

# **BONE MARROW TRANSPLANTATION IN THALASSEMIA—THE EXPERIENCE OF PESARO, ITALY**

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## **Thalassemia Major**

Beta homozygous thalassemia, or thalassemia major, is a genetic disease. Defective synthesis of the beta-chains of adult hemoglobin A leads to an imbalance of beta-chain production and the accumulation of free alpha-chains in red cell precursors and in red blood cells. This in turn causes intramedullary destruction of red cell precursors and marked ineffective erythropoiesis, which results in severe hemolytic anemia. Infants with thalassemia major who receive no treatment will die in early infancy from complications of severe anemia.

Red cell transfusion therapy will reduce mortality derived directly from anemia, but patients will develop complications due to severe organ iron overload. Because of this, attempts have been made to enhance iron mobilization and excretion with the use of an iron chelating agent such as desferrioxamine. This treatment, when rigorously adhered to, substantially reduces, but does not eliminate, the iron overload for patients on hypertransfusion therapy. The development of a regimen of hypertransfusion combined with regular iron chelation has transformed the prognosis of thalassemic children. If good compliance is obtained, patients no longer die from anemia.<sup>(7)</sup>

Children with thalassemia are sick mainly because of complications arising from the unavoidable organ iron overload, even if reduced by the adequate chelation treatment, from the hepatitis due to viral blood-borne infections, or from a combination of liver iron overload and hepatitis. Because of these complications, thalassemia major is a progressive, eventually fatal disease.

## **Bone Marrow Transplantation**

In December 1981, a one-year-old untransfused thalassemic patient was transplanted in Seattle from his HLA-identical sister. After more than 14 years<sup>(1)</sup> he is alive and well; he is the first ex-thalassemic after bone marrow transplantation.<sup>(8)</sup> At the same time, a 14-year-old thalassemic patient who had received 150 red cell transfusions was transplanted in Pesaro, but he had recurrence of thalassemia and returned to the pre-transplant condition.<sup>(3)</sup>

As of February 29, 1996, we had performed a series of 781 bone marrow transplantations in thalassemic patients aged 1 through 35 years: 756 from HLA-identical donors (22 parents and 734 siblings) and 25 from HLA partially matched donors. Overall results are reported in Figure 1.

In March 1989, statistical analyses were performed on a group of 222 patients aged 1 through 15 years who were treated in our Center with the same preparative regimen that had been adopted in June 1985.<sup>(4)</sup> The analysis of potential risk factors for the outcome of transplantation indicated that the poor quality of previous iron chelation therapy, marked hepatomegaly and portal fibrosis were factors associated with a reduced

probability of survival or disease-free survival. Using these factors as criteria, we were able to categorize patients into three classes of risk for the outcome of marrow transplantation. Patients with none of these risk factors were categorized as Class 1, patients with all three factors were categorized as Class 3 and all other patients were Class 2. All had been treated with a regimen that included busulfan, 14 mg/kg, and cyclophosphamide, 200 mg/kg, and cyclosporine alone. Results of the transplant, analyzed in March 1989, were good for both Class 1 and for Class 2,

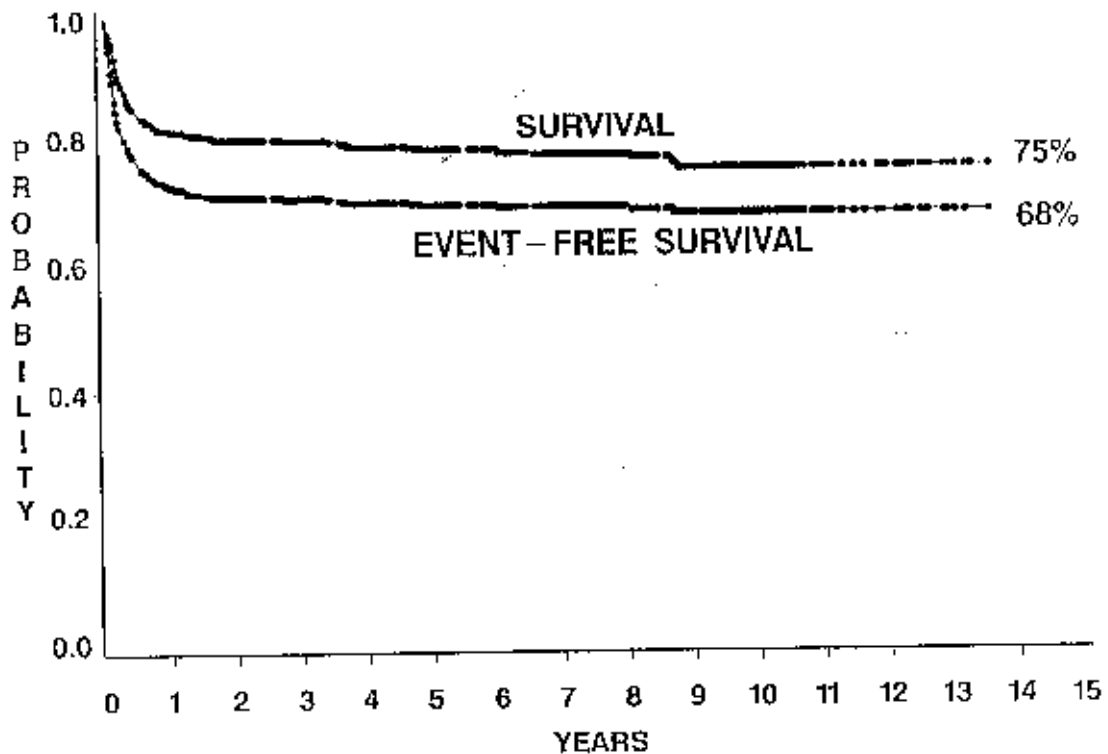
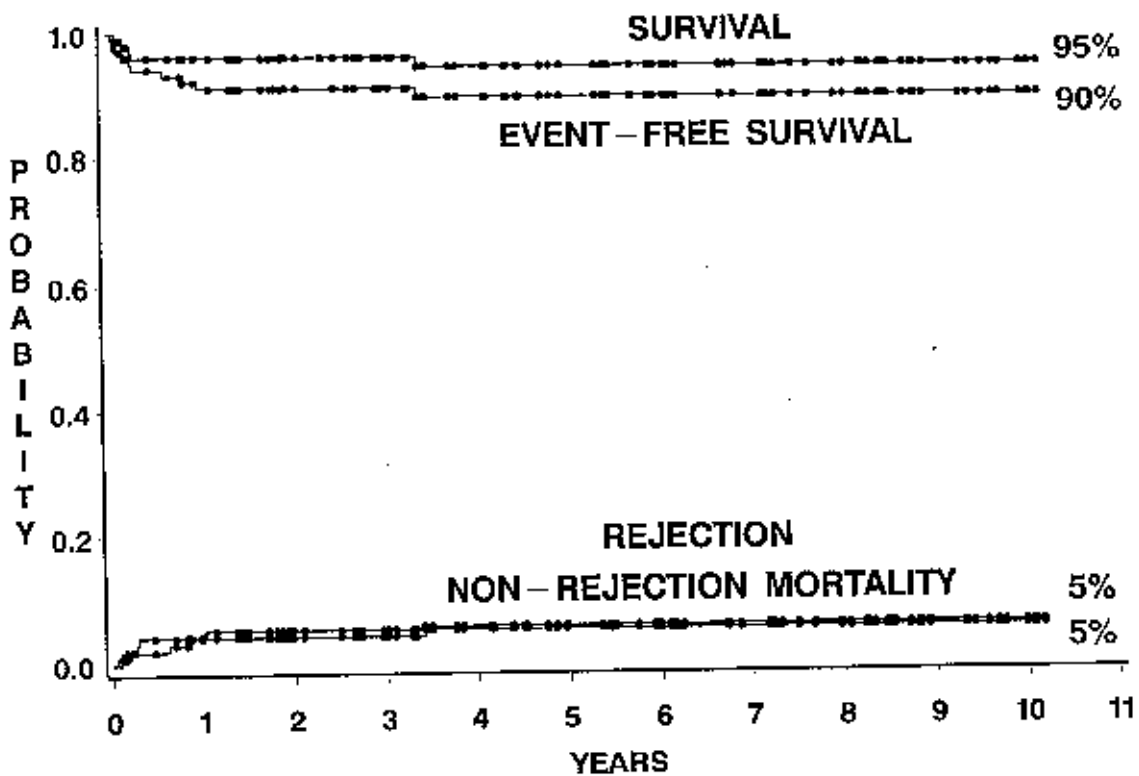


Fig. 1

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**Figure 1.** Kaplan-Meier probabilities of survival, event-free survival, rejection and non-rejection mortality for 781 thalassemic patients, age 1 through 38 years, transplanted in Pesaro from December 17, 1981, through February 29, 1996. (24 from partially HLA-matched family donors, one from HLA identical unrelated donor, 22 from HLA-identical parents and 734 from HLA-identical family members; all protocols used.)



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**Figure 2.** Kaplan-Meier probabilities of survival, event-free survival, rejection and non-rejection mortality for 104 Class 1 thalassemic patients aged less than 17 years, transplanted from HLA-identical donors (99 from sibling and 5 from parent) after preparation with busulfan 14 mg/kg, cyclophosphamide 200 mg/kg and cyclosporine alone from January 2, 1986, through February 1, 1996.

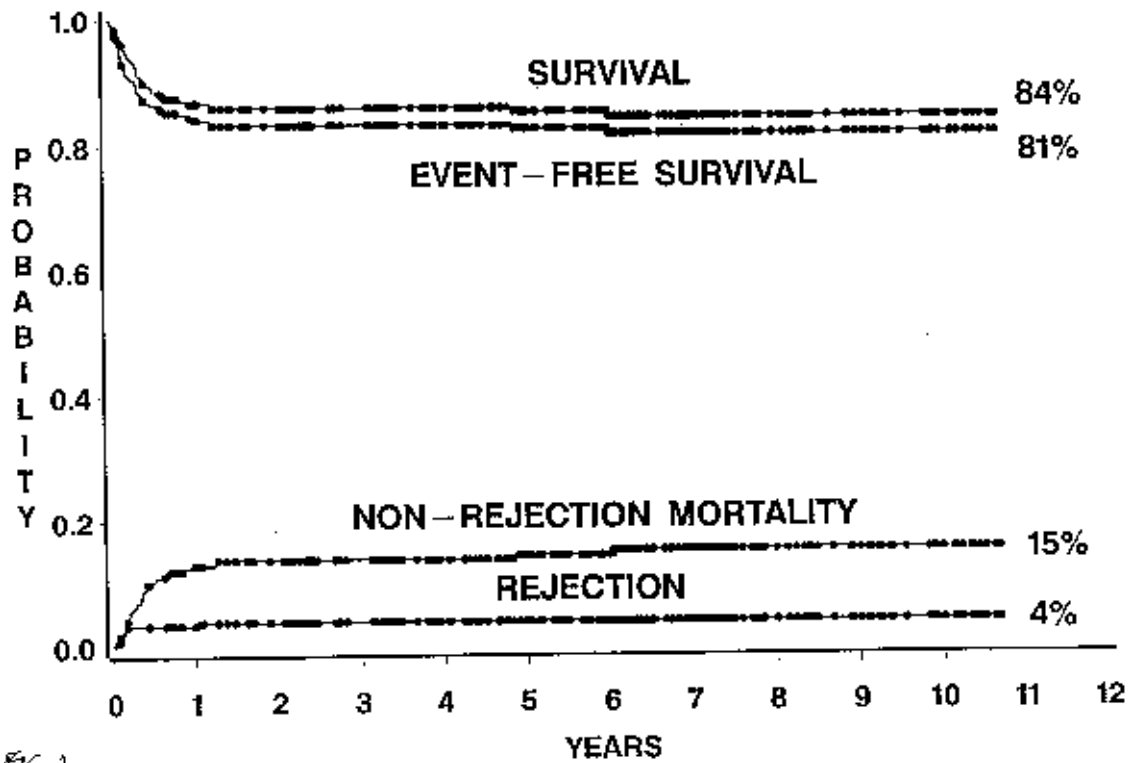


FIG. 2  
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**Figure 3.** Kaplan-Meier probabilities of survival, event-free survival, rejection and non-rejection mortality for 262 Class 2 thalassemic patients aged less than 17 years, transplanted from HLA-identical donors (258 from sibling and 4 from parent) after preparation with busulfan 14 mg/kg, cyclophosphamide 200 mg/kg and cyclosporine alone from June 6, 1985, through February 8, 1996.

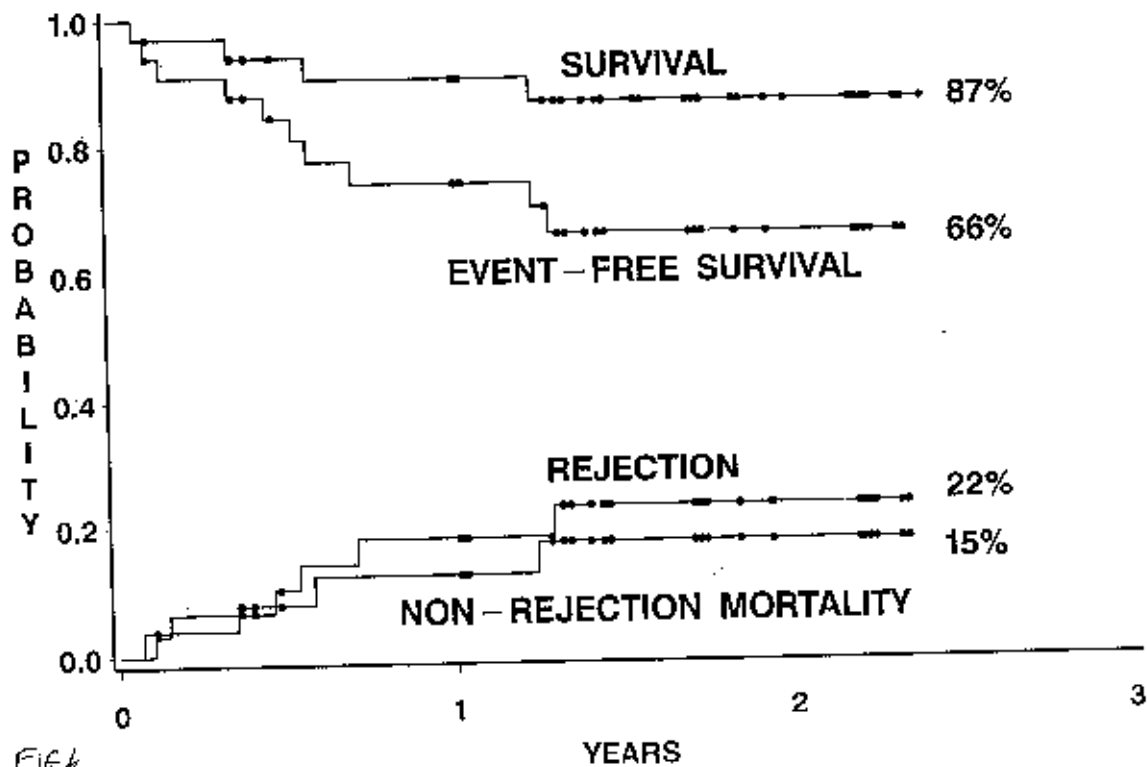
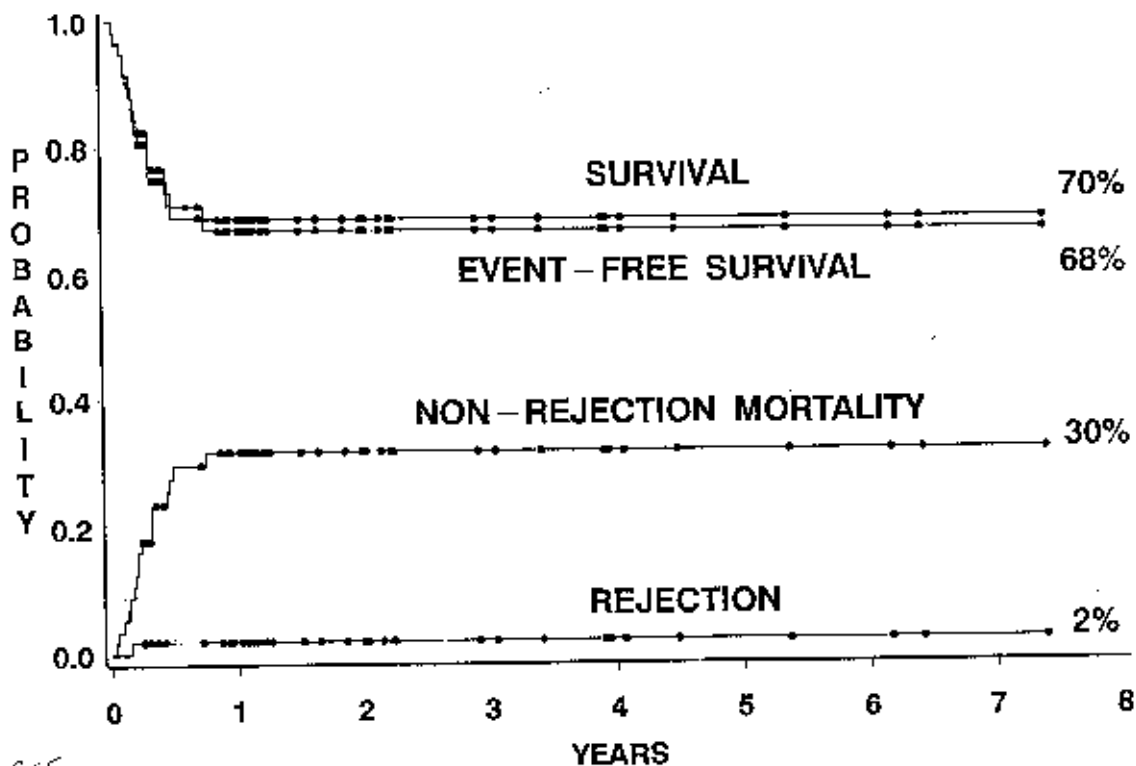


FIG 4  
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**Figure 4.** Kaplan-Meier probabilities of survival, event-free survival, rejection and non-rejection mortality for 33 Class 3 thalassemic patients aged less than 17 years, transplanted from HLA-identical siblings after preparation with busulfan 14 mg/kg, cyclophosphamide 160 mg/kg and cyclosporine and plus 'short' methotrexate from October 10, 1993, through January 25, 1996.



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**Figure 5.** Kaplan-Meier probabilities of survival, event-free survival, rejection and non-rejection mortality for 57 adult thalassemic patients aged more than 16 years (17 through 35 years of age) transplanted from HLA-identical siblings. Seventeen patients were in Class 2 and received the transplant after preparation with the protocol used for the Class 2 from October 13, 1988, through February 23, 1995, while 40 Class 3 patients received the transplant after preparation with the protocol actually in use for the Class 3, from November 26, 1993, through December 7, 1995.

but were poor for Class 3 as a consequence of intolerable cardiac and liver toxicity. This led us to adopt new preparative regimens for transplant in Class 3.<sup>(6)</sup> Since the adoption of new and less toxic preparative protocols for the transplant of patients in Class 3, patients older than 16 years of age have no longer been excluded from the transplant program and they form the group of adult thalassemia patients.<sup>(5)</sup>

## Results

We report here the results of bone marrow transplantation in thalassemia from HLA-identical family member donors and performed with the protocols actually in use at our Center and updated February 29, 1996. Starting in January 1986, 104 Class 1 and 262 Class 2 thalassemic patients aged less than 16 years were prepared for transplant with busulfan 14 mg/kg and cyclophosphamide 200 mg/kg and cyclosporine alone for prophylaxis of GVHD (Figures 2 and 3). Starting in November 1993, 33 Class 3

thalassemic patients less than 16 years old received busulfan 14mg/kg, cyclophosphamide 160 mg/kg and cyclosporine plus short methotrexate as prophylaxis for GVHD (Figure 4). Starting on November 1989, 17 Class 2 thalassemic patients older than 16 years of age received busulfan 14mg/kg and cyclophosphamide 200 mg/kg, while 40 Class 3 patients older than 16 years of age received busulfan 14 mg/kg and cyclophosphamide 160 mg/kg instead of 200 mg/kg (Figure 5).

### **The Ex-Thalassemic after Bone Marrow Transplantation**

At present only myeloablative regimens followed by marrow transplantation can eradicate hematologic thalassemia. For the thalassemic patients who have acquired normal bone marrows as a result of transplantation, the term “ex-thalassemic after transplant” has been proposed by us because there is uncertainty about the reversibility of the various lesions suffered by different organs as a result of the thalassemia and its treatment. In particular, we do not yet know how effectively excess iron deposits can be mobilized and excreted from the body once the patient’s marrow is functioning normally and transfusions are no longer needed. Some of the pre-existing lesions such as persistent and aggressive chronic hepatitis initiated by the hepatitis C virus may progress or may not readily be reversed.

After successful transplantation the body is left with a severe iron overload. Even under the best of circumstances, normal homeostatic mechanisms would take a long time to return the iron load and distribution to normal.

The use of chelating agents to hasten clearance in the ex-thalassemic after transplant has been effective in some young patients,<sup>(2)</sup> while periodic bleeding has been found to be the treatment of choice for older ex-thalassemics who maintain high levels of iron overload. There is some evidence that Class 1 patients will achieve relatively normal iron distribution within a year or two, but early indications are that this will be more difficult to achieve in patients with advanced disease. The need to retain the option for reversing thalassemia-induced lesions to organs other than the marrow is one of the factors that favor early rather than late transplantation.

Long-term complications arise from the allogeneic transplant itself. A small proportion of patients develop chronic GVHD, which may be occasionally be severely disabling. There are indications that gonadal function of some patients who have undergone marrow transplantation for thalassemia is impaired, but it is not clear how much of this effect is a result of previous iron overload or a consequence of the preparatory regimen.<sup>(1)</sup>

### **Conclusion**

The results of transplantation from HLA-identical family members are clear. Class 1 patients have a very high probability of cure with a very low early and late morbidity and mortality. There is no reason for denying these patients the advantages of a life free from daily tedious, expensive and uncomfortable therapy. We do not know the probability that a patient receiving conventional therapy will deteriorate into a worse risk category, but the fact is that every day transplant centers are confronted with patients in risk classes

2 and 3 who represent failures of conventional treatment. Delay of transplantation until the patient is in a risk category beyond Class 1 substantially reduces the probability of transplant success and jeopardizes the reversibility of liver and cardiac damage. We therefore believe that patients with b-thalassemia who have HLA-identical donors should be transplanted as soon as possible.

Approximately 60% of thalassemic children do not have HLA-identical family members. The use of family member donors genotypically identical for one HLA haplotype with minimal mismatching on the other haplotype has not been very rewarding, with only three successes in 11 patients mismatched for one antigen and only one success out of seven patients mismatched for more than one antigen. Clearly more studies are needed of partially matched transplants, but they are not at present an attractive option in the early management of patients who can obtain and tolerate conventional therapy. There is no extensive experience of the use of unrelated donors, but the results in the first three such transplants and the results of transplants from partially matched related donors indicate that unrelated donor transplants should not be performed except in the context of a well-defined research environment.

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