Unrelated cord blood transplantation for children with high risk myelodysplastic syndromes

We assessed the feasibility and toxicity of unrelated mismatched cord blood transplant (CBT) in five pediatric patients with high-risk myelodysplastic syndrome (MDS). Full donor chimerism was achieved in 4/5 cases on day 28 and two patients are in continuous complete remission more than 5 years after CBT.

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Allogeneic stem cells transplantation represents the only curative therapeutic option for patient with MDS; search of unrelated donor, including umbilical cord blood, should be mandatory for MDS who lack an HLA-identical sibling,[1-5] particularly in pediatric patients who have longer life expectancy than adults. We report the results of unrelated CBT in 5 children with high risk MDS transplanted at our Center: four were at high-risk according to the FAB criteria and one because of age > 2 years, hemoglobin F level greater than 10%, low platelet count, associated immunodeficiency and hemolytic anemia.[6] According to WHO classification of the myeloid neoplasm,[7] two children were considered as acute myeloid leukemia at UCB transplant. Patient characteristics are shown in table 1. Patients had neither an HLA identical sibling nor an unrelated bone marrow donor. Bone marrow back up, harvested after donor identification as a safety procedure before unrelated stem cell transplantation, was available in all cases; an informed consent was obtained by children's parents.

Before transplantation, two children were treated with chemotherapy: one failed 2 chemotherapy-induction cycles and one had a failure and disease progression after 1 locus mismatched allogeneic transplant from the mother. All patients received CBT as an up-front treatment and not as a post-remission consolidation. Median age was 2.9 years (range 1.3-6.6). Median number of nucleated cells, CD34+ cells and CFU-GM infused after thawing was 5×10^7/kg, 2.7×10^5/kg and 2.35×10^4/kg, respectively. Cord blood units were selected according to the number of NC per recipient's body weight and HLA compatibility. In case of more than one CB unit eligible for the above characteristics, AB0 matches were considered. According to serologic (class-I) or high resolution oligonucleotide HLA-typing (class-II), three patients received a CBT for 1 locus and two for 2 loci mismatched (Table 1). Three patients received six fractionated 12 Gy total body irradiation and one (< 3 years) oral busulfan at total dose of 600 mg/m^2 followed by cyclophosphamide 120 mg/kg. VP16 was included at total dose of 20 mg/kg, according to the Eurocord guidelines for high risk hematopoietic malignancies. The patient with JMML, who had already failed an allogeneic transplant from the mother using busulfan + cyclophosphamide preparative regimen, received an original regimen consisting of cytarabine, fludarabine, VP16 and thiotepa at total dose of 2 g/m^2, 5 mg/kg, 40 mg/kg and 10 mg/kg, respectively. All cases received horse anti-lymphocyte globulin at dose of 600 U/kg for 4 consecutive days during the conditioning regimen. GVHD prophylaxis consisted of intravenous cyclosporine (CsA) at a dose of 3 mg/kg/day followed by oral CsA as tolerated and methylprednisolone (2 mg/kg till day +28). In two cases of sepsis during aplasia, G-CSF was added after excluding the presence of residual marrow blasts. Four patients achieved neutrophil count > 500/mm^3 at a median time of 26 days (range 23-30) (Table 2); although the high cell dose infused, one patient (#4) reached a number of 300/mm^3 ANC on day + 15, but died of transplant related toxicity before achieving sustained engraftment. In this case, the severe gram-negative sepsis associated with pneumonitis could account for the delay in the hematological reconstitution. A self-sustained platelet count >25000/mm^3 was documented in 2 cases after 34 and 40 days, respectively. Full donor

Table 1. Assessment of Autoimmunhemolytic Anemia.

Child	*Age karyotype at diagnosis*	*FAB and at diagnosis*	*WHO blasts (%)*	*Marrow*	*Previous treatment diagnosis to UCBT*	*Mo. from karyotype at UCBT*	*FAB and at UCBT*	*WHO blasts (%)*	*Marrow at UCBT*	*bw CMV status*	*Recipient*	*Pairs sex*	*ABO d/r HLA ** mismatches*	*Number of NC x10^7/kg*	*Dose**
1	6 46XX	RA	RA	3	transfusions	30	RAEB 46XX	RAEB-2	12	18	pos	matched	A+/A-	2 (A)	2.7
2	2 46XY,-7	JMML	CMML-2	18	allo-PBSC	14	JMML 46XY,-7	CMML-2	15	12	pos	mismatched	B+/B+	2 (A, DRB1)	8.1
3	5 46XY	RA	RA	4	steroids + transfusions	48	RAEB 46XY	RAEB-2	14	25	pos	mismatched	0-/0+	1 (DRB1)	10.8
4	1.3 46XX	RAEB-t	AML	21	steroids + transfusions	2	RAEB-t 46XX	AML	25	10	pos	matched	A+/AB+	1 (DRB1)	5
5	3	RAEB 46XY	RAEB-2	15	2 induction courses	4	RAEB-t 46XY	AML	25	12	neg	matched	0+/0+	1 (A)	3.4

*UBCT=Umbilical Cord Blood Transplantation; RA=Refractary Anemia; RAEB=RA with excess of blasts; RAEB-t=RAEB in transformation; CMV=Cytomegalovirus; Mo.=Months; bw=body weight. * NC infused post-thawing procedure. ** HLA A and B was performed by serology and HLA-DRB1 by high resolution DNA typing.*

Table 2.

Child	*Chimerism*	*Neutrophil >0.5 x10^9/L*	*aGVHD*	*cGVHD*	*Survival (days)*	*Cause of death*
1	full donor	23	II	-	2260 +	
2	full donor	29	I	limited	1980 +	
3	full donor	24	-	n.e.	39	Heart failure
4	mixed	-	I	n.e.	29	Sepsis, VOD, Pneumonitis
5	full donor	30	IV	n.e.	36	aGVHD

aGVHD = acute graft versus host disease; cGVHD = chronic GVHD; VOD = Venocclusive disease.

chimerism evaluated either by FISH using X- and Y specific probes or Variable Number of Tandem Repeats PCR was documented in 4 cases on day +28; two children had marrow chimerism checked ahead of schedule on days +15 and +18, respectively, because of persistent fever and the necessity to start G-CSF. Two patients developed grade I, one grade II and one grade IV aGVHD. The patient with JMML experienced skin and gut involvement of cGVHD, resolved with immunosuppressive therapy. As of December 15, 2003, two patients are alive in CR after 2260 and 1980 days; three patients died of gram-negative sepsis associated with veno-occlusive disease, grade IV aGVHD, and hearth failure, respectively (table 2). Although all patients were considered at high risk of relapse because the proportion of marrow blasts ranged from 12% to 25% at transplant, full donor chimerism was achieved in 4/5 cases on day 28 and the two long term survivors are in continuous complete remission with no evidence of cGVHD. The anti-leukemic effect of the procedure, however, was supposed in one of them (#2) because of the appearance of cGVHD at the time of CsA withdrawal, which required 6 months of CsA and steroids treatment. Four patients showed WHO grade 3-4 stomatitis and sepsis that was fatal in one case. These data suggest that although the three-agent-regimen enables the achievement of full donor chimerism, absence of reject and promising long-term results in high risk MDS,[8] it carries high rate of severe mucosal damage that, combined to prolonged aplasia, increases the transplant related mortality. Otherwise, unrelated cord blood units in pediatric MDS could be transplanted with standard preparative regimen, reducing morbidity and mortality.[9] Results in adults indicate that reduced intensity conditioning regimen (RIC) followed by SCT allows the decrease of transplant related toxicity, although the experience with RIC is limited, especially in pediatric patients. Moreover, the use of cord blood for this transplant strategy is hampered by the high cell dose required for engraftment after RIC. Although timing of transplant and previous chemotherapy remain to be defined,[10, 11] our data indicate a potential role of CBT in the setting of pediatric MDS; nevertheless, due to the small number of patients, these findings must not be over-evaluated. The results of large cooperative studies indicate that standard risk MDS have a median survival of 5-7 years, significantly greater than high risk patients. Therefore, future investigation efforts in treatment of pediatric MDS should be addressed on both the timing of unrelated stem cell transplant and the intensity of the conditioning regimen.

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