Personal Practice

Common Queries in Thalassemia Care

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Beta thalassemia is a common genetic disorder in Indians. Around 10,000 thala-ssemia major cases are born every year. The treatment of thalassemia major patients imposes a financial burden on the family. Much progress has been made in last 15 years in understanding of the pathogenesis of thalassemia and development of effective management(1). These include development of a promising new oral iron chelator, intensive preparative regimens for stem cell transplantation and better vectors for gene therapy. In the present article, we highlight the common questions asked by the family and the general practitioners on thalassemia care.

Introduction

The beta thalassemia carrier rate in India is around 3-7% with higher frequency in certain ethnic groups like Sindhis, Lohanas, Bhanusalis, *etc.*(2). Thalassemia major is the severe transfusion dependent form, however, most of the patients do not receive adequate treatment. The queries commonly raised in relation to thalassemia are as follows:

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1. How to diagnose thalassemia major and when to start transfusions?

Thalassemia major patients are usually brought to the physician in the second half of infancy with complaints of decreased activity, increasing pallor of body and abdominal fullness. Examination reveals anemia and hepatosplenomegaly. High hemoglobin F (HbF) level on Hb electrophoresis or high performance liquid chromatography (HPLC, Biorad Variant^{TM}, Biorad Laboratories, Hercules, CA) establishes the diagnosis. Transfusions are indicated when hemoglobin is >7 g/dL.

2. What is the optimum hemoglobin level?

The Hb level is kept between 9-10 g/dL with transfusions given at intervals of 2-4 weeks. Lower hemoglobin levels may impair proper growth. Higher hemoglobin levels (>14 g/dL) may carry the risk of thrombotic complications and need more aggressive chelation therapy.

In presence of Hb <5 g/dL or in presence of congestive heart failure, packed red blood cells (PRBC) amount is given in aliquots, 5 mL/kg at one sitting with diuretic use.

3. In older child, can 3 units of blood be given at one sitting?

Transfusions should be given in form of one or two compatible PRBC units. A 40 kg child will require around 400 ml blood (10 mL/kg) and hence two PRBC units. An average PRBC unit contains 250 mL red cells (minus anticoagulant). With more number of units, there are chances of reactions arising from interactions between units of blood transfused. Also raising Hb levels to very high levels is not desirable.

4. If HbF level is low, can the patient still be thalassemia major?

In most patients of thalassemia major, the HbF level is very high indicating homozygous beta-thalassemia. But in some patients who have already been given few transfusions, the HbF level may be low, but clinically there is hepatosplenomegaly and severe anemia, say in a 1-year-old child. If there is any doubt, it is better to screen the parents for carrier status - both should show carrier state.

5. Should leucocyte filter be used in every thalassemia major patient?

The role of leucocyte filters is to help in leuco-reduction at the bedside. The presence of leucocytes in the transfused blood can give rise to non-hemolytic febrile transfusion reactions (NHFTR). Use of filters has been found to decrease substantially these re-actions. If the family can afford the use of filters, it is better to use them at the outset. They are available as single use or double use (Pall India Ltd., Mumbai, India/Baxter India Ltd, Gurgaon, India) for one or two blood bags at single sitting, costing around Rs. 500-600/-. In patients with frequent transfusions reactions (NHFTR), pre-medication with pheniramine maleate (Avil™, Hoechst) and paracetamol decreases the reactions, in addition to use of filters.

6. In a young child, how to differentiate between thalassemia major and thalassemia intermedia?

Suppose a child 2-3 years of age comes to the clinic and investigation reveals beta-homozygous thalassemia with high HbF levels on electrophoresis/HPLC. In absence of massive hepatosplenomegaly and Hb between 6-7 g/dL, one can follow up the patient and repeat Hb after 1 month. If Hb improves, or remains at steady level the patient is likely to be thalassemia intermedia. These patients may benefit from hydroxyurea (HU) therapy. Transfusion is required if there are pathological fractures, bony deformities, cardiac complications due to chronic anemia or significantly retarded growth and development.

7. How to determine whether a child who is HbsAg or anti-HCV positive requires treatment or not?

The HbsAg positively has declined over the years due to routine hepatitis B vaccination in these patients. However, hepatitis C can be a real problem, as the screening of blood bags for anti HCV is not done at all centers. The monitoring of hepatic transaminase levels is of prime importance. In active hepatitis C infection, there is persistent elevation of the transaminases. The treatment is done with alpha interferon with or without ribavirin therapy.

8. When to start iron chelation therapy?

With regular transfusions, there is increasing iron load, requiring removal with use of a chelator, usually after 15 transfusions. At 10 mL/kg PRBC given every 3 weeks, an amount of 150 mL/kg is reached by one year. Amount of 0.8 mg iron would be present per mL of PRBC in the bag, equivalent to 120 mg (*i.e.*, 150 × 0.8) iron/kg/year. For a child weighing 10 kg (1 year age), this would amount to 1200 mg iron per year from transfusions. In a normal individual, the intestinal iron absorption is 1-1.5 mg/day or 350-530 mg per year. Thus in a regularly transfused thalassemia major child, iron acquired from transfusions is 3-4 times above normal. After one year of transfusions, the serum ferritin reaches above 1500 μg/L. The serum ferritin level aids in the initiation of therapy but at least 2 values should be recorded before the start of chelation. The serum ferritin can be elevated if blood sample is taken during an active infection/ inflammation. If there was some undocumented fever/inflammation at one

sitting leading to high serum ferritin values, this can be clarified by a second testing. The aim of iron chelation is to keep serum ferritin below 1000 μg/L. Persistently high serum ferritin (>2500 μg/L) is asso- ciated with increased risk of cardiac complications.

9. Which iron chelator is better: desferrioxamine or deferiprone?

Desferrioxamine (Desferal^{TM}, Novartis) is a time tested iron chelator. It has to be given by S/C infusion by a pump over 5-7 hours at least 5 days in a week. The dose is 25-50 mg/kg/day. A higher dose increases risk of Desferal induced toxicity. The desferal therapeutic index or Porter index(3) is defined as mean daily dose of desferrioxamine in mg/kg, divided by serum ferritin in μg/L, calculated every 6 months should not exceed 0.025, to minimize sensorineural hearing loss. The main disadvantage of desferral is that it requires injection.

Deferiprone (Kelfer^{TM}, Cipla) is given at a dose of 50-75 mg/kg. The toxicity includes gastrointestinal problems, musculoskeletal pains, arthropathy and agranulocytosis. However, it has been successfully used in many Indian centers(4).

However, combination therapy is best for patients with very high serum ferritin levels. It provides more effective iron chelation due to 'shuttle effect' of deferiprone. It removes the tissue iron esp. cardiac iron to the plasma, which is then removed by desferrioxamine.

A newer oral iron chelator ICL 670 (Deferasirox, Exjade^{TM}, Novartis) is under clinical trials(1) and is as efficacious as desferrioxamine at a lower dose (20 mg/kg). It is expected to be available for routine use soon.

10. What is the role of vitamin C in increasing iron excretion?

Vitamin C at doses of 2-3 mg/kg/day, given along with desferrioxamine, increases iron excretion by increasing the availability of chelatable iron. However, the dose should not exceed 200 mg/day, as excessive doses may increase iron toxicity. It is better to avoid administration of vitamin C in excessively iron-overloaded patients.

11. When should splenectomy be done?

Splenectomy is advised if, (*a*) the PRBC requirement is more than 220 mL/kg/year(5), (*b*) there is evidence of hypersplenism in form of leucopenia or thrombocytopenia or reduced RBC survival with splenic sequestration on Cr^{51} radioisotope studies, or (*c*) there is presence of massive splenomegaly leading to persistent abdominal discomfort.

12. Should cholecystectomy be done along with splenectomy?

Cholelithiasis is common in thalassemia intermedia patients. So ultrasound should be done to detect gallstones prior to operation or gallstones should be checked at time of operation.

If there are gallstones, cholecystectomy should be performed along with splenectomy. Most thalassemia major patients do not develop gallstones.

13. When should vaccines be given before splenectomy?

The pneumococcal, meningococcal and H.influenzae vaccincs should bc given at least 4 weeks before the operation. Streptococcus pneumoniae accounts for more than 75% of documented bacterial infections in asplenic patients. Malaria is also more severe and carries increased risk of mortality in these patients.

14. What are the common hormonal problems in thalassemia?

Poor growth, short stature, delayed puberty and secondary amenorrhoea are common problems(6), mainly due to anemia and hypogonadism. Maintenance of a good Hb level and proper iron chelation reduces the magnitude of these problems.

For hypogonadism, replacement doses of testosterone or estrogen are required. Hypothyroidism (30%) is treated with eltroxin. For hypoparathyroidism, manifesting as body pains, muscular spasms, and tetany, vitamin D_3 and calcium are used.

Impaired glucose tolerance and diabetes can be detected by the oral glucose tolerance test. esp. in patients >10 years of age. Reduced bone mineral density in adolescent thalassemia patients requires treatment with oral calcium, bisphosphonates(7) and hormonal therapy.

15. Can thalassemia major patients marry and have children?

Fertility has been reported worldwide in well-treated thalassemia patients. If a thalassemia major patient marries a carrier, then there will be 50% risk of thalassemia major in offspring and will require prenatal diagnosis. If a thalassemia major female marries a normal male, who is neither carrier nor affected, then they can have asymptomatic (normal/carrier) children. Assisted reproductive techniques may be required in some of the cases.

16. When should bone marrow transplantation be done?

Bone marrow stem cell transplantation (SCT) requires a HLA-matched sibling donor. Only around 30% children are able to get a fully matched sibling donor. Earlier the transplantation is done in childhood better are the results. The patient characteristics associated with survival and event free survival following SCT depend on: (*a*) degree of hepatomegaly (>2 cm/<2 cm), (*b*) portal fibrosis on liver biopsy (present/absent), and (*c*) effectiveness of iron chelation (irregular/regular). If none of the adverse factors are present (Class I), results are very good. However, the Pesaro (Italy) group has recently tried an intensive protocol in class III patients <17 years age and found 93% survival(8). In India, one of the best centers for SCT is at Christian Medical College (CMC), Vellore.

17. Can we do umbilical cord blood transplantation?

Umbilical cord blood (UCB) transplantation and peripheral blood stem cell transplantation (PBSCT) have the advantages of easier processing and lower risk of GvHD and infection. However, large scale experience in these forms of therapy is less.

If there is a rejection following UCB transplantation, the success rate of subsequent bone marrow SCT further decreases. One can preserve the UCB and later use along with bone marrow SCT if it is HLA matched.

18. Can we not have a population-screening program for thalassemia?

Screening for any disease requires considerable inputs on part of the government. Screening the whole population will be expensive. In the present scenario in India, extended family screening and antenatal screening especially in high-risk communities are best options for prevention and control of thalassemia. In some communities, a β-thalassemia carrier state is considered a stigma. In these cases, screening after marriage is only feasible, though it can also cause marital tensions. Proper pre-test and post-test counseling are important in reducing the psychosocial problems arising from screening(9).

19. Is there any permanent cure for thalassemia?

Key Messages

- Proper management of thalassemia patients allows them to live a normal life.
- Severe thalassemia is preventable by screening and prenatal diagnosis.
- There is need for increasing awareness on thalassemia by community education programs.

A successful bone marrow SCT enables normal life and growth. Gene therapy strategies are being tried but clinical use for routine benefit of patients is still far off. Problem is with the finding of optimum mode of delivery and persistent expression of the gene. However, recent studies on self-inactivating lentiviral vectors (SIN-LV) have given encouraging results and renewed hope in gene therapy(10,11).

20. Will all children be affected if both partners are carriers?

Thalassemia being an autosomal recessive condition, when both parents are carriers, there is 25% risk in each pregnancy for a thalassemia major child. There is 75% chance that child will be unaffected (normal or carrier). In other words, the risk of unaffected and affected in each pregnancy is 3:1. But confirmation of individual fetus usually requires an invasive test, mainly a chorionic villus sampling (CVS).

21. What is the best time for prenatal diagnosis?

If mutations are identified in the previous affected child as both the partners (husband and wife), prenatal diagnosis is done on CVS sample at 12-14 weeks of pregnancy. The known mutations are checked in the CVS sample(9). If one or both mutations are unidentified, the options include linkage analysis, globin chain synthesis studies or cord blood HPLC(12). The legal limit for termination of pregnancy as per MTP Act is 20 weeks. Therefore, one should try to give a diagnosis before 20 weeks. At present, many couples come late in pregnancy, so it is necessary to increase awareness to enable early prenatal diagnosis and effective prevention.

22. Is there any benefit of use of anti-coagulants in thalassemia patients?

Splenectomized patients with thalassemia have thrombocytosis. Aspirin 50-100 mg/day can be given if platelet count exceeds 800,000/mm^3 till the counts fall to normal range. Anti-coagulants in form of unfractionated heparin or low molecular weight heparin are given to patients undergoing surgery or if an episode of thrombosis is documented.

23. What is the benefit of becoming a member of thalassemia society?

The thalassemia society organizes blood donation camps, screening camps and interactive sessions for thalassemia patients and families. One may also get iron chelating drug or infusion pumps at concessional rates. The interactive sessions are like a 'get together' for the patients where they can discuss with older thalassemia patients so as to allay fears and anxieties related to disease and its treatment.

24. What are the problems if one is a thalassemia carrier?

The thalassemia carrier is like any normal individual. Only the hemoglobin may be 1-2 g/dL lower, and peripheral smear usually shows red cell microcytosis. Folic acid supplementation can improve hemoglobin levels. Only when a carrier marries another

carrier, there is risk of thalassemia major child–this is preventable by timely prenatal diagnosis.

REFERENCES

1. Nienhuis AW. Eighth Cooley's anemia symposium: summation and perspective. Ann N Y Acad Sci 2005: 1054; 396-406.
2. Higgs DR, Thein SL, Wood WG. Distribution and population genetics of the thalassemias. *In:* Weatherall DJ, Clegg JB, eds. The Thalassemia Syndromes. 4th edn. Blackwell Science, Oxford 2001; p. 237-284.
3. Porter JB, Jaswon MS, Huehns ER, East CA, Hazell JW. Desferrioxamine otoxicity: evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. Br J Hematol 1989; 73: 403-409.
4. Naithani R, Chandra J, Sharma S. Safety of oral iron chelator desferiprone in young thalassemics. Eur J Hematol 2005; 74: 217-220.
5. Cohen A, Markenson AL, Schwarz E. Transfusion requirements and splenectomy in thalassemia major. J Pediatr 1980; 97: 100-102.
6. DeSanctes V. Growth and puberty and its management in thalassemia. Horm Res 2002: 58 suppl; 72-79.
7. Voskaridou E, Terpos E. New insights into the pathophysiology and management of osteoporosis in patients with beta thalassemia. Br J Hematol 2004; 127: 127-139.
8. Sodani P, Gaziev D, Polchi P, Erer B, Giardini C, Angelucci E, *et al*. New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years. Blood 2004; 104: 1201-1203.
9. Patrines GP, Kollia P, Papadkis MN. Molecular diagnosis of inherited disorders: lessons from hemoglobinopathies. Hum Mutat 2005; 26: 399-412.
10. Malik P, Arumugam PI. Gene therapy for beta thalassemia. Hematology (Am Soc Hematol Educ Program) 2005; 45-50.
11. Bank A, Dorazio R, Leboulch P. A phase 1/11 clinical trial of (beta)-globin gene therapy for (beta)-thalassemia. Ann NY Acad Sci 2005; 1054: 308-316.
12. Panigrahi I, Ahmed RP. Kannan M, Kabra M, Deka D, Saxena R. Cord blood analysis for prenatal diagnosis of thalassemia major and hemophilia. Indian Pediatr: 2005; 42; 577- 581.