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Outcomes of Transplantation with Related- and Unrelated-Donor Stem Cells in Children with Severe Thalassemia

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ABSTRACT

Recently published reports indicate that the outcome of unrelated donor transplantations in patients with leukemia is currently comparable to that of transplantation from identical family donors. We investigated the possibly favorable outcomes of related and unrelated transplantation in children with severe thalassemia. We reviewed transplantation outcome in 49 consecutive children with severe thalassemia who underwent allogeneic stem cell transplantation with related-donor (n = 28) and unrelated-donor (n = 21) stem cells between September 1992 and May 2005 at the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (Bangkok, Thailand). Analysis of engraftment, frequency of procedure-related complications, and thalassemia-free survival showed no advantage from use of related-donor stem cells. The 2-year thalassemia-free survival estimate for recipients of related-donor stem cells was 82% compared with 71% in the unrelated-donor stem cell group (P = .42). The present study provides evidence to support the view that it is quite reasonable to consider unrelated-donor stem cell transplantation an acceptable therapeutic approach in severe thalassemia, at least for patients who are not fully compliant with conventional treatment and do not yet show irreversible severe complications of iron overload.

KEY WORDS

Stem cell transplantation • Severe thalassemia • Children • Related donors • Unrelated donors

INTRODUCTION

Allogeneic bone marrow transplantation (BMT) from a genotypically identical family donor is the only curative therapy for patients with thalassemia. However, the probability of finding a histocompatibility (HLA)-identical donor within the family is <30%. For patients with thalassemia without an HLA-identical sibling donor, there was until recently no treatment other than chronic transfusion and iron chelation. Within the past few years, there has been a steady increase in the number of unrelated-donor BMTs in a variety of disorders, mainly due to the increase in the number of volunteer donors worldwide [1]. There are only 2 case-series reports, by La Nasa et al. [2] from Italy and Hongeng et al. [3] from Thailand, that are available about unrelated BMT in thalassemia and both series have indicated favorable outcomes. The present study investigated outcomes of related and unrelated stem cell transplantations (SCTs) and whether these compare favorably in children with severe thalassemia that was treated at a single institution (Ramathibodi Hospital, Mahidol University, Bangkok, Thailand).

METHODS

We studied 49 consecutive patients who received related-donor (n = 28) or unrelated-donor (n = 21) stem cells for severe thalassemia between September 1992 and May 2005. Some of the present patients

Table 1. *Characteristics of Patients, Frequencies of GVHD, Procedure-Related Complications, and Causes of Death in Related- and Unrelated-donor SCT**

	Related (n = 28)	Unrelated (n = 21)
Median age at transplantation, y (range)	7.2 (0.5-18.7)	4.0 (0.7-12.0)
Male/female	13/15	14/7
Type of thalassemia		
β/β thalassemia	8	8
β thalassemia/hemoglobin E	20	13
Lucarelli class		
1	15	13
2/3	13	8
Source of stem cells		
Bone marrow	12	21
Peripheral blood	12	—
Cord blood	4	—
HLA matching		
6/6 HLA antigen match	23	—
5/6 HLA antigen match	3	—
4/6 HLA antigen match	2	—
6/6 HLA allele match	—	13
5/6 HLA allele match	—	6
4/6 HLA allele match	—	2
Myeloablative		
Bu 16 Cy 200†	20	—
Bu 16 Cy 200 ATG 40‡	4	21
Nonmyeloablative		
Bu 8 Flu 175 ATG 20 TLI 500 cGy§	4	—
GVHD		
Acute, grade II-IV	9 (32%)	9 (42%)
Acute, grade III-IV	3 (11%)	3 (14%)
Chronic	4 (14%)	3 (14%)
Extensive chronic	2 (7%)	1 (4%)
Procedure-related complications		
Hemorrhagic cystitis	3 (11%)	4 (19%)
Sepsis	3 (11%)	3 (14%)
Autoimmune hemolytic anemia	—	1 (4%)
Seizure	2 (7%)	4 (19%)
Veno-occlusive disease	6 (22%)	5 (23%)
Causes of death		
Graft failure	1	—
Bleeding	—	1
Pneumonitis	—	1
Sepsis	1	—
Chronic GVHD	—	1
Median follow-up, mo (range)	51 (6-157)	35 (6-55)

*No statistical comparison showed significant differences in incidence of acute and chronic GVHD and procedure-related complications.

†Busulfan 16 mg/kg, cyclophosphamide 200 mg/kg.

‡Busulfan 16 mg/kg, cyclophosphamide 200 mg/kg, antithymocyte gloubulin 40 mg/kg.

§Busulfan 8 mg/kg, fludarabine 175 mg/m^2, antithymocyte gloubulin 20 mg/kg, total lymphoid irradiation 500 cGy.

were previously reported [3-5]. Patients and donors or their parents signed an informed consent before treatment. Characteristics of the 2 groups are presented in Table 1. Some of our patients could not be classified with the Pesaro risk classification because we did not perform routine pretransplantation liver biopsy before 2000 [6]. Although some of our patients did not have pretransplantation liver biopsy, these patients had severe anemia, marked hepatosplenomegaly, multiple blood transfusions, and high serum ferritin levels. Most of them received no or inadequate iron-chelation therapy. Therefore, these patients were classified as moderate to high risk (Lucarelli class 2 or 3) [6].

Histocompatibility

HLA was determined by conventional serologic typing for class I and II antigens. DNA typing with high-resolution sequence-specific oligonucleotide probes for class I and II loci was undertaken for patients with matched and mismatched HLA-unrelated or mismatched HLA-related donors.

Conditioning Regimen

Forty-five patients received myeloablative and 4 patients received nonmyeloablative conditioning regimen. A myeloablative regimen consisted of busulfan 1 mg/kg taken every 6 h for 4 days, and cyclophosphamide 50 mg/kg infused daily for 4 days. Antilymphocyte globulin (ATG; Fresenius, Graefelfing, Germany) 10 mg/kg/d was also infused daily for 4 days in patients with unrelated BMT and cord blood transplantation. A nonmyeloablative regimen consisted of busulfan 1 mg/kg taken every 6 hours for 2 days, fludarabine 35 mg/m^2 infused daily for 5 days, ATG 5 mg/kg/d infused daily for 4 days, and total lymphoid irradiation administered at a single fraction of 500 cGy [4,5]. The nonmyeloablative regimen was designed for patients who were classified as having Lucarelli class 3 and received stem cells from matched or mismatched related donors. All patients in risk class 3 were given hydroxyurea 20 mg/kg/d ≥3 months before BMT to decrease erythroid expansion and thus prevent graft rejection [3-5].

Preparation of Stem Cell Grafts

T-cell nondepleted bone marrow, peripheral blood, or cord blood stem cell graft was infused on day 0. Only 1 patient who underwent nonmyeloablative SCT received purified CD34$^+$ cells that were derived from 2 antigens and HLA-mismatched maternal peripheral blood stem cells with additional CD3$^+$ cells to a total of 1×10^5 CD3$^+$ cells/kg [5]. These purified CD34$^+$ cells were obtained with Clinimacs (Miltenyi, Bergisch, Germany). For peripheral blood stem cell graft preparation, donors received subcutaneous granulocyte colony-stimulating factor 10 μg/kg/d for 4 days before leukapheresis procedures.

Graft-versus-Host Disease

For graft-versus-host disease (GVHD) prophylaxis, 2 to 4 days before transplantation, patients received cyclosporin at a dose that was adjusted to