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Review article

Curative therapies: Allogeneic hematopoietic cell transplantation from matched related donors using myeloablative, reduced intensity, and nonmyeloablative conditioning in sickle cell disease

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ABSTRACT

Sickle cell disease (SCD) chronically damages multiple organs over the lifetime of affected individuals. Allogeneic hematopoietic cell transplantation (allo-HCT) is the most studied curative intervention. Fully matched related marrow, peripheral blood derived, or cord blood HCT have the best transplant outcome for symptomatic patients with SCD. For patients with asymptomatic or milder disease who have this donor option available, risks and benefits of HCT should be discussed among the patient, family, treating hematologist, and transplant physician, and decision to proceed to HCT should be individualized. Myeloablative conditioning with busulfan, cyclophosphamide, and ATG has been a commonly employed regimen for children and young adults. Recently, low intensity conditioning with low dose total body irradiation and alemtuzumab is emerging as an efficacious and safe regimen for adults, young adults, and possibly children. Mixed donor chimerism (minimum ≥20% myeloid cells), from myeloablative or nonmyeloablative conditioning regimen, produces robust normal donor erythropoiesis and is sufficient to provide a clinical cure. The proportion of patients remaining on immunosuppression beyond 2 years post-HCT is likely $<10\%$ with either myeloablative or low intensity regimens. Late effects from myeloablative or reduced intensity conditioning, or from several more months of immunosuppression in low intensity conditioning may be less common than those observed in HCT for malignant indications. Nonmyeloablative approaches with low toxicities should be the focus of future research efforts. Prevention of GVHD is a shared goal in all approaches of allo-HCT in SCD.

Sickle cell disease (SCD) is a monogenic, autosomal recessive disorder that repeatedly damages multiple organs over the life time of affected individuals. Clinical manifestations from injury to marrow (as vaso-occlusive crisis), spleen, vasculature, and brain parenchyma (stroke) occur in the first decade of life; injury to joints and vital organs (heart, lungs, liver, and kidneys) can be detected as early as in the second decade. Although hydroxyurea, red cell transfusion, and iron chelation are the backbone in treating this disorder, allo-HCT is the most studied curative intervention.

Myeloablative conditioning regimen

The first reported hematopoietic cell transplantation (HCT) in sickle cell disease (SCD) was performed over 30 years ago in a child who had acute myelogenous leukemia [1,2]. Although the HCT was performed for the malignant indication, the child was also cured of her SCD from a matched related donor (MRD) with hemoglobin (Hb) AS. This report demonstrated that SCD could be cured with HCT and that cure was achieved with a sickle trait (HbAS) allograft.

A small series of children and young adults in Belgium published a few years later expanded the literature on MRD allogeneic-HCT (allo-HCT), with a description of 12 patients with

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SCD who had to return to Africa and who would have limited access to optimal supportive care [3,4]. Some patients in this cohort had milder SCD phenotypes; all had MRD, 8 of 12 donors had HbAS. Conditioning consisted of myeloablative doses of oral busulfan, intravenous cyclophosphamide, and thoracoabdominal radiation for older recipients. All were cured of their SCD, with 1 patient requiring a second HCT due to secondary graft failure. No patient had a SCD crisis post-HCT, with Hb electrophoresis levels reflective of donor type. Four of 12 developed grade I-II acute graft-versus-host disease (GVHD). A larger cohort of Belgian HCT patients was later published with overall (OS) and disease-free survival (DFS) rates of 93% and 85%, respectively [5,6]. These reports replicated earlier results indicating that allo-HCT can be curative in SCD and further validated the use of HbAS MRD allografts.

The Multicenter Investigation of Bone Marrow Transplantation for SCD resulted in a landmark publication in 1996, with several follow-up manuscripts describing outcomes of myeloablative MRD HCT in children and adolescents with busulfan, cyclophosphamide, and serotherapy (usually antithymocyte globulin or ATG) [7,8]. Consensus eligibility criteria were established, many of which are still in use today. The OS and DFS rates were 91% and 73%, respectively. Updates on this cohort with additional subjects indicated OS of 93% and DFS of 85%. Deaths were usually due to GVHD, with 19% developing any GVHD and 3 deaths attributed to chronic GVHD. Five of the 50 subjects cured of SCD had mixed-donor chimerism, suggesting that full donor chimerism was not required for cure [9]. Importantly, all recipients who had donor levels of Hb S (HbS) were free of crises post-HCT and with stable cerebrovascular and pulmonary disease post-HCT.

The Société Française de Greffe de Moelle published results from a national registry in France, which has positioned MRD HCT as standard of care for symptomatic SCD in children and young adults [10,11]. ATG serotherapy was added to myeloabative busulfan and cyclophosphamide, resulting in an EFS of 95% since 2000, and no deaths in the latter 47 consecutive HCTs. Overall GVHD rates for the entire cohort of 87 patients were 20% for acute GVHD grades II-IV and 12.6% for chronic GVHD (2.4% extensive). Table 1 summarizes the experience with myeloablative HCT for children and young adults with SCD.

Matched related umbilical cord blood transplantation

The first report using fully matched related umbilical cord hematopoietic cells for SCD was published in 1998 [12]. Since then, >50 children have been transplanted using myeloablative conditioning (MAC). The OS was >90%, similar to the outcomes using marrow from MRD, and rates of grade IV acute or severe chronic GVHD were much lower [13,14]. In several children, umbilical cord blood cells were co-infused with marrow, with similarly successful results [15]. In contrast, HCT results from unrelated or mismatched umbilical cord products were suboptimal (discussed elsewhere in this journal). The use of this cell source is likely limited, since the cell dose for umbilical cord products is fixed and may be low for larger children or adults, and using only fully matched related cord units does not help to expand the donor availability.

MAC with busulfan, cyclophosphamide, and ATG has produced the best HCT outcomes, with marrow or umbilical cord blood cells from MRD. This regimen is commonly employed in children and young adults with acceptably low rates of GVHD and transplant-related morbidity.

Reduced intensity and nonmyeloablative conditioning regimens

Although MAC HCT achieves high rates of OS and DFS for SCD, acute and late toxicities remain a concern for many patients and physicians. Of particular concern is the risk of infertility with busulfan and the increased risk of toxicities with myeloablation in older recipients [16]. International registry data indicated that GVHD-free survival for HCT recipients over 16 years of age with SCD is only 77%, most of whom received MAC. With the already established high rates of cure with MAC in younger patients, fewer toxicities with reduced and low intensity regimens, and the aforementioned data showing mixed chimerism being curative in SCD, recent efforts have focused on HCT with less intensive conditioning protocols.

Several groups have described reduced intensity conditioning (RIC) strategies such as lower dose busulfan (8 mg/kg total) and fludarabine/low dose total body irradiation (TBI). Although the former approach cured 6/7 patients, the fludarabine/200 cGy TBI approach was curative in only 1/6 children [17-19]. A large series with RIC and MRD allo-HCT included 52 children with hemoglobinopathies, 43 of whom had SCD [20]. The conditioning regimen consisted of early (day-21) alemtuzumab, melphalan, and fludarabine and almost all recipients received bone marrow infusions, with 1 related umbilical cord blood allograft. The related cord blood allograft resulted in the only graft failure; rates of OS and EFS for those with SCD were 93% and 91%, respectively. GVHD outcomes were reported for all 52 subjects (including those with thalassemia major), with grade II-IV acute GVHD observed in 23% and extensive chronic GVHD in 13% of patients. All those with extensive chronic GHVD were over 14 years of age. Three subjects died from GVHD. Of those with SCD and 1 year of follow-up, 32/46 had full donor chimerism. Additionally, ovarian preservation was reported with this regimen [21]. Although graft failure rates were low with this approach, rates of GVHD, particularly chronic GVHD in older recipients, could be improved.

The National Institutes of Health (NIH) developed a very low intensity nonmyeloablative (NMA) regimen for adults with SCD using alemtuzumab (1 mg/kg total dose), 300 cGy TBI, and longer

Table 1
Myeloablative conditioning HCT for SCD.

Authors	*N*	Median Age (y)	Conditioning	OS (%)	Graft rejection (%)	DFS	cGVHD (%)	TRM (%)
Walters et al (2000)	50	9.4	Bu-Cy-ATG	94	10	84% @ 6 y	12	6
Bernaudin et al (2010)	144	9	Bu-Cy-ATG	95	<2	93% @ 3 y	10	7
Dedeken et a (2014)	50	8.3	Bu-Cy-ATG	94	8	86% @ 8 y	20	<5
Locatelli et al (2013)	160	-	Bu±Cy ± Thiotepa ± Flu	-	<2	91% @ 5 y	-	13
Lucarelli et al (2014)	40	12	Bu-Cy-ATG ± Flu	91	-	91% @ 9 y	<5	7.5
McPherson et al (2011)	27	8.6	Bu-Cy-ATG	96	0	96% @ 5 y	<5	<5
Vermylen et al (1998)	50	-	Bu-Cy ± ATG	93	10	85% @ 11 y	20	-
Bhatia et al (2014)	18	8.9	Bu-Flu-alemtuzumab	100	0	100% @ 2 y	11	0

ATG = antithymocyte globulin; Bu = busulfan; Cy = cyclophosphamide; Flu = fludarabine; TRM = transplant-related mortality; TLI = total lymphoid irradiation.