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Allogeneic Stem Cell Transplantation for Sickle Cell Disease

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Abstract

Purpose of Review—As the safety and availability of allogeneic hematopoietic stem cell transplantation (HSCT) have improved, this procedure is becoming a viable option for non-malignant conditions such as sickle cell disease (SCD). There are very few treatment options available for SCD, and even with optimal care SCD patients still suffer from a myriad of comorbidities to multiple organ systems and have a decreased life span. In this review we will summarize results from trials of HSCT for children or adults with SCD using a variety of graft sources as well as conditioning and GVHD prophylaxis regimens, and discuss the unique challenges that arise in these patients.

Recent Findings—AlloHSCT for SCD has been performed on small numbers of patients at multiple centers around the world using several different transplant platforms, and early outcomes are encouraging. Overall survival is excellent, although graft failure remains a challenge.

Summary—As alloHSCT becomes safer and more widely available, the procedure should be considered for patients with severe disease phenotypes in whom the potential benefits of transplantation outweigh the complications from the disease. AlloHSCT has been shown to reverse or at least halt the progression of end-organ damage secondary to SCD. More research is needed to understand the mechanisms underlying graft failure in SCD recipients, as well as to understand the biopsychosocial underpinnings of persistent pain in the post-transplant period to maximize the benefit from the transplant procedure.

Keywords

hematopoietic stem cell transplantation; sickle cell disease; haploidentical donor

Introduction

Hematopoietic stem cell transplantation (HSCT) was originally developed as a treatment for certain relapsed or refractory hematologic malignancies. In its infancy, allogeneic HSCT was only possible for patients with a fully human leukocyte antigen (HLA)- matched sibling donor. With the development of improved regimens for graft-versus-host disease (GVHD) prophylaxis, the donor pool has expanded to include matched unrelated donors, partially

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HLA-mismatched related donors, and unrelated umbilical cord blood. Transplant-related mortality is approximately 10% in most recent large studies.[1-5] As the safety of HSCT increases, the risk of undergoing HSCT for non-fatal diseases becomes more acceptable.

Sickle cell disease (SCD) is an inherited hemoglobinopathy that causes anemia and other serious morbidities such as retinopathy, nephropathy, acute chest syndrome (ACS), stroke, venous thromboembolism, chronic pain, and acute vaso-occlusive crises (VOC). There are over 100,000 people living with SCD in the United States alone, [6] and many more in Africa and the Middle East. SCD is an attractive target for transplantation given the comorbidities and lack of approved therapies, which currently consist only of red blood cell (RBC) transfusions and hydroxyurea (HU). Even with early identification of patients through newborn screening programs, use of available therapies, and optimal supportive care, SCD patients still have a decreased lifespan.[7] There is also a disproportionately high economic cost to patients with SCD due to disability.[8] AlloHSCT is a potentially curative therapy for SCD because engraftment results in the replacement of recipient blood cells, including RBCs, with those of the unaffected donor. AlloHSCT is reserved only for patients with severe complications of the disease such as stroke, recurrent ACS, or frequent VOC since for patients with a mild phenotype, the benefits of transplantation do not currently outweigh the risks.

HLA-matched sibling transplants

Historically, using a fully HLA-matched sibling as a donor for transplantation has been considered the gold standard in terms of safety, engraftment, and GVHD. The first use of HSCT in a SCD patient was actually performed in a child with acute myeloid leukemia. HSCT cured the leukemia but was also curative for SCD since the donor had hemoglobin AS.[9] Since that time other larger scale studies have been performed using myeloablative (MA) conditioning and HLA-matched donors and are summarized in Table 1 and below.

Walters published results of the first cohort of 22 patients who underwent transplantation for severe SCD. Two patients died, but 15 of the 20 survivors had successful engraftment and disease-free survival (DFS). End organ function was assessed prospectively, and for the patients who suffered a stroke pre-HSCT, MRI showed stable disease following transplant. In addition, patients with abnormal pulmonary function due to prior ACS had stable lung function following HSCT. This seminal study demonstrated that, although cure of SCD was possible, the high rate of graft failure was a challenge.[10]

The Center for International Blood and Marrow Transplant Research retrospectively analyzed 67 pediatric patients who were transplanted between 1989 and 2002. Patients received MA conditioning, mostly with busulfan/cyclophosphamide (Bu/Cy), and GVHD prophylaxis primarily with cyclosporine and methotrexate.[11] Acute GVHD was observed in 10% of patients at 100 days, but chronic GVHD was more common with the five-year probability being 22%. The 5-year probability of DFS was 85%. Graft failure occurred in nine patients and was associated with a history of multiple RBC transfusions pre-transplantation. Self-resolving veno-occlusive disease (VOD) developed in four patients, three patients died, and the (OS) survival at five years was 97%.[11]

Similar outcomes have been reported by Bernaudin et al. The 87 patients in this study received MA conditioning with Bu/Cy, and anti-thymocyte globulin (ATG) was later added to reduce the risk of graft failure.[12] The majority received grafts from HLA-matched siblings, but four patients had donors with one HLA allele mismatch. Graft failure occurred in seven patients and was associated with transplantation prior to using rabbit ATG for conditioning. There were six transplant-related deaths, with four secondary to severe GVHD. The incidences of acute and chronic GVHD were 20% and 12.6%, respectively. Factors associated with GVHD were age > 15 years and HLA-mismatch. Transplantation was complicated by posterior reversible encephalopathy syndrome (PRES) in seven patients. At long-term follow-up, 77 out of 81 living recipients had full donor chimerism and 79 patients were free of disease.[12]

Long-term follow-up data are available for a cohort of patients who underwent HLA-matched sibling transplantation in Belgium. The first study, published in 1998, reported on 50 subjects who were analyzed in two groups. The first group (n=36) underwent HSCT because of severe comorbidities, and the second group (n=14) had less severe disease but were transplanted because they were returning to their home countries where adequate care for SCD was unavailable. Graft rejection occurred in two cases, although one was salvaged by a second transplant using the same donor. There were six cases of durable mixed hematopoietic chimerism.[16] Patients in this initial study received cyclosporine or cyclosporine plus methotrexate for GVHD prophylaxis. Eighteen patients had seizures in the peri-transplant period, and addition of seizure prophylaxis did not decrease the incidence. [16] The same group published an updated study in 2014 on 50 consecutive patients transplanted between 1988 and 2013, thus including some patients from the original cohort. Rabbit ATG was added to the conditioning after 1991, and starting in 1995 all patients were treated with HU for at least three months prior to HSCT. There were no graft failures, and with a median follow-up of eight years, OS of the entire cohort was 94.1% and event-free survival was 85.6%. [13] The improvement in outcomes was attributed in part to the use of HU. In a small cohort of 24 patients they found that recipients who had received HU prior to HSCT and also received ATG as part of their conditioning regimen (n=13) had no graft failure.[17] They hypothesized that the decrease in $CD4^+$ cells from HU [18] led to decreased graft failure and hence better outcomes.

Another case series of 11 patients with SCD who underwent HLA-matched HSCT using MA conditioning and cyclosporine and methotrexate for GVHD prophylaxis was recently published by a group in Spain. Of these 11 patients, one died from acute GVHD of the gut, one had secondary graft failure with reoccurrence of SCD symptoms, and one had stable mixed chimerism.[14] This cohort had a particularly good rate of engraftment, although it’s not exactly clear why their outcomes were better since they used standard conditioning and GVHD prophylaxis regimens. Further analysis of this cohort should be undertaken to determine factors that contributed to high rates of engraftment.

There is valid concern in the field regarding both the short- and long-term effects of MA conditioning, and studies are ongoing to determine how to best reduce toxicity. Nonmyeloablative (NMA) conditioning is particularly appealing for adults since their comorbidities from SCD can contribute to being a poor candidate for myeloablation. Several

trials investigated the use of less toxic conditioning regimens, and are summarized in Table 2 and below.

Krishnamurti and colleagues reported on seven patients who received HLA-matched sibling bone marrow after a reduced-intensity conditioning (RIC) regimen of busulfan, fludarabine, equine ATG, and total lymphoid irradiation, with cyclosporine and mycophenolate mofetil for GVHD prophylaxis. Six of seven patients engrafted, experienced resolution of all disease-related symptoms, and remain stable mixed hematopoietic chimeras following discontinuation of immunosuppression. The seventh patient did not engraft but recovered autologous hematopoiesis.[19] Hsieh et al. developed a NMA protocol and, of 30 SCD patients who received HLA-matched grafts, there was no treatment-related mortality but one patient died from intracranial bleeding after relapse of SCD. An impressive 87% of patients had stable chimerism and no GVHD. Importantly, measures of morbidity such as days in hospital, narcotic use, cardiac function, and anemia were all improved after HSCT.[20]

Horan and colleagues tested the hypothesis that adding fludarabine to Bu/Cy and ATG would allow for dose-reduction of busulfan and cyclophosphamide. Cyclophosphamide was reduced by 55% without affecting engraftment, although when they attempted to reduce the busulfan dose two patients did not achieve full donor chimerism, which triggered trial-stopping rules. All patients survived and were disease free at follow-up ranging from 9-23 months. There was an increase in GVHD seen in patients who received lower doses of cyclophosphamide, although this represented only four patients, so more study will be needed to understand how the conditioning regimen influences GVHD.[21]

Iannone and colleagues published a report on outcomes following NMA transplantation using HLA-identical sibling grafts for six patients with SCD as well as one with thalassemia. The NMA conditioning used fludarabine, total body irradiation, and horse ATG. Only one patient had GVHD, none died, and six of seven had mixed chimerism early post-HSCT. However, as immunosuppression was tapered, all of these patients eventually lost their grafts and recovered with autologous hematopoiesis. Although the trial demonstrated that this NMA approach was safe, the outcome was disappointing and demonstrated the challenges of engraftment in this patient population.[22]

The Sickle Cell Unrelated Donor Transplant Trial used RIC and cord blood grafts for pediatric patients with severe SCD. In this trial only three out of eight patients engrafted and remained disease free, while the other five had autologous hematopoietic recovery. There was also one death from extensive chronic GVHD in this cohort.[23] Although the incidence of graft failure in this trial was high, patients did have autologous recovery of blood counts, demonstrating relative safety of the approach and justifying further studies into less toxic conditioning regimens.

Partially HLA-mismatched related donor (HLA-haploidentical) HSCT

Although the outcomes of HLA-matched sibling HSCT for SCD are encouraging, it is estimated that only 15% of SCD patients have an unaffected, HLA-matched sibling.[25] In

contrast, nearly every patient has an HLA-haploidentical first-degree relative, thus offering a potential solution to the problem of donor availability for patients with SCD.

Investigators at St. Jude's Research Hospital compared long-term outcomes in children receiving transplants from an HLA-matched sibling after MA conditioning versus a haploidentical parent after RIC. GVHD prophylaxis in this study was cyclosporine and methotrexate. At a median follow-up of nine years, 13 of 14 patients receiving an HLA-matched graft were alive, with the one death being attributed to chronic GVHD. At five years all survivors remained engrafted with > 85% donor chimerism. Six of eight patients receiving haploidentical transplant were alive at a median follow-up of seven years, with the two deaths again being attributed to GVHD. However, three of eight haplo recipients experienced graft failure and recurrence of symptoms, leaving only three out of eight patients engrafted and disease-free.[15] All patients in both cohorts who achieved sustained engraftment achieved transfusion independence and decrease in iron load. [15]

The Johns Hopkins experience of HSCT for SCD was published in 2012 and included three patients who had an HLA-matched donor and 14 with haploidentical-related donors. The NMA regimen included fludarabine, cyclophosphamide, TBI, and ATG. Patients received high dose post-transplantation cyclophosphamide, mycophenylate mofetil, and either tacrolimus or sirolimus for GVHD prophylaxis. The incidence of graft failure was 43% in haploidentical pairs. However, there was no mortality in this study and only one patient had GVHD of the skin only that did not require treatment. All patients who engrafted became transfusion independent, and of the 17 patients who started the trial, a striking 41% are no longer taking narcotics.[24] The results are encouraging that in the future, transplant can become a more widely utilized and safe option for patients with this chronic disease.

Unique challenges in transplantation for sickle cell disease

The experience with transplantation in this population has identified several unique challenges as outlined in Table 3. HSCT is known to affect fertility in all patient populations. A study assessed the ovarian reserve of young female SCD patients who had undergone HSCT. Of the nine HSCT patients assessed, all of them had undetectable anti-mullerian hormone and 89% has follicle-stimulating hormone levels in the menopausal range.[26] Similar results were found in the study by Dallas et al., in which only five of nine males and two of four females had normal gonadal function following transplantation.[15] Patients in this study had received MA conditioning, so further study must be done to assess the effect of NMA conditioning on fertility. In a separate prospective trial, over half of female recipients of HSCT had diminished ovarian reserve, and only three of 13 males had normal testosterone levels following HSCT, consistent with a diagnosis of hypogonadotropic hypogonadism.[27] Ovarian hyperstimulation and oocyte preservation has been done successfully in SCD patients prior to undergoing HSCT,[28] and sperm cryopreservation is also possible. It is particularly important for physicians to be proactive about discussing fertility preservation including the use of gamete or embryo cryopreservation since many SCD patients are being transplanted at young ages before they are ready to consider child-bearing.

The aforementioned studies demonstrate that graft failure is clearly a major challenge in transplantation for SCD. This is in stark contrast to alloHSCT for hematologic malignancies, where graft failure is below 5% in recent studies.[1,3,29,30] Unlike hematologic malignancy patients, SCD patients are not exposed to cytotoxic chemotherapy prior to transplant conditioning and so have intact immune systems that can mediate graft failure. Allosensitization through multiple RBC transfusions also increases the risk of graft failure for patients with SCD. Intensification of the conditioning regimen reduces the risk of graft failure but increases toxicity to vital organs and increases the risk of severe GVHD, an unacceptable complication of alloHSCT for non-malignant disorders. In our opinion, the biggest challenge in alloHSCT for SCD is to develop a conditioning regimen that minimizes toxicity without compromising engraftment.

AlloHSCT in the SCD population has a higher incidence of neurological toxicity than patients who are transplanted for other diseases. While the etiology of this is not known, many patients with SCD have pre-existing strokes or silent cerebral infarcts and so may have a low threshold for further damage. In the Belgian study, six out of 50 patients developed PRES. The majority of patients in this trial received cyclosporine and methotrexate for GVHD prophylaxis, with the remainder receiving cyclosporine alone (UCB recipients) or cyclosporine and mycophenolate mofetil. Changing GVHD prophylaxis to sirolimus significantly reduced the incidence of PRES in our cohort.[24] Patients who undergo HSCT for SCD also have a higher incidence of seizures in the peri-transplant period than do other populations. All patients receive anti-convulsants for prophylaxis but this has met with varying degrees of success. Further research is needed to understand the mechanisms behind the neurological complications unique to this population.

Conclusions

Allogeneic HSCT is a curative option for patients with HSCT. Currently it is only used for patients with severe manifestations of the disease, but as we optimize conditioning regimens and GVHD prophylaxis and safety continually increases, this may become a more widely utilized option. Small numbers of patients have undergone transplants from haploidentical donors, which has been shown to be safe and results are encouraging that in the future this procedure may be available for more patients as the donor pool expands. Graft failure remains the most significant challenge, and more research in preclinical models as well as clinical trials are needed.

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Key Points

- HSCT is a curative option for SCD, and may be an appropriate therapy for patients with severe manifestations of the disease.
- Graft failure remains the greatest challenge in transplantation for SCD.
- The use of RIC/NMA conditioning regimens has increased the safety of transplantation, and further research is needed to tailor conditioning regimen to optimize engraftement in this population.
- The use of haploidentical donors expands the donor pool and is a safe alternative when HLA-matched donor is unavailable.

Table 1

Summary of MA, HLA-identical HSCT for SCD.

Ref.	n, age range (years)	Graft failure	Acute GVHD, Grade II-IV	Chronic GVHD	Overall survival	Disease-free survival
Walters et al[10]	n=22 3-14	18%	9%	4.5%	91% at 4 years	73% at 4 years
Panepinto et al [**] [11]	n=67	13.4%	10%	22%	97% at 5 years	85% at 5 years
Bernaudin et al [12]	n=87 2-22	22.6%/ 3% [*]	20%	12.6%	93.1% at 6 years	86.1% at 6 years
Dedeken et al [13]	n=50 1-15	8%	22%	20%	94.1% at 8 years	85.6% at 8 years
García-Morin et al[14]	n=11 2-13	18%	55%	0%	90.9% at 3 years	81.9% at 3 years
Dallas et al (MRD cohort) [15]	n=14 5-17	0%	28%	21%	93% at 9 years	93% at 9 years

[*] Graft failure was 22% in patients who did not receive ATG during conditioning, and 3% in patients who received ATG during conditioning.

[**] Study included an unknown number of patients reported in Walters et al (1996).

Table 2

Summary of NMA/RIC and non-HLA-identical HSCT for SCD.

Ref.	Study period, n, age range (years)	Graft failure	Mean donor chimerism, myeloid/T cell compartments	Acute GVHD, II-IV	Chronic GVHD	Overall survival	Disease-free survival*
Krishnamurti et al[19]	~1999-2006, n=7, 6-18	14.3%	M: 78% (range 76-100%) T: 68.5% (range 50-90%)	28.6%	14.3%	100%	85.7%
Hsieh et al[20]	2004-2013, n=30, 16-65	13.3%	M: 86% (95% CI, 70-100% T: 48%, (95% CI, 34-62%)	0%	0%	96.7% at 3 years	87%
Horan et al [21]	2009-2013, n=14, 4-16	32%	M: 67% (95% CI, 55-80%) T: 96% (95% CI, 91-101%) (calculated)	14.3%	14.3%	100%	100%
Iannone et al [22]	1999-2001, n=7**, 3-20	14% primary graft failure, 86% secondary graft failure	Donor chimerism < 10% in long term follow up for all patients	14.3%	0%	100%	0%
Kamani et al [23]	~2008-2011, n=8, 7.4-16.2	62.5%	NR	25%	12.5%	87.5% at 2 years	37.5%
Dallas et al (RIC, haplo cohort) [15]	~2000-2012, n=8, 4.2-13.4	38%	Not reported	50%	37.5%	75% at 7 years	38%
Bolanos-Meade et al [24]	2006-2011, n=14 (11 haplo and 3 MRD),	21.4% overall, 43% for haplo	Unsorted: 80% T: 71% (calculated)	0%	0%	100%	64.7%

* defined as not requiring treatment for SCD

** 6 patients with SCD, and 1 patient with thalassemia

Table 3

Special considerations for HSCT in SCD populations

Challenge	Potential solutions
High incidence of graft failure	Consider HU pre-HSCT, consider early transplant before patients are allo-immunized from multiple transfusions.
High incidence of PRES	Use alternative methods such as sirolimus for GVHD prophylaxis. Use of anticonvulsants is standard but has not proven to be effective.
Incidence of infertility	Fertility preservation including offering gamete retrieval and cryopreservation should be discussed with all patients and their families prior to HSCT.
Chronic pain post-transplant	Consider a multi-disciplinary approach with psychiatry, neurology, and behavioral therapy.