Bone Marrow Transplantation in Thalassemia

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INTRODUCTION

Thalassemias represent the most common single-gene disorder to cause a major public health problem in the world[1]. The term “thalassemia” refers to various types of hereditary disorders characterized by a defective production of the globin chains which form the hemoglobin molecule. In ß homozygous thalassemia, or thalassemia major, there is a defective synthesis of ß-chains of adult hemoglobin A. This defect causes an imbalance in the chain production and the accumulation of free ß-chain in red cell precursors and in red blood cells, leading to their intramedullary destruction[2], apoptosis[3], ineffective erytropoiesis, and hemolytic anemia.

Over the last three decades, profound changes in the management of patients with thalassemia have been observed. The development of regular transfusion therapy and of regular iron chelation has dramatically improved the quality of life of thalassemic children and has led to the transformation of thalassemia from a rapidly fatal disease to a chronic disease compatible with prolonged survival[4]. Regular red blood transfusions eliminate the complications of anemia and compensatory bone marrow expansion[1]. Moreover, the introduction of regular iron chelation with deferoxamine extended survival, free of iron-induced complications[5]. These treatments are time consuming and uncomfortable. The lack of availability of proper medical care in developing countries and the frequent failure of compliance with regular chelation therapy still represents the unresolved social problems of thalassemia. Despite the increased life expectancy of thalassemia patients now, complications arising from the unavoidable iron overload in organs, and from hepatitis due to viral blood-born infections, make thalassemia major a progressive and eventually fatal disease.

Bone Marrow Transplantation

Because ß-thalassemia is a genetic disease in which the defect is expressed in the hemotopoietic marrow, it is rationally curable with allogeneic bone marrow transplantation (BMT). The first successful bone marrow transplant for ß-homozygous thalassemia was carried out by the Seattle group in 1981[6]. An 18 month-old untransfused child received bone marrow from his HLA identical sister and 18 years later he is well and free of disease. In the same period, a 14 year-old politransfused thalassemic patient was transplanted in Pesaro, but he had a reccurrence of thalassemia af-

ter a rejection of the graft. The following experiences reported in the literature were disappointing: among the first series of patients transplanted using high doses of cyclophosphamide (CY) and TBI, a high percentage of failure related to marrow rejection and early toxicity was observed[7]. This conditioning regimen was then abandoned and from 1983 on the conditioning regimen originally proposed by Santos et al.[8] for leukemias, including a combination of busulfan (BU) and CY, was adopted for all patients.

In 1989 a retrospective evaluation in an extensive series of transplanted patients showed that the risks of BMT using an HLA identical donor could be predicted according to the presence or absence of three criteria: hepatomegaly (enlargement of more than 2 cm below the costal margin), the evidence of liver fibrosis in the pre-transplant liver biopsy, and the quality of iron chelation received before transplantation[9]. The quality of chelation was considered regular when deferoxamine therapy was initiated within 18 months after the first transfusion and administered subcutaneously for 8-10 hours continuously for at least 5 days each week. The chelation was defined as irregular for any deviation from this requirement. These criteria were used as variables in categorizing patients into three classes of risk. Patients with none of these adverse criteria were assigned to Class 1; patients with one or more associations of adverse risk factors constituted Class 2; and patients for whom all three criteria were adverse formed Class 3[10]. Until October 1989 the graft versus host prophylaxis consisted of methotrexate (MTX) alone, then cyclosporine (CsA) was introduced. The conditioning regimen with BU14+CY 200 and CsA alone for the graft-versus-host disease (GVHD) prophylaxis, called Protocol 6, is actually in use in Pesaro for patients in Class 1 and in Class 2.

By far the most experience in the treatment of thalassemia with marrow transplantation has been reported by the Pesaro Bone Marrow Center. From December 1981 through October 1998, 824 patients with homozygous ß-thalassemia (with a mean age of 10 years and a range of 1-35) received marrow transplants from HLA identical related donors (794 siblings, 30 parents) and the probability of survival is 75% with a follow-up of 17 years (Figure 1). In this review we present the update of our overall clinical experience in allogeneic BMT in patients with thalassemia analysed on March 31st 1999.

UPDATE OF CLINICAL RESULTS

Class 1

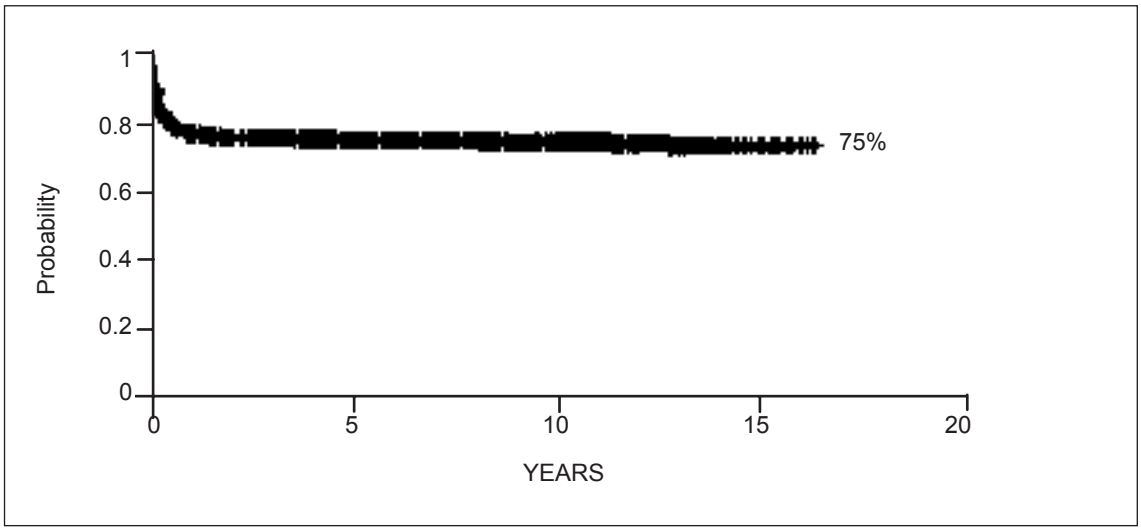

Figure 1. The Kaplan and Meier probabilities of survival and thalassemia-free survival for all the 824 patients with thalassemia aged 1 through 35 years who received HLA identical transplants from December 17 th 1981 through October 31 st 1998. Analysis was performed on March 31 st 1999.

Table 1. Pre-transplant characteristrics of patients

Characteristics	Mean (range) Class 1 (n = 291)	Class 2 (n = 291)	Class 3 (n = 126)	Adults (n = 11%)
Age (yr)	5.5 (1-16)	9 (2-16)	11 (3-16)	20.8 (17-35)
Number of TX	63 (1-250)	129 (1-430)	166 (4-435)	356 (58-900)
Ferritin (ng/ml)	1288 (48-52017)	2087 (33-8547)	3467 (604-12753)	2424 (322-9071)
LIC (mg/g dw)	7.65 (0.67-24.38)[a]	12.97 (0.67-53.78)[b]	20.57 (3.6-48.1)[c]	15.06 (1.36-46.75)[d]
Liver fibrosis				
Absent		63	0	0
Mild		101	29	33
Moderate		89	43	27
Severe		18	42	38
Chirrhosis		1	6	8
HCV-Ab*				
Pos/Neg	21/53	60/88	51/50	72/11
HCV-RNA**				
Pos/Neg	0/2	11/11	12/11	23/26

Abbrevations: TX, transfusions; LIC, liver iron concentration[a]; 72 patients studied[b]; 243 patients studied[c]; 88 patients studied[d]; 102 patients studied; HCV, hepatitis C virus; Pos/Neg, Positive/Negative.

* Serologic testing for HCV-Ab was started in March 1990.

** PCR for HCV-RNA was available from September 1993 (performed in only HCV-Ab positive patients).

Class 1 patients are defined by an absence of hepatomegaly, regular iron chelation therapy performed before transplant, and the absence of fibrosis in the pre-transplant liver biopsy[10]. Between October 1985 and October 31st 1998, 119 patients under the age of 17 years (with a mean age of 5.5, and a range of 1-16) were included in Class 1 and transplanted using a conditioning regimen with BU14 mg/kg and CY200 mg/kg; the GVHD prophylaxis was given with CsA. The pre-transplant characteristics of patients are reported in Table 1.

In patients receiving marrow transplants for thalassemia, liver fibrosis was not observed before the age of three. In the view of the known hazards of liver biopsy procedure in very young children, patients under the age of three years did not undergo liver biopsy unless hepatomegaly was present; such infants were considered not to have liver fibrosis. A quantitative estimation of the liver iron concentration by atomic absorption spectrophotometry has been obtained for 72 patients. The median liver iron concentration (LIC) was 7.65 mg/g dry weight (range 0.67-24.38). In a Kaplan-Meier analysis, the probabilities of survival, event-free survival, rejection, and non-rejection mortality are, respectively, 93, 91, 8, and 2% with a maximum follow-up of about 13 years (Figure 2). Nine patients (7.2%) died from causes related to the transplant procedure 5 of them within the first 100 days after transplant. Two patients rejected the graft and reconstituted autologous marrow.

Class 2

Between October 1985 and October 31st 1998, 291 patients aged less then 17 years (with a mean age of 9, and a range of 2-16), have been included in Class 2, identified by the presence of either one or various combinations of two of the

above risk factors. All patients were conditioned using Protocol 6. The pre-transplant characteristics of patients are reported in Table 1. A quantitative estimation of the liver iron content had been done in 243 patients: LIC ranged from 0.67 to 53.78 mg/g dw with a median of 12.97. The probabilities of survival, event-free survival, rejection, and non-rejection mortality are, respectively, 87, 82, 3, and 15% with a maximum follow-up of 13 years (Figure 3). Forty two (14%) patients died of transplant-related causes; 19 of them died within the first 100 days, mainly of acute GVHD (aGVHD) and infectious complications. Eleven patients rejected the graft: 9 of them showed an autologous reconstitution.

Class 3

Between October 1985 and March 1989, 55 patients were included in Class 3 as they had all three risk factors and had been transplanted according to the BU14 and CY200 protocol. The results of this clinical experience were disappointing because of a high incidence of early mortality due to toxicity and infections. Starting from March 1989, a new conditioning regimen with a reduced dose of CY was adopted for all Class 3 patients. Between March 1989 and October 1998, 126 Class 3 patients less than 17 years old received BMT with this protocol. The median age of the overall group was 11 years (range 3-16), the pre-transplant characteristics are reported in Table 1. LIC documented in 88 patients ranged from 3.65 to 48.1 with a median of 20.57 mg/g dw. In the Kaplan-Meier curves, the probabilities of survival, event-free survival, rejection, and non-rejection mortality for this group of patients are 79, 58, 28, and 19%, respectively, with a maximum follow-up of 9 years (Figure 4). Twenty six (20.6%) patients died from causes related to the transplant procedure (10 within the first 100 days). Thirty three patients rejected the graft; 26 of them are alive with autologous recontitution, with transfusional support.

Adult Patients

Most patients with thalassemia major, who are older than 16 years and presenting for transplantation, have disease characteristics which place them in Class 3 and, because of the improved results with the new Class 3 regimen in younger patients, we start to treat patients older than 16 years using treatment regimens assigned on the basis of disease Class. One hundred and fifteen consecutive patients aged more than 16 years old

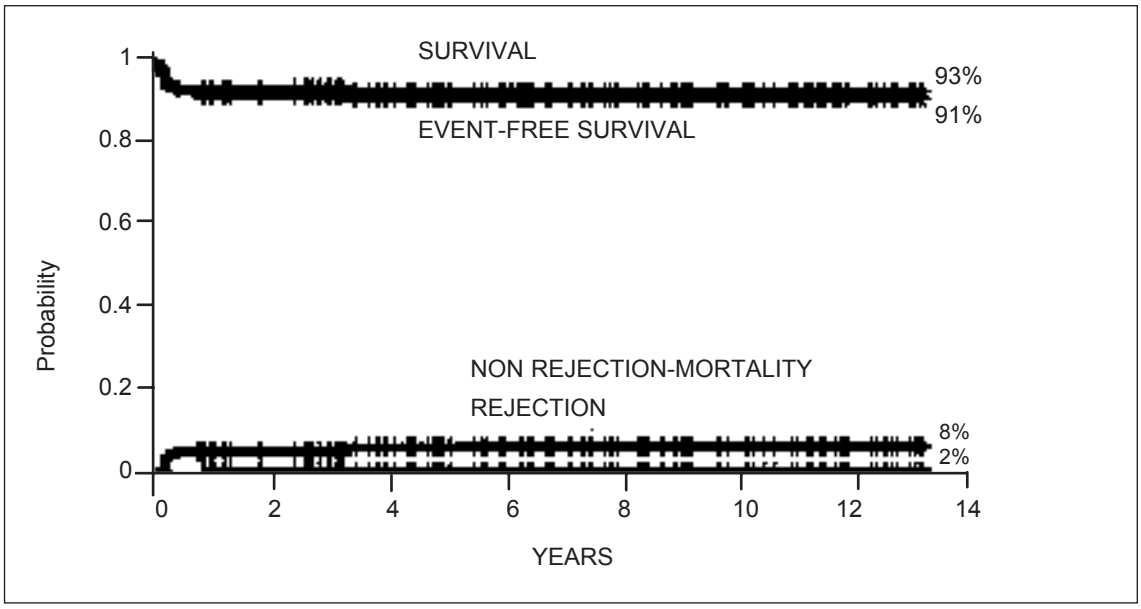

Figure 2. The Kaplan and Meier probabilities of survival, thalassemia-free survival, rejection and non rejection mortality for the 119 Class 1 thalassemia patients transplanted using Protocol 6.

Table 2. Causes of death (165 deaths among 785 consecutive transplants)

Transplant related deaths	Number of patients (%)
Acute grade III-IV GVHD and related complications	53 (32)
Marrow aplasia and related complications	15 (9)
Infectious disease	40 (24)
Respiratory disease (3 Adult Respiratory Distress Syndrome,	
2 idiopathic interstitial pneumonia)	5 (3)
Liver disease (3 veno-occlusive disease, 7 liver failure)	10 (6)
Cardiac disease (7 cardiac tamponade, 1 heart failure)	8 (4.8)
Bleeding (4 Central Nervous System, 1 Gastro-Intestinal)	5 (3)
B lymphoprolipherative disease	2 (1.2)
Chronic GVHD and related complications	15 (9)
Unknown	1 (0.6)
Thalassemia related deaths	
(occurring >1 year after BMT, an absence of chronic GVHD)	
Heart failure (In autologous reconstitution)	4 (2.4)
Overwhelming post-splenectomy infection	2 (1,2)
Other causes of deaths	
Car accident	4 (2.4)
Mushroom poisoning	1 (0.1)

Deaths occurring in uncontrolled GVHD have been considered caused by GVHD as a major cause.

were transplanted from HLA identical donors between October 1988 and October 1998. All Class 2 patients received BU 14 and CY 200 and the remaining 93 Class 3 patients were prepared with BU 14 and CY 120 or 160. The ages ranged from 17 to 35 years (median 20). A liver biopsy was performed before transplant in all 115 patients. The median value of LIC varied from 1.36 to 46.75 mg/g dw with a median of 15.06 (Table 1). According to the Kaplan-Meier analysis, the probabilities of survival, event-free survival, rejection, and non-rejection mortality are 66, 62, 5, and 35%, respectively (Figure 5). Thirty eight (33%) patients died from causes directly related to the transplant procedure. Five patients rejected the allogeneic marrow and they are alive with complete autologous reconstitution.

Acute Graft-Versus-Host-Disease

Graft versus host disease is one of the major complications of allogeneic BMT[11]. The disease can be divided into two distinct clinical entities: acute forms occurring in the first one or two months after transplantation and the chronic disease developing at least two or three months after transplantation. The current understanding of the pathogenesis of acute GVHD (aGVHD) suggests that alloreactive donor T lymphocytes recognize histocompatibility antigens on host cells and initiate secondary inflammatory injury leading to the clinical symptoms of GVHD[12]. Even with current immunoprophylaxis, 25-50% of patients receiving HLA-identical sibling donor marrow and 70-90% of patients receiving unrelated donor marrow develop aGVHD[13,14]; approximately 15-40% of deaths among patients receiving BMT result from GVHD or related causes[14-16].

Among the 724 patients evaluated for aGVHD 528 (72.9%) had grade 0-I aGVHD, 195 (26.9%) had grade II-IV aGVHD. Forty-four patients (6.1%) developed grade IV aGVHD. Class 1,

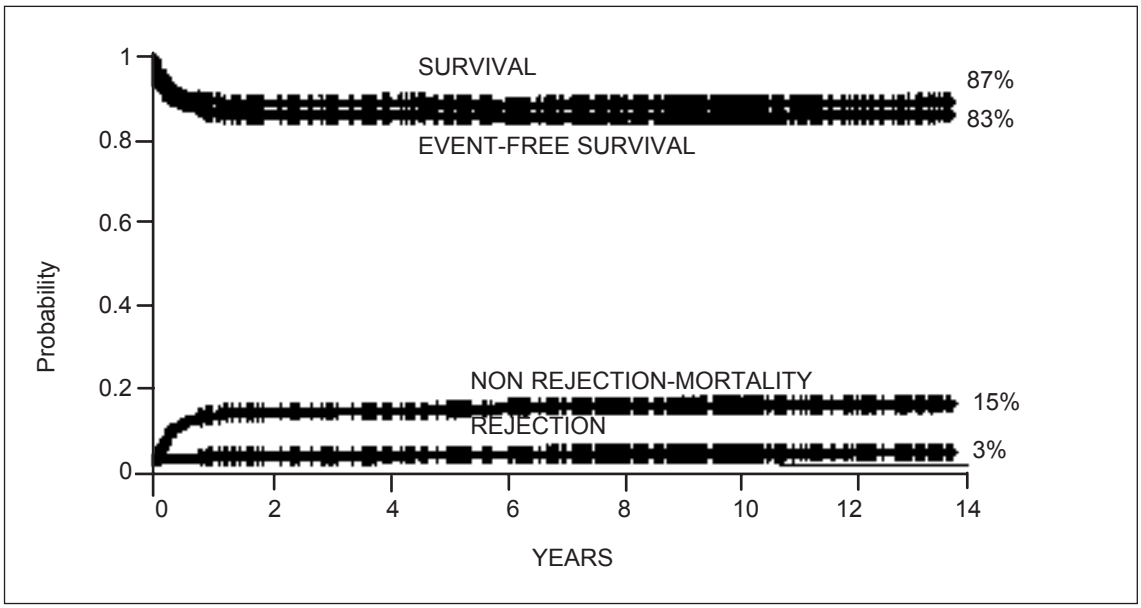

Figure 3. The Kaplan and Meier probabilities of survival, thalassemia-free survival, rejection, and non rejection mortality for the 291 Class 2 thalassemia patients aged less than 17 years transplanted using Protocol 6.

Class 2, and Class 3 patients had an incidence of aGVHD of 27, 32.4 and 20.7%, respectively[17]. The cumulative incidence of grade II-IV aGVHD was 32% in patients receiving CsA/MTX or MTX/methylprednisolone (MP) and 17% in patients receiving CsA/MTX/MP. The mortality rate was similar in patients with grade 0-I or II aGVHD (13.4%) and increased in patients with grade II-IV aGVHD (56.1%)[17].

Mixed Chimera

The presence of residual host cells (RHS) in a transplanted patient represent a risk factor for graft failure. The presence of mixed chimera (MC) is a frequent event after BMT in patients transplanted for thalassemia[18]. In an analysis of 351 patients, we observed that MC was present in 98 patients (27.9%) within the first 2 months after the transplant and it was, respectively, 13.6 and 10.6% at 1 and to 2 years from the time of transplant[19]. Mixed chimera may be transitory resulting from full donor chimera or rejection, and the amount of RHS in the early phase is an important factor in determining its outcome. In space fact, rejection occurred in 10 of 77 patients (12.9%) with an amount of RHS < 25% and in 19 of 21 patients (90%) with RHS > 25%[19]. A group of patients (n = 24) showed a persistence of mixed chimerism[20]. The yearly assessment of these patients for a period between 2 and 11 years showed that the percentage of donor-engrafted cells was variable (30%-90%). Although the presence of large amounts of residual host hematopoiesis were widely distributed in the different hematologic lineages, including the erytroid precursors, patients with persistent MC produced sufficient donor beta globin chain synthesis and maintained hemoglobin levels between 10-13.5 gm/dl and survived transfusion free. MC appears to be an active phenomenon that results from the interactions of various subsets of donor and recipient cells, but the mechanism of immunological tolerance between donor and host is not clear. A better understanding of the mechanism that induces the MC will allow for substantial modifications on the basic aspect of transplantation in thalassemia patients.

LONG-TERM BMT-RELATED COMPLICATIONS

Chronic Graft-Versus-Host-Disease

Chronic GVHD (cGVHD) developes in 30-40% of allograft recipients and usually manifests itself

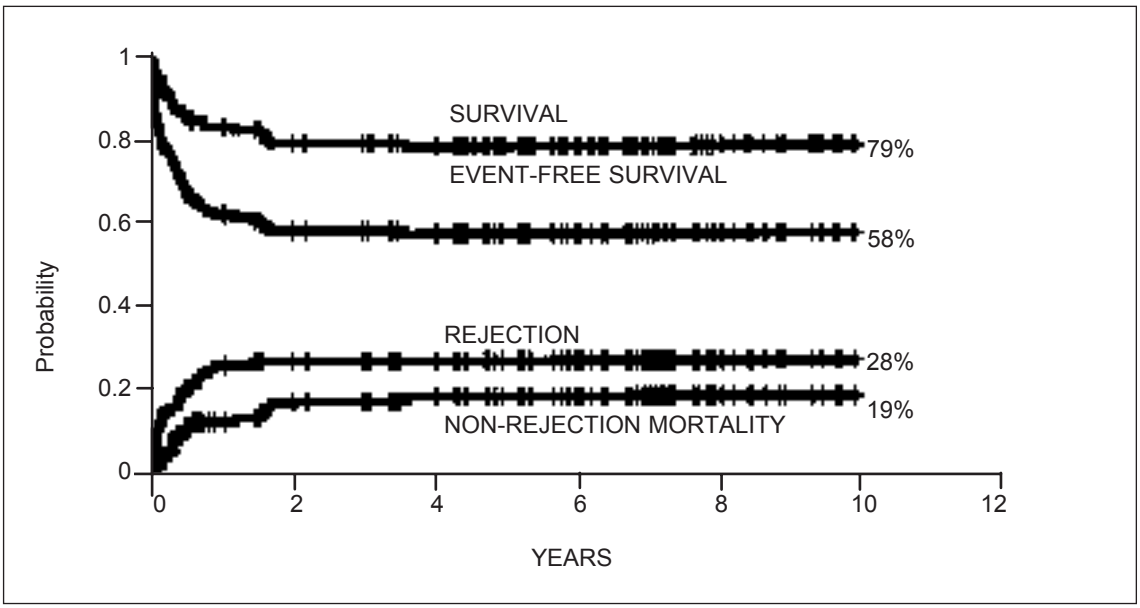

Figure 4. The Kaplan and Meier probabilities of survival, thalassemia-free survival, rejection and non rejection mortality for the 126 Class 3 thalassemia patients aged less than 17 years transplanted after March 1989 with the conditioning regimen with a reduced dose of cyclophosphamide (< 200 mg/kg).

between 90 and 150 days after transplantation[21]. It occurs most frequently in patients with preceding aGVHD, but may also occur in 10% of the siblings of allograft recipients de novo, without any preceding aGVHD[22]. The manifestations of cGVHD resemble connective tissue disorders characterized by autoimmune reactions, and the severe form of this syndrome can adversely affect the quality of life of patients. In our series, cGHVD developed in 168 (27.3%) of 614 evaluated patients[17]. Twenty-five (22.5%) patients in Class1, 90 patients (30.6%) in Class 2, and 53 (26.9%) in Class 3 developed cGVHD. Fifty-one patients developed de novo cGVHD (8.2%). Eighty-two patients (48.8%) developed cGVHD within 6 months, 65 (38.6%) between 6 months and 1 year, and only 21 (12.5%) patients developed cGVHD after the discontinuation of CsA at 1 year after transplantation. One hundred fifteen patients (18.7%) had mild, 42 (6.8%) had moderate and only 11(1.8%) patients had severe cGVHD[17].

Secondary Malignancies

The patients who received hematopoietic stem cell transplantation have an increased risk of developing secondary malignancies[23,24]. Some high-risk situations have been recognized, including an underlying diagnosis of immunodeficiency or other genetic defects, high-dose irradiation for conditioning, T-cell depletion of the marrow, HLA nonidentity of the donor, and cGVHD and its treatment[23-25]. We have peviously reported a total of 5 patients with a secondary malignancy after BMT for thalassemia[26]. Three patients developed EBV-associated B-cell lyhmphoma: two of them died of the progressive disease and one is alive and well more than 10 years after radiotherapy. Two patients developed solid tumors: one patient with spinocelluler cancer of the lip died 6 years after the diagnosis from a recurrence of the disease, and one case of Kaposi Sarcoma while in treatment for mild cGVHD[27]; the disease regressed after discontinuation of immunosuppressive treatment. The low incidence of lymphomas (0.4%) and solid tumors (0.3%) in our series showed that the transplant procedure does not increase the incidence of secondary malignancies in patients transplanted for thalassemia.

MORTALITY AND CAUSE OF DEATH

The allogeneic BMT is a therapeutic procedure with a significant risk of mortality and morbidity.

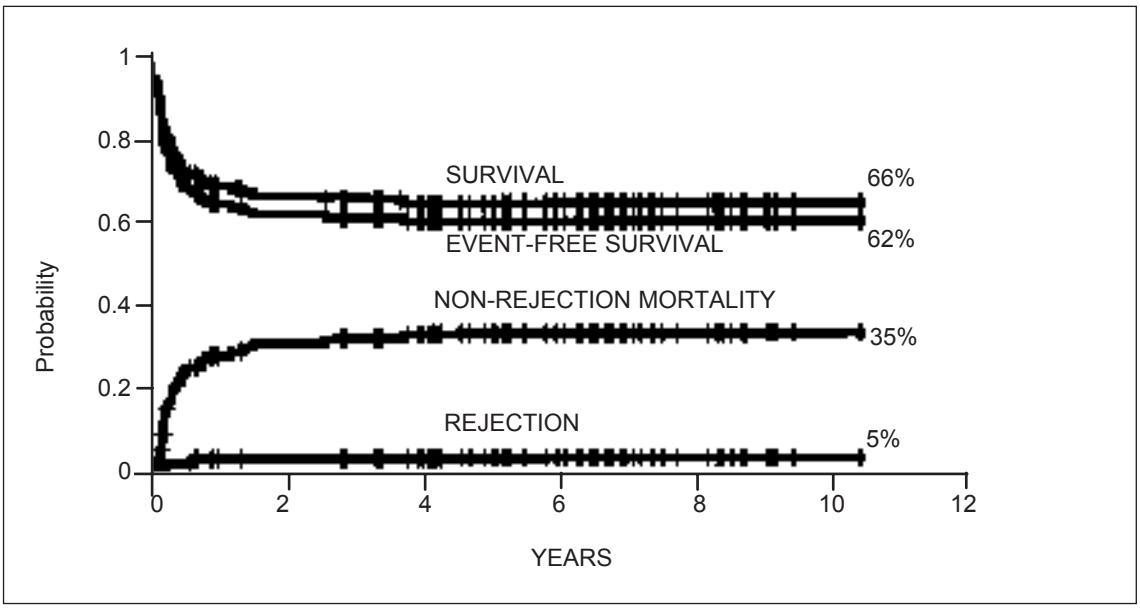

Figure 5. The Kaplan and Meier probabilities of survival, thalassemia-free survival, rejection and non rejection mortality of the 115 patients older than 16 years. Twenty-two of these patients were in Class 2 and were transplanted using Protocol 6, 93 were in Class 3 and were transplanted with regimens containing decreased doses of cyclophosphamide (< 200 mg/kg).

In a recent study, the causes of death among 785 consecutive patients transplanted for thalassemia in our center have been reported[28]. One hundred and sixty-five (21%) patients died after transplant (Table 2): acute GVHD and infectious complications represent the primary causes of death, contribuiting to 56% of all deaths (Table 2). Fifteen (9%) patients without autologous hemopoietic reconstitution after rejection, or a “no-take” of the graft, died of causes directly related to the marrow aplasia. The acute cardiac tamponade is an extremely insidious event in thalassemics undergoing BMT; this complication occurred in 8 (1%) cases and was fatal in seven (4%). The syndrome is characterized by a sudden onset of circulatory shock and cardiac arrest due to rapid fluid accumulation in the pericardial space[29]. The underlying mechanism of fluid formation is not clear, but the susceptibility of the pericardial membranes aggravated by chemotherapy has been supposed. The only treatment is immediate fluid removal by emergency pericardiocentesis[29]. Two patients (1.2%) died of an overwhelming post-splenectomy infection 4 and 6 years after BMT with a functioning graft and without cGVHD. Four patients (2.4%) died of causes unrelated to the transplant procedure (car accidents); these patients had been censored from the Kaplan-Meier analysis on the day of the event.

Thalassemia Patients After Bone Marrow Transplantation (Ex-Thalassemic)

A successful allogeneic BMT for thalassemia can cure the underlying hematological defect, but can not eliminate the multisystem organ damage sustained during the years before the transplant. We use the term 'ex-thalassemic' to define individuals cured from the hematological defect by BMT, but with residual organ damage due to pretransplant red-cell transfusions and associated complications. Therefore, the management of ex-thalassemics must also include the treatment of complications acquired during the years of thalassemia and its treatment. We have previously shown a progressive clearance of iron deposits for younger patients, while heavily iron laden patients maintained high serum ferritin levels and histological evidence of liver iron deposits throughout the years following transplantation[30]. A persistence of iron overload after the transplant is likely

to be associated with ongoing tissue damage, contributing to the progression of hepatic[31], cardiac[32], and endocrine disfunctions[33]. In order to prevent progressive multiorgan damage (i.e by accelerating the clearance of iron deposits), a program of regular venesection or deferioxamine therapy beginning 1-2 years after BMT has been started[30]. Both phlebotomy and iron-chelation therapy with deferoxamine have been found to be safe and effective in removing excess iron from the body after a succesful transplantation, without any adverse side effects[34,35]. A substantial improvement in cardiac functions in a group of patients who had been iron depleted by a phlebotomy program has been demonstrated[36].

The liver is the organ mainly effected in multitransfused thalassemic patients. Both hepatic parenchymal iron accumulation and transfusion-transmitted viral hepatitis contribute to fibrosis, which has been documented in these patients. Before the introduction of routine blood screening for hepatitis C, many patients who came for transplants were already infected with the hepatitis C virus (HCV)[37]. HCV infection does not have a relevant short-term impact on the outcome of BMT. But in the long-term it may have a significant role in the morbidity and mortality by causing a gradual progression to cirrhosis and liver failure[38]. To prevent a progression to cirrhosis, anti viral therapy should be considered in long-term BMT survivers with chronic hepatitis C infections. The role of liver iron in predicting the response to interferon the predictive role of liver iron in response to interferon therapy for chronic hepatitis C infection is well known[39]. Therefore, in ex-thalassemics with chronic hepatitis C, phlebotomy and chelation therapy should be considered before interferon therapy; to reduce hepatic iron stores the mobilization of iron may increase the chance of response.

Hypogonadism is the most frequent endocrine disorder in thalassemia patients; a spontaneous pubertal development was observed in 50% of patients treated with conventional therapy[40]. The post-transplant growth and pubertal development in ex-thalassemic patients have been reported in several studies[33,41,42]. The data show that young children transplanted in the early phase of thalassemia regain a normal growth rate after BMT[41], while older children, especially those who develop cGHVD, often have severely impaired growth[43]. The cytotoxic agents given during the conditioning regimen and the iron overload due to thalassemia are the major factors influencing the endocrine functions of ex-thalassemics[41,42]. In a study including 68 ex-thalassemics, 34% of the women and 63% of the men reached advanced or complete puberty spontaneously[41]. A careful monitor of growth and pubertal development before and after transplant is of primary importance in order to detect abnormalities and to initiate appropriate and early treatment.

Successful pregnancy following BMT for other hematological disorders using Bu and CY conditioning has been reported[44]. In our extensive series only a young woman transplanted at the age of 11 years became pregnant naturally and delivered a normal (thalassemia minor) child[45]. It is not possible at present to accurately predict the effect of BMT on fertility at least for females; but considering regimen-related gonadal damage after transplant, patients need to be counselled accordingly.

NEW APPROACHS

BMT From Matched Unrelated Donor

The possibility of finding a healthy sibling donor for most patients suffering from a genetic disease is very low and is estimated at about 10%[46]. For a thalassemic patient the probability of having a HLA identical sibling is around 30%[47], and only 8.5% of these were found to be phenotypically identical to one parent[48]. The development of a registry network, including more than 4 million HLA-typed volunteers, has extended the availability of allogeneic BMT to patients without a suitable family member. In thalassemia patients, a careful selection of donors, with an extensive DNA study of class II antigens, is requested and the patient should proceed to transplant only if a fully matched donor is available. The first unrelated marrow (UD) tranplant in thassemia has been reported in 1994[49]. Until December 1998, a total of 15 thalassemia patients received UD

transplant (G. La Nasa personal comunication). Graft rejection with autologous reconstitution occurred in 3 patients (20%); one patient died and 11 had successful transplants with a median follow up of more than 1 year. The incidence of aGVHD was 33% and the incidence of limited cGVHD was 25%. In Pesaro two patients have been transplanted; one in Class 2 and with extended HLA haplotype is well and free of disease 6 months after BMT, the second patient (transplanted in December 1998) was assigned to Class 3 and rejected the graft with autologous reconstitution.

Unrelated donor marrow transplant offers an additional therapeutic choice for patients without suitable family members and thalassemia patients can be successfully transplanted with UD marrow.

CONCLUSIONS

Since bone marrow transplantation was first introduced, its primary use has been in patients with malignancies or other rapidly fatal disorders. Actually, BMT has being accepted as the preferred form of treatment for a wide variety of diseases including hemoglobinopathies. Unfortunately, since 1982 when the first successful BMT for thalassemia was reported, the role of this treatment has been the subject of vigorous debate and, despite the successful results obtained thus far, there is still considerable opposition to marrow transplantation in thalassemia. In the case of hemoglobinopathies, BMT has not been considered a life-saving procedure, but an elective one. Therefore the ethical aspect of this therapeutic option continues to be the basic subject of discussions. Because of improvements in the symptomatic management of thalassemia, many clinicians do not feel able to recommend to their patients a form of treatment that is associated with acceptable but significant mortality and morbidity. On the other hand, many physicians do not consider transplantation, even for patients with a matched sibling, in the hope that the corrective gene therapy will be avaiable soon. Gene therapy is an exiciting prospect, although there are still formidable obstacles to be overcome before it is likely feasible for the ß thalassemias. The efficient gene transfer, especially of a large gene segment like the beta-globin gene and its regulators, into hemopoietic stem cells, and sustained gene expression, have not yet been achieved. Therefore gene therapy in the treatment of thalassemia is still far from a routine clinical application and must await further research.

As today the allogeneic BMT is the only available procedure that may lead to a definitive cure of disease, BMT program for ß thalassemia major have now been established in most parts of the world. The results of BMT from HLA identical family members are clear. Class 1 patients have a high probability of being cured with a very low, early, and late morbidity and mortality. The delay of transplantation, until the patient is in a risk category beyond Class 1, substantially reduces the probability of transplant success. On the other hand, there is no reason for denying these patients the chance of having a transplant and the advantages of a life free of disease and free of daily, tedious, and uncomfortable therapy.

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