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Original Article

Hematopoietic Stem Cell Transplantation in Severe Pediatric Sickle Cell Disease: Outcome and long-term complications, Saudi experience at King Faisal Specialist Hospital, Riyadh, Saudi Arabia

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Abstract. ***Background*: Hematopoietic stem transplantation (HSCT) from matched related donors (MRD) is offered as a curative therapeutic option in children with Sickle cell disease (SCD).**
Objective: **We wanted to assess the outcome and long-term complications observed in children undergoing HSCT at a single transplant center in Saudi Arabia.**
Patients and Methods: **One hundred and twenty-nine children were transplanted for severe Sickle cell disease (SCD) consecutively from 2006 to 2020 at our center. The main transplant indication was cerebral vasculopathy in 57 (43%), followed by the recurrent vaso-occlusive crisis (VOC) in 47 (36%). Median age at transplant was 9.1 years (range, 1.5-13.9 years). All patients received myeloablative conditioning with Busulfan, Cyclophosphamide, and Anti T-Lymphocyte Globulin (Grafalon®): BU/CY/ATG in 114 (88.4%), BU/CY in 13 (10%) and other in 2 (2%). Bone marrow was the main stem cell source in 123 (95%).**
Results: **All patients showed granulocyte engraftment. Acute graft-versus-host-disease (aGVHD) and chronic GVHD were observed in 26 (20%) and 12 (9%) patients, respectively. At a median follow-up of 4.36 years (range, 0.13-15.5 years), 10-year overall survival (OS) and event-free survival (EFS) of 94% and 91% was observed. The OS and EFS were significantly better in patients receiving BU/CY/ATG when compared to BU/CY (OS: 97.4%±1.5%, vs. 76.2%±12.1 *P=0.003* and EFS: 94.7%±2.1% vs. 76.2%±12.1%, *P=0.019*).**
Conclusion: **HSCT for children with sickle cell disease from fully matched siblings offers the best outcome using myeloablative conditioning. However, significant toxicities were observed secondary to myeloablative regimens, in particular long-term complications, which demands exploring the use of less toxic regimens.**

Keywords: Pediatrics; Hematopoietic stem cell transplantation; Sickle cell disease; Graft vs host disease; Chimerism; Survival.

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Introduction. Sickle cell disease (SCD) is a group of autosomal recessive red blood cell disorders characterized by mutations in the beta-globin genes that lead to a faulty hemoglobin (Hb) protein called hemoglobin S (Hb S). A homozygous mutation in the gene for b globin, a subunit of adult hemoglobin A (HbA), is the proximate cause of sickle cell disease (SCD). Hb S shows peculiar biochemical properties, which lead to polymerizing when deoxygenated, changing the shape of red blood cells into rigid, sickle-shaped cells called the "sickle cells," blocking blood flow and causing pain and organ damage.[1-3] Sickle cell disease is a lifelong, chronic illness that is associated with high morbidity, impaired quality of life, and reduced life expectancy.[3,4] Disease manifestation includes vaso-occlusive crisis (VOC), acute chest syndrome (ACS), stroke, and other cerebral vasculopathy.[3-5]

Sickle cell disease (SCD) is one of the most frequently reported inherited diseases worldwide, affecting approximately 300,000 newborns yearly.[3] Saudi Arabia is reported to have a high prevalence of sickle cell trait, ranging from 2% -to 27%, with up to 1.4% having SCD in some areas.[6-10] Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative option for SCD, and HLA-identical, sibling donor transplant is the standard of care with excellent overall survivals.[2,11-14] However, the procedure is not without risks that include severe chronic graft-versus-host-disease (GVHD), graft rejection, onset of transplant-related complications, and mortality.[2,11]

The Pediatric Stem Cell Transplantation unit at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia (KFSH&RC-R) is the major tertiary care referral center for children with SCD indicated for HSCT with a suitable donor. In this study, we present a pediatric cohort of patients (age at transplant ≤ 14 years) who underwent HSCT for SCD from a fully matched-related donor (MRD).

Material and Methods. We report a single-center, retrospective review of pediatric patients (aged ≤ 14 years) who underwent HSCT from MRD for SCD from January 2006 to December 2020. Written informed consent was taken from the patient at the time of transplantation that explained to the patient/family the risks and benefits involved with the procedure; in addition, it was explained to the family that data is being collected anonymously for all patients undergoing transplant that will be used for HSCT outcomes research. The study was approved by the institutional review board as a retrospective chart review study with a waiver of written/verbal consent (IRB Approval No. 2221219).

Study data was collected from the institutional medical charts using the case report form, which was divided into three sections: 1) Demographic data, transplant indication, donor-type, conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, and cell dose (CD34 x 10^6/kg and TNC x 10^8), 2) Transplant-related outcomes data included engraftment data (neutrophil and platelet recovery) and chimerism data, 3) Transplant-related complications data included graft-versus-host-disease (GVHD), veno-occlusive disease (VOD), posterior reversible encephalopathy syndrome (PRES) and infectious toxicity.

Study endpoints and definitions. The primary endpoint of the study was 10-year overall survival (OS), measured from the date of stem cell infusion to the last contact, and death due to any cause was considered as an event. In contrast, events for event-free survival (EFS) were graft failure and death. Secondary endpoints of the study were stem cell dose, neutrophil recovery defined as the first of three consecutive days with a neutrophil count of $\geq 0.5\times10^9$/L, platelet recovery defined as the first of three consecutive days with platelets count of $>20\times10^9$/L, sustained without transfusion for a minimum of seven-days, chimerism assessment was done using short tandem repeats. Full donor chimerism was defined as donor content of ≥95%, and mixed donor chimerism was defined as donor content of <95% of both myeloid and lymphoid cells.[15] Graft rejection was considered in symptomatic patients who showed evidence of recurrence of disease with changes in Hb level and Hb electrophoresis results, which were further confirmed by a reduction of donor cells (lymphoid /myeloid cells). Post-transplant infectious and non-infectious complications were also measured in this study.

Pre-Transplant evaluation and clearance. All patients had a pre-transplantation evaluation, including hemoglobin electrophoresis, molecular studies, and MRI evaluations. Prior to each patient's HSCT, a multidisciplinary team meeting was conducted with a validated medical decision.

Transplant conditioning regimen. All patients were conditioned using myeloablative regimen that included Busulfan (BU) IV dose 16mg/kg divided over 4 days Day -5, - 2 and cyclophosphamide (CY) dose 200 mg /kg over 4 days Day -10, -7), after 2007 subsequent patients 88% of the patients had additional ATLG- GRAFALON (10 mg/kg/day×4 days Day -5, -2). GVHD prophylaxis consisted of a short MTX dose given on days 1, 3, and 6. Cyclosporin A (CSA) was started on day -3 and continued for 6- 12 months post-HSCT. Levetiracetam (Keppra) was administered in all patients as prophylaxis to mitigate the risk of seizures in all patients for 6-12 months. Graft monitoring was done by molecular PCR.

Statistical methods. Quality assurance measures were applied to ensure data completeness and accuracy.

Baseline clinical characteristics and demographic data were described using frequencies and percentages for categorical values, while continuous data were described as non-parametric tests. Descriptive statistics were used to report the incidence of infectious and non-infectious toxicities. Kaplan-Meier survival analysis was used to estimate the 5-year OS and EFS. The Breslow (Generalized Wilcoxon) test was utilized to test the significance of differences between the survival times between groups, and the p-value of <0.05 was considered statistically significant in this study. All data was analyzed using the IBM SPSS Statistics for Windows, version 20.0 (IBM Corporation, Armonk, N.Y., USA).

Results. In total, 129 children underwent allogeneic MRD-HSCT between January 2006 and December 2020. There were 62 males (48%) and 67 females (52%). The median age at transplantation was 9.1 years (range: 1.5 to 13.9 years). Disease phenotype, as determined by Hemoglobin electrophoresis, showed Hemoglobin SS in 123 (95%) patients and Hemoglobin Sβ in 6 (5%); confirmatory testing by molecular PCR was achieved in 109 (89%) patients. The primary transplant indication was cerebral vasculopathy in 57% (74), followed by vascular occlusive disease (VOC) in 36% (47), recurrent acute coronary syndrome (ACS) in 4% (5), and osteonecrosis/avascular necrosis (AVN) in 2% (3), respectively (Table 1). Variable compliance (60%) to hydroxyurea (HU) was observed in the cohort prior to transplantation. Regular monthly blood transfusion with iron chelation therapy was observed in 52% (66) of the patients with cerebral vasculopathy.

All donors were HLA-identical siblings in 82% (106) cases, followed by parents in 18% (23) cases. The sickle cell trait was observed at 67% (86), and the remaining demonstrated normal hemoglobin electrophoresis patterns. Bone marrow (BM) was the main source of stem cells in 95% (122), followed by peripheral blood stem cells (PBSC) in 4% (5), and BM + PBSC in 1% (2). Mean TNC and CD34 doses of 4.91 x 10^9/kg and 7.7 x 10^6/kg were observed, respectively (**Table 1**).

All patients were engrafted, with a median time to neutrophil recovery of 14 days (range, 9 to 29 days) and platelet recovery of 24 days (range, 14 to 100 days). Initial chimerism assessment on Day 100 revealed full chimerism in 70% (91) of patients and mixed chimerism in 28% (36); primary graft failure was observed in 2% (2) of patients. Among the patients who were alive at the last follow-up, 70% (85) of patients continued to maintain full chimerism, and mixed chimerism in 27% (33) and 2% (2) had secondary graft failure. Amongst patients with full to mixed chimerism, a minimum of 33% donor cell content was observed to maintain stable hemoglobin electrophoresis with no evidence of disease. Two patients with primary graft failure were symptomatic and on HU. One patient with secondary

Table 1. Patient and transplantation characteristics, n=129.

Characteristic	Number (%)
Age at transplantation, median (range) years	9.1 (1.5to 13.9) years
Follow-up, median (range) years	4.3 (0.13 to 15.6) years
Transplant indication	
Cerebral vasculpathy	74 (57%)
Vaso-occlusive crisis	47 (36%)
Recurrent acute chest syndrome	5 (4%)
Osteonecrosis	3 (2%)
Disease phenotype	
Hb SS	123 (95%)
Hb Sβ	6 (5%)
Gender	
Male	62 (48%)
Female	67 (52%)
Source of stem cell product, number (%)	
BM	122 (95%)
PBSC	5 (3%)
BM + PBSC	2 (2%)
TNC dose 10^9/Kg, median (range)	4.91 x 109 (0.03 to 129.12) /Kg
CD34 dose 10^6/Kg, median (range)	7.70 x 10^6 (0.04 to 70.20) / kg
Conditioning	
BU/CY	13 (10%)
BU/CY/ATLG	114 (88%)
Other	2 (2%)
GVHD prophylaxis	
CSA+MTX	88 (68%)
CSA	3 (2%)
CSA+MMF	9 (7%)
FK506+Steroids	11(9%)
Others	18 (14%)

graft failure did not require any support, and another patient is responding to HU.

The cumulative incidence of acute GVHD was 20% (26). Grade I-II, aGVHD was seen in 17% (22) and grade III-IV in 3% (4) patients. Skin was the major organ involved in 12% (16) of patients, the gut in 5% (6), and multiple organs in 3% (4). Chronic (c) GVHD was observed in 9% (12) patients, and 4 out of 12 patients developed extensive cGVHD with multi-organ involvement (**Table 2**).

Age at transplant and donor gender disparity were not found to be associated with the incidence of aGVHD (P=0.693 and P=0.547, respectively), although female donor to male recipient was associated with a higher incidence of aGVHD (8 of 30, 27%). However, the difference was not statistically significant (P = 0.310). Similarly, age at transplant and donor gender disparity were not associated with a higher incidence of cGVHD (P=0.273 and P=0.313, respectively). However, having a mother as a donor was associated with an increased risk for severe aGVHD and cGVHD, which was statistically significant (*P=0.001* and *P=0.025*, respectively).

Early non-infectious complications included hypertension in 65% (84), mucositis in 36% (46), encephalopathy in 27% (seizures, 16 (12 %); headache 15 (11%); PRES, 7 (5%), hemorrhagic cystitis in 12% (16), VOD in 7% (9), interstitial pneumonia 2% (2). Infectious complications included CMV re-activation in 48% (62), bacterial infections in 28% (36), viral infections in 11% (14), and fungal infections in 3% (4) (**Table 2**). Our center adopted the practice of exchange transfusion prior to transplant in 2019 (May), and this was not associated with reducing the risk of PRES (P=0.307).

At a median follow-up of 4.36 (range: 0.13 to 15.5) years, 122 (95%) of patients were alive, and 7 (5%) died. Five-year OS and EFS of the cohort were 94.3% and 91.2%, respectively. Overall and event-free survival was significantly better in patients receiving BU/CY/ATLG when compared to BU/CY (OS: 97.4%±1.5%, 3 of 114

Table 2. Transplant-related complications, n=129.

Post-transplant complications	**No. of patients (%)**
Non-Infectious	
aGVHD	26 (20%)
Skin	16 (12%)
Gut	6 (5%)
Skin + gut	3 (2%)
Gut + Liver	1 (1%)
cGVHD	12 (9%)
Skin	7 (5%)
Liver	1 (1%)
Gut	2 (2%)
Eye	1 (1%)
Lung	1 (1%)
Hypertension	84 (65%)
Mucositis	46 (36%)
Haemorrhagic cystitis	16 (12%)
Veno-occlusive disease	9 (7%)
Interstitial pneumonia	2 (2%)
Encephalopathy	36 (27%)
Infectious complications	
CMV re-activation	62 (48%)
Bacterial infection	36 (28%)
Viral infection	14 (11%)
Fungal infection	4 (3%)
Long-term complications	
Gonadal dysfunction	33 (46%)
Hypothyroidism	4 (3%)
Autoimmune disorders	3 (2%)
CNS complications	6 (5%)

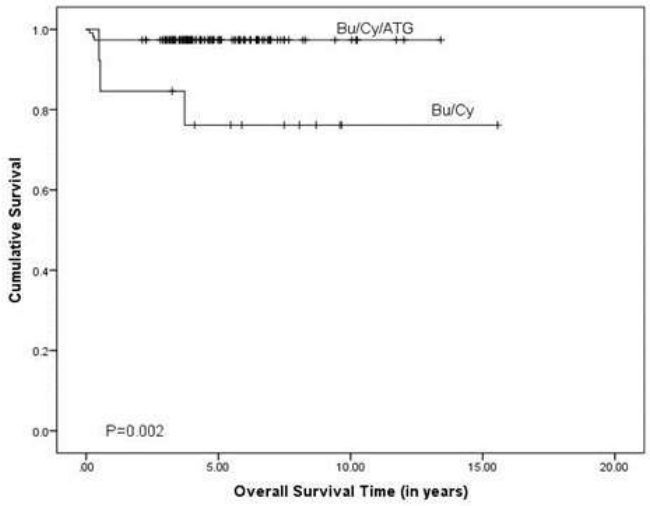

Figure 1. Overall survival by BU/Cy vs. BU/CY/ATG.

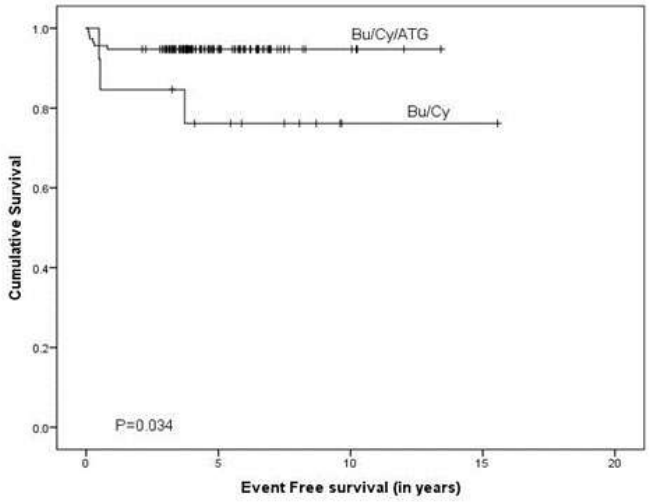

Figure 2. Event-free survival by BU/Cy vs. BU/CY/ATG.

events vs. 76.2%±12.1%, 3 of 13 events, P=0.003 and EFS: 94.7%±2.1%, 6 of 114 events vs. 76.2%±12.1%, 3 of 13 events, P=0.019), respectively (**Figure 1** and **2**).

A statistically significant difference in OS was not observed for recipient gender (female: 94.0%±2.9% vs. male: 94.5%±3.2%, P=0.664), age at HSCT (< 8 years: 97.3%±2.7% and >= 8 years: 91.8%±3.2%, P=0.075) and donor sickle cell trait (SCT) status (SCT: 93.7±2.8% and normal Hgb electrophoresis: 95.3±3.2%, P=0.823). Similarly, EFS statistically significant difference was not observed for gender (female: 91.0%±3.5% vs. male: 91.9%±3.5%, P=0.827), age at HSCT (< 8years: 92.9%±3.4% vs. >=8 years: 90.4%±3.4%, P=0.544) and donor sickle cell trait (SCT) status (SCT: 95.2±2.3% and normal Hgb electrophoresis: 100%, P=0.151%). Similarly, no significance in OS and EFS was observed when compared by disease phenotype and male patients to the female donor group (P=>0.05).

Among the seven patients who died, the cause of death was severe GVHD in two patients, refractory septic shock in two patients, pulmonary hemorrhage, and multi-organ failure in one patient each. One patient developed chronic lung disease with fibrosis four years after transplant and died.

Long-term complications. At the last follow-up, 55% (Female, 44 and Male, 27) of patients were above the age of 13 and were reviewed for long-term complications. A total of 33 (46%) patients showed long-term complications: 13 patients with ovarian failure on hormonal therapy and 8 patients with short stature needing growth hormone therapy. It was noted that patients who developed short stature and gonadal failure were transplanted at a median age of 9 (range: 8 to 13) years. Four patients were having hypothyroidism on replacement therapy. In terms of Central Nervous System (CNS) complications, four patients continued to have seizures, and two- patients had psychomotor disabilities. A post-HSCT comparison was made between patients who received exchange transfusion and those who did not, and a statistically significant difference was not observed. Three patients had autoimmune disorders (Autoimmune hemolytic anemia (AIHA), neutropenia, and arthropathy) and pulmonary restrictive disease in one patient. None of the patients developed a malignancy (**Table 2**).

Discussion. We report a cohort of 129 pediatric patients with severe SCD who had HSCT, representing the largest single-center experience from Saudi Arabia. Results from this study confirm and extend findings from similar published studies[12,16-18] with 10-year overall and event-free survival rates of 94.3% and 91.2%, respectively. HSCT is considered the standard of care treatment option in symptomatic children with SCD[13,19,20] when a fully HLA-matched related donor is available.[16,21,22] Earlier intervention has been shown to have an advantage in terms of overall and event-free survival outcomes.[16] At a median age at transplant of 9.1 years, an earlier age was associated with a survival advantage, similar to the outcomes reported by Vermylen et al.[16] We found cerebral vasculopathy (53%) was the major indication for transplantation, followed by recurrent vaso-occlusive crises (40%) when compared to the reported literature.[12,16-18]

A multicenter study reported outcomes from a retrospective review of patients post-HSCT for SCD, showing excellent outcomes by adding anti-thymocyte globulins (ATG) to busulfan and cyclophosphamide in terms of GVHD and graft rejection.[12] Moreover, a large multicenter study that included 1000 SCD recipients of HLA match sibling donors mostly received myeloablative conditioning in 87% of the patients with a 5-year OS and EFS of 92.9% and 91.4%, respectively.[2]

Transplantation conditioning in our cohort of patients consisted of myeloablative conditioning with busulfan (BU) and cyclophosphamide (CY), with or without anti-thymocyte globulin (ATG). Our findings confirm the

favorable survival outcomes with the addition of ATLG to BU/CY conditioning.[12]

Our results showed that all patients achieved engraftment, with a median time to neutrophil engraftment of 14 days and platelet recovery of 24 days. Chimerism data was routinely collected after HSCT in all patients, and sustained donor cell content was demonstrated at the last follow-up. Graft rejection was observed in 3% of the patients and was the main cause of transplant failure in our cohort. The most common post-HSCT complications observed were hypertension (65%), hemorrhagic cystitis (12%), seizures (12%), veno-occlusive disease (7%), encephalopathy (27%), and infectious complications such as CMV re-activation in 48%, bacterial infection in 28%, and other viral infections in 11% and fungal infections in 3%. These findings were comparable to those of other studies.[12,16-18] However, CNS sequelae, especially PRES, were less common in our patients, with a 5 % incidence, although it was reported to be higher (10% to 32%) in a similar study. Noteworthy, we have observed an increased risk of severe aGVHD and cGVHD when donors were the mothers.

Long-term complications were reviewed in a subset of patients aged 13 years or older. Among those patients, 46% experienced long-term complications, including ovarian failure requiring hormonal therapy, which is comparable to a published report by Dedeken et al.[24] Other complications included short stature, seizures and psychomotor disability, autoimmune disorders, and pulmonary restrictive disease. None of the patients developed a secondary malignancy post-HSCT.

Furthermore, it was noted that patients who developed short stature and gonadal failure had their transplantation at an older age of >9 years, and studies had shown that the gonads were significantly affected after myeloablative conditioning in patients who had HSCT and post-pubertal BU-based conditioning.[21,25,26] Nevertheless, our results show that pre-pubertal patients can be affected, and an earlier age of transplantation is preferable. Our findings advocate the utilization of gonadal cryopreservation to preserve fertility in eligible candidates.[27,28]

The study's findings are consistent with previous reports on the efficacy of HSCT in treating severe SCD from fully matched related donors. However, the study also highlights the importance of considering the potential long-term complications associated with HSCT, especially in patients who undergo the procedure at a younger age, which was considered the strongest predictor of EFS in fully matched HLA-identical sibling donors with more favorable outcomes.[4,5,29,30]

Reduced toxicity, myeloablative, and reduced intensity conditioning regimen studies have been reported with favorable outcomes in patients with SCD trying to avoid BU and CY complications. However, the increased frequency of mixed chimerism and the potential for rejection require further studies and a longer follow-up.[12,31-33] Therefore, prospective trials for the development of less toxic conditioning regimens and supportive care are warranted.

Conclusions. HSCT for children with sickle cell disease (SCD) from fully matched siblings offers the best outcome using myeloablative conditioning. The use of BU/CY/ATLG has proven to be a successful and effective conditioning regimen for patients with sickle cell disease. The outcome of the addition of ATLG to BU/CY was superior in terms of survival, rejection, and GVHD. This is in line with reports of studies from EBMT. However, significant toxicities were observed secondary to myeloablative regimens, in particular long-term complications, which demands further exploring the use of less toxic regimens. HSCT for pre-school-age patients is highly recommended to achieve the best outcome and reduce long-term complications.

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