Quality of life and survival of patients with β-thalassemia major

Up to the early sixties, patients affected by thalassemia major received blood transfusions only when they became symptomatic, with hemoglobin levels as low as 3g/dL. Their life span was very short; indeed, the vast majority of patients died very early in life of anemia or of infectious complications. Though aware of the risk of having other affected children, the parents continued to reproduce until the desired family was complete, usually with the birth of two normal children. The clinical management of thalassemia major changed radically when a regular transfusion program was introduced by Irvin Wolman in 1964[1] and later in 1969 by Sergio Piomelli.[2] Further progress was made with the regular use of intramuscular desferrioxamine (DF) with the purpose of removing the excess iron that accumulated as a result of blood transfusions.[3] Nevertheless, the target iron balance was only reached with continuous DF infusion, initially by the intravenous route[4] and subsequently subcutaneously.[5-6]

Regular blood transfusion in combination with iron chelation using subcutaneous DF infusion remarkably extended survival.[7-9] For instance, according to Zurlo *et al.*[8] the overall survival from birth of patients born in 1970-74 was 97.4% at 10 years and 94.4% at 15 years. In this issue of the journal, Caterina Borgna Pignatti and co-workers[10] report up-to-date results on survival and the causes of death in a large population of 977 Italian patients with thalassemia major born since 1960, on the whole confirming and extending previous findings. It is certainly gratifying to all workers in this field that 68% of the patients are alive at the age of 35. Of course survival is certainly better for those born more recently, most likely because of an improved compliance with DF treatment, as a longer survival has been shown in patients with a lower serum ferritin concentration. For some unknown reason females showed better survival rates than males, but certainly not because of better compliance, as can be seen from their ferritin levels, which were not significantly lower than in males. It is both interesting and useful to note that, although from recent studies serum ferritin would appear to be an imprecise parameter for evaluating the extent of iron overload, in this paper the level of serum ferritin was predictive both of the development of heart failure and of the length of survival. Besides living longer, we know that the large majority of thalassemic patients in the developed world are living better, their quality of life having improved dramatically. Many are in a good condition, lead a relatively normal life, and have obtained jobs that are appropriate to their academic achievements. Moreover, at least some of those women who have had regular transfusion and chelation therapy have succeeded in becoming pregnant either spontaneously or with the use of assisted reproductive technologies.

The most frequent causes of death are still heart failure and/or cardiac arrhythmia, which are mostly caused by myocardial iron overload. The second cause is intercurrent infections. However, Borgna-Pignatti's paper does not describe the type of infection. Most likely the most prevalent were overwhelming infections by encapsulated bacteria due to splenectomy, and *Yersinia enterocolitis* septicemia related to DF treatment. The rate of HIV infection is declining and will certainly disappear almost completely in the near future, because of accurate blood screening for the HIV. Thrombotic events are emerging as an important complication and relatively frequent cause of death. However, though with reduced frequency, in relation to the extent of iron overload, many patients still have cardiac disease and delayed pubertal development, and develop hypogonadism, hypothyroidism, hypoparathyroidism, and diabetes mellitus. Liver disease is a rare cause of death. Although not discussed in Borgna-Pignatti paper, the main causes of liver complications are chronic hepatitis C and iron overload.

The liver disease that develops in patients with thalassemia major is the topic of a second paper published in this issue of Haematologica by Prati[11] and co-workers for the Cooley Care Cooperative Group. In the large majority of the cases, the findings reconfirm the presence of a mild process of necrosis and inflammation, which essentially appear to be related to HCV infection. According to the authors, fibrosis seems to have a number of causes, including HCV infection and liver iron accumulation. They found, however, that the progression of fibrosis was strongly affected by the extent of iron overload. This is in partial contrast with other studies that observed that the development of fibrosis is markedly related and exacerbated by chronic hepatitis C.[12-14] The most important new result of this paper, however, concerns liver pathology in HCV negative patients, in whom a striking finding was the paucity of inflammation, which is certainly an indication against a role for putative blood-transmitted non-A non-B non-C hepatitis viruses in the development of liver disease. An unexpected result is the presence of marked iron accumulation in hepatocytes, which moreover show a lobular pattern typical of that found in hereditary hemochromatosis and anemias associated with ineffective erythropoiesis, and therefore indicative of iron hyperabsorption. According to the authors, this postu-

lated hyperabsorption may be secondary to the resurgence in thalassemia major of ineffective erythropoiesis secondary to the lower level of pretransfusional hemoglobin accepted with the current transfusional regimen. This provocative explanation should be demonstrated by evaluating the serum transferrin receptor and serum erythropoietin levels,[15] the percentage of peripheral erythroblasts, and the level of HbF.

A future perspective in the traditional management of thalassemia major is obviously the introduction of new types of iron chelation therapy that are more efficient and more acceptable to patients. Promising results are expected from the use of the combination of deferiprone and Desferal,[16] which appear to have a synergistic effect and possibly a better activity on removal of iron from the heart (related to deferiprone),[17] as well as the development of new iron chelators, some of which (ICL 670 and GT56-252) seem to have interesting properties and activities.[18-19]

The progress achieved in the clinical management of patients affected with thalassemia major should also be considered in the context of the development of methodologies for embryo or fetal diagnosis.[20] Following accurate genetic counseling, families at risk may have the option to plan their family, with antenatal diagnosis and, if they wish, interruption of the pregnancies of affected fetuses.[20] The introduction of HLA typing of fetuses, together with molecular analysis of the β-globin gene, has led to the identification of HLA compatibility between an affected fetus and a previous normal child, who may act as a donor of bone marrow stem cells.[21] A subsequent normal child may be a suitable donor of cord blood stem cells. Alternatively following counseling the couples at risk may opt for preconceptional or preimplantation diagnosis.[22]

Data on the survival of patients and on quality of life are very useful in the genetic counseling of couples at risk of having β-thalassemic offspring when planning a pregnancy, and in the discussion, with the parents of an affected child, on the available options for treatment of a newly diagnosed case. In both conditions the pros and cons of traditional treatment should be evaluated *vis-à-vis* the results of bone marrow or cord blood stem cell transplantation. In this counseling, it should be pointed out that the only treatment that may led to a definitive cure in thalassemia major is stem cell transplantation which, even in the best conditions, is still associated with a mortality of 5% when performed from an HLA identical family donor. Furthermore the follow-up of these patients following bone marrow transplantation shows impaired growth (at least in those transplanted after 7 years old), gonadal failure, and chronic graft-versus-host disease (in approximately 10% of the cases).[23] Optimizing the procedure for stem cell transplantation from HLA identical non-related donors, and the procedure for inducing a state mixed chimerism by non-myeloablative or reduced intensity conditioning regimens may result in progress in this field in the future. A great challenge for a family with affected children, which is nevertheless creating an enormous ethical dilemma, is preimplantation diagnosis associated with the selection of unaffected embryos HLA compatible with a previous affected child that may be a source of cord blood or bone marrow stem cells for curing the affected child.[22,24-25]

The great hope in the early 1980s of a rapid development of gene therapy was followed by profound disappointment. However, recent results on a β-thalassemia mouse model with a lentiviral virus vector are encouraging.[26]

This is the scenario of the present management of β-thalassemia in the developed world. We that live in this privileged world do, however, have a moral obligation to do everything possible to improve the disastrous management conditions of thalassemia major in the developing world, where the disease is highly prevalent and the resources and present organization preclude any chance of introducing modern clinical management. In this context it is extremely urgent that international health agencies, together with the governments of developed countries, should start to collaborate constructively with the governments of developing countries to begin organizing the most basic management in this field.

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Serum erythropoietin concentration as a diagnostic tool for polycythemia vera

Polycythemia vera (PV) is a chronic myeloproliferative disorder (CMD) with an incidence of about 10 cases per million population per year. Although its clinical course is indolent, PV has an impact on survival, the life expectancy of these patients (especially if younger than 50 years) being shorter thatn that of general population.[1,2]

Table 1. WHO criteria for polycythemia vera (PV)[5].

A criteria
A1. Elevated red blood cell mass (>25% more than mean normal predicted value) or Hb >18.5 g/dL in men, >16.5 g/dL in women*
A2. No cause of secondary erythrocytosis, including: absence of familial erythrocytosis; no elevation of erythropoietin (Epo) due to: hypoxia (arterial pO_2 ≤92%), high oxygen affinity hemoglobin, truncated Epo receptor, inappropriate Epo production by tumor
A3. Splenomegaly
A4. Clonal genetic abnormality other than Ph-chromosome or *BCR/ABL* fusion gene in marrow cells
A5. Endogenous erythroid colony formation *in vitro*.
B criteria
B1. Thrombocytosis >400×10^9/L
B2. WBC >12×10^9/L
B3. Bone marrow biopsy showing panmyelosis with prominent erythroid and megakaryocytic proliferation
B4. Low serum erythropoietin levels
Diagnostic use of A and B criteria
Polycythemia vera can be diagnosed when: • A1 + A2 and any other category A criterion is present. • A1 + A2 and any two of category B criteria are present.

**Or >99th percentile of method-specific reference range for age, sex and altitude of residence.*

Unlike chronic myeloid leukemia, PV lacks a molecular marker so far. In the last few years, there has been considerable interest in the overexpression of neutrophil *PRV-1* mRNA as a specific molecular marker of PV. *PRV-1* and *NB1* are alleles of the polymorphic gene *CD177*, which belongs to the Ly-6/uPAR superfamily, and their coding regions differ at only 4 nucleotides. We have recently shown that an elevated neutrophil *CD177* mRNA level is not a specific marker for the diagnosis of either PV or CMD.[3] From a clinical viewpoint, neutrophil *CD177* mRNA overexpression is rather a marker of abnormal neutrophil production and/or release in patients with CMD. Acquired uniparental disomy resulting in loss of heterozygosity of chromosome 9p represents the most frequent chromosomal aberration in PV, but is found in only one third of patients.[4]

The diagnosis of PV is still based on combinations of clinical and laboratory parameters: Table 1 reports the WHO criteria.[5] Serum erythropoietin is considered a B category criterion, i.e., a minor criterion. However, the role of serum erythropoietin appears to be equivocal in this classification, since criterion A2 includes: *no elevation of erythropoietin (Epo) due to hypoxia (arterial pO_2 ≤92%), high oxygen affinity hemoglobin, truncated Epo receptor or inappropriate Epo production by tumor.* While arterial pO_2 can be easily assessed, the only simple way of recognizing increased erythropoietin pro-