RELATED PEDIATRIC DONORS – HEMATOPOIETIC STEM CELL COLLECTION

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Hematopoietic stem cell (HSC) donation is considered a safe procedure and has been performed for more than 40 years. Particular attention should be paid to the donor and the donation process, considering both the safety of the donor and the recipient. Children may also be donors to their siblings, but with distinct peculiarities comparing to adult donation.

Several international accreditation committees monitor notifications of events and adverse reactions to donors participating in the registries worldwide. These committees periodically have published guidelines to ensure the health and well-being of these donors.[1]

This topic will analyze the assessment of a donor under the age of 18 who has been identified as compatible with a sibling. The general issues involved in selecting donors for allogeneic HSCT will be discussed elsewhere in the consensus.

DONOR ELIGIBILITY

Unlike the unrelated donor, the family donor, even if he or she has certain diseases such as some autoimmune diseases, diabetes, or even localized cancers, may still be eligible for donation as long as the risk is acceptable.[2]

The evaluation of the child as a donor should follow the same protocol used for the adult donor. In addition to the clinical history, the same evaluation tests are performed. If the recipient has a genetic disease like hemoglobinopathies, chronic granulomatous diseases, Fanconi anemia, among others, the sibling donor should be investigated for the same genetic condition.

PSYCHOLOGICAL EFFECTS

Children applying for HSC donation to their siblings, depending on their age, are unable to understand the act itself and are unable to voluntarily consent. Since the donation is considered safe for pediatric donors, there is a need to protect their mental and physical health differently from their sick sibling.[3]

A wide range of emotions related to the sibling donor experience has been reported. These include increased family closeness, improved relationships with the ill sibling, and a sense of tremendous pride in helping to save a life. Yet, negative responses for sibling donors have also been reported, including anxiety, depression, withdrawal, behavioral problems, anger, and responsibility for the transplant outcome.[4,5]

To minimize all the negative impacts of the donation procedure, the child donor should be evaluated by a specialized multidisciplinary team that at least the medical staff should be different from the one that takes care directly of the recipient to avoid the conflict of interest. In some countries, a kind of donor advocate has been determined, whose role would be to help parents and donors understand the medical procedure, as well as independently protect the interests and well-being of the donor.[6]

CONDITIONS UNDER WHICH A MINOR MAY PARTICIPATE AS A HEMATOPOIETIC STEM CELL DONOR

Worldwide, a person under 18 years old is not allowed to serve as a donor for a nonfamily member but may donate for a relative, most often a sibling. Currently, with the increased number of haploidentical transplants, a child or adolescent may be asked to donate to his or her sibling even to another relative.

In 2010, the American Academy of Pediatrics (AAP) published a policy statement regarding children as Hematopoietic stem cell donors.[7] The AAP recommends five conditions that should be fulfilled for a minor to be a donor:

There is no medically equivalent histocompatibility adult relative who is willing and able to donate

There is a solid personal and positive relationship between the donor and recipient

There is some likelihood that the recipient will benefit from transplantation

The clinical, emotional, and psychosocial risks to the donor must be minimized and reasonable in relation to the benefits expected to accrue to the donor and the recipient

Parental permission and donor assent (when possible) must be obtained

JUDGE'S AUTHORIZATION

In addition to the consent of parents and/or guardians, in Brazil, it is necessary to have a judge's authorization for a child to donate HSC to his or her sibling.[8]

BONE MARROW DONATION

The use of bone marrow from an HLA-identical sibling donor is considered the standard of care worldwide for children undergoing HSC transplantation. However, the number of allogeneic peripheral blood stem cells (PBSCs) among matched-sibling pediatric transplantations has increased recently.[9]

The European Group for Blood and Marrow Transplantation Pediatric Diseases Working Party published the experience of HSC collection in 453 pediatric donors, either bone marrow (BM) or PBCSs.[9] They investigated prospectively factors influencing the safety of HSC collection in those donors. Bone marrow harvest is frequently complicated by mild to moderate pain, fatigue, and transient changes in peripheral blood cell count. They reported an increased risk of allotransfusion after BM harvest associated with a donor age of < 4 years and a BM harvest volume of > 20 mL/kg of the donor. In a multivariate logistic regression model, only donor/recipient weight ratio <0.75 was associated with an increased risk of cardiac complications, presumably due to the volume of marrow collected relative to donor size. Donor/recipient weight ratio <0.75 was also associated with a greater risk of post-donation anemia. Allogeneic blood transfusion in pediatric donors should be avoided unless an unexpected life-threatening event occurs, so the authors appointed that the BM harvest of > 20 mL/kg is not an appropriate practice and should be discouraged.[9]

To minimize the most common complications of a bone marrow harvest in a young donor, it is recommended:

To start the iron supplementation with ferrous sulfate or equivalent (3 to 6 mg/kg elemental iron) one month before the day of collection and maintain one month after.

To have appropriate harvest needles for the size of the child

To collect autologous blood in children if there is an important discrepancy between donor and recipient body weight, two to three weeks before the BM harvest, and that the expected BM volume be superior of 20 ml/kg of the donor. But the procedure could be challenging due to the venous access, behavior of the child, and adequate material (needle size, bag etc)

To maintain appropriate analgesia during at least two to three days after the BM collection.

General anesthesia is recommended.

The bone marrow harvest is generally performed from the posterior iliac wing of the donor, about 2-3 cm below and laterally to the superior iliac spine. If it is necessary, the anterior iliac crest can be used, but the quantity that can be collected is clearly lower than that collected using the posterior iliac bone.[10] Once the needle has passed the bone cortex, aspirations should be made by vigorous suction of not more than 5-10 ml of bone marrow using a heparinized syringe, and it is possible to rotate the needle when there is a large bezel or move the needle to always aspirate different sites of the bone marrow to minimize contamination with peripheral blood. Only one or two punctures are made in the skin in each side, but through this orifice, dozens of punctures are performed in the iliac bone. The aspirated product is then filtered and transferred into an anticoagulant solution, usually heparin and/or anticoagulant citrate dextrose formula-A (ACD).[10]

There are few studies using 3-5 days G-CSF prior to bone marrow harvest that shown an increased number of nucleated and CD34 cells collected, which resulted in more rapid engraftment but with no increased risk of graft versus host disease (GVHD). However, Chu et al.[11] demonstrated the mortality risks were lower after transplantation of bone marrow compared to G-CSF primed bone marrow in adults with severe aplastic anemia (SAA), and the authors concluded that the bone marrow is the preferred graft for HLA matched sibling transplants for SAA. Therefore, additional randomized studies are needed to provide the optimal priming regimen and the benefit of G-CSF primed bone marrow collection, especially in a minor donor.

PERIPHERAL BLOOD PROGENITOR CELL (PBPC) COLLECTION

The use of G-CSF for stem cell collection in pediatric donors is a very controversial issue. None of the rare early complications described in adults after G-CSF administration, like vascular events, splenic enlargement, or rupture, have been reported in children. The long-term effects of G-CSF use in healthy children have not been registered. In some European countries, the use of G-CSF is not routinely allowed in healthy children.[9]

Eapen et al.[12] showed that pediatric patients received no benefit from PBSC transplantation, and an even worse outcome was reported than bone marrow transplant, primarily because of chronic GVHD. Meantime, more recent data do not confirm this experience in the related scenario but instead support the finding that PBSC transplantation in children leads to faster engraftment without an increased risk of acute and/or chronic GVHD.[13]

Although several studies in adult donors have not demonstrated any increased long-term complications such as increased cancer risk after short-term G-CSF administration for PBSC, sufficient long-term studies in children addressing this issue have not been performed.[14-16]

The procedure of PBSC collection in children has the potential of causing pain related to G-CSF administration (site of administration and/or bone pain), the risks associated with central venous catheter (CVC) placement, the occurrence of hypocalcemia during apheresis, and the risk of cardiovascular complications related to hypovolemia. In addition, children with less than 20kg may be exposed to heterologous red blood cells to prime an apheresis circuit of the machine.[9]

For all above, the use of children as PBSC donors is still not recommended routinely.

However, if there is a significant difference between the weight of the donor and recipient and it was necessary to collect PBSC, some precautions must be taken, such as:

Venous access: younger pediatric donors may require central catheter placement for collection. Pulsipher et al. [17] related that one-third of donors between ages 7 and 12 were successfully collected using peripheral access, but 97% of children under seven years needed a central venous line.

The catheter insertion should be performed with sedation or general anesthesia and by a well-trained staff. The site of the catheter insertion can vary according to the experience of the physician, but femoral vein catheterization has become an increasingly accepted method because of a lower complication rate during its insertion, especially when a rigid catheter is inserted.[18]

Complications of catheter placement are usually limited and mild. The most common is local pain.[17] The thoracic vascular puncture may cause pneumothorax, hemothorax, pleural laceration, among other complications. The main immediate complications of femoral vein puncture are inadvertent arterial puncture (9 to 15%) and hematoma (16%), of easy clinical management.[19,18]

More recently, ultrasound-guided catheterization has considerably reduced the number of jugular vein puncture accidents in children, as demonstrated by Leyvi et al.[20] Ultrasound, where available, should be used to guide vascular puncture also at other sites.[21]

HYPOVOLEMIA:

Children under 20 kg or when the extracorporeal machine volume of the circuit exceeds 10% to 15% of the total patient body volume, there is a significant risk of rapid decrease of hematocrit and pressure during an apheresis procedure, and the child may present hypotension, tachycardia, pallor and even hypovolemic shock. Therefore, it is an established practice in most centers to prime the apheresis machine with red blood cells or with 4% albumin solution. Orbach et al.[22] described a protocol using priming with 4% albumin or high molecular weight hydroxethylstarch in children under 15 kg. Before starting the procedure, red blood cell transfusion was performed in patients with hemoglobin below 12g/dl. In total, 38% of patients did not require red blood transfusion, suggesting that this approach can avoid unnecessary transfusions. More recently, Norooznezhad et al.[23] described their center's guideline for donors with less than 20 kg. The donors received irradiated (25Gy), leukoreduced red blood cell transfusion if their hemoglobin level was less than 13 g/dL at the night before the apheresis day. Moreover, the donors received 1:1 of the extracorporeal volume with normal saline 20-30 minutes at the beginning of the apheresis.

Japanese studies using regular donors less than 20 kg collected two or three 5–10 ml/kg autologous blood in sequential weeks before the PBSC harvest along with supplemental iron therapy. With this approach, they used only autologous blood priming for all their small donor.[24]

ANTICOAGULANTS AND ELECTROLYTE DISORDERS:

All leukapheresis procedures, including peripheral hematopoietic stem cell collection, require transient anticoagulation to prevent clot formation and system occlusion. The most used anticoagulant for leukapheresis is adenine citrate dextrose formula A (ACD-A). Anticoagulation is due to the citrate and calcium complex formation, which causes the most frequently observed side effect, especially in children, the hypocalcemia.[25,26] Probably, the reason that causes a higher frequency of hypocalcemia in younger children is that they have a lower hepatic metabolism of citrate. Signs and symptoms of hypocalcemia in children are generally nonspecific, and they could present as nausea, abdominal pain, agitation, hypotension, tachycardia, or even continuous crying. One option to reduce the risk of anticoagulant-related hypocalcemia is to infuse calcium in the patient in bolus or continuous infusion. Another option is to use only heparin for anticoagulation or the combination of heparin with ACD-A, but with a higher risk of bleeding. In addition to hypocalcemia, ACD-A can cause hypomagnesemia, hypopotassemia, and metabolic alkalosis.[27,28] The study published by Bolan et al.[29] thoroughly describes electrolyte changes observed in platelet donors during leukapheresis. The authors observed a ratio of serum citrate level and reduction of serum ionized calcium and magnesium of 33% and 39%, respectively, at the end of the procedure. They also observed a marked decrease in phosphorus. Total calcium and potassium levels decreased by 3% and 6%, while sodium and bicarbonate increased by 1% and 3%, respectively. Study data suggested that renal excretion of serum citrate overload causes increased renal excretion of cations, calcium, and magnesium. Increased renal excretion of potassium and sodium is likely to occur by metabolizing citrate to bicarbonate and continuous dextrose infusion from the anticoagulant solution. Therefore, to reduce the risks of electrolytes disturbances in a minor donor during leukapheresis, we suggest that children should receive an intravenous replacement of calcium, magnesium, and potassium.

IN CONCLUSION:

Most of the time, pediatric donors of hematopoietic stem cells can safely donate with parental consent and greatly benefit their recipients. They should be evaluated by a different and skilled medical staff to minimize their risks, the conflict of interest, and if there are increased risks of complications due to the collection, they should be deferred.

The use of G-CSF and heterologous red blood cell transfusion should be avoided in a child donor and when it is necessary to use, it should be discussed with the parents all the alternatives and risks.

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