CME Article

Evidence-based focused review of the status of hematopoietic stem cell transplantation as treatment of sickle cell disease and thalassemia

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Disclosures

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Learning objectives

1. Describe the indications for HSCT in SCD, as discussed in an evidence-based review.
2. Identify expected outcomes of HSCT for SCD.
3. Assess the indications for and outcomes of HSCT for transfusion-dependent thalassemia.

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Case presentation

Case 1. Kierra Malcom,† a 17 year old with homozygous sickle cell disease (HbSS), was on chronic erythrocytapheresis after she suffered a stroke at 8 years of age. With the intervention, her hemoglobin S level was consistently maintained between 25% and 35%. Iron chelation was commenced at the age of 10 years. She is currently on oral deferasirox and has a ferritin level of 1400 ng/mL. T2* liver magnetic resonance imaging is normal and indicates no iron overload. Her functional score is appropriate for her age, except for poor school performance mostly attributed to frequent absences from school for sickle cell complication–related hospital admissions. Specifically, after a period of well-being for 2 to 3 years following commencement of erythrocytapheresis, she reports increasing pain symptoms over the last 5 or 6 years, chronic opioid use, and hospital admissions lasting 4 to 5 days each time, 4 to 6 times per year, interrupting her education and resulting in poor quality of life (QOL). She is keen to discuss hematopoietic stem cell transplantation (HSCT) because she has heard that it promises a cure. Her hematologist concurs with her desire to meet the transplant team to discuss HSCT. Should Kierra undergo an HSCT?

Case 2. Sonal Scher† is a 13-year-old adopted child with β thalassemia major who commenced chronic red cell transfusion therapy 8 months after birth. Iron chelation with subcutaneous desferrioxamine was started at 7 years of age following adoption. Oral chelation therapy was substituted for desferrioxamine 3 years ago, but her ferritin has remained consistently >3000 ng/mL, suggesting poor compliance. By liver magnetic resonance imaging, her hepatic iron concentration was calculated as 20 mg/g dry weight. She is of small stature and has hepatosplenomegaly. The liver is palpable 3 cm below the right costal margin and the spleen is palpable 5 cm below the left. Otherwise, she appears to be in good health. Should Sonal undergo an HSCT?

The purpose of this evidence-based review is to discuss the indications and outcomes of HSCT for sickle cell disease (SCD) and transfusion-dependent thalassemia.

Literature search strategy

Published HSCT methods and outcomes were reviewed for both cases. Medline and Cochrane libraries were searched using SCD, thalassemia, stem cell transplant, bone marrow transplant, and cord

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†Patient names have been altered to conceal identity.

Table 1. Indications for HSCT in SCD

Matched sibling donor (if available)	Matched URD transplant	Mismatched marrow donor, haploidentical donor, unrelated cord blood transplant
Consider early,* prior to or at onset of SCD symptoms, with the highest priority given to patients with HbSS and HbSβ^0 thalassemia	Stroke	Recurrent stroke despite adequate chronic transfusion therapy; progressive CNS changes
Stroke	Elevated TCD velocity	Severe SCD symptoms and inability to tolerate supportive care resulting in symptom persistence/progression
Elevated TCD velocity	Recurrent acute chest syndrome despite supportive care	
Recurrent acute chest syndrome despite supportive care	Recurrent severe VOE despite supportive care	
Recurrent severe VOE despite supportive care	Red cell alloimmunization despite intervention + established indication for chronic transfusion therapy	
Red cell alloimmunization despite intervention + established indication for chronic transfusion therapy	Pulmonary hypertension	
Pulmonary hypertension	Recurrent priapism	
Recurrent priapism	Sickle nephropathy	
Sickle nephropathy	Bone and joint involvement	
Bone and joint involvement		
Sickle retinopathy		

For all genotypes, the morbidity of the disease is the driving factor in pursuing a HSCT. Preventative HSCT should be considered for children with higher-risk genotypes, HbSS, and HbSβ^0. HSCT for adults with SCD is better tolerated with a low-intensity regimen, with the caveat of requiring prolonged immune suppression to maintain mixed-donor chimerism.

AVN, avascular necrosis; TCD, transcranial Doppler; VOE, veno-occlusive episodes.

*Especially in children with difficult access to adequate lifelong supportive medical care, we recommend reviewing statistics for OS, DFS, GR, and GVHD with families as they weigh these options.

blood transplant as key words; data sets were limited to English language, human subjects, and clinical trial reports. References quoted by identified articles were also accessed; review articles were excluded. The list was screened for overlap and extractable data summarized. Data for publications included in this review were graded for quality by scoring based on Grading of Recommendations Assessment Development and Evaluation recommendations (based on a numerical score of likelihood of benefit from the intervention and a letter demonstrating the strength of the evidence) (see supplemental Data, available on the *Blood* Web site).[1] The search, extraction of data, and assessment of quality were completed by both authors individually and checked for agreement (100%). No prospective randomized trials comparing outcomes of conservative therapy vs HSCT or randomized studies between different transplant modalities were found for SCD or thalassemia.

Search results

SCD

The search was last performed on November 13, 2013. "Human stem cell transplant + sickle cell disease" resulted in 367 published studies. Reviews, non-English publications, case reports, abstracts, and mixed indications for HSCT were excluded, leaving 30 clinical trial reports. "Human bone marrow transplant + sickle cell disease" produced 369 studies that were restricted to 35 after exclusions. "Human cord blood transplant + sickle cell disease" produced 107 reports and 10 were retained. Deleting overlapping reports and condensing serial reports from the same group of patients selected 17 studies that were graded (supplemental Data). Of these, 4 reported on alternative donor (not HLA-matched family donors [MFDs]) transplants; 5 described HSCT toxicities and long-term outcomes/benefits post-HSCT. Eleven additional publications on care utilization and acceptance of HSCT were also reviewed.

Thalassemia

The search was last performed on November 13, 2013; "stem cell transplant + thalassemia," "bone marrow transplant + thalassemia," and "cord blood transplant + thalassemia" resulted in 559, 850, and 191publications, respectively. Based on similar exclusion/selection strategies described above to eliminate overlap, 37 (stem cell), 60 (bone marrow), and 11 (cord blood) publications were retrieved. Overlapping reports in these subsets were eliminated, leaving 22 reports, including 8 with alternative-donor transplants. Each was graded as described above (see supplemental Data). Five publications on care utilization and long-term follow up were also reviewed.

SCD (case 1)

SCD, a genetic disorder that results from the substitution of glutamine to valine at the sixth position in the β-globin chain of hemoglobin due to a single-nucleotide mutation, affects over 90 000 people in the United States and several thousands more worldwide (National Heart Lung and Blood Institute, 2009). HbSS causes red cell polymerization, vaso-occlusion, and vasculopathy. Children with HbSS have a 27% rate of neurologic complications (10% overt stroke), and 25% develop acute chest syndrome.[2-4] Vasculopathy also affects the kidneys, eyes, heart, bone and joints, muscles, and gut, resulting in chronic pain and irreversible sequelae. Median age at death is 40 years despite significant advances in care, even in developed countries.[5] Although HbSS and sickle β^0 thalassemia (HbSβ^0) genotypes typically represent those at highest risk for complications and the most likely to have a stem cell transplant, sickle cell hemoglobin C or sickle β thalassemia patients are not always spared the ravages of SCD, though the age at onset and symptom constellations vary. Symptoms are modified with hydroxyurea (HU) (the only US Food and Drug Administration–approved drug for SCD) and blood transfusions (alloimmunization can

become a complication limiting the use of this treatment modality). Observational studies of patients on long-term HU demonstrate reduced mortality.[6,7] Results from the BABY HUG trial offered evidence that daily HU for infants and toddlers with HbSS and HbSβ^0 genotypes reduced the number of painful events and the number of transfusions. However, BABY HUG did not provide any evidence that HU prevents central nervous system (CNS) disease.[8]

Allogeneic HSCT is curative. HSCT results in stabilization of organ function and gradual amelioration of CNS, pulmonary, and pain symptoms.[9] Given the risk of recurrent stroke and persistent morbidity, Kierra would be well served to pursue HSCT.

MFD transplants (blood, marrow, or cord blood) following predominantly myeloablative conditioning (MAC) have been reported from several countries and resulted in >90% overall survival (OS), 82% to 100% disease-free survival (DFS), graft rejection (GR) rates of 8% to 18%, and transplant-related mortality (TRM) of 4% to 14%.[10-13] The addition of anti–thymocyte globulin (ATG) to the regimen reduced GR rates to <10%.[10] Acute and chronic graft-versus-host disease (GVHD) rates varied between 6% and 35%. Nonablative conditioning strategies were undertaken in recent years to offset toxicities. Although well tolerated, significantly lowered-intensity preparative regimens for HSCT resulted in 67% to 100% GR rates.[14,15] A change to a more immune-suppressive regimen successfully achieved 86% to 90% DFS with reduced intensity conditioning (RIC), even in adult patients. However, prolonged immune suppression was necessary in 70% of recipients to maintain engraftment.[16] Continued attempts to improve conditioning strategies and reduce the intensity of the preparative regimen are targeted to offset transplant toxicities noted after MAC, including veno-occlusive disease, neurotoxicity (seizures, stroke, and hemorrhage), growth failure in postpubertal recipients, hypogonadism (as high as 70%), and sterility.[9] Toxicity is worse in older age groups (such as adolescents or young adults) and those with advanced SCD.[9,17-20] Mixed chimerism was noted in all patients with low-intensity conditioning but is also noted in 6% to 36% following MAC. However, stable donor chimerism (usually determined in cells of myeloid lineage) as low as 11% can ameliorate SCD symptoms and maintain low hemoglobin S levels, presumably secondary to an erythrocyte survival advantage.[21,22] The lower limit of erythrocyte donor chimerism associated with disease amelioration is unknown. Table 1 lists indications for which HSCT is considered, factoring in disease symptoms and donor availability.

If Kierra has a matched sibling donor, we suggest:

- The pursuit of a HSCT (grade 1B) over lifelong chronic red cell transfusion therapy and supportive care.
- The decision to choose a myeloablative (grade 1B) vs a nonmyeloablative (grade 1B/2B) preparative regimen has never been addressed in a randomized fashion. However, given the similar survival rates and tolerability of a nonmyeloablative approach, we would choose a less toxic approach (grade 2C).

Next steps if no matched sibling is available

Alternative donor transplantation for Kierra should be considered. Kierra is at risk for stroke recurrence despite continued transfusions (45% overt + silent; 22% overt).[23,24] Cognition declined with each year of age in a cross-sectional cohort of children with SCD, both with and without cerebral infarcts.[25] She also has continued pain (poor QOL). Both are established indications of severity, making her a candidate worthy of a discussion of HSCT. However, age (>16 years), organ toxicity, GVHD rates, GR, and increased mortality are risks of alternative donor transplants (unrelated or haploidentical).[26] Alternative-donor HSCT, defined as any donor other than MFD, constitutes less than one-quarter of SCD transplants reported to the Center for International Blood and Marrow Transplant Research.

Two national trials for severe SCD with an unrelated donor (URD) are underway: (1) the SCURT trial (NCT00745420) using an RIC regimen (alemtuzumab/fludarabine/melphalan) for children <19 years and (2) the STRIDE trial (NCT01565616) for adults (>16 years) using busulfan/fludarabine/ATG. Both require 8/8 matched marrow donors, and Kierra has a 20% to 30% chance of finding one (National Marrow Donor Program, 2011). The RIC regimens are based on past experience and seek to define DFS at 1 year and offset toxicities of MAC.[22,27] The SCURT trial closed to umbilical cord blood transplants (UCBT) after rates of GR (5/8) met stopping rules.[28] Unrelated UCBT predominantly after MAC was reported from retrospectively analyzed combined registry data.[29] OS was 94% and DFS was 50%; the study highlighted the importance of a high nucleated cell dose of $>5 \times 10^7$/kg (DFS 45% vs 13%). Optimizing unrelated UCBT requires formal trials targeting optimization of conditioning and cord products, some of which are in progress (NCT00920972, NCT01590628).

Kierra's other option is a haploidentical HSCT if a parent or sibling is eligible. Haploidentical transplantation has been reported following an RIC regimen and marrow infusion in 14 patients with posttransplant cyclophosphamide administered to thwart alloreactive T-cell expansion.[30] There was no mortality with this approach, though 42% had GR and 14% required continued immunosuppression to retain donor cell engraftment. Additional haploidentical HSCT trials using CD34-selected blood cells following a MAC or RIC regimen are in progress (NCT01461837, NCT00977691) for children and adults. Prospective trials that carefully define outcomes are the only way to better elucidate the risk/benefit ratios of the transplant intervention and improve upon them, particularly for adult patients.

In the absence of a matched donor in the family, we suggest the following approach to HSCT over supportive care without transplant:

- If an HLA match is identified at 8/8 loci by high-resolution typing and Kierra and her family are willing to proceed, then she should have an HSCT with an RIC regimen as opposed to continuing lifelong chronic transfusion therapy (grade 2B). If no URD is available, then she can pursue a haploidentical transplant or a cord blood transplant. With these stem cell sources, she can anticipate over 50% DFS and >85% OS.[29,30] RIC would be approached as a less toxic preparative regimen that would allow for greater OS, even if she is not cured of disease.
- Given the lower level of evidence and risk of graft failure, we suggest that these experimental treatments be pursued only as part of a clinical trial to provide best options for care while advancing this field.

Thalassemia (case 2)

Approximately 1000 people live with thalassemia major in the United States and several thousand worldwide (Centers for Disease Control and Prevention, 2011). Erythrocyte transfusion dependency commences during infancy. Hemolysis and ineffective erythropoiesis can result in hepatosplenomegaly and bone distortion, particularly if patients do not carefully maintain a regular transfusion regimen lifelong.[31] Allogeneic HSCT is the only established curative option currently. HSCT outcomes are influenced by a disease risk score (Pesaro): hepatomegaly >2 cm, portal fibrosis, and inadequate iron chelation therapy; class I, no risk factors (DFS 94% in children

following matched sibling donor transplants); class II, 1 or 2 risk factors (DFS 88%); and class III, all 3 present (DFS 62%).[32] A recently defined very high-risk group included patients >7 years of age with >5 cm hepatomegaly (DFS 24%).[33,34] Reasons for mortality (19%) included veno-occlusive disease (particularly with ferritin levels >2500 ng/mL), GVHD, infection, and marrow aplasia following GR. GR rates dropped (35% to 10%) following the addition of ATG; lower mortality and GR were achieved with the introduction of fludarabine, HU, thiotepa, and azathioprine in the preparative regimen.[35,36] Acute GVHD was described in 11% to 38% and chronic GVHD in 6% to 50% of MFD transplants depending on stem cell source (peripheral blood transplants had a higher GVHD risk than cord blood transplants), with a 15-year OS of 87% and DFS of 70% in MFD HSCT.[33,37-45] With increasingly successful outcomes demonstrated, especially in patients with risk class I and II disease and lowered toxicity following modification in transplant methods, this curative treatment modality should be discussed with all patients with HLA-matched family members following establishment of diagnosis and transfusion dependency, usually by about 2 or 3 years of age.

Thalassemia patient Sonal has only URD transplant options because she is adopted. Additional risk factors that influence HSCT outcomes in Sonal include age (>7 years), organomegaly, and poor efficacy of chelation. A liver biopsy (to determine histologic changes of cirrhosis such as bridging portal fibrosis) should be performed pretransplant.[46,47] URD peripheral blood stem cell and marrow transplants (following MAC) have an OS of 79% to 93% and DFS rates of 65% to 90%, with 7% to 11% TRM.[46,48-50] Changes that have improved HSCT outcomes include the agents described with MFD, lowered busulfan target dose (300-600 μg/L CSS), and substitution of busulfan with treosulfan in the MAC regimen.[48,50] UCBT outcomes are more variable, with OS and DFS ranging widely between 62% to 88% and 21% to 73%, respectively.[29,51] Acute GVHD (21% to 49%) and chronic GVHD (18% to 40%) should be discussed in detail. GR and TRM differences between blood/marrow and cord sources should be considered depending on the quality of the product available. GR (9% to 17% marrow; 17% to 57% cord) and TRM (7% to 11% marrow; 12% to 34% cord) reflect higher transplant risks with UCBT. However, GVHD risks are lower with cords. A national trial was just completed in the United States (the URTH trial) enrolling children (<17 years) with well-matched URD marrow (8/8 loci matched) and cord products (5-6/6 loci matched and with acceptable cell dose) using an RIC regimen (HU/alemtuzumab/fludarabine/melphalan/thiotepa) (NCT01005576) and restricted to children but excluding those with overt hepatic bridging fibrosis. The trial is in the follow-up phase. Immunosuppressive ablative protocols of haploidentical transplantation have reported a DFS of 54% with TRM of 15% and GR of 30%, leaving room for improvement.[52]

For Sonal, we suggest a discussion regarding URD HSCT in the risk class III recipient followed by a registry search to identify the best-available unrelated stem cell source (marrow, peripheral blood stem cells, or cord blood).

- If a matched marrow or suitably matched cord (5-6/6) with adequate cell dose is identified, we recommend that she proceed to HSCT (grade 1B) over continuing lifelong transfusions and chelation therapy. Recent "reduced toxicity" transplant methods incorporating immunosuppression with lower doses or alternate chemotherapy agents can provide a DFS of >70%, even in high-risk disease. Sonal will need to be educated regarding the variables associated with HSCT outcomes, such as TRM, GVHD, and infection, before she decides on the acceptability of HSCT.

Discussion

Attitudes regarding transplant are based on provider knowledge/belief, acceptance of HSCT as a treatment modality, and family perceptions and understanding.[53] A retrospective study of families of 113 children on chronic transfusion therapy revealed that only 58% with siblings opted for free HLA typing. A total of 5 of 8 matched sibling pairs with SCD refused HSCT for fear of mortality. It was also reported that <50% of parents/patients believed that SCD would negatively impact long-term prognosis without transfusions. In contrast, 62% of adult SCD surveyed were willing to accept >10% TRM, but 80% stated they wanted no GVHD.[54,55] Based on a decision-tree analysis of QOL, in severe disease, estimations suggest that HSCT will not be a preferred strategy if TRM is >11%.[56] This holds true based on availability of continued supportive care, especially chronic transfusions and lifelong chelation therapy.[57]

It is necessary to carefully weigh the pros and cons of continued disease vs HSCT, especially in the URD setting. There are no trials comparing the monetary efficacy of HSCT and conservative care. The cost of conservative care is $9000 to $13 000 more per year per child with SCD.[58] With transfusions and chelation, that increases to a median of $38 607 per 14 months of care.[59] The availability of such care lifelong vs the variable cost of HSCT is an impetus to develop trials designed to improve outcomes and decrease risks and cost.

Although SCD-related organ damage can progress despite conservative therapy, there is always the dilemma of choosing between continued conservative supportive care and HSCT for thalassemia. Although QOL following HSCT or transfusion therapy in thalassemia has not been studied extensively or in randomized fashion, a report noted that 89% of transplant recipients reported satisfaction on a HSCT choice when queried after the intervention,[60] and patients led a productive life posttransplant in the absence of chronic GVHD and when transplanted young.[61] Monetary costs (a cost-analysis effort from Thailand), though higher for HSCT than for transfusions ($114 000 vs $73 928), afforded better QOL gain (26.49 vs 14.11) and long-term gain when performed successfully in children and young adults.[62]

HSCT for hemoglobinopathies should be considered from the point of view of a risk/benefit ratio. HSCT offers a cure, but with variable levels of mortality, GVHD, or GR, and probabilities and options should be discussed with patients and families for shared decision making. Clinical trials are the best way to continue to make progress in both HSCT and supportive care arenas to continue to improve outcomes and reduce risks.

Authorship

Contribution: A.K. participated in collecting and reviewing the data and writing the manuscript; and S.S. was responsible for collecting published data, organizing data, and writing the manuscript.

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