2. Bone Marrow Transplantation in Thalassemia

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Introduction

The term *thalassemia* is used to define various hereditary anemias that are identified by a reduced production of one of the globin chains that form the hemoglobin molecule. Thalassemia syndromes are widely distributed throughout Mediterranean, Middle Eastern, and Asian countries, and occur with a significant incidence worldwide in populations that originated in these regions. The thalassemias probably represent the most common single gene disorder to cause a major public health problem in the world [1]. In the Mediterranean area alone there are more than 200,000 β-homozygous thalassemia patients, and according to the World Health Organization approximately 180 million people are heterozygous for one of several forms of genetic disorder of hemoglobin synthesis [2]. In β-thalassemia there is deficient or absent synthesis of the β-globin chains that constitute the adult hemoglobin molecule. Because β-thalassemia is a genetic disease in which the known expression of the genetic defect is located in the hematopoietic system, it is rationally curable by allogeneic bone marrow transplantation. The first successful transplant in β-thalassemia was in an untransfused 14-month-old child and was reported by Thomas in 1982 [3]. At about the same time a 14-year-old thalassemic patient who had received 150 red cell transfusions was transplanted in Pesaro but had recurrence of thalassemia after rejection of the graft. The first report from Pesaro on this topic was in 1984 [4], and since then several centers have reported experience with marrow transplantation for thalassemia (Table 1).

Through 1993, the Pesaro team has performed 652 transplants in thalassemic patients from HLA-identical donors, 632 of them from genotypically identical siblings and 20 from phenotypically identical parents. This large experience in a single institution has allowed a sequence of protocol design, completion, and analysis that has been reported [5–10] and that has resulted in marrow transplantation becoming established therapy for patients with thalassemia who have suitable donors. This chapter brings the publication of this experience up to date, as well as considering new developments and experimental approaches.
Table 1. Published experience of transplantation in Thalassemia

| Transplant center                     | Number of patients | Alive | Alive disease free | Disease recurrence | Ref. |
|--------------------------------------|--------------------|-------|--------------------|-------------------|------|
| Taiwan (1989)                        | 14                 | 9 (64%)| 6 (43%)           | 5 (36%)            | 30   |
| Paris, France (1990)                 | 17                 | 14 (82%)| 10 (59%)        | 4 (24%)            | 31   |
| Pescara, Italy (1993)                | 61                 | 54 (89%)| 51 (84%)         | 3 (5%)             | 32   |
| Bangkok, Thailand (1993)             | 10                 | 9 (90%)| 4 (40%)           | 5 (50%)            | 33   |
| Cagliari, Sardinia (1993)            | 10                 | 6 (60%)| 6 (60%)           | 0 (0%)             | 34   |
| USA (1994)                           | 30                 | 24 (80%)| 17 (57%)         | 7 (23%)            | 35   |
| United Kingdom (1994)                | 38                 | 27 (71%)| 24 (63%)         | 4 (11%)            | 36   |

**Prediction of outcome**

We have described a system for assigning patients undergoing marrow transplantation for thalassemia to prognostically useful categories [7]. Three risk factors are evaluated. These are the degree of hepatomegaly (greater than or not greater than 2 cm below the intercostal margin), the presence or absence of portal fibrosis in the pretransplant liver biopsy, and the quality of chelation (regular or irregular) given through the years before transplant. The quality of chelation is characterized as regular when desferoxamine therapy was initiated not later than 18 months after the first transfusion and administered subcutaneously for 8–10 hours continuously for at least 5 days each week. The chelation variable is defined as irregular for any deviation from this requirement. Class 1 patients have none of these adverse risk factors, class 3 patients have all three, and class 2 patients have one or two adverse risk factors. We have reported the evaluation of liver biopsies in a large series of patients receiving marrow transplants for thalassemia, and portal fibrosis was not observed in patients less than 3 years of age [11]. In view of this and the known hazards of liver biopsy in very young children, patients less than 3 years of age do not undergo liver biopsy unless hepatomegaly is present, and infants who do not have liver biopsies are considered not to have portal fibrosis.

**Bone marrow transplantation in class 1 patients**

Class 1 patients are identified by the absence of hepatomegaly, by regular iron chelation performed before transplant, and by the absence of any degree of fibrosis in the pretransplant liver biopsy. In Pesaro we have not seen a class 1 patient older than 17 years. In a previous study, the outcome for 64 patients included in class 1 and transplanted between June 1985 and July 1992 using a conditioning regimen that consisted of 14 mg/kg busulfan (BU) and 200 mg/kg cyclophosphamide (CY) with cyclosporine as pro-