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Transfusion-dependent β-Thalassemia Major Bangladeshi Child Treated Successfully with Combination of Hydroxyurea and Low-Dose Thalidomide : A Case Report

MD ANWARUL KARIM[1], SHARMIN AKHTER[2], CHOWDHURY YAKUB JAMAL[1]

Abstract:

Beta thalassemia results from absent or reduced production of beta globin gene leading to excess of alpha chain which causes ineffective erythropoiesis and marked anemia. β-thalassemia major patients usually present early within 2 years of life mostly in 2nd six months of first year of life. Only curative treatment till date is bone marrow transplantation. However, it is not feasible for all because of rarity of matched donar and obviously for its high cost and unavailability of services particularly in a developing country like Bangladesh. Hence regular blood transfusion remain the ultimate choice of their survival, growth and development with the cost of iron overload in the resource constraints country like ours. Recently HbF inducing drugs are showing promising result in the management of thalassemia children by inducing fetal hemoglobin. However, data are scarse from Bangladesh.Here we are reporting a case of beta-thalassemia who was diagnosed at 18 months of age and treated with only blood transfusion upto 2 years then hydroxyurea was given for 12 months with no response and then she was kept on regular blood transfusion with iron chelation up to 6 years with regression splenic size to normal and to maintain normal growth and development. After then she was given hydronix plus thalidomide in combination and responded well and remained transfusion free for last 3 years.

Keywords: *Beta thalassemia major, Hemoglobin, Hydroxyurea, Transfusion, Thalidomide.*

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Introduction:

β- hemoglobinopathies are the commonest monogenic blood disorders with autosomal recessive inheritance and become public health concern.[1] â-thalassemia has a high prevalence in regions bordering the Mediterranean Sea, Middle East, Central Asia, India, south China, Far East, northern Africa and South America and the highest prevalence of β-thalassemia carriers has been reported in Cyprus (14 %), Sardinia (10.3%) and Southeast Asian regions.[2]Annually about 50,000 children with a transfusion dependent thalassemia (β-thalassemia major and HbE β-thalassemia) born globally among which 26,000 require regular blood transfusion.[3-4] About 70-75% patients are found in southeast asia & eastern mediterranean region.[5] In Bangladesh approximately 2500 thalassemia major cases born annually in addition to the existing 60,000–70,000 thalassemia patients.[6] In β-thalassemia major, patient usually present early month in 2nd half of first year of life.The clinical feature in patients, who are untreated or poorly transfused, is characterised by growth retardation, pallor, jaundice, hepatosplenomegaly, typical craniofacial changes and requirement of regular blood transfusion for their survival with adequate growth and development.

The definitive curative treatment option for homozygous thalassemia patients is hemopoietic stem cell transplant (HSCT) from an HLA matched donor[3-7] and

1. Professor, Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University
2. Consultant, Pediatric Hematology and Oncology, Asgar ali Hospital

Correspondence: Professor Dr. Md. Anwarul Karim, Professor, Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University, Room #312,Block D, Level 2, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka 1000. Mobile: 01711-269052. E-mail: drkarim1990@gmail.com

Gene therapy.But transplant accessibility is limited due to lack of HLA-matched donor, vast initial expences, lack of dedicated centers with ample expertise and risk of transplant related morbidity and mortality.[3-4,8] Though gene therapy is a promising therapy, its long-term efficacy yet to be evaluated .[9] So, patient have to depend on regular blood transfusion for their survival.[3-4] However, it is very difficult even impossible to manage regular transfusion due to scarcity of blood, lack of safe blood transfusion center in low-and-middle-income countries like Bangladesh. Additionally, longterm blood transfusion causes iron overload (heart, liver, and endocrine systems) which ultimately restricts children's physical and sexual growth, spread transfusion transmitted infections and development of alloimmunization.[4] These patients need iron chelation for optimal growth and development and longivity. Therefore, effective, safe and affordable treatments for TDT patients other than blood transfusion are under investigation.[10]

In this connection, Fetal Hb inducing drugs show promising result by preventing ineffective erythropoiesis thereby decreasing the need for transfusion. Hydroxyurea (HU) has been shown to improve clinical and hematological outcome in thalassemia patients.[11] HU increase hemoglobin (Hb) by inducing HbF and is also known to reduce inflammation and hypercoagulability[12].Thalidomide, having immune-modulating and anti-angiogenic properties, has been shown to induce c-globin gene expression and increase the proliferation of erythroid cells.[13] It possibly works through the amplification of reactive oxygen species (ROS)-p38 mitogen-activated protein kinase (MAPK) signaling and histone H4 acetylation during erythropoiesis.[14] There are numerous research looking at the effectiveness of HU in treating beta-thalassemia patients, and a small number of papers reporting the usage of thalidomide; however, there are relatively few studies looking at the effectiveness of combination of both drugs and data are lacking from Bangladesh. Here we are presenting a baby girl who was diagnosed at 18 months of her age and was treated with transfusion at her 6 years. Initially she was given hydoxyurea form 1 year without effect at 2 year of age. Again at the age of 6 years, hydroxyurea and thalidomide combination was started and she remains transfusion free for more than 3 years.

Case report:

A 9-year- old girl, from Savar, Bangladesh, presented to the Pediatric Hematology and Oncology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) of Dhaka, at 18 months of age with history of pallor, abdominal distension, poor feeding, recurrent bouts of fever and pneumonia and growth failure. She has a13 years old brother who is on good health. On examination she was found to be irritable, severely pale (+++), mildly icteric (+), early facial changewith frontal bossing and depressed nasal bridge, and presence of moderate hepato-splenomegaly (liver: 4 cm,spleen: 6 cm), she was severely wasted (weight 6.7 kg Z score<-6.1) and sevely stunted (length 70 cm, <-3.98).

Her Investigations revealed: Hb–4.7g/dl, HCT–12.5%, MCV-68fl, MCH-20.9pg, MCHC-30g/dl, RDW-30.5, TWC–5600/dl, neutrophils 30% , Lymphocytes-60%, Monocytes 6%, Eosinophils 4% , Platelets-348 k/l, ESR –19 mm in 1st hour, Reticulocyte count-5.8%, PBF smear showed gross anisocytosis and poikilocytosis, fragmented cells with some target cell and tear drop cell and numerous nucleated RBC, WBC and Platelets were normal.

S. Ferritin-100 ng/ml, S.bilirubin: 2.6 mg/L, indirect bilirubin: 2mg/L, LDH: 300 U/L,. USG abdomen revealed hepatomegaly and massive splenomegaly. High Performance liquid chromatography (HPLC) showed Hb A-7.8% and Hb F-90%, A2-2.2%. With all these findings, she was diagnosed as a case of â Thalassemia Major. Both of her parents are thalassemia trait.

We treated her with packed cell transfusions. She required blood Transfusions every 3-4 weeks to maintain pre-transfusion Hb e" 9 gm/dl up-to 6 years of age. At 2 years of age, she was started Hydroxyurea 20 mg/kg/ day with escalating dose upto 30 mg/Kg along with regular transfusion for period of 1 year and then stopped as there was no response and however, transfusion along with chelation with deferox was continued. At this stage the child was maintaining normal growth potentials with regression of liver and spleen size.

At the age of 6 years, she was started with thalidomide 2mg/kg/day in combination with hydroxyurea 30 mg/kg/day and in the next visit after 3 weeks she showed good response. And over a period of 3 months her hemoglobin rises to > 9 gm/dl without transfusion and 10 gm/dl in next 3 months. Now she is maintyaining her Hb ≥10 gm /dl without transfusion. Now she is anthropometrically well thrived, there is no organomegaly and facial dysmorphism.Periodic assessment of serum ferritin shows rise during transfusion up to 2000 µg/dl, with deferox and now to 300 µg/dl without any iron chelator. Her TSH and serum FT4 level remains nomal. Patients experience only occasional abdominal pain and mildly elevated transaminase level that was managed with Ursodeoxycolic acid given at a dose of 10 mg/kg/day.

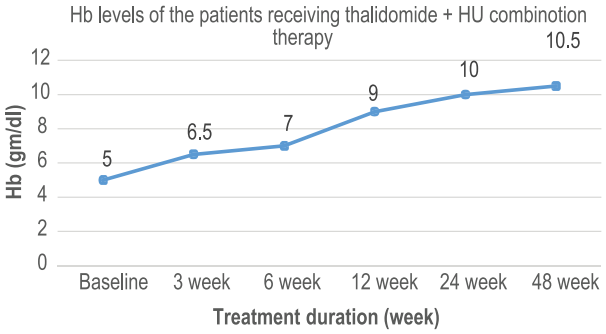

Fig.-1: *Hb levels of the patients receiving thalidomide + HU combinotion therapy*

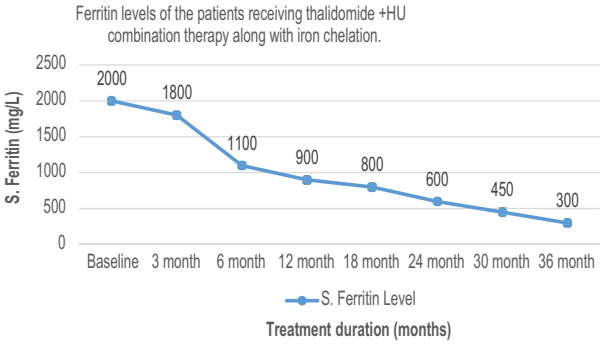

Fig.-2: *Ferritin levels of the patients receiving thalidomide +HU combination therapy along with iron chelation.*

Discussion:

Hydroxyurea got first FDA approval in 1998 for the treatment of sickle cell anaemia in adult population and in 2017 for children, which acts by inducing fetal hemoglobin to reduce the frequency of painful crises and decrease the need for blood transfusion.[15*] It is also one of the drugs that has been prescribed for decades for improvement of Hb in patients with NTDT and TDT.[16,17] The variable efficacy of Hydroxyurea in β thalassemia was reported in different studies and a recent meta-amalysis also reported the effecfiveness by increasing Hb and decreasing need for transfusion in significant number of cases.[17,18] Our patient failed to respond to hydroxyurea which was continued for1 year with escalating dose upto 30 mg/kg.But she had started response with combination of HU and thalidomide within 3 weeks and Hb rises to >9 gm/dl in 3 months time, to ≥10 gm/dl over 6 months period and now she has been maintaining around 10 gm/dl till date (>3 years) without transfusion. Now she has no organomegaly and she is maintaing nomal growth potentials.

Shah et al.,[4] in their retrospective single center retrospective observational study evaluating the efficacy and safety of the combination therapy in 25 patients. They included Thalassemia major and intermedia and reported the overall response rate to be 68.2% at 3 months and that for Thalassemia major with 50% and conservatively suggested that thalidomide and HU combination therapy is effective in high-risk patients ineligible or not willing to undergo bone marrow transplant and could be used as a bridge to transplantation in ineligible thalassaemia patients who are awaiting identification of a donor.

Yang et al.,[19] in their multicenter study observed the effect of thalidomide and demonstrated a 2.9 g/dl

increment of Hb from the baseline in transfusion-dependent thalassemia (TDT) patients, and additionally significant decrease in transfusion frequency. In this present case, though thalidomide was not used as single agent but when used with combination of hydroxyurea, Hb level increased from baseline 4.6 gm/dl to 10 gm/dl, which is much higher than the level achieved after thalidomide use and the patient required no transfusion for last 3 years. Ansari et al , in 2022 in a single arm randomized trial on 144 cases of â thalassemia showed the efficacy of combination of thadidomide and hydroxyurea and recommended this combination use particularly in developing countries where safe blood transfusion is hard to achieve and also in developed countries in selected cases. The authors have given emphasis on establishing the efficacy and safety of the combination of thalidomide and HU for patients with thalassemia through larger randomized trials.

Although some study shows some serious side effect of combination therapy including neutropenia, hyperbilirubinemia, sedation , neuropathy and thrombosis but our patients experience some less serious side effect like abdominal pain and mildly elevated transaminase level which was managed with ursodeoxycolic acid. Hence the promising results observed in this case suggest that introduction of combination of thadidomide and hydroxyurea in the treatment of â thalassemia might show a new horizon in the management of severe thalassemia in coming days.

Conclusion:

In our case, combination of HU and thalidomide shows excellent result in an improvement in Hb levels, transfusion independence and improvement in growth parameter and maintaining a healthy life style with minimal side effect.It could be considered in the treatment of TDT, however,larger-scale randomized controlled trials would validate efficacy and safety of combination hydroxyurea and thalidomide treatment in transfusion dependent thalassemia.

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