Risk factors and outcomes according to age at transplantation with an HLA-identical sibling for sickle cell disease

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for sickle cell disease (SCD).[1-4] Several barriers prevent its widespread application, including the lack of a suitable donor, risk of early and late onset of regimen-related toxicities, rejection and mortality. Despite these limitations, the number of transplants for hemoglobinopathies has been increasing in the last decade. The overall probability of survival (OS) for patients with SCD transplanted with a human lymphocyte antigen (HLA)- identical sibling graft ranges between 91 and 100% with an event-free survival (EFS) of 73-100%.[3] A controversial issue is the ideal age to perform HSCT in SCD patients. In fact, whilst early age HSCT could prevent SCD-related organ damage, resulting in better patient outcomes, the emergence of new available SCD supportive care, promising curative thera-

Table 1. Patient, disease, donor and HSCT characteristics.*

	All patients N=736	Age 0-5 yrs N=175	Age 6-15 yrs N=436	Age>15 yrs N=125	Test *P* between age groups
Sex: Female/Male	345/391 (47%/53%)	76/99 (43%/57%)	215/221 (49%/51%)	54/71 (43%/57%)	0.279
Hb Genotype					
HbSS	551 (90 %)	139 (94%)	325 (91 %)	87 (82 %)	
HbSb0	37 (6 %)	6 (5 %)	19 (5%)	12 (11 %)	NA
Other	24 (4 %)	3 (1 %)	14 (4 %)	7 (7%)	
Age at Transplant (IQR)	9.4 (1-39)	4.3 (3-5)	9.9 (8-12)	17.6 (15-39)	NA
Median Year of HSCT (range)	2009 (1986-2017)	2008 (1986-2015)	2009 (1987-2017)	2010 (1989-2017)	0.034
Pre HSCT Characteristics					
CNS Vasculopathy	311 (75%)	42 (68%)	66 (74%)	203 (77%)	0.267
Stroke	244 (42%)	48 (34%)	158 (46%)	38 (39%)	0.048
Acute Chest Syndrome	215 (52%)	35 (44%)	128 (49%)	52 (71%)	0.001
Vaso Occlusive Crises	413 (80%)	82 (73%)	250 (81%)	81 (87%)	0.029
Osteonecrosis	67 (12%)	4 (3%)	38 (11%)	25 (29%)	<0.001
Performance Status ≥ 80%	461 (97 %)	106 (100 %)	269 (97 %)	86 (94 %)	0.045
Red Blood Cell Transfusions >20:	253 (45 %)	47 (34 %)	153 (46 %)	53 (60 %)	0.001
Red Blood Cell Immunization:	64 (12 %)	10 (8 %)	38 (12%)	16 (18 %)	0.067
Treatment with Hydroxyurea:	256 (53 %)	37 (34 %)	152 (53%)	67 (77 %)	0.001
Splenectomy	119 (19%)	25 (16%)	74 (19%)	20 (20%)	0.629
Conditioning regimen					
RIC	48 (7%)	7 (4%)	19 (4%)	22 (18%)	<0.001
MAC	681 (93%)	168 (96%)	413 (96%)	100 (82%)	
T cell depletion					
No	117 (16 %)	44 (26 %)	62 (14%)	11 (9 %)	
ATG	530 (74 %)	113 (67 %)	324 (77 %)	93 (76%)	<0.001
Campath/OKT3	63 (10 %)	11(7 %)	34 (9 %)	18 (15%)	
GvHD Prophylaxis:					
CSA alone	160 (25 %)	60 (40 %)	82 (22 %)	18 (16 %)	
CSA+MTX + other	388 (60 %)	75 (49 %)	241 (64 %)	71 (62 %)	<0.001
other	94 (15 %)	17 (11%)	54 (14 %)	25 (22 %)	
SOURCE HSCT :					
BM	595 (81%)	130 (74 %)	367 (84 %)	98 (78%)	
PB	51 (7 %)	6 (4%)	19 (4 %)	26 (21%)	<0.001
CB	90 (12 %)	39 (22%)	50 (12 %)	1 (1 %)	
Median donor age at donation (IQR)	9.6 (4-15)	7 (3-11)	9 (4-15)	18 (11-23)	<0.001
Donor trait	174 (53%)	39 (59%)	111 (54%)	24 (41%)	NA

ATG: anti-thymocyte globulin; BM: bone marrow; CB: cord blood; CNS: central nervous system; CSA: cyclosporine A; GvHD: graft-*versus*-host disease, Hb: hemoglobin; HbSS: homozygotes beta S globin; HbSb0: severe double heterozygotes for HbS and β^0 thalassemia; HSCT: hematopoietic stem cell transplantation; IQR: interquartile range,; MAC: myeloablative conditioning regimen; MTX: methotrexate; NA: not applicable; OKT3: muromonab-CD3; PB: peripheral blood, RIC: reduced intensity conditioning regimen, yrs: years.

pies could justify not proceeding with HSCT in certain cases.[2,5,6]

Herein, we report the outcomes of 736 SCD patients who underwent HSCT from an HLA-identical sibling between 1986 and 2017 and were reported to the European Blood Society for Blood and Marrow Transplantation (EBMT)/Eurocord registries. Based on previous reports suggesting improved HSCT outcomes in preschoolers[1] and worst outcomes in adults, usually defined as patients older than 16 years in the SCD literature,[7] three different groups were defined according to the age at transplant: 0-5 years: group 1 (n=175), 6-15 years: group 2 (n= 436) and more than 15 years: group 3 (n=125). Patients, donor and transplant characteristics are shown in Table 1. The cumulative incidence of neutrophil engraftment at day +60 was 96%, 98% and 95% in group 1, 2 and 3 respectively (*P*=0.017); platelet engraftment was 98%, 96% and 95% in the three groups respectively (*P*=0.033). In univariate analysis, in group 1, the cumulative incidence for neutrophil engraftment was higher for patients who received HSCT from a donor older than 9.6 years [98% (95% Comorbidity index (CI) 93-100%), *P*=0.031]; in group 2, it was also higher for patients who received HSCT from a donor older than 9.6 years [99% (95%CI 98-100%), *P*=0.037], who had an ABO blood group system compatibility or a minor incompatibility [99% (95%CI 97-100%), *P*=0.021] or who received anti-thymocyte globulin (ATG) [98% (95%CI 97-100%), *P*=0.003]; in group 3, none of the analyzed factors had a significant impact on neutrophil engraftment.

Primary graft failure was reported in 2% of the patients in group 1 (n=4) and in group 2 (n=9), and 5% in group 3 (n=6), whereas late graft failure occurred in 2% of the patients irrespective of the group (n=4, 9 and 2 in the three groups respectively).

At day +100, full chimerism was achieved in 63% of the patients in group 1 and 2 and in 50% of group 3; mixed chimerism in 35 % of patients in group 1 and 2 and 46% in group 3; autologous reconstitution was achieved in 2% of the patients of group 1 and 2 and in 4% of the patients in group 3.

The overall cumulative incidence of grade II-IV acute graft-*versus*-host disease (GvHD) was 16% (95%CI 13-18%) [group 1: 10% (95%CI 6-15%); group 2: 18% (95%CI 1-22%); group 3: 17% (95%CI 11-25%), *P*=0.047]. A univariate analysis of group 2 showed a higher incidence of acute GvHD in male patients [21% (95%CI 17-28%) *versus* 13% (95%CI 10-19%), *P*=0.038], in patients who received the grafts from donors older than 9.6 years [28% (95%CI 22-36%), *P*<0.001] or from a donor with positive cytomegalovirus (CMV) serology [22% (95%CI 17-27%) *P*=0.001].

The overall 4-year cumulative incidence of chronic GvHD was 12% (95%CI 10-15%) [group 1=9% (95% CI 6-15%), group 2=11% (95% CI 8-15%) and group 3=20% (95% CI 14-30%), *P*=0.007]. Chronic GvHD was extensive in four patients in group 1, in 21 patients in group 2 and in five patients in group 3.

Four-year OS was 95 ± 1% for the whole cohort, being 100%, 95% and 88% for groups 1, 2 and 3, respectively (*P*<0.001) (Figure 1).

Four-year event free survival (EFS) was, overall, 89 ± 2% (93% in group 1, 89% in group 2 and 81% in group 3, *P*=0.003). We did not observe any risk factor for OS and EFS in the univariate analysis. All children in group 1 were alive at the last follow-up; 36 patients died: 21 (5%) in group 2 and 15 (12%) in group 3. The most common causes of death were infections and GvHD. Outcomes according to the age group are shown in Table 2.

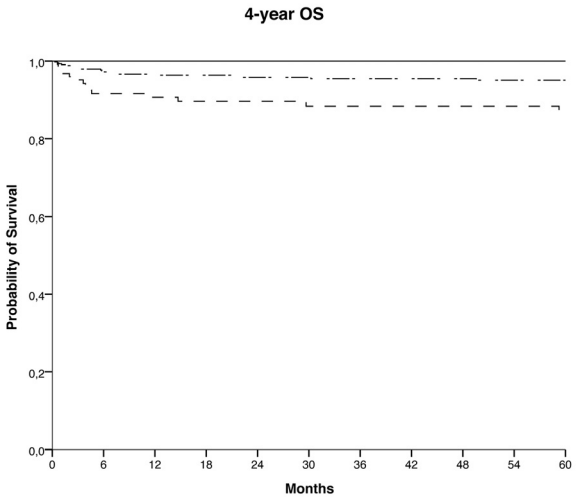

Figure 1. Overall Survival (OS), defined as the probability of survival, regardless of disease status, from the time of HSCT to the time of death or of the last follow-up, according to the age group; 4-year OS was 95 ± 1% : 100% in group 1 (solid line), 95% in group 2 (dash-dotted line), and 88% in group 3 (dashed line) (*P*<0.001).

Optimal timing for HSCT in patients with SCD with an available HLA-identical sibling donor is not well established. In our previous international report on patients transplanted from an HLA-identical sibling, we analyzed outcomes of 1000 patients transplanted before December 2015 in the EBMT and CIBMTR (Center for International Blood and Marrow Transplant Research) centers and showed that age was a prognostic factor for both EFS and OS 3. Recently, Arnold *et al.* suggested that a HSCT performed in patients before the age of 10 years is associated with better outcomes.[8] Moreover, it is known that both the number and severity of SCD-related complications tend to increase with age.[9] This was confirmed in our study where patients older than 15 years had more SCD related organ damage and a worse performance status at HSCT. In addition, because many adverse events may be exacerbated by HSCT, historically, patients aged >16 years were not considered eligible for HSCT due to SCD-related organ damage and inability to tolerate myeloablative conditioning.[10] Nevertheless, the low percentage of primary graft failure was surprising in these heavily transfused patients. However, optimal pre-transplant methodology could not be determined due to the heterogeneity of the conditioning regimen, stem cell source and GvHD prophylaxis.

Despite improvements in immunosuppressive prophylaxis, GvHD remains one of the major causes of morbidity and mortality after HSCT. In our series, patients younger than 5 years had both less grade 2-4 acute GvHD and chronic GvHD, compared to older patients. This could be, partially, explained by the fact that the majority of peripheral blood stem cell (PBSC) transplantations were performed in patients from group 2 and 3. When analyzing bone marrow (BM) recipients only, group 1 patients had a total nucleated cells (TNC) count higher than the other two groups which may have accounted to better engraftment rates (median TNC=$4.6x10^8$, $3.3x10^8$ and $2.7x10^8$ for groups 1, 2 and 3, respectively). Of note, BM recipients who received stem cells from a donor older than 9.6 years received a higher number of TNC (median $3.56x10^8$ *versus* $2.96x10^8$ for

Table 2. Outcomes according to age.*

	All patients N=736	Age 0-5 yrs N=175	Age 6-15 yrs N=436	Age>15 yrs N=125	Test *P* between age groups
4-year OS	95%	100%	95%	88%	<0.001
4-year EFS	89%	93%	89%	81%	0.003
CI Neutrophil engraftment	97%	96%	98%	95%	0.017
CI Platelet engraftment	96%	98%	96%	95%	0.033
Graft failure					
Primary	19 (3%)	4 (2%)	9 (2%)	6 (5%)	0.419
Late	15 (2%)	4(2%)	9(2%)	2(2%)	
Chimerism at 100 days					
Full donor>95%	304 (61%)	73 (63%)	191 (63%)	40 (50%)	0.290
Mixed 5-94%	185 (37%)	40 (35%)	108 (35%)	37 (46%)	
Auto rec <5%	13 (3%)	3 (2%)	7 (2%)	3 (4%)	
Chimerism at last follow up					
Full donor >95%	193 (51%)	40 (48.19%)	120 (53%)	33 (49%)	0.847
Mixed 5-94%	161 (43%)	38 (45.78%)	91 (41%)	32 (47%)	
Autore rec <5%	21 (6%)	5 (6.02%)	13 (6%)	3 (4%)	
CI acute GvHD grade II-IV	115 (16%)	17 (10%)	77 (18%)	21 (17%)	0.047
CI chronic GvHD	74 (12%)	15 (9%)	42 (11%)	17 (20%)	0.007

GvHD: graft-*versus*-host disease; Auto rec: autologous reconstitution; CI: cumulative incidence; EFS: event-free survival; OS: overall survival; yrs: years. * % of evaluable patients.

donors younger than 9.6 years old); therefore we cannot discard the possibility that the higher incidence of acute GvHD was related to the cell dose rather than the age of the donor. In the setting of non-malignant disease, where graft-*versus*-leukemia is not needed, an efficient GvHD prophylaxis strategy is mandatory to lower the risk of GvHD and its deleterious effect on morbidity and survival.

Importantly, besides GvHD, other complications such as graft rejection, growth impairment, gonadal dysfunction, infertility, life threatening infections can occur after HSCT and need to be taken into account when proposing HSCT to very young children with a non-malignant disorder.[11] The occurrence of these undesirable late effects must be balanced with the potential complications of SCD itself (cognitive deficits, iron overload, asplenism, and low quality of life). Although the high EFS observed in our cohort suggests a good quality of life after HSCT, studies comparing long term quality of life among patients with SCD undergoing HSCT in contrast with patients receiving standard treatment are needed to further illustrate the pros and cons of each therapeutic approach.[12,13]

Furthermore, because SCD is a chronic disease associated with costly complications and uncertainties that worsen throughout the patient's life, a curative therapy such as HSCT may be also warranted to reduce healthcare costs. In fact, although HSCT seems to be an expensive alternative, it constitutes a more economic path over a short period of years. Given that the cost of treating SCD increases significantly with time, transplantation at a younger age can have significant economic implications.[14] Nevertheless, the excellent OS and EFS we observed for patients younger than 5 years, strongly indicate that HLA-identical sibling HSCT should be proposed early in life, before complications occur. In the present study, only univariate analyses were performed; adjusted multivariate analyses were not performed due to the low number of events, especially in the youngest age group. Although this is a limitation of our study, as it makes controlling for potential confounders problematic, it also highlights the remarkable results observed for HSCT for SCD in this setting.

In conclusion, the comparison of these three age groups might help physicians to elaborate recommendations for transplant indications and to design conditioning protocols adapted to age, given the better OS and EFS and the lower incidence of acute GvHD and chronic GvHD in younger patients. These findings outline the importance of early referral to HSCT and the importance of adapting indications and protocols according to age. Decision making on time of transplant in 2019 is highly complex and we acknowledge the difficulties in providing advice to the families affected by SCD with respect to transplant, not least because of the progress in gene therapy/editing and new molecules currently in trial in SCD.

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