferal® use is contraindicated. (However, there is no formal evaluation in children < 10 years of age)

Deferiprone is given 75 – 100 mg/kg/day in 3 divided doses. It can also be used in combination with Desferal®, using a lower dose of 50mg/kg/day.

There is a small risk of reversible agranulocytosis, arthritis, or gastrointestinal disturbance. Weekly full blood counts are advised. Stop if neutropaenic (<1,500/mm³).

Deferasirox (Exjade®) is recently approved for use in transfusional iron overload in patients 2 years or older. The dose is 20-30 mg/kg/day in liquid dispersible table, taken once daily. There is a small risk of transient skin rash, GI disturbance and a reversible rise in serum creatinine below upper limit of normal (ULN) in some patients. Monthly monitoring of renal function is required.

Monitoring of patients

During each admission for blood transfusion, the following should be done:

- clinical assessment – height, weight, liver & spleen size assessment
- pre transfusion Hb, platelet count, post transfusion Hb (half hour post transfusion)
- volume of blood transfused: volume of *pure RBC (PRBC)* based on haematocrit (HCT) of packed red cells given (usually > 50 - 55%)
i.e. volume of PRBC = volume blood given x HCT of blood given (e.g. 600 mls x 0.55 = 330 mls)
- other medications

Every 3- 6 months

- evaluate growth and development
- serum ferritin
- liver function test

Every year or more frequent if indicated

- evaluate growth and development
- endocrine assessment - RBS, T4/TSH, Ca, PO4 (If Ca low - check PTH & Vit. D)
- pubertal and sexual development from 10 years onwards
- Tanner stage of breast and genitalia
- follicle stimulating hormone (FSH), luteinizing hormone (LH) levels, oestradiol or testosterone levels
- infection screen (6 monthly) – Hepatitis B and C, HIV, VDRL
- calculate transfusion indices (*Volume of Pure red blood cell transfused / median weight*)
- evaluate iron balance
- bone – osteoporosis & skeletal abnormalities

Cardiac assessment at variable intervals and especially after 10 years of age

- yearly ECG
- annual cardiac echocardiography
- cardiac T2* MRI (available in Hospital Sentosa, Kuala Lumpur)

Liver iron assessment

- liver biopsy for liver iron concentration and the assessment of hepatitis, fibrosis or cirrhosis in selected cases and prior to bone marrow transplant.

Splenectomy

Indications

- blood consumption volume of PRBC > 1.5X normal or >200-220 ml/kg/year in those > 5 years of age to maintain average haemoglobin levels.
- evidence of hypersplenism.

Note:

- give pneumococcal and HIB vaccinations 4-6 weeks prior to splenectomy
- meningococcal vaccine required in endemic areas
- penicillin prophylaxis for life after splenectomy
- low dose aspirin (75 mg daily) if thrombocytosis > 800,000/mm³ after splenectomy

Diet and supplements

- oral folate at minimum 1 mg daily may benefit most patients.
- low dose Vitamin C at 3 mg/kg augment iron excretion for those on Desferal.
 - dose: <10 years, 50mg daily; >10yrs, 100mg daily given only on deferral days
 - only to be given for patients on Desferal
- avoid iron rich food such as red meat and iron fortified cereals or milk.
- tea may help decrease intestinal iron absorption.
- dairy products are recommended as they are rich in calcium.
- vitamin E as antioxidant.

Bone marrow transplantation (BMT)

- potential cure option when there is a HLA -compatible sibling.
- classification of patients into 3 risk groups based on presence of hepatomegaly, iron chelation status and presence of liver fibrosis.

Table 4. Survival following BMT (Pesaro group, Lucarelli et al)

Class	No. of risk factors	Survival %	Disease free survival (>10 yrs) %
1	0	92	85
2	1-2	84	80
3	3	61	53

best results if BMT is done at the earliest age possible in Class 1 patients.

Note: in newly diagnosed cases, the family should be informed of this option and referred to a Paediatrician for counseling & HLA typing of patient and unaffected siblings to identify a potential donor.

Antenatal diagnosis

- can be done by chorionic villous sampling at 9-11 weeks period of gestation

Support groups

- various state and local Thalassaemia Societies are available
- provides support and education for families
- organises fund raising activities and awareness campaigns
- health professionals are welcomed to participate