



Review Article

Hematopoietic Stem Cell Transplantation for Sickle Cell Disease: A Review

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Abstract

Sickle cell disease is an autosomal recessive disorder widely spread over the world. The disease is associated with continuing morbidity, multi-organ damage, and mortality. Hematopoietic stem cell transplantation is the only established curative therapy. The probability of 5-year survival post HSCT extends beyond 90%. The therapy is continuously evolving in all aspects of transplantation. This review focuses on the recent trends in multiple facets of the procedure from indications to details of newer technologies. It reviews data related to age at transplantation, indications as proposed by various researchers, donor selection, multiplicity of conditioning regimens, various immunosuppressive methodologies in use and expected outcomes. Transplant at an early age is recommended if MSD is available. The complications profile differs, depending on the age. Practically every single serious complication requiring admission in SCD, is an indication for the transplant. The major challenges faced in HSCT include non-acceptance by the patients and non-availability of fully matched donors. The technology is completely gearing up to make haploidentical transplants more successful with lesser side effects like GVHD, rejections and infections. Different intensity levels of conditioning regimens are in use. Various manipulations with T cells also form the part of transplant. The review reinforces the current knowledge about methodologies, utility and feasibility of HSCT in SCD.

Introduction

Sickle cell disease (SCD) is an autosomal recessive disorder widely spread over the world but more prevalent in few parts of Africa and India. It is characterized by continuous intravascular hemolysis and microvascular occlusion resulting in recurrent vaso-occlusive events causing pain crisis. [1] Acute complications manifest as stroke, acute chest syndrome (ACS), priapism and increased risk of infection. The disease leads to chronic multiorgan dysfunction- pulmonary hypertension, chronic lung damage, nephropathy, hepatopathy, progressive brain damage, neurocognitive changes, retinopathy and chronic bone damage. SCD is associated with chronic morbidity and early mortality [2, 3].

Hematopoietic stem cell transplantation (HSCT) is the only established curative therapy for SCD. [4-6] The probability of 5-year SCD free survival following HSCT from HLA-matched sibling donor is >90%. [5,7-11] HSCT results in erythropoiesis reconstitution with donor cells, thereby reducing major issue of intravascular vaso-occlusive crisis, the main pathophysiological mechanism of SCD resulting in organ damage. While being used in clinical practice for many years, it continues to evolve in terms of indications, donor selection, conditioning regimens, cell harvesting techniques, expected outcomes, and GVHD prophylaxis strategies. With the advancement in

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supportive care and the advent of new drugs, the calculations of benefit from HSCT are also being reevaluated. With reduced toxicity, HSCT success rates are improving. There is a constant ongoing debate on the short-term and the long-term risks of HSCT in comparison to novel available treatment and developing technologies.

Patient's and relatives understanding of the transplant depends on the patient's geographical location. The understanding and knowledge of the patients and caregivers varies significantly based on educational level. A positive correlation was found between the knowledge about HSCT and people with higher education. Transplant dilemmas include short and long term complications due to transplant and non-realization of the long-term side effects of the disease. The majority are not aware of this modality, making it even more difficult to take decisions on this curative option.

Age and HSCT

SCD is a genetic disorder, requiring intervention from birth. HSCT can be offered as a treatment at any time during the disease- in childhood or adulthood. In patients with an indication, transplant at an earlier age rather than at an older age, is recommended especially when matched sibling donor (MSD) is available.[12,13] Recommendations point to evidence suggesting that children under age 13 who receive HSCT from a MSD have better outcomes than those older than age 13. [12] For non-MSD, the recommendations are still not mature. Eapen et al reported highest event free survival (EFS) in children <13 years with MSD HSCT receiving myeloablative conditioning regimen (MAC) regime. Patients older than 13 years had both lower EFS and lower overall survival (OS) and higher incidence of chronic Graft versus host disease (GVHD) risk. [14] With MAC, the risk of chronic GVHD is significantly higher in patients older than 15 years of age. Nonmyeloablative conditioning showed no chronic GVHD or transplantation related mortality, but reduced EFS of 87%. There were 13 % graft rejections. [15,16] With advancing age, the risk of transplantation related complications also varies. In early childhood viral complications during procedure are high, while at older age group GVHD related complications predominate. CMV serostatus is an important parameter to keep in mind. EFS was highest in children (≤13 years old) and with an HLA matched sibling and there is almost no sickle cell disease related mortality and low morbidity. In older age group, mainly beyond, 20 years, transplantation associated systemic vasculopathy: neurotoxicity, posterior reversible encephalopathy syndrome, veno-occlusive disease, sinusoidal obstruction syndrome become more common. Acute and chronic GVHD are more prevalent in this group. Other complications in older age groups include-alloimmunization, delayed immune reconstitution and graft rejection.

In children aged < 5 years, outcomes are better, if

patients are transplanted at young age and found to have lower incidence of acute GVHD and chronic GVHD. With more and more experience in transplantation technology and biology, more and more adult patients are being taken up for transplant.[16] More so, use of non-myeloablative regimens is increasing the acceptance of HSCT and abolishing the dependence on the age, as a variable. SCD associated organ damage starts from very early age and is progressive, so earlier intervention may lead to better outcomes. Unfortunately, the organ damage is visible when substantial time lapse has occurred. Nephropathy, retinopathy, damage to spleen, cognitive neurological damage become obvious later in life. Silent splenic infarctions and brain infarctions are common. The organ damage is irreversible. So logically, earlier intervention is desirable. In Low and Low- middle income countries (LMIC), when detailed investigation is neither feasible nor available, the decision making may even be more difficult. MSD HSCT though, is most preferred type of HSCT, the availability of such donors is very limited. Similar is the problem with matched unrelated donor. Keeping in view these facts, more consideration should be given to haploidentical transplant and the research should focus on improving results in this group. With more and more adults coming forward with request for transplant, the issue of the choice of donor is becoming more pertinent.

Indications

The majority of SCD patients keep experiencing multiple clinical situations leading to morbidity and end organ damage. Initial symptoms are related to pathophysiology of the disease involving vaso-occlusive phenomenon. The prevalence and progression of disease-related multiple chronic conditions (MCC) among this cohort of patients in relation to their age has been examined by Jang et al. By the age of 20 years or older, 28.6% of SCD patients suffered at least two disease related chronic morbidities. The prevalence increased to 40.7% (P value- 0.01) by age 40 years or above, and 55% (by age 60 years or above (P- value= 0.002). [17] The age of onset of the first SCD-related chronic conditions strongly predicted the risks for disease-related MCC. SCD patients who suffered their first disease-related chronic condition before age 30 years developed MCC at a rate of 19.1 times faster than those at a later age. [17]

Frequent pain crises are the hallmarks of the disease. Veno-occlusive events are commonest indications for transplant. [15, 18-20] Patients with recurrent episodes of VOC and ACS with history of hospitalization should be considered for HSCT, especially if they are non-respondent to hydroxyurea. A German Austrian group has indicated more than 5 lifetime admissions for SCD as an indication for HSCT (Table 1).

Neurological manifestations are common in patients with SCD. Nearly, a quarter of patients are affected by stroke.

Table 1: Indications for HSCT (Abridged)

Ven-occlusive crisis- Pain events requiring hospitalization, recurring more than 3 times per year
Acute chest syndrome
Neurological events-stroke, Transient Ischemic Attacks, MRI changes in brain, increased Trans Cranial Doppler velocity
Transfusion dependency and alloimmunization
Any hospitalization despite hydroxyurea usage and transfusions.
Organ damage-Hepatopathy, Nephropathy, Retinopathy, Cardiac injury

Patients with neurological injury, who have experienced an overt stroke, transient ischemic attack, abnormal MRI finding suggestive of silent infarct, any significant neurological event lasting more than 24 hours with associated MRI changes, are candidates for HSCT. (NCT04362293) Increased transcranial Doppler ultrasound (TCD) measurement (high MCA velocity), of > 200 m/s is also an indication for HSCT. Transplantation done for neurologic injury in children younger than 16 years of age has better outcome than for older than 16. [12] With recurring events neurocognitive deficit tends to set in and progressive rise. This also serves as an indication. Supportive care therapy and chronic red cell transfusion are useful, but their long-term use is associated with sequelae of alloimmunization and transfusion iron overload. If there are more than two antibodies detected, then it should immediately be taken up as an indication. More than 8 transfusions in a year are considered by many groups as a condition for evaluation for HSCT (NCT04362293).

The other indications for transplant include early-stage sickle lung disease, sickle cell nephropathy (GFR, 90 mL/min/1.74 m² or presence of microalbuminuria (urine albumin >300 mg/g creatinine), retinopathy, hepatopathy, avascular necrosis of multiple joints, recurrent priapism or any end organ damage. Bilateral proliferative retinopathy with major visual impairment in at least one eye should be reviewed for transplant. Newer indications have also been used like elevated TRJV (≥ 2.7 m/s), pulmonary hypertension defined by a mean pulmonary artery pressure > 25 mmHg, Echocardiogram finding of tricuspid valve regurgitation (TRJ) velocity ≥ 2.5 m/sec. If HLA-matched related donor available, the HSCT could be performed earlier but if there is an availability of alternate donor only, then prior trial of hydroxyurea and chronic red cell transfusion therapy is preferable. [12]

Risk Stratification

More objectivity is required for taking a decision on the need of HSCT in a given patient. With newer disease modifying drugs and treatments, becoming accessible, the need of risk stratification is gaining further importance. In an attempt to develop a risk stratification model, an analysis of 1425 children was performed. Brazauskas et al have proposed a risk score based on age at transplantation and type of donor. It calculates 3-year probability of EFS,

death without graft failure and graft failure rate. [21] This score may guide patients and physicians who are considering allogeneic transplantation as a curative treatment. This could also help in predicting outcomes after HSCT. [21]

Sourcing of Stem Cells

Bone marrow, peripheral blood stem cell and umbilical cord blood serve as major sources of stem cells for transplantation, the commonest being peripheral stem cells. Stem cells can be sourced from HLA-matched sibling, HLA matched related donors, HLA-matched unrelated donors, haploidentical related donors and haploidentical unrelated donors.

Stem cells from HLA-MSD are preferred source for transplantation. It is estimated that only 15 % of SCD patients have HLA-matched related donors. [22] Due to limited availability and improvements in immunosuppressive therapy, other sources-matched unrelated donor, haploidentical donor and umbilical cord blood, are being more commonly utilized. Results using haploidentical related donors are also encouraging. In an analysis of 910 patients who underwent transplant, 558 (61%) were matched sibling donors, 137 (15%)- haploidentical related donors, 111 (12%) matched unrelated donors and 104 (11%) mismatched unrelated donors.

In a recent meta-analysis published by Aydin et al it was concluded that, adjustments to the conditioning regimens, robust pre transplantation strategies, post transplantation T-cell depletion and improved supportive care have resulted in reduced graft failure and improved OS following haploidentical HSCT. [5]

Cord blood can serve as an alternative source of stem cells. [8] If HLA-identical cord blood unit is available with good cell dose and viability, it is preferred over bone marrow. Cell dose is a limiting factor in usage of cord blood. With less dose, chances of failure increase. [23] The generally recommended target cell dose is 4×10^8 to 5×10^8 TNC per kg for bone marrow and 4×10^7 to 5×10^7 for cord blood. Post cord transplant, engraftment is delayed compared to marrow transplant. There are no engraftment or infection related challenges. There is a trend towards lower incidence of acute and chronic GVHD. There are no differences in EFS or OS.

Children with SCD had 90% disease free survival after cord blood transplant with 6 years of follow up compared to 92% disease free survival, following bone marrow transplantation. The cumulative OS in the cord blood recipient cohort was 97+/- 3% and similar to the marrow cohort (95 +/- 1%). [24]

Donor Selection

MSD transplant remains the ideal situation for transplant in sickle cell disease. HSCT from alternate donors including matched unrelated donors and haploidentical donors should only be considered in the presence of at least one of the indications and in experienced centers only. Siblings, which are probable donors may possess Hb AS trait, which is acceptable for transplant. The following factors may be considered for donor selection-donor age, donor weight, ABO typing, cytomegalovirus serostatus. Donor age beyond one year and weight >10 kg is considered safe. ABO major and minor mismatch both should be avoided as it might led to delayed RBC engraftment and pure red cell aplasia.

Haploidentical related donors appear today to be the largest donor group, capable of offering HSCT as a curative option to larger population. [25] Strategies to improve results using haploidentical donors are ongoing, those include using ATG, CD3/Cd 19+ depleted T-cell transplants and so on. [26-28] Alternate donor strategies could lead to more patients undergoing the curative approach of HSCT.

Pretransplant Evaluation and Management

As SCD is associated with multi-organ damage, it is important to review the status of various organs like brain, liver, spleen, and kidney before the transplant. Various investigations like transcranial doppler brain, MRI of brain, liver-spleen nuclear scan, renal scan, GFR are important investigations to be carried out. Donor directed HLA antibodies in haploidentical HSCT may predict the higher risk of graft rejection. This may be reduced by desensitization procedures. [29-31]

Pediatric and adolescent young adults who receive multiple transfusions are at higher risk of developing donor specific antibodies (DSA). DSA has been recognized as an important barrier against successful engraftment of donor cells. This could be result of alloimmunization of multiparous females against offspring. DSAs with mean fluorescence intensity of greater than 500 have been associated with significant graft failure, but lower values between 2000 and 500 may result in poor graft function after HSCT. [7] Desensitization strategies have been developed to reduce DSA, especially in recipients of HLA-mismatched haploidentical HSCT, using multiple agents like rituximab, daratumumab, bortezomib, IVIG and plasma exchange. [32, 33] Desensitization techniques result in successful HSCT.

Conditioning Regimens

Stem cell engraftment and functioning remains the major aim of the HSCT. Myeloablation of host cells with growth of newer donor stem cells should occur with host lymphodepletion to prevent graft rejection and allow restoration of myeloid functioning. The conditioning regimens may be of varied intensity causing varied levels of myelo and immunosuppression (Table 2). Operational definitions of conditioning intensity are based on the expected duration of pancytopenia and the need for stem cell support for hematopoietic recovery. [34,35] MAC refers to using total body irradiation and/or alkylating agents at doses that will not allow autologous hematological recovery. Non-myeloablative (NMA) conditioning cause lesser cytopenia and can be safely used in elder population. Reduced intensity conditioning (RIC) is an intermediate category. Doses are generally reduced by 30%. The strategies may employ usage of TBI, non-chemotherapy strategies and other. [18, 36-40]

In children with MSD, use of myeloablative regimens is recommended over reduced dose regimens. Whereas, in adult SCD with MSD, NMA/RIC are more preferred. Chemotherapy based regimens using busulfan and cyclophosphamide, with or without serotherapy with anti-thymocyte globulin, is the preferred standard of care for pediatric patients with HLA matched HSCT. In fact, a 2017 database reported that 87% of myeloablative conditioning for pediatric patients was this regimen. [5]

In an attempt to study the effect of intensity of conditioning regimen on the outcome of children with sickle cell disease, an analysis of 48 patients by Alsultan et al showed that EFS at 2 years was 100% in the MAC group compared to 29% in the RIC group. With a median follow up of 43.4 months all events in RIC group were secondary graft failure. [41]

Cyclophosphamide is being replaced with fludarabine in many regimens. In adult patients, combinations of fludarabine with melphalan or low doses of busulfan have been tried, which resulted in improvements in EFS and OS and low rates of acute or chronic GVHD. For allogeneic HSCT chemotherapy based conditioning regimens with total body irradiation-TBI-(#300-400 cGy) are commonly prescribed.

In adult patients, nonmyeloablative regimens based on low dose TBI have been developed. [16, 42] Myeloablative regimens are associated with risk of higher toxicity due to comorbidities and organ dysfunction.

There prevails an understanding that complete chimerism is unnecessary for SCD symptoms to resolve. [34] Mixed donor chimerism after HSCT for sickle cell disease can result in resolution of disease symptoms. This philosophy has allowed newer strategies using non myeloablative and reduced intensity conditioning with lesser toxicity. Minimum donor myeloid chimerism of 20-25% has been reported to

Table 2: Conditioning regimens

Author	HSCT Type	Type of conditioning regime & GVHD prophylaxis	No. of patients (Median age)	Survival
Alzahrani et al [42]	MRD HSCT NHLBI, UIC, and the KAMCR	NMA (3 Gy TBI, Alemtuzumab, unmanipulated filgrastim-mobilized peripheral blood HPC and sirolimus GVHD prophylaxis- Sirolimus	122 (Median age- 29 years)	5 Year OS – 93% 5 year SFS- 85%
Carabante et al [66]	MRD ; Spanish Group for BMT	MAC- BuCy (120-200 mg/kg) and the TTF included Treosulfan (Treo) 42 g/m ² , Thiotepa (Thi) 10 mg/kg and Fludarabine (Flu) 160 mg/m ² . In vivo T-cell depletion with either thymoglobulin (ATG) (2.5 mg/kg x 3 days for MSD and 3.75 mg/kg x 3 days for one antigen mismatched related donor) or alemtuzumab (0.1 mg/kg x 3 days)	45 (Median age- 9.18 years)	3 Year OS – 92.1% 3 year EFS- 89.4% <5 year- 100% EFS, OS Grade III–IV acute GvHD- 6.8% and chronic GvHD- 6.8%
Gulicher et al [67]	MSD (NIH)	NMA(Alemtuzumab 0.2 mg/kg/dose s/c x 5 days + 300 cGy TBI GVHD prophylaxis- Sirolimus	16(Median age- 12 years (range, 3 to 18 years)	100% EFS & OS
Strocchio et al.[63]	MSD/MUD	Thiotepa (10 mg/kg), Treosulfan (14 g/m ² /day), Fludarabine (160 mg/m ² /day),ATG	15 (Median age= 9.2 (1.7–16.5)	5 year DFS=93%, 5 year OS=100%
Cairo et al [68]	Haploidentical	MAC (ATG + + Thio +Flu + Cyclo + Bu + 5 Gy TBI) GVHD Prophylaxis-	19 (Mean age (Range)= 13.12 (3.3-20))	2yr EFS and OS- 84% Grades 2 to 4 acute GVHD-6.2%
Kharya et al [62]	Haploidentical (Apollo protocol)	RTC (Thio+Flu+Cy+2Gy TBI+ ATG) GVHD prophylaxis- PTcy+ Sirolimus+ MMF	22 (Median age was 7 years (range 1–27 years)	88% DFS and OS Grade II/IV acute GvHD – 5 (20%) patients

reverse the SCD phenotype. [43-45] Despite MAC dosing in the conditioning regimen, mixed donor chimerism can be consistently observed. [45-47] This mixed chimerism is sufficient to produce donor type hemoglobin and revert SCD phenotype. In a study by Abraham et al on 95 patients over 2 years, 35 patients maintained full donor chimerism, 13 patients had graft failure and remaining 47 patients had mixed chimerism (range 10% to 94%). All patients with donor chimerism ≤ 17% had recurrent disease. [43] So, there had been attempts to use lesser intensity regimens, especially in young adults and elderly population.

In fact, there is good data available on the use of reduced intensity regimens using fludarabine, thiotepa and busulfan with anti-thymocyte globulin and muromonab-CD3 experienced reaction. [26] They are better tolerated than chemotherapy based conditioning regimens. They have the advantage of fertility preservation. In an attempt to reduce rejection rates after UCB transplantation, thiotepa was added to a reduced intensity regimen in order to ameliorate the results. This regimen was able to achieve donor engraftment in majority of patients. [38] A higher graft failure has been reported with RIC. [48]

NIH platform is a non-myeloablative regimen used in MSD HSCT and is aimed at tolerance induction and includes

low dose TBI and alemtuzumab and has demonstrated efficacy in children and adults. [49] A nonmyeloablative approach using alemtuzumab/total body irradiation was reported with acceptable efficacy. [50] Alzahrani et al analyzed 122 patients who received non-myeloablative HSCT from matched related donors using TBI of 300cGy, alemtuzumab, filgrastim induced unmanipulated stem cells and sirolimus. Median neutrophil and platelet engraftment occurred on day 22 and 19 respectively. Overall sickle free survival at one year and five year were 93% and 85% respectively. [42] A team of John-Hopkins unit has described a non-myeloablative approach for haploidentical HSCT using ATG, Fu-CY, TBI and subsequently an RIC version that added thiotepa. The median age of the group was 22 years, and showed 100% OS and 93% EFS. This further allowed Nickel et al to suggest reserving myeloablative regimens for a second transplant in minority of patients with graft failure. [51] The ASH guidelines suggest fludarabine-melphalan conditioning regimen for adults with SCD who have a transplant indication. [12]

One of the important challenges with intensity of the conditioning regimens is leveraging between toxicity and engraftment. TBI is an important tool to affect engraftment. Various doses of TBI are being used. In one such attempt dose of TBI was raised from 200 to 400 cGy, substantially reduced graft failure in HSCT.

Multiple reports conclude that conditioning regimen intensity is not associated with survival. [13,18] If survival is not affected than other parameters of importance are rejection, GVHD and chimerism. In case of rejection with NMA and RIC approach a second attempt may be feasible. Mixed chimerism has been reported in all three conditioning settings, in fact up to 29 % even with MAC. [52]

The CIBMTR data included a cohort of 910 patients who underwent HSCT. [48] Myeloablative regimen was busulfan based and non-myeloablative consisted of low-dose TBI with in-vivo T-cell depletion. RIC regimens consisted of melphalan/fludarabine with or without thiotepa. With reduced intensity conditioning regimens, the incidence of graft failure is higher. The rate of chronic GVHD was highest in patients treated with myeloablative regimens, less high in those receiving RIC regimens, and lowest in those receiving NMA conditioning regimens. When OS is compared across three regimens, nonmyeloablative conditioning has the highest survival advantage. [48] A non-myeloablative regimen is recommended in older patients over RIC because HR for EFS was significantly higher (1.00 vs 1.97, 95% CI, 1.15-3.36, p-.013). [48]

American society of hematology guidelines recommend using myeloablative conditioning regimens over reduced intensity in children with matched donor. [12]

In summary, there is no direct comparison between various intensity of conditioning regimens. The issue of conditioning remains investigative and probably should be addressed with keeping some important questions in mind. Looking into the very high prevalence of the disease and very low availability of transplants, the strategies should try to broaden acceptability at scale both by physicians and patients. Philosophies of low cost, low toxicity, mixed chimerism appear to appeal best.

T-Cell Depletion

Some of SCD patients go through multiple blood transfusions in their lifetime. This may increase exposure to minor histocompatibility antigens and thereby, may increase the likelihood of immunologic reactions. [34] ATG, Alemtuzumab, direct T-cell depletion from the stem cell product and other strategies have been employed to reduce the risk. [27, 42, 53] There may be selective removal of the subpopulation of the T-cells. As reported by Bernaudin et al, the addition of ATG allowed them to reduce rejection rate from 23% to 3%. [54] But these strategies may have an impact on engraftment. Removal of specific subset of T cells may be of help in reducing rejection as well as better engraftment.

Outcomes-Advantages of HSCT

HSCT in SCD is associated with reversal of SCD phenotype and resolution of the symptoms. [26, 55] As

majority transplants are done at an early age, their late term side effects are of significant consequence. The late effects are mainly related to reproductive organs, chronic skin and organ damage because of GVHD. The main concern is related to fertility preservation. Damage to reproductive organs is a known complication of chemotherapy. Risk of chronic GVHD and the need to preserve fertility might be indications for a non-myeloablative conditioning. [47] In young adults it may be partially resolved by procedure like oocyte or sperm preservation but remains a challenge in younger children.

Outcomes for pediatric patients have been excellent with Bu/Cy regimen, overall survival ranging from 90-100 % and event free survival from 77 to 100 %. [47, 54, 56] While grade II-IV GVHD has been reported in 11-39% of the patients. Patient reported outcomes of pain intensity improved post-HSCT in a subset of patients with intermittent pain pre-HSCT. However, nearly 40 % of the patients continue to experience pain post HSCT. It may not ameliorate chronic pain. ACS no longer occurs post successful HSCT. It offers improvement in quality of life and prolonged survival.

SCD presents with vaso-occlusive complications with cerebral vasculopathy as one of the most serious complications and overt stroke occurs in 7 to 13% of children, which can lead to motor disability, neuropsychiatric complications, even death and can be a reason chronic morbidity. [57, 58] About 5% to 17% of patients with SCD can develop stroke during childhood and adolescence. [59] The recurrence rate of infarction without regular monthly transfusion in patients who have had a prior clinical stroke can be as high as 67%. [60] Similarly, it has been observed that HSCT in high-risk patients before development of stroke and cerebral vasculopathy reduces the risk of subsequent neurologic complications. [26, 54]

Newer Directions

HSCT has been established as a sole curative option for SCD. Its acceptance rate is still low. [61] There is a wide gap between the number of transplants indicated and performed. There is a need to find novel strategies to shorten this gap. The new research is needed in reviewing the indications and making indications more acceptable by the patients. Recruitment of haploidentical donors with lower toxicity could increase the recruitment for the curative approach. Availability of donors remains the largest challenge. Toxicity is one concern which dissuades patients and physicians, both, from accepting the challenge of transplant. Toxicities can be mitigated by changing pretransplant strategies, conditioning regimes, post-transplant care. [62, 63] Pretransplant strategies focus towards reduction of graft failure. The strategies being investigated include usage of cyclophosphamide, fludarabine, hydroxyurea, azathioprine. [31, 62] T cell depletion strategies are also becoming popular. With more

and more data available, lesser intensity regimens would find a major place in the conditioning. Lessening of transplant related morbidity and mortality would increase the chance of higher acceptability. The post-transplant care with usage of immunosuppression of shorter duration, will also add to more transplants in future. The focus on genetic engineering combined with transplant will be game changer in the patient care of SCD. [64, 65]

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