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Abstract

Although a number of published trials exist of HLA-identical sibling hematopoietic cell transplantation (HCT) for sickle cell disease (SCD) that span 2 decades, when and for whom this therapy should be pursued is a subject of debate. Assessments of the therapeutic value of HLA-identical sibling HCT for children with SCD and serve as the basis for a strong recommendation in favor of the option of HCT when a suitable donor is available. The experience of HLA-identical sibling HCT in adults with SCD is limited but appears to be similar to results in children. These preliminary observations, however, warrant further investigation.

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Introduction

Hematopoietic cell transplantation (HCT) for sickle cell disease (SCD) is curative in most individuals who receive this treatment, but it is a treatment option that very few families and patients pursue [1-4]. The principal reason why so few transplants are performed is that most affected people lack a suitable donor. Even so, it is estimated that 18% of affected individuals will have an HLA-identical (HLA-ID) sibling donor [5]. Yet, far less than 1% of the SCD population in the United States has received a transplant. Many barriers to transplant exist, and these are detailed in other reports [6-8]. A key barrier is a prevailing assumption that HCT is risky and carries a mortality rate that exceeds mortality experienced with a supportive care approach. In addition, there are risks of infertility and of graft-versus-host disease (GVHD), which can cause a chronic debilitating disorder.
Table 1
Indications for HCT in Children with SCD (HbSS or HbS-β-thalassemia)

<table>
<thead>
<tr>
<th>One or more of the following complications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or central nervous system event lasting longer than 24 hours</td>
</tr>
<tr>
<td>Impaired neuropsychological function with abnormal cerebral magnetic resonance imaging and angiography</td>
</tr>
<tr>
<td>Recurrent acute chest syndrome</td>
</tr>
<tr>
<td>Stage I or II sickle lung disease (defined in [14])</td>
</tr>
<tr>
<td>Recurrent vaso-occlusive painful episodes or recurrent priapism</td>
</tr>
<tr>
<td>Sickle nephropathy (glomerular filtration rate 30%-50% of predicted normal)</td>
</tr>
</tbody>
</table>

In this brief review the basis for assumptions about mortality risk is examined in an update of the contemporary experience of HLA-ID sibling HCT for SCD.

An important benefit of successful HCT is the elimination of sickle erythropoiesis, thereby significantly reducing, or in most instances, ending the risk of sickle-related complications [1,9,10]. Thus, most agree that quality of life after successful HCT should be very much improved compared with that in individuals who continue to live with SCD. These comparisons about protection from sickle-related damage are difficult because prospective comparisons between groups of subjects treated by HCT and by supportive care have never been conducted. Thus, most analyses rely on comparisons with historical control subjects, which weakens their impact. In addition, some recipients have experienced events soon after HCT, such as pain, intracranial hemorrhage, and infection, thus, protection is not universal in those who survive with engraftment of donor cells, although these events eventually resolve. For these reasons the benefit of HCT with regard to symptom abatement and organ function is not the focus of this review. However, the importance of conducting studies that systematically monitor prospective outcomes in comparison cohorts that might establish unequivocal indications for HCT cannot be overstated.

HCT IN CHILDREN WITH SCD

In developing eligibility criteria for HCT in early studies, investigators selected clinical features of SCD that carry a high burden of ongoing supportive care with a risk of cumulative organ injury and an association with early mortality [11]. In childhood, supportive care delivered at comprehensive sickle cell centers is currently associated with excellent survival to adulthood, with a risk of mortality before age 18 that ranges from 1% to 2% by age 20 in the East London Cohort to 6.1% in the Dallas Newborn Cohort [12,13]. Thus, transplantation studies in childhood focused initially on minimizing the risks of early transplant-related death and of sickle-related clinical complications after successful transplantation. Currently, HCT in children with SCD is typically restricted to those with a clinical stroke or who have experienced recurrent vaso-occlusive complications such as pain and/or acute chest syndrome despite receiving optimal supportive care. The eligibility criteria used in the largest pediatric clinical trials completed 10 to 15 years ago are presented in Table 1. In the current era as the survival rates in transplant and nontransplant cohorts converge, restricting HCT solely in children who have had a significant complication such as stroke is no longer appropriate, as suggested below. A liberalized approach to indications for HCT would also increase its utilization.

TRANSPLANT RESULTS IN CHILDREN: HLA-ID SIBLING HCT

A compilation of the most recent single-center patient series in children with SCD treated by HLA-ID sibling HCT is presented in Table 2. In a series of 40 patients treated in Rome, Italy, the rates of overall survival and event-free survival (EFS) were both 91% after an HLA-ID sibling bone marrow transplantation (BMT) with a conventional preparative regimen of busulfan (BU)/cyclophosphamide/horse antithymocyte globulin (ATG) with or without fludarabine (Flu) [15]. In a series from Belgium, 37 of 38 children treated since 1995, who also received hydroxyurea (HU) well before HCT, survived free of SCD with an 8-year estimate of EFS of 97.1% [16]. In a series of children treated in New York who received a combination of BU, Flu, and alemtuzumab (Alem) before HLA-ID sibling HCT, all 18 children survived free of SCD after HCT [17]. Another single-center series from Atlanta observed 24 of 25 patients who were treated by HLA-ID sibling HCT between 1993 and 2007, after preparation with BU/cyclophosphamide/horse ATG, who survived free of SCD [19]. A recent multicenter investigation of 43 children with SCD who received Alem/Flu/melphalan before HLA-ID sibling BMT reported survival and EFS probabilities of 93% and 90.7%, respectively [21]. Finally, the experience from Pavia was also recently reported in which all 30 recipients survived after HLA-ID HCT after preparation with BU/thiotepa/Flu or treosulfan/thiotepa/Flu and ATG [20]. Together these combined series include 218 recipients, of whom 208 (95%) survived after transplantation and 200 (92%) survived free of SCD. These updated published results strongly suggest that survival after HCT from an HLA-ID sibling in children with SCD is not inferior to survival among those treated by standard supportive care. At last follow-up only 6 survivors (3%) were receiving immunosuppressive therapy to treat chronic GVHD.

Similar results have been reported from transplant registry data where there are approximately 1200 SCD transplant cases from related and alternate donor sources [22]. Among the HLA-ID sibling donor cohorts, the rates of overall survival in the Center for International Blood and Marrow Transplant Research (N = 412) and Eurocord/European Blood and Marrow Transplant (EBMT; N = 487) registries were 91% and 95%, respectively [22]. In a separate analysis comparing outcomes in 160 children with SCD who received HLA-ID sibling BMT and umbilical cord blood transplantation between 1994 and 2005 in the United States and Europe, there was no statistically significant difference in overall survival and EFS between these 2 donor sources [23]. Moreover, the combined 6-year disease-free survival rate was 92%.

These retrospective registry data also were reviewed critically by an international expert panel on behalf of the EBMT Inborn Error and EBMT Paediatric Working Parties [24] and the following recommended for HLA-ID HCT for children:

- Young patients with symptomatic SCD who have an HLA-ID sibling donor should be transplanted as early as possible, preferably at preschool age.
- Unmanipulated BM or umbilical cord blood (whenever available) from HLA-ID sibling donors are the recommended stem cell source.

However, an alternate view recently expressed by SCD experts is that additional research is still needed to
address the potential risks of this therapy, such as failure of engraftment and chronic GVHD before HCT can be widely used [25]. The objective of reducing the risk of HCT in children with SCD has been largely accomplished [25,26]. The notion is further strengthened by a recent report that described a cohort of 469 children and adults with SCD in Belgium in which the 15-year survival rate of patients treated by with [26].

There is limited but growing transplant experience in adults with SCD. The eligibility criteria used in 2 active trials after HCT [28].

### Table 2
Clinical Outcome of HLA-ID Sibling HCT for Children with SCD

<table>
<thead>
<tr>
<th>Center</th>
<th>Preparative Regimen</th>
<th>GVHD Prophylaxis</th>
<th>n</th>
<th>Follow-Up (yr)</th>
<th>Death (no)</th>
<th>Complications</th>
<th>Latest Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rome</td>
<td>Lucarelli, 2014</td>
<td>CsA, MTX, pred</td>
<td>40</td>
<td>2-17</td>
<td>1-10</td>
<td>3 deaths from GVHD</td>
<td>1 of 40</td>
</tr>
<tr>
<td>Brussels</td>
<td>(Dedefken, 2014)</td>
<td>CsA, MTX or MMF (UCB)</td>
<td>50</td>
<td>1.7-15.3</td>
<td>2 (6, 78)</td>
<td>4, sepsis, 1 IMI, seizures 21%, 6, PRES</td>
<td>1 of 50</td>
</tr>
<tr>
<td>New York</td>
<td>Bhatia, 2014</td>
<td>Tacrolimus, MMF</td>
<td>18</td>
<td>2.3-20.2</td>
<td>.4-7.5</td>
<td>None</td>
<td>ICH in 1, PRES in 1, CMV react in 4</td>
</tr>
<tr>
<td>Mississippi</td>
<td>Majumdar, 2010</td>
<td>CsA, Pred</td>
<td>10</td>
<td>2.8-16.3</td>
<td>2.9-9.9</td>
<td>1</td>
<td>1 death from sepsis, 1 AIHA</td>
</tr>
<tr>
<td>Atlanta</td>
<td>McPherson, 2013</td>
<td>CsA, MTX</td>
<td>27</td>
<td>3.3-17.4</td>
<td>.1-10</td>
<td>1 (3)</td>
<td>8 VOD, 16% seizures, 2 ICH</td>
</tr>
<tr>
<td>Pavia</td>
<td>Strocchio, 2015</td>
<td>CsA, MTX or MMF</td>
<td>30</td>
<td>1.7-18.8</td>
<td>.5-14</td>
<td>None</td>
<td>Stomatitis (43%), GI toxicity (17%); no VOD</td>
</tr>
<tr>
<td>United States</td>
<td>(King, 2015)</td>
<td>CsA or tacrolimus</td>
<td>43</td>
<td>3-20.3</td>
<td>.75-11.83</td>
<td>3 (11, 18, 21)</td>
<td>3 deaths from GVHD</td>
</tr>
</tbody>
</table>

IST indicates immunosuppressive therapy; CY, cyclophosphamide; rATG, rabbit ATG; CsA, cyclosporine; MTX, methotrexate; pred, prednisone; aGVHD, acute GVHD; ceGVHD, chronic GVHD; MMF, mycophenolate mofetil; UCB, umbilical cord blood; IMI, invasive mold infection; PRES, posterior reversible encephalopathy syndrome; ICH, intracranial hemorrhage; CMV, cytomegalovirus; AIHA, autoimmune hemolytic anemia; VOD, veno-occlusive disease; Treo, treosulfan; cGVHD, chronic extensive GVHD; TT, thiotepa; GI, gastrointestinal.

### Table 3
Indications of HCT in Adult Recipients with SCD

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>SCD and 1 or more of the following complication</th>
<th>HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-40</td>
<td>Clinically significant neurologic event (stroke) or any neurologic deficit lasting &gt; 24 hr</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>History of 2 or more episodes of acute chest syndrome in the 2-yr period preceding HCT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>History of 3 or more severe pain crises per year in the 2-yr period preceding enrollment despite the institution of supportive care measures (ie, asthma therapy and/or HU)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Administration of regular RBC transfusion therapy, defined as receiving 8 or more transfusions per year for &gt; 1 yr to prevent vaso-occlusive clinical complications (ie, pain, stroke, and acute chest syndrome)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

An echocardiographic finding of tricuspid valve regurgitant jet ≥ 2.7 m/s.
Table 4
Recent Results of HLA-Matched HCT in Adults with SCD

<table>
<thead>
<tr>
<th>Center</th>
<th>Preparative Regimen</th>
<th>GVHD Prophylaxis</th>
<th>n Age Range (yr)</th>
<th>Follow-Up (yr)</th>
<th>Death (mo)</th>
<th>Complications</th>
<th>IST</th>
<th>GVHD</th>
<th>Donor Chimerism</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHLBI (Hsieh, 2009, 2014) [5,41]</td>
<td>Alem 1 mg/kg, TBI 300 cGy</td>
<td>Sirolimus</td>
<td>30 17-65</td>
<td>1.8-6</td>
<td>1 (ICH)</td>
<td>GR (n = 4)</td>
<td>11 of 26 None</td>
<td>Median T cell 48%</td>
<td></td>
</tr>
<tr>
<td>France (Kuentz, 2011) [40]</td>
<td>BU 14 mg/kg, CY 200 mg/kg, CsA, MTX</td>
<td>rATG 10 mg/kg</td>
<td>15 16-27.5</td>
<td>1-16.1</td>
<td>1 (ICH)</td>
<td>SDH (n = 1), seizures</td>
<td>8 aGVHD 75-100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NHLBI indicates National Heart, Lung, Blood Institute; TBI, total body irradiation; GR, graft rejection; SDH, subdural hematoma.

having >4 pain crises per year or those with a higher organ severity score [30]. Thus, if the 2-year mortality probability after HCT in adults is <20%, it is very likely that transplantation will confer a long-term survival advantage in adult recipients.

Doppler transthoracic echocardiography has been validated in several cohorts as a screening tool to identify high-risk patients for early mortality. In 3 large screening studies approximately 30% of patients had a tricuspid valve regurgitant jet velocity (TRV) > 2.5 m/s and 10% had a TRV > 3 m/s. In all epidemiologic studies performed to date, the risk ratio of early death in adults with a TRV > 2.5 m/s ranged from 9.24- to 15.9-fold [32-34]. More recently, a larger cohort of 483 patients was screened in the Walk-PHASST (Walk-Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy) screening study [35,36]. In this cohort, 67 participants (9.1%) had a TRV > 3 m/s that was associated with a 2-year mortality of 11.9%. Using a 2-variable positive predictive value assessment of 2-year mortality risk in this same cohort, it was possible to identify very high-risk patients. Subjects who had a combination of TRV > 3 m/sec with WBC counts > 13,500 or chronic transfusion therapy had a 2-year mortality rate that exceeded 20% [37]. Finally, 43 of 240 subjects from a cohort of adults with SCD died between 2000 and 2005, with a median survival of 40 years [38]. The authors concluded that HU protected from acute sickle-related events but not from cardiopulmonary complications, which were the leading cause of death. Thus, in selected groups of adults with SCD, even if the 2-year probability of transplant-related mortality is approximately 20%, survival in the short term compared with those who lack a donor might be acceptable.

TRANSPLANT RESULTS IN ADULTS: HLA-ID SIBLING HCT

The possibility of successful HCT in young adults with SCD was suggested by a report of 15 patients from a French group and by parallel efforts in thalassemia major in which myeloablative regimens with reduced toxicity were developed to lower the risk of transplant-related mortality [39,40] (Table 4). Although reduced-intensity and nonmyeloablative conditioning regimens have been successful in treating hematologic malignancies where there are comorbidities, these have been less successful in hemoglobinopathies [42,43]. However, results of more recent trials suggest progress that might be extended to clinical practice. Between 2004 and 2013, 30 patients with severe disease ages 16 to 65 years were treated with Alem, total body irradiation (300 cGy), and sirolimus followed by HLA-ID sibling filgrastim-mobilized peripheral blood stem cell transplantation in a single-center trial [9,41]. With a median follow-up of 3.6 years (range, 1.8 to 6), 87% of recipients had long-term engraftment without acute or chronic GVHD and overall survival was 97%. However, 11 of 26 surviving patients who had mixed donor-host chimerism were still receiving immunosuppressive therapy at last follow-up because of concerns about late graft failure. Recently, a multicenter pilot trial of HCT for SCD reported results in 22 adults with severe SCD treated by HLA-ID related (n = 17) or unrelated (n = 5) donor HCT after a myeloablative combination of BU, Flu, and rabbit ATG. Twenty-one of 22 patients survived after HCT, all with engraftment of donor cells [44]. Together, these initial series have generated very good results and if confirmed in a larger, multicenter investigation of HLA-ID sibling HCT in adults could support the notion that survival after transplantation is not inferior to survival in those not treated by HCT.

SUMMARY

Just as refinement in supportive care for SCD has improved the likelihood of survival to adulthood, results after HLA-ID sibling HCT have also improved significantly in the past 15 years. In addition, the goal of cure is achieved in 90% or more of transplant recipients. Because there appears to be very little if any survival disadvantage after HCT compared with those who receive supportive care, a broadened view about transplant eligibility is warranted [45]. The role of HCT in adults with symptomatic SCD is less well defined because of the small number of published reports; however, projections based on the risk of early mortality in adults with severe SCD also warrants broader endorsement of HCT as a therapeutic option, particularly when investigated in National Institutes of Health–funded prospective clinical trials.

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