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Allogeneic hematopoietic stem cell transplantation from sibling and unrelated donors in pediatric patients with sickle cell disease—A single center experience

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Abstract

HSCT is curative in SCD. Patients with HLA-identical sibling donor have an excellent outcome ranging from 90%-100% overall and event-free survival. However, due to the lack of matched sibling donors this option is out of reach for 70% of patients with SCD. The pool of potential donors needs to be extended. Transplantations from HLA-matched unrelated donors were reported to be less successful with shorter event-free survival and higher incidences of complications including graft-vs-host disease, especially in patients with advanced stage SCD. Here we report transplantation outcomes for 25 children with SCD transplanted using HLA-matched grafts from related or unrelated donors. Overall survival was 100% with no severe (grade III-IV) graft-vs-host disease and a 12% rejection rate. Mixed donor chimerisms only occurred in transplantations from siblings, while transplantations from unrelated donors resulted in either complete donor chimerism or rejection. Despite the small patient number, overall and disease-free survival for unrelated donor transplantations is excellent in this cohort. The advanced disease state, higher alloreactive effect and stronger immunosuppression in unrelated donor transplantations raises patient risk, for which possible solutions could be found in optimization of transplant preparation, graft manipulation or haploidentical transplantation using T cell receptor α/β-depleted grafts.

KEYWORDS

allogeneic HSCT, chimerism and engraftment, matched sibling donor, matched unrelated donor, SCD

Abbreviations: GvHD, graft-vs-host disease; HSCT, hematopoietic stem cell transplantation; MSD, matched sibling donor; MUD, matched unrelated donor; SCD, sickle cell disease; STR, short tandem repeat.

Oevermann and Schulte authors equally contributed to this work.

1 | INTRODUCTION

SCD is one of the most frequent inherited diseases worldwide, affecting approximately 300 000 newborns each year.[1] HSCT is the standard of care for SCD in children with a MSD.[2] Unfortunately, an HLA-identical sibling donor is available for fewer than 30% of the patients.[3-5] Without HSCT, median life expectancy ranges from 40 to 50 years in high-resource healthcare settings, emphasizing the urgency for optimized curative approaches for these patients.[5-8] HLA-MUD are available for approximately 10%-43% of cases.[3,4,9,10] While results after HSCT using HLA-identical grafts from siblings are excellent and exceed 95% overall survival, complication rates are higher in patients receiving grafts from unrelated donors.[11,12] In a cohort of 29 patients with SCD undergoing HSCT from unrelated donors, Shenoy et al reported event-free and overall survival of only 70% and 80%, respectively.[13] A recent large analysis comparing different donor choices found event-free survival was significantly worse in unrelated donor transplantations for SCD compared to transplantations from HLA-identical siblings.[14] To date, there is no standardized protocol for conditioning regimens in SCD patients. Early studies used a myeloablative conditioning regimen of busulfan and cyclophosphamide, and produced 73% and 91% event-free and overall survival, respectively, at 4 years, with most failures occurring as a consequence of graft rejection or disease recurrence.[15,16] Following studies used fludarabine-based reduced intensity conditioning regimens and reported improved outcomes with event-free and overall survival ranging between 91% and 100%.[11,17] Additional studies tried to reduce transplant-related toxicities (eg, infertility) by introducing non-myeloablative conditioning regimens, resulting in higher graft rejection rates.[8] A new immunosuppression strategy using sirolimus and alemtuzumab instead of the standard regimen with cyclosporine and anti-thymocyte globulin showed promising results with minimal graft rejection and a low incidence of graft-vs-host disease.[18,19] Transplant strategies always need to consider the patient's comorbidities. In SCD, the existing systemic vasculopathy is worsening with time and complications (eg, stroke, renal impairment, cardiac insufficiency).[8,20,21] As SCD is a steadily advancing chronic disease, age is a critical issue and will directly affect transplant outcome.[22,23] Efforts to reduce transplant-related toxicity, optimize conditioning regimen strategies and expand the donor pool to include alternatives who are unrelated or haploidentical are necessary to offer safe options to a larger proportion of patients with SCD.[5,6]

Here, we present a pediatric cohort of patients with sickle cell disease undergoing allogeneic HSCT in Berlin from either an HLA-identical sibling or HLA-matched unrelated donor.

2 | PATIENTS AND METHODS

2.1 | Ethics

Informed consent for HSCT was obtained in accordance with the Declaration of Helsinki. Data were retrospectively collected from 25 pediatric patients, treated at the Charité between 2013 and 2018.

2.2 | Patients

Between March 2013 and July 2018, 25 patients with SCD received HSCT using MSD or MUD grafts at the Department of Pediatric Oncology and Hematology, Charité – Universitätsmedizin Berlin (Germany). All patients received in vivo T cell depletion using anti-thymocyte globulin. An autologous back-up was collected prior to allogeneic HSCT for all patients undergoing HSCT from an unrelated donor. Patient and donor characteristics are summarized in Table 1.

2.3 | Donors and grafts

Seventeen patients were transplanted using grafts from an HLA-identical sibling donor. The remaining eight patients received an allograft from unrelated donors. High-resolution HLA typing was performed for all MUD transplantations. Six patients received transplants from a 10/10 HLA-matched unrelated donor, the other two patients were transplanted with grafts having 9/10 HLA matches due to low donor availability. The hemoglobin donor genotype was A/A in eleven cases and S/A (sickle cell trait) in 12 cases. Two donors had beta thalassemia minor. Peripheral blood stem cells were the source for four of eight MUD transplantations. These grafts were selected for CD34-positive cells and repleted with 30×10^6 CD3-positive cells/kg bodyweight. All other patients were transplanted using bone marrow grafts (see Table 1).

2.4 | Conditioning regimens and immunosuppression

Three different conditioning regimens were used in this cohort. Seven patients received the busulfan (14 mg/kg total dose) and cyclophosphamide (200 mg/kg total dose) regimen published by Lucarelli et al in 2014.[24] A conditioning regimen using fludarabine (160 mg/m^2), thiotepa (10 mg/kg), and treosulfan (3×14 g/m^2) according to the published general guidelines was used in eight patients.[2] The other ten patients received a fludarabine (160 mg/m^2), thiotepa (10 mg/kg), and melphalan (140 mg/m^2) conditioning regimen according to Matthes-Martin et al that aimed to improve the retention of fertility by reducing toxicity.[25] All patients received serotherapy with anti-thymocyte globulin. Immunosuppression was started using cyclosporine in all 25 patients, but was replaced by tacrolimus due to renal insufficiency in two patients. Mycophenolate mofetil was used as a second immunosuppressive agent in all patients receiving the fludarabine, thiotepa, melphalan regimen.

2.5 | Chimerism analysis

Post-transplant monitoring of donor-recipient chimerism was assessed by quantitative polymerase chain reaction analysis of (STR analysis) markers on DNA obtained from peripheral blood. 16 different short

TABLE 1 Summary of patient, donor and transplant characteristics

	Total	MSD	MUD
Number of patients	25	17	8
Age at HSCT	11.84 (1-21)	10.71 (1-20)	14.25 (3-21)
Disease subtype			
HbSS	19	15	4
HbS/ß-Thal	6	2	4
SCD-related comorbidities			
Vaso-occlusive pain crises	17	13	4
Acute chest syndrome	9	6	3
Stroke/cerebral vasculopathy	2	1	1
Splenic sequestration	9	5	4
Osteonecroses	8	3	5
Aplastic crisis	2	1	1
Arterial hypertension	2	0	2
Priapism	1	0	1
Hemosiderosis	2	0	2
Endocarditis	1	0	1
Chronic exchange transfusions	4	2	2
Graft source			
Bone marrow	21	17	4
Peripheral blood stem cells	4	0	4
Conditioning regimen			
Busulfan/Cyclophosphamid	7	5	2
Fludarabin/Thiotepa/Treosulfan	8	5	3
Fludarabin/Thiotepa/Melphalan	11	7	3
GVHD prophylaxis			
Ciclosporin A + Mycophenolate mofetil	13	10	3
Ciclosporin A + Methotrexate	4	3	1
Ciclosporin A	5	4	1
Tacrolimus + Methotrexate	2	0	2
Ciclosporin A + Mycophenolate mofetil + Methotrexate	1	0	1
Donor characteristics			
Hb genotype			
HbA/A	11	6	5
HbS/A	12	10	2
HbA/ß-Thal	2	1	1
Donor age (years)	19		
Gender			
Female	11	9	2
Male	14	8	6
Gender mismatch	10	6	4
AB0 compatibility			
Matched	13	11	2
Major mismatch	4	2	2
Minor mismatch	8	4	4
Neutrophil engraftment in days (range)	21.36 (12-37)	22.35 (12-37)	19.25 (12-35)
Median follow-up in days (range)	981 (225-2496)	1083 (225-2496)	830 (329-1841)

TABLE 2 Donor chimerism at last follow-up in the pediatric SCD cohort

	Total	MSD	MUD
Full donor chimerism (%)	13 (52)	7	6
Mixed chimerism (%)	9 (36)	9	0
<10% host cells (%)	4 (16)	4	0
10%-25% host cells (%)	2 (8)	2	0
26%-50% host cells (%)	1 (4)	1	0
>50% host cells (%)	2 (8)	2	0
Graft rejection (%)	3 (12)	1	2
Donor chimerism = Total nuclear cells			

TABLE 3 Different conditioning regimens in the pediatric SCD cohort

	Bu/Cy	Flu/TT/Treo	Flu/TT/Mel
Total	7	8	10
Full donor chimerism	3	4	6
Mixed chimerism	4	3	3
<10% host cells	2	1	1
10%-25% host cells	0	1	1
26%-50% host cells	0	1	0
>50% host cells	1	0	1
Graft rejection	1	1	1
Donor chimerism = Total nuclear cells			

Abbreviations: Bu, busulfan; Cy, cyclophosphamid; Flu, fludarabin; Mel, melphalan; Treo, treosulfan; TT, thiotepa.

tandem repeats were used for each analysis. Lineage specific chimerism was assessed for CD34, CD3, CD56, CD235a subpopulations. Blood samples were collected around 30, 60, 100, and 180 days and 365 days after transplantation and every following 6-12 months. Hemoglobin pattern and HbS fraction quantification were assessed in parallel with donor-recipient chimerism, every 6-12 months.

2.6 | Statistical analysis

A retrospective review was performed in 25 pediatric patients with SCD who underwent matched related or unrelated donor stem cell transplantations between 2013 and 2018. All statistical analyses were performed using SPSS software.

3 | RESULTS

3.1 | Overall survival and treatment-related morbidity

Overall survival was 100% (median follow-up time, 981 days) in our cohort of 25 patients transplanted for SCD from either HLA-matched siblings or unrelated donors (Table 1). Mild acute GvHD occurred in only eight patients. The most severe cases (grade II) occurred among the oldest patients. No patient developed a severe acute GvHD (higher than grade 2) or chronic GvHD (Table 1). Patients were tested regularly for possible virus reactivations with adenovirus, BK virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, and parvovirus B19. Systemic virus reactivations occurred in 13 patients, with one of six viruses reactivating in eight patients and the reactivation of both Epstein-Barr virus and cytomegalovirus in five patients. All viral infections were treated and resolved without sequelae. Interestingly, all four patients that had received peripheral stem cell grafts from a matched unrelated donor had at least two different systemic virus infections after HSCT.

3.2 | Engraftment and chimerism

Primary engraftment was achieved in 24 of 25 patients. A primary graft rejection occurred in one patient, who reconstituted autologously and chose not to undergo a second HSCT. Another patient rejected shortly after HSCT. She received her autologous back-up directly after graft rejection and was re-transplanted successfully 6 months later with a haploidentical graft from her father. At last follow-up, a complete donor chimerism was detected in 13 patients and a stable mixed chimerism in nine patients (23%-94% donor cells). Late graft rejection with <20% donor cells and a return of SCD-related symptoms (vaso-occlusive crisis) occurred in one patient after sibling donor transplantation (Table 2). A mixed donor chimerism occurred in nine of the 16 patients receiving MSD grafts who reached primary engraftment. At last follow-up none of them presented with recurrence of SCD-related symptoms, but three of them are still at risk for late graft rejection (Table 4). None of the eight patients who received a graft from an unrelated donor developed a mixed chimerism, but full graft rejection occurred in two patients.

3.3 | Comparison of the three different conditioning regimens

Transplant outcomes for the three different conditioning regimens used in this cohort do not differ significantly in regard to GvHD, systemic virus reactivations, chimerism, and rejection rate, with a balanced distribution of sibling and unrelated donors among conditioning regimens (Table 1). Of note, a graft rejection occurred in each group, and >90% donor chimerism was achieved in more than 60% of the patients in each group (Table 3).

4 | DISCUSSION

We describe the outcomes of allogeneic HSCT from matched sibling or unrelated donors in a pediatric cohort of patients with SCD

TABLE 4 Courses of chimerism in pediatric SCD patients after sibling donor transplantation

Patient N°	Age at SCT	Diagnosis	Donor	Graft source	Conditioning	SCD recurrence	Chimerism day 30	Chimerism day 60	Chimerism day 100	Chimerism day 180	Chimerism day 365	Chimerism last follow-up	Follow-up in days
1	9	HbSS	MSD	BM	Bu/Cy	0	n.d.	n.d.	n.d.	n.d.	73	23	2496
2	1	HbSS	MSD	BM	Bu/Cy	0	98	98	n.d.	95	n.d.	95	225
3	9	HbSS	MSD	BM	Bu/Cy	0	n.d.	n.d.	n.d.	n.d.	100	100	2205
4	18	HbSS	MSD	BM	Bu/Cy	0	96	100	100	100	96	99	1778
5	12	HbSS	MSD	BM	Bu/Cy	0	100	100	100	100	100	100	1888
6	15	HbSS	MSD	BM	Flu/TT/Mel	0	100	100	100	100	100	100	1304
7	9	HbSS	MSD	BM	Flu/TT/Mel	0	60	97	82	84	84	78	1464
8	20	HbSS	MSD	BM	Flu/TT/Mel	0	100	n.d.	100	100	100	100	730
9	14	HbSS	MSD	BM	Flu/TT/Mel	1	100	60	35	26	22	15	1527
10	7	HbSS	MSD	BM	Flu/TT/Treo	0	100	100	100	100	100	100	786
11	17	HbSS	MSD	BM	Flu/TT/Mel	0	100	100	100	100	100	100	741
12	14	HbS/bThal	MSD	BM	Flu/TT/Treo	0	100	100	100	100	100	100	737
13	7	HbSS	MSD	BM	Flu/TT/Mel	0	100	100	100	100	99	98	1091
14	2	HbSS	MSD	BM	Flu/TT/Mel	0	100	93	85	61	44	41	1083
15	8	HbSS	MSD	BM	Flu/TT/Treo	0	99	99	100	96	88	85	873
16	15	HbS/bThal	MSD	BM	Flu/TT/Treo	0	97	95	95	78	68	67	776
17	5	HbSS	MSD	BM	Flu/TT/Treo	0	100	98	92	90	94	92	735

Note: Chimerism = Donor chimerism in total nuclear cells.

Abbreviations: BM, bone marrow; Bu, busulfan; Cy, cyclophosphamid; Flu, fludarabin; Mel, melphalan; Treo, treosulfan; TT, thiotepa.

who were treated at the Department of Pediatric Oncology and Hematology at the *Charité – Universitätsmedizin Berlin* between 2013 and 2018 using three alternative conditioning regimens. Overall survival was 100% in this cohort. Graft-vs-host disease - to be avoided completely in non-malignant diseases - did not affect any of the patients severely. The different conditioning regimens used in this cohort did not seem to have a significant impact on transplant outcomes, taking into account that patient numbers were small.

Patients transplanted with MSD grafts did reveal higher percentages of mixed chimerisms without disease recurrence or total graft rejection until last follow-up. One patient had a late graft rejection and recurrence of SCD symptoms 3 years after transplant. At last follow-up, three of the nine patients who had a mixed chimerism are still at risk for late graft rejection as their donor chimerism is constantly dropping. Donor lymphocyte infusions were given repetitively but did not stop the development. None of them presented with SCD-related symptoms so far (Table 4). The absence of mixed donor chimerisms in patients receiving grafts from unrelated donors can be explained by the stronger alloreactive potential present in unrelated donor transplantations.[26,27] A higher risk for acute GvHD is associated with alloreactivity requiring an intensive GvHD prophylaxis. Moreover, patients receiving unrelated donor transplants are generally older and/or have a more advanced stage SCD resulting in comorbidities that raise the risk for transplant-related complications. Advanced stage vasculopathy or HLA-antibodies due to multiple red cell transfusions lead to a higher risk for GvHD and graft rejection. In our cohort patients transplanted from unrelated donors were significantly older than those in the sibling donor group (15 vs 9 years). One patient (13 years), who had received multiple red cell transfusion and was alloimmunized did not reach engraftment, but rejected the graft immediately. Fortunately, none of the patients in our cohort were affected by a severe (grade III-IV) GvHD, and GvHD occurrence did not differ according to the conditioning regimen used. Systemic GvHD therapy delays immune recovery after HSCT and leads to systemic virus infections increasing treatment-related complications and mortality.[28] Here, systemic virus reactivations with two or more viruses occurred predominantly in patients who received peripheral blood stem cell grafts from matched unrelated donors. These grafts were selected for CD34-positive cells, and repleted with 30×10^6 CD3-positive cells/kg bodyweight. This graft manipulation strategy was necessary to successfully avoid severe GvHD, but resulted in deeper immunodeficiency and slower immune reconstitution, which enhanced viral complications and resulted in rejection of one graft.

With 100% overall survival and no severe GvHD our results for unrelated donor transplantations are excellent. Results for unrelated donor transplantation in other studies were diverse with high rates for GvHD and viral infections,[29] low overall survival[13] and high rejection rates.[4] More successful studies were limited by the number of patients treated with unrelated donor grafts[22,30]; the same is true for our study. Moreover, graft rejection rates need to be improved for our patients. Strategies to optimize transplantation outcomes for SCD are manifold. Reducing transplant-related toxicity further and simultaneously inducing tolerance to avoid graft rejection has been attempted in different ways.[14] Non-myeloablative conditioning regimens are successful in MSD transplantations, but graft rejection rates were significantly higher when applied in transplantation from unrelated or haploidentical donors.[14,18,31] Alloimmunization, vasculopathy and vascular end-organ damage affect transplant outcomes. The individual patient risk has to be considered when planning for unrelated transplantation. Pre-conditioning procedures, for example repetitive exchange transfusions could improve the physical patient condition and lead to less treatment-related complications. At our center, every SCD patient receives an exchange transfusion prior to transplantation and an anticonvulsive prophylaxis. We always search for HLA-antibodies. Alloimmunized patients are treated with immunoglobulins, bortezomib and/or plasmapheresis prior to transplantation. Blood pressure is monitored closely and antihypertensive therapy is started early to avoid posterior reversible encephalopathy syndrome.

In addition, the chance of finding an unrelated donor for patients with SCD is also limited and sparsely extends the donor pool.[9,10] Haploidentical stem cell transplantation has been performed on a number of patients with SCD to expand the donor pool and offer a cure for a large proportion of patients with SCD.[5,6,27,32] Risks for different complications are higher after haploidentical transplantation due to T cell depletion.[33] One possible solution could be found in haploidentical transplantation with T cell receptor α/β-depleted grafts. This HSCT strategy was first introduced in leukemia patients, where it lowered the incidence of GvHD and relapse while maintaining sufficient immune function and rapid immune reconstitution.[34] Promising results were also achieved using haploidentical HSCT with T cell receptor α/β-depleted grafts in 23 pediatric patients with non-malignant diseases.[35] Haploidentical transplantation with either CD3/CD19 or T cell receptor α/β-depleted grafts resulted in 90% overall survival and low GvHD graft rejection rates in another cohort of pediatric patients with advanced stage SCD.[5,36] An obstacle to this graft manipulation option is that it is only available in a few experienced centers, but more data should be gathered to further evaluate this promising transplantation strategy.

5 | CONCLUSION

Outcomes for pediatric SCD patients are excellent in this cohort especially for unrelated donor transplantation. The individual patient risks have to be considered and are crucial especially in patients with advanced stage disease. Optimization of graft manipulation and pre-transplant treatment is necessary to avoid transplant-related complications. Lacking both, a matched sibling and unrelated donor, haploidentical stem cell transplantation should be considered to further expand the donor pool, spare toxicity and improve immune reconstitution.

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CONFLICT OF INTEREST

The authors disclosed no potential conflicts of interest.

AUTHORS' CONTRIBUTIONS

FK, DH, and LO data collection, FK, LO, and JHS manuscript composition, PS, PL, JSK, PH, AK, and AE manuscript revision.

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