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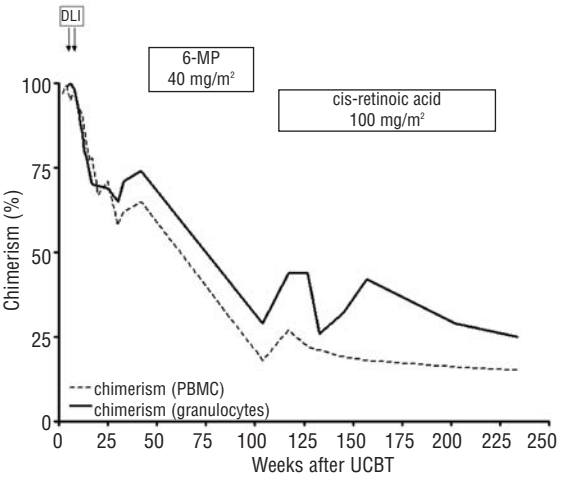

Figure 1. DLI: donor lymphocyte infusion (week 10 and 12); 6-MP: 6-mercapto-purine; PBMC: peripheral blood mononuclear cells; UCBT: umbilical cord blood transplantation; % chimerism reflects the percentage of donor bone marrow in the patient.

HLA-identical umbilical cord blood transplantation from a sibling donor in juvenile myelomonocytic leukemia

As recently described by Flotho *et al*. juvenile myelomonocytic leukemia (JMML) is a rare type of childhood leukemia not only characterized by young age, hepatosplenomegaly, thrombocytopenia and monocytosis, but also by molecular aberrations in the RAS-RAF-MEK-ERK signaling pathway and GM-CSF-hypersensitivity.[1] Although progress has been made in unraveling the molecular background of JMML, the only curative treatment option for these children is stem cell transplantation (SCT).[2,3] Previous studies have shown that in JMML the graft versus leukemia (GvL) effect of the SCT plays an important role in the prevention of relapse.[2,4] Hence, donor and stem cell source selection could play an important role in the outcome of JMML patients. SCT using unrelated, immunological naive, umbilical cord blood (UCB) has shown to be effective for pediatric JMML.[3] UCBT has increased the available pool of hematopoietic stem cell transplantation donors, especially for young children.[5] This is important for patients with rare HLA-haplotypes and with diseases that may rapidly progress like JMML. However, it is conceivable that the relatively immunological naivety of cord blood stem cells from a newborn HLA identical sibling donor may be a negative factor for outcome.[4,6]

In this report we describe 5 JMML patients registered in the database of the European Working Group on Childhood MDS (EWOG-MDS), who have received umbilical cord stem cells from an HLA-identical sibling (Table 1). So far only MacMillan *et al*. has described a JMML patient who received HLA-identical sibling umbilical cord cells.[7] More information is available on unrelated UCBT in JMML.[3,7,8] Recently, from the combined EWOG-MDS/EBMT registry, Locatelli *et al*. described 100 JMML patients of whom 7 received an unrelated UCBT. These 7 patients showed a delayed hematologic recovery, but the outcome was comparable to the children treated with other stem cell sources.[3] Rocha *et al*. reported that children receiving a related UCBT for malignancies, bone marrow failure syndromes, hemoglobinopathies, inborn errors of metabolism or immunodeficiencies, had a slower hematopoietic recovery and a lower risk of acute and chronic GVHD than children receiving a related bone marrow transplantation.[9] Gluckman *et al*. have shown that the amount of acute GVHD in related UCBT is lower (18%) than in unrelated UCBT (32%).[10] These studies underscore the relative immune naivety of the UCB cells and the feasibility of the use of UCBs especially for childhood transplantation settings. However, especially in JMML, where the GvL-effect is an important contributor to the success of the transplantation procedure, it could be questioned whether these relatively naive umbilical stem cells from sibling donors should be used in all patients, especially when alternative donors would be available.

In all cases full donor-chimerism was found after transplantation. In the cases that relapsed, a mixed chimerism was found prior to clinical progression. In addition, in Patient 1 increasing mixed donor-chimerism developed from day 42 onwards without clinical signs of relapse (Figure 1). Mixed donor-chimerism after SCT in JMML has been shown to be an important predictor for relapse, therefore discontinuation of immunosuppressive therapy (IST) is the first step to prevent relapse if this occurs early after transplantation.[11] To avoid relapse, a second stem cell transplantation was considered, but the parents were very reluctant to proceed, because of the absence of any clinical signs of JMML and the excellent clinical condition of the child. Therefore, 6-mercaptopurine (6-MP) (average dose 40 mg/m^2) was started on day 145 after SCT. When, after initial improvement, donor-chimerism increased, 6-MP was replaced by 13-cis-retinoic acid (100 mg/m^2/day every other week) for 2.5 years until the age of five years. Thereafter, the child remained well with a current follow-up of five years after SCT. At present the percentage of donor cells is 15%, without any clinical sign of JMML. At the moment no series are available on the use of 6-MP and 13-cis-retinoic acid in a relapse setting after SCT for JMML. Although Locatelli *et al*. showed that second SCT was successful in 7/15 cases with a relapse after SCT, the issue whether to proceed to a second SCT in all cases of

Table 1. (A) Patients' characteristics of the JMML patients. (B) Transplantation characteristics of the JMML patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Table 1A					
Age at diagnosis (months)	18	18	27	14	30
Sex	F	F	F	M	M
Peripheral blood counts at diagnosis					
Hb (g/dL)	7.2	10.9	12.1	7.7	5.8
WBC ($\times 10^9$/L)	68	4.6	116	20.9	11
% blasts	4	0	0	1	13
% monocytes	24	35	14	5	23
PLT ($\times 10^9$/L)	70	14	115	23	64
%HbF	2.5	1.3	64.3	0.6	18
Bone marrow (% blasts)	6	2	3	11	7
GM-CSF hypersensitivity	yes	no	n.a.	no	n.a.
NF1/PTPN11/RAS gene mutation	no	no	n.a.	no	*PTPN11*
Karyotype	46, XX	46, XX	46, XX	45, XY, -7	45, XY, -7
Table 1B					
HLA-match	10/10 identical	10/10 identical	10/10 identical	10/10 identical	10/10 identical
Cell dose ($\times 10^8$ MNC/kg)	1	n.a.	0.2	0.4	0.5
Conditioning					
Cy/etoposide /TBI					
Total body irradiation			12 Gy		
Methotrexate intrathecal			2×12 mg		
day –4: etoposide (iv)			60 mg/kg		
day –3-2: cyclophosphamide (iv)			60 mg/kg		
Bu/Cy/Mel					
day –9-6: busulphan (iv/oral)	4-6mg/kg	120 mg/m^2		5 mg/kg	120 mg/m^2 oral
day –4-3: cyclophosphamide (iv)	60 mg/kg	60 mg/kg		60 mg/kg	60 mg/kg
day –1: melphalan (iv)	140 mg/m^2	140 mg/m^2		140 mg/m^2	140 mg/m^2
Engraftment					
ANC > 500/uL (day)	33	35	10	20	33
PLC >20,000/uL (day)	48	77	38	42	53
GVHD-prophylaxis					
cyclosporine	2 mg/kg	2 mg/kg	5 mg/kg	3 mg/kg	none
tapering	day 28	day 42	n.a.	n.a.	–
stop	day 42	day 70	day 87	day 7	–
Signs GVHD					
acute	no	no	grade 1	grade 2	grade 2
chronic	no	no	no	no	no
Therapy after transplantation	2x DLI	no	re-transplantation	no	5x DLI re-transplantation
Relapse	no	no	yes	no	yes
Time till first relapse (months)			4 months		30 months
Survival from (last) SCT	alive	alive	died	alive	alive
Follow-up time (months)	60	18		84	66

Hb: hemoglobin; WBC: white blood cells; Plt: platelets; GM-CSF= granulocyte-macrophage colony stimulating factor; M: male; F: female; MNC: mononuclear cells; ANC: absolute neutrophil count; PLC: platelet count; DLI: donor lymphocyte infusion; GVHD: graft versus host disease; n.a.:not available.

mixed donor-chimerism without any clinical signs of JMML has not been clarifed.[3]

We conclude that in JMML umbilical cord stem cells can be considered a good alternative source for HSCT. However, whether the use of sibling HLA-identical UCB should be advocated needs to be confirmed in larger series of JMML patients.

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