Editorial

Advances in Management of Thalassemia

Thalassemias represent the most common single-gene disorder causing a major public health problem in India. Over the last 3 decades, the development of regular transfusion therapy and iron chelation has dramatically improved the quality of life and transformed thalassemia from a rapidly fatal disease to a chronic disease compatible with prolonged survival. Today, in the developed world, the life expectancy of patients with thalassemia varies between 25 and 55 years, mainly depending on compliance with medical treatment(1).

However, these conventional modalities are expensive, time consuming and inconvenient. In developing world, especially India, poor availability of proper medical care, safe and adequate red blood cell transfusions together with high cost and poor compliance with chelation therapy remain major obstacles. Despite the increased life expectancy of thalassemia, complications keep arising. These relate to inadequate transfusions, transfusion transmitted viral diseases, allo-sensitization, iron overload related endocrine, liver and cardiac disturbances as well as toxicities of iron chelators. These make conventional treatment of thalassemia a difficult and often fatal therapy(1).

Vaccination is an effective tool to prevent hepatitis-B. Effective screening has reduced HIV and HCV infections. However, all of these still remain significant problems in Indian subcontinent. Treatment of HIV infection with HAART therapy and hepatitis-B and hepatitis-C infection with pegylated interferon, lamivudine (for hep-B) and ribavarin (for hep-C) are important advances. Cost, however, remains prohibitive(1).

Endocrinopathies secondary to iron overload include hypogonadism, hypothyroidism, diabetes mellitus and hypoparathyroidism. Most of these occur towards the end of second decade of life. These often require lifelong replacement therapy(2). Iron related cardiac disorders include rhythm disturbances and cardiac failure. These form the chief modality of death in young adults with thalassemia major. They need inotropic and anti-arrhythmic medications(3,4). Hepatic iron concentration (HIC) greater than 15 mg/g dry weight is a risk factor for cardiac disease. However, the exact relationship between HIC and heart disease is ill-understood. Iron related hepatic cirrhosis and fibrosis are also important issues(1).

Effective management of iron overload requires frequent evaluation of the body iron stores(5). There is, therefore, a need for quantitative, non-invasive methods for measuring body iron that are safe, accurate and readily available. Serum ferritin measurement, although easy to perform frequently, has too great a variability, still at present, no other serum test is a better predictor. Direct assessment of hepatic iron content (HIC) by liver biopsy is the best predictor of the total body iron, but the procedure is invasive, risky and difficult to perform repeatedly. At present, Super-conducting Quantum Interference Device Biomagnetic Liver Susceptometry (SQUID-BLS) provides the most accurate and best-validated non-invasive method for measuring liver iron, however, its

clinical availability is restricted, and its use is limited to the liver and spleen(6). The development of high-transition temperature ferritometers may improve clinical access in the future.

Magnetic resonance imaging (MRI) is a widely available test, and in principle allows the evaluation of iron overload in all organs that may be affected by iron overload. Studies are, however, needed to compare the precision and repeatability of the MRI-derived HIC estimates, obtained by measuring T2*, R2 or the liver-to-reference SIR(7,8).

Cardiac iron overload cannot be accurately and easily assessed by repeated endomyocardial biopsies owing to the heterogeneity of iron distribution and the risk of complications. Once again, one can utilize the non-invasive method of MRI based relaxation parameters T2 and T2*. Low T2* suggests high myocardial iron content and it is associated with poor ventricular function, myocardial arrhythmias and need for cardiac medication. These can be used for repeated estimations. These results are in the process of being validated(7,8)

Desferrioxamine (DFO) and the orally effective deferiprone (DFP), either alone or together, are effective tools for iron chelation. DFO-related problems include poor compliance and local reactions at the site of injection. On the other side, DFP remains a less effective chelator and it has the problems of marrow toxicity, arthritis, GI intolerance, zinc deficiency and the controversial hepatic fibrosis(9). Recent data has favored DFP as a more powerful iron chelator for the cardiac iron overload. The two together probably form the best modality of iron chelation. The combination fulfils the shuttle hypothesis, according to which, DFP mobilizes iron from the stores while DFO puts it out of the body. ICL 670 is the new oral iron chelator with better efficacy and lack of side-effects. This should make the future of conventional therapy of thalassemia, relatively more comfortable(10).

Implantable central vascular access devices (CVAD) are becoming common. They are useful both for red blood cell transfusions as well as intravenous DFO infusion. These, however, can lead to infections including staphylococcal bacteremia which can be fatal(1).

Overall, the standards of conventional treatment for thalassemia patients have improved, resulting in almost doubling of the average life expectancy. As a consequence, however, additional previously undescribed complications are now been recognised. Prothrombotic haemostatic abnormalities leading to a chronic hypercoagulable state have been noted. These lead to frequent occurrence of thromboembolic complications. Increased arterial stiffness secondary to iron induced lipid peroxidation and development of atherogenesis-related pathologies have been noted(11).

Osteopenia and osteoporosis have been noted in aging population of thalassemia major. There is serious loss of bone mineral density (BMD). This loss of BMD is of multifactorial origin, however, increased osteoclast activity plays the most important role. Osteoprotegrin (OPG) levels are low while the levels of soluble receptor activator of nuclear factor-kappa B legend (sRANKL) have varied. Disturbed bone remodeling results from concerted hormonal changes such as growth hormone, insulin-like growth factor I and sex hormones. Administration of pamidronate has shown a significant increase in BMD of the lumber spine and it is now recommended that pamidronate at a monthly

dose of 30 mg is an effective treatment for thalassemic osteoporosis(12).

Hepatocellular carcinoma (HCC) can complicate liver cirrhosis secondary both to iron overload and viral infections. Italians have published 22 cases of HCC in thalassemia major, 15 of them were males and the mean age of diagnosis was 45 ± 11 years(13). Eighty-six percent were infected by hepatitis-C virus and majority were diagnosed after 1993, suggesting that the problem is becoming more frequent with the aging population of thalassemia patients(13).

Since 1982, hematopoietic stem cell transplantation (HSCT) has become an alternative modality of treatment(14). It is the only available procedure that may lead to cure. HSCT program for beta thalassemia major is now well established in India chiefly at CMC, Vellore. The advantages of a life, free from disease and free from daily, tedious and uncomfortable therapy, are far too many. However, there is a real risk of dying which is related to patient's age, iron overload and liver viral infections. Adults have a worse outcome than children; among children, three classes of risk have been identified on the basis of regularity of previous iron chelation, liver enlargement and presence of portal fibrosis. The results of HSCT from HLA identical related donor are clear. Class 1 patients have a high probability of cure with very low, early or late morbidity and mortality. The delay in transplantation allows patients to move to a risk category beyond class 1 and this substantially reduces the probability of success. If a donor is available, there is no reason for denying these patients the chance of cure(14).

Although, majority of HSCT have been from HLA-identical related donor, the same from an unrelated volunteer, carefully selected by high-resolution HLA-typing, is an alternative for those lacking a compatible family donor. The results obtained using such donors are comparable with those obtained employing an HLA-identical sibling(14).

Recently, it has also been demonstrated that cord-blood is as effective as, and possibly safer than, bone marrow for transplantation in pediatric patients. It is also possible that, in near future, thalassemic adults with poor organ function may tolerate and benefit from transplantation employing non-myeloablative, less toxic, conditioning regimens which induce mixed chimerism. This may make an allogeneic HSCT safer for adults as well as heavily iron-overloaded subjects(14).

Unfortunately, HSCT for thalassemia has remained a subject of vigorous debate. However, it is not a life-saving procedure. It is an elective option and has significant morbidity and mortality. The ethical aspects remain debatable, especially as the conventional management of thalassemia keeps improving. Also, there are hopes for the corrective gene therapy(14).

After successful HSCT, iron overload still remains an important cause of morbidity. Regular two weekly phlebotomy programme is a safe, efficient and easily applicable to the ex-thalassemics(14).

Gene therapy is an exciting prospect, although, there are still formidable obstacles to be overcome before it is likely to become feasible for the thalassemics. The efficient gene transfer, especially of a large gene segment like the *b*-globin gene and its regulators, into hematopoietic stem cells, and sustained gene expression, have not yet been achieved. Therefore, gene therapy must await further research(14).

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REFERENCES

1. Cunningham MJ, Macklin EA, Newfeld EJ, Cohen AR. Complications of ß-thalassemia major in North America. Blood 2004; 104:34-39.
2. De SV. Growth and puberty and its management in thalassemia. Horm Res 2002; 58 Suppl 1: 72-79.
3. Hui L, Leung MP, Ha SY, Chau AKT, Cheung YF. Early detection of left ventricular dysfunction in patients with beta thal major by dobutamine stress echocardiography. Heart 2003; 89: 669-670.
4. Westwood M, Anderson LJ, Pennell DJ. Treatment of cardiac iron overload in thalassemia major (Ed). Hematologica 2003; 88: 481-482.
5. Jensen PD. Evaluation of iron overload. Br J Haematol 2004; 124: 697-711.
6. Fischer R, Longo F, Nielsen P, Engelhardt R, Hider RC, Piga A. Monitoring long-term efficacy of iron chelation therapy by deferiprone and desferrioxamine in patients with beta thalassemia major: Application of SQUID biomagnetic liver susceptometry. Br J Hematol 2003; 121: 938-948.
7. Anderson LJ, Davis HB, Prescott E, Charrier CC, Bunce NH, Firmin DN, *et al*. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001; 22: 2171-2179.
8. Jensen PD, Jansen FT, Christensen T, Eiskjaer H, Baandrup U, Nielsen JL. Evaluation of myocardial iron by magnetic resonance imaging during iron chelation therapy with desferrioxamine indication of close relation between myocardial iron content and chelation iron pool. Blood 2003; 101: 4632-4639.
9. Wanless IR, Sweeney G, Dhillon AP, Guido M, Piga A, Galanello R, Gamberini MR, *et al*. Lack of progressive hepatic fibrosis during long-term therapy with deferiprone in subjects with transfusion-dependent beta-thalassemia. Blood 2002; 100: 1566-1569.
10. Agarwal MB. ICL 670 : A new oral chelator : A major breakthrough in treatment of thalassemia. Ind J Hematol Bl Trans 2003, 31: 26-28.
11. Cheung YF, Chan GCF, Ha SY. Arterial stiffness and endothelial function in patients with beta-thalassemia major. Circulation 2002; 106: 2561-2566.
12. Voskardou E, Terpos E, Spina G, Palermos J, Rahemtulla A, Loutradi A, *et al*. Pamidronate is an effective treatment for osteoporosis in patients with ß-thalassemia. Br J Hematol 2003;123: 730-737.
13. Borgna-Pignatti C, Vergine G, Lombardo T, *et al*. Hepatocellular carcinoma in the thal syndromes. Br J Haematol 2004; 124:114-117
14. Erer B, Lucarelli G. Bone marrow transplantation in thalassemia. Turk J Hematol 1999; 16: 147-159.