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

Permalink
https://escholarship.org/uc/item/2vr9t477

Journal
Blood, 129(11)

ISSN
0006-4971

Authors
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Publication Date
2017-03-16

DOI
10.1182/blood-2016-10-745711

Peer reviewed

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

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Key Points

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

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 Society for Blood and Marrow Transplantation, 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 a Cox regression models. The median age at transplantation was 9 years, and the median follow-up was longer than 5 years. Most patients received a myeloablative conditioning regimen (n = 873; 87%); the remainder received reduced-intensity conditioning regimens (n = 125; 13%). Bone marrow was the predominant stem cell source (n = 839; 84%); peripheral blood and cord blood progenitors were used in 73 (7%) and 88 (9%) patients, respectively. The 5-year event-free survival and overall survival were 91.4% (95% confidence interval, 89.6%-93.3%) and 92.9% (95% confidence interval, 91.1%-94.6%), respectively. Event-free survival was lower with increasing age at transplantation (hazard ratio [HR], 1.09; *P*<.001) and higher for transplantations performed after

Submitted 14 October 2016; accepted 1 December 2016. Prepublished online as *Blood* First Edition paper, 13 December 2016; DOI 10.1182/blood-2016-10-745711.

There is an Inside *Blood* Commentary on this article in this issue.

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2006 (HR, 0.95; *P* = .013). Twenty-three patients experienced graft failure, and 70 patients (7%) died, with the most common cause of death being infection. The excellent outcome of a cohort transplanted over the course of 3 decades confirms the role of HLA-identical sibling transplantation for children and adults with SCD. (*Blood*. 2017;129(11):1548-1556)

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Disclosures

CME questions author Laurie Barclay, freelance writer and reviewer, Medscape, LLC, owns stock, stock options, or bonds from Pfizer. Author Mark C. Walters serves as Medical Director for ViaCord's Processing Laboratory. Associate Editor Robert Zeiser and the remaining authors declare no competing financial interests.

Learning objectives

1. Distinguish characteristics of HLA-identical sibling transplantation for sickle cell disease (SCD) and hematopoietic recovery, based on an international, retrospective, registry-based survey.
2. Describe graft-versus-host disease and event-free survival in HLA-identical sibling transplantation for SCD.
3. Determine overall survival and risk factors associated with survival in HLA-identical sibling transplantation for SCD.

Release date: March 16, 2017; Expiration date: March 16, 2018

Background

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy worldwide. SCD affects more than 100 000 Americans and occurs in about 1 in 500 African-American births and in 1 in every 1000 to 1400 Hispanic-American births.[1] Similar rates are reported in European and Caribbean countries; for example, 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 4 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 of severe SCD, but access is limited for several reasons, including donor availability and sociocultural and economic barriers. SCD and transplant physicians alike debate the burden of morbidity from a chronic disease and mortality from the disease vs the curative option with transplantation and the risk for 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 preschool 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 study sought to describe outcomes after HLA-identical sibling transplantation for SCD 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 the Center for International Blood and Marrow Transplant Research (CIBMTR), European Society for Blood and Marrow Transplantation (EBMT), and Eurocord databases. Children and adults who underwent HSCT as first transplant before December 31, 2013, were included. All donors were HLA-identical siblings; stem cell source included BM, peripheral blood (PB), or CB. Recipients of HLA-mismatched related donor (including haploidentical 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.

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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)
Sex, 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)

Missing data: in vivo TCD = 20 patients; conditioning (RIC/MAC) = 2 patients.

ATG, anti-thymocyte globulin; Bu, busulfan; CsA, cyclosporin A; Cy, cyclophosphamide; FK506, tacrolimus; MMF, mycophenolate mofetil; MTX, methotrexate; OKT3, mouse monoclonal anti-CD3 antibody; PBSC, PB stem cell; TCD, T-cell depletion.

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 to IV acute GVHD or extensive chronic GVHD.

Conditioning regimen was defined, according to published criteria,[18] as reduced intensity conditioning (RIC) if fludarabine (Flu) was associated with less than 6 Gy total-body irradiation (TBI), or busulfan 8 mg/kg or less, melphalan 140 mg/m^2 or less, or other nonmyeloablative drugs; conditioning was defined as myeloablative conditioning (MAC) if TBI was higher than 6 Gy and busulfan was higher than 8 mg/kg with or without other drugs being used.

All patients meeting the inclusion criteria were included in the study. 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 0.5×10^9/L. Platelet recovery was defined as the first of 3 consecutive days with platelets $>20 \times 10^9$/L, sustained without transfusion for at least 7 days. Graft failure was defined as having never achieved absolute neutrophil count 0.5×10^9/L, 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 percentage. 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 function[20] 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 percentage 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,[21] stratified by registry (EBMT vs CIBMTR). All factors associated with a P value $<.10$ 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 2-sided, and P values $\leq .05$ were considered to be statistically significant. Analyses were performed using 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 months (range, 3-325 months). Four hundred thirty-nine patients

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

	BM		PB		
	Children	Adults	Children	Adults	CB (children only)
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)

Tx, transplant.

were transplanted in the United States, 513 in Europe, and 48 in non-European countries.

Patients and transplant characteristics are shown in Tables 1 and 2. Patients were mainly children (n = 846; <16 years), with a median age at HSCT of 9 years (range, 0.3-16 years). The median age for adults (n = 154) was 19 years (range, 16-54 years). The median age at transplantation for recipients of BM, PB, and CB was 9.4, 18.7, and 6.1 years, respectively ($P < .001$). The most frequent indications were stroke, acute chest syndrome, and recurrent vaso-occlusive disease. Before 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 Flu (n = 110). One hundred twenty-five patients (13%) received RIC regimens, and Flu with cyclophosphamide was the most commonly used regimen (n = 46). Most recipients of BM (88%; 742/838) and CB (95%; 84/88) transplantation received MAC regimens. In contrast, only 65% (47/72) of PB transplantation recipients received MAC regimens ($P < .001$). Most regimens included in vivo T-cell depletion (n = 807) with either antithymocyte globulin (n = 692) or alemtuzumab (n = 113). The most frequently used stem cell source was BM (n = 839), whereas 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 with CB cells (27 days), ($P < .001$). 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 with CB cells (37 days), ($P < .001$). Twenty-three patients experienced graft rejection. Data on chimerism were available for a subset of patients (N = 614), of whom 68% were full-donor chimera, 29% were mixed chimera and 3% had autologous reconstitution.

GVHD

The cumulative incidence of grade II-IV acute GVHD was 14.8% (95% CI, 12.6%-17.1%), whereas that of chronic GVHD was 14.3% (95% CI, 12%-16.9%). In multivariate analysis, the risk for acute GVHD was higher with increasing age (hazard ratio [HR], 1.04; 95% CI, 1.01-1.07; $P = .008$). For every 1-year increment in age at transplantation, there was a 4% increase in the HR 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 with those younger, 19.6% (95% CI, 13.3%-26.8%) vs 13.3% (95% CI, 10.9%-16%), respectively ($P = .015$; 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 vs ≥16 years), and results of multivariate analysis revealed a 2% increase in the HR for chronic GVHD (HR, 0.5; 95% CI, 0.32-0.90; $P = .020$).

OS and EFS

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 younger than 16 years and those aged 16 years or older, respectively ($P < .001$); the corresponding EFS was 93% (95% CI, 92%-95%) and 81% (95% CI, 74%-87%; $P < .001$). The 5-year probability of GVHD-free survival was 86% and 77% for patients younger than 16 years and 16 years or older, respectively ($P < .001$).

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 HR for treatment failure (graft failure or death). Similarly, for every 1-year increment in age, there was a 10% increase in the HR 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

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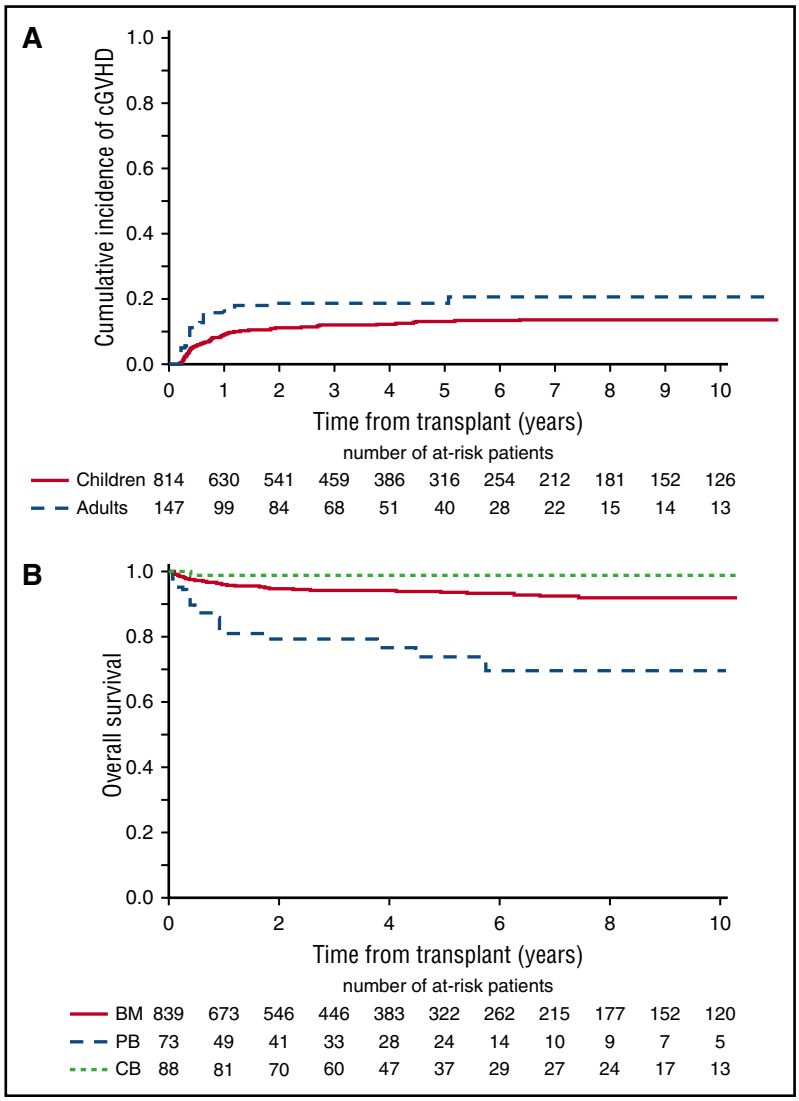

Figure 1. Outcomes after HSCT for SCD. (A) Unadjusted chronic GVHD, according to age; and (B) OS, according to stem cell source.

(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 our knowledge, 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 and reported to observational registries and that the majority of patients were not enrolled on clinical trials.[22-27] Further, we were able

Table 3. Multivariate analysis for EFS and OS

	EFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PB vs BM	1.93 (0.87-4.26)	.104	2.62 (1.17-5.89)	.019
CB vs BM	0.55 (0.13-2.31)	.412	Not applicable*	
Age	1.09 (1.05-1.12)	<.001	1.10 (1.06-1.14)	<.0001
Transplant year, ≥2007 vs ≤2006	0.95 (0.90-0.99)	.013	0.96 (0.91-1.00)	.101
Conditioning regimen, RIC vs MAC	1.13 (0.46-2.81)	.793	0.83 (0.29-2.39)	.735
In vivo T-cell depletion, yes vs no	1.34 (0.63-2.82)	.445	1.10 (0.49-2.48)	.806

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

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

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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.[28] The 5-year OS of 95% in patients younger than 16 years after HLA-identical transplantation compares favorably with that reported by Quinn et al in their study of the Dallas Newborn Cohort.[28] For patients aged 16 years or older, 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 among nontransplanted adults with severe SCD who were at risk for early death as they transition from pediatric to adult care.[28]

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 can we 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 comorbidities, 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 for mortality from transplant-related complications and the potential risk for severe GVHD, which adds to the burden of morbidity and mortality.[29,30] Standard of care (ie, nontransplant therapies) has very low toxicity, but it offers no cure for the underlying disease, and the risk for death is higher later in life; the expected mortality is 4.4 per person-years.[31,32] As a consequence, the ideal comparison between these 2 very different treatments would be a randomized trial of the treatment options. However, such trials are difficult to conduct and are 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 groups (donor vs no donor), according to the availability of a suitably matched donor. One such trial was recently opened in the United States (NCT02766465), 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 was reported after HLA-identical sibling PB transplants for aplastic anemia.[33] 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 on EFS or 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. Although 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. Flu, treosulfan, melphalan, and low-dose TBI[24,34-36] have all been shown to decrease toxicity from the regimen per se, but the risk for rejection is higher.[16] Others have used 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. As a consequence, 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,[1,37] 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.[38] Consensus reports on indications for transplantation may increase awareness, with early referral for accepted indications.[17,39] Others have reported the observation that HLA-matched sibling transplantation performed in view of abnormal transcranial 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 in the general population.[7] Yet, in carefully controlled situations such as structured comprehensive clinics that include transitioning of care of the older adolescent from a pediatric to an adult setting, the median survival for adults is 67 years,[40] but structured comprehensive clinics are not the norm.

In the absence of systematic referral and tracking of those unable to proceed with transplantation because of a lack of a matched related donor, the potential number of patients with SCD 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. On the basis of 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.[41] The option of directed family CB banking from nonaffected siblings of patients with SCD should be offered to families at risk.[42] Strategies that explore the use of mismatched related donors are ongoing[43,44] as are studies of gene therapy and gene editing, all of which are aimed at improving survival for SCD.[45-47] Transplantation of grafts from HLA-identical siblings offers excellent 5-year survival, and our results confirm this is an accepted treatment of severe SCD worldwide. Nevertheless, it is also important to study the effects of transplantation in the long term and to develop prospective trials of comparable patient cohorts to determine the relative merits of transplantation vs supportive care, especially in older patients with severe SCD.

Acknowledgments

The authors thank Arnaud Dalissier from the EBMT for helping collecting and preparing the data.

This work is supported by a Monaco government grant to the International Observatory on Sickle Cell Disease Monacord at the

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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 Institutes of Health National Cancer Institute, the National Heart, Lung, and Blood Institute and the National Institute of Allergy and Infectious Diseases, and HHSH234200637015C (Health Resources and Services Administration/Department of Health and Human Services).

The content is solely the responsibility of the authors and does not represent the official policy of the National Institutes of Health or the Health Resources and Services Administration or any other agency of the US Government.

Authorship

Contribution: E.G., F.B., B.P.S., A.R., and M.E. designed the study; E.G., F.V., F.L., A.R., and M.E. wrote the manuscript; B.C., F.V., and A.R. prepared the data for analysis; M.L. and A.R. performed statistical analysis; B.C. and F.B. collected and verified data; J.C., H.E., and C.K. helped with data management; F.B., B.P.S., L.K., J.K., S.M.-M., and F.L. edited the manuscript; and F.B., B.P.S., A.F., S.D., J.d.l.F., J.-H.D., M.Z., M.C.W., L.K., M.B., K.L., G.Y., J.K., N.D., M.K., G.M., J.A., P.L., B.N., Y.B., J.P.V., M.A., M.C., S.M.-M., V.R., P.B., and F.L. transplanted patients and provided data for the study. All authors read and approved the manuscript.

Conflict-of-interest disclosure: M.C.W. serves as Medical Director for ViaCord's Processing Laboratory. The remaining authors declare no competing financial interests.

A list of the members 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 appears in "Appendix."

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The following transplant centers contributed with patients, participated in this study, and are members of the European Society for Blood and Marrow Transplantation or the Center for International Blood and Marrow Transplant Research: 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; Vanderson 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 Jubert, Centre Hospitalier Universitaire Pellegrin Enfants, Bordeaux; Jean Perrin, Centre Hospitalier Universitaire Hospital Hotel Dieu, Clermont-Ferrand; Francoise Bernaudin and Mathieu Kuentz, Referral center for sickle cell disease, Centre Hospitalier Intercommunal Créteil, Créteil; Jean Yves Cahn, 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 Brabois, Nancy; Francoise Mechinaud, Hospital Hotel Dieu, Nantes; Jean Paul Vernant, La Pitié, Paris; Bénédicte Neven and Marina Cavazzana, Hospital Necker-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 Suttorp, Universitate Klinikum Carl Gustav Carus, Dresden; Brigitte Strahm, University of Freiburg, Freiburg; Claudia Bettoni da Cunha, Hannover Medical School Dept. Pediatric Haematology/Oncology, Hannover; Birgit 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 Naeimi, Shariati Hospital Teheran; Israel: Tsila Zuckerman, Rambam Medical Center, Haifa; Pantel Bakst Sharon, Hadassah University Hospital, Jerusalem; Isaac Yaniv, Schneider Childrens Medical Center, Petach-Tikva; Toren Amos, Edmond and Lily Safra Children's Hospital, Tel-Hashomer; Italy: Arcangelo Prete, S.Orsola-Malpighi, Bologna; Luca Lo Nigro, Ospedale Ferrarotto, Catania; Edoardo Lanino and Maura Faraci, Instituto G. Gaslini, Genova; Fabio Ciceri and Sarah Marktel, Ospedale San Raffaele, Milano; Giusy De Simone, Ematologia Pediatrica, Napoli; Chiara Messina, Clinica di Oncoematologia Pediatrica, Padova; Marco Zecca, Istituto di Ricovero e Cura a Carattere Scientifico San Matteo, Pavia; Paolo DI Bartolomeo and Stella Santarone, Ospedale Civile, Pescara; Daniele Vallisa, Hospital Guglielmo da Saliceto, Piacenza; Alice Bertaina and Franco Locatelli, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Pediatrico Bambino Gesu, Roma; William Arcese, Roma-Policlinico Tor Vergata and Transplant Network, Roma; Roberto Foa, Università La Sapienza, Roma; Massimo Berger, Ospedale Infantile Regina Margherita, Torino; Natalia Maximova, Istituto Burlo Garofolo, Trieste; The Netherlands: Sylwia Wallet, Malicka–University Hospital, Leiden; Nigeria: G.N. Bazuaye, University of Benin, Benin; Russia: Alexei Maschan, Russian Childrens Hospital, Moscow; Saudi Arabia: Mouhab Ayas, King Faisal Hospital & Research Centre, Riyadh; Spain: Cristina Diaz de Heredia, Hospital Vall d'Hebron, Barcelona; C Belendez Bieler, Hospital Gregorio Marañon, Madrid; Julia Ruiz Pato, Niño Jesus Hospital, Madrid; Inmaculata Heras, Hospital Morales Meseguer, Murcia; South Africa: Reyhana 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 Ljugman, Karolinska Hospital, Stockholm; Switzerland: Marc Ansari, Hopitaux Universitaires Pediatric Department, Genève; Tayfun Güngör, Universitats Kinderspital Eleonorenstiftung, Zurich; Turkey: Emel Unal, Cebeci Hospital, Ankara; Mustafa Pehlivan, Gaziantep University, Gaziantep; Sema Anak and Gulyuz Ozturk, Istanbul University, Istanbul; Ali Unal, Erciyes Üniversitesi, Kapadokya Kayseri; United Kingdom: Sarah Lawson, Birmingham Childrens Hospital,

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