

Comparison of Umbilical Cord Blood Transplantation with Bone Marrow or Peripheral Blood Derived Stem-Cell Transplantation in Transfusion Dependent Thalassemia Patients: A Single Center Propensity Score Matching Analysis

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Abstract

Background: Successful hematopoietic stem cell transplantation (HSCT) could cure the hematological manifestations of transfusion-dependent thalassemia (TDT) but introduces risks of morbidity and mortality. Umbilical cord blood transplantation (UCBT) is considered as an acceptable strategy, by providing a condensed graft versus host disease (GvHD). This paper compares the outcomes of UCBT with HSCT from peripheral blood and bone marrow in TDT patients.

Methods: Between 1998 and 2014, 10 patients with TDT underwent UCBT, which were matched with 20 patients undergone BMSCT and 20 patients undergone PBSCT, by using propensity score matching (PSM) for age, gender and thalassemia class. All patients received the same myeloablative conditioning regimen and were transplanted from a fully HLA matched sibling donor.

Results: The median follow-up time after HSCT was 5.7 years. Rejection incidence was 70.0% (95% CI = 28.1%-90.4%) after UCBT, 25.6% (95% CI = 8.9%-46.4%) after BMSCT, and no rejection occurred in the PBSCT group. Acute GVHD incidence was 20.0% (95% CI = 2.6%-49.0%), 35.0% (95% CI = 15.1%-55.8%), and 40.0% (95% CI = 18.6%-60.6%) in patients undergone UCBT, BMSCT and PBSCT, respectively (P=0.62). The incidence of chronic GVHD was 7.2% (95% CI = 0.3%-28.7%), and 35.2% (95% CI = 13.7%-57.8%) in patients undergone BMSCT and PBSCT, respectively (P=0.026) and none of the patients in the UCBT group experienced chronic GvHD.

Conclusions: Although the overall survival is not significantly influenced by the graft source, due to the high incidence of rejection after UCBT, the probability of thalassemia free survival is very low in these patients.

Abbreviations: HSCT: hematopoietic stem cell transplantation; TDT: transfusion-dependent thalassemia; UCBT: umbilical cord blood transplantation; GvHD: graft versus host disease; BMSCT: bone marrow stem cell transplantation; PBSCT: peripheral blood stem cell transplantation; PSM: propensity score matching; MSD: matched sibling donors; OS: overall survival; TFS: thalassemia-free survival; TRM: transplant-related mortality

Introduction

Thalassemia is the most common monogenic hematologic disorder, affecting millions of people worldwide. Allogeneic hematopoietic stem cell transplantation (HSCT), as the only clinically available curative modality for transfusion dependent thalassemia (TDT), has grown to have major developments by becoming less toxic and more successful for a larger number of patients. Initial experiences on HSCT for TDT patients were confined to those who were relatively young with limited comorbidities and from HLA-matched sibling donors (MSD). However, less than 30% of patients have an unaffected MSD available [1]. Umbilical cord blood transplantation (UCBT) could be considered as an alternative strategy to overcome the shortage of matched donors, considering that a less stringent HLA matching is acceptable while

implementing this graft source. Moreover, UCBT has the theoretical advantage of having condensed GvHD incidence and especially in non-malignant diseases such as TDT, the potential of GVHD abolition, greatly improves the quality of life for transplanted patients [2]. However, UCBT may be underprivileged by higher primary graft failure incidence and delayed immune reconstitution after HSCT [3]. Not all centers have experienced HSCT in TDT patients from different stem cell sources, in view of that and in the absence of conclusive recommendations on UCBT for thalassemia, current research is focused on comparing the results of TDT patients undergone UCBT with those who underwent bone marrow stem-cell transplant (BMSCT) or peripheral blood stem-

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Key words: thalassemia, transfusion, transplantation, umbilical cord blood, UCBT, graft failure, GvHD, survival

Received: December 14, 2020; **Accepted:** December 24, 2020; **Published:** December 28, 2020

cell transplant (PBSCT) in our center, in order to assess the safety and efficacy of UCBT compared with BMSCT or PBSCT in TDT patients in the setting of a comparable situation.

Patients, materials, and methods

Clinical data were obtained from the Hematology, Oncology and Stem Cell Transplantation Research Center (HORCSCT) database, Tehran, Iran.

Included in this retrospective analysis were 10 TDT patients, aged 2-15 years, undergone a single unmanipulated umbilical cord blood (UCB) unit between January 1998 and December 2014, in our center, matched at a ratio of 1:2 with 20 from 66 patients undergone BMSCT and 20 from 338 patients undergone PBSCT during the same period. So, we extracted 50 patients out of total 414 patients to have unbiased results.

Prior to HSCT, all patients were assigned to 1 of 3 classes of risk according to the criteria proposed by Lucarelli, *et al* [4]. Only class 1 and 2 patients were included in our study.

The donor/recipient HLA matching in patients undergone UCBT was accomplished by low-resolution molecular typing for class I HLA-A and -B alleles, and high-resolution molecular typing for HLA-DRB1 alleles. HLA typing (A, B, C, DR, DQ) in bone marrow and peripheral blood grafts were determined by high-resolution molecular typing using polymerase chain reaction sequence-specific primers. All patients were transplanted from HLA matched sibling donors (6/6 in the UCBT group and 10/10 in the BMSCT and PBSCT groups).

All patients received the same non total body irradiation myeloablative conditioning regimen comprising busulfan and cyclophosphamide. In PBSCT, antithymocyte globulin was also included. Regarding GVHD prophylaxis, cyclosporine was administered in all patients but methotrexate was only administered after PBSCT and BMSCT.

Considering the infused stem cells at the time of HSCT, the median number of leukocytes infused in the UCBT group was $4.30 \times 10^7/\text{kg}$ (ranging from 2.10 to $14.76 \text{ cells}/\times 10^7/\text{kg}$), in the BMSCT group was $4.75 \times 10^8/\text{kg}$ (ranging from 2.97 to $9.40 \text{ cells}/\times 10^8/\text{kg}$), and in the PBSCT group was $9.02 \times 10^8/\text{kg}$ (ranging from 1.44 to $17.30 \text{ cells}/\times 10^8/\text{kg}$). All patients received essentially the same supportive care.

End points

The primary indicator of hematopoietic recovery was the time of myeloid and platelet engraftment (i.e., the date of first of 3 consecutive days in which the absolute neutrophil count was at least $0.5 \times 10^9/\text{L}$ and an unsupported platelet count was at least $20 \times 10^9/\text{L}$, respectively). Primary engraftment failure was defined as graft rejection occurrence less than 42 days after transplantation. Acute and chronic GVHD were diagnosed and recorded according to standard criteria (i.e., grade 0 to IV for acute GVHD and the classification of none, limited, or extensive for chronic GvHD) [5]. The incidence of chronic GVHD was evaluated in patients surviving 100 days or longer after HSCT with allogeneic engraftment. Overall survival (OS) was calculated from date of HSCT to death from any cause. Thalassemia-free survival (TFS) was defined as being thalassemia free and alive. End points were calculated at the last contact, the date of the latest follow-up being 21st of September 2019.

Written informed consent was sought from all patients or from their parents and the study protocol was approved by the ethical board of the Tehran University of Medical Sciences.

Statistical Analysis

We performed propensity score matching (PSM) using a 1:2 ratio to remove the effect of gender and age, between three group of patients undergone UCBT, BMSCT, and PBSCT. This was done to obtain unbiased statistical results as the sample size in the three groups were extremely unbalanced. Homogeneity between graft sources was evaluated using the chi-square test for qualitative variables and Kruskal-Wallis test for continuous variables. Kaplan-Meier method was derived to estimate the OS and TFS and were compared by means of the log-rank test. Median follow-up time calculated by the reverse Kaplan-Meier method. The differences between cumulative incidence curves in the competing risk analysis were compared using Gray's tests. Death without rejection (engraftment) was considered as a competing event for rejection (engraftment). A 2-sided P = 0.05 or lower was considered to be statistically significant. Analyses were conducted using Stata (Corp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.) and the R package MatchIt.

Results

By the end of September 2019, the median follow-up time after HSCT in our patients was 5.7 years (95% CI: 4.75-7.02), totally. While the median follow up time between the three groups of UCBT, BMSCT, and PBSCT were 4.94 (95% CI: 0.12 - 14.49), 5.43 (95% CI: 0.93 - 5.83), and 7.52 (95% CI: 3.76 - 9.13) years, respectively.

Considering the graft source, 10 patients had received UCBT, 20 PBSCT and 20 BMSCT. The age range was between 3.1 to 10.25 years at the time of HSCT. The characteristics of the patients and donors in the three source groups are outlined in Table 1, showing the greatness of matching in the three considered groups.

Engraftment, GVHD, and length of hospitalization

Among patients who received UCBT as compared with those received BMSCT and PBSCT, the mean time for neutrophil engraftment was 14 days and 15.5 days longer, respectively (P < 0.001). The mean time for platelet engraftment in patients who received UCBT as compared with those received BMSCT and PBSCT, was also 13 days and 15 days longer, respectively (P=0.0139).

At the time of this report, 13 patients (25.5%) had experienced graft failure, totally. Primary graft failure was recorded in 5 (10%) patients, among which 4 patients had undergone UCBT and one patient was from the BMSCT group.

The cumulative incidence of rejection was 70.0% (95% CI = 28.1%-90.4%) after UCBT, 25.6% (95% CI = 8.9%-46.4%) after BMSCT, and no rejection occurred in the PBSCT group.

Acute GVHD developed in 42% of patients, totally. The cumulative incidence of acute GVHD until 100 days after HSCT was 20.0% (95% CI = 2.6%-49.0%), 35.0% (95% CI = 15.1%-55.8%), and 40.0% (95% CI = 18.6%-60.6%) in patients undergone UCBT, BMSCT and PBSCT, respectively. Demonstrates that acute GvHD incidence is not significantly different among the three source groups (P=0.62).

Chronic GVHD developed in 5 patients, among which 4 patients were from the PBSCT group and one patient was from the BMSCT

Table 1. Patients and Donors Characteristics Compared in the three Graft Source Groups

Patients	UCBT	BMSCT	PBSCT	P-value
Gender (F/M)	4/6	13/7	9/11	0.38
Thalassemia class (I/II)	3/7	7/8	6/9	0.78
Extent of ABO matching (match/mismatch)	5/5	11/7	12/7	0.86

group. Three recipients developed extensive GVHD. In patients who survived more than 100 days after HSCT, the incidence of chronic GVHD was the incidence of chronic GVHD was 0 %, 7.21% (95% CI = 0.38%-28.77%), and 35.29% (95% CI = 13.77%-57.86%) in patients undergone UCBT, BMSCT and PBSCT, respectively. Exhibits the statistically significant difference of chronic GvHD incidence in the three source groups (P=0.026).

The median duration of hospital stay was 39.5, 43, and 19.5 days in the UCBT, BMSCT and PBSCT patients, respectively. The median duration of hospitalization for UCBT recipients was significantly longer than that for other recipients (P=0.002).

Survival and mortality rate

Among the included 50 patients, 3-year OS was 80.44% (95% CI 65.74-89.33%) and the 5-, 10- and 15-year OS were 77.72% (95% CI 62.38-87.40%). The 3-year TFS was 59.46% (95% CI 44.48-71.64%) and the 5, 10 and 15-year TFS were 57.13% (95% CI 42.11-69.61%).

The 5-, 10- and 15-year OS and TFS in the three groups are compared in Table 2. BMSCT compared with UCBT is able to increase the probability of thalassemia free survival up to 68% and PBSCT compared with UCBT is able to increase the probability of thalassemia free survival up to 71%. However, the incidence of non-rejection mortality was 5.3% (95% CI 0.3%-22.3%), and 35.3% (95% CI 15.2%-56.3%) in patients undergone BMSCT and PBSCT, respectively. As demonstrated patients who underwent UCBT, no incidence of non-rejection mortality was reported (P=0.015).

Discussion

Allogeneic stem cell transplantation is the only curative treatment which is clinically available for TDT patients [6]. However, the absence of HLA identical donors and the non-negligible risk of transplant-related mortality (TRM) and post-HSCT complications are major barriers which confine the desirability of this modality for eligible patients. In order to circumvent these barriers, alternative strategies such as transplantation using umbilical cord blood (UCB) units are being employed with significant involvement in progress. Since the first report of a successful UCBT in 1989, this option has been used increasingly to treat patients with hematologic diseases. Although initial reports about UCBT were not rewarding with unacceptably high rate of rejection, due to smaller cellularity and volume compared to other stem cell sources, the relatively lower reported rate of acute and chronic GvHD, made UCBT a potentially attractive option for non-malignant diseases such as hemoglobinopathies [7]. However, few number of anecdotal studies on UCBT in TDT patients have been conducted and so meticulous data on HSCT outcomes in TDT patients using UCB derived stem cells compared with other graft sources is not easily within reach [8]. The present report is claimed to be the first fully matched and detailed study addressing the outcomes of UCBT compared with PBSCT and BMSCT for patients with TDT.

Graft failure is the main faced apprehension after UCBT. An increased risk of graft failure in UCBT recipients compared with patients given BMSCT has already been reported [9]. It is postulated

that the competition between cord blood derived stem cells and the residual hematopoietic progenitors in the host bone marrow, plays an unfavorable role [10]. In UCBT, the number of infused stem cells is one log less than the quantity which is received in the BMSCT recipients and this disadvantage could be a hypothetical cause for the observed high rate of graft failure after UCBT. In nonmalignant diseases, the cell dose of the UCB unit has been reported to be a major factor affecting engraftment probability and disease free survival (DFS) [11]. Ruggeri, *et al.* have stated that engraftment and DFS were higher after transplantation of UCB units containing $>5 \times 10^7$ nucleated cells/kg at the time of infusion [12]. However, in our study the number of infused nucleated cells did not correlate with the probability of rejection after UCBT and even transplanted patients with UCB units containing more than 5×10^7 nucleated cells/kg, experienced graft rejection. Radiation-containing regimens are conveyed to be efficient in achieving better engraftments, though, the significant early and late toxicities associated with these regimens limits their applicability [13]. Implementation of a non-TBI conditioning regimen could be a tallying reason for the high incidence of graft failure in our study.

On the other side of the coin, the lower risk of GvHD associated with UCBT seems appealing. Acute GVHD (grade II-IV) occurs in 17–55% of thalassemia patients undergone HSCT from HLA-matched related donors, and this problem is escalated when using alternative donors. Chronic GVHD is encountered in 27% of patients with thalassemia undergone BMSCT from a compatible relative and this reported incidence is even higher in patients undergone PBSCT [14]. It is stated that extensive chronic GVHD certainly worsens the quality of life in thalassemia patients undergone HSCT compared with those treated with supportive therapy [15]. Moreover, in patients with nonmalignant disorders, who do not benefit at all from the associated graft-versus-tumor effect, implementation of UCBT that is associated with a lower risk of GvHD, is postulated to be desirable [16]. Several studies have documented that patients receiving transplants from placental blood have a significantly lower relative risk of both acute and chronic GVHD [17]. Locatelli, *et al.* have reported that the incidence of acute and chronic GVHD after UCBT in hemoglobinopathies was 11% and 6%, respectively [18]. In our study, the incidence of acute GVHD after UCBT was 20.0% compared with 35.0% and 40.0% in patients undergone BMSCT and PBSCT, respectively. None of the patients in the UCBT group had experienced chronic GvHD among our patients. Our results endorses the less significant chronic GvHD probability after UCBT compared with other graft sources.

In thalassemia patients, HSCT from a fully HLA matched sibling donor, delivers an OS of 88%, TFS of 85%, a rejection rate as low as 4% to 7% and TRM of 12% [19]. In our study, in patients undergone UCBT, the 10-year OS was about 86% and the 10-year TFS was only 30%, which was much lower than the TFS brought about after BMSCT and PBSCT. Kabbara, *et al.* have reported that the OS after related HLA-matched sibling donor UCBT is similar to OS after BMSCT in children with thalassemia [20]. In our study, the OS among the three source groups did not differ significantly.

Takahashi, *et al.* have compared transplantation outcomes from the three different mentioned sources in adults with hematologic

Table 2. Fifteen-Year OS and TFS for three categories of patients

Patient Category	OS			P value	TFS			P value
	5 years	10 years	15 years		5 years	10 years	15 years	
UCBT	86.67 (36.15-98.01)	86.67 (36.15-98.01)	86.67 (36.15-98.01)	0.15	30.0 (7.11-57.79)	30.0 (7.11-57.79)	30.0 (7.11-57.79)	0.02
BMSCT	88.57 (61.53-97.01)	88.57 (61.53-97.01)	88.57 (61.53-97.01)		63.46 (38.15-80.69)	63.46 (38.15-80.69)	63.46 (38.15-80.69)	
PBSCT	64.66 (39.80-81.35)	64.66 (39.80-81.35)	64.66 (39.80-81.35)		64.66 (39.80-81.35)	64.66 (39.80-81.35)	64.66 (39.80-81.35)	

malignancies, and reported no apparent differences in TRM (9% in UCBT and 13% in BMSCT/PBSCT recipients), and DFS (70% in UCBT and 60% in BMSCT/PBSCT recipients) between groups [21]. The lower TRM associated with UCBT in malignant disease is persuasive and the high incidence of graft failure may not be considered as a significant interferer on the DFS. However, in hemoglobinopathies, as the main goal of transplantation is becoming disease-free, the high rate of rejection, practically makes the entire procedure useless. This may bring in to mind that stem cells from bone marrow or mobilized peripheral blood are better choices compared with cord blood stem cells for patients with thalassemia.

Conclusion

The outcome of UCBT has improved in recent years, largely due to the better donor choice (cell dose and HLA matching) and improvement in supportive care. However, compared with the two other graft sources, UCB does not seem to be an efficient stem cell source to be used in transplantation of thalassemia patients.

Acknowledgments

The authors acknowledge the pediatric staff of nurses especially A. Hoseini and M. Pourabbas. Our gratitude goes to Dr M. Nikbakht and Dr M.R. Ostadali for being involved in the processing of cord blood derived stem cells and HLA typing.

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