Shifting paradigms from myeloablation to immune modulation: pre-transplant immune-suppression and post-transplant cyclophosphamide in human leukocyte antigen-identical related-donor hematopoietic stem cell transplantation for sickle cell disease

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Abstract

Excellent outcomes of human leukocyte antigen-identical related-donor hematopoietic stem cell transplant (HSCT) in patients with sickle cell disease (SCD) have put it as a standard of care in symptomatic patients especially after a failed hydroxyurea therapy, however a large part of this data comes from resource-rich settings. These encouraging outcomes are in-turn due to patients being considered for HSCT in relatively well-preserved condition, safer transplant conditioning, better graft-*versus*-host disease (GVHD) prophylaxis strategies and improved overall supportive care. Large-scale real-world data from resource-constraint settings is however missing. We retrospectively analyzed baseline characteristics and longitudinal data of 85 pediatric and young adults who underwent matched sibling donor HSCT for SCD over a decade. Patients received conditioning as per APOLLO protocol from May 2019. Median age was 8 years (range, 10 months-32 years). Median time to neutrophil and platelet engraftment was 13 days (range, 10-19) and 14 days (range, 6-48). None experienced primary graft failure and one had secondary graft failure. Acute GVHD was seen in five patients (4 acute skin GVHD, grade 1/2; 1 gut GVHD, grade 4). At a median follow-up of 1,191 days (range, 23-4,226), Kaplan-Meier estimated event-free survival and overall survival is 94.11% and 96.47%, respectively. Overall survival in APOLLO protocol cohort was 100% and 91.4% using conventional (busulfan-cyclophosphamide or thiotepa-treosulfan-fludarabine-based conditioning). Age >10 years turned out to be the only significant risk factor affecting outcome (100% *vs*. 89.28%; *P*=0.007). This emphasizes the need of early intervention <10 years of age for best clinical outcomes.

Introduction

Early identification of the disease and initiation of optimal supportive care remains the mainstay of treatment for sickle cell disease (SCD). Although better understanding of the disease pathophysiology has allowed progress on more focused pharmacological therapies and the development of new treatment modalities, including L-glutamine, crizanlizumab, and voxelotor only hydroxycarbamide has stood the test of the time and continues to be the mainstay of pharmacological therapy for SCD. While considering the curative modalities, CRISPR/Cas9-based exagamglogene autotemcel marketed as (Casgevy) and lentiviral vector-based lovotibeglogene autotemcel marketed as (Lyfgenia) have been approved by Food and Drug Administration but their large-scale application remains far beyond the reach of majority of patients in need primarily due to cost and logistic issues. This puts the focus back on allogenic hematopoietic stem cell transplant (HSCT) as the only viable curative option for SCD patients. [1-14]

HSCT is currently the most feasible curative treatment option for symptomatic SCD. Five-year overall survival (OS) and event-free survival (EFS) of patients who received HSCT from a human leukocyte antigen (HLA)-identical sibling donor (matched sibling donor [MSD]) have been reported to be 93-100% and 85-96% using myeloablative conditioning (MAB) and 97-100% and 87-100%, respectively using non-myeloablative/reduced intensity conditioning (NMA/RIC).[15-29]Although a risk-based approach has widely been used and propagated to identify patients who can be benefited by HSCT (HLA-identical related/unrelated/haploidentical) different investigators have used different set of criteria to identify patients who would benefit from HSCT.[30] To address the lack of clarity about the indications of HSCT in SCD, a multidisciplinary expert panel formed by the American Society of Hematology made eight recommendations with very low certainty in the evidence, as a guidance for patients who might benefit from allogeneic HSCT.[31]

A large European Society for Blood and Bone Marrow Transplantation, Eurocord and Center for International Blood and Marrow Transplant Research survey of over 1,000 patients who underwent an HLA-identical donor HSCT using MAB and bone marrow as a source in majority (84%) showed an EFS and OS of 91.4% (95% confidence interval [CI]: 89.6-93.3%) and 92.9% (95% CI: 91.1-94.6), respectively with an improved OS in children younger than 16 years (95% *vs*. 81%; *P*<0.001). It was also noted that with yearly increment in age at the time of HSCT, the hazard ratio for graft-*versus*-host disease (GVHD) and graft failure (GF)/death increased by 4% and 10%, respectively.[32]

In the present retrospective analysis, we tried to analyze our decade-old experience of MSD HSCT for SCD. The analysis was aimed at identifying the risk factors that might influence the outcomes in resource constraint settings.

Methods

Patients

All consecutive patients (pediatric and young adults) with a diagnosis of SCD (homozygous sickle or sickle β thalassemia) presenting to the Center for Bone Marrow Transplant & Cellular Therapy (BMT&CT), Indraprastha Apollo Hospital, New Delhi between November 2014 and November 2025 undergoing MSD HSCT were included. For patients <12 years, consent was obtained from either of the parents, for patients 12-18 years written and informed assent along with parents' consent was obtained and patients >18 years signed the consent on their own after detailed counseling. The use of laboratory and clinical data was approved by institutional ethics committee (IAH-BMR/049/09-25) (details in Table 1).

Donors

In all the cases, the donors were HLA-identical siblings. Siblings with sickle cell trait were accepted as donors. None of the donors had any associated comorbidity. For patients <12 years, consent was obatined from either of the parents, for patients 12-18 years written and informed assent along with parents' consent was obatined and patients >18 years signed the consent on their own after detailed counseling (details in Table 1).

Pre-transplant preparation

The initial cohort of 35 (41.17%) patients received hydroxyurea, azathioprine and hyper-transfusion as pre-HSCT preparation, subsequently from May 2019 onwards all the patients received one/two courses of pre-transplant immune suppression (PTIS) as per the APOLLO protocol at 3 weekly intervals[33] (details in Figure 1 and Table 2).

Table 1. Demographic details of recipient and donor.

Baseline characteristics	N (%)
Patients	85
Median age, years (range)	8 (10 months-32)
Sex	
Male	49 (57.64)
Female	36 (42.35)
Ethnicity	
African	78 (91.76)
Indian	5 (5.88)
Others	2 (2.35)
Genotype	
Hb SS	84 (98.8)
HbS β thalassemia	1 (1.2)
HLA matching	
10/10	37 (49.4)
12/12	38 (50.6)
Indications of HSCT	
Severe VOC	67 (78.82)
Stroke	6 (7.05)
ACS	15 (17.64)
SLD	0 (0)
AVN	2 (2.35)
PRC transfusion >2-3	29 (34.11)
Graft source	
Bone marrow	17 (20)
PBSC	67 (78.82)
Cord blood	1 (1.17)
Donor's median age, years (range)	11 (0.8 months-33)
Donor's sex	
Male	39 (45.8)
Female	46 (54.2)
Donor status	
Sickle cell trait	33 (38.82)
Non-sickle cell trait	52 (61.17)

ACS: acute chest syndrome; AVN: avascular necrosis; PRC: packed red cell; PBSC: peripheral blood stem cell; SLD: sickle liver disease; VOC: veno-occlusive crisis.

Conditioning regimen and graft-*versus*-host disease prophylaxis

The initial cohort of patients received busulfan-cyclophosphamide (BU-CY)/thiotepa-treosulfan-fludarabine-(TTF) based conditioning whereas after May 2019, protocol was amended and subsequently the patients received conditioning as per APOLLO protocol.[40] Prior to protocol amendment, patients received calcineurin/mTOR inhibitors in combination with methotrexate (MTX) or mycophenolate mofetil (MMF) as GVHD prophylaxis but after May 2019, all the patients received post-transplant cyclophosphamide (PTCY) in combination with mTOR inhibitors and MMF. The details of PTIS, conditioning and GVHD prophylaxis are provided in Table 2.

Graft source

Initial cohort of patients received bone marrow as a stem cell source with few receiving granulocyte colony-stimulating factor-(GCSF) mobilized peripheral blood stem cells (PBSC). From May 2019 onwards after protocol amendment, all the patients received GCSF and plerixafor-mobilized PBSC as a graft source. GCSF 10 µg/kg was given subcutaneous (S/C) once daily for 5 days with plerixafor 0.24 mg/kg S/C stat 10-12 hours before initiation of harvest. Peripherally harvested stem cells were collected with a target CD34 dose of 5 million cells per kg recipient body weight. The majority of donors being sickle trait were given strict instructions to maintain hydration after starting GCSF and to report immediately in case of any new symptom suggestive of sickle crisis. All the donors were admitted on day 4 of GCSF administration and were started on intravenous (iv) hydration. Post-harvest, all the donors were closely monitored for 1 week. Decision to add plerixafor to GCSF was based on work by Rutella *et al*. which highlighted that a mega dose of $CD34^+$ cells can be collected without affecting the dose of naïve/memory T and B cells, NK cells and myeloid/plasmacytoid dendritic cells.[34]

Chimerism analysis

Sixteen short tandem repeat (STR) loci and one amelogenin locus were used to identify informative loci between donor and recipient. The amplicon was resolved by capillary electrophoresis on Dx 3500 platform. Chimerism was sent at the time of engraftment and then at day +30, +60, +100, +180, +270, and +365 using peripheral blood.

Ethics statement

For patients <12 years, consent was obtained from either of the parents, for patients 12-18 years written and informed assent along with parents' consent was obtained and patients >18 years signed the consent on their own after detailed counseling. Informed consent about data sharing and its use for analytical research and publication was obtained from all the patients from a competent person in accordance with the Declaration of Helsinki. The use of laboratory and clinical data was approved by the institutional ethics committee (IAH-BMR/049/09-25). All the data was anonymized prior to analysis.

Statistical analysis

Our last follow-up on all surviving patients who completed day +100 post HSCT was December 1, 2025. All outcomes have been presented using descriptive statistics. The Kolmogorov-Smirnov test was used to assess the normality of the data. We presented continuous variables as medians and range, categorical variables as numbers and percentage. The comparison of data was analyzed by the χ^2 test/Fisher exact test. OS and disease-free survival (DFS) was calculated using the Kaplan-Meier method and the differences in subgroups were assessed by log-rank test. Median follow-up was determined using the reverse Kaplan-Meier method. Competing risks analyses were separately applied to estimate the incidence of GVHD, neutrophil and platelet engraftment. Statistical analyses were performed using SPSS.

Table 2. Details of pretransplant immune-suppression, conditioning regimen and graft-*versus*-host disease prophylaxis details of the entire cohort.

SN	Variable	N=85
1	Pre-transplant immunosuppression, N (%) Flu-Cy-Dex x 1 Flu-Cy-Dex x 2 Hydrea-azathioprine- hyper-transfusion Not given	 16 (18.8) 33 (38.82) 35 (41.1) 1 (1.17)
2	Pre-transplant immunosuppression complications, N Febrile neutropenia Pain crisis CMV reactivation	 11 7 3
3	Conditioning regimen, N (%) Myeloablative Reduced toxicity	 17 (20) 68 (80)
4	Conditioning details, N (%) Thio-Flu-Cy-ATG-TBI Bu-Cy-ATG-TBI Thio-Treo-Flu-ATG-TBI Thio-Treo-Flu-ATG Thio-Flu-Cy-ATG	 57 (67.05) 17 (20) 3 (3.5) 7 (8.2) 1 (1.17)
5	GVHD prophylaxis, N (%) CNI + MTX Siro + MMF Siro + MMF + PTCY Others	 34 (40) 1 (1.17) 49 (57.64) 1 (1.17)

ATG: anti-thymocyte globulin; Bu: busulfan; CNI: calcineurin Inhibitor; Cy: cyclophosphamide; CMV: Cytomegalovirus; Dex: dexamethasone; Flu: fludarabin; GVHD: graft-*versus*-host disease; MMF-mycophenolate mofetil; MTX: methotrexate; PTCy: post-transplant cyclophosphamide; Siro:sirolimus; SN: serial number; TBI: total body irradiation; Thio: thiotepa; Treo: treosulfan.

Results

Patients

Eighty-five patients with SCD underwent HLA-identicalHSCT during the aforementioned period, 84 with homozygous sickle whereas one had sickle β thalassemia. The majority (N=49, 57.64%) were male and median age was 8 years (range, 10 months-32 years). Major indication of HSCT was frequent severe veno-occlusive crisis (VOC) (N=67; 78.8%). Among 67 patients, all had severe episodes of VOC; 44 had ≤4 episodes and 23 had >4 episodes of VOC in the past 6 months. Baseline characteristics of patients and donors are detailed in Table 1.

Donors

All the donors were HLA-identical siblings. Median age was 11 years (range, 10 months-33 years), 39 were male, 36 were female. Thirty-three donors were heterozygous sickle whereas, 52 were normal. Seventeen donors were taken up for bone marrow collection without GCSF mobilization and one patient received cord blood. Sixty-seven patients received PBSC graft. Most common complication encountered during mobilization was bone pain. Of 67 donors who underwent GCSF +/- plerixafor mobilization, two donors had mild VOC, which was managed with paracetamol and one had vomiting during the procedure (Table 1).

Graft source and characteristics

The median $CD34^+$ cells infused were 5 million $CD34^+$ cells/kg body weight (BW) (range, 1.8-11.1). Median $CD3^+$ cells infused were 1.7×10^8/kg recipient BW (rBW) (range, 2.35-84). Median volume infused was 76 mL (range, 11-1,200 mL). The infusion was well tolerated with no significant adverse effects noticed in any of the recipients.

Engraftment characteristics

Median time to neutrophil engraftment (first day of absolute neutrophil count [ANC] >0.5×10^9/L) was 13 days (range, 10-19) and median time to platelet engraftment (PC >20×10^9/L unsupported for more than 5 days) was 14 days (range, 6-48) (Figure 1). None of our patients experienced primary graft failure. One developed a secondary graft failure and underwent subsequent second MSD HSCT using same donor and has 100% chimerism at last follow-up (Table 3).

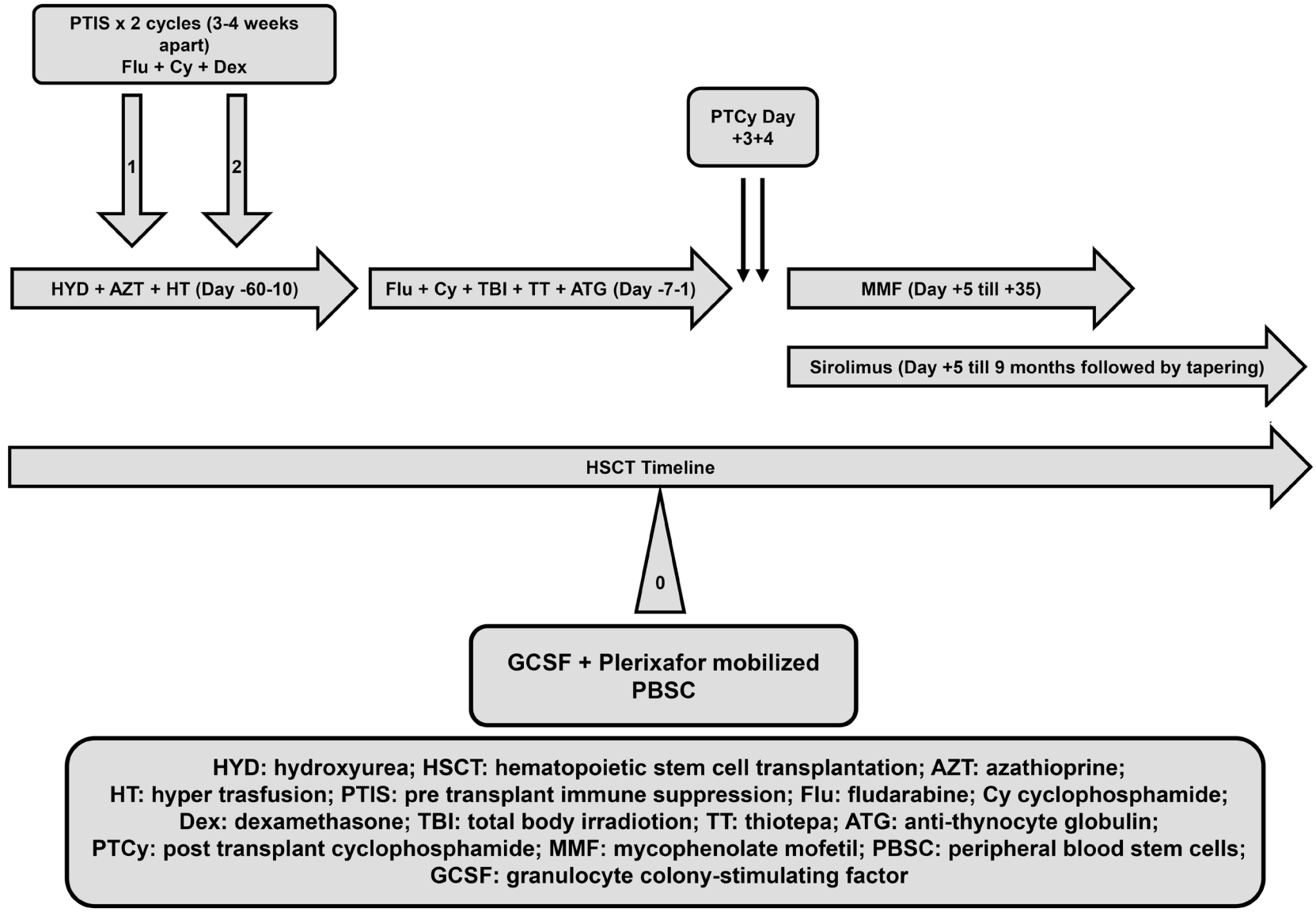

Figure 1. Schema of APOLLO protocol.

Complications and recovery post hematopoeitic stem cell transplantation

Mucositis

Grade 1/2 mucositis was seen in 30 (35%) patients. Enteral nutrition was maintained in all and none of the patients requited total or partial parenteral nutrition. None of our patient experienced grade 3/4 mucositis (Table 3).

Sinusoidal obstruction syndrome and posterior reversible encephalopathy

One patient developed mild sinusoidal obstruction syndrome (SOS) and responded to conservative management. None of our patients experienced posterior reversible encephalopathy (PRES) (Table 3).

Bacterial/fungal infection

Culture-positive bacterial infection was seen in 21 (24.7%) patients with *Escherichia coli* being the commonest pathogen. Possible invasive fungal infection (IFI) was seen in six (7%) patients. All patients responded to appropriate antimicrobials and none progressed to shock or organ dysfunction (Table 3).

Cytomegalovirus reactivation

Cytomegalovirus (CMV) reactivation with a cut-off of ≥500 copies/mL was seen in 31 (36.5 %) patients. All patients responded to ganciclovir and none required addition of cidofovir or foscarnet. We also observed CMV reactivation pre HSCT post PTIS in three (3.52%) patients which responded to ganciclovir (Table 3).

BK polyoma virus and Eppstein-Bar virus reactivation

Grade 1/2 BK virus hemorrhagic cystitis was seen in five (5.88%) patients which responded well to supportive care and cidofovir. One patient had non-BK-positive hemorrhagic cystitis which settled with supportive care. None of our patients experienced Epstein-Barr visus (EBV) reactivation (Table 3).

Acute and chronic graft-versus-host disease

Five patients developed acute GVHD (Figure 2). Four had acute skin GVHD, grade 1/2 which responded to topical steroids. One patient had grade 4 steroid refractory acute gut GVHD which did not respond to second- or third-line drugs and succumbed to it. One patient had chronic extensive GVHD and succumbed to it. Both these patients received combination of cyclosporine with methotrexate as GVHD prophylaxis with PBSC as source. None of the patients on APOLLO protocol developed grade 3/4 acute or chronic GVHD (Table 3).

Pain crisis post-transplant

Five patient experienced VOC post HSCT. One experienced VOC on day +15 of HSCT and responded to hydration, iv paracetamol and red cell transfusion. One patient, aged 32 years has multiple episodes of severe VOC, post-transplant, requiring hospitalization on two occasions and is on opioids for the pain control till the last follow-up. Three patients had mild VOC (non-specific body pains), which was managed with analgesics.

Chimerism analysis

Median chimerism at day +100 was 99.15% (range, 70.18-100%). Of 85 patients, 75 patients had >95% donor chimerism at the last follow-up, however in ten patients a drop in chimerism was noticed subsequent to which immune suppression was tapered and donor lymphocyte infusion was initiated. Ten patients had mixed chimerism post HSCT for which they received escalated DLI (1 million/kg; 5 million/kg and 10 million/kg) with median number of 3 (range, 1-4). Post DLI, two patients had full donor chimerism, one patient had secondary graft failure and seven patients had

Table 3. Post-transplant complications in patients of sickle cell disease undergoing matched sibling donor hematopoietic stem cell transplantation.

SN	Variable	N=85
1	Acute GVHD with overall grade, N (%) Grade 0 Grade 1 Grade 2 Grade 3 Grade 4	 80 (94.11) 03 (3.52) 01 (1.17) 0 (0) 01 (1.17)
2	Mucositis with overall grade, N (%) Grade 0 Grade 1 Grade 2	 55 (64.70) 16 (18.82) 14 (16.47)
4	Infection profile, N (%) Fungal Yes No Bacterial Yes No Post-transplant CMV Yes No BK virus Yes No	 06 (7.05) 79 (92.94) 21 (24.70) 64 (75.29) 31 (36.47) 54 (63.52) 05 (5.88) 80 (94.11)
5	Non-infectious complications, N (%) Hemorrhagic cystitis Yes No VOD Yes No PRES Yes No	 06 (7.05) 79 (92.94) 01 (1.17) 84 (98.82) 0 (0) 85 (100)

CMV: Cytomegalovirus; GVHD: graft-*versus*-host disease; PRES: posterior reversible encephalopathy syndrom; SN: serial number; VOD: veno-occlusive disease.

mixed stable chimerism. The median chimerism at day+ 365 for the nine patients was 80.6 (67.86-100%).

Immune reconstitution

Immunoglobulin levels (G, M, A) and lymphocyte subsets (CD3, 4, 8, 19 and 56) were assessed at days +30, +60, +100, +180, +270 and +365 to see the immune reconstitution patters. Median IgG levels at day +100 was 893 mg/dL (range, 305 -2,119); IgM was 32.5 mg/dL (range, 08-174); and IgA was 98.7 mg/dL (range, 12-308). Median $CD4^+$ counts at day +100 were 282 cells/mm^3 (range, 51-850); $CD8^+$ were 513 cells/mm^3 (range, 15-3,289); $CD19^+$ were 100 cells/mm^3 (range, 0-1,514) and that of $CD56^+$ was 207 cells/mm^3 (range, 26-1,223). The CD19 recovery was delayed in the cohort of patients which received rituximab on day -1 post may 2019 protocol amendment.

Transplant outcome

At a median follow-up of 1,191 days (range, 23-4,226) (as on December 1, 2025), Kaplan-Meier estimated EFS and OS is 94.11% and 96.47%, respectively (Figure 3). The OS in children <10 years was 100% whereas it was 89.28% in children >10 years (*P*=0.007). Three patients expired in our cohort, one succumbed to bacterial infection, one had steroid-refractory grade 4 GVHD and one had extensive chronic GVHD. On subgroup analysis, the OS in APOLLO protocol cohort was 100% whereas it was 91.4% using conventional (BU-CY- or TTF-based conditioning) (Figure 3).

Discussion

Despite being caused by the same point mutation, the clinical manifestations of SCD show marked global variability, reflecting the role of epigenetic regulation and other genetic modifiers in determining disease severity. In the past few years, autologous gene corrected therapies have emerged as a promising curative option but their large-scale

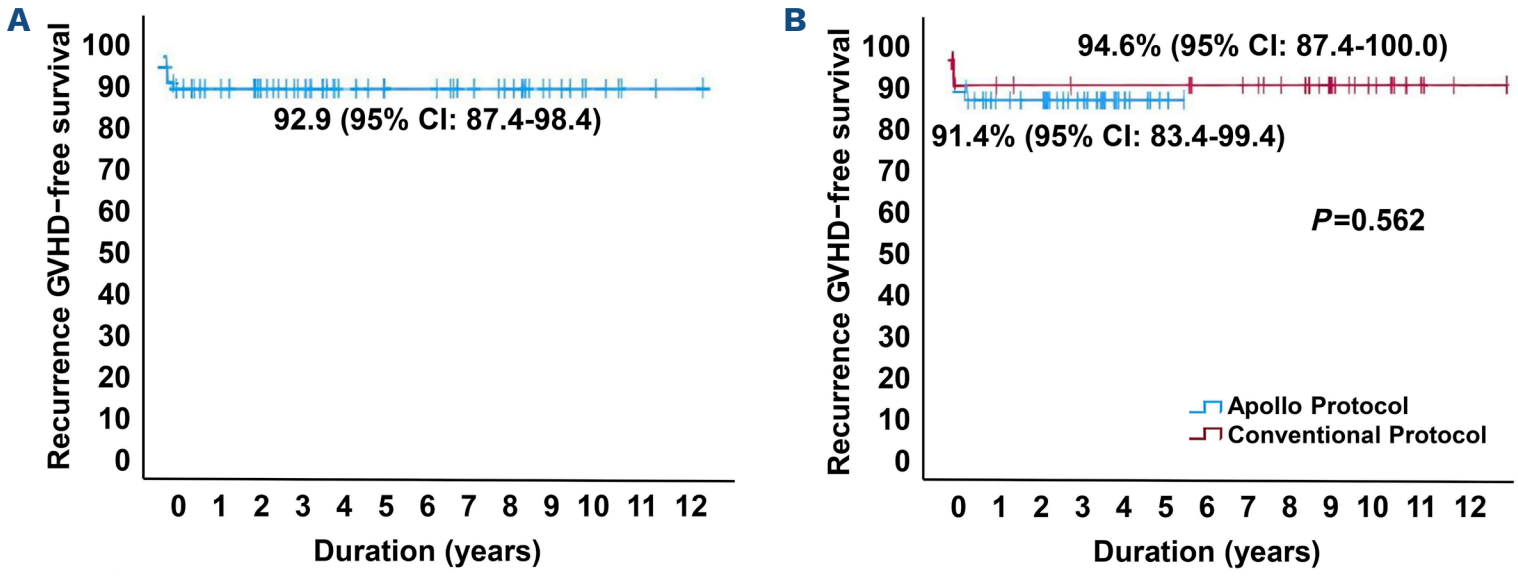

Figure 2. Kaplan-Meier survival curves of recurrence-free, graft-*versus*-host disease-free survival of HLA-identical related donor hematopoietic stem cell transplantation for sickle cell disease. (A) Recurrence-free, graft-*versus*-host disease (GVHD)-free survival of the entire cohort. (B) Recurrence-free, garft-*versus*-hsot disease (GVHD)-free survival in APOLLO protocol *versus* rest. CI: confidence interval.

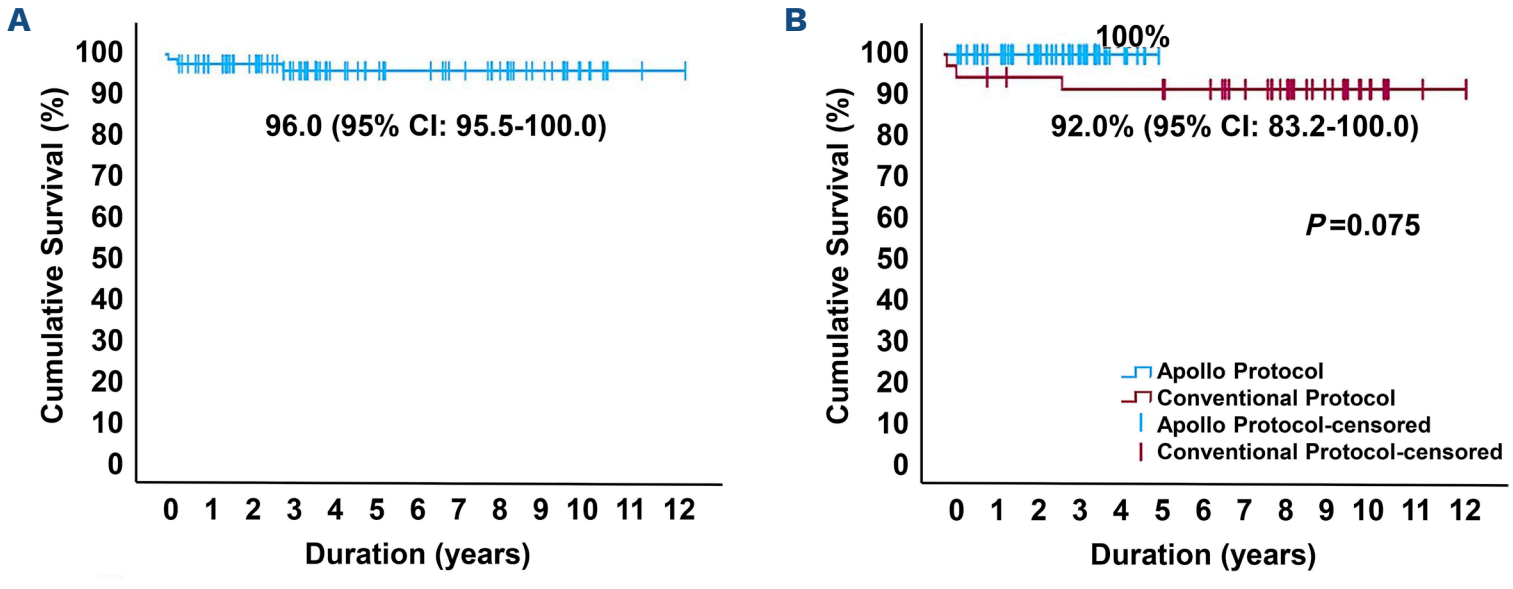

Figure 3. Kaplan-Meier survival curves of overall survival of HLA-identical donor hematopoietic stem cell transplantation for sickle cell disease. (A) Overall survival of entire cohort. (B) Overall survival in APOLLO protocol *versus* rest. CI: confidence interval.

use is limited by exorbitant cost and logistic challenges in manufacturing and scaling-up such therapies. This puts the focus back on HSCT as the only viable curative option.

In the present retrospective analysis, we tried to look at OS and EFS of patients undergoing HLA-identical sibling donors HSCT for SCD presenting from resource constraint settings at Center for BMT & CT. We also tried to look at the factors affecting the outcomes of HSCT. The present manuscript also highlights the protocol amendments done over a period of time to improve the outcomes.

Of 85 patients, 78 (91.76%) were of African ethnicity, five (5.88%) were Indians and two (2.35%) were of other ethnicities. All the patients were from resource-constraint settings with improper access to routine supportive care.

Ten (11.76%) patients had a major blood group mismatch whereas 13 (15.2%) had a minor blood group mismatch and two (2.3%) had a bi-directional mismatch. Sixty (70.5%) donor recipient pair had the same blood group with O+ being the commonest combination. This might be due to the fact that majority of our patients were from African ethnicity where O+ is the commonest blood group. Fifty-eight (68.23%) donor/recipient combinations were CMV seropositive whereas just seven (8.2%) were seronegative. This is in contrast to the previous studies in which majority of donor/recipient pairs were O-. Despite higher number of recipients/donors being seropositive in our cohort, we did not notice any significant increase in CMV reactivation which we attribute to valganciclovir prophylaxis which was initiated at day +3 of engraftment and continued till day +60 post HSCT.

Bone marrow (cord blood in 1 patient) was used primarily in the initial cohort of patients prior to shifting to APOLLO protocol from May 2019 onwards. This shift was primarily guided by the success of APOLLO protocol in the haploidentical patients published by our group in 2020.[40] This observation in our cohort was different from the previous studies where bone marrow was used as a preferred source. The reason to shift from BM to PBSC was to ease out the logistic challenges with bone marrow harvest which becomes a rate limiting step in resource constraint settings. Two patients who received PB as graft source developed life threatening GVHD (1 steroid-refractory acute gut grade 4, stage IV and 1 extensive chronic GVHD). Both these patients were from the initial cohort and did not receive PTCY as GVHD prophylaxis. None of the patients in PBSC and PTCY cohort developed acute GVHD grade 3 and beyond or extensive chronic GVHD. Our findings re-enforce the fact PTCY is an emerging platform beyond haploidentical settings which can very well mitigate the increased risk of GVHD using PBSC as graft source. This can also be explained by using GCSF + plerixafor-based mobilization which is known to modify the graft favorably to reduce the risk of GVHD. Another key observation in our study is that most of the donors, who had sickle cell trait and underwent GCSF +/- plerixafor-based PBSC mobilization did not experience any significant complications, thus, reinforcing the idea that GCSF mobilization is safe in individuals with sickle cell trait.[35,36]

The initial cohort of patients received BU-CY/TTF as conditioning with no PTIS. After May 2019, all the patients were enrolled in APOLLO protocol and received 1/2 cycles of PTIS comprising of fludarabine, cyclophosphamide and dexamethasone 3 weeks apart along with hydroxyurea and azathioprine. This was subsequently followed by fludarabine/thiotepa (5/10 mg/kg)/TBI (2/4 cGy)/low-dose cyclophosphamide (29 mg/kg) as conditioning chemotherapy. This conditioning was well tolerated and none of our patients experienced grade 3/4 toxicities. We feel, introduction of PTIS helped us reduce the intensity of conditioning chemotherapy thereby reducing the risk of conditioning-related toxicities. This is a novel concept primarily tried in haploidentical HSCT for SCD but ours is the first study documenting the safety, efficacy and feasibility of this approach in HLA identical sibling donor settings as well.

The two patients who developed life threatening GVHD, one steroid-refractory acute gut GVHD and one, extensive chronic GVHD were both from the initial cohort where PBSC was used as a graft source without PTCY as GvHD prophylaxis. We observed that the patients who received either bone marrow as graft source or PBSC along with PTCY as GVHD prophylaxis had an excellent GVHD-free survival.

We also observed that our change in strategy from BU-CY/TTF with bone marrow as source to APOLLO protocol did not increase the risk of GVHD or viral reactivations. The immune reconstitution was robust with median CD4/CD8/CD56 cell count of 282/513/207 cells/μL respectively at day 100. In subset analysis between APOLLO Protocol *versus* conventional (BU-CY/TTF) based protocols, we did observe poor CD19 reconstitution along with low IgG and IgM levels at day 100 post HSCT in APOLLO protocol which we attribute to addition of rituximab on day -1 of conditioning in APOLLO protocol.

The key finding in our study is the incorporation of PTIS which might have helped us to reduce the risk of graft failure by addressing the allo-reactive T cells. Incorporation of PTIS also helped us to reduce the intensity of conditioning chemotherapy which was very well tolerated. Another key finding in our study is that use of PBSC in combination with PTCY did not increase the risk of GVHD, or GF or led to poor immune reconstitution thus increasing the risk of viral reactivations. The only secondary graft failure was seen in a child who received the APOLLO protocol without PTIS. The same patient subsequently underwent a second HSCT using the same donor and APOLLO protocol with one course of Flu-Cy-Dex-based PTIS and engrafted on day 13 and continues to have complete donor chimerism at last follow-up. Over the years there has been a visible shift of graft source from BM to PBSC for obvious reasons but this shift comes with the increased risk of GVHD (acute/chronic). The incorporation of PTCY to this strategy negates the risk of GVHD. This strategy can easily be replicated in

resource-constraint settings where a bone marrow harvest becomes difficult due to a number of reasons.

In contrast to previous investigators where 16 years has been used as a cut-off affecting outcomes of HSCT, we observed 100% OS for children <10 years and 89.28% for patients >10 years.[32] This, we feel is on account of early disease progression in these patients who presented to us from resource constraint settings with improper access to care. This observation makes a strong point to advocate early HSCT for patients <10 years of age in resource limited settings.

To best of our knowledge, this is the first large scale study documenting encouraging outcomes of HLA-identical sibling donor HSCT for patients from resource-limited settings. This is also the first study documenting the safety, efficacy and feasibility of PTIS, thiotepa-based reduced-toxicity conditioning, PBSC as graft source and PTCY as GvHD prophylaxis in HLA-identical sibling donor settings for SCD.

Despite encouraging outcomes, our study has certain limitations. It is a retrospective single center non-randomized study over an extended period of time. The data is quite heterogeneous due to the change of strategies over a period of time thus making the meaningful statistical analysis a limiting factor.

Disclosures

No conflicts of interest to disclose.

Contributions

GK prepared the concept note and the basic framework of the manuscript. GN subsequently worked on the details of the manuscript and did the data compilation and analysis together with SS and VC. The data was further refined with inputs from NG, EPB, AB, SM, SV, AJ, MC, KKS, and HY. The final manuscript was revised by GK and shared with all the authors for their approval. The corresponding author has complete access to data, takes full responsibility of authenticity of data and of the decision to submit the manuscript for publication.

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Data-sharing statement

The anonymized data is stored in hospital database. The center also reports the data to EBMT (Center number 464) and Indian society of Bone Marrow Transplant (Center number 123). Request to access the anonymized data by authorized personal can be sent to the correspondence email. The application should have IEC approvals from their parent institute for access of data. All the applications shall be reviewed by IEC and data governance committee. After getting approvals from IEC at IAH, the data can be shared with requesting authority. Liabilities and litigations of any subsequent data breech shall fall upon the requesting authority.

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