Management of Thalassemia

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Introduction

Over the last three decades, clinical observations and research have established that thalassemia major is a treatable condition. Studies have shown that regular transfusion therapy with safe and appropriately processed blood, combined with regular and effective iron chelation tremendously increase patients' survival and quality of life. This recommended treatment regime is focused on fighting the anemia prevalent in thalassemia and all its consequences, and on preventing progressive tissue iron loading that may result from the disease itself and from the blood transfusion therapy used to treat the anemia.

Blood transfusion

Regular blood transfusions greatly contribute to the quality and length of life of patients with thalassemia major, and have been a central aspect of the treatment of thalassemia since the 1960's[1]. Children with hemoglobin values below 6–7 g/dl should be observed very carefully at regular intervals, with particular respect to their activity, growth and development, spleen size and any suggestion of early skeletal changes. Any infant who is showing deleterious effects of anemia of this kind, which would include most of those with hemoglobin values much below 6–7g/dl, will require transfusion. Because of the dangers of transfusion reactions there is no place for the use of whole blood or untreated packed red blood cells. In order to avoid leucocyte sensitization, leucocytes should be removed from the blood to be transfused, either by washing with saline or by the use of filters which remove the majority of leucocytes from banked blood[2]. The objective of a transfusion regimen is to correct the anemia and clinical manifestations of the disease and to suppress the patient's endogenous erythropoiesis. In practice patients are transfused every 3–4 weeks with 10–15ml/kg of packed red cells keeping the Hb level between 9 and 12 g/dl.

Iron chelation therapy

With the delivery of 200–250 mg of elemental iron with each unit (200 ml) of packed RBCs, iron overload is inevitable. As the body has no effective means of removing iron, the only way to remove excess iron is to use drugs called iron chelators (iron binders), which form a compound with iron that can be excreted from the body through the urine and/or stools. Without regular chelation therapy to control iron accumulation, transfusion dependent children with severe forms of thalassemia die during the second decade of life[3]. There are now three iron chelators are available

Desferrioxamine (DFO, Desferal™)

Desferrioxamine (DFO) was the first iron chelation drug to be manufactured. It is a hexadentatechelator, binds iron tightly, and the iron- DFO complex is excreted in both urine and stool. The standard regimen to remove excess iron is by subcutaneous (sc) infusion of DFO over 8-12 hours, on 5 to 7 days each week because the plasma half-life is short [4]. DFO chelates iron from two main sources or pools of iron in the body. The first pool is iron formed by the breakdown of red blood cells. This pool accounts for

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70% of the iron chelated by DFO, and is passed out of the body in the urine. The second pool of iron chelated by DFO comes from the liver which is the biggest iron-storing organ in the body. Iron stored in the liver is released when ferritin and haemosiderin are broken down in the liver cells (hepatocytes). DFO in the hepatocytes then binds with the iron, before being passed out of the body in stools. DFO does not bind with iron already bound to transferrin[5].

Deferiprone (DFP, Ferriprox™, Kelfer™, L1, CP20): Deferiprone was the first orally-active iron chelating drug to be developed[6,7]. DFP was first licensed for use in 1995 in India, for use by patients who cannot use DFO because of toxicity, or inability to comply with recommended dosage. DFP appears to be rapidly and completely absorbed after oral administration, with peak plasma levels typically occurring about 1 hour after administration[8,9]. The drug is rapidly eliminated from the body with a half-life of about 2 hours due to hepatic biotransformation, with glucuronidation accounting for almost the entire

metabolism. About 90% of the drug is excreted in the urine as the glucuronide. Deferiprone often causes gastrointestinal symptoms, idiosyncratic side effects that are potentially severe include erosive arthritis (5% to > 20%) and neutropenia (up to 5% of patients), including severe agranulocytosis (up to 0.5% of patients). Therefore close monitoring is required.

Deferasirox(ICL 670, Exjade™, Desirox™,Asunra™)

Deferasirox is a tridentate oral iron chelator with a 2/1 stoichiometry for iron [10], has the longest half-life of all 3 iron chelators. With a plasma half-life of 8 to 16 hours, it is practical to administer the drug once a day and to maintain effective plasma level of the drug. It is able to scavenge non– transferrin-bound "labile plasma iron, the chemical species responsible for tissue damage in iron-overloaded subjects, by means of toxic oxygen intermediaries. After chelation with deferasirox, e" 90% of iron is excreted in feces and < 10% is excreted in urine. Deferasiroxoften causes gastrointestinal symptoms and may increase the serum transaminase levels.

Table 1 Comparison of three different iron chelators

Agent	Route	$T_{\frac{1}{2}}$, hours	Schedule	Clearance
Deferoxamine	Slow infusion	0.5	8 - 24 hours 5 - 7 days per week	Renal and hepatic
Deferiprone	Oral	2 - 3	3 daily	Renal
Defrasirox	Oral	12 - 16	1 daily	Hepato-biliary

Splenectomy

In untransfused or rarely transfused patients, the size of the spleen inevitably increases with time, with consequent worsening of the anemia (which may require red blood cell transfusion), and, sometimes, neutropenia and thrombocytopenia. Splenectomy usually reverses the process, allowing discontinuation of transfusion in the majority of the thalassemia intermedia patients.

Bone Marrow Transplant

Currently the only available curative treatment of thalassemia is allogeneic bone marrow/stem cell transplantation. This cure was pioneered and developed by Guido Lucarelli and his group in Pesaro [11]. The first successful transplantation for a patient with β thalassemia was carried out by

Thomas *et al* in 1982[12]. In India there are six centers which perform BMT[13]. A current limitation to the general applicability of this therapy is the availability of a related HLA-matched donor. Only one in four siblings on average is HLA identical. Improved management of graft-versus-host disease and the development of technologies for bone marrow transplantation from unrelated donors may expand the pool of potential donors in the near future. The use of cord blood stem cells and unrelated donors is extending the donor pool and number of patients who may receive bone marrow transplantation[14,15]

HbF Reactivation

Reactivation of fetal γ globin expression is appealing as a therapeutic approach to the β

thalassemia. Three classes of potential therapeutic agents have been investigated in β thalassemia syndromes: chemotherapeutic agents (Hydroxyurea and 5-azacitidine), short-chain fatty acid derivatives (SCFADs) (of which some are histone deacetylase(HDAC) inhibitors), and the recombinant growth factor erythropoietin (EPO). Increases in total hemoglobin levels of 1-5 g/dL above baseline have been achieved by these agents when administered for at least 3-6 months' duration[16].

Antioxidant Therapy

Oxidative damage is believed to be one of the main contributors to cell injury and tissue damage in thalassemia. Supplements with Vitamin E[17], Vitamin C[18], N-acetylcysteine[19], and Tea polyphenols [20] is often recommended to reduce the oxidative damage.

Molecular therapies

Gene Therapy: The transfer of a regulated β globin gene in autologous Hematopoietic Stem Cells is a highly attractive alternative treatment. This strategy, which is simple in principle, raises major challenges in terms of controlling expression of the globin transgene, which ideally should be erythroid specific, differentiation- and stage-restricted, elevated, position independent, and sustained over time.

Therapeutic antisense mRNA: About half of the β-thalassemia mutations are caused by aberrant RNA splicing. The use of morpholino oligonucleotides has enabled high level correction of transcribed mutant β-globin mRNA. These are oligonucleotides where the deoxyribose rings linked to nucleic acids by anionic phosphates have been substituted with morpholine rings that are linked with phosphorodiamidate groups, which are uncharged. This renders the oligonucleotides resistant to RNAses[21,22].

α *hemoglobin stabilising protein.* The α hemoglobin stabilizing protein (AHSP) binds free α globin chains, limiting the oxidative effects of αHb and prevents its precipitation. In humans, it is directly regulated by GATA-1. Upregulation of AHSP protein or the synthesis of an AHSP mimic to chaperone the free redundant β globin in α thalassemia represent potential molecular therapies [23].

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