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Hematopoietic Stem Cell Transplantation for Sickle Cell Disease: More Options and Many Unanswered Questions

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Sickle cell disease (SCD) is an inherited hemoglobinopathy leading to polymerization of hemoglobin S in the deoxygenated state. The resulting vaso-occlusion with ischemia and reperfusion injury accounts for most of the morbidity and shortened life-expectancy. Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only established curative therapy for SCD. Initial trials included only the most severely affected patients, using a myeloablative conditioning and HLA-identical sibling donors, resulting in event-free survival (likely cure) of >85% [1]. While successful HSCT can halt the progression of SCD existing organ damage may not be reversible. Therefore it seems reasonable to extend this procedure to the less severely affected patients at a younger age. Based on registry data, HSCT is much underutilized for SCD and that is due to several unresolved issues. Less than 15% of patients with SCD have a matched, related donor and those identified have often been reluctant to participate. For the majority of SCD patients an alternative donor is required. While there are more than 10 million adult volunteers in various registries around the world, finding a well-matched unrelated donor has been difficult for patients of African-American ancestry due to their unique HLA-phenotypes. Umbilical cord blood cells (UCB) from siblings have been used successfully as a source of stem cell for HSCT. Unrelated cord blood transplants have been increasingly used for other HSCT indications and may represent an attractive option for SCD patients, due to the better tolerance of HLA-disparity. A recent report from three international registries showed the feasibility of this approach. Despite the use of myeloablative conditioning, engraftment failure remained a challenge, especially when a high cell dose was not available [2]. Haploidentical related donors are theoretically a much more readily available stem cell source. The difficulties encountered with this approach included the technical complexity of T-lymphocyte depletion, risk of rejection and delayed immunologic recovery. Intensive chemo-radiotherapy has therefore been required. Recently a novel approach with the use of post-transplantation high dose cyclophosphamide showed engraftment without excessive graft-versus-host disease [3]. If the success is confirmed more SCD patients may be considered for HSCT.

The most commonly used myeloablative regimen involves high-dose busulfan. The acute and long-term sequelae are considerable. Hepatic veno-occulsive disease is a known complication with the use of myeloablative regimens and can be fatal. Permanent sterility and thyroid dysfunction are common. To families and physicians these complications provide substantial deterrent in considering HSCT instead of other symptomatic treatment for sickling crises. Laboratory and clinical data both suggest healthy donor erythrocytes have survival advantage over sickle cells. In a stable mixed chimerism (MC) state small fraction of donor red cells can be adequate to prevent symptoms of SCD. For example, donor chimerism of 11% was associated with a low HbS of 7% and freedom from vaso-occlusive crisis [4]. Since complete replacement by donor cells is not required reduced intensity conditioning (RIC) utilizing an immunoablative approach to facilitate engraftment, even partial, is an attractive option. Initial experience of RIC was associated with a high incidence of delayed graft loss [5], but more recent reports appeared more encouraging. Hsieh et al. employed a chemotherapy-free protocol including 3 Gy of total body irradiation and alemtuzumab, followed by continual maintenance immunosuppression with sirolimus. After matched sibling donor HSCT 9 of 10 adults engrafted with stable MC and became asymptomatic [6].

The RIC regimen of alemtuzumab, fludarabine, and melphalan has led to successful engraftment in children with various non-malignant hematologic disorders [7,8]. It unique design includes early administration of alemtuzumab, three weeks before transplant. This allows depletion of recipient immune cells, but ensures that the monoclonal antibody will be mostly cleared at the time when donor stem cells are infused. Most of the experience using this RIC regimen was derived from matched sibling and unrelated adult donor HSCT. We have reported that engraftment after this regimen was affected by the stem cell source and the pathophysiology of the underlying disorder [9]. Compared to other stem cell sources, unrelated UCB was associated with a higher incidence of MC.

A Blood and Marrow Transplant Clinical Trial Network (BMT-CTN) study utilized this regimen for unrelated donor HSCT in children with SCD. As reported by Kamani et al. 5 of the 8 recipients in the cord blood donor cohort developed autologous hematologic recovery [10]. Further enrollment into this stratum has been suspended. The authors retrospectively reviewed a number of factors that may account for the unsuccessful outcome. Due to limited cell dose and frequent donor-recipient mismatch, engraftment failure is more frequent after UCB transplants. In the BMT-CTN study strict donor selection (at least 5 of 6 HLA match) and cell dose requirement (an adequate, albeit modest, 3 x 107 per kg,) were employed. Yet early graft loss was common. Recently the presence of anti-donor-specific HLA antibody has been correlated with graft rejection in unrelated donor HSCT; this was not detected in any of the cases. The cohort of matched unrelated adult donor HSCT continues in the BMT-CTN and its result shall provide much needed information on efficacy of this regimen.

The negative results from the BMT-CTN showed that a number of challenges still remain. Areas to be explored included:

(1) Further modification of the conditioning regimen. Kamani et al. suggested intensifying the regimen by adding other chemotherapeutic

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agents, such as thiotepa and hydroxyurea [10]. Treosulfan, an analog of busulfan, is being investigated as a conditioning agent since it has a better toxicity profile. However the long-term sequelae remain to be seen [11]. European centers have more experience with the use of this agent, but a few patients with SCD have been treated. The optimal dosage and its role in a conditioning regimen remain to be determined.

(2) Because low number of cord blood cells infused adversely affects engraftment, a number of strategies can be considered to increase the effective cell dose received. Most experience has come from the infusion of multiple cord blood units [12]. This is an established approach in cases of hematologic malignancies but no systemic analysis on SCD is available. *Ex vivo* expansion of a single cord blood unit has been tested and only preliminary results are available. Another approach, with favorable engraftment kinetics, has been the direct administration of UCB into the marrow cavity. Finally some studies have also shown co-administration of third party mesenchymal stromal cells has the potential to enhance engraftment of UCB cells [13].

(3) The current approach of selecting cord blood units based on numeric value (allowing a single mismatch of a HLA A or B antigen or 1 DRB1 allele) may not be optimal. There is recent information that HLA-C match may also be critical. In addition a mismatch involving shared maternal HLA antigen (Non-inherited maternal antigens or NIMA) has resulted in better outcome instead of a random disparity [14].

In summary there are major ongoing efforts to expand the availability of HSCT for SCD. Increasing donor availability is critical, and the use of unrelated UCB cells as a donor source should not be abandoned without additional evaluation. Optimizing the safety of transplant preparative regimens is also important, especially if HSCT is used for adults who have sustained morbidity from SCD. The recent trend is clearly towards the use of RIC for HSCT. However, not all RIC regimens are equal and the definition can be vague. To make interpretation more difficult most series only consisted of a small number of cases, with a mixture of patients receiving different stem cell sources and a relatively short period of follow up. As more options become available to patients with SCD there are clearly many unanswered questions to be addressed.

References

1. Panepinto JA, Walters MC, Carreras J, Marsh J, Bredeson CN, et al. (2007) Matched-related donor transplantation for sickle cell disease: report from the Center for International Blood and Transplant Research. Br J Haematol 137: 479-485.
2. Ruggeri A, Eapen M, Scaravadou A, Cairo MS, Bhatia M, et al. (2011) Umbilical cord blood transplantation for children with thalassemia and sickle cell disease. Biol Blood Marrow Transplant 17: 1375-1382.
3. Brodsky RA, Luznik L, Bolaños-Meade J, Leffell MS, Jones RJ, et al. (2008) Reduced intensity HLA-haploidentical BMT with post transplantation cyclophosphamide in nonmalignant hematologic diseases. Bone Marrow Transplant 42: 523-527.
4. Walters MC, Patience M, Leisenring W, Rogers ZR, Aquino VM, et al. (2001) Stable mixed hematopoietic chimerism after bone marrow transplantation for sickle cell anemia. Biol Blood Marrow Transplant 7: 665-673.
5. Iannone R, Casella JF, Fuchs EJ, Chen AR, Jones RJ, et al. (2003) Results of minimally toxic nonmyeloablative transplantation in patients with sickle cell anemia and beta-thalassemia. Biol Blood Marrow Transplant 9: 519-528.
6. Hsieh MM, Kang EM, Fitzhugh CD, Link MB, Bolan CD, et al. (2009) Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. N Engl J Med 361: 2309-2317.
7. Shenoy S, Grossman WJ, DiPersio J, Yu LC, Wilson D, et al. (2005) A novel reduced-intensity stem cell transplant regimen for nonmalignant disorders. Bone Marrow Transplant 35: 345-352.
8. Marsh RA, Vaughn G, Kim MO, Li D, Jodele S, et al. (2010) Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. Blood 116: 5824-5831.
9. Chan KW, Grimley M, Jude V, McDonald L, Luke J, et al. (2010) Reduced intensity conditioning regimen of Alemtuzmab, fludarabine, and melphalan for transplantation of pediatric non-malignant congenital hematologic disorders (NMHD): outcome affected by stem cell source. Blood 116: 1434.
10. Kamani NR, Walters MC, Carter S, Aquino V, Brochstein JA, et al. (2012) Unrelated donor cord blood transplantation for children with severe sickle cell disease: Results of one cohort from the phase II study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Biol Blood Marrow Transplant 18: 1265-1272.
11. Danylesko I, Shimoni A, Nagler A (2012) Treosulfan-based conditioning before hematopoietic SCT: more than a BU look-alike. Bone Marrow Transplant 47: 5-14.
12. Jaing TH, Yang CP, Hung IJ, Chen SH, Sun CF, et al. (2007) Transplantation of unrelated donor umbilical cord blood utilizing double-unit grafts for five teenagers with transfusion-dependent thalassemia. Bone Marrow Transplant 40: 307-311.
13. Macmillan ML, Blazar BR, DeFor TE, Wagner JE (2009) Transplantation of ex-vivo culture-expanded parental haploidentical mesenchymal stem cells to promote engraftment in pediatric recipients of unrelated donor umbilical cord blood: results of a phase I-II clinical trial. Bone Marrow Transplant 43: 447-454.
14. Rocha V, Spellman S, Zhang MJ, Ruggeri A, Purtill D, et al. (2012) Effect of HLA-matching recipients to donor noninherited maternal antigens on outcomes after mismatched umbilical cord blood transplantation for hematologic malignancy. Biol Blood Marrow Transplant 18: 1890-1896.