

## *Oration*

**Late Hony. Surg. Cmde. Dr. Shantilal C. Sheth Oration Presentation during PEDICON 2006 Delhi, January 6th, 2006.**

### **Progress in the Management of Thalassemia**

Thalassemia is one of the commonest single gene disorders prevalent in our country. It is estimated that world over there are more than 200 million (1.5% of the world's population) carriers of  $\beta$ -thalassemia gene, out of which about 40 million (20%) are in South-East Asia, and 20 million of them are in India alone. Every year approximately 100,000 children with thalassemia major are born world over, of which 10,000 are born in India. The carrier rate for  $\beta$ -thalassemia gene varies from 1 to 3% in Southern India to 3% to 15% in Northern India.

Until the last few decades, thalassemia was regarded as a uniformly fatal disease and death was expected during the second decade of life before adulthood. However, better understanding of molecular biology and pre-natal diagnosis, better laboratory techniques for diagnosing complications, availability of blood components and provision of comprehensive care has resulted into better and prolonged survival (even upto the 3rd and 4th decades of life) for thalassemic children. Concerns that need to be addressed now are problems of growth and development, adolescence, education, employment, marriage and parenthood.

#### **What has resulted in the change?**

A comprehensive management plan for

thalassemics with regular packed red cell transfusions, chelation therapy and management of complications has impacted the lives of these children. When feasible some subjects have been cured of the ailment by stem cell transplantation. However, the disease burden has been reduced by antenatal diagnosis and genetic counseling.

#### **A. Blood transfusion practices**

##### **Ambulatory outpatient transfusion practices**

This should be carried out in well equipped centers and it has considerably reduced the cost of management. Compared to Rs.800/day for transfusion in hospitalized children, it costs only about Rs.180/day for transfusion on an outpatient basis. Besides costs, the other benefits of this approach are there is less school absenteeism and parents lose fewer workdays, the threat of acquiring nosocomial infections is substantially eliminated, and both parents and children are happy to be with other children and parents who share the same problems. There are at present more than 25 outdoor transfusion centers all over the country. Blood bank support is crucial to sustain this programme and with the support of non-governmental organizations, it has been possible to organize blood donation camps to sustain this transfusion programme.

##### **Transfusion practices**

Hypertransfusion therapy with an aim to maintain hemoglobin  $>12$  g/dL is the most accepted practice for thalassemic children today. Group and type specific, triple saline washed or filtered (leucodepleted) packed red cells with a hematocrit of 65 to 75% should be

used. Ideally, thalassemic children should receive completely matched red cells and hence, it is important to know the complete genotype of red cells in the patients. This would prevent red cell alloimmunisation following repeated transfusion. As this is not possible in our country, ABO and Rh matched red cells are transfused. To avoid hemolytic transfusion reactions, a coomb's cross-match during each transfusion is strongly recommended. Non hemolytic febrile transfusion reactions have been drastically reduced in our institution from 15.2% to 2.3% by using saline washed red cells for transfusion.

#### **Transfusion transmitted infections(1-3)**

The most common infections are Hepatitis B, Hepatitis C, HIV, Malaria, CMV and Yersinia sepsis. Hepatitis B is reported in 5% to 30.6% of multiply transfused individuals, Hepatitis C in 11% to 69% of transfused patients and HIV in 0% to 70 %. Prevention of infection can be possible if the following guidelines are adhered to.

- Stringent donor selection (voluntary donation drives and not replacement donations) and screening of donors' blood for HIV, HbsAg, HCV and malaria.
- Hepatitis B can be prevented by vaccination. All children diagnosed to have thalassemia major/Intermedia should be immunized with double dose intense regimen of 0, 1, 2, & 12 months with a booster dose after 5 years.
- CMV infection risk can be reduced by centrifugation, saline washing and filtration with bedside filters. However, the available filters are very expensive (Rs. 650-1000).

#### **B. Iron chelation**

One of the major problems encountered in

the management of thalassemia major is iron overload. Multiple transfusions, ineffective erythropoiesis and excessive dietary absorption of iron from gut to compensate the large turnover of red cell mass contribute to the iron load.

Desferrioxamine. Though several hundred compounds have been developed and tried, desferrioxamine (DFO) is yet the gold standard therapy. It is the most effective and safe iron chelator. The drug is usually given as a continuous subcutaneous infusion but can be used as an intravenous infusion which may be given through an implanted intravenous devise like Port-a-Cath. Intravenous route is indicated when there are cardiac complications, very high ferritin level, patient awaiting bone marrow transplantation or if there is persistent local reaction at injection site.

The high cost of Desferrioxamine and the need for continuous subcutaneous injection over 6-8 hours, poor compliance, particularly in the adolescent group has prompted the need for another simpler chelator. L1 or Deferiprone is one such chelator.

1,2 Dimethyl, 3-Hydroxy, Pyrid-4-one (L1), (4,9) Deferiprone. It is cheaper and therefore affordable to majority of our patients. As it is an oral drug, compliance has considerably improved. Deferiprone has a better protective effect on myocardial tissue as shown in various studies.

#### **New oral iron chelators**

HBED-HydroxyBenzyl-Ethylenediamine - Diacetic acid(10,11). It is twice as active as desferrioxamine. It is given orally and has unacceptable toxicity. It may be useful in combination therapy with Deferiprone.

Pyridoxal Isonicotinoyl Hydrazones (PIH)(12,13). A number of PIH analogs have

been synthesized and can be administered orally, and can be given alone or along with DFO. Safety evaluation showed no systemic toxicity. However, as these drugs are not patentable, pharmaceutical interest in this drug seems limited at present.

ICL 670(4- [3,5-bis (2-hydroxyphenyl) - 1,2,4-triazol-1-yl] benzoic acid)(14-16). It is a new class of tridentates iron chelator. It is highly selective for iron, rapidly absorbed from G.I. tract. Oral ICL670 is twice as effective as subcutaneous DFO. In animal models, on molar basis, it has shown five times more potency than DFO and ten times more potency than Deferiprone. It is already approved for use in the USA and is likely to be available in our country shortly.

#### **Combination chelator therapy - shuttle hypothesis(17)**

To reduce cost, to improve compliance, to increase efficacy and to reduce the side effects, combination chelator therapy has been tried. Oral Deferiprone 75 mg/kg/day for 4-5 days in a week and DFO 20-40 mg/kg/day subcutaneously for 2 days/wk have been found to be more efficacious than either alone. Combination therapy has been effective with HBED and L1 as well as with ICL 670 and DFO too.

#### **C. Stem cell transplantation**

This is the only curative therapy available today for thalassemia major. The various sources for stem cells include bone marrow, peripheral blood, cord blood and fetal liver. Though expensive, it is cost effective as compared to yearly cost of regular packed red cell transfusions and ideal chelation therapy. Stem cell transplantation costs around Rs 8 to 10 lakhs. For those in Class I (hepatomegaly <2 cm, no fibrosis and regular chelation) the success rate is around 93% and for the rest it is

about 60%.

#### **Future perspectives**

##### **Prevention of thalassemia**

It is distressing to note that only 5-10% of thalassemic children born in India receive optimal treatment due to non-affordability. The cost of treatment of an average weight 4-year-old thalassemic child is around Rs. 100,000 annually. Therefore, the emphasis is a shift from treatment to prevention of birth of such children in future. Prenatal diagnosis can be done by chorionic villous sampling, amniocentesis or cord blood sampling. Newer diagnostic techniques in the horizon include pre-implantation diagnosis by biopsy of blastula or analysis of a single blastomere from an eight cell embryo after *in-vitro* fertilization or pre-conception diagnosis by analysis of the first polar body of an unfertilized egg. However, it is technically demanding, difficult to organize and very expensive.

##### **Gene therapy**

It is aimed at addition of a normal copy of the gene along with key regulatory sequences. This approach, however, has been impeded by difficulty of attaining high-titer vectors for sustained expression. Lentiviral vectors derived from Human Immunodeficiency Virus, where a large fragment of human beta gene and its locus control region, can be introduced has shown definite promise, though yet experimental. Hopefully, more effective therapies will become available in near future to cure the disease

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