Chapter 11

Stem Cell Transplantation in Patients with Sickle Cell Disease

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Abstract

Hematopoietic stem cell transplantation (HSCT) is currently the only established cure for sickle cell disease (SCD). Replacement of the stem cell that has the defective beta globin allele with the normal gene decreases hemoglobin S and the risk of complications of SCD. The first case reported was a girl with acute myeloid leukemia and SCD who received HSCT and achieved long-term SCD and leukemia-free survival. Given the favorable outcomes of HSCT with thalassemia major using myeloablative preparative regimens, this approach became widely used in the initial studies of HSCT in SCD. The current standard of care is to use a myeloablative stem cell transplantation in patients with severe disease who have human leukocyte antigen–identical sibling. HSCT improves organ function, quality of life, and overall and disease-free survival. However, this is associated with high risk of gonadal dysfunction and graft versus host disease in addition to the mortality associated with the myeloablative HSCT. Reduced-intensity HSCT has also been reported with high rates of engraftment and favorable outcomes. This has been introduced to lower the gonadal dysfunction, mortality, and graft versus host disease associated with myeloablative approaches. Other approaches include HSCT using matched unrelated donors, cord blood units, and human leukocyte antigen haploidentical donors. Unfortunately, graft rejection is a common complication with these approaches. In this chapter, we review the indications of HSCT for SCD and outcomes of different transplant strategies including alternative donor transplant, graft rejection, and infertility after transplantation.

Keywords: sickle cell disease, hemoglobinopathy, stem cell transplantation, myeloablative, reduced intensity, graft rejection

1. Introduction

Replacement of the stem cell that has the defective beta globin allele with the normal gene decreases Hemoglobin S and the risk of complications of sickle cell disease (SCD). This could be achieved through gene therapy or allogeneic Hematopoietic stem cell transplantation (HSCT). The proof of principle case was an 8-year-old girl with acute myeloid leukemia (AML) and SCD who received HSCT for AML. Her AML was in remission 22 months posttransplantation and she was free of SCD.

The utility of HSCT in patients with SCD was shown in multiple studies since over 20 years with disease-free survival (DFS) of 90% [1, 2]. The improved organ function and decreased risk of SCD-related complications are attractive goals of therapy in these patients [3, 4]. Furthermore, SCD cure by HSCT is associated with improved quality of life scores in the physical, social, and emotional domains [5, 6].

Despite the promising results of HSCT in SCD, there are a number of unresolved issues limiting its' widespread application. The number of HSCT for SCD remains less than expected and cost is one of the major factors behind this knowing that the disease is much more prevalent in countries with low income [7, 8]. The course and severity of the disease cannot be accurately predicted with the currently available tools making it difficult to recommend HSCT early before end organ damage [9, 10]. This is especially important in children without end organ damage where one can debate the utility of HSCT for mild disease before damage occurs. In addition, most of the preparative regimens used are myeloablative [11] and these have led to high rates of gonadal dysfunction in patients who have not yet completed their family. This is even more of an issue in cultures where SCD is prevalent. Another issue is the limited number of siblings in families with SCD potentially giving rise to two problems, the low probability of finding a matched sibling donor (MSD) and the risk of mobilization of siblings with sickle cell trait. Unfortunately, for patients with no MSD, the probability of finding a matched unrelated donor (MUD) is low [12]. The theoretical risk of mobilizing donors with sickle cell trait is probably not real and the safety has been shown in multiple small studies [13].

2. Indications of HSCT in SCD

HSCT is the only curative treatment option for patients with SCD. However, it can be associated with significant toxicities making it a good treatment option for patients with severe disease who have a human leukocyte antigen (HLA) MSD [11]. Therefore, its initial use was limited to severe SCD, which is defined by the presence of one or more of SCD complications that include stroke or central nervous system event lasting longer than 24 hours, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions, recurrent vasoocclusive pain (≥2 episodes per year for several years, recurrent priapism), impaired neuropsychological function and abnormal cerebral MRI scan, stage I or II sickle lung disease, sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30–50% of the predicted normal value), bilateral proliferative retinopathy and major visual impairment

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in at least in one eye, osteonecrosis of multiple joints, and/or red cell alloimmunization (≥2 antibodies) during long-term transfusion therapy [14]. Unfortunately, besides fetal hemoglobin there are no well-established prognostic markers that can indicate which patients are most likely to develop severe disease making it difficult to determine risk benefit ratio of HSCT for patients with less severe disease.

The indications above were adopted from the inclusion criteria of the first major trial of HSCT in patients with SCD involving 22 children [14]. There is no evidence-based medicine guideline to inform practice and all available guidelines are expert and consensus recommendations. A recent evidence-based focused review [15] divided the indications according to the donor source; however, the quality of evidence is not superior to expert and consensus recommendations. The review suggests that as the severity of SCD worsens, more experimental approaches could be utilized. Below, we list the indications of HSCT according to the donor source as recommended in the review [15].

When MSD is available:

- Stroke or high risk of stroke (elevated transcranial Doppler velocity).
- Recurrent acute chest syndrome.
- Recurrent severe acute painful crises.
- Red cell alloimmunization in patients on chronic transfusion protocol.
- Pulmonary hypertension.
- Recurrent priapism.
- Sickle nephropathy.
- Bone and joint involvement.
- Sickle retinopathy.

When MUD is available:

- Stroke or high risk of stroke (elevated transcranial Doppler velocity).
- Recurrent acute chest syndrome.
- Recurrent severe acute painful crises.
- Red cell alloimmunization in patients on chronic transfusion protocol.
- Pulmonary hypertension.
- Recurrent priapism.
- Sickle nephropathy.
- Bone and joint involvement.

When neither MSD nor MUD is available, mismatched marrow, haploidentical, or unrelated cord blood donor transplantation could be considered when:

- Recurrent stroke in patients on chronic transfusion therapy.
- Failure to tolerate the supportive care (e.g., chronic transfusion) in severe SCD.

HSCT for SCD offers a cure, but with variable morbidity especially graft versus host disease (GvHD) and treatment-related mortality. The risk benefit ratio should be considered when offering HSCT for patients and their families. The risks of complications and options should be discussed with the patients and their families for shared decision making. Outcomes and the nature of evidence for the available transplant donor should be balanced with the severity of SCD and the two should be presented to the patients and their families before a decision to undergo the procedure is made. Finally, the new and experimental approaches should only be performed in experienced transplant centers. Comparison of different transplant outcomes between the different transplant strategies is summarized in **Figure 1**.

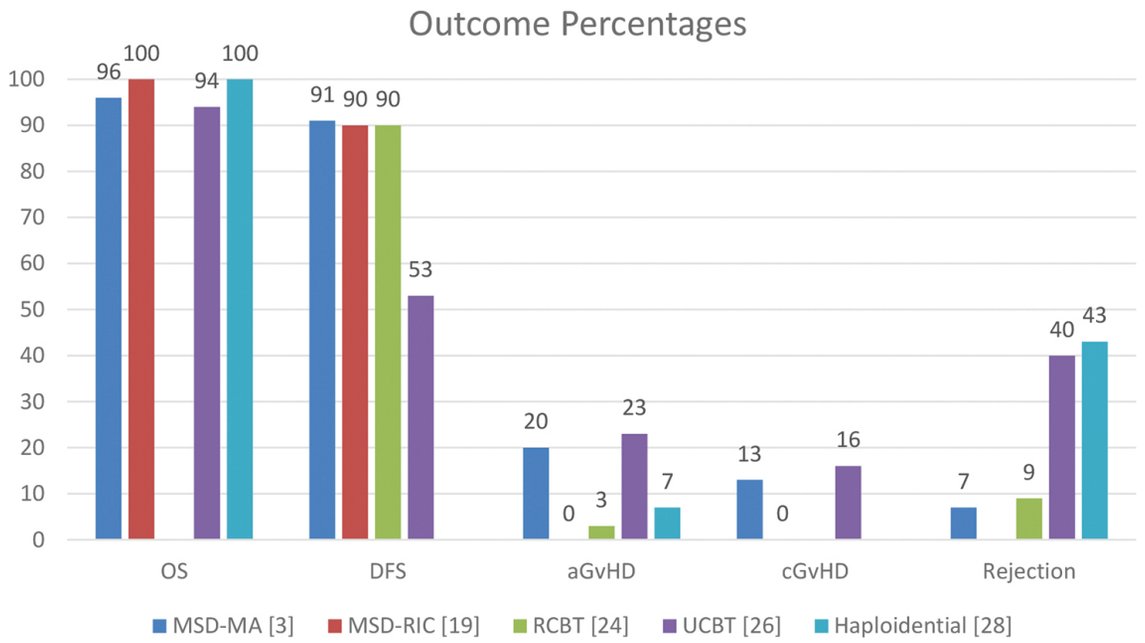

Figure 1. Comparison of transplant outcomes between different transplant strategies. Abbreviations: MSD-MA, matched sibling donor-myeloablative; MSD-RIC, matched sibling donor-reduced intensity conditioning; RCBT, related cord blood transplantation; UCBT, unrelated cord blood transplantation; OS, overall survival; DFS, disease free survival; aGvHD, acute graft versus host disease; cGvHD, chronic graft versus host disease. Note: The numbers in the figure are summarized for representative study of each transplant strategy. In MSD-MA study, the aGvHD rate only represents the high grade.

3. HSCT from MSD using a myeloablative preparative regimen

Preparative regimens and outcomes of HSCT in thalassemia major have influenced the strategies used in HSCT in patients with SCD. Myeloablative, nonradiation-based regimens were commonly used with high rates of engraftment and DFS [11]. The most commonly used was busulfan with cyclophosphamide at myeloablative doses and this became the preferred

regimen in many of the future SCD transplant studies [11]. One of the earliest prospective studies was reported by Walters et al. [14]. In this study, a myeloablative regimen using busulfan and cyclophosphamide with antithymocyte globulin (ATG) was used in 22 patients with severe SCD. With a median follow-up of 2 years, overall survival (OS), and DFS were 91 and 73%, respectively. The high grade acute graft versus host disease (aGvHD) and chronic graft versus host disease (cGvHD) rates were 15 and 12%, respectively.

Another study reported by Bernaudin et al. [3] included 87 children with SCD, most of which had cerebrovascular event as the indication of the HSCT. The preparative regimen used was busulfan with cyclophosphamide at myeloablative doses. The ATG was later added to the regimen. The DFS was 91% with OS of 96%. The rates of high grade aGVHD and cGvHD were 20 and 13%, respectively. Two other studies using a similar preparative regimen reported OS of 85–96% [16, 17]. Given the high rates of DFS and OS, myeloablative preparative regimen using MSD is considered the standard of care for patients with SCD undergoing HSCT.

4. HSCT from MSD using reduced intensity preparative regimen

After the encouraging results of myeloablative preparative regimens in children, attempts to include adults using reduced intensity regimens were tried. The rationale was based on the assumption that mixed chimerism may be enough to ameliorate the complications of SCD and unlike in malignant conditions, myeloablation is not needed [18]. The use of reduced intensity regimens has expectedly resulted in less transplant-related organ dysfunction and may have preserved fertility, which is an important limitation of myeloablative transplantation.

Hsieh et al. [19, 20] investigated this approach in 30 adult patients using peripheral stem cell transplants. The preparative regimen constituted of 300 cGy of total body irradiation (TBI) with alemtuzumab and using sirolimus for GvHD prophylaxis. Most patients (26 out of 30) had a successful engraftment and no treatment related mortality, or GvHD was reported. This was attributed to the intensive GvHD prophylaxis using alemtuzumab and sirolimus. The DFS of 90% and OS of 100% were very encouraging. No data are yet available on the gonadal dysfunction of this approach.

Another study by Bhatia et al. [21] using a reduced toxicity, albeit myeloablative, preparative regimen with busulfan, fludarabine, and alemtuzumab in 18 patients with a median age of 8.9 years reported 17% of high grade aGvHD and 11% cGvHD. There was no graft rejection and all patients were alive at the time of the study report.

5. HLA matched unrelated donor transplantation

The probability of finding an HLA MUD is lower than desired in patients with SCD. In a report from the National Marrow Donor Program, the probability of finding a 6/6 MUD for patients with SCD was 60% [12]. The probability is much lower, 20%, when a more strict criteria using

8/8 matching at the allelic level is used [22]. This is likely due to the underrepresentation of the haplotypes of this genetic group in the international stem cell donor registries. Overall, the studies of MUD transplantations in SCD are scarce and include very small number of patients. There is a high risk of graft failure and other transplant-related complications with the MUD approach [23]. A number of prospective studies are currently running and results should be available in the near future. At this time, transplantation for patients with SCD from a MUD donor should only be done in a clinical trial setting.

6. Related cord blood transplantation (RCBT)

Related cord blood transplantation (RCBT) achieves OS and DFS rates similar to that of MSD transplantation, except for a significantly longer engraftment time for neutrophils and platelets. In a comparative study [24] of bone marrow HSCT versus RCBT in patients with hemoglobinopathies, 30 patients received RCBT for SCD. Patients in the RCBT group were mostly children and received a myeloablative preparative regimen. Serotherapy was given in more than half of the patients. The median total nucleated count (TNC) was 3.9×10^7/kg. With a median follow-up of 70 months, the DFS at 6 years for this group was 90% and no patient developed grade IV aGvHD or extensive cGvHD. The cumulative incidence of primary graft failure in the entire RCBT group was 9%. For those who engrafted, the cumulative incidence of day 60 neutrophil and day 180 platelet recovery was 90% (median 23 days) and 83% (median 38 days), respectively. Although the results of RCBT are not markedly different than that of MSD, the delayed recovery of neutrophils and platelets increases the risk of infection and bleeding complications, particularly, the central nervous system. In addition, the probability of finding RCBT unit is limited given the limited number of siblings in families with SCD. Finally, the availability of the RCBT is limited in areas where it is mostly needed, such as Africa.

7. Unrelated cord blood transplantation (UCBT)

The outcomes of unrelated cord blood transplantation (UCBT) are inferior to that of RCBT for patients with SCD. Two of the largest series are the Eurocord study [25] and the SCURT trial [26]. In the Eurocord study [25], 16 patients were transplanted with a mixture of myeloablative (10 received busulfan with cyclophosphamide or fludarabine) and reduced intensity preparative regimens (6 received fludarabine with busulfan, melphalan, or cyclophosphamide). Most patients received serotherapy with either ATG or alemtuzumab. All units were at least 4/6 HLA matched with a median TNC of 6 and 4.9×10^7/kg at the time of collection and infusion, respectively. The engraftment was only 60% with a 2-year OS and DFS of 94 and 53%. The rates of acute and chronic GvHD were 23 and 16%, respectively. In the SCURT trial [26], only eight patients were studied and all received similar nonmyeloablative preparative regimen using melphalan, fludarabine with alemtuzumab. All patients received at least 5/6 HLA matched units with a median TNC of 6.4×10^7/kg. Only three patients engrafted and one died of extensive cGvHD. In a similar small study [27] of eight patients (only five evaluable) using

busulfan, fludarabine, and alemtuzumab, only 63 and 50% engrafted neutrophils and platelet, respectively. Twenty-five percent of patients had high grade aGvHD. The overall event-free survival and OS at 2 years were 50 and 63%, respectively.

Given the high rates of graft rejection and the delayed immune reconstitution that is associated with UCBT, this modality should only be used in a study. Possible ways to improve this modality are using higher intensity preparative regimens, using higher TNC, and lower mismatches. Double cord blood or cord blood supplemented with bone marrow are two promising options especially with children.

8. Haploidentical stem cell transplantation

HLA haploidentical HSCT is a promising alternative for patients with SCD with no available MSD. Nevertheless, it is characterized by high rate of graft failure. In a prospective study of 17 patients with SCD [28], 14 patients received a haploidentical transplantation. The preparative regimen was similar to the most widely used T cell-replete haploidentical HSCT with cyclophosphamide, fludarabine, and TBI using bone marrow as the stem cell source. The mycophenolate and the calcineurin inhibitor were used in addition to the posttransplant cyclophosphamide as aGvHD prophylaxis. In this study, ATG was added for 3 days starting Day -9. With a median follow-up 711 days, 10 patients were asymptomatic from SCD and 6 stopped immunosuppression. No deaths were reported and only one patient had GvHD of the skin. Unfortunately, the probability of graft failure was high at 43%. The use of haploidentical transplantation in SCD should be only used in a study setting.

9. Graft rejection

HSCT using myeloablative preparative regimen and HLA MSD has relatively low risk of graft rejection [11]. Bernaudin et al. reported an overall cumulative incidence of rejection of 7.0% at 5 years [3]. The addition of ATG to the preparative regimen resulted in a significant decrease in the 5-year cumulative incidence of rejection from 22.6 to 2.9% in patients who received ATG. A number of other studies using similar myeloablative regimens reported rejection rates of up to 10% [14, 17].

The rejection rate is different outside myeloablative transplantation; graft loss may not be uncommon complication of transplant using nonmyeloablative preparative regimens [11]. Attempts to improve this with higher intensity of nonmyeloablative regimens improved the rejection rate but with high proportion of mixed chimerism [20, 29, 30]. The mixed chimerism, if stable, may be enough to ameliorate the complications SCD [18]. Locatelli et al. reported rejection rate of 9% with RCBT which is similar to the MSD transplantation using myeloablative protocol. The URCB and the HLA haploidentical transplantation are associated with high risk of graft rejection of over 40% [25, 28, 31].

10. Infertility

The risk and fear of infertility is a major limiting factor on the widespread use of HSCT in patients with SCD. This high risk of infertility from HSCT in a benign condition limits the referral of patients. In addition, it also adds to the worries and deferral factors for patients to undergo the procedure.

The assessment of infertility post HSCT in children and young adults is difficult and only surrogate endpoints like gonadal dysfunction are used which limits the interpretation of studies of fertility post HSCT. The use of a standard approach of HSCT in SCD is associated with high risk of gonadal dysfunction. In the prospectively U.S. study [4], the use of a myeloablative preparative regimen lead to hypogonadotropic hypogonadism in most of the pubertal males and primary ovarian failure in the majority of postpubertal females. In another study using a similar preparative myeloablative regimen with ATG or radiation [17], all patients who were transplanted after puberty had gonadal dysfunction. The use of reduced intensity preparative regimens may lower the risk of gonadal dysfunction; however, it is yet to be shown prospectively.

11. Quality of life and long-term complications

Sickle cell disease impacts health related quality of life (HRQL) in children and adults [32–35]. The impact is worse in females and older children [34]. In adults, HRQL scores may be similar to patients receiving hemodialysis [36]. Unfortunately, it is not yet known with confidence that HSCT improves HRQL in patients with SCD. Studies addressing this question are small in number and sample size and predominantly examined reduced intensity HSCT [5, 6, 37]. HRQL scores improved in patients who received reduced intensity chemotherapy-based HSCT. The improvement was more marked with longer follow-up after transplant [5]. The improvement was noticed across all domains of and in parent-reported HRQL. Similar results were observed in patients who received chemotherapy-free (TBI-/alemtuzumab-based) HSCT [37]. The improvement in scores included the bodily pain, general health and vitality.

Long-term complications and reintegration have not been well addressed in literature despite a relatively long history of HSCT in SCD. In a study with a median follow-up of 9 years of 22 children with SCD who received HSCT from MSD [38], the overall survival was 93% and there was no recurrence of graft failure. This study was able to demonstrate that even with long-term follow-up; the engraftment and protection against SCD-related complications were sustained.

12. Conclusions

HSCT for severe SCD offers cure and a chance of amelioration of SCD-related complications. Myeloablative HSCT using HLA MSD remains the standard of care. RCBT offers similar results

but longer time to count recovery. Transplantation from MUD, UCBT, or HLA haploidentical donors should only be practiced in a study setting in experienced transplant centers. Reduced intensity transplantations from MSD offer stable mixed chimerism and may decrease the risk of gonadal dysfunction in these young patients. Attempts to expand the pool of donors should continue.

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