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Intravenous busulfan in young children with thalassaemia undergoing haplo-identical haematopoietic stem cell transplantation from mother

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IN THALASSEMIA AND SICKLE CELL ANEMIA

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Abstract

Hematopoietic stem cell transplantation (HSCT) remains the only curative option for patients with Thalassemia. Advances in hematopoietic SCT, supportive care and tissue typing techniques have steadily led to consider this curative approach also for patients who lack matched related donor Using mismatched related donor. Preparatory regimen for BMT of patients with thalassemia must achieve two objectives: elimination of the disorder marrow and establishment of a tolerant environment that will permit transplanted marrow to survive to treatment.

High-dose busulfan (Bu) combined with cyclophosphamide (Cy) is the preferred preparatory regimen for patients with thalassemia. In the present study, we hypothesized that intravenous Bu is safe and associated with low toxicity, a high engraftment rate, low severe acute or chronic GVHD. Eleven patients with thalassemia major were conditioned with 60 mg/kg hydroxyurea and 3 mg/kg azathioprine from day -59 to -11, fludarabine 30 mg/m^2 from day -17 to -11, starting on day -10 patients were given weight-based iv. busilvex with targeted dose adjustment (target AUC range, 900-1350µMol min) instead of oral Bu, and 200 mg/kg cyclophosphamide,10 mg/kg Thiotepa, and 10 mg/kg ATG (Fresenius) daily from day -5 to -2. Intravenous Bu doses were based on actual patient body weight and were administered over 4 consecutive days in 4 divided doses as an intravenous infusion (concentration, 0.6 mg/mL) for 2 hours. No hepatic VOD prophylaxis was given. Patients received CD34$^+$ mobilized peripheral and bone marrow progenitor cells from mismatched mother. T-cell dose was adjusted to 3 x 10^5/kg by fresh marrow cell add back at the time of transplant. Two patients reject their grafts, and 9 showed full chimerism with functioning grafts at a median follow-up of 16 months. None of the 9 patients who showed full chimerism developed acute GVHD and organ toxicity.

Days of treatments	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
Fludarabine 30 mg/m2/d																		
ivBusulfan dose weight based																		
iv Cy 50 mg/kg daily																		
Thiotepa 10 mg/kg																		
ATG-F 10 mg/kg																		

Outcome

Two patients reject their grafts, and 9 showed full chimerism with functioning grafts at a median follow-up of 16 months. None of the 9 patients who showed full chimerism developed acute GVHD and organ toxicity. These results suggest that maternal haploidentical HSCT is feasible for patients with thalassemia who lack a matched related donor, and the low toxicity profile observed in our study resulted from the use of intravenous Bu and the more conservative target range with therapeutic drug monitoring.

Introduction

Hematopoietic stem cell transplantation (HSCT) from a suitable related or unrelated matched donor provides the only cure for patients with thalassemia.1-3. High-dose busulfan (Bu) combined with cyclophosphamide (Cy) is the preferred preparatory regimen for patients with thalassemia.

A recently developed intravenous formulation of Bu exhibits less interpatient as well as dose-to-dose variability, leading to more reliable and consistent PK estimations.

Intravenous Bu doses were based on actual patient body weight and was administered over 4 consecutive days in 4 divided doses as an intravenous infusion (concentration, 0.6 mg/mL) for 2 hours.

Actual Body Weight	<9 kg	9 to <16 kg	16 to 23 kg	>23 to 34 kg	>34 kg
Dose of ivBusulfan (D)	1.0 mg/kg	1.2 mg/kg	1.1 mg/kg	0.95 mg/kg	0.8 mg/kg

Patients and methods

Two-step selection (CD34 positive selection leukapheresis followed by negative selection using anti-CD3 and anti-CD19 monoclonal antibodies) of bone marrow cells was employed for eight donors.We attempted to suppress erythropoiesis by intensive hypertransfusion and chelation. Between day -59 and day -11 before the transplantation, 40 mg/kg deferoxamine was continuously infused through a central venous catheter each 24 hours. Red cells were transfused every 3 days to maintain the hemoglobin level between 140 and 150 g/L (14 and 15 g/dL). During this time interval hydroxyurea 60 mg/kg daily and azathioprine 3 mg/kg daily were administered to eradicate marrow, and growth factors, granulocyte colony-stimulating factor and erythropoietin, were given twice weekly to maintain stem cell proliferation in the face of hypertransfusion, thereby facilitating the effect of the hydroxyurea.

Fludarabine was administered at a dosage of 30 mg/m2/d from day -17 through day -13.

Starting on day -10, 14 doses of busulfan (BU) 1 mg/kg were administered orally 3 times daily over 4 days (total dose 14 mg/kg over 4 days) in the first 17 patients, and corresponding dose of busulfan give intravenous in the following 14 patients, followed by intravenous cyclophosphamide (CY) 50 mg/kg daily on each of the next 4 days (total dose 200 mg/kg), and 10 mg/kg Thiotepa, and 10 mg/kg anti-thymocyte globulin daily from days -5 to -2 (ATG-Fresenius S). No hepatic VOD prophylaxis was given.

Table 1. Patient characteristics at transplantation for 14/ 31 patients younger than 17 years

Age in yrs	Sex	Class	Ferritin	GOT	GPT	FS	N°TX	CI	Outcome
12	M	3	19801	16	28	Mo	50	100	Alive and well
3	M	1	578	35	23	No	12	49	Rejection
8	F	2	2980	36	27	Mi	51	80	Alive and well
6	F	1	1240	28	18	Mi	68	100	Alive and well
14	M	3	2568	31	23	Mi	125	100	Alive and well
3	M	2		30	25		12	100	Alive and well
16	M	3	2780	35	37	Se	140	100	Alive and well
12	F	3	2300	28	31	Se	98	100	Alive and well
11	F	3	1780	27	33	Mo	95	100	Rejection
16	F	3	1890	34	32	Se	167	100	Alive and well
5	M	2	1289	32	26	Mo	56	100	Alive and well
7	M	2	1345	27	24	Mo	78	100	Alive and well
4	M	2	1300	29	25	Mo	56	100	Alive and well
6	M	3	1789	24	35	Mo	26	80	Alive and well

No. of Tx, number of red cell transfusions before transplantation; CI, chelation index; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase;; FS, portal fibrosis (Mi, mild; Mo, moderate; Se, severe; Ci, cirrhotic).

Conclusions

High-dose busulfan (Bu) combined with cyclophosphamide (Cy) is the preferred preparatory regimen for patients with thalassemia and is a valid alternative to regimens that include total body irradiation.

The introduction of i.v. Busulfan allows better drug delivery and control of systemic esposure, to minimize adverse effects and improve the safety of the treatment.

The addition of Busilvex to -Cy-Fluda -Thiotepa in thalassemics patients who lack a matched donor appear to be tolerable regimen.

There was no correlation between intravenous Bu PK parameters and toxicity, graft failure, mixed chimerism, hepatic VOD, acute GVHD, chronic GVHD, and transplantation-related mortality (data not shown). One of the important findings of this study is that, despite pre-existing disease and treatment-related liver damage, intravenous Bu was well tolerated with no significant toxicity.

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