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.

C. Dean Buckner (ed.), TECHNICAL AND BIOLOGICAL COMPONENTS OF MARROW TRANSPLANTATION.

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-

phylaxis against graft-versus-host disease (GVHD) were analyzed [9,12]. The mean age was 6 years, the mean number of pretransplant red cell transfusions was 70 (range 0–223), and the mean serum ferritin level was 1576 ng/ml (range 239–5207). Twenty percent of patients had serologic markers of hepatitis B infection and 42% (6 out of 14 patients tested) had markers of hepatitis C. In two patients (4%), the pretransplant liver biopsy showed severe liver iron overload, and there was active chronic hepatitis in another 2 (4%) (Table 2).

The probabilities of survival, event-free survival, rejection-free mortality, and rejection were 97%, 93%, 3%, and 4%, respectively, with a maximum follow-up of about 8 years (Table 3). All curves showed a plateau after the first year. Twenty percent of these patients (actuarial probability 0.31) developed grade II or grater acute GVHD, and nine patients (14%) developed clinical extensive chronic GVHD. Two patients died on days 94 and 101, one with severe acute GVHD and the other with infectious com-

Table 2. Pre-transplant characteristics of patients less than 17 years of age

Characteristics	Class 1	Class 2	Class 3
Number of patients	64	188	47
Age: mean years (range)	6 (1–15)	9 (1–16)	11 (5–15)
Transfusions: mean no. (range)	70 (0–223)	125 (0–404)	70 (24–435)
Serum ferritin: mean ng/ml	1576	2300	3996
AST: mean IU/L (range)	18 (5–136)	24 (5–86)	36 (7–101)
ALT: mean IU/L (range)	32 (4–412)	45 (2–170)	61 (10–340)
Liver histology — number of patients (%)			
Severe iron overload	2 (4%)	29 (17%)	26 (55%)
Chronic active hepatitis	2 (4%)	34 (20%)	21 (44%)
Moderately severe fibrosis	None	70 (41%)	38 (80%)
Serologic hepatitis markers — number of patients (%)			
Hepatitis B virus antibody	13 (20%)	44 (24%)	15 (32%)
Hepatitis C virus antibody	6/14 (42%)	25/48 (52%)	16/31 (52%)

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 3. Summary of results by category of patient

Class[a]	Number of patients	Age (range in yr)	Protocol[b]	Follow-up (months)	Probability		
					Survival	DFS[c]	Rejection
1	64	1–16	A	12–97	0.97	0.93	0.04
2	188	1–16	A	12–97	0.88	0.85	0.04
3	47	1–16	B	12–52	0.95	0.64	0.32
Adults	41	17–32	A or B	12–57	0.85	0.82	0.05

[a] Eleven adults were class 2 and 30 adults were class 3.
[b] Protocol A consisted of 14 mg/kg BU and 200 mg/kg CY. Protocol B consisted of 14 mg/kg BU and 120 mg/kg CY or 160 mg/kg CY.
[c] DFS = thalassemia-free survival.

plications of chronic GVHD. Two patients rejected their grafts on days 305 and 366: One patient had a complete autologous thalassemic reconstitution and the other had documented persistent mixed chimerism. This patient is now 6 years after transplant with a stable normal hemoglobin level without transfusion support.

In a more recent evaluation of the correlation of categorization and the outcome of transplantation, the Kaplan-Meier statistics were calculated for 107 patients retrospectively classified as class 1 and transplanted since 1982 who were treated with a regimen consisting of 14 mg/kg BU and 200 mg/kg CY. The estimated probabilities of survival, event-free survival, rejection and nonrejection mortality at 8 years were 0.93, 0.86, 0.09, and 0.06, respectively (Figure 1). This figure includes all class 1 patients conditioned with this regimen either using methotrexate (before 1985) or cyclosporine for GVHD prophylaxis. After the first year post-transplant, three patients died in automobile accidents. If survival at the time of death is censored for these patients to facilitate evaluation of the categorization, the 10 year estimated probabilities of survival, event-free survival, rejection, and non-rejection mortality were 0.95, 0.87, 0.09, and 0.05, respectively. There are no statistically significant differences between this group and the previous one (64 patients) that included only patients conditioned with the same dose of CY. The oldest of the 90 class 1 thalassemia-free survivors is now 21 years old, and 10 are older than 17 years.

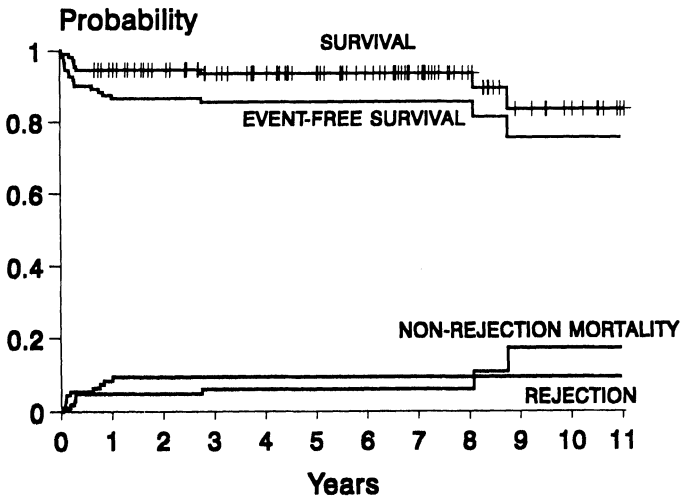

Figure 1. Kaplan-Meier probability statistics on survival, event-free survival, rejection, and nonrejection mortality for 107 class 1 patients less than 17 years old transplanted from HLA-identical family members after 14 mg/kg busulfan and 200 mg/kg cyclophosphamide. The three deaths after 1 year were due to automobile accidents.

Bone marrow transplantation in class 2 children

Between June 1985 and July 1992, 188 patients less than 17 years of age were categorized as class 2 on the basis of the presence of various combinations of two of the risk factors hepatomegaly, a history of irregular chelation before transplant, or histological evidence of liver fibrosis. The mean age was 9 years (range 1–16), the mean total number of red cell transfusions was 125 (range 0–404), and the mean serum ferritin level was 2300 ng/ml (113–8000). Forty-four patients (24%) had serological markers of hepatitis B infection, and 52% (25 out of 48 patients tested) had markers of hepatitis C. In 29 patients (17%), the pretransplant liver biopsies showed severe iron overload. Chronic active hepatitis was present in 34 patients (20%); fibrotic liver damage from moderate to severe was present in 70 patients (41%) (Table 2). The probabilities of survival, event-free survival, rejection, and nonrejection mortality were 0.88, 0.85, 0.04, and 0.12, respectively, with a plateau after the first year of follow-up (Table 3) [13]. A total of 51 patients (28%) developed grade II or worse acute GVHD; 25 patients (16%) developed chronic GVHD (mild in 19 patients, moderate in 5, and severe in 1 patient). A total of 23 patients died from transplant-related causes. Of these deaths, 14 occurred within the first 100 days (most of them during the pre-engraftment aplasia or during early engraftment, of septic-hemorrhagic causes or acute GVHD). A total of nine patients died after the first 100 days, five of them during the first year while on immunosuppressive therapy with cyclosporine. Seven patients rejected their grafts and five of these patients are alive with autologous reconstitution, receiving transfusional support [13].

A more recent evaluation has been conducted of all 256 patients less than 17 years of age, categorized (some retrospectively) as class 2 and transplanted since 1982 using regimens containing 14 mg/kg BU and 200 mg/kg CY. The estimated 10 year probabilities of survival, event-free survival, rejection, and nonrejection mortality were 0.85, 0.81, 0.06, and 0.13, respectively (Figure 2). The only death more than 1½ years after transplant was in a patient who died in the same automobile accident that killed his brother who had been transplanted in class 1 and whose death is reported earlier. The oldest of the 210 thalassemia-free surviors from this group of patients is now nearly 23 years old, 81 are 17 years of age or more, and 20 are older than 20 years.

Bone marrow transplantation in class 3 children

Between June 1983 and March 1989, 55 patients less than 17 years old were categorized as class 3 because of the presence of all the above-mentioned risk factors and transplanted using the above regimen with 200 mg/kg of CY. The results of this clinical experience were published in 1989 [7], and are

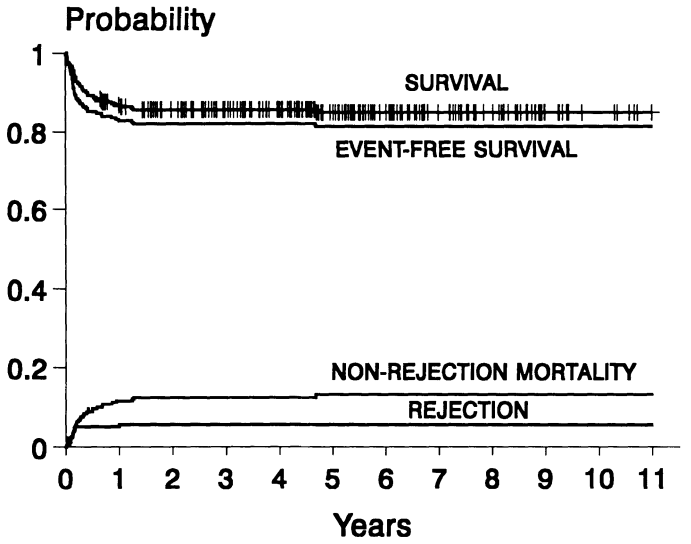

Figure 2. Kaplan-Meier probability statistics on survival, event-free survival, rejection, and nonrejection mortality for 256 class 2 patients less than 17 years old transplanted from HLA-identical family members after 14 mg/kg busulfan and 200 mg/kg cyclophosphamide. The only death after 1½ years was due to an automobile accident.

updated in Figure 3 with estimated probabilities of survival, event-free survival, rejection, and nonrejection mortality of 0.57, 0.53, 0.13, and 0.42. These outcomes were considered unsatisfactory because of a high incidence of early mortality due to regimen-related toxicity and infections. It was thought that this toxicity was a consequence of high-dose CY in patients with pre-existing liver damage, and treatment of class 3 patients with regimens containing 200 mg/kg Cy was then abandoned. Since March 1989 the use of new conditioning regimens with less cyclophosphamide and, hopefully, less toxicity has been the subject of clinical studies.

From March 1989 to August 1992, 47 patients aged 1–15 years (median 11) have been included in class 3 following the reported criteria [14]. The mean age at transplant was 11 years (range 5–15), the mean number of pretransplant transfusions was 70 (range 24–435), and the mean serum ferritin was 3996 ng/ml (range 1262–12,753). A total of 15 patients (32%) had serological markers of hepatitis B infection, and 52% (16 out of 31 patients tested) had markers of hepatitis C. The pretransplant liver biopsies showed a severe iron overload in 26 patients (55%), chronic active hepatitis in 21 patients (44%), and moderate to severe fibrotic liver damage in 38 patients (Table 2). All patients were conditioned with protocols that included a reduced dose of cyclophosphamide (from 120 to 160 mg/kg). This reduction was made mainly with the purpose of reducing the acute toxicity of the ablative chemotherapy following the Tutschka experience [15]. A total of two patients died, one from systemic aspergillosis and the other from

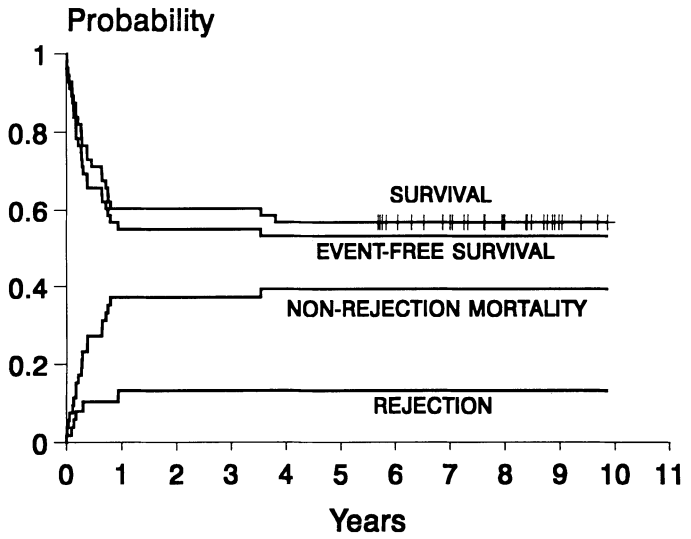

Figure 3. Kaplan-Meier probability statistics on survival, event-free survival, rejection, and nonrejection mortality for 55 class 3 patients less than 17 years old transplanted from HLA-identical family members after 14 mg/kg busulfan and 200 mg/kg cyclophosphamide.

infectious complications of severe acute GVHD. A total of 12 patients rejected their grafts between day 36 and 548 with complete autologous thalassemic reconstitution. The probabilities of survival, event-free survival, and rejection as of 1993 were 0.95, 0.64, and 0.32, respectively (Table 3) [14]. A total of three patients developed grade II acute GVHD (6%), and one patient (2%) developed grade IV acute GVHD. Out of 40 evaluable patients, one developed chronic GVHD in a moderate form.

The most recent analysis of outcome for 66 class 3 patients less than 17 years old transplanted since 1989 using a protocol with a reduced dose of CY is presented in Figure 4. The estimated 5-year probabilities of survival, event-free survival, rejection, and nonrejection mortality were 0.84, 0.58, 0.31, and 0.16, respectively.

The introduction of new protocols with a reduced dose of cyclophosphamide represents a promising step in the attempt of reducing the transplant-related mortality in this patient population. In fact the 5 year estimated nonrejection mortality is reduced from 0.42 to 0.16. At the same time the rejection rate increased from 0.13 to 0.31. The balance of risks for class 3 patients suggests that regimens with lower doses of CY might reduce the risk of transplant-related mortality in circumstances in which rejection was not associated with early death. As the much improved survival estimates show, the large majority of patients who rejected the graft had a complete autologous reconstitution with return to a pretransplant thalassemic condition. New conditioning protocols are currently being studied for young class 3 thalassemia patients in an attempt to reduce the incidence of rejection without

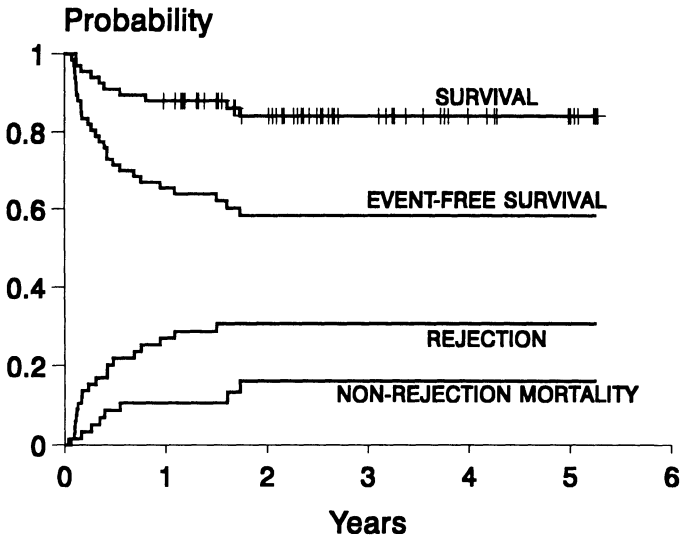

Figure 4. Kaplan-Meier probability statistics on survival, event-free survival, rejection, and nonrejection mortality for 66 class 3 patients less than 17 years old transplanted from HLA-identical family members after 14 mg/kg busulfan and 120 mg/kg or 160 mg/kg cyclophosphamide.

increasing the nonrejection mortality. An important need in this respect is to develop an improved understanding of the biology of rejection and the associated recurrence of thalassemia. It would be particularly useful if we could identify the class 3 patients at highest risk for rejection so that more intensive conditioning protocols could be reserved for such patients without jeopardizing the survival prospects of patients with a high susceptibility to transplant-related toxicity and a low risk of rejection.

A total of 90 patients transplanted while younger than 17 years and in class 3 survive without thalassemia, and 41 of these patients are now 17 years or older, while 14 are older than 20 years. The oldest thalassemia-free survivor from this group is now nearly 24 years old.

Bone marrow transplantation for adults with thalassemia

The early experience with transplantation for patients older than 16 years was disappointing, and for a time we discontinued transplantation for adults with thalassemia. Most adult patients presenting for transplantation have disease characteristics that place them in class 3, and as a consequence of the improved results with the new class 3 regimens we broadened patient eligibility in October 1988 to include thalassemic patients of all ages, with the preparative regimen selected on the basis of disease status [8,16]. Through June 1992, 41 patients were evaluated for transplant with a protocol that included radiographic studies of the skeleton, abdominal ultrasound,

liver biopsy, and cardiologic and endocrine evaluation. All patients had a history of irregular iron chelation at the time of the pretransplant evaluation. Ages ranged from 17 to 32 years (mean 20). The mean serum ferritin level was 2624 (range 329–9071). Thirty-one patients (75%) had serological markers of hepatitis B infection, and 90% (24 out of 27 patients tested) had markers of hepatitis C. Liver biopsies were performed before transplant in all 41 patients, and 7 patients had mild, 21 had moderate, and 13 had severe iron overload; while 11 patients had moderate and 16 had severe liver fibrosis. Nineteen patients had chronic active hepatitis.

Eleven patients were categorized as class 2 and 30 as class 3. Patients in class 2 received the regimens with 200 mg/kg CY, and for patients in class 3 the conditioning regimen consisted of BU 14 mg/kg and the lower dose of CY (120 mg/kg). All patients achieved engraftment but two patients rejected their transplants and were alive at the time of analysis with autologous reconstitution. The estimated probability of developing grade II or worse acute GVHD was 0.18, and this condition was fatal for two patients. Of 33 evaluable patients, 8 (24%) developed mild (7 patients) or moderate (1 patient) chronic GVHD. One patient in class 2 (9%) and five in class 3 (17%) died of transplant-related causes, mainly of septic-hemorrhagic type, within the first 100 days. The estimated probabilities of survival, event-free survival, rejection, and nonrejection mortality were 0.88, 0.82, 0.05, and 0.13, respectively [16].

More patients have accrued to this study and, from 1988 through 1993, 60 patients aged from 17 through 32 years have now been transplanted for thalassemia using conditioning regimens prescribed on the basis of risk class. The estimated 5 year probabilities of survival, event-free survival, rejection, and nonrejection mortality were 0.65, 0.62, 0.04, and 0.30, respectively (Figure 5). The only death later than 1.2 years post-transplant was associated with sudden septic shock, which occurred in a 17-year-old patient, without chronic apparent GVHD, 3.73 years after transplant. There are 42 thalassemia-free survivors from this group of patients, of whom 34 are currently older than 20 and 10 older than 25 years. The oldest survivor is 30 years of age.

Obviously adult patients who are in class 3 may have had slower clinical deterioration than younger class 3 patients. It is interesting that older class 3 patients are less likely to reject their transplants after the lower dose of CY than are younger patients and can therefore benefit from the lessened toxicity associated with this regimen. We are examining the possible reasons for this unexpected finding.

Mortality and causes of death

In a review of the outcome of transplantation for 546 patients transplanted from HLA-identical donors, 92 (17%) died from transplant-related causes

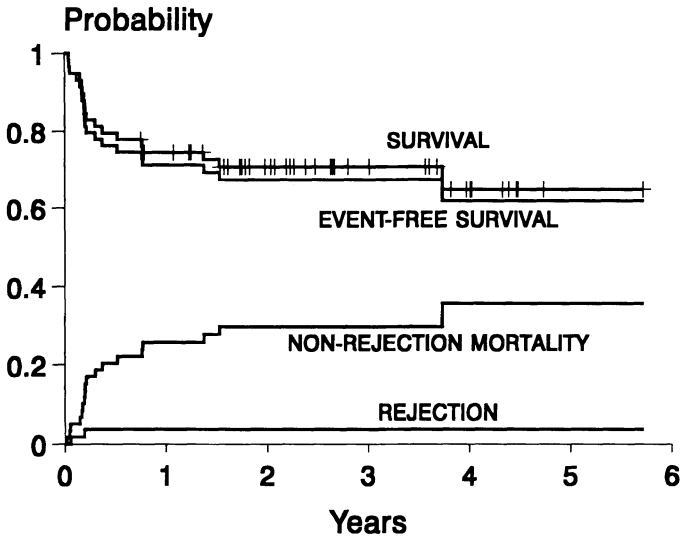

Figure 5. Kaplan-Meier probability statistics on survival, event-free survival, rejection, and nonrejection mortality for 60 patients 17 years of age or older transplanted from HLA-identical family members from 1988 through 1993. The conditioning regimens were selected on the basis of risk class. Fourteen patients in class 2 were prepared with 14 mg/kg busulfan and 200 mg/kg cyclophosphamide, while 46 class 3 patients received 14 mg/kg busulfan and 120 mg/kg or 160 mg/kg cyclophosphamide.

Table 4. Causes of death (other than recurrent thalassemia)

Causes of death	Number of patients (% of deaths)
Infection	47 (51%)
Bacterial	4 (5%)
Fungal	23 (25%)
Viral	18 (19%)
Protozoal	2 (2%)
Graft-versus-host disease	15 (16%)
Cardiac tamponade	6 (6%)
Hemorrhage	3 (3%)
ARDS[a]	3 (3%)
B-cell lymphoma	2 (2%)
Veno-occlusive disease of liver	1 (1%)
Died at home (cause uncertain)	15 (16%)
Total deaths	92

[a] ARDS = adult respiratory distress syndrome.

and the causes of death are presented in Table 4. The incidence of infections was 51% (47 patients), with a prevalence of fungal (23 patients) and viral infections (18 patients). The large majority of lethal infections occurred during the period of bone marrow aplasia. Acute and chronic GVHD have

been direct or indirect causes of death in 15 patients (16%). A worrisome complication and cause of death after bone marrow transplantation has been sudden cardiac tamponade, which occurred in six cases (6%), most likely related to a special susceptibility of the pericardial membrane of these patients [17,18]. In view of reports of liver toxicity of BU in patients transplanted for the treatment of leukemia [19], the incidence of fatal veno-occlusive disease of the liver has been surprisingly low (one patient in 92 deaths).

Experimental approaches

A current limitation of the general applicability of this therapy is the availability of a related HLA-matched donor. There is a one in four chance that any given sibling will be HLA identical, which for families of the Mediterranean area provides a 35–40% probability that a thalassemic patient will have an HLA-identical sibling who is not homozygous for thalassemia. For patients who lack bone marrow donors, transplantation from related donors mismatched for one or more HLA-A,-B, or-DR loci or from unrelated phenotypically matched donors can be considered. At present such transplants for the treatment of thalassemia are experimental. Clinical experience accumulated in patients with hematologic malignancies suggests that these transplants will be attended by a relatively high mortality rate and an increased incidence of severe GVHD. For this reason, at the moment transplants from donors other than HLA-identical family members should be considered only in special situations (for example, chronic hemolysis with consequent difficulty in maintaining a stable hemoglobin level, allergy to desferoxamine, or nonavailability of the drug with consequent impossibility of performing regular chelation) in which life expectancy is drastically shortened.

Transplantation from mismatched related donors

Through July 1994, 18 transplants from mismatched family donors have been performed in Pesaro, 12 from one antigen–mismatched donors and 6 from donors with whom they were two or three antigens mismatched. Ten patients were from Italy and three of these (aged 1, 1, and 6 years) had never been transfused due to religious reasons. Eight patients were from other countries: three from Iran, two from India, one from Pakistan, one from Argentina, and one from Azerbaijan. For 12 patients chelation therapy had not been 'regular' by our criteria. Five of these patients practically had no chelation, even though they had received many years of transfusional support. The conditioning for eight patients consisted of the standard BU (14 mg/kg) and CY (200 mg/kg) regimen, while six patients received this

regimen plus anti-lymphocytic globulin (Lymphoglobuline Merieux®). Two patients were conditioned with total lymphoid irradiation, and two patients received total body irradiation. The GVHD prophylaxis consisted of 100 days of methotrexate in three patients, cyclosporine alone in one, and cyclosporine plus a modified short course of methotrexate in 14 patients. In this group of patients the probabilities of survival, disease-free survival, and rejection were 0.58, 0.26, and 0.41, respectively. The transplant-related mortality has been high (eight patients died), and the incidence of severe acute GVHD was very high. There was no significant difference in outcome between patients transplanted from donors with whom they were one HLA antigen–mismatched compared with disparities of two to three HLA antigens, but the number of patients in the each arm was very small. Similarly, no significant differences could be found when analyzing the outcome on the basis of conditioning regimen [20].

Transplantation from phenotypically identical unrelated donors

As of July 1994, three patients have been transplanted from unrelated volunteer donors. One child was transplanted in Paris (E. Gluckman, personal communication) after a regimen of BU 16 mg/kg over 4 days followed by CY 200 mg/kg over 4 days. Another patient was transplanted in Seattle after BU 24 mg/kg over 4 days followed by CY 120 mg/kg over 4 days (E.D. Thomas, personal communication). The third patient was transplanted in Cagliari [21], after BU 14 mg/kg and CY 160 mg/kg. In each case the unrelated donor was HLA identical with the recipient. The Paris and Seattle patients promptly rejected their grafts and developed recurrent thalassemia, while the patient transplanted in Cagliari is alive with full allogeneic chimerism, normal hematopoiesis, and no evidence of acute GVHD 17 months after BMT.

As already mentioned, the worldwide experience in transplanation from unrelated donors for the treatment of leukemia suggests that this type of transplant entails a high mortality and a strong probability of severe GVHD. Thalassemia is not a disease that is imminently life threatening, and there are several ethical perplexities for exercising this therapeutic option, except in the context of a well-defined research environment and for patients who cannot obtain and tolerate efficiently delivered conventional therapy.

Post-transplant clinical and laboratory follow-up

Marrow transplantation is a therapeutic maneuver with significant risk, but mortality and risk of rejection are concentrated within the first year and subsequently most survival curves level out. Because the longest survivors are now more than 10 years post-transplant, we can reasonably claim that

these patients are definitively free of the genetic disorder and that there is no longer a significant risk of late transplant-related mortality. We refer to these individuals as ex-thalassemics after transplant. The only probability of transplant-related or thalassemia-related disability is in patients with the chronic form of GVHD. Although this can be severely disabling and has a major impact on the quality of life, it is fortunately a rare complication in young patients. In our experience of transplanting patients with thalassemia, it affects approximately 3.5% of evaluable patients still under immunosuppressive therapy, with a Karnofsky score usually ranging from 60 to 80 overall. The quality of life for all other ex-thalassemics is the same as that of their nonthalassemic, nontransplanted siblings, and those who were transplanted under 8 years of age have a near normal growth and pubertal development [22–24].

The outcome is less optimistic when transplantation is delayed until the patient is older and has more organ damage from thalassemia and its treatment. In the course of their disease, polytransfused thalassemic patients may develop multiple endocrine deficits that often necessitate substitutive therapy. Also sexual and pubertal development is often retarded and incomplete due to iron overload of specific endocrine organs, causing progressive fibrosis and functional deficits. Bone marrow transplantation can stop this progression, and removal of the continuing cause for the extramedullary organ damage can reverse the phenomenon and sometimes permit healing of the damaged organs [17,25] as the iron deposits are slowly cleared or metabolized [26]. For heavily transfused patients, or for those in whom previous suboptimal chelation programs produced heavy iron overload, this natural process of 'clearance' may take many years to be completed. An Italian multicentric study is in progress to study the possibility of accelerating the clearance of iron deposits with periodic phlebotomy [27] or, in selected cases, by restarting subcutaneous desferoxamine [28] in ex-thalassemic patients with persistent high iron overload 2 years after the transplant. Preliminary results of this polycentric study are encouraging.

Conclusions

Allogeneic bone marrow transplantation is at present the only rational therapeutic modality for the eradication of β-thalassemia major [29]. The first thalassemic patient was transplanted more than 12 years ago, and since then the results have improved steadily, with major progress in the management of transplant-related complications. This is due to the introduction of cyclosporine for prophylaxis against GVHD, more effective treatment for cytomegalovirus infection, improvement of aseptic techniques, and the evolution of systemic antibiotic therapy. At present a patient in class 1 has a 3% probability of dying, a 3% probability of rejection, and a 94% probability of disease-free survival if transplanted. In patients in classes 2 and 3 the

organ damage related to iron overload is more advanced, and therefore transplant-related mortality is higher. However, these are patients who have developed progressive and significant organ damage while receiving conventional treatment. The survival expectations of such patients are poor in the absence of intervention by marrow transplantation.

Several forms of experimental therapy are the subject of vigorous and ongoing research, and possible options for the future include artificial hemoglobin substitutes, the development of oral and more effective iron chelators, gene therapy, and agents for stimulating fetal hemoglobin production (azacytidine, hydroxyurea, or butyrate derivatives). All of these experimental approaches are far from offering routine clinical applicability. Bone marrow transplantation in β-thalassemia started as clinical experimentation about 12 years ago, and in 1994 it is a genuine option for the management of severe forms of the disease. A large body of clinical experience permits the definition of the risk related to this therapeutic maneuver for any individual patient. At present bone marrow transplantation is a therapeutic option for patients who have HLA-identical donors within the family. This option offers benefit to patients who live in regions where conventional transfusion-chelation therapy can be effectively administered. For patients who live in areas where safe transfusions and properly supervised chelation therapy are not consistently available, travel to a transplant center may be the only option that offers any reasonable expectation of prolonged survival for the patient with a suitable donor.

Hopefully in the future improved management of GVHD and the development of technologies for bone marrow transplantation from unrelated donors may expand the pool of potential candidates.

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