Peripheral Blood Stem Cell Transplantation in Patients with Beta-Thalassemia Major

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Abstract

From 1996 to 2002, fifty three patients with major beta-thalassemia received allogeneic peripheral blood stem cell transplantation (PBSCT). Median age was 6 years .Twenty two were class I, 17 class II and 14 class III. All of the donors were HLA-identical. Conditioning regimen for class I and II patients consisted of Cyclophosphamide (CY) 50 mg/kg/day for 4 days + Busulfan (Bu) 3.5 mg/kg for 4 days, while class III patients received 4 mg/kg/day Busulfan for 4 days and 40mg/kg/day Cyclophosphomide for 4 days. G-CSF (Neopogen) 5µ/kg IV was given to donors. Graft Versus Host Disease (GVHD) prophylaxis regimen consisted of Cyclosporin-A (CsA) 3 mg/kg/day plus Methotrexate (MTX) 10 mg/m^2 on day+1 and 6 mg/m^2 on days +3 and +6. The median time for neutrophil and platelet engraftment was day +16 and day +23 post transplantation, respectively. Chronic GVHD (cGVHD) was observed in 30 patients (56%). Ten patients (18.8%) died. Forty patients are well and transfusion independent. Median time of follow-up was 23 months. Recurrences have been seen at 3 pts, one patient 21 months, the other one 6 months and the last one 8 months after transplantation, who received Donor Lymphocyte infusion (DLI). Event free survival was 72% and overall survival was 80%. In conclusion, we suggest that PBSCT can be considered a safe and effective treatment for children with Beta-thalassemia major and cGVHD is tolerable and manageable in these patients.

Key words: Peripheral blood stem cell transplantation, Beta thalassemia, GVHD

Introduction

Stem cells are often harvested by bone marrow aspiration technique in the operating room under general anesthesia. In fact, aspiration was the rule for all kind of diseases, including thalassemia, intended to be cured by stem cell transplantation till 1981, when peripheral blood was introduced as a stem cell harvesting source.[1,2] The classical stem cell source, being the bone marrow (BM) was introduced by E.D. Thomas in 1963. Two decades later, in 1981, peripheral blood (PB) was introduced as a second source and, in 1988, cord blood (CB) was introduced to the scientific society as a third source for stem cell extraction. Peripheral blood stem cell transplantation is increasingly used. Some authors have suggested PBSCT has some advantages as compared with bone marrow stem cell transplantation.

Diaz, et al, reviewed the use of cytokine-mobilized PBSC for allogeneic transplantation and reported that it appears to be safe for both pediatric donors and patients, leading to a rapid hematopoetic recovery with similar incidence of acute graft-versus host disease (aGVHD).[3] Vialla and Kawano reported that using PBSC instead of BM leads to faster hematological recovery, a similar risk of GVHD, and improved survival.[8,9] We retrospectively analyzed 53 children in our center with beta-thalassemia major, given PBSCT.

Material and methods

Fifty three patients with Beta-thalassemia major received PBSCT from 1996 to 2002 in our center. All of the patients were transfusion-dependent before stem cell transplantation. The female to male ratio was 24/29 and the median age of the patients was 6 years (range 2-12 years). Twenty two of them were class I, 17 class II and 14 were class III. Their weight was between 10-37 kg. Fifty of the donors were fully HLA-matched siblings and 3 were parents. Conditioning regimens consisted of 3.5 mg/kg busulfan for 4 days and 50 mg/kg/day CY for 4 days in the class I and II patients. All class III patients received 4 mg/kg/day Bu for 4 days and 40mg/kg/day CY for 4 days as a conditioning regimen. G-CSF (Neopogen) 5µ/kg IV was given to donors of peripheral blood stem cell mobilization for 5 days. Antecubital veins were used for harvesting in older children and adults and central veins were used in other child donors. Peripheral blood stem cell apheresis was performed on the fifth day but continued on days 6 and 7 when necessary. The median apheresis session was one (range 1-2). Median apheresis time was 240 min (180-360 min). The

mean number of WBC for transplantation was 10.6×10^8 cells/kg, the mean number of MNC was 8.2×10^8 cells/kg and the mean number of CD34 was 0.42×10^6 cells/kg. Forty patients received 5 µg/kg G-CSF starting on day +1.

For GVHD prophylaxis, the patients received CsA 3 mg/kg/day iv from -2 to +5 followed by 12.5 mg/kg/day PO, which was tapered according to the patient's condition and MTX (10 mg/m^2 on day+1 and 6 mg/m^2 on days +3 and +6. Successful engraftment was defined as the first consecutive 3 days of the absolute neutrophil count exceeding 0.5×10^9/L for neutrophil engraftment and the first of 7 consecutive days with an untransfused platelet count exceeding 20×10^9/L for platelets.

GVHD was graded as previously described by the International Blood and Marrow Transplantation Registry (IBMTR).

Results

Engraftment was achieved in 40 patients. The median neutrophil and platelet engraftment times were 16 days (14 to 93 days) and 23 days (14-65), respectively.

Ten patients died during time period of 4 to 343 days after transplantation. Causes of death were aGVHD(2), cGVHD(2), VOD(1), infection(2), and multiple organ failure(3). None of them died due to recurrence. Twenty two patients were in class I and 5 of them (22.7%) expired due to aGVHD(1), cGVHD(1), VOD(1) and multiple organ failure(1), infection(1). Seventeen patients were in class II, 2 of them (11.6 %) expired due to aGVHD and multiple organ failure. Thalassemia relapsed in two of these patients. Of the 14 class III patients, 3 (21.4%) expired due to cGVHD complications, infection and multiple organ failure. GVHD was graded according to standard criteria (IBMTR). Acute GVHD was observed in 52 patients (91%), Grade I in 11 patients, Grade II in 13 patients, Grade III in 21 patients, and Grade IV in 7 patients (Table 1).

Table 1: Acute and Chronic GVHD

aGVHD	
I-II	24/52 (46.1%)
III-IV	28/52 (53.7%)
cGVHD	
Limited	17/35 (48.5%)
Extensive	18/35 (51.4%)

Seventeen (48.5%) showed limited and 18 (51.4%) showed extensive GVHD. But gradually some of extensive ones regressed toward limited type chronic GVHD, and finally 12 patients (22.6%) remained in extensive chronic GVHD and 17 limited chronic GVHD reduced to 12 (22.6%) after the cure of 5 limited diseases.

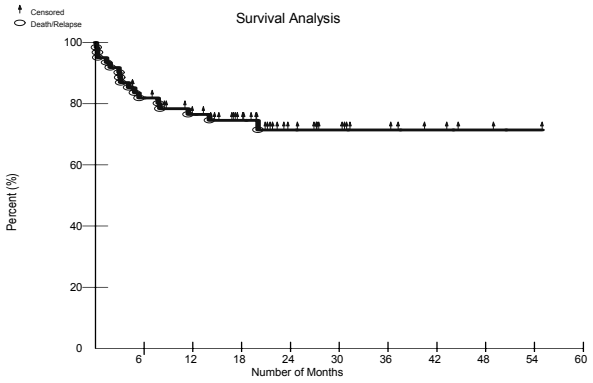
Veno-occlusive disease (VOD) occurred in 3 patients.

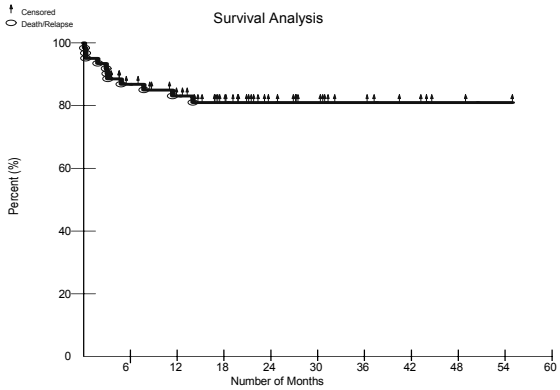
Forty of the patients are well and transfusion-independent .Median time of follow-up was 23 months (range 3-56 months)(Table 2).

Table 2: Current status

Transfusion independent	40
Alive/dead	43/10
Overall survival	80%
Disease free survival	72%
Follow up(Median time; months)	23 (3-56)

Recurrences have been seen in 3 patients. Overall survival was 80% and event free survival was 72% (Figure 1,2).





Discussion

Beta thalassemia major is a health problem in children and teenagers in Iran. Before stem cell transplantation, there was no potentially curable treatment. Our center started stem cell transplantation in 1991 and beta-thalassemia major is one of our main concerns in this field. Following successful results of Lucarelli et al,(4) we naturally adopted stem cell harvesting from the iliac crest. The main difficulty of this kind

of harvesting is general anesthesia and severe blood loss in some donors during aspiration from the iliac crest.[5,7] Gradually, we used the PBSCT technique and now it is our main method of harvesting in beta-thalassemia major. According to our report and study,[11] neutrophil and platelet engraftment occurred 18.8 days and 21.2 days after PBSCT, respectively. In BMT, this was 26.2 and 34.2 days, respectively. So engraftment occurs about 8 days earlier in PBSCT compared to stem cell harvesting from the iliac crest .According to the number of patients in each class, our mortality is higher in class I and class III but because each class group is not enough, we can not draw any conclusions concerning the relationship between the probability of mortality and the class group. Conditioning and GVHD prophylaxis are the same in both groups. Referring again to our report, the incidence of severe aGVHD (grade 3 and 4) was the same in PBSCT and BM harvesting methods (21% in PBSCT and 20% in the comparison group). We have not used any technique of T-Cell purging in our center for PBSCT in beta-thalassemia major, and, aGVHD incidence in both groups shows that T-cell purging is not mandatory in these patients. In our previous study, cGVHD occurred in 37.8% of 147 patients from which 58.4% occurred in PBSCT and 41.55% in the bone marrow harvesting method. According to our paper [12] the most important predictive factor for developing cGVHD in beta-thalassemia major recipients is the type of transplantation: 78.9% (15/19) of patients who underwent allogeneic PBSCT developed cGVHD compared with only 34.3% (24/70) of those who underwent allogeneic BMT ($P<0.001$). Risk of developing cGVHD within one year of transplantation was 17.9% higher in PBSCT thalassemic recipients, which is treatable. This seemed to be the only disadvantage of PBSCT in comparison to the BM harvesting method in our previous report, but, as previously mentioned in the result section, cGVHD is not a main cause of mortality or morbidity in our series and by this time it is improving. We use the phlebotomy technique in some patients as an iron reducing technique but, we advise strong tea after each meal to them. Yesilipelc reported PBSC in 15 patients. Conditioning regimen in their study consisted of Bu and CY with or without ATG. The median neutrophil and platelet engraftment time were day 12 and 16.[10] Overall, PBSCT for beta-thalassemia major Patients seems safe and effective and with a lower risk in comparison to the BM harvesting method.[6,7]

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