

Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation

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Key points :

1. HLA-identical sibling transplantation for SCD offers excellent long-term survival.
2. Mortality risk is higher for older patients; EFS has improved in patients transplanted after 2006.

Abstract

Despite advances in supportive therapy to prevent complications of sickle cell disease (SCD), access to care is not universal. Hematopoietic cell transplantation is, to date, the only curative therapy for SCD, but its application is limited by availability of a suitable HLA-matched donor and lack of awareness of the benefits of transplant. Included in this study are 1000 recipients of HLA-identical sibling transplants performed between 1986 and 2013 and reported to the European Blood and Marrow Transplant, Eurocord and the Center for International Blood and Marrow Transplant Research. The primary endpoint was event-free survival, defined as being alive without graft failure; risk factors were studied using Cox regression model. The median age at transplantation was 9 years and the median follow-up, longer than 5 years. Most patients received a myeloablative conditioning regimen (n=873; 87%) and the remainder, reduced-intensity conditioning regimens (n=125; 13%). Bone marrow was the predominant stem cell source (n=839; 84%), while peripheral blood and cord blood progenitors were used in 73 (7%) and 88 patients (9%), respectively. The 5-year event-free and overall survival was 91.4% (95% CI 89.6%-93.3%) and 92.9% (95% CI 91.1%-94.6%), respectively. Event-free survival was lower with increasing age at transplantation (hazard ratio [HR] 1.09; p<0.001) and higher for transplantations performed after 2006 (HR 0.95, p=0.013). Twenty-three patients experienced graft failure; 70 patients (7%) died, the most common cause of death being infection. The excellent outcome of a cohort transplanted over 3 decades confirms the role of HLA-identical sibling transplantation for children and adults with SCD.

Background

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy worldwide. SCD affects over 100,000 Americans and it occurs in about 1 in 500 African-American births and in 1 in every 1000-1400 Hispanic-American births.¹ Similar rates are reported in European and Caribbean countries; it is estimated that there are, approximately, 12,000 cases in France. In Brazil, the mean incidence of SCD is 1 per 1000 births with 3000 new cases per year.² However, the frequency of the disease worldwide is uncertain and is likely to be underestimated in Asia and Africa. The implementation of newborn screening, penicillin prophylaxis, vaccination, narcotics, transfusions and hydroxyurea (HU) has improved survival, with more than 95% of children in developed countries surviving to adulthood.³⁻⁵ Further, the completion of four major randomized clinical trials, since the 1990s, has provided evidenced-based guidelines for primary and secondary stroke prevention in SCD.⁶ Survival in children has improved to an extent that the mortality rate is now 0.5 per 100,000 persons.⁷ In contrast, survival is lower in adults, with a mortality rate exceeding 2.5 per 100,000 persons.⁷ Despite these remarkable advances in supportive therapy of SCD, most patients suffer from considerable disabilities and early mortality.^{1,2,8-10}

Allogeneic hematopoietic stem cell transplant (HSCT) is currently the only curative treatment for severe SCD, but access is limited for several reasons, including donor availability, socio-cultural and economic barriers. SCD and transplant physicians alike debate the burden of morbidity from a chronic disease and mortality from the disease, versus the curative option with transplantation and the risk of transplant-related complications and mortality. In this regard, a panel of experts published consensus recommendations reporting that young patients with symptomatic SCD with a HLA-identical sibling should be transplanted, as early as possible, preferably at pre-school age.¹¹ They also recommended that unrelated or alternative donor transplantation should only be considered in the presence of markers of disease severity, such as cerebral vasculopathy, recurrent acute chest syndrome, severe vaso-occlusive disease, sickle nephropathy, osteonecrosis, priapism, severe erythroid allo-immunization and failure to benefit from or an unwillingness to continue supportive therapy, including HU.¹¹ Although several reports have demonstrated that HLA-identical sibling transplantation with bone marrow (BM) or umbilical cord blood (CB) establishes normal hematopoiesis and is associated with excellent survival, most studies

were conducted at single institutions or in the context of clinical trials.¹²⁻¹⁷ The current analyses sought to describe outcomes after HLA-identical sibling transplantation for sickle cell disease worldwide.

Methods

Study design

With the goal of analyzing the role of HSCT for patients affected by SCD, we designed an international, retrospective, registry-based survey. Data were collected from CIBMTR (Center for International Blood and Marrow Transplant Research), EBMT (European Society for Blood and Marrow Transplantation) and Eurocord databases. Children and adults, who underwent HSCT as first transplant, before December 31st, 2013, were included. All donors were HLA-identical siblings and stem cell source included BM, peripheral blood (PB) or CB. Recipients of HLA-mismatched related donor (including haplo-identical donors) and HLA-matched or mismatched unrelated donor transplants were excluded.

All patients or legal guardians gave informed consent for research. The study was conducted in compliance with the Declaration of Helsinki. The Internal Review Board of EBMT/Eurocord and the Institutional Review Board for the National Marrow Donor Program approved the study.

Study endpoints, definitions and statistical methods

The primary endpoint was event-free survival (EFS), defined as the probability of being alive with sustained donor cell engraftment. Death from any cause and primary or secondary graft failure were considered events. Surviving patients were censored at last follow-up. Secondary endpoints included overall survival (OS), neutrophil and platelet recovery, graft failure, and graft-versus-host disease (GVHD), according to standard criteria. GVHD-free survival was defined as the probability of being alive without having experienced either grade III-IV acute GVHD or extensive chronic GVHD.

Conditioning regimen was defined, according to published criteria,¹⁸ as reduced intensity (RIC) if fludarabine (Flu) was associated with <6 Gy total-body irradiation (TBI), or busulfan \leq 8 mg/kg, melphalan \leq 140 mg/m², or other non myeloablative drugs; conditioning

was defined as myeloablative (MAC) if TBI>6Gy, busulfan >8mg/kg with or without other drugs were used.

All patients meeting the inclusion criteria were included in the analysis. Start time for all endpoints was the date of HSCT. Neutrophil recovery was defined as the first of 3 consecutive days with a neutrophil count of at least $0.5 \times 10^9/L$. Platelet recovery was defined as the first of three consecutive days with platelets $>20 \times 10^9/L$ sustained without transfusion for at least seven days. Graft failure was defined as having never achieved ANC $0.5 \times 10^9/L$ or autologous recovery, or loss of donor engraftment.

Quantitative variables are described with median, range and interquartile range (IQR). Categorical variables are reported with counts and percent. Patient's age was tested as a continuous variable. EFS, OS and GVHD-free survival were calculated using the Kaplan-Meier estimator.¹⁹ Cumulative incidence function²⁰ was used to estimate probabilities of hematopoietic recovery and GVHD, considering death as the competing risk for hematopoietic recovery, and death and rejection for GVHD. Comparison of probability estimates was performed using Gray's test for cumulative incidence of hematopoietic recovery and GVHD and the log-rank test for EFS and OS. Probability estimates are reported as a percent with a 95% confidence interval (CI). Patient and transplant characteristics associated with EFS and OS were evaluated in multivariate analysis, using Cox proportional-hazard model²¹, stratified by registry (EBMT versus CIBMTR). All factors associated with a p value <0.10 by univariate analysis were included in the models. Variables retained in the final model were: stem cell source (PB vs. BM/CB), age at HSCT, conditioning regimen intensity (RIC vs. MAC), *in vivo* T-cell depletion and transplant period. All p-values are two-sided, and p-values ≤ 0.05 were considered to be statistically significant. Analyses were performed using the R statistical software version 3.2.3 (available online at <http://www.R-project.org>).

Results

Patient and transplant characteristics

From 1986 to 2013, 1000 patients received an HLA-identical sibling transplant for SCD at 106 centers in 23 countries worldwide. The median follow-up for surviving patients was 55 (range 3-325) months. Four hundred and thirty nine patients were transplanted in the USA, 513 in Europe and 48 in non-European countries.

Patients and transplant characteristics are shown in Tables 1 and 2. Patients were mainly children (<16 years) (n=846) with a median age at HSCT of 9 (range 0.3-16) years. The median age for adults (n=154) was 20 (range 16-54) years. The median age at transplantation for recipients of BM, PB and CB were 9.4, 18.7 and 6.1 years, respectively ($p<0.001$). The most frequent indications were stroke, acute chest syndrome, and recurrent vaso-occlusive disease. Prior to transplant, most patients had been transfused and had been treated with HU. Most conditioning regimens were MAC (n=873; 87%), based on the combination of busulfan with either cyclophosphamide (n=723) or fludarabine (n=110). One hundred and twenty five patients (13%) received RIC regimens, and fludarabine with cyclophosphamide was the most commonly used regimen (n=46). Most recipients of BM (88%; 742 of 838) and CB (95%; 84 of 88) transplantation received MAC regimens. In contrast, only 65% (47 of 72) of PB transplantation recipients received MAC regimens ($p<0.001$). Most regimens included *in vivo* T-cell depletion (n=807) with either anti-thymocyte globulin (n=692) or alemtuzumab (n=113). The most frequently used stem cell source was BM (n=839), while PB (n=73) and CB (n=88) were used less frequently.

Hematopoietic recovery

The cumulative incidence of neutrophil recovery at day+60 was 98% (95% CI 97.1%-98.9%). The median time to granulocyte recovery was 19 days; recovery was faster after transplantation of BM (18 days) and PB (15 days) progenitors compared to CB cells (27 days), ($p<0.001$). The cumulative incidence of platelet engraftment at 6 months was 96% (95% CI 95%-97.7%). The median time to platelet recovery was 25 days and it was faster after transplantation of PB (18 days) and BM (25 days) progenitors compared to CB cells (37 days), ($p<0.001$). Twenty-three patients experienced graft rejection. Data on chimerism was available for a subset of patients (N=614) of whom 68% were full donor chimera, 29% mixed chimera and 3% had autologous reconstitution.

Graft-versus-host disease

The cumulative incidence of grade II-IV acute GVHD was 14.8% (95% CI 12.6%-17.1%), while that of chronic GVHD was 14.3% (95% CI 12%-16.9%). In multivariate analysis, the risk of acute GVHD was higher with increasing age (HR=1.04 95% CI 1.01-1.07, $p=0.008$). For every 1-year increment in age at transplantation, there was a 4% increase in the hazard ratio for acute GVHD. No other risk factors for acute GVHD occurrence were identified. Although results of univariate analysis suggested higher chronic GVHD rates in patients 16 years and older compared to those younger, 19.6 % (95%CI 13.3%-26.8%) versus 13.3% (95%CI 10.9%-16%), respectively ($p=0.015$; Figure 1A), none of the variables tested were associated with chronic GVHD in multivariate analysis (age tested as continuous variable). To further test the observed effect of age, we tested age as a binary variable (<16 years versus ≥ 16 years) and results of multivariate analysis revealed a 2% increase in the hazard ratio for chronic GVHD (HR 0.5 (95% CI 0.32 – 0.90), $p=0.020$).

Overall survival and event-free survival

The unadjusted overall 5-year probabilities of OS and EFS were 92.9% (95%CI 91.1%-94.6%) and 91.4% (95%CI 89.6%-93.3%), respectively. The 5-year OS was 95% (95%CI 93%-97%) and 81% (95%CI 74%-88%) for patients aged <16 years and those aged ≥ 16 years, respectively ($p<0.001$); the corresponding EFS was 93% (95%CI 92%-95%) and 81% (95%CI 74%-87%), $p<0.001$. The 5-year probability of GVHD-free survival was 86% and 77% for patients aged <16 and ≥ 16 years, respectively ($p<0.001$).

Multivariate analysis results confirmed the significant association of age at HSCT and transplant period with EFS and of age at HSCT and graft type with OS (Table 3). The EFS and OS were both lower with increasing age, and OS was lower for PB transplant recipients (Figure 1B). EFS was higher for transplantations performed after 2006. For every 1-year increment in age there was a 9% increase in the hazard ratio for treatment failure (graft failure or death). Similarly, for every 1-year increment in age, there was a 10% increase in the hazard ratio for death. Transplant conditioning regimen intensity and in vivo T-cell depletion were not associated with OS or EFS (Table 3).

Overall, 70 patients died: 52 after BM, 17 after PB, and 1 after CB transplantation. The most common cause of death was infection ($n=14$), followed by GVHD ($n=9$), toxicity ($n=9$), hemorrhage ($n=3$), secondary malignancy ($n=2$; 1 CNS lymphoma and 1 cerebral tumor) and other or not specified causes ($n=33$). Seven (~10%) deaths occurred beyond 5

years, this finding underscores the need for long-term follow-up. These deaths were attributed to transplant-related toxicities (n=2), liver failure (n=1), original disease (n=1), secondary malignancies (n=1) and causes not specified for 2 patients (who died at 11.5 and 11.65 years after HSCT, respectively).

Discussion

This is the first study to analyze a large number of SCD recipients of HLA-identical sibling transplantation. Five-year survival is excellent considering that these transplants were performed worldwide, reported to observational registries and that the majority of patients were not enrolled on clinical trials.²²⁻²⁷ Further, we were able to interrogate for risk factors associated with survival and identified important factors: age, graft type and transplant period. In the context of SCD, HSCT is an elective intervention. Our data support early referral for transplantation when an indication is identified, so that donor search and transplantation of BM, PB or banked CB from an HLA-identical sibling can be initiated in a timely manner. Further, better supportive care during the immediate and later periods after transplantation has also improved survival. Concurrently, advances in caring for children and adolescents with SCD has also improved substantially to an extent that 93.4% of children with sickle cell anemia and 98.4% of children with milder forms of SCD now live to become adults.²⁴ The 5-year overall survival of 95% in patients aged <16 years after HLA-identical transplantation compares favorably to that reported by Quinn and colleagues in their study of the Dallas Newborn Cohort.²⁴ For patients aged ≥16 years, we observed lower survival rates, namely 80% at 5 years, confirming age is a significant prognostic factor for both OS and EFS. Others have also reported higher mortality amongst non-transplanted adults with severe SCD who at risk for early death as they transition from pediatric to adult care.²⁴

Despite the excellent 5-year EFS and OS reported here, in 10% of patients death occurred beyond 5 years. End organ damage from SCD in addition to transplantation is a likely explanation for the observed late mortality. Only with longer follow-up, we can study the very late outcomes, including mortality after transplantation for SCD. Acute GVHD risk was also associated with increasing age; therefore, early referral for transplantation, as soon as it is indicated, may mitigate some of the risks for higher acute GVHD.

Severe SCD affects several organs and the higher age-associated mortality risk may in part be attributed to several factors, notably co-morbidities, end organ function or performance score at transplantation, as well as other unknown or unmeasured factors. Under the circumstances, when counseling patients for transplantation, it is important to balance the potential benefits of long-term survival as a result of a curative treatment against the risks of mortality from transplant-related complications and the potential risk of severe GVHD, which adds to the burden of morbidity and mortality.^{28,29} Standard of care (i.e., non-transplant therapies) has very low toxicity, but it offers no cure for the underlying disease and the risk of death is higher later in life; the expected mortality is 4.4 per person years.^{30,31} Consequently, the ideal comparison between these two very different treatments would be a randomized trial of the treatment options. However, such trials are difficult to conduct and usually lengthy, as less than a third of potentially eligible patients will have a suitably HLA-matched donor. An alternative approach is the concept of biologic assignment to the treatment arms (donor versus no donor) based on the availability of a suitably matched donor. One such trial was recently opened in the USA (NCT 02766465) with the results anticipated by 2021.

In the current analysis, most transplants used BM graft. Our data support the notion that use of PB grafts is associated with higher mortality. This is similar to what reported after HLA-identical sibling PB transplants for aplastic anemia.²⁵ In the current study, 125 (12.5%) transplantations used a variety of RIC regimens. We did not observe an effect of transplant conditioning regimen intensity neither on EFS nor on OS. Our inability to detect differences by regimen intensity may be explained by the modest numbers of RIC recipients and heterogeneity of regimens used. While MAC-regimens offer long-term protection from common complications of SCD, including stroke and acute chest syndrome, growth retardation and sterility are concerning.²⁵ Efforts to decrease the early and late complications of transplantation attributed to conditioning regimens have led to RIC regimens. Fludarabine, treosulfan, melphalan, and low-dose TBI,^{24,32-34} have all been shown to decrease toxicity from the regimen per se, but the risk of rejection is higher.¹⁶ Others have utilized regimens with minimal toxicity but that has required prolonged immune suppression to sustain engraftment.²⁴ Ours is not the ideal dataset to test for an effect of conditioning regimen intensity considering the heterogeneity of regimens used.

Consequently, we are unable to recommend one type of regimen over another. It is noteworthy mentioning that a recent report on HLA-matched unrelated donor BM transplants for SCD in children that used a reduced intensity melphalan and alemtuzumab-containing regimen reported very high rates of chronic GVHD, which then led to high mortality rates.²⁹ Only carefully controlled prospective clinical trials will identify the effects of regimen intensity on transplantation outcomes.

SCD is recognized as a global public health issue by both national and international organizations^{1,35} and SCD, along with other hemoglobinopathies and hemolytic anemia, is reported to contribute to 0.6% of all global disability-adjusted life years (DALYs). This is a substantial contribution to global burden of disability by a rare disease, considering that other high burden diseases, such as cardiovascular/circulatory diseases and diabetes mellitus, account for 11.8% and 1.9% of all DALYs, respectively.³⁶ Consensus reports on indications for transplantation may increase awareness, with early referral for accepted indications.^{17,37} Others have reported the observation that HLA-matched sibling transplantation performed in view of abnormal trans-cranial Doppler velocities allowed for discontinuation of transfusions in all patients.¹² Although survival in children has improved substantially over the years, the median survival of adults is about 20 years shorter than the general population.⁷ Yet, access to comprehensive clinics, including transition of care of the adolescent from a pediatric to an adult setting, the median survival for adults is 67 years³⁸ but, structured comprehensive clinics are not the norm.

In the absence of systematic referral and tracking of those unable to proceed with transplantation due to lack of a matched related donor, the potential number of SCD subjects who might benefit from transplantation is unknown. For a patient seeking a donor, each full sibling has a 25% chance of being an HLA identical match. Based on an average of 2 to 3 children per family, it is estimated that an individual has approximately a 30% chance of identifying a matched sibling, and the likelihood of identifying a matched sibling is lower for younger patients.³⁹ The option of directed-family cord blood banking from non-affected siblings of patients with SCD should be offered to families at risk.⁴⁰ Strategies that explore the use of mismatched related donors are ongoing^{41,42} as are studies of gene therapy and gene editing, all of which are aimed at improving survival for SCD.⁴³⁻⁴⁵ Transplantation of grafts from HLA-identical siblings offers excellent 5-year survival and our results confirm this

is an accepted treatment for severe SCD worldwide. Nevertheless, it is also important to study the effects of transplantation on the long term and to develop prospective trials of comparable patient cohorts to determine the relative merits of transplantation versus supportive care, especially in older patients with severe SCD.

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Author Contributions

EG, FB, BPS, AR, and ME designed the study; EG, FV, FL, AR and ME wrote the manuscript. BC, FV, AR prepared the data for analysis; ML and AR performed statistical analysis, BC, FB collected and verified data; CK, HE and JC helped with data management; FB, SMM, FL, BPS, JK and LK edited the manuscript; FB, BPS, AF, SD, JF, JHD, MZ, MCW, LK, MB, KL, GY, JK, ND, MK, GM, JA, PL, BN, YB, JPV, MA, MC, SMM, VR, PB, FL transplanted patients and provided data for the study. All authors read and approved the manuscript.

Conflict of Interest Disclosures

The authors have no conflict of interest to disclose.

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Table 1. Patients and transplant characteristics (n=1000)

Variables		Total (n=1000)	Children (n=846)	Adults (n=154)
Follow-up, months median (range)		54.5 (0.3-324.6)	56.4 (0.3-324.6)	48.0 (2.18-305.9)
Age, years median (range)		9.4 (0.26-54.37)	8.3 (0.3-16.0)	19.3 (16.0-54.4)
Year of transplantation median (range)		2007 (1986-2013)	2007 (1986-2013)	2008 (1989-2013)
Gender, n (%)	male	498 (49.8)	416 (49.2)	82 (53.2)
	female	502 (50.2)	430 (50.8)	72 (46.8)
Source of HSC, n (%)	BM	839 (83.9)	728 (86.1)	111 (72.1)
	PBSC	73 (7.3)	30 (3.5)	43 (27.9)
	CB	88 (8.8)	88 (10.4)	---
GVHD prophylaxis, n (%)	CsA	188 (19.9)	168 (21.1)	20 (13.5)
	CsA+MTX	533 (56.5)	470 (59.1)	63 (42.6)
	CsA+MMF	73 (7.7)	54 (6.8)	19 (12.8)
	FK506±other	110 (11.7)	89 (11.2)	21 (14.2)
	other	39 (4.1)	14 (1.5)	25 (16.9)
in vivo TCD, n (%)	None	173 (17.7)	161 (20.8)	12 (9.1)
	ATG	692 (70.6)	605 (78.1)	87 (65.9)
	OKT3	2 (0.2)	1 (0.1)	1 (0.8)
	Campath	113 (11.5)	8 (1.0)	32 (24.2)
Conditioning, n (%)	MAC	873 (87.4)	760 (89.8)	113 (73.4)
	Bu+Cy	721 (82.6)	660 (86.8)	61 (54.0)
	Bu+Flu±other	79 (9.0)	57 (7.5)	22 (19.5)
	Flu±other	33 (3.8)	27 (3.6)	6 (5.3)
	TBI±other	26 (3.0)	6 (0.8)	20 (17.7)
	Other or missing	14 (1.6)	10 (1.3)	4 (3.5)
	RIC	125 (12.5)	85 (10.0)	40 (26.0)
	Bu+Cy	3 (2.4)	2 (2.4)	1 (2.5)
	Bu+Flu±other	22 (17.6)	14 (16.5)	8 (20.0)
	Flu±other	62 (49.6)	45 (52.9)	17 (42.5)
	TBI±other	20 (16.0)	8 (9.4)	12 (30.0)
	Other or missing	18 (14.4)	16 (18.8)	2 (5.0)

Kg means kilogram; HSC, hematopoietic stem cell; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; GVHD, graft-versus-host disease; CsA, cyclosporin A; MTX, methotrexate; MMF, mycophenolate mofetil; FK506, tacrolimus; TCD, T-cell depletion; ATG, anti-thymocyte globulin; OKT3, mouse monoclonal anti-CD3 antibody; MAC, myeloablative conditioning; Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; TBI, total body irradiation; RIC, reduced intensity conditioning. **Missing data:** in vivo TCD=20, conditioning (RIC/MAC)=2, detailed conditioning MAC=13, detailed conditioning RIC=18

Table 2. Patients and transplant characteristics according to stem cell source

	Bone marrow		Peripheral blood		Cord blood (children only)
	Children	Adults	Children	Adults	Children
N	728	111	30	43	88
Median follow-up, months (range)	57.8 (0.3-325.4)	48.46 (2.65 - 306.67)	51.0 (1.1-227.9)	47.88 (2.19 -168.4)	54.2 (3.7-161.9)
Median age, years (range) [IQR]	8.4 (0.3-16) [5.8-11.8]	18.5 (16-46.2) [16.8-23.3]	12.7 (2.2-15.9) [9.9-14.6]	23.4 (17.3-54.4) [19.8-30.1]	6.1 (1.9-15.5) [4.1-8.5]
Median year of TX (range) [IQR]	2007(1986-2013) [2001-2010]	2008(1989-2013) [2003-2010]	2003(1999-2011) [2001-2008]	2008(1997-2012) [2003-2011]	2009(1994-2012) [2004-2011]
Registry: n (%)					
EBMT	400 (55.0)	54 (48.7)	19 (63.3)	17 (39.5)	71 (80.7)
CIBMTR	328 (45.0)	57 (51.4)	11 (36.7)	26 (60.5)	17 (19.3)
Conditioning type: n (%)					
MAC	653 (89.7)	89 (80.9)	23 (79.3)	24 (55.8)	84 (95.5)
RIC	75 (10.3)	21 (19.1)	6 (20.7)	19 (44.2)	4 (4.6)
GVHD prophylaxis: n (%)					
CsA	102 (14.9)	13 (12.0)	6 (27.3)	5 (12.5)	56 (64.4)
CsA+MTX	447 (65.2)	57 (52.8)	9 (40.9)	5 (12.5)	16 (18.4)
CsA+MMF	41 (5.9)	17 (15.7)	2 (9.1)	2 (5.0)	9 (10.3)
FK506+/-other	82 (12.0)	17 (15.7)	3 (13.6)	4 (10.0)	4 (4.6)
other	14 (2.0)	4 (3.7)	2 (9.1)	24 (60.0)	2 (2.3)

IQR means inter quartile range; EBMT, European Society for Blood and Marrow Transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; GVHD, graft-versus-host disease; CsA, cyclosporin A; MTX, methotrexate; MMF, mycophenolate mofetil; FK506, tacrolimus

Table 3. Multivariate analysis for event free survival and overall survival

	EFS		OS	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
PB vs. BM	1.93 (0.87 – 4.26)	0.104	2.62 (1.17 – 5.89)	0.019
CB vs. BM	0.55 (0.13 – 2.31)	0.412	Not applicable*	
Age	1.09 (1.05 – 1.12)	<0.001	1.10 (1.06 – 1.14)	<0.0001
Transplant year ≥2007 vs. ≤2006	0.95 (0.90 – 0.99)	0.013	0.96 (0.91 – 1.00)	0.101
Conditioning regimen RIC vs. MAC	1.13 (0.46 – 2.81)	0.793	0.83 (0.29 – 2.39)	0.735
In vivo T cell depletion Yes vs. no	1.34 (0.63 – 2.82)	0.445	1.10 (0.49 – 2.48)	0.806

* Not evaluable as there was only 1 event in the CB group; therefore for OS, the CB transplants were included with BM transplants.

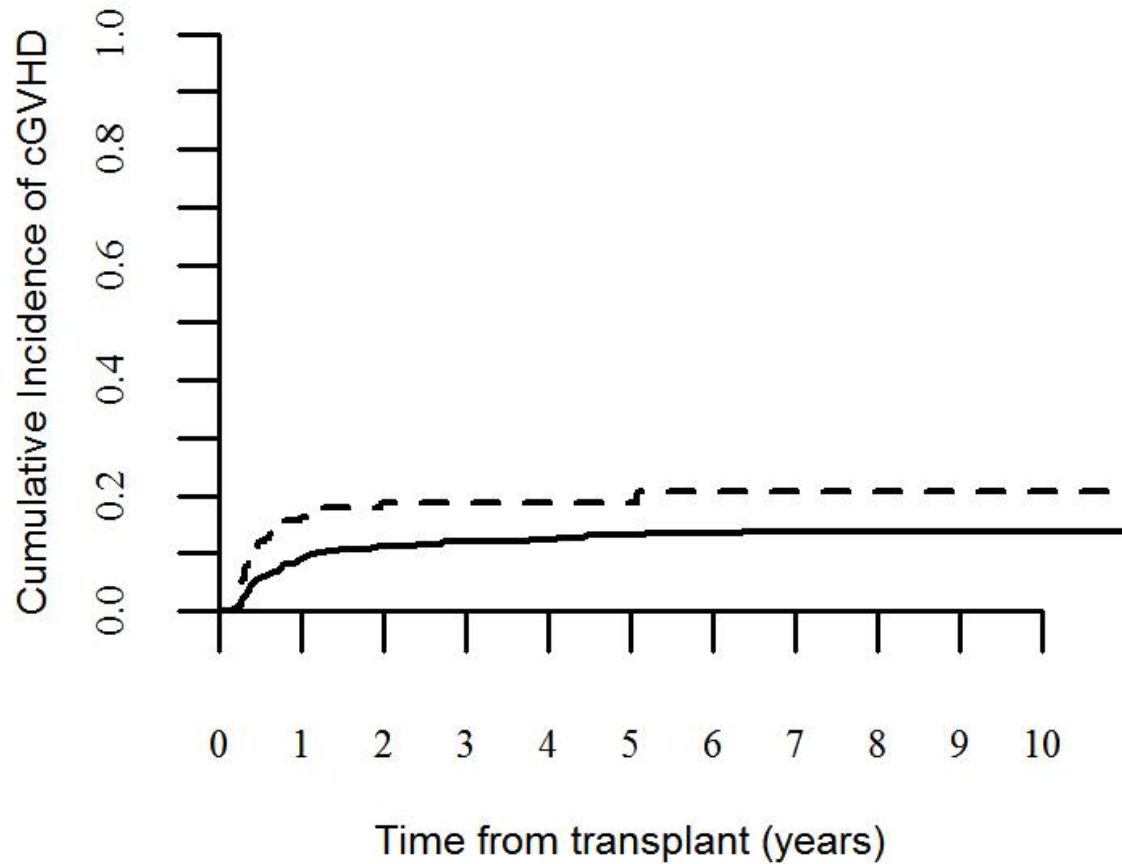
EFS means event free survival; OS, overall survival, PB peripheral blood stem cell; vs, versus; BM bone marrow; CB, cord blood; Tx, transplant; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; TCD, t-cell depletion; HR, hazard ratio; CI, confidence interval.

The adjusted Cox regression analysis was stratified by registry (EBMT and CIBMTR); Age was considered as a continuous variable; when considering the graft source, PB and CB were compared, separately, to BM (baseline) for the EFS.

Figure Legend:

Figure 1. Unadjusted chronic graft-versus-host disease (1A) according to age and overall survival (1B) according to stem cell source

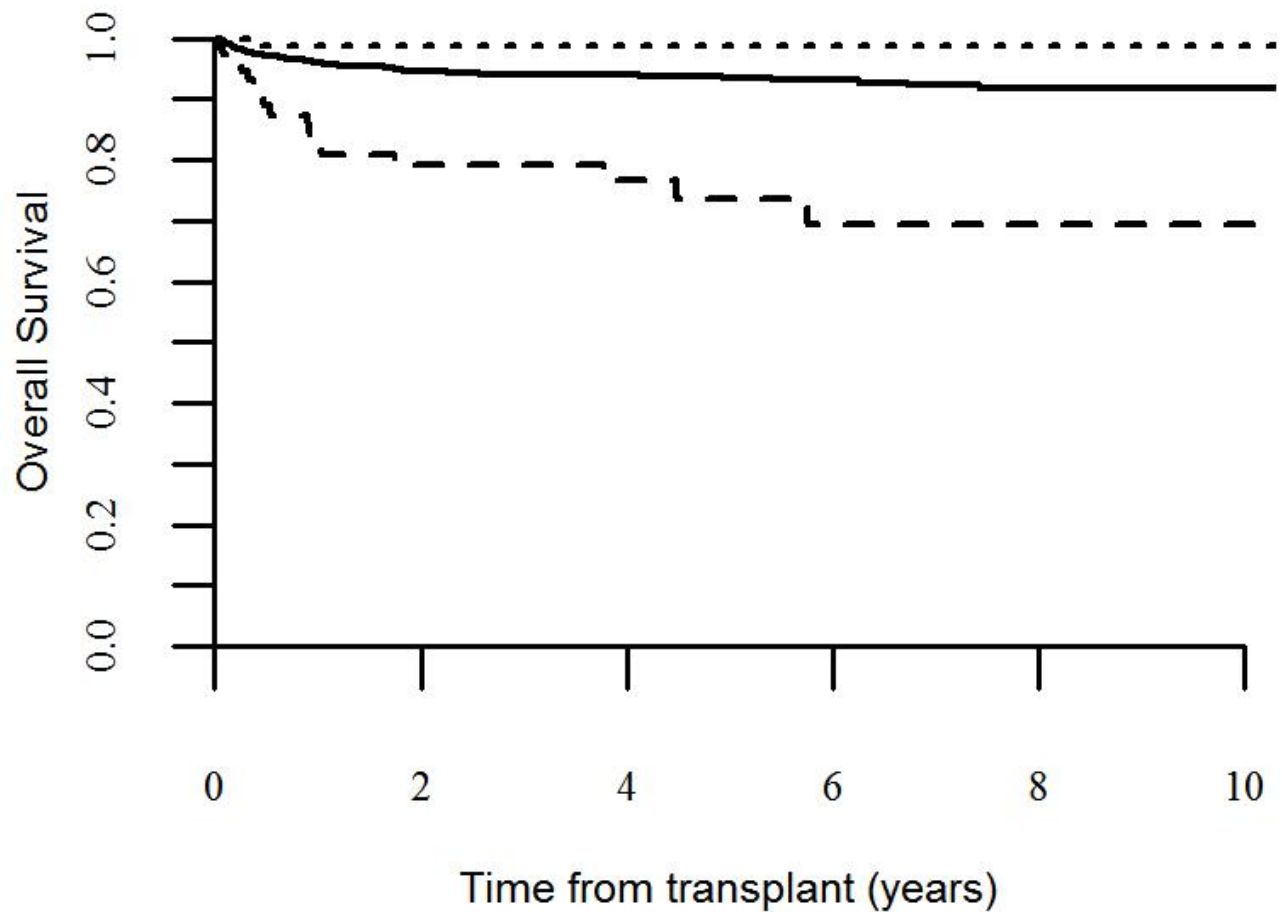
Figure 1A. Chronic graft-versus-host disease according to age



number of at-risk patients

— Children	814	630	541	459	386	316	254	212	181	152	126
- - Adults	147	99	84	68	51	40	28	22	15	14	13

Figure 1B. Overall survival according to stem cell source



		0	2	4	6	8	10					
—	BM	839	673	546	446	383	322	262	215	177	152	120
- -	PB	73	49	41	33	28	24	14	10	9	7	5
· · ·	CB	88	81	70	60	47	37	29	27	24	17	13



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Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation

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