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Research Article

Management of Thalassemia Minor & Major

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Abstract

Thalassemia is most frequent inherited genetic disorders in the World. There are 270 million carriers Worldwide however it has high prevalence in the Mediterranean area & South East Asia. Over the last three to four decades there has been major development in the management of thalassemia & nearly 95% of children are surviving who were born after 1995 in the developing countries. The current protocols recommends that pre-transfusion hemoglobin should be maintained around 10 gm/dl by repeated leukodepleted & NAT tested blood transfusions and serum ferritin should be maintained between 800-1000 ng/ml by adequate chelation therapy to prevent complications of iron overload. Hematopoietic stem cell transplant offers complete cure and the results of HSCT have significantly improved over the last two decades. It is unfortunate that sibling matched donors are available in 30% of cases. It is believed that with further improvement in HLA-matching techniques, conditioning regimens and management of graft versus host disease (GVHD) & veno-occlusive disease (VODs) the survivals in allo-HSCT or haplo-transplant will improve significantly & will become standard form of therapy in near future.

Newer therapies in form of gene therapy, gene editing & drugs to correct ineffective therapy are at various stages of development & it is expected that with these newer therapies every child with thalassemia will have option of complete cure in future.

INTRODUCTION

Thalassemia is an inherited hemoglobin disorder which affects α or β globin gene resulting in inadequate or absence of α or β chain synthesis. In β globin disorder β chain synthesis is reduced & thus excess of α chain precipitate in red cells resulting in reduced red cell survival, anemia, hemolytic facies, hepato-splenomegaly, and growth retardation. It has been estimated that there are 270 million carrier of thalassemia worldwide (1). High rate of carrier is attributed to natural selection & consanguinity. Heterozygous are selected as they have protection against malaria (Plasmodium falciparum). β thalassemia was first discovered in Mediterranean & it was called as Mediterranean anemia but with human migration now it is prevalent all over the World. In the eastern Mediterranean and Pakistan has highest number of infants born with β thalassemia because of high rate of consanguinity. (2) In India there are nearly 5 crore persons with thalassemia minor and 12000 children with thalassemia major are born every year. (3) Children with thalassemia major require repeated blood transfusion for their survival from infancy onwards along with regular chelation for their survival. Children without blood transfusion survive up to 5 years and even with regular transfusion & chelating therapy only 50-65% of individuals live beyond 35 years of age. (4)

PATHOPHYSIOLOGY

Hemoglobin is a tetramer made up of globin (2 alpha & 2 beta chains) attacked to heme molecule carrying an iron molecule. Its synthesis is controlled by 2 multi-gene clusters on chromosomes16. (3 homologous genes, the zeta gene, alpha 1 (HBA1) and alpha 2 genes (HBA2) and two genes on chromosome11 (containing five functional genes (ε (HBE), Gy (HBG2), Ay (HBG1), δ (HBD), & β (HBB)) which are arranged along the chromosome to produce different tetramers during different stages of embryonic & fetal development. Upstream of β globin gene on chromosome is the locus control region (LCR) which plays a major role in β globin gene expression as enhancer of globin gene transcription. (5) Normally there is balanced production of alpha & non-alpha chains which ensures reciprocal pairing into the tetramers. Each individual inherits two α genes from both parents & thus genotype is αα/ αα. Alpha thalassemia results from deletion of α gene or from a mutation which inactivates one of the pair. The homozygous state is written as – –/– – & heterozygous as – –/αα. In situation in when one α gene is lost then heterozygous states may be termed as –α/αα and –α/– α. Clinical classification of α thalassemia along with clinical presentation is given in (Table 1). In β thalassemia this equilibrium is disturbed because defective production of β globin chains due to mutation in the beta-globin gene leading to accumulation of α globin chains which results in increase of total hemoglobin (HbF) and HbA_2. β thalassemia results from single nucleotide substitutions (insertion / deletion) within HBB gene. Presently 1811 hemoglobin gene variants have been identified & 404 mutations are associated with thalassemia. (6) Generally 5-8 mutations in any country account for nearly 95 percent of cases. Common mutation which are common in India are IVS 1-5 (G→C),

Table 1: Classification of A-Thalassemia.

Syndrome	Number of globin gene affected	Clinical picture	Hemoglobin pattern
Silent carrier	One	Asymptomatic No anemia No010rmal red cells	1–2% Hb Bart (rμ)
α-thalassemia trait	Two	Mild anemia Microcytic hypochromic red cells	5–10% Hb Bart (rμ) at birth low MCV and MCH
HbH disease	Three	Significant anemia hypochromic and microcytic picture hepato-splenomegaly	5–30% HbH Bart (rμ)
Hydrops fetalis	Four	Severe anemia in fetal life. Hepato- splenomegaly, death in utero because of anemia	Mainly Hb Bart's, small amount of HbH

IVS -1-1(G→T), codons 8/9 (+ G), codons 41/42 (– CTT), 619 bp deletion, codon 15 (G→A) – 88 b (C→T), frameshift mutation 8/9 (+ G) etc.

Individuals with β thalassemia may have additional hemoglobin structural disorders such as hemoglobin E (HbE), sickle cell disease, hemoglobin D, HbD Iran, hemoglobin q etc. Among these hemoglobin E (HbE) & sickle cell disease (HbS) are common in India while HbD Iran is common in Iran. HbE-beta globin variant G→A at codon 26 is associated with decreased beta globin production. Clinical phenotype of HbE beta thalassemia is variable from mild to severe transfusion dependent thalassemia (TDT). HbS results from glutamic acid → valine amino acid substitution at 6th position of β chain. Phenotype in these cases is variable depending upon whether it is associated with β^0 or β^+ inheritance. HbD Iran is found among Iranian, Pakistanis, Jamaican black. There is a mutation GAA→CAA at codon 22 of β chain in HbD Iran & phenotype picture is mild to moderate.

Clinical presentation

It has very wide variation from asymptomatic to other extreme where anemia is severe which presents by 4-6 months of age and it may result in congestive heart failure along with cardiomegaly, thalassemic facies & hepato-splenomegaly based upon the genetic mutation (homozygous or heterozygous state), interaction of various gene modifiers, presence of structural disorders such as HbE, HbS, HbD-Punjab, HbD-Iran etc. Based upon the natural course four type of clinical presentation have been identified depending upon (a) age at presentation, (b) severity of anemia, (c) clinical evidence of hemolysis, congestive heart failure, (d) growth retardation etc. Currently confirmation of these disorders is based on hemoglobin electrophoresis by HPLC & molecular studies (Table 2).

Thalassemia minor / carrier: It is heterozygous state and affected persons have a mutation in one chain of β globin located on chromosom11. They may be completely asymptomatic or may have mild anemia with hemoglobin between 9-11 gm/dl. Anemia often worsens in presence of deficiencies due to iron, folic acid or vitamin B_{12}. Red cell indices reveal mean corpuscular volume (MCV) is below 78 fL/cell and mean corpuscular hemoglobin (MCH) below 27 picogram/cell & red cell count is higher for hemoglobin levels. Peripheral smear shows microcytic hypochromic picture with minimal target cells, anisocytosis & poikilocytosis and its diagnosis can be confirmed with HbA_2 levels of over 3.5%. Rarely HbA_2 may be less than 3.5 % in presence of severe iron deficiency. One should repeat HbA_2 estimation after correcting iron deficiency. Thalassemia minor individuals have same risk of developing iron deficiency as general population. Unfortunately general physicians have impression that iron therapy should not be given to individuals with thalassemia therefore many persons with thalassemia minor develop severe iron deficiency especially during pregnancy when iron requirements are more. In fact iron therapy should be given to them whenever they have evidence of iron deficiency. The difference between thalassemia minor & iron deficiency anemia are given in (Table 3).

Silent thalassemia carrier state has been identified when persons are asymptomatic and all their RBC indices such as hemoglobin level MCV, MCH are within normal limits along with normal HbA2 levels. Silent carriers are suspected when their children are diagnosed as Thalassemia minor or major. Silent thalassemia carrier are diagnosed by identification of mutations on molecular studies such as (a) Cap + 1 (A-C) (4% of carriers in Punjab have this mutation (b) IVS-II – 844 (c) 92 C (C-T) and (d) 101 ?(C-T). At times some individuals with homozygous state with these mutations are asymptomatic. It is essential to exclude silent carrier while counseling a thalassemia minor for marriage.

Person with thalassemia often have mild pallor and may have weakness, tiredness, fatigue, exhaustion on exertion besides mood disturbances. Recently Eren et al (7) have observed that thalassemic minor have more depression or anxiety and poor quality of life. These individuals are at higher risk of developing anemia due to other causes such as iron or vitamin B_{12}, folic acid, deficiency, refractory anemia, anemia due to blood loss (menorrhagia / piles) coeliac disease etc. Thus anemia should be investigated & treated accordingly. Women often develop iron deficiency during pregnancy which need to be treated accordingly. (8) All individuals should receive folic acid, psycho social support for anxiety, depression in families who have thalassemia major children. Their problems get compounded with problems of their children. Thus they need counseling and psycho-social support, to improve their quality of life.

Thalassemia major: WHO has estimated that 4.5% of world's population is affected by thalassemia & hemoglobinopathies. Thalassemia –passes across countries such as Italy, Greece, Cyprus, Turkey, Sardinia, Saudi Arabia, Afghanistan, Pakistan, India, Ceylon, Indonesia, Burma, Thailand. (9) The prevalence of thalassemia in different countries in the World are given in figure

Table 2: classification of β-thalassemia.

Syndrome	β-globin gene affected	Clinical presentation	Hemoglobin pattern	Confirmatory diagnosis
Silent carrier	Heterozygous state	Asymptomatic persons without anemia	Normal with normal HPLC	Molecular studies
Thalassemia trait/carrier	Heterozygous state	Mild anemia ↑ RBC count ↓ MCV and MCH	HbA_2> 3.5%	Molecular studies
Thalassemia intermedia (NTDT)	Homozygous/ heterozygous state	Moderate anemia not dependent on blood transfusion, hepatosplenomegaly Growth retardation Bone abnormalities May require blood transfusion occasionally	Raised HbF or HbA_2 level and or Changes of hemoglobinopathies on HPLC	Molecular studies
Thalassemia major	Homozygous state	Develops severe anemia below 2 years, hepatosplenomegaly, blood transfusions dependent	Markedly raised HbF level	Molecular studies

Table 3: differences between ida & thalassemia minor.

	Thalassemia Minor	IDA
Hemoglobin	Normal / low	Low
Erythrocyte count	Normal / Slightly increased	Decreased
Peripheral smear	Microcytic & Hypochromic	Microcytic & Hypochromic
S. Iron,	Normal	Reduced
UIBC,	Normal	Reduced
TIBC	Normal	Increased
Transfusion saturation	Normal	Decreased
S. Ferintin	Normal	Reduced
Protoporphrin & Haem Ratio	Normal	Increased
Hb A2 level	Increased	Normal

1. (6) There are 270 millions carrier and 0.3 – 0.4 million children are born every year. (6) While in India there are nearly 5 crores people with thalassemia minor, 12000 children with thalassemia major are born every year & nearly 1.25 lakh thalassemic children are receiving treatment as estimated. (3)

Clinical presentation

It is dependent on interaction and severity of four factors (a) reduced hemoglobinization of red cells (b) reduced red cell survival (c) ineffective erythropoiesis & (d) extramedullary hematopoiesis. (10) Children at birth are normal & develop anemia between 3 months to 2 years of age. Anemia is progressive, persistent & there is no response to iron or any hematinic therapy. They are irritable & develop hemolytic facies (prominence of forehead & facial bones). They develop recurrent infections, abdominal distension as a result of hepato-splenomegaly, growth retardation & have poor weight gain. These children succumb to severe anemia leading to congestive heart failure by 4-6 years of age if left untreated.

Diagnosis is based upon (a) presence of moderate to severe anemia (b) reduced red cell indices (MCH, MCV, MCHC), (c) red cells changes of microcytic hypochromic picture along with evidence of hemolysis and increased erythropoiesis (d) increased fetal hemoglobin with normal HbA_2 levels (e) molecular studies to identify the mutations. Presence of other hemoglobinopathies along with thalassemia can be identified on hemoglobin electrophoresis by HPLC and by other appropriate tests if required. Unconjugated bilirubin may be raised in some while iron studies may be normal or raised depending upon the age & in children who have received blood transfusion. Radiological changes are seen in older untreated children who are secondary to marrow expansion such as cortical thinning of long bones, sun-ray appearance of skull, osteoporosis & flattening of vertebrae and small bones of hand. (Table 4).

Management: The management of children with thalassemia has improved significantly over the years which has resulted that over 95% of children are surviving who were born after 1995. (11) Currently principles of management (Table 2) are based upon several guidelines. (7) (12-13) Investigations such as (a) complete blood groups ABO, Rh, Kell, Kidd, M, N lewis system (b) HLA studies on patient & sibling for future possibility of hematopoietic stem cell transplant (HSCT) (c) family studies for genetic counseling & future pregnancies (d) hepatitis B vaccination at diagnosis if child has not received & it should be repeated every five years.

Among various transfusions regimens currently moderate transfusion therapy is recommended in which pre-transfusion hemoglobin level is maintained at 10 gm/dl. Fresh leucodepleted, NAT tested blood is preferred to (a) prevent the suppression of immune system due to donor's lymphocytes (b) reduce the risk of non-hemolytic febrile reaction (c) prevent development of alloimmunisation of HLA class I antigens (d) prevent cytomegalovirus (CMV) infection and (e) prevent transfusion transmitted infections. Blood transfusion therapy is initiated when hemoglobin levels are below 7 gm/dl on two occasions. Packed cell transfusion of 10-15 ml/kg should be transfused 2-4 weekly intervals over 3-4 hours to maintain pre-transfusion hemoglobin above 9.5 gm/dl. Children with congestive heart failure should be given slowly (5-10 ml/kg) with close monitoring. Generally blood requirement varies between 150-180 ml/kg yearly.

Chelation therapy: Current transfusion regimens are

Table 4: Risk factors and outcome of bone marrow transplantation.

Risk Factors
1. Hepatomegaly > 2 cm
2. Liver fibrosis
3. Irregular chelation (high serum ferritin level)

Class	Overall survival (%)	Thalassemia free survival (%)
I. Absence of all risk factors	94	87
II. Presence of one or two factors	84	81
III. Presence of all three factors	70	58

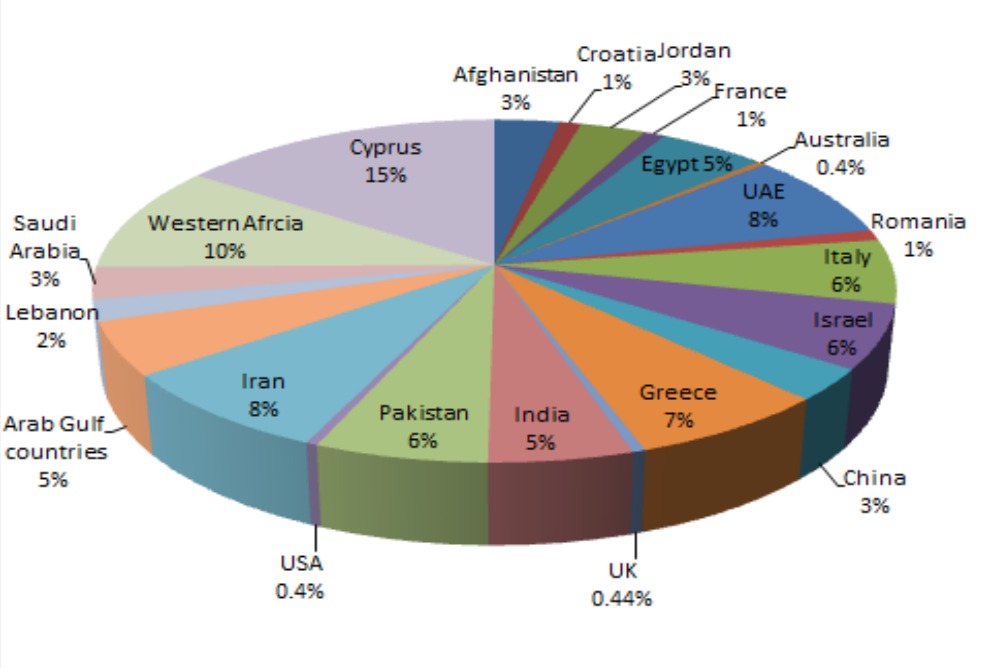

Figure 1 Worldwide incidence of β-thalassemia in Afghanistan, Jordan, France, Cyprus (2016), Croatia, Austrailia (2016), Egypt, Romania, UK, UAE, Turkey (2007), Italy & Israel (2013), USA, China, India (2016), Pakistan (2011), Greece, Iran (2017), Arab Gulf Countries, Lebanon, Saudi Arabia (2020) Western Africa (2016) based on data obtained from IthaGenes (2,126-135).

responsible for excessive iron accumulation in the body as there is no mechanism in the body to excrete iron. Transfusion dependent thalassemia (TDT) children receive 0.3 - 0.6 mg of iron per kg daily & are expected to accumulate 6-12 gm of iron every year. (14) Excess of iron is toxic to various tissues wherever it gets deposited such as liver, heart, endocrine glands resulting in increase in morbidity & mortality. (15) Among various methods to assess the iron overload serum ferritin is widely used & it should be done every 3 months & its levels should be maintained between 800-1000 ng/ml by chelating therapy. Use of magnetic resonance imaging (MRI T_2*) is a noninvasive tool to assess liver & cardiac iron levels. Recently it is also being used to assess iron overload in endocrine glands in some countries. Iron chelation therapy should be initiated once serum ferritin levels exceed 1000 ng/ml in TDT. Serum ferritin levels more than 2500 ng/ml is associated with increased risk of cardiac, liver & multiple endocrine disorders.

There are 3 major iron chelators (a) deferoxamine (DFO) a hexadentate, (b) deferiprone (DFP) a bidentate & (c) deferasirox (DFX) tridentate. DFO was first iron chelator & was developed from siderophore derived from Streptomyces pilosus with high molecular weight of 657 & short half-life of 8-10 minutes & needs to be administered by subcutaneous or intravenous route over 8-12 hours, 5-7 days a week depending upon the ferritin level. DFO enters the hepatic parenchymal cells, chelates iron as feroxamine molecule which is excreted through bile while iron released from senescent RBC is excreted through urine. Iron excretion is dependent on the (a) initial iron overload, (b) DFO dose and (c) duration of administration. Initially it is recommended in 30-40 mg/kg dose over 5-7 days a week after the serum ferritin levels exceeds 1000 ng/ml or child has received 20 units of pack cells. Efficiency of chelation may be low during the initial years & its dose need to be increased to 50-60 mg/kg daily. Deferiprone (DFP) is a synthetic compound which was first oral chelating agent developed in London & was made commercially available for first time in India in 1995. It is well absorbed from gastrointestinal tract (GI) with plasma half-life of 2-4 hours. It chelates iron which is predominantly excreted through urine which becomes light red colour. It has higher chelating efficacy from heart. Its dose is 75-100 mg/kg daily in three divided doses. Its side effects include arthralgia, arthropathy, GI disturbances, and rarely neutropenia.

(17) Therefore it is essential to monitor complete blood counts monthly. Deferasirox (DFX) is second oral iron chelator which is well absorbed from GI tract with a half-life of 12-18 hours & needs to be given once a day. It is five times more effective as compared with DFO and 10 times when compared with DFP. (16) It has minimal side effects & is currently considered as gold standard iron chelator as it chelates iron effectively from liver & heart which is excreted through GI tract. Its recommended initial dose is 30 mg/kg/daily but its dose needs to escalated to 40-45 mg/kg daily to maintain serum ferritin between 800-1000 ng/ml. It has minimal side effects and is well tolerated. It has minimal G.I side effects such as nausea, abdominal pain/discomfort and may cause transient increase in transaminases and serum creatinine.

Combination therapy: TDT children with high serum ferritin levels or having cardiac/liver/endocrine dysfunctions and if serum ferritin levels cannot be controlled by maximum recommended doses of any single agent should be treated with combination therapy. Various combinations such as (a) DFO twice or thrice a week with daily DFP, (b) DFO and DFX and (c) DFP & DFX. The advantages of combination therapy includes (a) access to different iron pools, (b) prevents non-transfusion bound iron accumulation, (c) better compliance because of lesser side effects, (d) improved chelation efficacy, (e) better quality of life. Among various combinations combination of DFP & DFX is preferred as both are oral chelators having minimal side effects & high efficacy. Doses of both these agents can be 75% of the normal dose.

Splenectomy: With current adequate transfusion therapy generally TDT children do not develop splenomegaly. Under transfused TM or children in combination with other hemoglobinopathies such as HbE disease, develop splenomegaly & hypersplenism. Hypersplenism is suspected in presence of leucopenia or thrombocytopenia and increase in blood transfusion requirement in absence of allo-immunization. If blood transfusion requirement exceeds 200ml/kg over a year it is evidence of hypersplenism. Splenectomy should be undertaken only after 6 years of age to avoid risk of sepsis. Children needing splenectomy should receive pneumococcal, meningococcal & H influenzae vaccine 4-5 weeks prior to surgery. Family should be counselled regarding the benefits & risk of splenectomy. Penicillin prophylaxis is advised for life long. These children should be treated with broad spectrum antibiotics with the onset of fever at home and should be hospitalized for appropriate therapy. Now all thalassemia centers are following current therapies and rarely children with TDT are undergoing spleenectomy.

Fetal hemoglobin inducer drugs: Several drugs such as 5-azacytidine, butyrates, decitabine, thalidomide, erythropoietin (EPO) and hydroxyurea either singly or in combination have been used to increase the fetal-hemoglobin to decrease the imbalance between alpha globin versus non-alpha globin chains. Among these drugs hydroxyurea is most promising and has been found to improve the hemoglobin levels in (a) δβ-thalassemia (b) β-thalassemia intermedia with homozygous for Xmn polymorphism (c) alloimmunized children requiring frequent blood transfusions (d) extramedullary-hematopoiesis or pseudo-tumors and (e) patients with hypercoagulability, pulmonary hypertension, leg ulcers. Several studies have clearly shown that hydroxyurea is safe & effective on prolonged use. This drug is well tolerated given in dose of 10 mg/kg/day and it should be gradually increased to maximally tolerated dose of 20 mg/kg/day. Folic acid supplementation is essential. Response usually occurs within 6 months of therapy. Hydroxyurea augments HbF levels & hemoglobin levels. Its effectiveness is dependent on genetic makeup of patient & is proven treatment option for thalassemia intermedia. (18) Recently short term studies have shown Thalidomide is useful but still not recommended for general use till the results from larger & long term clinical trials are available. (19)

Hematopoietic stem cell transplant (HSCT): Donald Thomas performed first successful HSCT in 18 month old TM using HLA matched sibling donor. (20) The principles of HSCT include (a) to destroy defective stem cell to inhibit its proliferation (b) to suppress the immune system of the host to ensure engraftment (c) infuse normal stem cells and (d) to prevent graft vs host disease (GVHD). Procedure has been further categorized on source of progenitor cells such as (a) progenitor stem cells from recipient (autologous transplant) (b) stem cell from other than recipient (allogeneic transplant) or (c) umbilical cord blood transplant. In allogeneic transplant stem cell donor can be sibling or unrelated donor. Selection of suitable donor in HSCT is of greater importance. HSCT with fully HLA matched sibling donor offers best results. (21) Unfortunately sibling donor match is available in 30% of children with TM. TDT children who do not have sibling matched donor may undergo HSCT from (a) HLA matched unrelated donor (b) unrelated cord blood stem cells (c) HLA mismatched related donors (haplo donor) (22) but the success of HSCT in these situation is poor. It is expected that with further improvement in HLA matching, conditioning regimens & treatment of GVHD results of HSCT in these cases will improve.

Outcome of HSCT is dependent on (a) age of HSCT (b) presence of hepatomegaly (c) fibrosis of liver (d) iron chelation status (e) presence of co-morbidities i.e. cardiac status, diabetes (f) histocompatibility match (full/partial) & source of stem cells. Pesaro group identified three groups based upon three variable factors in sibling fully matched HSCT (a) presence of hepatomegaly, (b) liver/portal fibrosis & (c) quality of chelation therapy before HSCT (Table 4). (23) Presence of active hepatitis infection has a strong negative impact on overall survival of HSCT. (24) HSCT failure occurs due to GVHD as 10-50% of individuals with HLA matched related donor who develop grade II-IV GVHD. Veno-occlusive disease (VODs) of liver may occur following HSCT. Incidence of VODs is high in Indian population as compared with other population.(25) Problem of infertility is high after HSCT and it needs to be addressed by cryopreservation of ovarian tissue and sperm banking. Over the years with improvement in conditioning regimens, HLA matching techniques, treatment of GVHD the results of HSCT have greatly improved. Similarly HSCT from alternative sources such as HLA matched unrelated donor, haplotransplant are being undertaken & may become standard form of treatment in near future.

Novel therapies: HSCT which offers complete cure is possible in nearly 30% of TDT cases. The standard therapy needs to be continued for life long and is associated with poor quality of life. Novel therapies are being developed to offer cure to all

which include (a) drugs correcting ineffective erythropoiesis (b) gene therapy (c) gene editing & (d) drugs correcting the iron dysregulation.

Drugs correcting ineffective erythropoiesis: Activins are key regulators of human hematopoiesis & modulate erythroid proliferation, differentiation & apoptosis. A modified activin type II B receptor inhibiting signaling induced by TGF-β promotes maturation of erythroblasts. Sotatercept (ACE-011) inhibits negative regulators at late stage of erythropoiesis & corrects ineffective erythropoiesis. (26) It inhibits transforming growth factor beta (TGF- β). Similarly luspatercept (ACE-536) has similar effect in the phase I & II studies. Based upon these results US FDA has approved it for the treatment of TDT in November 2019. In large scale randomized double blind trail in over 60 centers across 15 countries in which luspatercept (dose 1.0-1.5 mg/kg SC every 3 weekly) was used for 48 weeks. Over 40 percent of patients in treatment group achieved more than 33% reduction in transfusion requirement. Adverse effects were mild which were well tolerated such as anemia, increased liver iron concentration, hyper-uricemia, bone pain, arthralgia, and hypertension. These results are encouraging and large studies are in progress. This drug is very expensive beyond the reach of majority & needs to be administered subcutaneously. (27)

It has been observed that erythropoietin binding with cell membrane receptor activates cytoplasmic JAK-2 which in turn activates multiple signal pathways to increase cell proliferation differentiation & survival of erythroid progenitors. JAK-2 inhibitors administration has resulted to improve erythropoiesis & reduce splenomegaly in mouse model of NTDT. Further studies are in progress to evaluate its efficacy & safety in phase I studies. (6)

Gene therapy: Gene therapy is now being considered as an effective cure for monogenic blood disorders such as TM, sickle cell anemia, hemophilia. (28) Retroviral vectors act as powerful tools for auto HSCT (AHSCI) as they have long terminal repeats with efficient & universal enhancers. There is fear that retroviral vectors may integrate near proto-oncogenes causing genotoxicity. (29) Development of lentiviral vector which is self-inactivating & without any genotoxicity will offer cure for TM. Globin-expressing lentiviral vectors (GLOBE) with transplanted transduced HSCs offered cure in patients of TM & intermedia. (30) There are several hurdles such as (a) collection adequate number of HSCs (CD-34) cells (b) transduction of HSC at therapeutic levels and (c) large quantities of lentiviral vectors are required for efficient therapeutic effects & its high cost of production. It is expected that with further development in near future gene therapy will become a reality.

Gene editing: Over the last few years different engineered nucleases e.g. Zinc Finger Nucleases, Clustered Regularly Interspaced Short Palindromic Repeats (Crisper)- associated-nuclease 9 (Crisper-cas9), Transcription Activator-Like Effector Nucleases (TALENS) which act like molecular scissors & cut human DNA at very precise locations. These nucleases are very precise, specific, efficient and have greater ability to make single/double standard edits in the target sequence of DNA. Among these Crisper-cas9 is very efficient and has been effectively used for gene editing using pre-designed 42 nucleotide sequence. BCL11A which controls the switch from HbF to HbA provides an excellent target for gene editing for hemoglobinopathies. It is being postulated that HbF production can be triggered in TM patients to a sufficient degree to ameliorate anemia & need of transfusion therapy by suppression of BCL11A. Developing specific deletion in the erythroid specific enhancer region of BCL11A gene is promising which is being used in experimental study models. Another approach to increase HbF synthesis is to create a mutation as present in patients with high persistent foetal hemoglobin by making gene edits in HBB gene. Pre-clinical studies are in progress & these approaches require higher degree of precision so that endogenous production of globin proteins is not disrupted. Currently phase I, studies are in progress and it is expected in future the gene editing will evolve as an alternative form of therapy for treatment of hemoglobinopathies.

Correction of iron dysregulation: Body iron balance is controlled by 25 amino acid peptide hormone hepcidin (HAMP) which is produced in the liver in response to serum & intracellular iron levels. Normally hepatocytes increase hepcidin release proportionately to increasing serum iron levels. High levels of hepcidin binds with target ferroportin (FPN1) leading to its degradation within lysosomes.[31] It has been observed that hepcidin levels are low in TM which results in increase iron absorption in TDT in spite of high serum ferritin levels. Thus it is possible to reduce the iron overload in TM by increasing the hepcidin production in TM. Clinical data is encouraging where use of mini-hepcidins & transmembrane protein serin-6 (TMPRSS-6) inhibitors have resulted reduced iron absorption & increased iron retention in splenic macrophages and control of anemia in β thalassemia mice.[32] It is expected that by manipulating of hepcidin synthesis by these agent will reduce the iron burden which will reduce the need of iron chelating agents and improvement in hemoglobin levels which in turn will reduce the blood transfusion requirements.

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