Collection of HSC in Children

16

Volker Witt and Christina Peters

16.1 Introduction

Collecting or harvesting HSCs from children is a challenge, not only because children have different physiological and therefore anatomical situations but also because psychological, legal and ethical concerns in minors are sometimes more difficult compared to adult donors. In addition, parents and/or legal guardians have to be addressed in all issues. This chapter will focus on the technical, physiological, and ethical problems in the field of HSC collection from children rather than indications.

The main difference to the adult setting is the small bodyweight; the difficulties in accessing venous access, especially in the leukapheresis setting; and the need for blood cell substitution in case of BM harvest. In children the indications for autologous HSC harvesting is well-established (Passweg et al. 2014). Using children in the allogeneic setting as donors is a complete different issue (Bitan et al. 2016). Children should not donate HSCs if a comparable compatible adult volunteer HSC donor is available, if the indication for the stem cell therapy is not first line, or if the therapy is experimental (Sheldon 2004; Zinner 2004).

The main resources to harvest HSCs are BM and PBSCs. The basic techniques are quite similar to the techniques used in adults. For BM collection punctures of the iliac crests or in very small children, the tibia is used. For harvesting HSCs from the PB, leukapheresis is used with the same apheresis systems as in adults.

To perform these procedures in children, physicians and nursing practitioners must have working knowledge about the normal age-dependent physiological parameters, like vital signs, growth, and psychological and motorical development, and should be trained in the communication with children, parents, and/or their legal guardians (Anthias et al. 2016).

16.2 Bone Marrow Harvest (See Chap. 14)

The collection of HSCs from the BM is the historical oldest technique. Multiple punctures of the iliac crest are performed in general anesthesia by experienced physicians and practitioners. The bone marrow is harvested by aspirations through adequately dimensioned needles. In very small children and if the iliac crest is anatomically not suitable for punctures, the aspirations could also be performed by punctures of the proximal tibia.

V. Witt
Department of Pediatric Hematology and Oncology, St. Anna Kinderspital, Medical University Vienna, Vienna, Austria

C. Peters (✉)
Stem Cell Transplantation Unit, St. Anna Children's Hospital, Vienna, Austria
e-mail: christina.peters@stanna.at

E. Carreras et al. (eds.), *The EBMT Handbook*, https://doi.org/10.1007/978-3-030-02278-5_16

For successful HSCT, it is necessary to obtain enough progenitor cells during the BM harvesting procedure. Most centers are using multiple aspirations of maximum 2 mL BM, while other centers are using few larger amount aspirations for BM harvesting (20–100–250 mL). It could be shown that the latter methods result in comparable grafts for transplantation (Witt et al. 2016). For some young donors with anatomically tiny situations or in diseases where a suitable donor should be used for more than one recipient a minimal harming procedure is warranted for the bone marrow harvest (Biral et al. 2008; Furey et al. 2018).

More recently, adult donors have received G-CSF because stimulated BM is richer in HSCs and therefore results in quicker engraftment (Ji et al. 2002). Experience with G-CSF-mobilized BM in pediatrics is limited. Recent data showed that a dose of 3–5 × 10^6 CD34+ HPC/kg of recipient bodyweight is the optimal CD34+ cell dose infused to attain GVHD relapse-free survival in children with an HLA-matched sibling donor. A higher CD34+ cell dose did not impact clinical outcome. G-CSF-primed BM harvest might have a better impact on smaller amount of BM harvest volume needed for a sufficient stem cell graft, but the study was underpowered to give an answer on this urgent question (Frangoul et al. 2007; Furey et al. 2018).

16.3 Peripheral Blood Stem Cell Harvest

PBSCs are harvested by leukapheresis in very small children even below 6 kg bodyweight and are described since the 1990s of the last century (Kanold et al. 1994; Klingebiel et al. 1995; Diaz et al. 1996; Moon et al. 2013). Special experience and techniques are required to perform safe leukapheresis procedures in pediatric patients using apheresis systems who are constructed for the use in adults. Due to the large extracorporeal volume of the apheresis systems available on the market (ca. 160–220 mL), there is a need to calculate the expected blood loss in the set during procedure (Witt et al. 2007). This has to be done in each procedure to decide whether a priming of the set is needed with blood (Moon et al. 2013). In most of the newest versions of the apheresis systems, an algorithm guides the user through this pediatric priming procedure. For priming only irradiated and leukodepleted packed RBCs should be used. In order to gain enough flow for the apheresis systems in very small children, a central venous catheter is needed, but also alternative line management with arterial lines is possible (Goldstein 2012; Even-Or et al. 2013; Hunt et al. 2013). It is important to know that in reports from registries, up to 50% of vascular access lines were peripheral venous access lines only in pediatric patients (Witt et al. 2008). For anticoagulation, citrate is used even in very small children. To avoid side effect, a calcium substitution is recommended (Kreuzer et al. 2011; Maitta et al. 2014).

For mobilization of the HPC into the PB, the longest experience exists with G-CSF in combination with chemotherapy in the autologous setting, but also plerixafor is reported in case series as suitable and safe in the use in children (Chambon et al. 2013). As in adults, a leukapheresis should be performed if a meaningful number of CD34+ HPCs are mobilized in the peripheral blood, to achieve the harvest of 2–5 × 10^6/kg recipient with a minimum number of procedures (Fritsch et al. 2010).

16.4 Risk Analysis BM Versus PBMNC

A study from the EBMT Pediatric Diseases Working Party describes which factors influenced the safety of HSC collection. In this prospective evaluation, 453 pediatric donors were included. The children donated either BM or PBSCs according to center policy. A large variability in approach to donor issues was observed between the participating centers. Significant differences were observed between BM and PBSC donors regarding pain, need for blood allotransfusion, duration of hospital stay, and iron supplementation; however, differences between the groups undergoing BM vs PBSC donation preclude direct risk comparisons between the two procedures. The most common adverse event was pain, reported mainly by older children after BM

harvest but also observed after CVC placement for PBSC collection. With regard to severe adverse events, one patient developed a pneumothorax with hydrothorax after CVC placement for PBSC collection. The risk of allo-transfusion after BM harvest was associated with a donor age of <4 years and a BM harvest volume of >20 mL/kg. Children <4 years were at higher risk than older children for allo-transfusion after BM harvest, and there was a higher risk of complications from CVC placement before apheresis. It was concluded that PBSC and BM collection are both safe procedures in children (Styczynski et al. 2012).

16.5 Pediatrics as Allogeneic Donors

Pediatric-aged donors vary widely in their ability to assent or consent to the risks of a donation procedure. There are key regulations and ethical imperatives, which must be addressed in deciding which donation procedure is appropriate for minors (van Walraven et al. 2013). In order to have general guidance, the American Academy of Pediatrics published in 2010 a recommendation on this issue. The authors strongly recommend the inclusion of the potential child donor in all decision-making process to the extent that they are capable. A minor's advocate should be an independent person who will help to prevent the delay of the donation procedure (Chan and Tipoe 2013).

The decision to take a minor family donor especially in inherited diseases is complicated to the fact that phenotypically healthy or minor symptomatic siblings with mild carrier status might be eligible for the severely ill recipient. One simple example is a sibling with thalassemia minor for a recipient with a thalassemia major (Biral et al. 2008). There are many other major diseases, including primary immunodeficiencies, chronic granulomatous disease, or sickle cell disease, where carriers are used as HSC donors. Potential family sibling donors with medical or psychological reasons not to donate should not be HLA typed (Bitan et al. 2016).

Key Points

- Pediatric donors can safely donate HSCs if an experienced team is performing the harvest procedure.
- Donors below 4 years of age have a higher risk for harvest-associated complications: With BM harvest, they have a higher need for Allo-transfusions, and there is a higher risk of complications from CVC placement before apheresis.
- Minors should only be recruited as HSC donors if no medically equivalent histocompatible adult person is available for donation and if there is a reasonable likelihood that the recipient will benefit.
- An informed consent (child assent) for the HSC donation has to be obtained by the legal guardians and from the pediatric donor. A donor advocate with expertise in pediatric development should be appointed for all individuals who have not reached the age of majority and who are considered as potential HSC donor.
- Long-term follow-up data should be collected to help determine the actual medical and psychological benefits and risks of child donors.

References

Anthias C, O'Donnell PV, Kiefer DM, et al. European group for blood and marrow transplantation centers with FACT-JACIE accreditation have significantly better compliance with related donor care standards. Biol Blood Marrow Transplant. 2016;22:514–9.

Biral E, Chiesa R, Cappelli B, et al. Multiple BM harvests in pediatric donors for thalassemic siblings: safety, efficacy and ethical issues. Bone Marrow Transplant. 2008;42:379–84.

Bitan M, van Walraven SM, Worel N, et al. Determination of eligibility in related pediatric hematopoietic cell donors: ethical and clinical considerations. Recommendations from a working group of the Worldwide Network for Blood and Marrow Transplantation Association. Biol Blood Marrow Transplant. 2016;22:96–103.

Chambon F, Merlin E, Rochette E, et al. Mobilization of hematopoietic stem cells by plerixafor alone in

children: a sequential Bayesian trial. Transfus Apher Sci. 2013;49:453–8.
Chan TK, Tipoe GL. The policy statement of the American Academy of Pediatrics–children as hematopoietic stem cell donors–a proposal of modifications for application in the UK. BMC Med Ethics. 2013;14:43.
Diaz MA, Villa M, Alegre A, et al. Collection and transplantation of peripheral blood progenitor cells mobilized by G-CSF alone in children with malignancies. Br J Haematol. 1996;94:148–54.
Even-Or E, Grunspan A, Swerdlow Y, et al. Peripheral blood stem-cell harvest using percutaneous arterial lines in children. Pediatr Blood Cancer. 2013;60:946–8.
Frangoul H, Nemecek ER, Billheimer D, et al. A prospective study of G-CSF primed bone marrow as a stem-cell source for allogeneic bone marrow transplantation in children: a Pediatric Blood and Marrow Transplant Consortium (PBMTC) study. Blood. 2007;110:4584–7.
Fritsch P, Schwinger W, Schwantzer G, et al. Peripheral blood stem cell mobilization with pegfilgrastim compared to filgrastim in children and young adults with malignancies. Pediatr Blood Cancer. 2010;54:134–7.
Furey A, Rastogi S, Prince R, et al. Bone marrow harvest in pediatric sibling donors: role of granulocyte colony-stimulating factor priming and CD34(+) cell dose. Biol Blood Marrow Transplant. 2018;24:324–9.
Goldstein SL. Therapeutic apheresis in children: special considerations. Semin Dial. 2012;25:165–70.
Hunt EA, Jain NG, Somers MJ. Apheresis therapy in children: an overview of key technical aspects and a review of experience in pediatric renal disease. J Clin Apher. 2013;28:36–47.
Ji SQ, Chen HR, Wang HX, et al. Comparison of outcome of allogeneic bone marrow transplantation with and without granulocyte colony-stimulating factor (lenograstim) donor-marrow priming in patients with chronic myelogenous leukemia. Biol Blood Marrow Transplant. 2002;8:261–7.
Kanold J, Rapatel C, Berger M, et al. Use of G-CSF alone to mobilize peripheral blood stem cells for collection from children. Br J Haematol. 1994;88:633–5.
Klingebiel T, Handgretinger R, Herter M, et al. Autologous transplantation with peripheral blood stem cells in children and young adults after myeloablative treatment: nonrandomized comparison between GM-CSF and G-CSF for mobilization. J Hematother. 1995;4:307–14.
Kreuzer M, Ahlenstiel T, Kanzelmeyer N, et al. Regional citrate anticoagulation—a safe and effective procedure in pediatric apheresis therapy. Pediatr Nephrol. 2011;26:127–32.
Maitta RW, Vasovic LV, Mohandas K, et al. A safe therapeutic apheresis protocol in paediatric patients weighing 11 to 25 kg. Vox Sang. 2014;107:375–80.
Moon JH, Kim MJ, Song SY. Safety and efficacy of G-CSF mobilization and collection of autologous peripheral blood stem cells in children with cerebral palsy. Transfus Apher Sci. 2013;49:516–21.
Passweg JR, Baldomero H, Peters C. Hematopoietic SCT in Europe: data and trends in 2012 with special consideration of pediatric transplantation. Bone Marrow Transplant. 2014;49:744–50.
Sheldon M. Children as organ donors: a persistent ethical issue. Camb Q Healthc Ethics. 2004;13:119–22.
Styczynski J, Balduzzi A, Gil L, et al. Risk of complications during hematopoietic stem cell collection in pediatric sibling donors: a prospective European Group for Blood and Marrow Transplantation Pediatric Diseases Working Party study. Blood. 2012;119:2935–42.
van Walraven SM, Straathof LM, Switzer GE, et al. Immediate and long-term somatic effects, and health-related quality of life of BM donation during early childhood. A single-center report in 210 pediatric donors. Bone Marrow Transplant. 2013;48:40–5.
Witt V, Beiglbock E, Ritter R, et al. Performance of a new separator system for routine autologous hematopoietic progenitor cell collection in small children. J Clin Apher. 2007;22:306–13.
Witt V, Pichler H, Fritsch G, Peters C. Multiple small versus few large amount aspirations for bone marrow harvesting in autologous and allogeneic bone marrow transplantation. Transfus Apher Sci. 2016;55:221–4.
Witt V, Stegmayr B, Ptak J, et al. World apheresis registry data from 2003 to 2007, the pediatric and adolescent side of the registry. Transfus Apher Sci. 2008;39:255–60.
Zinner S. Cognitive development and pediatric consent to organ donation. Camb Q Healthc Ethics. 2004;13:125–32.