Title

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Journal

The Lancet Haematology, 6(11)

ISSN

2451-9960

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Publication Date

2019-11-01

DOI

10.1016/s2352-3026(19)30154-1

Peer reviewed

Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study

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Summary

Background Donors other than matched siblings and low-intensity conditioning regimens are increasingly used in haematopoietic stem cell transplantation. We aimed to compare the relative risk of donor type and conditioning regimen intensity on the transplantation outcomes of in patients with sickle cell disease.

Methods For this retrospective cohort study, we collected data from 90 US centres reported to the Center for International Blood and Marrow Transplant Research. Eligible patients were younger than 50 years, had genetically confirmed sickle cell disease (Hb SS) or sickle beta thalassemia (Hb Sβ), and underwent allogeneic haematopoietic cell transplantation between Jan 15, 2008, and Dec 28, 2017. We considered transplants from donor-recipient pairs matched at the allele-level (*HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1*), including HLA-matched sibling donors, haploidentical related donors, matched unrelated donors, or mismatched unrelated donors. The main outcome was event-free survival. The effect of donor type, conditioning regimen intensity (myeloablative, non-myeloablative, and reduced-intensity regimens), age (≤12 or 13-49 years), sex, performance score, comorbidity index, recipient cytomegalovirus serostatus, graft type (bone marrow, peripheral blood, or umbilical cord blood), and transplantation period (2008–12 and 2013–17) on outcomes was studied using Cox regression models.

Findings Of 996 patients with sickle cell disease and who underwent transplantation in 2008–17, 910 (91%) were included (558 [61%] patients had HLA-matched sibling donors, 137 [15%] haploidentical related donors, 111 [12%] matched unrelated donors, and 104 [11%] mismatched unrelated donors). The median follow-up was 36 months (IQR 18–60) after transplantation from HLA-matched siblings, 25 months (12–48) after transplantation from haploidentical related donors, 37 months (23–60) after transplantation from HLA-matched unrelated donors, and 47 months (24–72) after transplantation from mismatched unrelated donors. Event-free survival was worse in recipients aged 13 years or older than in those younger than 13 years (hazard ratio 1·74, 95% CI 1·24–2·45; p=0·0014) and in those who received a transplant from haploidentical related donors (5·30, 3·17–8·86; p<0·0001), matched unrelated donors (3·71, 2·39–5·75; p<0·0001), and mismatched unrelated donors (4·34, 2·58–7·32; p<0·0001) than in patients who received a transplant from matched siblings. There was no significant difference in event-free survival between recipients of transplants from non-sibling donors: haploidentical related donors (1·43, 0·81–2·50; p=0·21) or mismatched unrelated donors (1·17, 0·67–2·05; p=0·58) versus HLA-matched unrelated donors, or mismatched unrelated donors versus haploidentical related donors (1·22, 0·65–2·27; p=0·98). Event-free survival was also worse in patients conditioned with reduced-intensity regimens (1·97, 1·15–3·36; p=0·013) than in those conditioned with non-myeloablative regimens, but did not differ between those who received myeloablative compared with non-myeloablative regimens (1·57, 0·95–2·61; p=0·079). Interpretation Our data suggest that event-free survival is improved in patients with sickle cell disease who receive an allogenic transplantation at age 12 years or younger and those with an HLA-matched sibling donor. For patients without a matched sibling available for transplantation, our data do not favour one alternative donor type over another in this setting.

Funding National Institutes of Health and US Health Services Research Administration, Department of Health and Human Services.

Introduction

Sickle cell disease is the most common inherited haemoglobinopathy and occurs in one in 500 African-American and one in 1000–1400 Hispanic-American births. Worldwide, over 270 000 affected infants are born annually. For children with access to modern health care, overall survival at 18 years of age is 85·6% (73·4–97·8).[1] The life expectancy of adults with sickle cell disease is shortened by at least two decades compared to the general population.[2,3] Risk factors associated with mortality in adults include age, gender, elevated tricuspid valve regurgitation velocity, intensity of haemolytic anaemia, and elevated blood concentrations of ferritin, creatinine, and aspartate transaminase.[3,4] Haematopoietic

Lancet Haematol 2019

Published Online
September 5, 2019
http://dx.doi.org/10.1016/S2352-3026(19)30154-1

See Online/Comment
http://dx.doi.org/10.1016/S2352-3026(19)30150-4

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Research in context

Evidence before the study

We searched MEDLINE from Jan 1, 2011, to Aug 29, 2018, for articles on sickle cell disease published after 2010, with the search terms "sickle cell disease", "HLA-matched sibling", "haploidentical", "unrelated", and "transplant". In addition to two reports of transplantations from HLA-matched sibling donors, we identified five reports of transplantations from haploidentical and unrelated donors but they were limited to small numbers of patients. We did not identify any reports that compared outcomes after transplantations from HLA-matched siblings, haploidentical donors, or unrelated donors in patients with sickle cell disease. Furthermore, the heterogeneity of transplant conditioning regimens in the reports made it impossible to assess the effect of conditioning regimen intensity on transplantation outcomes for patients with sickle cell disease.

Added value of the study

To our knowledge this is the first study to compare transplant outcomes by donor type for sickle cell disease. In a population of 910 patients we recorded improved event-free survival and overall survival for patients who received transplantation from HLA-matched siblings compared to other allogeneic transplantation types. The occurrence of graft failure was increased after transplantation from alternative donors compared with transplantations from HLA-matched sibling.

Implications of all the available evidence

There are publications with fewer than 30 patients that have reported outcomes using alternative donors but not a direct comparison as we have undertaken. A direct comparison of available donor types has offered an unique opportunity to address barriers to success after alternative donor transplantation. Well designed phase 2 trials that investigate strategies to overcome graft failure after transplantation from alternative donor and increased prevalence of graft-versus-host disease after transplantation from unrelated donors are needed.

cell transplantation is potentially curative for sickle cell disease but the treatment itself is associated with substantial risks which can limit its use. Although the probability of overall survival is approximately 90% at 5 years after transplantation in recipients of a human leukocyte antigen (HLA)-matched sibling transplant,[5–8] access is limited by donor availability. As a result, alternative donor sources have been explored. Because of the rarity of HLA haplotypes observed in patients of African-descent, matched unrelated donors are infrequent,[9] therefore grafts from haploidentical related or mismatched unrelated donors often have to be used.[10–13] Treatment failure is primarily attributed to graft failure after transplantations from mismatched related donors[10] and to development of chronic graft-versus-host disease (GVHD) after transplantation from matched unrelated donors.[11]

Data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) indicate increasing numbers of transplantations from alternative donors, in particular for young adults, and the use of conditioning regimens that are not full intensity (ie, myeloablation) in the USA. Therefore, this study sought to compare the relative risks of donor type and conditioning regimen intensity on outcomes after allogeneic transplantation for sickle cell disease in 2008–17, a period during which alternative donors and reduced intensity and non-myeloablative conditioning regimens were increasingly used for transplantation.

Methods

Study design and participants

The CIBMTR is a working group of more than 300 transplant centres worldwide that contribute data on consecutive allogeneic and autologous transplantations for different indications. Patients are followed longitudinally until death or lost to follow-up. Accuracy of data reported to the CIBMTR and compliance are monitored by on-site audits. Consent for research is sought from patients or their legal guardians. The Institutional Review Board of the National Marrow Donor Program approved this study.

We retrospectively reviewed data from 90 US centres reported to the CIBMTR. We included patients younger than 50 years (7 patients aged 50 years or older were excluded, this group are more likely to have transplant-related complications including death), who had genetically confirmed sickle cell disease (Hb SS) or sickle beta thalassemia (Hb Sβ), and underwent allogeneic haematopoietic cell transplantation between Jan 15, 2008, and Dec 28, 2017, including transplants from HLA-matched sibling donors, haploidentical related donors, matched unrelated donors, or mismatched unrelated donors.

We excluded patients from two transplant centres that failed data accuracy audit, including patients who received conditioning regimens rarely used for sickle cell disease (ie, off-label regimens containing treosulfan and total body irradiation [TBI] ≥1000 cGy), patients who did not receive prophylaxis for GVHD, and patients who were inadequately followed up after transplantation.

Procedures

We retrieved the following information for all eligible patients from the CIBMTR: donor type (patients were grouped by donor type, including HLA-matched sibling, haploidentical related donors, and HLA-matched and mismatched unrelated donors, and donor-recipient pairs

were HLA-matched at the allele-level [*HLA-A, HLA-B, HLA-C,* and *HLA-DRB1*]), conditioning regimen intensity (myeloablative, non-myeloablative, and reduced-intensity regimens), age, sex, performance score (Lansky play scale or Karnofsky performance score), comorbidity index (hematopoietic cell transplant comorbidity index score), recipient cytomegalovirus serostatus, graft type (bone marrow, peripheral blood, or umbilical cord blood), and transplantation period (2008–12 and 2013–2017).

Conditioning regimen for patients was either myeloablative, reduced intensity, or non-myeloablative, and was established on the basis of previously defined criteria.[14] Briefly, regimens were considered myeloablative when busulfan was administered orally at a concentration greater than 8 mg/kg or intravenously at a concentration greater than 6 mg/kg, or melphalan was administered at concentrations greater than 150 mg/m². Regimens using lower doses of busulfan or melphalan (administered without another alkylating agent) were considered reduced intensity. TBI regimens (dose 200–400 cGy) were considered non-myeloablative. Myeloablative conditioning is the regimen with highest intensity and non-myeloablative is the one with lowest intensity, whereas the reduced-intensity regimens fall into an intermediate intensity category that does not fit the definition of myeloablative or non-myeloablative conditioning.

The main outcome measure was event-free survival (defined as time from transplantation to death or graft failure) assessed throughout the entire follow-up period. Graft failure was defined as: failure to achieve an absolute neutrophil recovery (ANC) of $0 \cdot 5 \times 10^9$ cells per L or more for 3 consecutive days; a decline in ANC to less than $0 \cdot 5 \times 10^9$ cells per L without recovery, after having achieved an ANC $0 \cdot 5 \times 10^9$ cells per L or more; myeloid donor chimerism (<5%); or second transplant.[15] Our definition of graft failure considered donor chimerism information collected up to 2 years after transplantation. Thereafter, our standardised data-collection forms asked whether the patient experienced graft failure (<5% donors) and the date of failure.

Other outcomes studied were overall survival (death from any cause was considered an event) assessed throughout the entire follow-up period, and acute and chronic GVHD graded using standard criteria (modified Glucksberg grading for acute GVHD and National Institute of Health criteria for chronic GVHD).[16,17] GVHD is an immunologically mediated complication of transplantation affecting multiple organs. Acute GVHD occurs primarily within the first 3 months after transplantation and chronic GVHD ensues thereafter. Occurrence of acute GVHD of grade 2–4 and any chronic GVHD were considered events.

Statistical analysis

The characteristics of patients grouped by donor type were compared using the χ^2 test for categorical variables. The proportion of patients with graft failure and acute and chronic GVHD were calculated using the cumulative incidence estimator to accommodate competing risks (ie, death).[18] Risk factors associated with event-free survival, overall survival, graft failure, and acute and chronic GVHD were examined using the Cox proportional hazards model;[19] hazard ratios (HRs) and their associated 95% CIs were estimated for all outcomes. The probabilities of event-free survival and overall survival were generated from final Cox regression models.[20] Surviving patients were censored at last follow-up.

Variables considered were age, sex, performance score, comorbidity index, recipient cytomegalovirus serostatus, donor type, conditioning regimen intensity, graft type, and transplantation period (2008–12 *vs* 2013–17, chosen arbitrarily). Age was treated as a binary variable (≤12 years *vs* 13–49 years). The age cutoff at 13 years was determined statistically using the minimum p-value approach. To determine the optimal age cutoff, we used a series of two-sample tests for multiple possible candidate dichotomisations of age. For each candidate cutoff, an appropriate Cox model with a single binary covariate for age was constructed and the p value for the Wald test was obtained. The optimal age cutoff was defined as that candidate cutoff with the smallest p value. All variables met the assumption of proportional hazards and there were no first-order interactions between the variables held in Cox models.

The level of significance set for the study was p less than 0·05. All p values are two-sided and all analyses were done using SAS version 9.4.

Role of the funding source

The funder of the study played no role in study design, data collection, data analysis, data interpretation, or

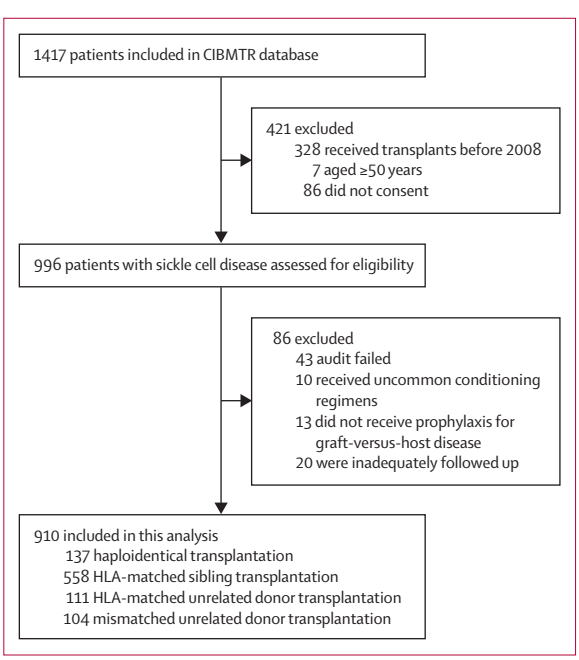

Figure 1: **Study profile**

writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 1417 patients with sickle cell disease who had a transplantation reported to the CIBMTR, 996 (70%) underwent transplantation during the period of interest, of whom 910 (91%) were eligible for this study (figure 1). We excluded 43 (4%) of 996 patients from two transplant centres that failed data accuracy audit: 10 patients received uncommon conditioning regimens (ie, regimens containing treosulfan [n=8] and TBI dose ≥1000 cGy [n=2]), 13 did not receive prophylaxis for GVHD, and 20 (2%) were inadequately followed up after transplantation. Treosulfan can only be used as an investigational new drug in the USA and high-dose TBI (≥1000 cGy) regimens are rarely used for sickle cell disease. 185 (20%) of these 910 patients were included in earlier reports[7,8,10–13] (111 [12%] received a transplant from HLA-matched siblings, 39 [4%] from haploidentical relatives, 28 [3%] from HLA-matched unrelated donors, and seven [1%] from HLA-mismatched unrelated donors).

There were no differences in sex distribution or recipient cytomegalovirus serostatus between the groups. However, recipients of transplants from HLA-matched siblings and from HLA-matched and HLA-mismatched unrelated donors were younger and more likely to have performance scores of 90 or 100 and a HCT-comorbidity index of 0–2 than recipients of transplants from haploidentical related

	HLA-matched sibling, n=558	Haploidentical relative, n=137	HLA-matched unrelated donor, n=111	HLA-mismatched unrelated donor, n=104
Genotype				
Hb SS (sickle cell disease)	534 (96%)	132 (96%)	106 (95%)	95 (91%)
Hb Sβ (sickle β-thalassemia)	24 (4%)	5 (4%)	5 (5%)	9 (9%)
Age at transplant, years				
Median	11 (6–17)	19 (13–27)	14 (9–17)	10 (6–16)
≤10	295 (53%)	22 (16%)	35 (32%)	56 (54%)
11–17	139 (25%)	38 (28%)	54 (49%)	34 (33%)
18–29	82 (15%)	50 (36%)	17 (15%)	12 (12%)
30–49	42 (8%)	27 (20%)	5 (5%)	2 (2%)
Sex				
Male	311 (56%)	74 (54%)	53 (48%)	51 (49%)
Female	247 (44%)	63 (46%)	58 (52%)	53 (51%)
Cytomegalovirus serostatus				
Positive	288 (52%)	64 (47%)	54 (49%)	49 (47%)
Negative	269 (48%)	72 (53%)	57 (51%)	55 (53%)
Not reported	1 (<1%)	1 (<1%)	..	..
Performance status				
≤80	80 (14%)	42 (31%)	18 (16%)	20 (19%)
90–100	472 (85%)	90 (66%)	90 (81%)	80 (77%)
Not reported	6 (1%)	5 (4%)	3 (3%)	4 (4%)
HCT-comorbidity index				
0–2	404 (72%)	76 (55%)	79 (71%)	79 (76%)
≥3	154 (28%)	61 (45%)	32 (29%)	25 (24%)
Graft type				
Bone marrow	437 (78%)	63 (46%)	99 (89%)	32 (31%)
Peripheral blood	78 (14%)	74 (54%)	12 (11%)	13 (13%)
Umbilical cord blood	43 (8%)	..	..	59 (57%)
HLA-match score				
8/8	558 (100%)	..	111 (100%)	..
7/8	..	..	..	55 (53%)
≤6/8	..	137 (100%)	..	49 (46%)

(Table 1 continues on next page)

	HLA-matched sibling, n=558	Haploidentical relative, n=137	HLA-matched unrelated donor, n=111	HLA-mismatched unrelated donor, n=104
(Continued from previous page)				
Conditioning regimen				
Myeloablative	348 (62%)	34 (25%)	49 (44%)	47 (45%)
Busulfan plus cyclophosphamide	250 (45%)	21 (15%)	14 (13%)	27 (26%)
Busulfan plus fludarabine	85 (15%)	6 (4%)	26 (23%)	17 (16%)
Busulfan plus fludarabine and thiotepa	2 (<1%)	7 (5%)	2 (2%)	2 (2%)
Melphalan plus fludarabine	11 (2%)		7 (6%)	1 (<1%)
Reduced intensity	129 (23%)	14 (10%)	57 (51%)	51 (49%)
Busulfan plus fludarabine	5 (1%)	..	..	..
Melphalan plus fludarabine	110 (20%)	1 (<1%)	41 (37%)	24 (23%)
Melphalan plus fludarabine and thiotepa	14 (3%)	13 (9%)	16 (14%)	27 (27%)
Non-myeloablative*	81 (15%)	89 (65%)	5 (5%)	6 (6%)
TBI plus cyclophosphamide	14 (3%)	6 (4%)	..	..
TBI plus cyclophosphamide and fludarabine	9 (2%)	55 (40%)	3 (3%)	3 (3%)
TBI plus cyclophosphamide, fludarabine, and thiotepa	1 (<1%)	9 (7%)	..	..
TBI plus melphalan	2 (<1%)	..	1 (1%)	2 (2%)
TBI plus fludarabine	..	4 (3%)	1 (1%)	..
TBI alone	55 (10%)	15 (11%)	..	1 (<1%)
In-vivo T-cell depletion				
Anti-thymocyte globulin	249 (45%)	95 (69%)	29 (26%)	25 (24%)
Alemtuzumab	289 (52%)	30 (22%)	75 (68%)	66 (63%)
None	20 (4%)	12 (9%)	7 (6%)	13 (13%)
Graft-versus-host disease prophylaxis				
Ex-vivo T-cell depletion	..	10 (7%)	1 (1%)	..
CD34 cell selection	2 (<1%)	22 (16%)	4 (4%)	12 (12%)
Post-HCT cyclophosphamide plus sirolimus and mycophenolate	3 (1%)	47 (34%)	1 (<1%)	1 (1%)
Post-HCT cyclophosphamide plus sirolimus	..	21 (15%)	..	..
Post-HCT cyclophosphamide plus calcineurin inhibitor and mycophenolate	4 (1%)	14 (10%)	1 (<1%)	..
Calcineurin inhibitor plus mycophenolate	129 (23%)	10 (7%)	27 (24%)	57 (55%)
calcineurin inhibitor plus methotrexate	324 (58%)	4 (3%)	65 (59%)	26 (25%)
Calcineurin inhibitor plus sirolimus	2 (<1%)	..	2 (2%)	1 (1%)
Calcineurin inhibitor alone	26 (5%)	9 (7%)	10 (9%)	7 (7%)
Sirolimus alone	68 (12%)	..	..	..
Transplantation period				
2008–12	211 (38%)	33 (24%)	38 (34%)	45 (43%)
2013–17	347 (62%)	104 (76%)	73 (66%)	59 (57%)

Data are n (%) and median (IQR). HLA=human leukocyte antigen. HCT=haematopoietic cell transplantation. TBI=total body irradiation. *TBI dose for HCTs from HLA-matched siblings was 300 cGy for the TBI alone and TBI plus cyclophosphamide regimens and 200 cGy for all other TBI-containing regimens (except for two patients who received TBI 300 cGy with the TBI plus cyclophosphamide and fludarabine regimen); TBI dose for HCTs from haploidentical related donors was 400 cGy for TBI alone regimen (except for one patient who received a TBI dose of 300 cGy), 400 cGy for the TBI plus cyclophosphamide regimen, 200 cGy for most patients receiving the TBI plus cyclophosphamide and fludarabine regimen (except for six patients who received TBI 300 cGy and 14 patients who received TBI 400 cGy), and 200 cGy for the TBI plus cyclophosphamide, fludarabine, and thiotepa regimen and the TBI plus cyclophosphamide regimen; TBI dose for HCTs from matched unrelated donors was 300 cGy for the TBI plus cyclophosphamide and fludarabine regimen and the TBI plus cyclophosphamide regimen and 200 cGy for the TBI plus melphalan regimen; TBI dose for HCTs from mismatched unrelated donors was 400 cGy for the TBI alone regimen, 300 cGy for the TBI plus cyclophosphamide and fludarabine regimen, and 200 cGy for one patient and 400 cGy for the other patient who received the TBI plus melphalan regimen.

Table 1: **Baseline characteristics**

	Events/patients	Hazard ratio (95% CI)	p value
Event-free survival			
Age, years			
≤12	72/491	1 (ref)	..
13–49	102/418	1·74 (1·24–2·45)	0·0014
Regimen intensity			0·046
Non-myeloablative	36/181	1 (ref)	..
Myeloablative	75/478	1·57 (0·95–2·61)	0·079
Reduced intensity	63/250	1·97 (1·15–3·36)	0·013
Donor type	..	..	<0·0001
HLA-matched sibling	52/557	1 (ref)	..
Haploidentical related	45/137	5·30 (3·17–8·86)	<0·0001
HLA-matched unrelated	38/111	3·71 (2·39–5·75)	<0·0001
HLA-mismatched unrelated	39/104	4·34 (2·58–7·32)	<0·0001
Graft type			
Bone marrow	105/630	1 (ref)	0·33
Peripheral blood	40/177	1·01 (0·66–1·54)	0·98
Umbilical cord blood	29/102	1·52 (0·87–2·65)	0·14
HCT comorbidity index			
0–2	125/637	1 (ref)	..
≥3	49/272	0·86 (0·61–1·24)	0·42
Performance status			
≤80	29/160	1 (ref)	..
90–100	143/731	1·33 (0·87–2·04)	0·19
Recipient cytomegalovirus serology			
Negative	81/454	1 (ref)	..
Positive	93/455	1·33 (0·98–1·80)	0·065
Sex			
Male	95/488	1 (ref)	..
Female	79/421	0·86 (0·63–1·16)	0·31
Transplantation period			
2008–12	73/327	1 (ref)	..
2013–17	101/582	0·98 (0·71–1·36)	0·89
Graft failure			
Age, years			
≤12	54/491	1 (ref)	..
13–49	59/418	1·17 (0·76–1·82)	0·47
Regimen intensity			0·28
Non-myeloablative	31/181	1 (ref)	..
Myeloablative	44/478	1·04 (0·56–1·91)	0·91
Reduced intensity	38/250	1·46 (0·77–2·79)	0·25
Donor type	..	..	<0·0001
HLA-matched sibling	32/557	1 (ref)	..
Haploidentical related	36/137	6·58 (3·55–12·21)	<0·0001
HLA-matched unrelated	16/111	2·88 (1·54–5·37)	0·00090
HLA-mismatched unrelated	29/104	4·38 (2·31–8·31)	<0·0001

(Table 2 continues on next page)

donors. HLA-matched siblings were the predominant donor group and bone marrow was the predominant graft for HLA-matched sibling and HLA-matched unrelated donor transplants. The predominant graft source was peripheral blood for transplants from haploidentical related donors and umbilical cord blood for transplants from HLA-mismatched unrelated donors. The predominant conditioning regimen was myeloablative for recipients of transplants from HLA-matched sibling donors and non-myeloablative for recipients of transplants from haploidentical related donors. Myeloablative and reduced-intensity regimens were equally likely to be used for recipients of transplants from HLA-matched and HLA-mismatched unrelated donors. Transplantations were more common in the period 2013–17 than in 2008–12, especially those from haploidentical related donors. The median follow-up of surviving patients after transplantation was 36 months (IQR 18–60) for recipients of transplants from HLA-matched siblings, 25 months (12–48) for recipients of transplants from haploidentical related donors, 37 months (23–60) for recipients of transplants from HLA-matched unrelated donors, and 47 months (24–72) for recipients of transplants from HLA-mismatched unrelated donors (table 1).

Event-free survival was decreased in patients aged 13 years or older versus those aged 12 years or younger (HR 1·74, 1·24–2·45), in those who received reduced-intensity conditioning regimens versus non-myeloablative regimens (1·97, 1·15–3·36), and after transplantation of grafts from donors who were not HLA-matched siblings versus HLA-matched siblings (5·30, 3·17–8·86, for haploidentical related donors; 3·71, 2·39–5·75, for HLA-matched unrelated donors; and 4·34, 2·58–7·32, for HLA-mismatched unrelated donors; table 2 and figure 2A). Event-free survival did not differ between myeloablative and reduced-intensity regimens (0·80, 0·56–1·13; p=0·21), between HLA-matched unrelated donors and haploidentical related (1·43, 0·81–2·50; p=0·21) or mismatched unrelated (1·17, 0·67–2·05; p=0·58) donors, or between mismatched unrelated and haploidentical related donors (1·22, 0·65–2·27; p=0·98). 3-year event-free survival is shown in the appendix (p 1).

Donor type was associated with graft failure. Compared with recipients of transplants from HLA-matched sibling the proportion of patients with graft failure increased among recipients of transplants from haploidentical relatives (HR 6·58, 95% CI 3·55–12·21) and HLA-matched (2·88, 1·54 –5·37) and HLA-mismatched (4·38, 2·31–8·31) unrelated donors (table 2, figure 2B). Graft failure occurred in a greater proportion of recipients of transplants from haploidentical relatives (2·27, 1·09–4·76; p=0·028), but not HLA-mismatched unrelated donors (1·52, 0·71–3·24; p=0·28), than from HLA-matched unrelated donors. Graft failure did not differ between mismatched unrelated and haploidentical related donor transplants (0·67, 0·31–1·44; p=0·30). Graft failure occurred less frequently in women than in

men (0·61, 0·42 – 0·90; table 2). The proportion of patients with graft failure at 3 years is shown in the appendix (p 1).

Overall survival was lower in patients aged 13 years or older than in those younger than 13 years (HR 3·15, 95% CI 1·86–5·34), in those who received myeloablative (4·62, 1·87–11·44) and reduced-intensity (3·79, 1·46–9·84) conditioning than in those who received nonmyeloablative regimens, and after transplantation of grafts from donors who were not HLA-matched siblings than HLA-matched siblings (2·94, 1·26–6·87, for haploidentical related donors; 5·12, 2·79–9·40, for HLA-matched unrelated donors; and 4·88, 2·22–10·75, for HLA-mismatched unrelated donors; table 2, figure 2C). Overall survival did not differ between myeloablative and reduced intensity regimens (1·22, 0·74–2·02; p=0·44). Compared with recipients of transplants from HLA-matched unrelated donors, overall survival did not differ in recipients of transplants from haploidentical related donors (0·57, 0·24–1·35; p=0·20) or from mismatched unrelated donors (0·95, 0·44–2·05; p=0·90). Similarly, overall survival did not differ between mismatched unrelated donors and haploidentical related donors (0·60, 0·24–1·49; p=0·27). 3-year overall survival is shown in the appendix (p 1).

The proportion of patients with acute GVHD was increased with myeloablative (HR 4·14, 95% CI 1·68–10·22) and reduced-intensity (4·43, 1·73–11·35) conditioning versus non-myeloablative regimens; after transplantation of grafts from haploidentical related donors (2·27, 1·08–4·77), HLA-matched unrelated donors (3·84, 2·22–6·63), and HLA-mismatched unrelated donors (6·14, 3·66–10·28) versus HLA-matched siblings, and in the transplantation period 2013–17 (1·74, 1·06–2·84) versus 2008–12 (table 3). The proportion of patients with acute GVHD at 100 days is shown in the appendix p 1.

Acute GVHD risks did not differ between myeloablative and reduced-intensity conditioning regimens (0·93, 0·60–1·46; p=0·77). The risk of acute GVHD did not differ between transplants from HLA-matched unrelated donors and recipients of transplants from haploidentical related donors (0·63, 0·27–1·47; p=0·29) or mismatched unrelated donors (1·27, 0·62–2·59, p=0·51), or between recipients of transplants from HLA-mismatched unrelated donors and from haploidentical related donors (0·37, 0·20–1·20; p=0·12). The severity of acute GVHD did not differ by donor type (p=0·35; data not shown).

The proportion of patients with chronic GVHD was increased in patients aged 13 years or older versus those younger than 13 years (HR 1·46, 95% CI 1·06–2·00), those treated with myeloablative (2·82, 1·51–5·27) and reduced-intensity (4·00, 2·11–7·55) conditioning versus non-myeloablative regimens, and those who received a transplant from an HLA-matched unrelated donor (1·70, 1·14–2·54) versus an HLA-matched sibling (table 3). The proportion of patients with chronic GVHD also increased

	Events/patients	Hazard ratio (95% CI)	p value
(Continued from previous page)			
Graft type			
Bone marrow	60/630	1 (ref)	0·09
Peripheral blood	28/177	1·02 (0·61–1·70)	0·95
Umbilical cord blood	25/102	2·07 (1·08–3·96)	0·028
HCT comorbidity index			
0–2	81/637	1 (ref)	..
≥3	32/272	0·77 (0·49–1·21)	0·26
Performance status			
≤80	23/160	1 (ref)	..
90–100	88/731	1·03 (0·62 –1·70)	0·92
Recipient cytomegalovirus serology			
Negative	53/454	1 (ref)	..
Positive	60/455	1·32 (0·90–1·92)	0·16
Sex			
Male	71/488	1 (ref)	..
Female	42/421	0·61 (0·42–0·90)	0·013
Transplantation period			
2008–12	47/327	1 (ref)	..
2013–17	66/582	1·01 (0·67–1·51)	0·96
Overall survival			
Age, years			
≤12	22/491	1 (ref)	..
13–49	54/418	3·15 (1·86–5·34)	<0·0001
Regimen intensity	..	..	0·004
Non-myeloablative	7/181	1 (ref)	
Myeloablative	41/478	4·62 (1·87–11·44)	0·00093
Reduced intensity	28/250	3·79 (1·46–9·84)	0·0062
Donor type	..	..	<0·0001
HLA-matched sibling	21/557	1 (ref)	
Haploidentical related	13/137	2·94 (1·26–6·87)	0·013
HLA-matched unrelated	26/111	5·12 (2·79–9·40)	<0·0001
HLA-mismatched unrelated	16/104	4·88 (2·22–10·75)	<0·0001
Graft type			
Bone marrow	50/630	1 (ref)	0·09
Peripheral blood	19/177	1·02 (0·61–1·70)	0·95
Umbilical cord blood	7/102	0·58 (0·22–1·55)	0·27
HCT comorbidity index			
0–2	53/637	1 (ref)	..
≥3	23/272	1·15 (0·68–1·93)	0·60
Performance status			
≤80	10/160	1 (ref)	..
90–100	65/731	1·71 (0·85–3·45)	0·13
Recipient cytomegalovirus serology			
Negative	34/454	1 (ref)	..
Positive	42/455	1·35 (0·85–2·14)	0·20

(Table 2 continues on next page)

	Events/patients	Hazard ratio (95% CI)	p value
(Continued from previous page)			
Sex			
Male	31/488	1 (ref)	..
Female	45/421	1·49 (0·94–2·38)	0·09
Transplantation period			
2008–12	31/327	1 (ref)	..
2013–17	45/582	0·94 (0·57–1·56)	0·81

Data are n/N, unless otherwise indicated. Overall p values for multiple comparison are reported when more than two exposure categories are tested. HCT=haematopoietic cell transplantation. ref=reference.

Table 2: **Risk factors for event-free survival, graft failure, and overall survival**

See Online for appendix

after reduced intensity compared with myeloablative conditioning regimens (1·41, 1·03–1·96; p=0·031). The risk of chronic GVHD did not differ between recipients of transplants from HLA-matched unrelated donors and haploidentical related donors (1·03, 0·54–1·96, p=0·93) or HLA-mismatched unrelated donors (0·93, 0·52–1·67, p=0·82), or between recipients of transplants from HLA-mismatched unrelated and from haploidentical related donors (1·09, 0·54–2·22, p=0·79). The severity of chronic GVHD did not differ by donor type (p=0·12; data not shown). The proportion of patients with chronic GVHD at 3 years is shown in the appendix p 1.

A subset analysis of 558 recipients of transplants from HLA-matched sibling was done to assess the effect of conditioning regimen intensity. Conditioning regimen intensity was not associated with overall survival. However, prevalence of graft failure increased after reduced-intensity conditioning compared with myeloablative (HR 0·28, 95% CI 0·13–0·57; p<0·0001) and non-myeloablative (0·29, 0·08–1·00; p=0·049) regimens. Consequently, event-free survival was decreased after reduced-intensity conditioning compared with myeloablative (0·38, 0·21–0·67; p=0·00080) and non-myeloablative (0·36, 0·13–0·94; p=0·036) regimens. Consistent with the main analysis, the HR for overall survival was three-times higher in patients aged 13 years or older (3·25, 1·27–8·29, p=0·014) than in those younger than 13 years.

Six (1%) of 910 patients developed malignant neoplasm (acute myeloid leukemia [n=2], myelodysplastic syndrome [n=2], hepatic myelofibroblastic tumor [n=1], and TCR-β gene rearrangement positive T-cell large granular lymphocytic leukemia [n=1]; appendix p 2). Three of six patients with malignant neoplasm died. The point estimate for the risk of developing a post-transplantation malignancy was seven times higher with non-myeloablative than with reduced-intensity regimens, although it was not significant (HR 7·08, 95% CI 0·82–60·63; p=0·07). None of the six patients had chronic GVHD. There were no cases of post-transplantation malignant neoplasm with myeloablative regimens. Nine patients developed Epstein-Barr

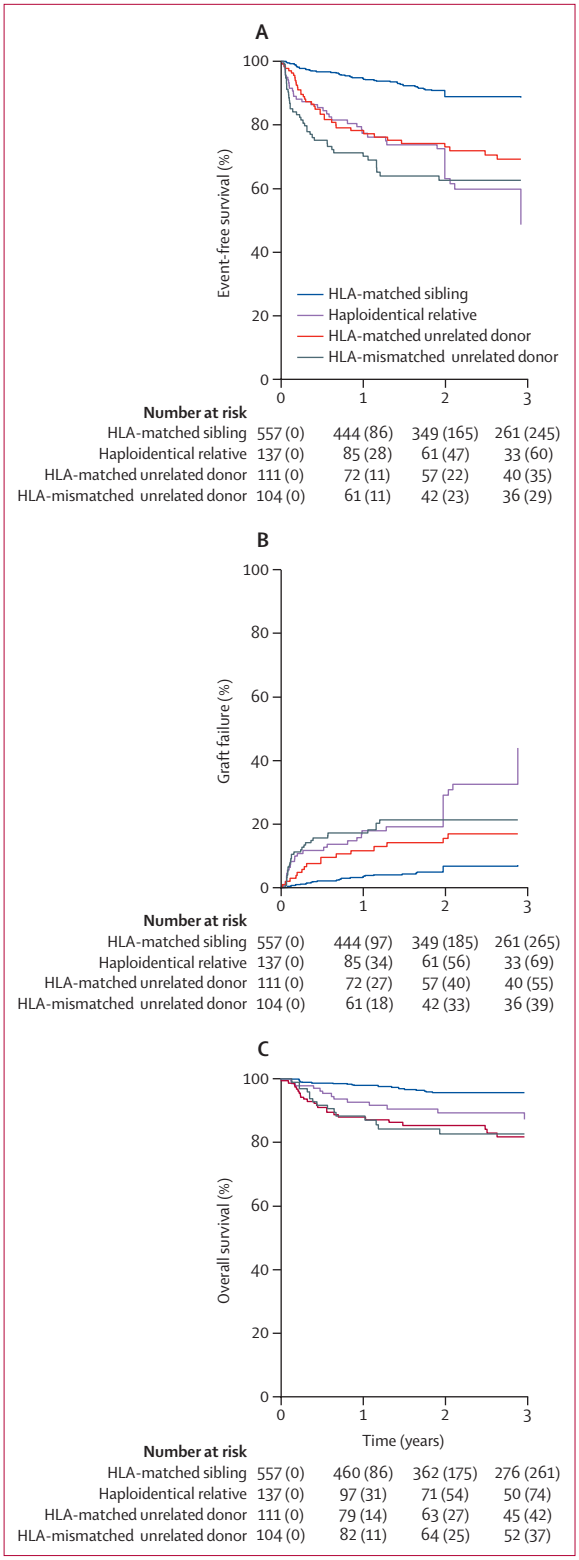

Figure 2: **Event free survival (A), graft failure (B), and overall survival (C) by donor type**

Data are number at risk (numbers censored). HLA=human leukocyte antigen. HR=hazard ratio.

virus-positive lymphoproliferative disease at a median of 5 months (IQR 3–12) after transplantation with all having had in-vivo T-cell depletion with anti-thymocyte globulin or alemtuzumab. Notably, one (<1%) of 421 patients for whom pre-transplantation and post-transplantation sickle cell disease-specific data were available reported acute chest syndrome and six (1%) patients had a stroke; all seven patients had full donor myeloid chimerism.

Discussion

There were two key findings in this retrospective analysis that warrant caution when considering alternative donor transplantation as a potentially curative option for patients with sickle cell disease. Mortality and prevalence of graft failure were increased after any alternative donor transplantation compared with HLA-matched sibling transplantation, which resulted in substantially decreased event-free survival. To our knowledge, this is the first study to assess allogeneic transplantation outcomes for patients with sickle cell disease who received transplantations from HLA-matched sibling donors or transplantations from alternative donors (haploidentical related donors, HLA-matched unrelated donors, and HLA-mismatched unrelated donors). The study also addressed the effect of conditioning regimen intensity on transplant outcomes. Myeloablative and reduced-intensity regimens were associated with increased mortality as well as acute and chronic GVHD. Conditioning regimen intensity was not associated with graft failure.

Increased mortality and prevalence of graft failure after transplantation from HLA-mismatched unrelated donors has been reported for non-malignant diseases but those studies[21,22] did not include many patients who received transplants for haemoglobinopathies. Our findings confirm the adverse effect of HLA disparity on survival outcomes and graft failure after transplantation in patients with sickle cell disease. The timing of graft failure differed by donor type in patients with sickle cell disease. Graft failure after transplantation from HLA-matched siblings and unrelated donors primarily occurred within 1–2 years after transplantation. By contrast, graft failure was more common 2–3 years after haploidentical related donor transplantation. This is particularly relevant in light of the improved outcomes reported in two recent phase 2 trials[23,24] of transplantations from haploidentical related donor with 15 and 12 patients with sickle cell disease. Both trials used the post-transplantation cyclophosphamide approach to overcome the HLA barrier. One trial[23] reported donor engraftment in 14 (93%) of 15 patients at 6 months[23] and the other trial[24] reported full or mixed donor engraftment 11 (92%) of 12 patients in the first year after transplantation. Longer follow-up of these patients is needed to confirm sustained donor engraftment. We did not find an association between graft failure and conditioning regimen tested (myeloablative, reduced intensity, and non-myeloablative).

	Events/patients	Hazard Ratio (95% confidence interval)	p value
Grade 2-4 acute graft-versus-host disease			
Age, years			
≤12	46/446	1 (ref)	..
13–49	49/377	1·39 (0·89–2·18)	0·14
Regimen intensity	..	..	0·0062
Non-myeloablative	7/171	1 (ref)	
Myeloablative	51/440	4·14 (1·68–10·22)	0·0020
Reduced intensity	37/212	4·43 (1·73–11·35)	0·0019
Donor type	..	..	<0·0001
HLA-matched sibling	32/513	1 (ref)	..
Haploidentical related	11/126	2·27 (1·08–4·77)	0·03
HLA-matched unrelated	23/97	3·84 (2·22–6·63)	<0·0001
HLA-mismatched unrelated	29/87	6·14 (3·66–10·28)	<0·0001
Graft type			
Bone marrow	58/565	1 (ref)	0·37
Peripheral blood	15/163	0·98 (0·50–1·91)	0·95
Umbilical cord blood	22/95	1·61 (0·81–3·20)	0·18
HCT comorbidity index			
0–2	65/564	1 (ref)	..
≥3	30/259	0·94 (0·59–1·49)	0·79
Performance status			
≤80	22/149	1 (ref)	..
90–100	72/658	0·71 (0·42–1·19)	0·19
Recipient cytomegalovirus serology			
Negative	45/411	1 (ref)	
Positive	50/412	1·19 (0·79–1·80)	0·39
Sex			
Male	45/439	1 (ref)	
Female	50/384	1·16 (0·77–1·76)	0·47
Transplantation period			
2008–12	24/285	1 (ref)	
2013–17	71/538	1·74 (1·06–2·84)	0·028
Chronic graft-versus-host disease			
Age, years			
≤12	98/491	1 (ref)	
13–49	92/419	1·46 (1·06–2·00)	0·019
Regimen intensity			<0·0001
Non-myeloablative	17/181	1 (ref)	
Myeloablative	97/478	2·82 (1·51–5·27)	0·0012
Reduced intensity	76/250	4·00 (2·11–7·55)	<0·0001
Donor type			0·017
HLA-matched sibling	101/557	1 (ref)	
Haploidentical related	22/137	1·75 (0·55–3·11)	0·055
HLA-matched unrelated	37/111	1·70 (1·14–2·54)	0·0087
HLA-mismatched unrelated	30/104	1·59 (0·95–2·67)	0·08

(Table 3 continues on next page)

	Events/patients	Hazard Ratio (95% confidence interval)	p value
(continued from previous page)			
Graft type			
Bone marrow	146/630	1 (ref)	0·09
Peripheral blood	20/177	0·55 (0·32–0·94)	0·028
Umbilical cord blood	24/102	0·84 (0·49–1·46)	0·54
HCT comorbidity index			
0–2	135/637	1 (ref)	
≥3	55/272	1·13 (0·81–1·57)	0·47
Performance status			
≤80	34/160	1 (ref)	
90–100	152/731	0·86 (0·57–1·28)	0·44
Recipient cytomegalovirus serology			
Negative	93/454	1 (ref)	
Positive	97/455	1·05 (0·79–1·40)	0·74
Sex			
Male	89/488	1 (ref)	
Female	101/421	1·32 (0·99–1·77)	0·06
Transplantation period			
2008–12	76/327	1 (ref)	
2013–17	114/583	1·07 (0·79–1·46)	0·65

HCT=haematopoietic cell transplantation. ref=reference value.

Table 3: **Risk factors for acute and chronic graft-versus-host disease**

The concept of less intense conditioning regimens (reduced intensity or non-myeloablative) was introduced to overcome mortality risks associated with myeloablation in less fit patients or for diseases for which myeloablation was not desirable. Therefore, the finding that mortality risks were four times higher with both myeloablative and reduced-intensity regimens than with non-myeloablative regimens was unexpected. The recorded increased mortality might be explained in part by the increased risks of acute and chronic GVHD with myeloablative and reduced intensity regimens. These regimens relied on standard GVHD prophylaxis, which included a calcineurin inhibitor alone or with methotrexate, mycophenolate, or sirolimus. The non-myeloablative regimens used a different strategy. In the setting of HLA-matched sibling transplantation, the low-dose TBI approach incorporates an attempt at tolerance induction through the use of lymphocyte reduction with alemtuzumab plus mTOR inhibition with sirolimus during recovery.[25] This tolerance is blocked in vitro and in animal models with calcineurin inhibitor.[25] Similarly, for transplantation from haploidentical related donors, post-transplantation treatment with cyclophosphamide induces early immune tolerance mediated by the destruction of alloreactive donor and recipient T cells, and any remaining alloreactivity is counterbalanced by increasing the number T regulatory cells.[26] A delayed but long-lasting intrathymic clonal deletion of anti-host T cells maintains long-term immune tolerance.[26] Tolerance induction and low prevalence of GVHD associated with low-intensity regimens are likely to have contributed to the high event-free survival and overall survival in these patients. Increased prevalence of acute GVHD after the 2008–12 period can be explained by the increasing numbers of transplantation from unrelated donors.[27] On the basis of these observations, we hypothesise that immune tolerance induction, rather than regimen intensity per se, is the key driver of survival after transplantation for treatment of sickle cell disease.

Age at transplantation was an important predictor of survival in this study. The risk of death is three times higher in a patient aged 13 years or older than in a younger patient, assuming the type of donor and conditioning regimen intensity are the same for both patients. Although almost half the study population was aged 13 years or older, we did not find another age cutoff associated with survival differences. Only seven transplantations were reported in patients aged 50 years or older and they were not included in the current analyses. The effect of age in adults can only be studied properly in a larger adult population than represented in our population, and this is a limitation of our study. The timing of transplantation is dependent on physician and patient choice, donor availability, and access to health care. With the exception of stroke, severity of symptoms of sickle cell disease that prompts referral for transplantation is variable. In the absence of a comparative study of transplant recipients and those receiving non-transplantation therapies with comparable disease severity, we cannot comment on whether transplantation from HLA-matched sibling should be offered in the first decade of life. With 3-year prevalence of chronic GVHD of 18% (95% CI 15–22) after transplantation from HLA-matched siblings we cannot recommend transplantation for asymptomatic children or for children without severe disease. Consistently with a published study,[28] we did not record an association between comorbidity index and survival.

There are several limitations to our study because of its retrospective nature, which include the fact that the decision to offer transplantation and its timing, choice of conditioning regimen intensity, and choice of alternative donor in the absence of a matched sibling were made by the treating physicians at each participating institution. We acknowledge transplantation strategies are best studied in the setting of multicentre trials. Yet, prospective studies are challenging as accrual can extend over 5 years for funded multicentre transplantation trials.[5,11] We did not consistently collect information on haemoglobin S concentration after transplantation. Our definition of graft failure considered donor chimerism collected up to 2 years after transplantation. Thereafter, our standardised data-collection forms asked whether the patient experienced graft failure (<5% donors) and the date of

failure. We did not have data on red blood cell chimerism. The occurrence of events such as acute chest syndrome and stroke in the setting of full donor chimerism deserves further study and such research is best achieved through careful longitudinal follow-up focusing on sickle cell disease-related complications. We did not collect detailed data on sickle cell disease-related complications after transplantation to study the occurrence of stroke in patients with full myeloid donor chimerism.

Similarly, because of limited follow-up, the recorded increased risk of post-transplantation myeloid malignancy after non-myeloablative regimens should be further investigated. Whether this finding is a result of age, transplantation per se, regimen intensity, or some other unknown or unmeasured factor cannot be addressed in this study. A 2017 study[29] found that the standardised incidence ratio for haematologic cancer in an unselected population with sickle cell disease is 1·72 (95% CI 1·17–2·44) and that patients were diagnosed with their first primary cancer at a median age of 46 years. With increasing numbers of transplantations in young adults, in a few years it might be possible to design comparative studies on cancer prevalence amongst patients with sickle cell disease who received or did not receive transplantation. Although our data does not favour one alternative donor over another, a decrease by 20 percentage points in 3-year event-free survival between recipients of transplants from haploidentical relatives and HLA-matched unrelated donors cannot be ignored. To detect a significant difference with 80% power, 271 patients are needed but our analyses only included 248 patients.

Allogeneic transplantation is potentially curative, but we do not know whether appropriate follow-up might reduce the mortality caused by the transplantation procedure to less than the mortality caused by complications of sickle cell disease. A phase 2 trial (NCT02766465) of young adults with severe sickle cell disease in the USA addresses this question by assigning eligible participants (eligibility criteria are based on disease severity and organ function) to either a donor group (if they have a suitably matched sibling or unrelated donor) or a no-donor group (if they do not have a suitable donor). Participants in the donor group are expected to undergo transplantation and those in the no-donor group are expected to receive best available standard of care. We acknowledge monetary coverage for access to health care is critical to improve survival. Access to transplantation for young adults with sickle cell disease is also challenging in the USA. The introduction of the Coverage with Evidence Determination programme by the Center for Medicare and Medicaid Services is likely to broaden access to allogeneic transplantation. Another potentially curative treatment for sickle cell disease that is being pursued is the use of a lentiviral vector to add an anti-sickling β-globin gene variant into autologous haematopoietic cells.[30] This approach is being studied in small numbers of patients and definitive conclusions will require confirmation of success in larger numbers of patients as well as longer follow-up.

In conclusion, our data suggest that event-free survival is improved in patients with sickle cell disease who receive an allogenic transplantation at age 12 years or younger and those with an HLA-matched sibling donor. For patients without a matched sibling donor available, our data do not favour one alternative donor type over another in this setting. Transplantation from alternative donors broadens access to this treatment. However, strategies aimed at lowering graft failure and GVHD are needed before transplantation from these donors can be as effective as that from HLA-matched siblings.

Contributors

ME, RB, MCW, FB, CDF, JSH, JK, JJM, JB-M JAP, DR, SS, JEW, and JFT designed the study. RB and KBS did the statistical analysis. All authors contributed to writing the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

This work was undertaken through conversations with the members of the American Society of Hematology guideline panel on sickle-cell disease-related transplantation.

The Center for International Blood and Marrow Transplant Research is supported by grant U24-CA76518 from the National Institutes of Health and grant HHSH 250201200016C from Health Services Research Administration, Department of Health and Human Services, USA.

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