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Indications and Results of Human Leukocyte Antigen-identical Sibling Hematopoietic Cell Transplantation for Sickle Cell Disease

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Abstract

Although there are a number of published trials of human leukocyte antigen (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 risks of transplant-related complications that include infertility and debilitating graft-versus-host disease and long-term quality of life after successful HCT are difficult to perform without prospective trials in transplant and non-transplant cohorts. However, it is possible to assess the risk of mortality and to compare published rates of survival in individuals with sickle cell disease treated and not treated by HCT. In this brief review, projections about mortality risk based upon recent published reports are reviewed and summarized. The published data show overall survival and event-survival rates of 95% and 92%, respectively, in children treated by HLA-identical sibling

HCT. The overall survival in the Center for International Blood and Marrow Transplant Research (CIBMTR) (N=412) and European Blood and Marrow Transplant (EBMT) (N=487) registries was 91% and 95%, respectively. These results provide broad support for the therapeutic value of HLA-identical sibling HCT for children with sickle cell disease 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 similar to results in children, and these preliminary observations warrant further investigation.

Introduction

Hematopoietic cell transplantation (HCT) for sickle cell disease (SCD) is curative in the majority of 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 US has received a transplant. Many barriers to transplant exist, and these are detailed in other reports[6, 78]. 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) that can cause a chronic debilitating disorder. 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 to 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 upon comparisons to historical controls, which weakens their impact. In addition, some recipients have experienced events soon after HCT such as pain, intra-cranial 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 will not be 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 1–2% 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 non-transplant 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 overall survival and event-free survival were both 91% after an HLA-ID sibling bone marrow (BM) transplantation with a conventional preparative regimen of busulfan (BU)/cyclophosphamide (CY)/horse anti-thymocyte globulin (ATG) with or without fludarabine (Flu)[14]. In a series from Belgium, 37 of 38 children treated since 1995, who also received hydroxyurea (HU) well before HCT, survive free of SCD with an 8-year estimate of event-free survival (EFS) of 97.1%[15]. 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[16]. 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/CY/horse ATG[17] survived free of SCD. A recent multicenter investigation of 43 children with SCD who received Alem/Flu/melphalan (Mel) before HLA-ID sibling bone marrow transplantation reported survival and EFS probabilities of 93% and 90.7%, respectively[18]. Finally, the experience from Pavia was also recently reported in which all 30 recipients survive after HLA-ID HCT after preparation with BU/thiotepa(TT)/Flu or Treosulfan(Treo)/TT/Flu and ATG. Together these combined series include 218 recipients, of whom 208 (95%) survive after transplantation, and 200 (92%) survive 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[19]. Among the HLA-ID sibling donor cohorts, the overall survival in the Center for International Blood and Marrow Transplant Research (CIBMTR) (N=412) and European Blood and Marrow Transplant (EBMT) (N=487) registries was 91% and 95%, respectively (Figure 1). In a separate analysis comparing outcomes in 160 children with SCD who received HLA-ID sibling BM and umbilical cord blood (UCB) transplantation between 1994 and 2005 in the US and Europe, there was no statistically significant difference in overall survival and EFS between these 2 donor sources[20]. Moreover, the combined 6-year disease-

free survival 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[21] which made the following recommendations about 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 pre-school age.
- Unmanipulated BM or UCB (whenever available) from HLA-ID sibling donors are the recommended stem cell source.

However, an alternate view recently expressed by sickle cell disease experts is that "additional research is still needed that addresses the potential risks of this therapy (e.g., failure of engraftment and chronic graft-versus-host disease, GVHD) before HCT can become a widely used therapy"[22]. The objective of reducing the risk of HCT in children with SCD has been largely accomplished when an HLA-ID sibling donor is used, which challenges this opinion. The 2-year transplant-related mortality risk after HLA-ID sibling donor HCT appears very similar to the risk in children with SCD who receive standard supportive care. This 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 after transplantation compared to supportive care was not significantly different (mortality rate of 0.38 and 0.36/100 patient years, respectively, in supportive care and transplant groups), although survival was superior in a group treated by HU[23]. Novel methods in preserving fertility after HCT should hasten a revision of the current indications for HLA-ID sibling HCT, extending this therapeutic option to all children who have a sickle cell anemia genotype. Oocyte cryopreservation has been reported in a patient with sickle cell disease[24]. Cryopreservation of ovarian tissue is available as a research procedure, and this tissue might be utilized to restore endocrine and reproductive function after HCT[25].

Eligibility Criteria – Adults with SCD

There is limited but growing transplant experience in adults with SCD. The eligibility criteria used in 2 active trials are shown in Table 3. There is a potential for a wider acceptability of HCT in adults with severe SCD for several reasons. First, unlike the experience in childhood during which survival to adulthood improved significantly after the institution of comprehensive care, the mortality rate among adults has changed very little in the past several decades[26, 27]. Patients with symptomatic SCD who participated in the Multicenter Study of Hydroxyurea (MSH) represent a cohort that mirrors adult patients referred for HCT.[28] The annual mortality rate in the long-term (17.5 years) follow-up cohort from the MSH study was 4.4 per 100 person-years. The mortality rate was quite similar across groups who received HU for less than 5 years, 5 to <10 years, and 10 to <15 years. After roughly 13 years of continuous HU treatment, however, the mortality rate declined to 2.5% per year and 2.25% per year in the groups of patients treated for the longest periods of time. Another recent report of a cohort that included 534 adults with SCD showed 25% mortality at the end of the 10-year study. The mortality was even higher among those having >4 pain crisis per year or those with a higher organ severity score[27]. 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 trans-thoracic 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 the epidemiological 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[29–31]. 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[32, 33]. In this cohort, 67 participants (9.1%) had TRV was > 3 m/sec which was associated with a 2-year mortality of 11.9%. Using a two-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> 13,500 or chronic transfusion therapy had a 2-year mortality rate that exceeded 20%[34]. Finally, 43 of 240 subjects from a cohort of adults with SCD died between 2000–2005 with a median survival of 40 years[35]. The authors concluded that HU protected from acute sickle-related events but not from cardiopulmonary complications that 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 to 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 have been developed to lower the risk of transplant-related mortality[36, 37]. While reduced intensity and non-myeloablative conditioning regimens have been successful in treating hematological malignancies where there are co-morbidities, these have been less successful in hemoglobinopathies[38, 39]. However, results of recent trials suggest progress that might be extended to clinical practice. Between 2004 and 2013, 30 patients with severe disease who were 16 to 65 years of age were treated with Alem, total-body irradiation (TBI, 300 cGy), and sirolimus followed by HLA-ID sibling filgrastim-mobilized peripheral blood stem cell transplantation in a single center trial[9, 40]. With a median follow-up of 3.6 (range, 1.8 – 6) years, 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 due to concerns about late graft failure. More recently, a multicenter pilot trial of HCT for SCD reported results in 22 adults with severe sickle cell disease 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 survive after HCT, all with engraftment of donor cells[41]. 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 sickle cell disease 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 to those who receive supportive care, a broadened view about transplant eligibility is warranted[42]. The role of HCT in adults with symptomatic SCD is less well defined because of the small number of published reports; however, projections based upon the risk of early mortality in adults with severe SCD also warrants broader endorsement of HCT as a therapeutic option, particularly when investigated in NIH-funded prospective clinical trials.

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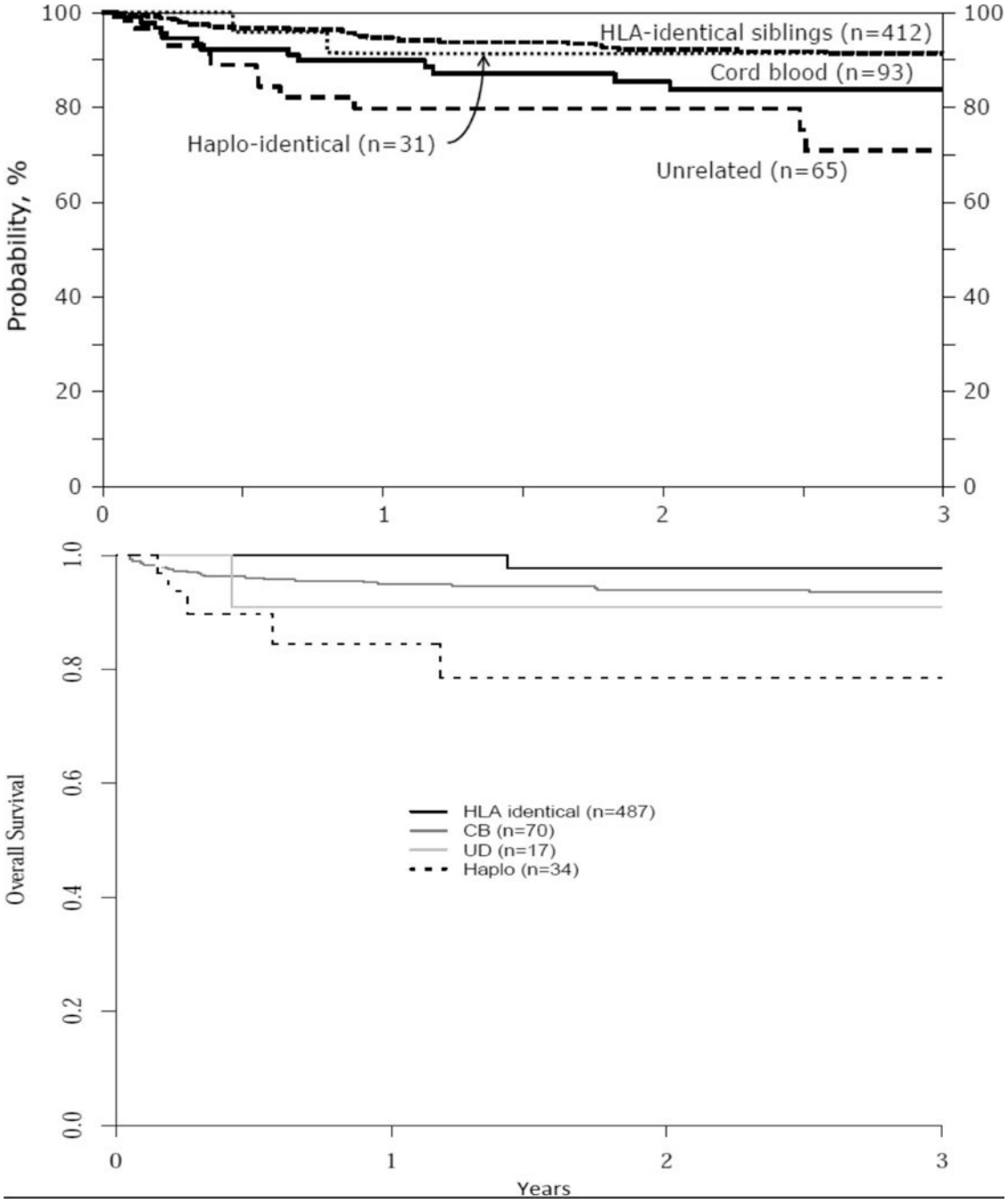

Figure 1.

Depictions of overall survival after HCT for sickle cell disease according to donor source, as analyzed from the CIBMTR (upper panel) and European (EBMT) (lower panel) registries. Hematopoietic cell source is indicated in both panels. Reproduced with permission[19].

Table 1

Indications for hematopoietic cell transplantation in children with sickle cell disease

Patients with sickle cell disease (HbSS or HbSβ°-thalassemia) less than 16 years of age
One or more of the following complications:
Stroke or central nervous system event lasting longer than 24 hours
Impaired neuropsychologic function with abnormal cerebral magnetic resonance imaging and angiography
Recurrent acute chest syndrome
Stage I or II sickle lung disease (defined in[43])
Recurrent vaso-occlusive painful episodes or recurrent priapism
Sickle nephropathy (glomerular filtration rate 30–50% of predicted normal)

Table 2

Clinical outcome of HLA-ID sibling HCT for children with SCD

Center	Preparative regimen	GvHD prophyl	n	Age range (yrs)	Published outcomes			Latest follow up		
					Follow up (yrs)	Death (mos)	Complications	IST	GvHD	% donor chimerism
Rome (Lucarelli, 2014)[14]	BU14 mg/kg, CY 200 mg/kg/rATG 10 mg/kg, ±Flu 150 mg/m^2	CsA, MTX, pred	40	2–17	1 – 10	3 (2.5, 6, 15)	3 deaths from GVHD	1 of 40	17.5% aGVHD, 5% cGVHD	25 – 100%
Brussels (Dedeken, 2014)[15]	BU 13–18 mg/kg, CY 200 mg/kg, ±rATG (10–20 mg/kg), ±HU	CsA, MTX Or MMF (UCB)	50	1.7 – 15.3	0.4 – 21.3	2 (6, 78)	4, sepsis, 1 IMI, seizures 21%, 6, PRES	1 of 50	20.5% aGVHD, 20% cGVHD	15 – 100%
New York (Bhatia, 2014)[16]	BU 12.8 – 16 mg/kg, Flu 180 mg/m^2, Alem 54 mg/m^2	Tacrolimus, MMF	18	2.3 – 20.2	0.4 – 7.5	none	ICH in 1, PRES in 1, CMV react in 4	none	17% aGVHD, 11% cGVHD	Mean 88% at 1 year
Mississippi (Majumdar, 2010)[44]	BU 14 mg/kg, CY 200 mg/kg, ATG 90 mg/kg	CsA, Pred	10	2.8 – 16.3	2.9 – 9.9	1	1 death from sepsis, 1 AIHA	1 of 10	40% aGVHD 10% ceGVHD	15 – 100%
Atlanta (McPherson, 2011)[17]	BU 14 mg/kg, CY 200 mg/kg, ATG 90 mg/kg	CsA, MTX	27	3.3 – 17.4	0.1 – 10	1 (3)	8 VOD, 16% seizures, 2 ICH	none	12% aGVHD, 1 death from cGVHD	62 – 100%
Pavia (Strocchio, 2015)[45]	BU 16 mg/kg, TT 10 mg/kg, Flu 160 mg/m^2 **or** Treo 14 gm/m^2, TT 10 mg/kg, Flu 160 mg/m^2, ATG	CsA, MTX or MMF	30	1.7 – 18.8	0.5 – 14	none	Stomatitis (43%), GI toxicity (17%); no VOD	none	7% Gr I–II aGVHD, 7% cGVHD in BU group, none in treo group	50% (BU) and 36% (Treo) at 1 year
USA (King, 2015)[18]	Alem 48 mg, Flu140–150 mg/m^2, Mel 140 mg/m^2	CsA or tacrolimus	43	3 – 20.3	0.75 – 11.83	3 (11, 18, 21)	3 deaths from GVHD	19% by 1yr; 9% by 2 yrs	23% aGVHD, 13.4% cGVHD	29 – 100%

Abbreviations: Alem, alemtuzumab; ATG, anti-thymocyte globulin [r(rabbit)]; BU, busulfan; CMV, cytomegalovirus; CY, cyclophosphamide; Flu, fludarabine; Treo, treosulfan; TT, thiotepa; TBI, total body irradiation; aGVHD, acute GVHD; cGVHD, chronic GVHD; ceGVHD, chronic extensive GVHD; CsA, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate; Pred, prednisone; VOD, veno-occlusive disease; PRES, posterior reversible encephalopathy syndrome

Table 3

Indications of HCT in adult recipients with SCD

Age, 15 – 40 years with SCD AND one or more of the following
Clinically significant neurologic event (stroke) or any neurological deficit lasting >24 hours
History of 2 or more episodes of acute chest syndrome (ACS) in the 2-year period preceding HCT despite the institution of supportive care measures (i.e. asthma therapy and/or HU)
History of 3 or more severe pain crises per year in the 2-year period preceding enrollment despite the institution of supportive care measures (i.e. a pain management pain and/or treatment with HU)
Administration of regular RBC transfusion therapy, defined as receiving 8 or more transfusions per year for≥1 year to prevent vaso-occlusive clinical complications (i.e. pain, stroke and acute chest syndrome)
An echocardiographic finding of tricuspid valve regurgitant jet (TRJ) ≥ 2.7 m/sec

Table 4

Recent results of HLA-matched HCT in adults with SCD

Center	Preparative regimen	GvHD prophyl	n	Age range (yrs)	Published outcomes			Latest follow up		
					Follow up (yrs)	Death (mos)	Complications	IST	GvHD	% donor chimerism
NHLBI (Hsieh, 2009, 2014)	Alem 1mg/kg,TBI 300 cGy	Sirolimus	30	17–65	1.8–6	1 (ICH) after GR	GR (n=4)	11 of 26	none	Median T-Cell 48%
France (Kuentz, 2011)	BU 14 mg/kg, CY 200 mg/kg, rATG 10 mg/kg	CsA, MTX	15	16 – 27.5	1 – 16.1	1 (ICH)	SDH (n=1), seizures	–	8 acute GVHD, 2 chronic GVHD	75 – 100%