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Original Article

Unrelated-donor, peripheral blood stem cell transplantation in thalassemia major

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Abstract: Objective: To investigate the clinical efficacy and complications of unrelated-donor peripheral blood stem cell transplantation (URD-PBSCT) for treating thalassemia major and to evaluate its safety and efficacy. Methods: As study subjects, forty-six children diagnosed with thalassemia major in The Second Affiliated Hospital of Hainan Medical College between October 2014 and November 2016 were selected. Busulfan + Cyclophosphamide + fludarabine + antithymocyte globulin (Bu + Cy + Flu + ATG) was used as a preconditioning approach to perform URD-PBSCT. The hematopoietic stem cell engraftment, adverse reactions, complications, and survival were observed. Results: After completion of the graft infusion, hematopoietic function was rapidly reconstructed except for one patient with severe hemolysis. After the reconstitution of hematopoietic function, acute graft-versus-host disease (aGVHD) at stage II to IV was observed in 12 patients, and the incidence rate was 26.1% (12/46). One case of severe aGVHD was observed. There were 29 cases of oropharyngeal mucositis, including 4 cases of severe oral mucositis. There were 2 cases of cytomegaloviremia, which immediately received ganciclovir treatment and improved after 14 days. Bacterial infection occurred in 6 cases. No fungal infection was found. All patients were successfully implanted and the median follow-up time was 2.7 years. Both the implantation rate and the survival rate were 100.0%. Conclusion: The use of Bu + Cy + Flu + ATG as a pretreatment regimen for allo-PBSCT in treating infants with β-thalassemia major is safe and effective, with no signs of severe GVHD, and can be further expanded in case studies.

Keywords: Thalassemia major, unrelated-donor peripheral blood stem cell transplantation, graft-versus-host disease

Introduction

Thalassemia major is a hereditary hemolytic disease that is caused by a lack of synthesis of the globin peptide chain. Major clinical symptoms of thalassemia major include chronic progressive hemolytic anemia, hepatosplenomegaly, and significantly increased hemoglobin (Hb) levels [1, 2]. Once a child has an episode of thalassemia major, the demand for regular blood transfusions is high and the patient requires taking iron-removal drugs to stay alive [3, 4]. However, due to the relatively long treatment time, high medical costs, and poor treatment compliance, these methods severely affect the children's quality of life, and bring a heavy burden on the family. The rapid development of unrelated-donor peripheral blood stem cell transplantation (URD-PBSCT) in recent years has resulted in a cure for thalassemia [5, 6]. However, transplanting bone marrow in children with β-thalassemia major is challenging because of the characteristics of blood cells within autogenous bone marrow and the susceptibility physique caused by long-term blood transfusion. Continuously improving the pretreatment regimen and strengthening supportive care have become the focus of transplantation research. In this study, Busulfan + cyclophosphamide + fludarabine + antithymocyte globulin (Bu + Cy + Flu + ATG) was used as a preconditioning approach to perform unrelated-donor peripheral blood hematopoietic stem cell transplantation (URD-PBSCT) to provide clinical evidence for the treatment of thalassemia major.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of The Second Affiliated Hospital of

Table 1. General information about the patients and donors

	Patient data	Donor data
Cases	46	46
Gender		
Male	20	26
Female	39	7
Age (year)	6.7 (2.0~10.0)	12.6 (4~31.0)
Clinical indexing		
I	14	
II	28	
III	4	
HLA matching		
10/10 matched	27	
9/10 matched	15	
8/10 matched	4	

Hainan Medical College. Forty-six patients diagnosed with thalassemia major and treated in The Second Affiliated Hospital of Hainan Medical College between October 2014 and November 2016 were enrolled in the study. The age range was 2.0-10.10 years and the median age was 6.7 years. The study included 20 males and 26 females. The Italy Pesaro Transplantation Center indexing criteria were used for indexing and it was as follows: grade I in 14 cases, grade II in 28 cases, and grade III in 4 cases [7].

Inclusion criteria: (1) Patients diagnosed with thalassemia based on the Criteria for diagnosis and efficacy of hematological diseases; (2) Hb content 30-60 g/L in the absence of blood transfusion; (3) Children and their families were informed of the study and signed the consent form [7].

Exclusion criteria: (1) Hemolytic anemia as a result of other causes; (2) Children with abnormal coagulation and severe liver and kidney dysfunction; (3) Children with poor compliance and failure to cooperate with treatment.

All patients received URD-PBSCT from non-blood allogeneic donors. The 46 cases of donors included 39 males and 7 females, aged 4.0 to 31.0 years, with a median age of 12.6 years. A total of 31 patients had mismatched blood group recipients. There were 27 cases of human leukocyte antigen (HLA) matching, including 10/10 matched, 15 cases of HLA 9/10 matched, and 4 cases of HLA 8/10 matched (**Table 1**).

Methods

Prior to transplantation, the patients were given the following treatment: (1) high frequency blood transfusion at regular times, 45 days before transplantation to correct anemia and maintain Hb levels above 150.0 g/L; (2) deferoxamine 40.0 mg/kg/d was continuously administered intravenously by micro-pumps for 8 to 12 hours for 10 consecutive days; deferiprone was given 75.0 mg/kg/d twice daily for iron removal; (3) roughly 3 months prior to transplantation, hydroxyurea 30.0 mg/kg/d and azathioprine 3.0 mg/kg/d were administered to inhibit a bone marrow hyperproliferation state and to prepare for pretreatment to reduce the incidence of rejection [8]. During this period, the blood parameters were routinely monitored. When leukocytes were reduced to $2*10^9$/L, the drug treatment was stopped.

The collection and preparation of hematopoietic stem cells was performed simultaneously: the blood donors were given a subcutaneous injection of 5 μg/kg granulocyte colony-stimulating factor (G-CSF) once daily for 5 consecutive days [8]. On day 6, peripheral blood hematopoietic stem cells were collected using a CS-3000 blood cell separator. The circulating blood volume was required to reach 15 L, and the number of nucleated cells was required to reach $10*10^9$/L. If these parameters did not meet the required standards, blood was collected again on day 7. After collecting the cells, 2 mL of cells was removed for examination. The $CD34^+$ and $CD3^+$ cells were counted, and blood smears were prepared to evaluate the morphology of the leukocytes.

Pretreatment and graft infusion: (1) Pretreatment plan: Pretreatment with Bu + Cy + Flu + ATG was performed using BU at 2.8-4.4 mg/kg/d, and the dose was adjusted according to the age and disease of the children. Moreover, it was administered orally four times from the 8th to the 5th day prior to surgery; Cy at 50.0-60.0 mg/kg/d was given by intravenous drip for 2 days from the 10th to the 9th day prior to the operation; Flu at 40.0 mg/m^2/d was given once a day by intravenous drip from the 6th to 2nd day prior to the operation. ATG at 5.0 mg/kg/d was given once a day by intravenous drip from the 5th to 2nd day prior to the operation. (2) Graft infusion: dexamethasone and promethazine hydrochloride were given as

anti-allergy treatment prior to the infusion of the graft and hydration and alkalinization of urine were given. At the beginning of the infusion, electrocardiograph monitoring was continued, and changes in heart rate, blood pressure, respiration, and urine color were monitored until 4-6 hours after the completion of the graft infusion. During treatment, the patients were admitted to laminar wards and antibiotics were given to prevent infection. When leukopenia was observed, itraconazole was given to prevent fungal infections. Granulocyte colony-stimulating factor (300 μg/d) was administered subcutaneously on the first day after graft infusion and was continued for 20 days [8].

Prevention of GVHD: A cyclosporine + mycophenolate mofetil + methotrexate (CsA + MMF + MTX) regimen was given with CsA of 1.5-3.0 mg/kg/d. The day before transplantation, when the gastrointestinal symptoms were relieved and the patients could take oral medication, the dosage was changed 6.0 to 8.0 mg/kg/d, and the dosage was administered by two times orally every day. At the same time, according to the CsA plasma concentration (maintained at 150-400 μg/mL), the dosage of drugs was adjusted and used for a total of 3 to 6 months. MMF was administered 600.0-1,000.0 mg/m^2 each time and once every 12 h orally, beginning on the 3rd day before transplantation and lasting for 35 days. MTX was administered 15.0 mg/m^2 on the first day after transplantation, and 10.0 mg/m^2 on days 3, 6, and 11 after transplantation.

The number of returned cells: The range of the $CD34^+$ cells was 3.0-26.8*10^6/kg, and the MNC range was 5.6-23.5*10^8/kg. Successful implantation: Peripheral blood neutrophils ≥0.5*10^9/L. In the absence of platelet (PLT) transfusion, PLT ≥20*10^9/L. In the absence of red blood cell transfusions, Hb was maintained above 90 g/L. If the above conditions were sufficient, the implant was considered successful.

Post-transplant treatment: (1) Prevention and treatment of infection. To prevent infection, the patient entered the laminar sterile ward 5-7 days prior to pretreatment. If the patient was a hepatitis B virus carrier, lamivudine was administered orally to prevent hepatitis virus replication. At day 7 prior to transplantation, ganciclovir, voriconazole, compound sulfamethoxazole, and cefoperazone were administered to prevent cytomegalovirus, fungi, *pneumocystis carinii*, and bacterial infection. The blood parameters were routinely checked. (2) Symptomatic support treatment: If the patient needed to fast, parenteral nutrition was given. When red blood cells ≤80 g/L, red blood cells needed to be transfused. When PLT ≤10*10^9/L, and there was a tendency to bleed, PLT transfusion was given. (3) GVHD prevention: A triple regimen of cyclosporine + mycophenolate + methotrexate was used to prevent the occurrence of GVHD. If GVHD occurred, methylprednisolone was added for the treatment [9].

Observation indicators

Primary observation indicators: (1) Hematopoietic function reconstruction: Hematopoietic function reconstitution after graft infusion was evaluated; (2) Complications: The incidences of aGVHD, infection, gastrointestinal symptoms, toxic shock, pulmonary hemorrhage, hepatic vein occlusive disease, and hemorrhagic cystitis were determined after allo-PBSCT.

Secondary observation indicators: Follow-up was performed to observe the occurrence of chronic graft-versus-host disease (cGVHD) as well as the survival rate of patients.

Statistical analysis

SPSS 17.0 software was used for the data analysis. GraphPad Prism image processing software was used for the data plotting.

Results

Hematopoietic function reconstitution

After the graft infusion was complete, the hematopoietic function was rapidly reconstructed except for one patient who presented with severe hemolysis. Among the patients, the time it took the absolute neutrophil count in the peripheral blood to reach ≥0.5*10^9/L was 10-19 days, and the median time was 18.2 days. The time it took PLT to reach ≥20*10^9/L was 11-21 days, and the median was 18.5 days. The time it took Hb to reach ≥90 g/L was 15-51 days with a median of 31 days. During the follow-up period at 1 year after transplantation, the Hb level was maintained above 100 g/L (**Table 2**).

Table 2. Time of hematopoietic function reconstitution

	Time range (d)	Median time (d)
Neutrophil ≥0.5*10^9/L	10-19	16.2
Platelet ≥20*10^9/L	11-21	18.5
Hemoglobin ≥90 g/L	15-51	31.0

GVHD occurrence

After reconstitution of the hematopoietic function, a total of 12 patients developed grade II-IV aGVHD with an incidence of 26.1%. Of these, 1 case was intestinal severe aGVHD and 2 cases were grade III skin aGVHD, and they all improved after treatment. A total of 8 cases (17.4%) developed cGVHD, and most of them showed grade I-II skin and liver lesions. Liver GVHD showed elevated bilirubin, alanine aminotransferase. Skin GVHD manifested the symptoms of skin congestion, macular papules, and itching pain. All the symptoms were relieved after glucocorticoid therapy (**Tables 3**, **4** and **Figure 1**).

Incidence of infection

After reconstitution of the hematopoietic function, 29 cases of oropharyngeal mucositis occurred, 4 of which were severe oral mucositis; 2 cases of cytomegaloviremia occurred, and the patients immediately received ganciclovir treatment, which improved the symptoms after 14 days. Bacterial infections occurred in 6 cases, including 2 cases of cystitis, 1 case of otitis media, 1 case of sinusitis, and 2 cases of G + bacterial infection after blood culture, which was considered to be a catheter-related infection, and the infection was improved after anti-infective treatment. There was no fungal infection in this group (**Table 5** and **Figure 2**).

Other compliance

During pretreatment, the main toxic and side effects included nausea and vomiting, diarrhea and other gastrointestinal symptoms, transient bilirubin, and elevated transaminase, which disappeared after symptomatic treatment. In the course of transplantation, epilepsy occurred in two cases, which was considered to be related to the drugs and was just a transient attack. After sedation, the condition improved and no further attacks occurred. What's more, the one case of otitis media and the one case of sinusitis improved after the antimicrobial therapy. There were two cases of hemorrhagic cystitis after the transplantation, which were quickly improved after administering alkali and hydration of urine. After transplantation, none of the patients experienced severe complications, such as toxic shock, multiple organ failure, cerebral hemorrhage, hepatic venous occlusion, or pulmonary toxicity. All the patients survived the implantation. Hemolysis occurred in one patient, which was mainly due to the incompatibility of the blood group.

Follow-up and outcome

The follow-up period ended on April 19, 2018, with the shortest being 2 months, and the longest 43 months, with a median time of 2.7 years. All the patients were successfully implanted and the implantation rate was 100%. As of the follow-up date, all the cases survived, the survival rate was 100%, and the mortality rate was 0%. Two of the children developed autoimmune hemolytic anemia at six months and 11 months after transplantation, respectively. Their conditions became stable after treatment with hormones and a rituximab injection. The other children were all in good condition.

Discussion

Regular blood transfusion and iron-removal therapy are critical treatment methods for patients with β-thalassemia major. Although long-term survival can be achieved, the costs associated with treatment are high and treatment compliance is poor, which seriously affects a patient's quality of life [10]. Currently, URD-HSCT is the only clinical cure for β-thalassemia major [11, 12]. After successful hematopoietic stem cell transplantation, patients may completely dispose of blood transfusion and iron-removal treatment. Based on different donors, the types of hematopoietic stem cells include bone marrow, peripheral blood, umbilical cord blood, and HLA matching. Irfan et al. compared the therapeutic effects of bone marrow and peripheral blood stem cell transplantation on thalassemia and found no significant differences in the disease-free survival rate [13]. Moreover, Ghavamzadeh et al. [14] reported that although no differences were

Table 3. aGVHD occurrence

	Skin damage	Intestinal damage	Total
Grade			
I	0	0	0
II	6	2	8
III	2	1	3
IV	0	1	1
Total (n, %)	8 (17.4)	4 (8.7)	12 (26.1)
Median time (d)	34.7	31.9	
Treatment	Methylprednisolone, 2 mg/kg, Q12h, IVGTT; improved after local hormone application	Hormone therapy similar to the treatment of skin damage. Patients with grade III were also treated with an anti-CD25 monoclonal antibody	

Table 4. cGVHD occurrence

	Skin damage	Liver damage	Total
Grade			
I	4	3	7
II	1	0	1
III	0	0	0
IV	0	0	0
Total (n, %)	5 (10.9)	3 (6.5)	8 (17.4)
Median time (d)	34.7	17.9	
Treatment	Methylprednisolone, 2 mg/kg, Q12h, IVGTT; improved after local hormone application	Hormone therapy similar with the treatment of skin damage	

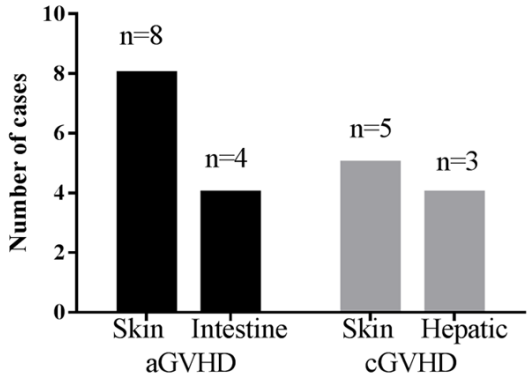

Figure 1. Distribution of GVHD.

observed in the disease-free survival rate of bone marrow and peripheral blood stem cell transplantation, the GVHD of peripheral blood stem cell transplantation was more serious.

We chose non-blood allogeneic hematopoietic stem cell transplantation for the treatment of β-thalassemia major. Except for the severe hemolysis observed in one patient, the hematopoietic function was all rapidly reconstructed. One year after transplantation, the Hb levels of all the patients were maintained above 100 g/L, and all the patients were successfully transplanted. Among them, the median time for absolute neutrophil in peripheral blood that reached ≥0.5*10^9/L was 18.2 days, which was consistent with the data reported in the literature and was significantly shorter than that of bone marrow transplantation. Rapid reconstitution of hematopoietic function better relieves the financial burden on children, shortens hospital stays, and reduces the incidence of infection. By the end of follow up, all the patients were implanted successfully and the implantation rate was 100.0%. As of the follow-up date (median follow-up time, 2.7 years), all cases survived, the survival rate was 100.0%, and the mortality rate was 0%.

Pretreatment was the immunosuppressive treatment of choice prior to URD-PBSCT [15]. The purpose of pretreatment is to remove abnormal hematopoietic cells in the patient's bone marrow and suppress the immune system as much as possible, so that the stem cells of the donor are not repelled and the recipient's bone marrow is emptied, ensuring

Table 5. Incidence of infection

	Case
Viral infection	
Oropharyngeal mucositis	29
Cytomegaloviremia	2
Bacterial infections	
Cystitis	2
Otitis Media	1
Sinusitis	1
Catheter-Related Infection	2

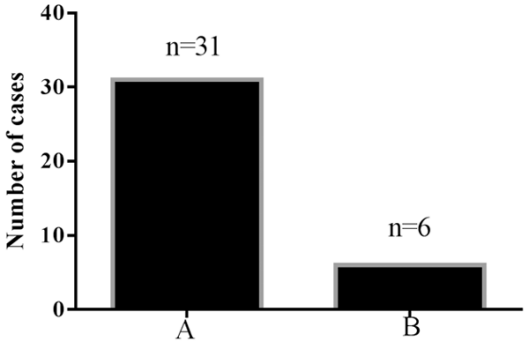

Figure 2. Distribution of different infections.

the donor's stem cells are implanted. Pretreatment is divided into a myeloablative and non-myeloablative approach. Bone marrow proliferation in children with thalassemia major is extremely prosperous, and immune function is more complete than it is in other malignant hematological diseases. Multiple blood transfusions can cause alloantigen sensitization; therefore, bone marrow clearance and immune clearance are more challenging. Thus, in this study, we employed the myeloablative protocol of treating with Bu + Cy + Flu + ATG. Unlike previous myeloid protocols, the dose of Bu and ATG was decreased and thiotepa (TT) was not used in this protocol. TT has a high degree of bone marrow clearance and immunosuppressive effects. The addition of TT to the classical BuCy protocol constitutes a BCT protocol that can significantly reduce the recurrence rate [16]. However, pulmonary hemorrhages, hemorrhagic cystitis, cardiotoxicity, skin toxicity, and related mortality may occur. Therefore, in this study, TT was not used. Cy plays an immunosuppressive role in the pretreatment regimen. In previous studies, it has been reported that the risk of life-threatening cardiac toxicity can reach 5.0% to 10.0% when a Cy dose of greater than 200.0 mg/kg is used [17]. In this study, the dose of Cy was lower than 200.0 mg/kg, and it was used in combination with Flu. Flu has a strong immunosuppressive effect and no overlap toxicity in combination with Bu and does not affect the implantation rate. All the patients in this study were successfully implanted with an implantation rate of 100%. As of the follow-up date, the median follow-up time was 2.7 years. Both the patients' survival rate and mortality rate were 0%. Additional observations of pretreatment-related complications were performed. During the pretreatment in our study, the main toxic and side effects included nausea and vomiting, diarrhea and other gastrointestinal symptoms, transient bilirubin, and elevated transaminase, which disappeared after symptomatic treatment. All patients were implanted successfully without serious GVHD and infection after surgery, which might be associated with the drug doses of this therapeutic regimen, indicating the clinical feasibility of the pretreatment used in this study. This results are consistent with the relevant studies in the literature.

The major complications of allo-HSCT include the toxic side effects of pretreatment, severe infection in the desolation of the bone marrow, GVHD, and multisystem organ failure, which are important indicators in evaluating the effect of allo-HSCT treatment [18, 19]. In the course of transplantation, epilepsy occurred in two cases, which was mainly connected with the use of calcineurin inhibitors. GVHD is a common complication of URD-PBSCT, and it's also one of the main causes of transplant failure and early death in patients [20, 21]. The earlier GVHD is diagnosed, the less hormones are used and the fewer corresponding infections occur. Methylprednisolone is the first choice for the treatment of GVHD. In this study, aGVHD occurred in 12 patients after transplantation, with an incidence of 26.1%, which was consistent with the study reported previously [22]. The GVHD mainly includes lesions of the skin and intestines. Among those GVHD patients, only two cases of skin lesions were III grade GVHD, and one case was intestine lesion was IV degree GVHD, and the symptoms were relieved after hormone and symptomatic treatment. Infections after hematopoietic reconstitution include cytomegalovirus infection, fungal infection, bacterial infection, and the infection

sites include pulmonary infection, oral infection, urinary tract infection, and pulmonary infection. A study revealed that 10%-40% of patients might die from pulmonary complications [8]. Infection is an important cause of pulmonary complications, and post-transplantation GVHD, hormone therapy, and cytomegaloviremia are all risk factors for pulmonary infection. Therefore, a timely diagnosis of GVHD, the monitoring of cytomegalovirus infection, and active treatment can reduce the occurrence of pulmonary infection to some extent and improve the prognosis of patients. In this study, there were 31 cases of viral infections, 29 of which were oral mucosal infections and 2 cases were cytomegalovirus viremia. After active antiviral treatment, the symptoms improved rapidly. The results showed that the transplant-related protocol used in this study is relatively safe. No toxic shock, multiple organ failure, cerebral hemorrhage, hepatic vein occlusive disease, pulmonary toxicity, pulmonary infection, or other serious complications were found after transplantation, and the incidence of serious complications was low. The main reasons are related to the age (under 7 years old), the standard blood transfusion and iron removal therapy before transplantation, as well as the adjustment of disease grading and preconditioning program. Therefore, the pretreatment regimen used in this study effectively controls disease and ensures a smooth implantation of hematopoietic stem cells. However, the effects of this study on the growth and development of thyroid function are still under follow-up observation. In cooperation with pediatric doctors specializing in growth and development, all the children are monitored for growth and development after transplantation to assist in treatment and to pay attention to the growth and development of the children.

In summary, the data presented in this study suggest that Bu + Cy + Flu + ATG as a preconditioning regimen for non-blood URD-PBSCT for the treatment of β-thalassemia major can quickly achieve the reconstruction of hematopoietic function. The incidence of severe GVHD was low, and sufficient disease-free survival can be achieved. However, the sample size of this study was limited, and further multi centers and large-scale trials are needed.

Disclosure of conflict of interest

None.

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