EDITORIAL

Beta-Thalassemia Major in Malaysia, an On-Going Public Health Problem

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Thalassemias are a heterogeneous group of disorders of hemoglobin synthesis which are characterized by the absence or reduced output of one or more globin chains of hemoglobin. This disease is a public health problem in Malaysia and can be confusing for the patients and the doctors as the picture varies from one patient to another. About 4.5% of the people in Malaysia are heterozygous carriers for beta-thalassemia and the couples are at risk of producing a child with beta-thalassemia major where affected births annually would be 2.1/1,000. During the last ten years, the spectrum of molecular defects and the clinical severity of the mutations that cause thalassemia have been identified. This information has resulted in improved patient management. The most common beta-thalassemia mutations are IVS 1-5 (G to C) and CD 41-42 (-TCTT) in the Malays and Chinese respectively.

Management of Beta-Thalassemia Major

Beta-thalassemia major is the most severe form of beta-thalassemia and results from the inheritance of the homozygous state for the phenotype β^0 (β^0/β^0). Patients present at age one and two years of life and are transfusion dependent for life. The aim of transfusion is to keep the mean hemoglobin level > 10gm/dl so as to suppress the ineffective erythropoiesis which is the basis for the clinical features of this disease. Iron derived from the transfused red blood cells and from increased gut absorption of iron accumulates with iron mediated damage to the heart, liver, and endocrine organs. The excess of iron needs to eliminated by iron chelation. Properly managed patients have life expectancies that extend to the third decade.

In Malaysia, the management of patients with transfusion dependent thalassemias constitutes a heavy burden for health authorities. Less than 20% of patients receive adequate iron chelation therapy and the majority are destined to die in the second or third decade of life from complications of multiple organ failure secondary to iron overload. Iron chelation therapy is currently available in two forms, desferrioxamine given via subcutaneous route at a dose of 35 - 40mg/kg costing RM 12 - 17 a vial of 500mg, and deferiprone (L1) an oral chelator which has yet to be registered for use in Malaysia. Desferrioxamine if started too early may result in growth retardation and toxicity increases when serum ferritin levels fall below 1000ug/L. Desferrioxamine is commonly commenced when the serum ferritin reaches 1000ug/L or when the child has reached 3 years of age or has had about 20 transfusions. L1 the oral chelator of iron, is a cheaper drug when compared to desferrioxamine and has been used as an alternative drug in those who are allergic to desferrioxamine or cannot afford desferrioxamine. A proportion of patients on L1 may develop agranulocytosis with an increased risk to overwhelming infection, arthritis, zinc deficiency and fluctuation of liver transaminases. Some studies indicate it may not remove iron adequately from the liver and

current concerns are that it may not provide adequate sustained control of body iron in a substantial proportion of patients with beta-thalassemia major. Trials are on going with L1 in many countries including Malaysia. Only after these trials are complete will it be possible to say with certainty whether L1 is going to be a useful long term alternative to standard desferrioxamine as a single agent or when used in combination with desferrioxamine.

Liver iron is the most reliable predictor of complications from iron overload where serum ferritin levels may not be clinically reliable in the presence of infection and inflammation. Liver iron studies necessitates serial liver biopsies for monitoring iron overload. A new technique which encompasses magnetic resonance imaging (MRI), which is non-invasive has been found to be comparable to liver iron as a tool for monitoring iron status.

Regular maintenance blood transfusions which is the main stay of therapy for transfusion dependent thalassemia patients exposes them to transfusion related viruses and immunomodulation. Donated blood in Malaysia are screened for HBV, HCV, HIV and syphilis. Nucleic amplification testing (NAT) which has improved sensitivity has been performed on virtually all blood collected in the United States since early 1999. The testing focused on HIV-1, and HCV. In Malaysia it has not been introduced on routine basis. Immunization to HBV is provided at the time of diagnosis before the first transfusion to all patients with beta-thalassemia major.

Stem cells sourced from bone marrow, peripheral and cord blood for transplantation offers a permanent cure. Recent studies of experiences with bone marrow transplantation (BMT) in class 1 indicate 90% relapse-free survival between 1.5 and 9 years after transplantation. Bone marrow transplantation has a higher risk as the patient gets older where the risks identified are poor quality previous iron chelation, enlarged liver, exposure to transmitted viruses and portal fibrosis. However 70% may not have matching siblings for bone marrow transplantation (BMT) and cord blood as source for stem cells has potential when transplantation is the modality of treatment. A landmark case was the first cord transplantation done in a 5 year old Malaysian-Chinese boy with thalassemia major in August 2001. In Malaysia, three medical centers (two public and one private) offer bone marrow and peripheral blood stem cell transplantation but the priority at these centers remain for malignant disorders and for aplastic anemia rather than for thalassemia where the waiting list is long. BMT results in cure and is likely to restore life expectancy to normal. This suggests that BMT should be offered to all thalassemia major patients, even when optimal medical care is available. It is, nevertheless, essential that the risks and disadvantages are explained to all families considering this option. Uncertainty over fertility remains and children even in class 1 may experience severe chronic graft versus host disease (GVHD) or fatal transplant-related complications. For the children in class III who are known to have poor prognosis with medical treatment, should be identified promptly and transplanted early before major organ damage occurs.

Transplantation of stem cells from umbilical cord blood (UCB) has several theoretical advantages as an available suitable cord blood collection many allow the transplantation to be carried out 1-2 years early and spares the donor the discomfort and risks of bone marrow donation. Studies indicate that the incidence of GVHD was low however recurrent disease was the primary reason for failure, suggesting that the best strategy for improving outcome is to modify the immunosuppression before and after the UCB transplantation to overcome immunologic rejection by host cells.

In this issue of the journal, Chan LL, Lin HP, Ariffin WA, and Ariffin H report their experience with stem cell transplantation (SCT)

in beta-thalassemia major patients where they had 76% cure rate, and their success will hopefully lead to SCT being offered as first line therapy to all patients when a matched donor is available in Malaysia.

Prevention of Beta-Thalassemia

Carriers are reliably detected by a screen that includes measurement of the red cell indices generated by automated blood counter (a mean cell volume < 80 fl, and an mean cell hemoglobin, MCH < 27 pg may be indicative of thalassemia), accurate quantitation of Hb A_2 by automated chromatography (Hb A_2 levels by HPLC >4.0% indicative of beta-thalassemia), automated hemoglobin electrophoresis for abnormal hemoglobins, and followed by definite diagnosis tests (DNA).

Each ethnic group has 4 - 5 common mutations that form more 95 % of the mutations seen. A number of DNA techniques incorporating polymerase chain reaction (PCR) are currently available for DNA characterization. In Malaysia the amplification refractory mutation system (ARMS) and the reverse dot blot hybrization (RDBH) are the techniques used. With these techniques about 90% of the mutations will be identified with the unknowns being further investigated by sequencing. There are on going research studies using micro array DNA analysis to investigate multiple of mutations in one go. This latter technique will be useful in ethnic groups with many possible mutation interactions as this will screen for the mutation easily and will not require preparations of agarose for runs. The main problem will be the necessary equipment and reagents, which would be more costly than the ARMS and RDBH.

Malaysia has yet to establish a nationally endorsed program for population screening for thalassaemia. Currently a pilot project is on going for the screening for thalassemia in pregnant females in Kota Bahru at first antenatal care visit When a carrier is identified her partner will be offered testing. This retrospective screen for thalassemia will not prevent the births of beta-thalassemia major. It is possible to support primary care screening with information materials made available, education and dissemination of information. A control programme for thalassemia depends upon adequate education of public and health professionals. It has been suggested that approximately 10% of the budget of the control program should be set aside for providing educational materials and professional training. Primary care teams have counselling skills but most lack precise genetic information needed for basic counselling. Prenatal diagnosis for thalassemia was introduced in Malaysia in 1994 as a routine technique in the two centers in Malaysia, with first trimester diagnosis at 10-16 weeks gestation following chorionic villus sampling and fetal blood sampling at 18-23 weeks. Expertise with chorionic villus sampling is not as widely available as fetal blood sampling as a source for fetal DNA studies. Majority of those who seek prenatal diagnosis have been Chinese. Abortion is illegal in Malaysia, and there a need to discuss the social and religious implications of prenatal diagnosis. Analysis of data where all at-risk couples learn of their risk prior to marriage gives an insight into their choices. Less than 4% of the almost 100% fall in beta-thalassemia major birth prevalence in Cyprus is due to avoidance of at-risk marriages. Seventy six (76%) is due to use of prenatal diagnosis, and 20% due to at-risk couples limiting their final family size.

Recommendations and future prospects. The dilemma of selecting the best treatment for patients with thalassemia in Malaysia remains a difficult one for the attending physician where constraints are the exorbitant costs of iron chelation therapy, exposure to transfusion related viruses and limitations of available stem cell transplantation. As the magnitude of beta-thalassemia major as a public health problem is related to the prevalence of the heterozygotes, there is an urgent need in Malaysia for a concerted effort to screen for thalassemia, so that at risk couples can be identified and

informed prospectively before they have affected children. In parallel, we need to make available iron chelation therapy to every patient with beta-thalassemia major to treat the inexorable accumulation of tissue iron that results with blood transfusions. The possibility of cure for beta-thalassemia major patients with stem cell transplantation makes this an attractive first line of therapy when a matched sibling donor is available.

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