Carter BloodCare
SPECIALTY SERVICES

Blood Matters

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News for Blood Bank Medical Directors, Physicians and the Lab

Blood Matters is a quarterly news *outlet with important medical information for you, our customers and colleagues, from Carter BloodCare. We hope you will share it with others interested in the work we do together.*

IN THIS ISSUE

HOT TOPICS

Cord Blood Transplantation

Todd Nishimoto, MD

Umbilical cord blood (UCB) or cord blood (CB) is found in the blood vessels of the placenta and the umbilical cord. Procurement is a generally safe procedure for the newborn baby and mother since the UCB is collected after the baby is delivered and after the umbilical cord is cut. Cord blood contains hematopoietic stem and progenitor cells (HSPC).

Umbilical cord blood transplantation (UCBT) is an alternative source of HSPC for pediatric and adult patients with hematological malignancies and non-malignant diseases lacking a related or an unrelated donor. Increased levels of HLA disparity that can be tolerated makes UCBT an attractive alternative source of HSPC. This feature is particularly important for patients from racial and ethnic minorities, as it can be difficult to find an unrelated donor (URD) for such patients. However, the downside is that a single UCBT does not contain sufficient HSPC to allow for both hematopoietic and immunologic recovery in a large child or adult.

There are two strategies proposed to overcome the limitations of using UCB in both hematopoietic and immunologic recovery. First, enhancing homing capacity of HSC for more efficient engraftment. Second, ex-vivo expansion of collected HSPC and increasing proliferation of the engrafted cells in the bone marrow (BM).

Enhancing the homing capacity of the infused UCB for more efficient engraftment is under investigation. Besides attempts of IV injection or infusion, some current efforts include inhibition of enzymes by using prostaglandin E, increasing the affinity to endothelial cells by fucosylation, and a combination of fucosylation with mesenchymal stromal cell (MSC) presentation.

Ex-vivo expansion of collected UCB and increasing proliferation of the engrafted cells in the BM studies include mimicry of the BM micro-environment with MSC, notch ligand, and copper chelation to inhibit differentiation, nicotinamide to inhibit differentiation and increase function of HSC.

Many of these methods are currently being tested in late phase multi-center clinical trials; the data show promise with rapid neutrophil and platelet engraftment but the studies have been limited by small sample size and complex technology.

Since the first UCBT in 1988, the practice of UCBT has advanced considerably by establishing a minimum transplantable cell dose, dual CB to compensate for the paucity of HSPC, refinement of UCB unit selection, and infection prevention. However, limitations remain with single UCB unit having insufficient cell dose which challenges the hematopoietic and immune recovery. If homing and expansion techniques prove successful, larger studies on long term safety, engraftment success, and cost will be a few of the major challenges ahead.

Reference:

J Clin Invest. 2014;124(7):3121-3128

Intrauterine Transfusions: A Procedure of Last Resort

William Crews, MD

Intrauterine transfusion (IUT) is a highly complex, invasive procedure where RBCs are transfused into the fetal abdomen or directly transfused via the umbilical cord vein. Hemolytic disease of the fetus and newborn (HDFN) is the most common indication for a fetus to be transfused. The most common cause of HDFN is due to ABO incompatibility between the mom and fetus where the mom produces anti-A,B, or isolated anti-A or anti-B, but this form of HDFN rarely causes severe hemolysis. HDFN that occurs when the mother is alloimmunized, typically from exposure to fetal RBCs from a previous pregnancy, produces an IgG antibody which crosses the placenta and destroys fetal RBCs that express the paternally inherited corresponding antigen. Anti-D, anti-c and anti-K are often implicated in severe HDFN, although many other antibodies have been implicated. Other indications for IUT include non-immune hemolysis due to infection, hemoglobinopathies, membrane/cytoskeletal defects, and RBC enzyme deficiencies (G6PD,PK).

The typical prenatal workup of an alloimmunized mother includes monthly or bimonthly antibody titers to determine when a critical level (four to eightfold increase from baseline) is reached. Once the antibody titer has reached a critical threshold, testing to predict fetal antigen status and/or ultrasound fetal monitoring with middle cerebral artery (MCA) Doppler assessment may be pursued.

When paternity is certain, paternal RBC phenotyping can be performed to determine fetal risk of inheriting the corresponding RBC antigen. If the father is negative for the corresponding antigen, the fetus will also be negative, and no further workup or monitoring is needed. When paternity is uncertain, or the known father is heterozygous for the antigen, additional testing and monitoring will be required since there is a 50% chance of inheriting the antigen. Noninvasive tests to determine fetal genotype are becoming increasingly available using fetal DNA extracted from maternal plasma to determine RHD zygosity. If noninvasive fetal genotyping is unavailable, amniocentesis, cordocentesis, or chorionic villus sampling can be performed to obtain fetal DNA.

Fetal anemia can be detected with Doppler ultrasound and measurement of MCA peak systolic blood flow velocity (MCA-PSV). This test is based on the principle that fetal anemia increases cardiac output and decreases blood viscosity, resulting in increased blood flow velocity. An MCA-PSV >1.5 multiples of the median for gestational age is used to identify a fetus with potentially severe anemia, and fetal blood sampling, or percutaneous umbilical blood sampling (PUBS) is indicated.

Before the PUBS can be performed, a multi-departmental team must be assembled to ensure the procedure is performed smoothly and quickly as possible. This team typically consists of a Maternal-Fetal-Medicine physician, anesthesiologist, ultrasound operator, someone to guide the needle, someone to control the syringe for sampling fetal blood and transfusing blood, and a runner to deliver fetal blood to lab for testing and pick up the blood to be transfused from the blood bank.

General guidelines for RBC selection for use in IUT include: ABO compatible with mother and fetus, negative for antigens to which mother has been alloimmunized, hematocrit between 70-80%, less than 7 days old, leukocyte reduced or CMV seronegative, and Hgb S negative.

Summary of Procedure:

1. An intrauterine fetal blood transfusion is done in the hospital. Mom may have to stay overnight after the procedure
2. Mom is sedated, an ultrasound image is obtained to determine the position of the fetus and placenta

HOT TOPICS Continued

3. Mom's abdomen is cleaned with an antiseptic solution, she is given a local anesthetic injection to numb the abdominal area where the transfusion needle will be inserted
4. Medication may be given to the fetus to temporarily stop fetal movement
5. Ultrasound is used to guide the needle through the mother's abdomen into the fetus' abdomen or an umbilical cord vein
6. A sample of fetal blood is obtained to determine ABO/Rh, Hgb, and Hct
7. If Hgb is too low a compatible blood type is delivered into the fetus' abdominal cavity or into an umbilical cord blood vessel
8. The mother is usually given antibiotics to prevent infection. She may also be given tocolytic medication to prevent labor from beginning

Due to the complexity of determining if the fetus is a candidate for IUT, and up to a 5% risk of fetal death with the procedure, PUBS/IUT is only performed when there is evidence of accelerated hemolysis and all other treatment options have been exhausted.

MEDICAL MINDS

What topics would you like to see in a future issue of Blood Matters?

Click **here** to submit your choice.

PHYSICIAN RESOURCES

Download updates

- Feb 2020 – Blood Bulletin Vol. 20, No. 1: Transfusion-Associated Circulatory Overload (TACO): Undereported and Underappreciated
- May 2020 - Blood Bulletin Vol. 20, No. 2: "COVID-19 Convalescent Plasma - a Potentially Effective Therapeutic Modality" Revised to Reflect May 1st Change to FDA Guidance

New Therapies in Hemophilia A – Will They Help?

Geeta Paranjape, MD

Hemophilia A is an X linked bleeding disorder due to clotting factor VIII deficiency. Patients with severe disease (factor level less than 1%) have spontaneous bleeding in joints, muscles, and soft tissues, patients with moderate disease (factor level 1-5%) rarely have spontaneous bleeding but will bleed with minor trauma, and patients with mild disease (factor level 6-30%) will only bleed with trauma or with invasive procedures.

Factor VIII replacement is the standard mode of treatment, it can be given to treat a bleeding episode or in severe deficiency to avoid such bleeding episodes. Since patients with severe hemophilia lack the factor VIII protein they are at a risk of developing antibodies to the administered factor which is perceived as "foreign". These antibodies referred to as "inhibitors" – since they inhibit the function of infused factor – pose a serious problem when patients with severe hemophilia bleed since factor VIII infusion is ineffective. The way to bypass the inhibitors is to use either activated factor VII (aVII) or prothrombin complex concentrate (PCC). These treatments carry significant risks and are also very expensive. These cannot be used to prevent but only to treat bleeding episodes. Immune tolerance by gradual administration of factor VIII has been tried in patients with inhibitors, but it is expensive, time consuming and patients often do not comply.

Clearly, new therapies are needed to treat hemophilia A.

Patients who get factor VIII infusions for prevention typically need infusions at least 2-3 times per week due to short half-life of infused factor. A lot of work has been done to have factors with extended half-life (EHL) with modifications in the structure of the factor or attaching it to carrier molecules. While theoretically sound it does not translate into practice, and results vary greatly from patient to patient; this therapy also does not eliminate the risk of developing inhibitors.

So, if not the factor VIII, can we use non-factor therapy (NFT) for hemophilia?

Emicizumab is a factor VIII-like monoclonal antibody and has recently been approved by FDA for hemophilia A patients with inhibitors. In clinical trials it has been shown to decrease (but not eliminate) bleeding in hemophilia A patients with or without inhibitors.

Other agents directed against natural anticoagulants have been tried with encouraging results. These can be administered subcutaneously and with a patient friendly frequency of once a week or once a month leading to much better patient compliance. They also are unaffected by presence of inhibitors. The problem with these agents (none has been licensed for use) is how to treat patients safely if they bleed while on these agents.

Gene therapy using a safe viral vector carrying the gene for factor VIII is the most attractive option. Work has been done using adenovirus vector carrying a factor VIII gene that will get integrated in liver cells and make factor VIII. Clearly the ideal gene therapy would require a small dose, produce sufficient factor and not lead to immune response eliminating the vector virus and the gene – this of course is a tall order and currently not available.

There is hope that with new therapies all hemophilia patients will be able to have the same quality of life as someone with no bleeding disorder. There is hope that this dream will become reality in a not too distant future.

Reference:

F1000Research 2018, 7(F1000 Faculty Rev):489