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Stem cell mobilization and collection from pediatric patients and healthy children

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ABSTRACT

Today, hematopoietic stem cell transplantation (HSCT) is a standard treatment for a variety of conditions in children, including certain malignancies, hemoglobinopathies, bone marrow failure syndromes, immunodeficiency and inborn metabolic disease. Two fundamentally different types of HSCT are categorized by the source of the stem cells. The first, autologous HSCT represents infusion of patient's own hematopoietic stem cells (HSCs) obtained from the patient; the second, allogeneic HSCT refers to the infusion of HSCs obtained from a donor via bone marrow harvest or apheresis. Bone marrow has been the typical source for HSCs for pediatric donors. Bone marrow harvest is a safe procedure mainly related to mild and transient side effects. Recently, a dramatically increased use of mobilized peripheral blood stem cells (PBSCs) in the autologous as well as allogeneic setting has been seen worldwide. There are limited data comparing mobilization regimens; also mobilization practices vary widely in children. The most commonly used approach includes granulocyte colony stimulating factor (G-CSF) at 10 mg/kg/day as a single daily dose for 4 days before the day of leukapheresis. G-CSF induced pain was less reported in children compared to adult donors. For the collection, there are several technical problems, derived from the size of the patient or donor, which must be considered before and during the apheresis. Vascular access, extracorporeal circuit volume, blood flow rates are the main limiting factors for PBSC collection in small children. Most children younger than 12 years require central vascular access for apheresis; line placement may require either general anesthesia or conscious sedation and many of the complications arise from the central venous catheter. In this review, we discuss that the ethical considerations and some principals regarding children serving as stem cell donors and the commonest sources of HSCs are presented in children, together with a discussion of how to collect and process these cells.

1. Introduction

Today, hematopoietic stem cell transplantation (HSCT) is a standard treatment for a variety of conditions in children, including certain malignancies, hemoglobinopathies, bone marrow failure syndromes, immunodeficiency and inborn metabolic disease. The pluripotent hematopoietic stem cells (HSCs) arise in the bone marrow. These cells can be isolated from bone marrow, which can be aspirated from long bones or the pelvis. Alternatively, HSCs can be obtained from the blood by apheresis, and are termed peripheral blood stem cells (PBSCs); also they can be obtained from umbilical cord blood (UCB). The preferential source of these stem cells remains controversial, depending on different factors such as underlying specific diseases, and donor characteristics (unrelated vs. related, and infant vs. adolescent donor). The proportion of PBSCs circulating

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in the blood is normally very low, but can be significantly increased by the administration of chemotherapy, and sequential growth factors such as granulocyte colony stimulating factor (G-CSF), and some signaling pathway inhibitors [1,2]. The sufficient target yields of PBSCs for transplantation are usually obtained with one to three apheresis, although this may vary with the different conditions of the patients, and underlying diseases; in addition to these factors the weight ratio between the recipient and the donor must be taken into account. Moreover recent alpha beta depleted haploidentical HSCTs require higher numbers of PBSC to provide the Tsunami effect.

Two fundamentally different types of HSCT are categorized by the source of the stem cells, depending on the indication and the patient's features. The first, autologous HSCT involves infusion of patient's own HSCs obtained from the patient, with the sole intent to restore hematopoietic function following the administration of bone marrow ablative doses of cytotoxic agents. The second type of HSCT is allogeneic HSCT which refers to the infusion of HSCs obtained from a donor via bone marrow harvest or apheresis.

Bone marrow has been the typical source for HSC collection for more than 40 years. Since 1990, a dramatically increased use of mobilized PBSCs in the autologous as well as allogeneic setting has been seen worldwide [3]. According to data from the European Group for Blood and Transplantation (EBMT) registry, pediatric recipients undergoing transplantations from any donor received bone marrow in 64%, PBSCs in 30%, and UCB in 6% of cases [4,5]. Today, almost all autologous transplants are performed from PBSCs in pediatric population as well as adult patients.

In this review, we discuss that the ethical considerations and some principles regarding children serving as stem cell donors and the commonest sources of HSCs are presented in children, together with a discussion of how to collect and process these cells.

1.1. Children as hematopoietic stem cell donors

Children often serve as hematopoietic stem cell donors, most commonly for their siblings. HLA matched biological siblings are generally preferred as donors because of reduced risks of transplant related complications as compared with unrelated donors. According to EBMT registry, sibling donors have been recruited in 39%–48% of all childhood transplantations [4,5]. In rare cases, children may also be considered as potential donors for an adult sibling, parent, or other family member. The American Academy of Pediatrics (AAP) reports that children can ethically participate as hematopoietic stem cell donors. This statement includes a discussion of the ethical considerations regarding children serving as stem cell donors using the traditional benefit/burden calculation from the perspectives of both the donor and the recipient. Ethically, to determine if a stem cell donation by a child is permissible, one must examine the risks and benefits from the perspective of the donor as well as the risks and benefits to the recipient and to his or her family [6]. There is no direct medical benefit from serving as a stem cell donor. The benefit is always stated as the psychosocial benefit of helping a sibling or other close family member. The medical risks of stem cell collection depend on its source and the modality of collection [6,7].

1.2. Ethical considerations for pediatric donors

There is a small but growing literature on the psychosocial risks and harms caused by hematopoietic stem cell donation by children. Data show that many children experience distress related to their role as a donor [6,8,9]. Many pediatric donors believe that they did not have a choice about whether to serve as a marrow donor.

Currently, there is no guideline regarding participation of children as hematopoietic stem cell donors. The AAP established the ethically permissible for children to participate as donors if some criteria are fulfilled. Children can be a hematopoietic stem cell donors if there is no medically equivalent histocompatible adult relative, if there is some likelihood that the recipient will benefit from transplantation, if there is a strong personal and emotionally positive relationship between the donor and recipient, if the clinical, emotional, and psychosocial risks of the donors are minimized and parental permission or child assent have been obtained where appropriate [6]. Also, each donor should be regularly examined for the presence of any disease or condition that may affect his or her ability to donate stem cells safely, including viruses and other infectious diseases.

2. Bone marrow stem cells as stem cell source in children

2.1. Bone marrow collection (harvest)

Bone marrow is typically collected from the posterior iliac crest of the donor. The procedure is usually performed under general, or rarely, regional anesthesia. The collection is usually performed at the posterior superior iliac spine. The anterior iliac crest can be used if necessary, but the quantity that can be collected is clearly lower than that collected using the posterior iliac crest [1,10–13]. A normal collection will require about 200 to 300 punctures performed directly through the skin or across a small incision. 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. The aspirated product is then filtered and transferred into an anticoagulant solution, usually anticoagulant citrate dextrose (ACD), in a concentration of 1/6–10 volume (ACD/bone marrow) and/or 10 IU heparin per milliliter bone marrow.

The harvested bone marrow is always contaminated with normal blood. The degree of peripheral blood contamination is related to the total volume of bone marrow harvested, but clearly also to the collection technique; careful and vigorous small amount of aspirations result with less peripheral blood contamination [4,12]. The required cell dose empirically established over four decades relies on the amount of nucleated cells, which should be at least $1–2 \times 10^8$/kg for autologous transplants and at least 2×10^8/kg, or better $4–6 \times 10^8$/kg, for allogeneic transplants [1,2,4,12].

Recently, using 3–5 days G-CSF prior to bone marrow harvest have been shown to increase the number of nucleated and CD34+ cells collected, which results in more rapid