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

Eliane Gluckman,1,2 Barbara Cappelli,2 Francoise Bernaudin,3 Myriam Labopin,4 Fernanda Volt,1,2 Jeanette Carreras,5 Belinda Pinto Simões,6 Alina Ferster,7 Sophie Dupont,8 Josu de la Fuente,9 Jean-Hugues Dalle,10 Marco Zecca,11 Mark C. Walters,12 Lakshmanan Krishnamurti,13 Monica Bhatia,14 Kathryn Leung,15 Gregory Yanik,16 Joanne Kurtzberg,17 Nathalie Dhedin,18 Mathieu Kuentz,3 Gerard Michel,19 Jane Apperley,20 Patrick Lutz,21 Bénédicte Neven,22 Yves Bertrand,23 Jean Pierre Vannier,24 Mouhab Ayas,25 Marina Cavazzana,26,27,28 Susanne Mathes-Martin,29 Vanderson Rocha,1,30,31 Hanadi Elayoubi,1,2 Chantal Kenzey,12 Peter Bader,32 Franco Locatelli,33 Annalisa Ruggeri,12,34 Mary Eapen5

An international study on behalf of Eurocord, the Pediatric Working Party of the European Society for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research

1Eurocord, Paris-Diderot University EA 3518, Hospital Saint Louis, Paris, France
2Monacord, International Observatory on Sickle Cell Disease. Centre Scientifique de Monaco, Monaco
3Department of Pediatrics, Referral Center for Sickle Cell Disease, CHIC Hospital, Paris XII University, Créteil, France
4EBMT Statistical Unit, Hospital Saint Antoine, AP-HP, Paris, France
5Department of Medicine, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee WI, USA
6Ribeirão Preto Medical School, University of São Paulo, Brazil
7Hematology-Oncology Unit, Hospital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles (ULB), Brussels, Belgium
8Cliniques Universitaires Saint Luc, Hemato-Oncology Unit, Brussels, Belgium
9Centre for Haematology, Imperial College London, London, United Kingdom
10Hematology-Immunology, Hospital Robert Debré and Paris-Diderot University, Paris, France
11Pediatric Hematology-Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
12UCSF Benioff Children's Hospital, Oakland, CA, USA
13Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA, USA
14Morgan Stanley Children's Hospital of New York, NY, USA
15Baylor College of Medicine, Houston, Texas, USA
16Children's Hospital of Michigan, Detroit, MI, USA
17Pediatric Blood and Marrow Transplant Program, Duke University Medical Center, Durham, NC, USA
18Adolescent and Young Adults Hematology Department, Hospital Saint-Louis, Paris, France
19Department of Pediatric Hematology and Oncology and Research Unit EA 3279 Aix-Marseille University and Children Timone Hospital Marseille, France
20Imperial College London, Hammersmith Hospital, UK
21Service D'hématologie Pédiatrique, CHU de Strasbourg, Strasbourg, France
22Pediatric Hematology-Immunology Department, Hospital Necker-Enfants Malades, AP-HP, Paris, France
23Department of Pediatric Hematology and Oncology, University Hospital of Lyon, France
24EA 3829, IRIB, Faculté de Médecine-Pharmacie, Rouen, France
25Paediatric Haematology/Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia
26Biotherapy Department, Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, France

Copyright © 2016 American Society of Hematology
Short title: HLA-Identical sibling HSCT for SCD

Abstract word count: 250
Text word count: 2980
Table: 3
Figure: 1
References: 45

Corresponding Author:
Eliane Gluckman, MD
Eurocord Hospital Saint Louis
1 avenue Claude Vellefaux, 75010 Paris, France
E-mail: eliane.gluckman@aphp.fr
Phone: +33 1 42 49 96 44 Fax: +33 1 42 38 53 90

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. 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, as reduced intensity (RIC) if fludarabine (Flu) was associated with <6 Gy total-body irradiation (TBI), or busulfan ≤ 8 mg/kg, melphalan ≤ 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 0.5x10^9/L. Platelet recovery was defined as the first of three consecutive days with platelets >20x10^9/L sustained without transfusion for at least seven days. Graft failure was defined as having never achieved ANC 0.5x10^9/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. Cumulative incidence function 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 model, 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. 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. 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. 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, have all been shown to decrease toxicity from the regimen per se, but the risk of rejection is higher. Others have utilized regimens with minimal toxicity but that has required prolonged immune suppression to sustain engraftment. 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. 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 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. Consensus reports on indications for transplantation may increase awareness, with early referral for accepted indications. 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. Although survival in children has improved substantially over the years, the median survival of adults is about 20 years shorter than the general population. 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 years 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. The option of directed-family cord blood banking from non-affected siblings of patients with SCD should be offered to families at risk. Strategies that explore the use of mismatched related donors are ongoing as are studies of gene therapy and gene editing, all of which are aimed at improving survival for SCD. 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.
Acknowledgements

We thank all the participating transplant centers below:

**Austria:** Susanne Matthes-Martin- St. Anna Kinderspital, Vienna; **Belgium:** Alina Fester- Hôpital Universitaire des Enfants Reine Fabiola, Brussels; Sophie Dupont- Cliniques Universitaires St. Luc, Brussels; Victoria Bordon-University Hospital Gent, Gent; Veerle Labarque- University Hospital Gasthuisberg, Leuven; Maguy Pereira - University of Liege, Liege; **Brazil:** Belinda Pinto Simões Medical School University of São Paulo, Ribeirão Preto; Vanessa Rocha- Hospital Sirio-Libanes, São Paulo; **Canada:** Henrique Bittencourt- Ste-Justine Hospital, Montréal; **Denmark:** Heidi Petersen- Rigshospitalet, Copenhagen; **France:** Eric Deconninck- Hospital Saint Jacques, Besançon; Charlotte Juberthie- CHU Pellegrin Enfants, Bordeaux; Jean Perrin- CHU Hospital Hotel Dieu, Clermont-Ferrand; Francoise Bernardin and Mathieu Kuentz –Referral center for sickle cell disease, CHIC Hospital, Créteil; Jean Yves Cahm- Hospital La Tronche, Grenoble; Bénédicte Bruno-CHU Jeanne de Flandre, Lille; Yves Bertrand-University Hospital Department of Pediatric Hematology/Oncology, Lyon; Gérard Michel- Hospital La Timone, Marseille; Pierre Bordigoni- Hospital Brabos, Nancy; Françoise Mechinaud- Hospital Hotel Dieu, Nantes; Jean Paul Vernant- La Pitié, Paris; Bénédicte Neven and Marina Cavazzana-Hospital Neckers-Enfants Malades, Paris; Jean Hugues Dalle-Hospital Robert Debré, Paris; Nathalie Dhedin- Hospital Saint-Louis, Paris; Jean Pierre Vannier- Hospital Charles Nicolle, Rouen; Jean Luis Stephan- Hospital Nord, Saint-Etienne; Patrick Lutz- Hospital Hautepierre, Strasbourg; **Germany:** Meinolf Suttrop- Universitäre Klinikum Carl Gustav Carus, Dresden; Brigitte Strahm- University of Freiburg, Freiburg; Claudia Bettoni da Cunha- Hannover Medical School Dept. Pediatric Haematology/Oncology, Hannover; Björk Garwer-Eppendorf, Hamburg; Margarete Rothmayer- Klinikum Grosshadern, Munich; Knut Wendelin- Klinikum Nürnberg, Nürnberg; **Greece:** Stelios Graphakos- St. Sophia Hospital, Athens; **Jordan:** Abdelghani Tbakhi- King Hussein Cancer Centre, Amman; **Iran:** Nooshin Naemi- Shariri Hospital Teheran; **Israel:** Tsila Zuckerman- Rambam Medical Center, Haifa; Pantel Bakst Sharon- Hadassah University Hospital, Jerusalem; Isaac Yaniv- Schneider Children’s Medical Center, Petach-Tikva; Toren Amos- Edmond & Lily Safra Children’s Hospital Tel-Hashomer; **Italy:** Angolo Prete- S. Orsola-Malpighi, Bologna; Luca Lo Nigro- Ospedale Ferrarotto, Catania; Edoardo Lanino and Maura Faraci- Instituto G. Gaslini, Genova; **Netherlands:** Alexei Maschan- Russian Childrens Hospital, Moscow; **Saudi Arabia:** Mouhmed Ays- King Faisal Hospital & Research Centre, Riyadh; **Spain:** Cristina Diaz de Heredia- Hospital Vall d’Hebron, Barcelona; C Belendez Bieler- Hospital Gregorio Marañon, Madrid; Julio Ruiz Pato- Niño Jesus Hospital, Madrid; Inmaculada Heras- Hospital Morales Meseguer, Murcia; **South Africa:** Rehyna Trevor and Kym Abayomi - Medi-Clinic Constantiaberg, Cape Town; Jackie Thomson- Pretoria East Hospital, Pretoria; **Sweden:** Anders Fasth- Sahlgrenska Hospital, Goteborg; Ulla Frödin- University Hospital, Linköping; Per Ljungan- Karolinska Hospital, Stockholm; **Switzerland:** Marc Ansari- Hospitals Universitaires Pediatric Department, Geneva; Tayfun Gungör- Universitäts Kinder- und Jugendklinik Zürich, Zurich; **Turkey:** Emel Unal- Çebeci Hospital, Ankara; Mustafa Pehlivan- Gaziantep University, Gaziantep; Sema Anak and Gulyüz Ozturk- Istanbul University, Istanbul; Ali Unal- Erciyes Universitesi, Kapadokya Kayseri; **United Kingdom:** Sarah Lawson-Birmingham Children's Hospital, Birmingham; Jane Apperley- Imperial College Hammersmith Hospital, London; Jagoda Keshani- Royal Free Hospital and School of Medicine, London; Andy Drake- St George, London; Josu de la Fuente- St. Mary’s Hospital Division of Paediatrics, London; Robert Wynn- NHS Trust, Manchester; Janet Williams- Royal Hallamshire, Sheffield; **United States:** Lakshmanan Krishnamurti-Children’s Healthcare of Atlanta at Egleston, Atlanta; Monica Bhatia-Morgan Stanley Children's Hospital of New York, New York; Kathrin
Leung- Baylor College of Medicine, Houston; Gregory Yanik- Children's Hospital of Michigan, Detroit; Mark Walters- Children's Hospital of Oakland, Oakland; Joan Kurtzberg- Duke University Medical Center; Pediatric BMT, Durham; Madan Jagsia- Vanderbilt University, Nashville; Wing Leung- St Jude Children's Research Hospital, Memphis; Allstar Abraham- Children's National Medical Center, Washington, D.C.; Indria Sahdey- Cohen Children's Medical Center of New York, New York; David Margolis- Children's Hospital of Wisconsin, Milwaukee; Gretchen Eames- Cook Children's Medical Center, Fort Worth; Edwin Horwitz-Nationwide Children's Hospital, Columbus; Mortan Cowan-University of California, San Francisco; Neena Kapoor- Children's Hospital of Los Angeles; Scott Rowley- Hackensack University Medical Center; Hackensack; Gail Megason- University of Mississippi Medical Center, Jackson; Zora Rogers-Children's Medical Center, Dallas; Javier Bolaños-Mead-John-Hopkins Oncology Center, Baltimore; Michelle Hudspeth- Medical University of South Carolina, Charleston; Joseph-Rosenthal- City of Hope National Medical Center, Duarte; Timothy Olson- Philadelphia Children's Hospital, Philadelphia; Kimberly Kassow- University of North Carolina Hospitals, Chapel Hill; George Selby-Oklahoma University Medical Center, Oklahoma; Hillary Haines-University of Alabama Birmingham, Alabama; Sonali Chaudhury-Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago.

**Funding source**

This work is supported by a Monaco government grant to the International Observatory on Sickle Cell Disease Monacord at the Centre Scientifique de Monaco and by a grant of the Cordon de Vie organization (President Fabienne Mourou), Monaco. The Center for International Blood and Marrow Transplant Research is supported primarily by U24-CA76518 from the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Institute of Allergy and Infectious Diseases and HHSH234200637015C (HRSA/DHHS). The content is solely the responsibility of the authors and do not represent the official policy of the National Institutes of Health or the Health Resources and Services Administration or any other agency of the United States Government.

We also thank Arnaud Dalissier from the EBMT for helping collecting and preparing the data.

**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, UK, 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.
References

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Bone marrow</th>
<th></th>
<th>Peripheral blood</th>
<th></th>
<th>Cord blood (children only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>728</td>
<td>111</td>
<td>30</td>
<td>43</td>
<td>88</td>
</tr>
<tr>
<td><strong>Median follow-up, months (range)</strong></td>
<td>57.8 (0.3-325.4)</td>
<td>48.46 (2.65-306.67)</td>
<td>51.0 (1.1-227.9)</td>
<td>47.88 (2.19-168.4)</td>
<td>54.2 (3.7-161.9)</td>
</tr>
<tr>
<td><strong>Median age, years (range) [IQR]</strong></td>
<td>8.4 (0.3-16)</td>
<td>18.5 (16-46.2)</td>
<td>12.7 (2.2-15.9)</td>
<td>23.4 (17.3-54.4)</td>
<td>6.1 (1.9-15.5)</td>
</tr>
<tr>
<td><strong>Registry: n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBMT</td>
<td>400 (55.0)</td>
<td>54 (48.7)</td>
<td>19 (63.3)</td>
<td>17 (39.5)</td>
<td>71 (80.7)</td>
</tr>
<tr>
<td>CIBMTR</td>
<td>328 (45.0)</td>
<td>57 (51.4)</td>
<td>11 (36.7)</td>
<td>26 (60.5)</td>
<td>17 (19.3)</td>
</tr>
<tr>
<td><strong>Conditioning type: n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAC</td>
<td>653 (89.7)</td>
<td>89 (80.9)</td>
<td>23 (79.3)</td>
<td>24 (55.8)</td>
<td>84 (95.5)</td>
</tr>
<tr>
<td>RIC</td>
<td>75 (10.3)</td>
<td>21 (19.1)</td>
<td>6 (20.7)</td>
<td>19 (44.2)</td>
<td>4 (4.6)</td>
</tr>
<tr>
<td><strong>GVHD prophylaxis: n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CsA</td>
<td>102 (14.9)</td>
<td>13 (12.0)</td>
<td>6 (27.3)</td>
<td>5 (12.5)</td>
<td>56 (64.4)</td>
</tr>
<tr>
<td>CsA+MTX</td>
<td>447 (65.2)</td>
<td>57 (52.8)</td>
<td>9 (40.9)</td>
<td>5 (12.5)</td>
<td>16 (18.4)</td>
</tr>
<tr>
<td>CsA+MMF</td>
<td>41 (5.9)</td>
<td>17 (15.7)</td>
<td>2 (9.1)</td>
<td>2 (5.0)</td>
<td>9 (10.3)</td>
</tr>
<tr>
<td>FK506+/other</td>
<td>82 (12.0)</td>
<td>17 (15.7)</td>
<td>3 (13.6)</td>
<td>4 (10.0)</td>
<td>4 (4.6)</td>
</tr>
<tr>
<td>other</td>
<td>14 (2.0)</td>
<td>4 (3.7)</td>
<td>2 (9.1)</td>
<td>24 (60.0)</td>
<td>2 (2.3)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>EFS Hazard Ratio (95% CI)</th>
<th>EFS P-value</th>
<th>OS Hazard Ratio (95% CI)</th>
<th>OS P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB vs. BM</td>
<td>1.93 (0.87 – 4.26)</td>
<td>0.104</td>
<td>2.62 (1.17 – 5.89)</td>
<td>0.019</td>
</tr>
<tr>
<td>CB vs. BM</td>
<td>0.55 (0.13 – 2.31)</td>
<td>0.412</td>
<td>Not applicable*</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.09 (1.05 – 1.12)</td>
<td>&lt;0.001</td>
<td>1.10 (1.06 – 1.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Transplant year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2007 vs. ≤2006</td>
<td>0.95 (0.90 – 0.99)</td>
<td>0.013</td>
<td>0.96 (0.91 – 1.00)</td>
<td>0.101</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIC vs. MAC</td>
<td>1.13 (0.46 – 2.81)</td>
<td>0.793</td>
<td>0.83 (0.29 – 2.39)</td>
<td>0.735</td>
</tr>
<tr>
<td>In vivo T cell depletion</td>
<td>1.34 (0.63 – 2.82)</td>
<td>0.445</td>
<td>1.10 (0.49 – 2.48)</td>
<td>0.806</td>
</tr>
</tbody>
</table>

* 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
Figure 1B. Overall survival according to stem cell source

Overall Survival

Time from transplant (years)

number of at-risk patients

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

Eliane Gluckman, Barbara Cappelli, Francoise Bernaudin, Myriam Labopin, Fernanda Volt, Jeanette Carreras, Belinda Pinto Simões, Alina Ferster, Sophie Dupont, Josu de la Fuente, Jean-Hugues Dalle, Marco Zecca, Mark C. Walters, Lakshmanan Krishnamurti, Monica Bhatia, Kathryn Leung, Gregory Yanik, Joanne Kurzberg, Nathalie Dhedin, Mathieu Kuentz, Gerard Michel, Jane Apperley, Patrick Lutz, Bénédicte Neven, Yves Bertrand, Jean Pierre Vannier, Mouhab Ayas, Marina Cavazzana, Susanne Matthes-Martin, Vanderson Rocha, Hanadi Elayoubi, Chantal Kenzey, Peter Bader, Franco Locatelli, Annalisa Ruggeri and Mary Eapen

Information about reproducing this article in parts or in its entirety may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at: http://www.bloodjournal.org/site/subscriptions/index.xhtml

Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include digital object identifier (DOIs) and date of initial publication.