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ORIGINAL ARTICLE

Unrelated cord blood transplantation for severe combined immunodeficiency and other primary immunodeficiencies

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HCT is currently the treatment of choice for children with severe primary immunodeficiencies (PIDs). Frequently, these patients lack an HLA-identical sibling donor, and umbilical cord blood (UCB) transplantation may be an option; however, experience in this field remains scant. Fifteen children with PID (SCID 11, X-linked lymphoproliferative syndrome 2, Omenn's syndrome 1, Wiskott–Aldrich syndrome 1) received a UCB transplant. The donor was unrelated in 14 cases and related in 1. Median age at transplant was 11.6 months (range, 2.9–68.0) and median weight 7 kg (range, 4–21). Thirteen patients were conditioned with busulphan and cyclophosphamide and 2 with fludarabine and melphalan. Nine patients received antithymocyte globulin. Median NC $\times 10^7$/kg infused was 7.9 (range, 2.9–25.0) and median CD34 $\times 10^5$/kg 2.9 (range, 1.0–7.9). All patients engrafted. Median days to $>0.5 \times 10^9$/l neutrophils was 31. Eight patients developed acute graft-versus-host disease (GvHD) grades II–IV and one chronic GvHD. Viral and fungal infections were frequent. Four patients died: three from GvHD grade IV complicated by infection and one from progressive interstitial lung disease. Five-year survival was 0.73 ± 0.12. All surviving patients presented complete immunologic reconstitution. No patient is intravenous immunoglobulin (IVIg) replacement therapy-dependent. UCB transplantation is a valid option for children with PID who lack an HLA-identical sibling donor.

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Introduction

Severe primary immunodeficiencies (PIDs) are genetic diseases with high morbidity and mortality due to severe and recurrent infections. The severe combined forms (severe combined immunodeficiencies (SCIDs)) usually lead to death before the age of two[1] and, except for a few cases treated successfully with gene therapy,[2,3] haematopoietic cell transplant (HCT) is the only curative treatment.[4–6] Other PID (non-SCID) with a high risk of mortality can also be cured by HCT.[5,7,8]

In the first SCID case, cured by an HLA-identical sibling bone marrow transplant in 1968, immunologic reconstitution was achieved without a conditioning regimen.[9] Some years later in 1977, cure with complete lymphoid and myeloid chimaerism was achieved in a patient with Wiskott–Aldrich syndrome using myeloablative conditioning.[10] In those early years, only patients with an HLA-identical sibling donor (<20%) were able to benefit from this treatment.

At the beginning of the 1980s, haploidentical parents were found to be able to serve as donors provided the graft was T-cell depleted.[11] Results with these donors were inferior in terms of survival and immunologic recovery to those obtained with HLA-identical siblings.[4] However, results improved markedly in the 1990s when T-cell depletion methods were perfected and treatment of GvHD and infections became more effective.[5,6] Similarly, pre- or postnatal diagnosis of SCID and the use of HCT in the neonatal period led to significantly better results: 95% survival in a series of 21 neonates.[12] Despite these advances, immunologic recovery in haploidentical transplants continues to be slower and less complete than with HLA-identical siblings and over 60% of survivors require permanent intravenous immunoglobulin (IVIg) treatment.[5,6,13] On the other hand, results of non-SCID immunodeficiencies, particularly WAS and other T-cell deficiencies, remain poor.[5,8]

The results of matched unrelated donor (MUD) transplants were better in terms of survival and immunologic reconstitution than those of haploidentical donors.[5,14–16] The best were obtained in non-SCID immunodeficiencies.[15,16] Two disadvantages of MUD transplants are the

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time invested in the search for a donor, over 3 months in the majority of cases, and the high frequency and intensity of GvHD.[15] These problems could be overcome if the transplant is performed with previously typed umbilical cord blood (UCB) with a known number of CD34 cells to which a lower incidence of GvHD has been attributed.

The first three cases of PID successfully treated with UCB transplant from sibling donors were reported by Wagner *et al*.[17] in 1995 from an international registry data. In the mid-1990s, the first series of patients with malignant and non-malignant diseases treated with an unrelated UCB transplant showed similar results to those obtained with bone marrow or peripheral blood-matched unrelated transplants.[17–20] Since then, some cases of PID successfully treated with UCB transplant have been described.[21–27] The Eurocord group reported the preliminary results in 47 children from 25 centres with 69% survival at 2 years.[18,28,29] Experiences of single centres in St Louis, Newcastle and Tokyo were recently published.[30–32]

Our study presents the results of a series of 15 patients with different PID including 11 cases of SCID. This series, with the largest number of UCB transplants in SCID published, underlines the high survival rate of patients with complete immunologic reconstitution.

Patients and methods

Patients

A total of 15 patients (11 boys, 4 girls), from three hospitals of the Spanish Paediatric Bone Marrow Transplant Group (GETMON), with PID and without an HLA-identical sibling donor received a UCB transplant between May 1996 and October 2002. Eleven patients had SCID (seven had T−B−, three T−B+, one abnormal T cells B−) and four patients had other non-SCID PIDs (two had X-linked lymphoproliferative syndrome, one Omenn's syndrome, one Wiskott–Aldrich syndrome). Median age at diagnosis was 7.5 months (range, 1.6–60.5). Pre-transplant complications were failure to thrive in 11, lung disease 9, recurrent infections 6, erythroderma 3, chronic diarrhoea 3, B-cell lymphoma 2 and maternal engraftment 1. Main patient characteristics are shown in Table 1.

Methods

A total of 14 patients underwent a UCB transplant from an unrelated donor and 1 from an HLA-identical sibling. All transplants were performed in laminar airflow rooms. Median age at transplant was 11.6 months (range, 2.9–68.0). Main transplant characteristics are summarised in Table 2.

HLA compatibility and UCB unit origin. HLA identity was based on the study of class I antigens (A and B) measured by low-resolution molecular methods and class II antigens (DRB1) by high-resolution molecular techniques. UCB units were selected according to cellularity and compatibility. Units with less than 2.7×10^7/kg NC were not accepted. Three units had an HLA identity 6/6, eight had 5/6 (four differences in B, two in A and two in DRB1) and four had 4/6 (two differences in A and B, two in B and DRB1).

Five units were from the Cord Blood Bank of Barcelona, three from New York, two from Düsseldorf, one from Milan, one from Málaga, one from Denver and one from Paris.

Conditioning. All patients were conditioned in accordance with the EBMT guidelines of the Working Party of Inborn Errors. A total of 13 patients received busulphan 4 mg/kg per day in divided doses from days −9 to −6 (total dose 16 mg/kg) and cyclophosphamide 50 mg/kg per day once daily from days −5 to −2 (total dose 200 mg/kg). In addition, one of these patients with previous B-cell lymphoma received VP16 30 mg/kg in a single dose and another patient citarabine 3 g/m^2 per 12 h in four doses (total dose 12 g/m^2), respectively. Since 2001, patients with a degree of organ failure have received reduced-intensity conditioning. Consequently, a further two patients with previous lung disease were conditioned with fludarabine

Table 1 Patient characteristics

Patient	*Sex*	*Age at diagnosis (m)*	*Diagnosis*	*Complications pre-UCBT*
1	F	1.6	T–B− SCID	Failure to thrive; recurrent infections; lung disease
2	M	10.5	T–B+ SCID	Failure to thrive; recurrent infections; lung disease; B-cell lymphoma
3	M	10.5	T–B− SCID	Failure to thrive; chronic diarrhoea; lung disease
4	M	10	T–B+ SCID	Failure to thrive; recurrent infections
5	M	8.5	T–B− SCID	Failure to thrive; recurrent infections; chronic diarrhoea; lung disease
6	F	2.8	T–B− SCID	Failure to thrive; erythroderma
7	M	3.5	T–B− SCID	Failure to thrive; recurrent infections; lung disease
8	F	22	T–B− SCID	Failure to thrive; recurrent infections; chronic diarrhoea; lung disease
9	M	7.3	Abnormal T, B− SCID	Failure to thrive; erythroderma; lung disease
10	M	1.5	Wiskott–Aldrich syndrome	Intestinal bleeding
11	M	3	XLPS	B-cell lymphoma
12	M	60.5	XLPS	None
13	F	5	T–B+ SCID	Failure to thrive lung disease
14	F	7.5	T–B− SCID	Lung disease maternal engraftment
15	M	6.5	Omenn's syndrome	Failure to thrive-erythroderma

Abbreviations: SCID = severe combined immunodeficiency; UCBT = umbilical cord blood transplantation; XLPS = X-linked lymphoproliferative syndrome.

Table 2 Transplant characteristics

Patient	*Age at UCBT (m)*	*Weight at UCBT (kg)*	*HLA-identity*	*Conditioning*	*GvHD prophylaxis*	*NC × 10^7 per kg infused*	*CD34 × 10^5 per kg infused*	*Acute GvHD grade*	*Status*
1	3	4	5/6	BU CY	CsA PRED	14	1.5	II (S + GI)	Alive +131 mo
2	14	8	4/6	BU Citarabine CY	CsA PRED	4.4	1.8	III (S + GI)	Deceased Day + 69
3	12.5	8	5/6	BU CY ATG	CsA	5.6	4.5	II (S)	Alive +110 mo
4	12	8	5/6	BU CY ATG	CsA PRED	6.8	3.0	I (S)	Alive +101 mo
5	11.5	6.5	6/6	BU CY	CsA PRED	9.5	2.9	II (S + L)	Alive +80 mo
6	4	5.5	6/6	BU CY ATG	CsA PRED	10.1	1.5	I (S)	Alive +74 mo
7	7	6	4/6	BU CY ATG	CsA PRED	25	7.9	IV (S + L + GI)	Deceased Day + 52
8	25	7	5/6	BU CY ATG	CsA PRED	5.4	2.7	0	Alive +99 mo
9	7.5	7.5	5/6	BU CY ATG	CsA PRED	9	5.7	IV (S + L + GI)	Deceased Day + 103
10	2.9	6.7	5/6	BU CY ATG	CsA PRED	6.4	1.6	I (S)	Alive +58 mo
11	23.5	15	4/6	BU VP16 CY	CsA PRED	11	1.4	III (S + L + GI)	Alive +77 mo
12	68	21	6/6	BU CY	CsA MTX	2.9	1	I (S)	Alive +60 mo
13	9.5	7	5/6	FLU MEL ATG	CsA PRED	13.3	6.8	0	Alive +54 mo
14	9	9	4/6	FLU MEL ATG	CsA PRED	4.6	1	IV (S + L + GI)	Deceased Day + 84
15	20	9	5/6	BU CY ATG	CsA	4.2	1.5	I (S)	Alive +132 mo

Abbreviations: ATG = anti-thymocyte globulin; FLU = fludarabine; GI = gastrointestinal; GvHD = graft-versus-host disease; L = liver; MEL = melphalan; mo = months; PRED = prednisone; S = skin; UCBT = umbilical cord blood transplantation.

30 mg/m^2 per day from days −7 to −3 (total dose 150 mg/m^2) and melphalan 140 mg/m^2 on day −2. Nine of the fifteen patients received horse antithymocyte globulin (ATG) 60–90 mg/kg or rabbit thymoglobulin (SANG-STAT) 8 mg/kg.

Graft-versus-host disease prophylaxis. All patients received prophylaxis with cyclosporine started on days −2 or −1. In addition, 12 patients received methylprednisolone 1 mg/kg per day from day +5 and 1 patient methotrexate 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6 and +11.

Infection prophylaxis. All patients were nursed in laminar airflow rooms with strict anti-infection measures including fluconazole, acyclovir and intravenous nonspecific immunoglobulin. Cotrimoxazole was given until the day of transplant, suspended and reinstated with haematologic recovery.

Chimaerism studies. Chimaerism studies were carried out in peripheral blood by short tandem repeats in DNA (STRs) at 1 and 12 months post transplant. If required, more evaluations were made. Lineage-specific chimaerism analysis was not possible. Complete chimaerism was defined as the presence of more than 95% donor-derived cells in whole blood and mixed chimaerism as the presence of more than 5% host-derived cells. High-level mixed chimaerism was defined as 95–50% donor chimaerism.

Immunologic reconstitution studies. Immunologic reconstitution studies at 1–2, 3, 6, 9, 12, 15, 18 and 24 months

post transplant consisted of determination of IgG, IgA and IgM levels, lymphocyte subpopulations CD3, CD4, CD8, CD19 and CD56 by FACS analysis of peripheral mononuclear cells using fluorescein isothiocyanate–phycoerythrin-labelled antibodies against CD3, CD4, CD8, CD19, CD56 and T-cell function measured by the assay of PHA stimulation index (defined as the ratio of baseline-maximum stimulated levels of ^{3}H-thymidine uptake in a 3-day culture of peripheral blood mononuclear cells stimulated with a range of PHA concentrations). Age-specific normal ranges for CD3, CD4, CD8, CD19 and CD56 were used to ascertain times to normalisation.[33] B-cell function was assessed by response to tetanus and hepatitis B vaccines.

Statistical analysis

Results are expressed as medians and ranges for continuous variables with a symmetric distribution. Recovery of CD3, CD4, CD19 and CD56 to age-related normal levels after transplantation and survival probability was estimated by the product-limit method of Kaplan and Meier.

Results

Cell infusion

Median of NC $\times 10^7$/kg infused was 7.9 (range, 2.9–25.0) and of CD34 $\times 10^5$/kg cells was 2.9 (range, 1.0–7.9).

Engraftment and chimaerism

All patients engrafted. By day +39 all patients had reached $>0.5 \times 10^9$/l neutrophils with a median of 31 days (range, 10–39). The median in attaining $>20 \times 10^9$/l platelets was 56 days (range, 13–95) and 60 days for $>50 \times 10^9$/l.

At 1 month post transplant, all patients were alive and all except one had 100% donor chimaerism. One patient treated with a reduced-intensity conditioning regimen showed high-level mixed chimaerism at 1 month post transplant, which has persisted. Nevertheless, this patient attained immunologic reconstitution after transplant and made a good clinical recovery. At 1 year post transplant, all survivors except the aforementioned had complete donor chimaerism.

Graft-versus-host disease

Eight patients developed acute GvHD grades II–IV, five of whom were grades III–IV. One of these patients had received a UCB transplant with an HLA-identity 5/6 and the remaining four 4/6.

Only 1 of 11 evaluable patients developed chronic GvHD which evolved favourably.

Complications

Infectious complications were common: five patients presented viral infections (two adenovirus-induced pneumonia, two BK virus-induced haemorrhagic cystitis, one herpes zoster) and four had fungal infections (two candidaemia, one pneumocystis jirovecci-induced pneumonia, one fusariasis).

Three patients presented chronic interstitial lung disease; of these, two had suffered lung disease prior to transplant. One of the two required mechanical ventilation owing to severe respiratory failure and died from progressive interstitial lung disease. The second gradually improved although a long-term course of steroid and oxygen therapy was required. The third patient developed secondary pulmonary hypertension at 12 months post-UCB transplant and underwent a lung transplant which evolved satisfactorily.

One patient presented autoimmune haemolytic anaemia 8 months post transplant and responded well to a short course of steroids.

Causes of death

Eleven patients are alive and four died at 52, 60, 84 and 103 days post transplant, respectively. Causes of death were GvHD grade IV in three, complicated in two by adenovirus-induced pneumonia and in one by interstitial pneumonitis; the fourth died from progressive interstitial lung disease.

Immunologic reconstitution

At 3 months post transplant, 80% of surviving patients had normal age-related CD56 counts. At 6 months post transplant, 60% had age-related normal levels of CD3, CD4 and CD19. At 12 months, 80% of surviving patients had normal age-related levels of CD3 and 70% of CD4 and CD19. At 24 months, 100% of surviving patients had normal age-related levels of CD3, CD4 and CD19. Recovery of CD56, CD3, CD4 and CD19 to normal age-related values after transplant is shown in Figure 1. From 6 to 24 months post transplant, all these patients had normal

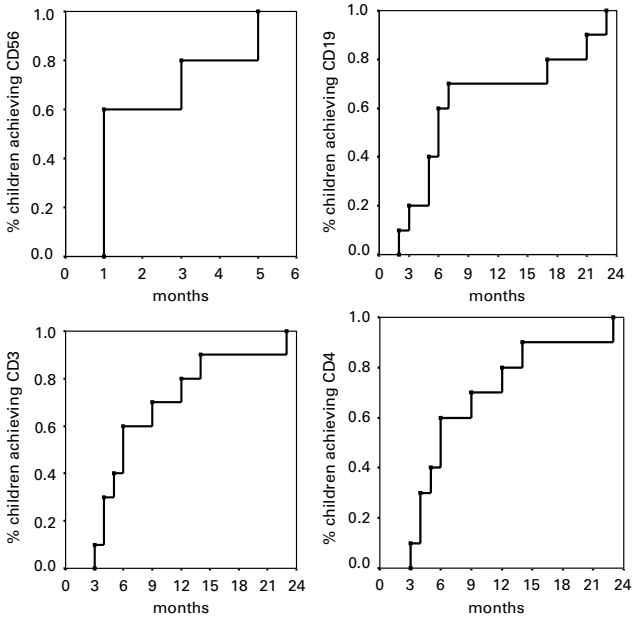

Figure 1 Recovery of lymphocyte subpopulations CD56, CD3, CD4 and CD19 to age-related normal levels post transplantation in 11 surviving PID patients.

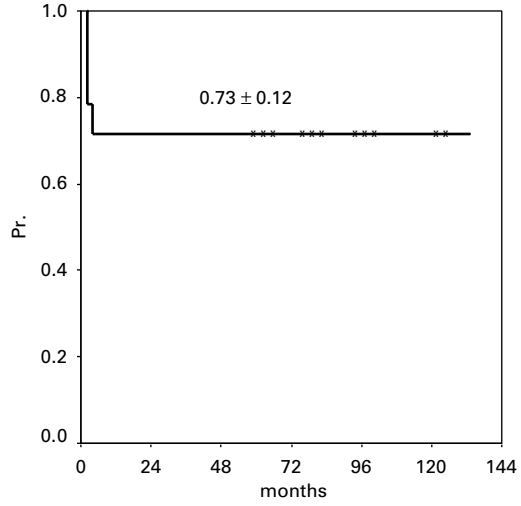

Figure 2 Survival of 15 PID patients undergoing cord blood transplantation. Four patients died from MRT before day 104. A total of 11 patients remain alive.

T- and B-cell function with normal immunoglobulin production and achieved good antibody titres after vaccination. Consequently, all surviving patients presented complete T- and B-immunologic reconstitution and were not IVIg replacement therapy-dependent.

Survival

Survival at 5 years was 0.73 ± 0.12 with a median follow-up post transplant of 64 months (range, 54–132) (Figure 2).

Discussion

Several studies have shown the overall results of UCB transplants to be similar to those of MUD transplants in both malignant and non-malignant diseases.[19,20] The recovery period of myeloid and lymphoid activity is longer in UCB transplants,[13,17,18,20,34–37] which raises the risk of severe infections. In contrast, advantages of UCB include easy availability and lower HLA-compatibility requirements. These advantages are notable in PID, particularly SCID.

Apart from sporadic reported cases of UCB transplants in PID,[21–27] only data from three centres have been published.[30,31,32] In the St Louis series, six of eight patients were cured and one remained alive with chronic interstitial pneumonitis.[30] In the Japanese experience, favourable results were obtained in five of seven patients.[31] The Newcastle series reported survival of 86%,[32] higher than the 73% in our series, probably due to reasons described below.[5,15,16,19]

In SCID patients, according to the European Registry data,[5] survival with MUD was 63 versus 54% with haploidentical transplants. In the recently published Japanese study, four of five patients with SCID who received a UCB transplant survived with complete immunologic reconstitution.[31] In the Newcastle study, eight patients had SCID (four with adenosine deaminase deficiency, two with T−B+NK+ SCID, one with undefined SCID, one with severe immunodeficiency with CHARGE association). All patients, except one, engrafted. Two patients died from pneumonitis. Chimaerism and T-cell immunologic reconstitution were complete in four patients and partial for B cells in two patients. Survival was 75%.[32] Our series comprised 11 SCID patients. Eight of them were T−B− with worse prognosis than SCID T−B+ according to the European Registry data. Similarly, it is noteworthy that 9 of the 11 patients had had lung disease, which became chronic in three; B-cell lymphoma was diagnosed in one patient. All patients engrafted. The incidences of viral and fungal infections and of GvHD were high. Seven patients survived with complete immunologic reconstitution.

Two of our four non-SCID patients had X-LPD. Up to 2005, 14 patients had been transplanted from different types of donors, with overall survival of 71%. The first case of a related UCB transplant was published in 1993[25] and the first two cases of UCB unrelated transplants in 2001;[21] all were successful. The first of our two patients had a brother who died from Epstein–Barr Virus-associated B-cell lymphoma. The patient himself also suffered a B-cell lymphoma which responded favourably to chemotherapy prior to transplant. The second patient, a first cousin of the first and diagnosed by genetic study, received a UCB transplant while asymptomatic; the clinical course was excellent with complete immunologic reconstitution as in the case of his cousin. As the short- or medium-term prognosis of X-LPD is poor, transplantation in the asymptomatic phase of the disease is recommended.[38] The remaining two patients had WAS and Omenn's syndrome, respectively. EFS with HLA-identical sibling donor transplants in WAS oscillates between 80 and 90%. In the absence of such donors, results with MUD transplants are superior to those with haploidentical donors.[16] Of 26 WAS patients treated with HCT at a single centre, 8 recipients of a matched sibling donor were cured versus 6 of 16 who received a haploidentical transplant.[8] Few cases of WAS patients treated with UCB transplant have been reported.[24,30–32] In the three series previously mentioned, only four patients had WAS: one died from respiratory complications and three were cured.[30–32] Our patient had presented intestinal bleeding prior to transplant; UCB transplant at the age of 3 months led to normal haematologic and immunologic reconstitution. In the absence of a sibling donor, results in Omenn's syndrome have been poor—only one of six patients who received either a haploidentical or an unrelated transplant survived.[39] Our previously reported Omenn's syndrome patient is the first case successfully treated by UCB transplant.[22]

Development of lymphocyte subpopulations and immunologic function in our SCID and non-SCID patients followed the pattern previously described,[34–37] with early recovery of normal NK cell values followed by CD19, CD3, CD4 and finally CD8. Response to mitogens and immunoglobulin production preceded the development of serologic responses to specific antigens. Immunologic reconstitution was complete. No patient is intravenous γ-globulin replacement therapy-dependent.

Although complete immunity in PID is achieved more frequently with myeloablative regimens, their complications are more toxic. The risks are higher if patients reach transplant with previous complications (lung disease, cholecystitis, chronic diarrhoea and viral infections). Reduced-intensity regimens (RIR) lower the risks and it has been shown that complete or stable mixed chimaerism and clinical cure can be achieved in a considerable proportion of MUD transplants with this approach.[40–42] In the Great Ormond Street Hospital series, survival in 33 patients with PID who received a MUD transplant with RIR (fludarabine, melphalan and ATG or CAMPATH) was 94%, almost double the 53% obtained at the same centre in 19 patients conditioned with a myeloablative regimen.[41] In our series, RIR was used in two patients with SCID and previous lung disease: one evolved favourably with a stable mixed chimaerism and complete immunologic recovery and is clinically asymptomatic; the other developed GvHD grade IV and died. It is even debatable whether any conditioning regimen at all should be used in PID, since favourable results have been obtained in some cases with no conditioning treatment.[31,32,43]

The fact that UCB transplants can be performed with greater tolerance to HLA disparity does not necessarily rule out the development of GvHD grades II–IV, the incidence of which oscillates between 33 and 37%.[17,18,20] Of note, 8 of 15 patients in our series (53%) developed GvHD grades II–IV and 5 of these were III–IV. Four of these five patients had received UCB transplants with 4/6 HLA-identities and the fifth patient with 5/6. Three of these five patients died: two had undergone 4/6 cord blood transplants and one 5/6. This high incidence contrasts with the 14% in the Newcastle series.[32] Possible explanations for this discrepancy could be the different conditioning regimens used in each series (Newcastle: no regimen in 4, RIR in 3 and myeloablative in 7 versus our series: RIR in 2, myeloablative in 13) and differences in HLA identity (Newcastle: 6/6 in all and even 10/10 in 10 versus our series: 6/6 in 3, 5/6 in 8 and 4/6 in 4). No differences were observed in the number of cells infused (total cells and CD34 +) in either series. The degree of HLA compatibility affects not only the incidence and intensity of GvHD, but also transplant-related mortality, as shown in a recent analysis of 608 HCT.[44] Therefore, the degree of HLA compatibility may exert a notable influence on results.

Although our 73% survival with cure could be considered satisfactory, the results could be improved with better HLA compatibility, selection of cord blood units and the use of RIR.

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