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Original article

Treosulfan-Based Conditioning Regimen in Sibling and Alternative Donor Hematopoietic Stem Cell Transplantation for Children with Sickle Cell Disease

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Abstract. ***Background and objectives:*** **Lack of suitable donors and regimen related toxicity are major barriers for hematopoietic stem cell transplantation (HSCT) in patients with sickle cell disease (SCD). The aim of the study is the assessment of efficacy and toxicity of Treosulfan-based conditioning regimen for SCD also when alternative donors such as mismatched unrelated donor and haploidentical donor are employed.**

Methods: **We report our single-center experience: 11 patients with SCD received HSCT with a Treosulfan/Thiotepa/Fludarabine/Anti-thymoglobulin conditioning regimen between 2010 and 2015. The donor was a matched sibling donor (n= 7), a haploidentical parent (n= 2), a matched unrelated donor (n= 1) or a mismatched unrelated donor (n=1). The haploidentical and mismatched unrelated donor grafts were manipulated by removing TCRαβ and CD19 positive cells.**

Results: **All patients survived the procedure and achieved stable engraftment. Stable mixed chimerism was observed in 5/11 patients. Grade III-IV regimen related toxicity was limited to mucositis and no grade III-IV graft-versus-host disease (GvHD) occurred. No SCD manifestation was observed post transplant and cerebral vasculopathy improved in 3/5 evaluable patients. Organ function evaluation showed no pulmonary, cardiac or renal toxicity but gonadal failure occurred in 1/4 evaluable patients.**

Conclusion: **Our data suggest that Treosulfan is associated with low toxicity and may be employed also for unrelated and haploidentical donor HSCT.**

Keywords: Hematopoietic stem cell transplantation, Treosulfan, Sickle cell disease, Haploidentical, T-cell depletion.

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Introduction. Sickle cell disease (SCD) is the most frequent haemoglobinopathy worldwide. A point mutation in the beta-globulin gene alters the hemoglobin structure and results in chronic hemolytic anemia and increased blood viscosity. This leads to an heterogeneous phenotypic

spectrum: increased morbidity and mortality is due to a higher susceptibility to infections, intermittent vaso-occlusive events and ischemic tissue injury with progressive organ dysfunction.[1]

Hematopoietic stem cell transplantation (HSCT) is the most consolidated curative treatment.[2] When considering HSCT for SCD patients, expected SCD morbidity should be balanced against the risk of transplant related mortality and morbidity, keeping in mind that SCD is a disease with a life expectancy of over 50 years with contemporary treatment.[3]

More than 200 matched sibling donor (MSD) transplants after a myeloablative conditioning regimen based on Busulfan and Cyclophosphamide were reported. The limitations associated with this strategy are the significant regimen related toxicity and the risk of graft failure. The transplant associated mortality is around 2-8% and graft failure is observed in around 10-15% of patients.[4,5,6,7,8,9,10,11] Although better outcomes have been recently reported with the use of targeted Busulfan therapy, the use of Busulfan-based conditioning regimen is established only in the setting of MSD transplant and only few SCD patients in need of a HSCT have a matched sibling available.[12,13,14,15] The use of alternative donors such as matched unrelated donor (MUD), mismatched unrelated donor (MMUD), unrelated umbilical cord blood (UCB) and haploidentical family members is associated with higher mortality and morbidity, due to pre-existing organ dysfunction, alloimmunisation and risk of GvHD.[2,16] Moreover, suitable matched unrelated donors are difficult to find and experience is limited for umbilical cord blood or haploidentical donor HSCT.[17,18,19,20,21] In order to overcome the limitations of Busulfan-based conditioning regimen and allow the use of alternative donors, different conditioning strategies have been proposed.[22,23] Recently, Treosulfan became attractive to substitute Busulfan due to its lower toxicity and good immune suppressive and myeloablative potential.[24,25,26,27,28] This led to the use of Treosulfan in patients with pre-existent morbidity (mainly primary immune deficiency or β-thalassemia) or receiving a second transplant for malignant disorders.[25,29,26,30,31,32,33,34,35] For these reasons, since 2010, at our institution Busulfan was substituted with Treosulfan as standard conditioning regimen for SCD patients.

We present our single-centre experience of HSCT performed for SCD patients employing Treosulfan-based conditioning regimen also in haploidentical and MUD HSCT .

Methods. From April 2010 to December 2015, all SCD patients undergoing HSCT at the Pediatric Hematology-Oncology Unit of the University of Padova received a Treosulfan-based conditioning regimen and are described in this retrospective cohort study. Eligibility for HSCT was determined on the basis of published guidelines and criteria included cerebral vasculopathy, recurrent episodes of acute chest syndrome (ACS) or vaso-occlusive crises despite hydroxycarbamide treatment.[36] Donors were chosen on the basis of availability and considered in the following order: MSD, MUD, Haploidentical donor and MMUD. The preferred stem cell source was bone marrow or umbilical stem cells for MSD, bone marrow for MUD and T-depleted peripheral blood stem cells for haploidentical donors and MMUD. The use of a combination of umbilical cord blood and bone marrow was employed in MSD HSCT if the cellularity of the umbilical cord graft was low.[20] Before T-cell depleted or MUD HSCT, autologous bone marrow stem cells were harvested and cryopreserved in order to be re-infused in case of graft rejection, due to the higher risk of this event after T-cell depletion.[37] All patients received either red cell exchange transfusion or simple transfusion the day before the start of conditioning regimen in order to obtain a proportion of HbS < 30% and an Hb level ≥ 100g/L.

The haploidentical donors underwent PBSC collection after mobilization with subcutaneous Filgrastim 10 µg/Kg twice daily from day -5 to day -1 and once on the day of collection. PBSC were collected using a COBE® Spectra Apheresis System (BCT Terumo, Lakewood, CO). T-cell depletion was performed by removing TCRαβ positive and CD19 positive cells through immuno-magnetic selection (CliniMACS; Miltenyi Biotec, Bergisch Gladbach, Germany).

All patients received Thiotepa (8 mg/kg or 10 mg/kg in 2 doses on day -7), Treosulfan (14 g/m2/day for 3 days from day -6 to day -4) and Fludarabine (40 mg/m^2/day for 4 days from day -6 to day-3).[29] Fresenius® anti-thymocyte globulins (ATG) at the dose of 20 mg/kg/day were administered for 3 days in MSD and MUD transplants and 5 mg/kg/day for 4 days in T-

depleted transplants. Patient 8 and patient 11 received Rituximab (200 mg/m^2) at day -1 to reduce the risk of EBV reactivation and GvHD after HSCT.[38] Graft-vs-Host Disease (GvHD) prophylaxis for T-replete transplants consisted in short term Methotrexate (10mg/kg for 4 doses), Cyclosporine 1 mg/kg/day on days -7 to -2, and Cyclosporine aiming at a pre-dose level of 100-200 µg/L for 6 months post HSCT. No GvHD prophylaxis was given for T-deplete transplants. The supportive measures, diagnosis and treatment strategy for acute GvHD employed at our institution were recently described.[39]

Engraftment and chimerism were serially tracked after HSCT. Samples were obtained every 2-3 weeks up to day +100 and monthly thereafter up to 18 months post-transplant in patient with complete donor chimerism. Follow up was longer for patients with mixed chimerism. Chimerism analysis was performed by PCR testing for informative short tandem repeats. Adverse events were graded according to common terminology criteria for adverse events (CTCAE) v4. Neutrophil and platelet recovery were defined as a neutrophil count $\geq 0.5\times10^9$/L for 3 consecutive days and as a platelet count $\geq 50\times10^9$/L independently of platelet transfusions for 7 consecutive days.

Organ function was assessed pre-transplant and every year post-transplant by pulmonary function testing, echocardiography, growth and puberty evaluation and hormonal dosage (estradiol/testosterone, FSH, LH, T4 and TSH levels). Transcranial Doppler Ultrasonography (TCD) was performed for all patients prior to the initiation of chronic transfusion and pre-HSCT; data were evaluated according to the criteria defined by the STOP trial.[40] Brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were performed pre-transplant, and repeated one year post transplant and every two years thereafter if lesions were detected. MRI and MRA were evaluated according to a standardized scoring system.[41,42] Cerebral vasculopathy was defined as abnormal Transcranial Doppler velocity associated with cerebral artery stenosis. Immune reconstitution was evaluated by total lymphocyte count, CD4+ cell count and immunoglobulin dosage. Data were recorded at day +30, +90, +180 and +365.

Results. *Patients:* Eleven consecutive children affected by SCD (7 females, 4 males) were transplanted at the Pediatric Hematology-Oncology Unit of the University of Padova. The origin of patients was African (n = 6), Caucasian (n = 4) or Caribbean (n = 1). Patient and transplant characteristics are summarized in **table 1**. Seven patients were diagnosed at birth due to family history, the remaining at their first disease manifestation, between 7 month and 5 years of age. The Hb genotype was HbSS (n = 10) or HbSβ0 (n = 1, P7). Before transplant patients were treated with chronic transfusion (n = 7), monthly red cell exchange transfusion (n = 2) and/or hydroxycarbamide (n = 5). Patients were eligible for HSCT due to cerebral vasculopathy (n=7), recurrent episodes of acute chest syndrome (ACS) or vaso-occlusive crises despite hydroxycarbamide treatment (n = 4). Patient 7 suffered also from recurrent splenic sequestration.[36] The median age at HSCT was 6.5 years (range: 4 – 16.3 years). At the time of HSCT, only two patients had significant comorbidities: relapsing autoimmune hepatitis (P8) and an association of Chiari I malformation and syringomyelia (P11). Donor source was an HbS/A MSD (n = 5), an HbA/A MSD (n = 2), a haploidentical HbS/A parent (mother, n = 1 and father, n = 1), HbA/A MUD (n = 1) or HbA/A MMUD (n=1, 8/12 HLA loci donor/recipient matching). Stem cell source was bone marrow (n=6, median total nucleated cells, TNC = 4,9 x 10^8/kg), combined bone marrow and umbilical cord blood (n=2, median TNC for bone marrow = 2,67 x 10^8/kg; median TNC for cord blood = 2,44 x 10^7/kg) or peripheral blood stem cells (PBSC) (n=3, two haploidentical grafts and one MUD graft, median CD34+ cells = 14,3 x 10^6/kg). One apheresis was sufficient to reach the target dose of CD34+cell (10 x 10^6/kg recipient) in both haploidentical donors. Both donors complained only grade I-II myalgia and fatigue.

Transplant-related outcomes: All patients achieved neutrophil and platelets engraftment at a median of 20 days (range: 15-34 days) and 22 days (range: 12-31 days) from HSC infusion, respectively. No patient experienced primary graft failure. All patients experienced Grade III anemia, grade IV thrombocytopenia and grade IV neutropenia. Grade III-IV non hematological toxicity occurred in 2 patients and consisted in grade IV stomatitis in one patient and acute

Table 1. Patient characteristics and outcomes. Abbreviations: ATG = antithymoglobulin; FLU = fludarabine in mg/m^2; RITUX = rituximab; TREO = Treosulfan in g/m^2; TT = Thiotepa in mg/kg.

n	sex	age at transplant (years)	HSCT indication	Conditioning	Treatment pre HSCT	Donor	Donor genotype	Stem cell source	Grade III-IV non hematological complication	GvHD	Chimerism	HbS proportion	Follow up (years)
1	M	3.9	Recurrent ACS/VOC	TREO42 TT8 FLU160 ATG	Hydroxycarbamide	MSD	HbAA	BM			100% donor	0	6.5
2	F	9.1	Cerebrovascular disease	TREO42 TT8 FLU160 ATG	Chronic transfusion	MSD	HbSA	BM			41% donor	40.4	5.6
3	F	6.5	Cerebrovascular disease	TREO42 TT8 FLU160 ATG	Chronic transfusion	MSD	HbSA	BM			53% donor	40.3	5.6
4	F	6.5	Cerebrovascular disease	TREO42 TT8 FLU160 ATG	Chronic transfusion + hydroxycarbamide	MSD	HbSA	BM + UCB			100% donor	38.8	4.3
5	F	13.8	Cerebrovascular disease	TREO42 TT8 FLU160 ATG	Monthly red cell exchange transfusion	Haploidentical father	HbSA	TCRαβ/CD19 depleted PBSC			88% donor	40.6	3.9
6	M	4.1	Recurrent ACS/VOC	TREO42 TT8 FLU160 ATG	Hydroxycarbamide	MSD	HbAA	BM + UCB			100% donor	0	2.3
7	M	4.3	Recurrent ACS/VOC	TREO42 TT8 FLU160 ATG	Chronic transfusion	MSD	HbAβ^0	BM	Acute disseminated encephalomyelitis		100% donor	0	2.2
8	F	16.3	Cerebrovascular disease	TREO42 TT10 FLU160 ATG RITUX	Monthly red cell exchange transfusion	Haploidentical mother	HbSA	TCRαβ/CD19 depleted PBSC	Grade IV mucositis	Grade II gastrointesinal aGvHD	100% donor	39.8	1.5
9	F	10.5	Recurrent ACS/VOC	TREO42 TT8 FLU160 ATG	Chronic transfusion + hydroxycarbamide	MUD	HbAA	BM		Grade II gastrointesinal aGvHD	100% donor	0	1.1
10	F	4.1	Cerebrovascular disease	TREO42 TT8 FLU160 ATG	Chronic transfusion + hydroxycarbamide	MSD	HbSA	BM			37% donor	41,4	1
11	M	6.5	Cerebrovascular disease	TREO42 TT10 FLU160 ATG RITUX	Chronic transfusion	MMUD	HbAA	TCRαβ/CD19 depleted PBSC	EBV reactivation	Grade II gastrointesinal aGvHD	61% donor	0	0.8

disseminated encephalomyelitis in one patient. All toxicity resolved completely. Grade I-II gastrointestinal acute GvHD was diagnosed in 3 patients (haploidentical transplant, n = 1; MUD transplant, n = 1, MMUD transplant, n=1). These patients were successfully treated with calcineurin inhibitors (n = 3), steroid (n = 1) and extracorporeal photochemotherapy (n = 3) as per institutional protocol.[39] No grade III-IV acute GvHD or chronic GvHD were observed. No secondary graft failure was observed.

Full donor chimerism was demonstrated in 6/11 patients and stable mixed chimerism was observed in 5/11 patients (45%). Donor hematopoiesis ranged from 37% to 90%, but did not affect the HbS proportion: HbS was absent after a transplant from HbA/A MUD (n=1) or compatible with HbS carrier (median 40.5%, range 40.3-41,4%) in patients transplanted from a HbS/A MSD (n=4).

The lymphocyte count reached normal values for age at day +180 in all patients except P11. Median time to reach a CD3+CD4+ cell count higher than 400/µL was 148 days for T-replete grafts (range 57-203 days) and 245 days (range 237-253 days) for T-deplete grafts. Immunoglobulin replacement was necessary only in one patient (P11) who experienced EBV reactivation and received one dose of rituximab. Despite serial monitoring no viral reactivation was documented in any other patient.

Organ damage and SCD-related outcomes: The median follow-up was 2.35 years (range: 0.8-6.5 years). All patients are alive and well. No episode compatible with acute chest syndrome, stroke or other sickle cell disease manifestation occurred.

No patient experienced renal or hepatic dysfunction following transplantation.

TCD was normal for patients without cerebral vasculopathy. Data for patients with cerebral vasculopathy are reported in **Table 2**. Brain MRI and MRA data are available for 10 patients. Three patients had normal pre-transplant brain imaging. Two patients had cerebral vasculopathy before transplantation, but no post-transplant imaging. Five patients had alteration on the pre transplant MRI and evaluable data on follow-up (**Table 3**). Resolution or improvement of the vascular stenosis was detected in 3/5 patients. Last post-transplant evaluation was performed after a median of 1315 days (range: 268-1417).

Pre-transplant organ function was within normal limits for all patients. Post-transplant lung function evaluation was performed in 7 patients (P1-3 and P5-8) and was normal for all of them after a median of 1104 days from transplant (range 369-2304 days). Hormonal function was evaluated in 7 patients (P1-3 and P5-8) after a median of 804 days from transplant (range 205-1518 days). Height, weight and thyroid function were normal for all explored patients. Three patients were pre-pubertal at last assessment. Puberty was evaluable in 4 patients (P1, P2, P5 and P8: 1 male and 3 females): 3 had normal pubertal development and 1 patient (P8) experienced secondary gonadal failure. Follow-up echocardiography (data available for 7 patients) and eye examination (data available for 5 patients) were normal.

Table 2. Brain imaging before and after HSCT for patients with cerebral vasculopathy. WHM: white matter hyperintensity; n/a: not available

	Magnetic resonance angiography		**White matter changes**	
patient	**Before HSCT**	**After HSCT**	**Before HSCT**	**After HSCT**
1	Moderate stenosis	Significant reduction of stenosis	Mild WHM in the hippocampus and temporal cortex	normal
2	Severe stenosis	Stable	WHM in the periventricular region	gliosis of affected region
3	Bilateral severe stenosis	Resolution of stenosis	WHM in the semioval centers	gliosis of affected region
4	Bilateral mild stenosis	n/a	Absent	n/a
5	Bilateral moderate stenosis	Significant reduction of stenosis	Minimal WHM in the left subcortical temporal region	Stable
8	Bilateral moderate stenosis	n/a	Absent	n/a
10	Bilateral severe stenosis	stable	Absent	Absent
11	Bilateral severe stenosis	n/a	Bilateral WHM in the semioval centers	n/a

Table 3. Transcranial Doppler Ultrasonography for patients with cerebral vasculopathy. Results were categorized as normal, conditional or abnormal according to the STOP trail criteria.[40] n/a: not available.

Patient	Before initiation of chronic transfusion	Before HSCT	After HSCT
1	The patient did not receive chronic transfusion	Abnormal	Normal
2	Abnormal	Normal	n/a
3	Abnormal	Normal	n/a
4	n/a	Normal	n/a
5	Abnormal	Normal	n/a
8	Abnormal	Normal	n/a
10	Abnormal	Conditional	n/a
11	Abnormal	Normal	n/a

Discussion: We report a retrospective case series of 11 SCD patients who received HSCT after a Treosulfan-based conditioning regimen. Sustained engraftment was observed in all patients. Stable mixed chimerism was detected in a significant proportion of patients (45%), did not change after the discontinuation of immunosuppressive treatment and resulted in a cure of SCD for all patients. Previous experiences have demonstrated that full donor chimerism is not needed to cure SCD due to the survival advantage for donor red cell in peripheral blood: pulmonary, gonadal and central nervous system status can be significantly ameliorated also when stable mixed chimerism is obtained.[43,44,45,46,47] Indeed, no clinical manifestation correlated with SCD occurred after HSCT in our cohort. Since cerebral vasculopathy was the cause for transplant in 7 patients, we focused our attention on the evaluation of TCD and brain MRI and MRA. Chronic transfusions resulted in normalization of pre-transplant TCD in all patients receiving this treatment. However, cerebral artery stenosis persisted on pre-HSCT MRA for all patients. Post-HSCT MRA data, evaluated with a standardized scoring system, were available for 5 patients and showed either a stabilization of the stenosis or amelioration. Although improvement in vascular stenosis has been previously described in patients treated with chronic transfusion, hydroxycarbamide or HSCT, the rate of improving patients in our cohort compares favorably with previous reports.[37,48,49,50,51] These satisfactory outcomes could be possibly due to the screening program for cerebral vasculopathy performed at our center that led to the fact that all patients were transplanted before any clinically evident stroke.[42]

The safety profile of Treosulfan conditioning regimen was excellent and incidence of adverse events was comparable to previous reports: no transplant-related mortality was observed and grade III-IV non hematological toxicity was limited to mucositis which resolved completely without sequelae.[25,26] The neurological event in our case series cannot be attributed with certainty to the Treosulfan conditioning. This toxicity profile is similar to results obtained in adult patients transplanted after a non-myeloablative conditioning.[52,53,54,55] Grade I-II acute GvHD was observed in 3/11 patients in our cohort (27%) with no grade III-IV acute GvHD or chronic GvHD. The GvHD cases were all among patients receiving an alternative donor transplant, no GvHD was observed among the 7 patients receiving a MSD HSCT and all the patients experiencing GvHD responded rapidly to first line treatment. To the best of our knowledge, data regarding organ damage related to HSCT has not been previously reported for SCD patients undergoing HSCT after a Treosulfan-based conditioning regimen. In our cohort, the decline in pulmonary and renal function observed after Busulfan-based conditioning regimen was not present and growth, thyroid and cardiac function were preserved after HSCT.[37,43] Although 3 patients had normal pubertal development, 1 patient that had reached puberty before HSCT and for whom pre-transplant ovarian cryopreservation was performed, experienced secondary gonadal failure. This event highlights the opportunity to attentively evaluate possible long term effects on reproductive health and propose mitigating strategies before HSCT.[56]

Current knowledge about outcomes of Treosulfan based conditioning regimen in SCD is limited to a single-center experience reporting 15 patients who received a MSD or MUD HSCT.[26] We have nearly doubled the number of reported patients and we have described the use of Treosulfan-based conditioning regimen for MMUD or haploidentical donor HSCT, which are considered investigational approaches in SCD.[16,37,57] To mitigate the risk of rejection and GvHD, TCRαβ+ and CD19+ cell depletion was performed.[38] In the MMUD setting, this approach was reported as safe and efficacious for patients with acute myeloid leukemia or Hurler syndrome but no SCD patient has been described yet.[58,59] If further investigations will confirm its feasibility and efficacy, haploidentical or MMUD HSCT in SCD may open the possibility of cure for many

patients without a MSD or MUD donor available.[17,18,19] When employing alternative donors, a higher risk of GvHD and delayed immune reconstitution should be taken into account; however, in our experience, these drawbacks can be managed by supportive therapy and are outweighed by the satisfactory outcomes. Although PBSC mobilization with G-CSF in HbS heterozygous parents is often perceived as risky, no significant adverse events were reported and, in our experience, both the haploidentical donors underwent PBSC mobilization and collection safely.[60,61]

The main limitation of our study is its retrospective nature and the report of a single center experience; sample size was also limited and warrants further confirmation. Moreover, in order to perform the TCRαβ and CD19 depletion, a facility with experience in stem cell manipulation is needed.

Conclusions. our data show that HSCT after Treosulfan based conditioning regimen for SCD patients is effective and associated with low toxicity. End organ damage may be halted or even ameliorated as shown by the regression of cerebral vessel stenosis and white matter changes. This strategy is suitable also for alternative donor transplants and, if our data are confirmed in larger cohorts, could pave the way for expanding the access to HSCT also to SCD patients lacking a matched sibling or matched unrelated donor.

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References:

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010 Dec;376(9757):2018-31. https://doi.org/10.1016/S0140-6736(10)61029-X
2. Talano J-A, Cairo MS. Smoothing the crescent curve: sickle cell disease. Hematology. 2014 Dec 1;2014(1):468-74. https://doi.org/10.1182/asheducation-2014.1.468 PMid:25696896
3. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood. 2010 Apr 29;115(17):3447-52. https://doi.org/10.1182/blood-2009-07-233700 PMid:20194891 PMCid:PMC2867259
4. Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Mentzer WC, Davies SC, Ohene-Frempong K, Bernaudin F, Matthews DC, Storb R, Sullivan KM. Bone Marrow Transplantation for Sickle Cell Disease. N Engl J Med. 1996 Aug 8;335(6):369-76. https://doi.org/10.1056/NEJM199608083350601 PMid:8663884
5. Vermylen C, Cornu G, Ferster A, Brichard B, Ninane J, Ferrant A, Zenebergh A, Maes P, Dhooge C, Benoit Y, Beguin Y, Dresse MF, Sariban E. Haematopoietic stem cell transplantation for sickle cell anaemia: the first 50 patients transplanted in Belgium. Bone Marrow Transplant. 1998 Jul;22(1):1-6. https://doi.org/10.1038/sj.bmt.1701291 PMid:9678788
6. Walters MC, Storb R, Patience M, Leisenring W, Taylor T, Sanders JE, Buchanan GE, Rogers ZR, Dinndorf P, Davies SC, Roberts IA, Dickerhoff R, Yeager AM, Hsu L, Kurtzberg J, Ohene-Frempong K, Bunin N, Bernaudin F, Wong WY, Scott JP, Margolis D, Vichinsky E, Wall DA, Wayne AS, Pegelow C, Redding-Lallinger R, Wiley J, Klemperer M, Mentzer WC, Smith FO, Sullivan KM. Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. Blood. 2000 Mar 15;95(6):1918-24. PMid:10706855
7. Bernaudin F, Socie G, Kuentz M, Chevret S, Duval M, Bertrand Y, Vannier J-P, Yakouben K, Thuret I, Bordigoni P, Fischer A, Lutz P, Stephan J-L, Dhedin N, Plouvier E, Margueritte G, Bories D, Verlhac S, Esperou H, Coic L, Vernant J-P, Gluckman E. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. Blood. 2007 Oct 1;110(7):2749-56. https://doi.org/10.1182/blood-2007-03-079665 PMid:17606762
8. Panepinto JA, Walters MC, Carreras J, Marsh J, Bredeson CN, Gale RP, Hale GA, Horan J, Hows JM, Klein JP, Pasquini R, Roberts I, Sullivan K, Eapen M, Ferster A. Matched-related donor transplantation for sickle cell disease: Report from the Center for International Blood and Transplant Research. Br J Haematol. 2007;137(5):479-85. https://doi.org/10.1111/j.1365-2141.2007.06592.x PMid:17459050
9. McPherson ME, Hutcherson D, Olson E, Haight A, Horan J, Chiang K-Y. Safety and efficacy of targeted busulfan therapy in children undergoing myeloablative matched sibling donor BMT for sickle cell disease. Bone Marrow Transplant. 2011 Jan 22;46(1):27-33. https://doi.org/10.1038/bmt.2010.60 PMid:20305698
10. Dedeken L, Lê PQ, Azzi N, Brachet C, Heijmans C, Huybrechts S, Devalck C, Rozen L, Ngalula M, Ferster A. Haematopoietic stem cell transplantation for severe sickle cell disease in childhood: a single centre experience of 50 patients. Br J Haematol. 2014 May;165(3):402-8. https://doi.org/10.1111/bjh.12737 PMid:24433465
11. Locatelli F, Pagliara D. Allogeneic hematopoietic stem cell transplantation in children with sickle cell disease. Pediatr Blood Cancer. 2012 Aug;59(2):372-6. https://doi.org/10.1002/pbc.24177 PMid:22544533
12. Walters MC, Patience M, Leisenring W, Eckman JR, Buchanan GR, Rogers ZR, Olivieri NE, Vichinsky E, Davies SC, Mentzer WC, Powars D, Scott JP, Bernaudin F, Ohene-Frempong K, Darbyshire PJ, Wayne A, Roberts IA, Dinndorf P, Brandalise S, Sanders JE, Matthews DC, Appelbaum FR, Storb R, Sullivan KM. Barriers to bone marrow transplantation for sickle cell anemia. Biol Blood Marrow Transplant. 1996 May;2(2):100-4. PMid:9118298
13. Gaziev J, Isgrò A, Mozzi AF, Petain A, Nguyen L, Ialongo C, Dinallo V, Sodani P, Marziali M, Andreani M, Testi M, Paciaroni K, Gallucci C, De Angelis G, Alfieri C, Ribersani M, Lucarelli G. New insights into the pharmacokinetics of intravenous busulfan in children with sickle cell anemia undergoing bone marrow transplantation. Pediatr Blood Cancer. 2015 Apr;62(4):680-6. https://doi.org/10.1002/pbc.25376 PMid:25557687
14. Maheshwari S, Kassim A, Yeh RF, Domm J, Calder C, Evans M, Manes B, Bruce K, Brown V, Ho R, Frangoul H, Yang E. Targeted Busulfan therapy with a steady-state concentration of 600-700 ng/mL in patients with sickle cell disease receiving HLA-identical sibling bone marrow transplant. Bone Marrow Transplant. 2014;49(3):366-9. https://doi.org/10.1038/bmt.2013.188

PMid:24317124
15. Lucarelli G, Isgrò A, Sodani P, Marziali M, Gaziev J, Paciaroni K, Gallucci C, Cardarelli L, Ribersani M, Alfieri C, De Angelis G, Armiento D, Andreani M, Testi M, Amato A, Akinyanju OO, Wakama TT. Hematopoietic SCT for the Black African and non-Black African variants of sickle cell anemia. Bone Marrow Transplant. 2014;49(11):1376-81. https://doi.org/10.1038/bmt.2014.167 PMid:25068420
16. Gluckman E. Allogeneic transplantation strategies including haploidentical transplantation in sickle cell disease. Hematology. 2013 Dec 1;2013(1):370-6. https://doi.org/10.1182/asheducation-2013.1.370 PMid:24319206
17. Krishnamurti L, Abel S, Maiers M, Flesch S. Availability of unrelated donors for hematopoietic stem cell transplantation for hemoglobinopathies. Bone Marrow Transplant. 2003 Apr;31(7):547-50. https://doi.org/10.1038/sj.bmt.1703887 PMid:12692619
18. Justus D, Perez-Albuerne E, Dioguardi J, Jacobsohn D, Abraham A. Allogeneic donor availability for hematopoietic stem cell transplantation in children with sickle cell disease. Pediatr Blood Cancer. 2015 Jul;62(7):1285-7. https://doi.org/10.1002/pbc.25439 PMid:25663074
19. Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, Hartzman R, Rizzo JD, Horowitz M, Confer D, Maiers M. HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry. N Engl J Med. 2014 Jul 24;371(4):339-48. https://doi.org/10.1056/NEJMsa1311707 PMid:25054717
20. Ruggeri A, Eapen M, Scaravadou A, Cairo MS, Bhatia M, Kurtzberg J, Wingard JR, Fasth A, Lo Nigro L, Ayas M, Purtill D, Boudjedir K, Chaves W, Walters MC, Wagner J, Gluckman E, Rocha V. Umbilical Cord Blood Transplantation for Children with Thalassemia and Sickle Cell Disease. Biol Blood Marrow Transplant. 2011 Sep;17(9):1375-82. https://doi.org/10.1016/j.bbmt.2011.01.012 PMid:21277376 PMCid:PMC3395002
21. Locatelli F, Kabbara N, Ruggeri A, Ghavamzadeh A, Roberts I, Li CK, Bernaudin F, Vermylen C, Dalle J-H, Stein J, Wynn R, Cordonnier C, Pinto F, Angelucci E, Socie G, Gluckman E, Walters MC, Rocha V. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood. 2013 Aug 8;122(6):1072-8. https://doi.org/10.1182/blood-2013-03-489112 PMid:23692854
22. King AA, Kamani N, Bunin N, Sahdev I, Brochstein J, Hayashi RJ, Grimley M, Abraham A, Dioguardi J, Wah Chan K, Douglas D, Adams R, Andreansky M, Anderson E, Gilman A, Chaudhury S, Yu L, Dalal J, Hale G, Cuvelier G, Jain A, Krajewski J, Gillio A, Kasow KA, Delgado D, Hanson E, Murray L, Shenoy S. Successful matched sibling donor marrow transplantation following reduced intensity conditioning in children with hemoglobinopathies. Am J Hematol. 2015 Dec;90(12):1093-8. https://doi.org/10.1002/ajh.24183 PMid:26348869
23. Matthes-Martin S, Lawitschka A, Fritsch G, Lion T, Grimm B, Breuer S, Boztug H, Karlhuber S, Holter W, Peters C, Minkov M. Stem cell transplantation after reduced-intensity conditioning for sickle cell disease. Eur J Haematol. 2013 Apr;90(4):308-12. https://doi.org/10.1111/ejh.12082 PMid:23369103
24. Burroughs LM, Nemecek ER, Torgerson TR, Storer BE, Talano J-A, Domm J, Giller RH, Shimamura A, Delaney C, Skoda-Smith S, Thakar MS, Baker KS, Rawlings DJ, Englund J a., Flowers MED, Deeg HJ, Storb R, Woolfrey AE. Treosulfan-Based Conditioning and Hematopoietic Cell Transplantation for Nonmalignant Diseases: A Prospective Multi-Center Trial. Biol Blood Marrow Transplant. 2014 Sep; https://doi.org/10.1016/j.bbmt.2014.08.020 PMid:25196857 PMCid:PMC4324724
25. Slatter MA, Boztug H, Pötschger U, Sykora K-W, Lankester A, Yaniv I, Sedlacek P, Glogova E, Veys P, Gennery AR, Peters C. Treosulfan-based conditioning regimens for allogeneic haematopoietic stem cell transplantation in children with non-malignant diseases. Bone Marrow Transplant. 2015 Dec 10;50(12):1536-41. https://doi.org/10.1038/bmt.2015.171 PMid:26259076
26. Strocchio L, Zecca M, Comoli P, Mina T, Giorgiani G, Giraldi E, Vinti L, Merli P, Regazzi M, Locatelli F. Treosulfan-based conditioning regimen for allogeneic haematopoietic stem cell transplantation in children with sickle cell disease. Br J Haematol. 2015 Jun;169(5):726-36. https://doi.org/10.1111/bjh.13352 PMid:25818248
27. Feit PW, Rastrup-Andersen N, Matagne R. Studies on epoxide formation from (2S,3S)-threitol 1,4-bismethanesulfonate. The preparation and biological activity of (2S,3S)-1,2-epoxy-3,4-butanediol 4-methanesulfonate. J Med Chem. 1970 Nov;13(6):1173-5. https://doi.org/10.1021/jm00300a034 PMid:5479859
28. Sjöö F, Hassan Z, Abedi-Valugerdi M, Griskevicius L, Nilsson C, Remberger M, Aschan J, Concha H, Gaughan U, Hassan M. Myeloablative and immunosuppressive properties of treosulfan in mice. Exp Hematol. 2006 Jan;34(1):115-21. https://doi.org/10.1016/j.exphem.2005.09.015 PMid:16413398
29. Bernardo ME, Piras E, Vacca A, Giorgiani G, Zecca M, Bertaina A, Pagliara D, Contoli B, Pinto RM, Caocci G, Mastronuzzi A, La Nasa G, Locatelli F. Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan. Blood. 2012 Jul 12;120(2):473-6. https://doi.org/10.1182/blood-2012-04-423822 PMid:22645178
30. Slatter MA, Rao K, Amrolia P, Flood T, Abinun M, Hambleton S, Nademi Z, Goulden N, Davies G, Qasim W, Gaspar HB, Cant A, Gennery AR, Veys P. Treosulfan-based conditioning regimens for hematopoietic stem cell transplantation in children with primary immunodeficiency: United Kingdom experience. Blood. 2011 Apr 21;117(16):4367-75. https://doi.org/10.1182/blood-2010-10-312082 PMid:21325599
31. Beier R, Schulz A, Hönig M, Eyrich M, Schlegel P-G, Holter W, Stachel KD, Ehlert K, Greil J, Nürnberger W, Wößmann W, Bader P, Urban C, Müller I, Suttorp M, Sauer M, Gruhn B, Meisel R, Zimmermann M, Sykora K-W. Long-term follow-up of children conditioned with Treosulfan: German and Austrian experience. Bone Marrow Transplant. 2013 Apr 22;48(4):491-501. https://doi.org/10.1038/bmt.2012.188 PMid:23085832
32. Lehmberg K, Albert MH, Beier R, Beutel K, Gruhn B, Kroger N, Meisel R, Schulz A, Stachel D, Woessmann W, Janka G, Muller I. Treosulfan-based conditioning regimen for children and adolescents with hemophagocytic lymphohistiocytosis. Haematologica. 2014 Jan 1;99(1):180-4. https://doi.org/10.3324/haematol.2013.094730 PMid:24162790 PMCid:PMC4007927
33. Dinur-Schejter Y, Krauss AC, Erlich O, Gorelik N, Yahel A, Porat I, Weintraub M, Stein J, Zaidman I, Stepensky P. Bone marrow transplantation for non-malignant diseases using treosulfan-based conditioning. Pediatr Blood Cancer. 2015 Oct;62(2):299-304. PMid:25284797
34. Boztug H, Zecca M, Sykora K-W, Veys P, Lankester A, Slatter M, Skinner R, Wachowiak J, Pötschger U, Glogova E, Peters C. Treosulfan-based conditioning regimens for allogeneic HSCT in children with acute lymphoblastic leukaemia. Ann Hematol. 2015 Feb 19;94(2):297-306. https://doi.org/10.1007/s00277-014-2196-8 PMid:25231927
35. Morillo-Gutierrez B, Beier R, Rao K, Burroughs L, Schulz A, Ewins A-M, Gibson B, Sedlacek P, Krol L, Strahm B, Zaidman I, Kalwak K, Talano J-A, Woolfrey A, Fraser C, Meyts I, Muller I, Wachowiak J, Bernardo ME, Veys P, Sykora K-W, Gennery AR, Slatter M. Treosulfan based conditioning for allogeneic HSCT in children with chronic granulomatous disease: a multicentre experience. Blood. 2016 May 23; https://doi.org/10.1182/blood-2016-03-704015 PMid:27216217
36. Angelucci E, Matthes-Martin S, Baronciani D, Bernaudin F, Bonanomi S, Cappellini MD, Dalle J-H, Di Bartolomeo P, de Heredia CD, Dickerhoff R, Giardini C, Gluckman E, Hussein AA, Kamani N, Minkov M, Locatelli F, Rocha V, Sedlacek P, Smiers F, Thuret I, Yaniv I, Cavazzana M, Peters C. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica. 2014 May 1;99(5):811-20. https://doi.org/10.3324/haematol.2013.099747 PMid:24790059 PMCid:PMC4008115
37. Dallas MH, Triplett B, Shook DR, Hartford C, Srinivasan A, Laver J, Ware R, Leung W. Long-Term Outcome and Evaluation of Organ Function in Pediatric Patients Undergoing Haploidentical and Matched Related Hematopoietic Cell Transplantation for Sickle Cell Disease. Biol Blood Marrow Transplant. 2013 May;19(5):820-30. https://doi.org/10.1016/j.bbmt.2013.02.010 PMid:23416852 PMCid:PMC4712646
38. Bertaina A, Merli P, Rutella S, Pagliara D, Bernardo ME, Masetti R, Pende D, Falco M, Handgretinger R, Moretta F, Lucarelli B, Brescia LP, Li Pira G, Testi M, Cancrini C, Kabbara N, Carsetti R,

Finocchi A, Moretta A, Moretta L, Locatelli F. HLA-haploidentical stem cell transplantation after removal of aß+ T and B cells in children with nonmalignant disorders. Blood. 2014 Jul 31;124(5):822-6. https://doi.org/10.1182/blood-2014-03-563817 PMid:24869942
39. Calore E, Marson P, Pillon M, Tumino M, Tison T, Mainardi C, De Silvestro G, Rossin S, Franceschetto G, Carraro E, Pescarin M, Varotto S, Destro R, Gazzola MV, Basso G, Messina C. Treatment of Acute Gvhd in Childhood with Extracorporeal Photochemotherapy/Phofotopheresis: the Padova Experience. Biol Blood Marrow Transplant. 2015;1-10.
40. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, Brambilla D. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998 Jul 2;339(1):5-11. https://doi.org/10.1056/NEJM199807023390102 PMid:9647873
41. Montanaro M, Colombatti R, Pugliese M, Migliozzi C, Zani F, Guerzoni ME, Manoli S, Manara R, Meneghetti G, Rampazzo P, Cavalleri F, Giordan M, Paolucci P, Basso G, Palazzi G, Sainati L. Intellectual function evaluation of first generation immigrant children with sickle cell disease: the role of language and sociodemographic factors. Ital J Pediatr. 2013 Jun 4;39:36. https://doi.org/10.1186/1824-7288-39-36 PMid:23735165 PMCid:PMC3704731
42. Manara R, Talenti G, Rampazzo P, Ermani M, Montanaro M, Baracchini C, Teso S, Basso G, Sainati L, Colombatti R. Longitudinal evaluation of cerebral white matter hyperintensities lesion volume in children with sickle cell disease. Br J Haematol. 2016 Mar 27;i.
43. Walters MC, Hardy K, Edwards S, Adamkiewicz T, Barkovich J, Bernaudin F, Buchanan GR, Bunin N, Dickerhoff R, Giller R, Haut PR, Horan J, Hsu LL, Kamani N, Levine JE, Margolis D, Ohene-Frempong K, Patience M, Redding-Lallinger R, Roberts IAG, Rogers ZR, Sanders JE, Scott JP, Sullivan KM. Pulmonary, Gonadal, and Central Nervous System Status after Bone Marrow Transplantation for Sickle Cell Disease. Biol Blood Marrow Transplant. 2010;16(2):263-72. https://doi.org/10.1016/j.bbmt.2009.10.005 PMid:19822218 PMCid:PMC2919571
44. Walters M., Patience M, Leisenring W, Rogers Z., Aquino V., Buchanan G., Roberts IA., Yeager A., Hsu L, Adamkiewicz T, Kurtzberg J, Vichinsky E, Storer B, Storb R, Sullivan K. Stable mixed hematopoietic chimerism after bone marrow transplantation for sickle cell anemia. Biol Blood Marrow Transplant. 2001 Dec;7(12):665-73. https://doi.org/10.1053/bbmt.2001.v7.pm11787529 PMid:11787529
45. Krishnamurti L, Kharbanda S, Biernacki MA, Zhang W, Baker KS, Wagner JE, Wu CJ. Stable Long-Term Donor Engraftment following Reduced-Intensity Hematopoietic Cell Transplantation for Sickle Cell Disease. Biol Blood Marrow Transplant. 2008;14(11):1270-8. https://doi.org/10.1016/j.bbmt.2008.08.016 PMid:18940682
46. Kean LS, Manci EA, Perry J, Balkan C, Coley S, Holtzclaw D, Adams AB, Larsen CP, Hsu LL, Archer DR. Chimerism and cure: Hematologic and pathologic correction of murine sickle cell disease. Blood. 2003;102(13):4582-93. https://doi.org/10.1182/blood-2003-03-0712 PMid:12933586
47. Andreani M, Testi M, Gaziev J, Condello R, Bontadini A, Tazzari PL, Ricci F, De Felice L, Agostini F, Fraboni D, Ferrari G, Battarra M, Troiano M, Sodani P, Lucarelli G. Quantitatively different red cell/nucleated cell chimerism in patients with long-term, persistent hematopoietic mixed chimerism after bone marrow transplantation for thalassemia major or sickle cell disease. Haematologica. 2011 Jan 1;96(1):128-33. https://doi.org/10.3324/haematol.2010.031013 PMid:20935000 PMCid:PMC3012776
48. Lefèvre N, Dufour D, Gulbis B, Lê P-Q, Heijmans C, Ferster A. Use of hydroxyurea in prevention of stroke in children with sickle cell disease. Blood. 2008 Jan 15;111(2):963-4; author reply 964. https://doi.org/10.1182/blood-2007-08-102244 PMid:18182580
49. Grace RF, Su H, Sena L, Poussaint TY, Heeney MM, Gutierrez A. Resolution of cerebral artery stenosis in a child with sickle cell anemia treated with hydroxyurea. Am J Hematol. 2009;85(2):NA-NA.
50. Abboud MR, Cure J, Granger S, Gallagher D, Hsu L, Wang W, Woods G, Berman B, Brambilla D, Pegelow C, Lewin J, Zimmermann RA, Adams RJ, STOP study. Magnetic resonance angiography in children with sickle cell disease and abnormal transcranial Doppler ultrasonography findings enrolled in the STOP study. Blood. 2004 Apr 1;103(7):2822-6. https://doi.org/10.1182/blood-2003-06-1972 PMid:14684415
51. Bernaudin F, Verlhac S, Arnaud C, Kamdem A, Hau I, Leveille E, Vasile M, Kasbi F, Madhi F, Fourmaux C, Biscardi S, Gluckman E, Socie G, Dalle J-H, Epaud R, Pondarre C. Long-term treatment follow-up of children with sickle cell disease monitored with abnormal transcranial Doppler velocities. Blood. 2016 Apr 7;127(14):1814-22. https://doi.org/10.1182/blood-2015-10-675231 PMid:26851292
52. Iannone R, Casella JF, Fuchs EJ, Chen AR, Jones RJ, Woolfrey A, Amylon M, Sullivan KM, Storb RF, Walters MC. Results of minimally toxic nonmyeloablative transplantation in patients with sickle cell anemia and ß-thalassemia. Biol Blood Marrow Transplant. 2003 Aug;9(8):519-28. https://doi.org/10.1016/S1083-8791(03)00192-7
53. Horan JT, Liesveld JL, Fenton P, Blumberg N, Walters MC. Hematopoietic stem cell transplantation for multiply transfused patients with sickle cell disease and thalassemia after low-dose total body irradiation, fludarabine, and rabbit anti-thymocyte globulin. Bone Marrow Transplant. 2005 Jan 8;35(2):171-7. https://doi.org/10.1038/sj.bmt.1704745 PMid:15531901
54. Hsieh MM, Kang EM, Fitzhugh CD, Link MB, Bolan CD, Kurlander R, Childs RW, Rodgers GP, Powell JD, Tisdale JF. Allogeneic Hematopoietic Stem-Cell Transplantation for Sickle Cell Disease. N Engl J Med. 2009 Dec 10;361(24):2309-17. https://doi.org/10.1056/NEJMoa0904971 PMid:20007560 PMCid:PMC3627532
55. Saraf SL, Oh AL, Patel PR, Jalundhwala Y, Sweiss K, Koshy M, Campbell-Lee S, Gowhari M, Hassan J, Peace D, Quigley JG, Khan I, Molokie RE, Hsu LL, Mahmud N, Levinson DJ, Pickard a S, Garcia JG, Gordeuk VR, Rondelli D. Nonmyeloablative Stem Cell Transplantation with Alemtuzumab/Low-Dose Irradiation to Cure and Improve the Quality of Life of Adults with Sickle Cell Disease. Biol Blood Marrow Transplant. 2016 Mar;22(3):441-8. https://doi.org/10.1016/j.bbmt.2015.08.036 PMid:26348889
56. Schattman GL. Cryopreservation of Oocytes. Solomon CG, editor. N Engl J Med. 2015 Oct 29;373(18):1755-60. https://doi.org/10.1056/nejmcp1307341
57. Bola-os-Meade J, Fuchs EJ, Luznik L, Lanzkron SM, Gamper CJ, Jones RJ, Brodsky R a. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood. 2012;120(22):4285-91. https://doi.org/10.1182/blood-2012-07-438408 PMid:22955919 PMCid:PMC3507140
58. Maschan M, Shelikhova L, Ilushina M, Kurnikova E, Boyakova E, Balashov D, Persiantseva M, Skvortsova Y, Laberko A, Muzalevskii Y, Kazachenok A, Glushkova S, Bobrynina V, Kalinina V, Olshanskaya Y, Baidildina D, Novichkova G, Maschan A. TCR-alpha/beta and CD19 depletion and treosulfan-based conditioning regimen in unrelated and haploidentical transplantation in children with acute myeloid leukemia. Bone Marrow Transplant. 2016 May 25;51(5):668-74. https://doi.org/10.1038/bmt.2015.343 PMid:26808573
59. Mainardi C, Tumino M, Gazzola M V, Rampazzo A, Scarpa M, Messina C. TCRaß CD19 depletion in allogeneic haematopoietic stem cell transplantation performed for Hurler syndrome. Bone Marrow Transplant. 2016 Mar 9;51(3):438-9. https://doi.org/10.1038/bmt.2015.258 PMid:26551775
60. Kang EM. Mobilization, collection, and processing of peripheral blood stem cells in individuals with sickle cell trait. Blood. 2002 Feb 1;99(3):850-5. https://doi.org/10.1182/blood.V99.3.850 PMid:11806986
61. Fitzhugh CD, Hsieh MM, Bolan CD, Saenz C, Tisdale JF. Granulocyte colony-stimulating factor (G-CSF) administration in individuals with sickle cell disease: time for a moratorium? Cytotherapy. 2009 Jan;11(4):464-71. https://doi.org/10.1080/14653240902849788 PMid:19513902 PMCid:PMC2747259