Sickle Cell Today

USA Comprehensive Sickle Cell Center

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TABLE OF CONTENTS

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TWiTCH is out!

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Clinical stroke is a dreadful and frequent complication in patients with sickle cell anemia (SCA). The peak incidence of stroke occurs in the first decade of life and before age 20, has an estimated cumulative incidence of 7–11%. Stroke handicaps a person not only physically, but also psychologically and socially. Thus, any treatment program that lowers the risk or prevents stroke is a worthwhile endeavor.

Transcranial ultrasonography screening (TCD) can effectively identify children at risk of stroke by determining how fast blood flows to the brain (blood flow velocity). A blood flow velocity of 200 cm/s or more is associated with a 10% increase in stroke risk each year after the initial finding and has a cumulative 3-year primary stroke incidence of 40%. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) showed that maintaining the sickle hemoglobin (HbS) to less than 30% with regular blood transfusions reduces the incidence of first overt stroke by 90% in this population. The STOP 2 trial assessed whether regular blood transfusion therapy in patients with abnormal TCDs could be discontinued if the TCD normalized. This study had to be terminated early because the TCD velocities again became abnormal in several children and overt strokes occurred in a few. Since then indefinite therapy has become the standard of care for this patient population even with its antecedent risks of allo- and auto- antibody formation, blood-borne infections, and iron overload with its associated organ damage. An alternative treatment that carries a reduced adverse event profile and an increased possibility of compliance had long been sought after until the recently closed TWiTCH (TCD with Transfusions Changing to Hydroxyurea) trial which assessed Hydroxyurea (HU) efficacy in SCA patients who were on regular blood transfusions for abnormal TCDs.

HU is the only medical therapy other than red cell transfusions proven to prevent known complications of SCA. It increases the hemoglobin level and the percentage of fetal hemoglobin along with a concurrent reduction in total white blood cell, platelet and reticulocyte counts. These effects on blood cells have been clinically found to reduce pain episodes, acute chest syndrome, hospitalizations, need for blood transfusions and likely prevention of organ damage. To compare HU with standard regular blood transfusion therapy in patients with a history of abnormal TCD velocity, the NHLBI sponsored multicenter TWiTCH trial was conducted at 26 sites in the USA and Canada including the University of South Alabama.

In TWiTCH, patients with SCA, ages 4–16 years, who had a documented abnormal TCD velocity (≥200 cm/s) and had received at least 12 months of regular blood transfusions were enrolled and randomized either to continue regular transfusion therapy or switch to HU. Every participant underwent baseline brain magnetic resonance imaging (MRI) and angiography (MRA), TCD examination, a measurement of liver iron concentration, neurocognitive testing, and quality of life assessments. Documented clinical stroke, transient ischemic attack, or severe cerebral

see "TWiTCH" on page 4

Visit the Comprehensive Sickle Cell Center website at:
http://www.usahealthsystem.com/sicklecellcenter

STEM CELL TRANSPLANTATION AS TREATMENT OF SICKLE CELL DISEASE

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Hematopoietic Stem Cell Transplantation (HSCT) is a treatment for some types of cancers and blood disorders. This article discusses the use of HSCT in sickle cell disease (SCD).

Bone marrow is the soft, spongy tissue inside bones. It contains cells called hematopoietic stem cells. These cells can turn into several other types of cells including red and white blood cells. In the past, stem cells could only be collected from the bone marrow, so patients who needed a stem cell transplant received a "bone marrow transplant." Today, stem cells are usually collected from the blood, instead of the bone marrow. For this reason, they are now more commonly called stem cell transplants. The infusion of hematopoietic stem cells from a healthy donor into a patient with SCD is a potentially curative treatment in that the SCD patient can now potentially make new healthy red blood cells. However, before stem cells can be infused in the patient, the patient must first be treated with a preparative regimen consisting of agents designed to create marrow space and suppress the patient's immune system to prevent rejection.

Although an effective treatment, HSCT can cause a number of different side effects, therefore patients are carefully selected and screened before proceeding to this huge undertaking. Moreover, it is prudent to find a donor whose bone marrow matches the patient. There are certain proteins on the stem cells called human leukocyte antigens (HLA). The best donor has fully matched HLA proteins. Matching HLA proteins, lowers the risk of a serious condition called graft-versus-host disease (GVHD).

The first patient with SCD who received HSCT was an 8 year old girl who also had leukemia. After the transplant she not only became cancer free, but also her hemoglobin S levels came down to that of her donor who had sickle cell trait and the patient no longer experienced pain crisis or acute chest syndrome. This was published in medical literature in 1984. Since then multiple clinical trials have been initiated across the United States and Europe. The goal of these clinical trials is to improve the overall survival and disease free survival of patients receiving HSCT. The key to success in HSCT depends on factors such as patient selection, donor selection, choice of preparatory regimens and aggressive supportive care measures.

Indications for HSCT: In SCD, selecting patients that are most suitable candidates to receive HSCT is one of the biggest challenges. Unfortunately, there are no clear indicators to predict, at an early age, the severity of a patient's SCD course. By the time, a decision is made to refer a patient for HSCT many of them have already developed severe respiratory and vascular complications. These complications deem them ineligible to receive HSCT. Besides, there are serious concerns about transplantation related deaths as well as the potential for treatment induced cancers over the long term.

The International Consensus Guidelines recommend HSCT for patients younger than 17 years of age, with severe symptoms of SCD that are unresponsive to hydroxyurea, or those who have had prior organ damage (e.g., stroke, acute chest syndrome, frequent painful episodes, multiple sites of osteonecrosis) if an HLA-matched sibling is available as a donor. This recommendation recognizes the SCD free survival of 80 to 90 percent after HSCT, and the 7 to 10 percent deaths associated with HSCT for such patients.

HSCT Donor Selection: Siblings with matching HLA, are always preferable as HSCT donors due to low risk of GVHD and rejection or failure of graft. About three quarters of the siblings of patients with SCD have sickle cell trait. Fortunately, the safety and feasibility of using HLA- matched sibling donors with sickle cell trait have been established. In a large multi-center study in the United States in 2000, 50 children with SCD were transplanted from HLA- matched siblings including those with sickle cell trait. After 3 years follow up, 84% of children were alive and free of SCD. Three children died from complications of HSCT and in 5 children, transplant was unsuccessful.

Early vs Late Transplant: In Belgium, a study was performed to compare the outcome of early versus late transplant. The late transplant group was comprised of 36 patients who had developed significant complications from SCD. The early transplant group was comprised of 14 patients who were picked up early in the course of their disease, with a history of less than 3 blood transfusions. The early group, after a follow up period of 11 years, showed 100% overall survival and all but one patient was free of SCD. Whereas the late group reported 12% deaths and 80% of patients were disease free. Similarly, fewer side effects associated with transplant were reported in the early group.

Preparative Regimen: Before the body can receive healthy stem cells, the diseased cells must be destroyed. This is done using chemotherapy and sometimes radiation. The destruction of diseased cells is called a preparative regimen. This treatment also suppresses the immune system to prevent graft rejection and GVHD. A non-myeloablative regimen, also termed reduced-intensity conditioning (RIC), is a newer treatment approach that uses doses of chemotherapy and radiation too low to destroy all the bone marrow cells of the recipient. This regimen significantly reduces treatment related toxicity. So far 2 studies have

been performed which comprised a total of 40 adult patients with SCD who received a non-myeloablative preparative regimen prior to HSCT. The transplant was successful in 90% of the patients and no patients experienced acute or chronic GVHD. Despite these encouraging results, non-myeloablative preparatory regimens remain experimental for SCD patients.

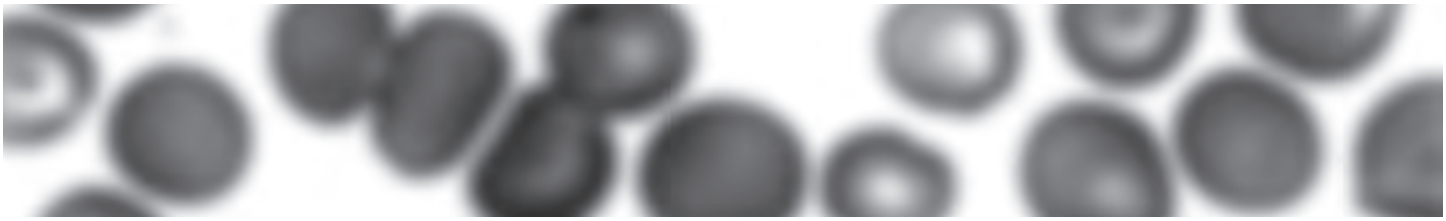
Alternative Donors: Another source of stem cells is the cord blood collected at the time of birth. Successful engraftment using cord blood transplant from matched sibling donors in patients with SCD have been reported. Eleven such patients were reported to the Eurocord Registry. There were no transplant-related deaths and one graft failure. The estimated disease free survival 2 years after transplant was 90 percent.

The role of unrelated cord blood transplants in patients with SCD remains uncertain. In one report, seven patients underwent transplant from unrelated, incompletely matched umbilical cord blood. Only three were successful.

The use of stem cell donors who only match half of the recipient HLA proteins (i.e., haploidentical donors mostly a parent) has been proposed as a means of increasing the size of the HSCT donor pool for patients with SCD, but remains experimental. In an observational study, 17 patients with severe SCD underwent haploidentical transplantation. This therapy was well tolerated and was successful in 65% of patients. Further studies are needed to determine the risk-benefit ratio of this approach outside of a clinical trial.

Conclusion / Recommendation: Hematopoietic stem cell transplantation (HSCT) is a potentially curative option in patients with sickle cell disease (SCD).

- In several series of patients who have undergone HSCT for SCD, five-year survival rates were 90 to 97 percent, and transplant-related deaths were 7 to 10 percent. SCD recurred in some patients, resulting in a SCD-free survival of 80 to 90 percent.
- Experts recommend HSCT for patients with severe symptoms of SCD that are unresponsive to treatment with transfusions and hydroxyurea if an HLA-matched sibling is available as a donor.
- Early HSCT in young children with SCD has been explored as a possible means of reducing SCD complications and transplant associated side effects and deaths. However, because accurate predictors that can prospectively define the severity of SCD in infants and children have not been identified, the role of this approach has yet to be defined.
- The use of alternative donors (e.g. umbilical cord blood, mismatched related donors, or matched unrelated donors) remains uncertain in patients with SCD.
- Non-myeloablative preparative regimens have been proposed to reduce regimen-related toxicity, but further data are needed to determine the long-term success.



GBT440: A Potential New Disease-Modifying Therapy in Sickle Cell Disease

A primary function of hemoglobin, the protein inside red blood cells (RBCs), is to carry oxygen from the lungs for delivery to the tissue (i.e., brain, skin, bone, etc). In sickle cell disease, hemoglobin undergoes a process called polymerization after it releases oxygen to the tissues. This polymerization process results in RBC sickling, RBC destruction and blockage of blood flow to vital organs, which causes organ damage.

In comparison to normal hemoglobin (hemoglobin A), sickle hemoglobin (hemoglobin S) does not bind oxygen as tightly. This observation has led scientists to investigate compounds that can make hemoglobin S bind oxygen to an extent that parallels that of hemoglobin A. If that is accomplished, the process of sickling, in theory, can be prevented.

At the American Society of Hematology meeting held in December 2015, Global Blood Therapeutics presented promising data from multiple preclinical studies on the compound, GBT440. In patients with sickle cell disease, GBT440 was found to: dose-dependently increase oxygen binding to hemoglobin S without impairing effective oxygen delivery; reduce RBC destruction and the number of circulating sickled cells; and improve RBC survival and tissue oxygen delivery. Further clinical investigation of GBT440 as a potential disease-modifying therapy for sickle cell disease is underway. The USA Comprehensive Sickle Cell Center will keep you updated on GBT440.

A Healthy Approach To Hot Weather

Pediatric-to-Adult Care Transition (PACT)
T'Shemika Perryman, RN-PACT Coordinator

Spring is here, and summer is quickly approaching. School is coming to an end, and vacation planning is about to begin. Whether you're planning a big trip or simply planning to be outside every day, you must remember to take care of yourself first.

We live in a very hot and humid region, and it's important to remember a few ways to stay reasonably healthy in such a climate. Here are a few tips for the spring and summer months:

- **Adequate hydration** — Dehydration can cause your cells to sickle, which can trigger a pain crisis. It is very important to stay well hydrated, especially during the hot and humid summer months. You should drink at least 8 glasses of water a day — more if you are outside directly in the heat.
- **Rest** — Make sure you get at least 8 hours of sleep at night. During the day, when you are outside playing with friends or doing an activity with family and you feel tired, take breaks as needed. You can always catch up.
- **Prevent Infections** — Try to avoid, if possible, people who are sick. Always implement proper handwashing skills with soap and water as a simple way to prevent infection.
- **Medications** — Take all medications as prescribed. Try to avoid missing any doses and do not double up on missed doses. If you are having trouble remembering when to take your medications and have access to a smartphone or tablet, download a medication reminder app to your device. Just type in Rx reminder in your app store.
- **Medical care** — Make and keep all routine check-up appointments with your health care providers. If you have to miss an appointment, make sure you call to reschedule.
- **Avoid extreme temperatures** — Try to avoid getting overheated. Dress appropriately. If it's too hot outside, stay inside. If the air conditioner is blowing too cold inside, cover up with a blanket.
- **Avoid stressful situations** — If a situation is stressful for you, it could potentially trigger a pain crisis. If possible, avoid stressful situations. If not, try to quickly resolve the matter or find the best coping mechanism for you so that your stress level does not get so high that you wind up in a pain crisis.

These are just a few tips to help you enjoy your spring and summer breaks. By adding these tips to your daily routine, you can decrease the potential of having a pain crisis this spring and summer. Have a great summer!!!

Content source: **www.cscfkids.org/living-with-sickle-cell/how-are-you-living-well**
www.cdc.gov/ncbddd/sicklecell/healthyliving-living-well.html

"TWiTCH" continued from page 1

vasculopathy (brain vessel narrowing) were exclusion criteria. Comparable maintenance of TCD velocity was the primary end point of the trial.

Between September 20, 2011, and April 17, 2013, 61 patients were randomly assigned to receive standard transfusions and 60 patients were assigned to HU treatment. The standard transfusion group continued to receive transfusions once per month to maintain HbS at 30% or lower and received Exjade (deferasirox) to manage iron overload. In the HU group, HU was initiated at 20 mg/kg per day (capsules or liquid formulation) with escalation to maximum tolerated dose (MTD), which was defined as the dose at which moderate blood counts suppression was achieved. Transfusions were slowly weaned over 4–9 months to protect against stroke during HU dose escalation. After discontinuing transfusions, patients receiving HU underwent serial phlebotomy to manage iron overload. The treatment period was 24 months after randomization and throughout that time monthly TCD velocities were measured.

Baseline TCD velocities were similar in the two treatment groups, but the final average velocity of the HU group was slightly lower (138 cm/s; 95% CI 135–142) than that of the standard group (143 cm/s; 95% CI 140–146). This finding lead to early termination of the study by the NHLBI after 50% of participants had exited. No child in either treatment group reverted from a normal to abnormal TCD velocity or had a stroke. Three events in each group were deemed transient ischemic attacks. Exit brain MRI examinations detected no new cerebral infarcts in either treatment group. Compared with the standard group, iron overload improved more in the HU group. Expected adverse events were mostly balanced between treatment groups but serious adverse events were more common in patients receiving HU (10 vs. 23 events; pain crises, acute chest syndrome, fever, neurologic and hepatobiliary issues).

In summary, children with abnormal TCD velocities but without severe vasculopathy now have an alternative therapeutic option after a period of transfusions, which represents an important advancement in management of stroke risk in high risk patients with SCA. As pediatric sickle cell providers, we are obligated to provide our children with SCA and their parents, the most up-to-date information on the best available therapy for their potentially incapacitating and progressive illness. If your child is receiving regular blood transfusions for abnormal TCD velocity, please ask their sickle cell provider about the possibility of switching them to HU at their next visit.

Community Efforts Lead to a Record Breaking Blood Drive in 2015

The annual blood drive sponsored by Alpha Phi Alpha Fraternity, Inc., the USA Comprehensive Sickle Cell Center, the Sickle Cell Disease Association of America, Mobile Chapter; and Franklin Primary Health Center was held on September 19, 2015 at the Franklin Memorial Complex Mall located at 1303 Martin Luther King Avenue, Mobile, Alabama. 2015 marked the 10th year of this partnership where the blood drive is conducted annually during the month of September which is National Sickle Cell Awareness Month. While the goal of this blood drive was to collect 50 units of blood, **a record shattering 72 units of blood were collected!!!** The largest drive held prior to 2015 was in 2013 which collected 57 units.

The success of the drive stems from growing support by the Mobile community. The USA Department of Physician Assistant Studies had the largest number of donors amongst participating organizations. Other supporters of the blood drive were the: Classic Corvette Club, Student National Medical Association, USA Leadership Scholarship Program, Alpha Elites, Pacesetters Motorcycle Club, Edith Mitchell Health Initiatives, JEM Scholars and donors from across the Mobile community. The sponsors express their sincere gratitude to the community, local organizations and volunteers who came out in support of the blood drive. **Thank you for giving the "Gift of Life" through blood donation.** We are looking forward to an even more successful blood drive in 2016 and hope to see you and your organization present.

The 2016 Blood Drive is tentatively scheduled for Saturday, September 17, 2016 at Franklin Primary Health Center Medical Mall located on Martin Luther King Drive, Mobile, Alabama.

THE 2016 ANNUAL SICKLE CELL CONFERENCE

Practical Issues in Sickle Cell Disease XV: More Is Not Always Better!

On Saturday, April 30, the USA Comprehensive Sickle Cell Center will host its 15th Annual Regional Sickle Cell Conference. National and local experts will present up-to-date information on treating patients with sickle cell disease.

A central theme of this year's conference will be red blood cell transfusions — indications and therapeutic targets as well as transfusion complications. Additionally, experts will focus on addressing sickle cell pain crisis as a diagnosis of exclusion.

The conference targets physicians, physician assistants, nurse practitioners, nurses and allied health professionals. It is supported by the Dr. Cecil L. Parker, Jr., Lectureship Endowment, which was created to address the educational needs of the clients and health care providers of the Gulf Coast community.

The conference will be held from 8 a.m. to 4 p.m. in the University of South Alabama's Health Sciences Building, College of Nursing Auditorium, Room 1013; 5721 USA Drive North; Mobile, AL 36688.

Register early for a chance to win complimentary admission to the 2017 Annual Regional Sickle Cell Conference. The early bird registration deadline is April 15, 2016. For additional conference information visit http://www.usahealthsystem.com/sicklecellcenter or call 251-470-5893.

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