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JOURNAL OF BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY

JBMTCT

IN THIS EDITION

Consensus Guidelines for pediatric hematopoietic stem cell transplantation from Brazilian Society for Blood and Marrow Transplantation and Cellular Therapy

7TH EDITION

JOURNAL OF BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY

JBMTCT

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SBTMO

SOCIEDADE BRASILEIRA DE TERAPIA CELULAR E TRANSPLANTE DE MEDULA ÓSSEA

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Dear transplant colleagues

In 2019 we celebrated the 40th anniversary of the first bone marrow transplant (BMT) in our country, with the pioneering spirit of Professor Ricardo Pasquini, Eurípides Ferreira and his team, a fact that was undoubtedly a milestone and the driving force for us to arrive where we are. Today, we are 84 BMT-enabled centers in Brazil and we have seen the great success of these teams, demonstrating a process of maturation of our transplant recipients.

Our company was founded in 1996 by a group of specialists and within this same premise. Today we are prominent in the worldwide transplanting community, having entered into several partnerships with international entities, such as ASCT, LABMT, CIBMTR, FACT, among others.

We have a research group at GEDECO (Grupo de Estudo Doença Enxerto Contra o hospedeiro e complicações tardias) ,coordinated by our dear Dr. Mary Flowers and Dr Afonso Celso Vigorito. This started small as a group of studies on graft disease and because of its quality and empathy, it has now become the gateway to cooperative studies on various topics in our society. SBTMO also maintains a Pediatrics Group, a flow cytometry group, a multidisciplinary group and one of data managers. Every two years, a consensus of indications and complications of transplants is performed, which serves as a guide for the guidance of specialists and public policies.

Faced with this scenario, in a natural way, arose the need to have a journal that could disseminate the work of this scientific community, doctors and multidisciplinary professionals, thus strengthening our interaction with transplantation professionals from various countries.

It is with this spirit of joy and hope that we launched this volume of JBMCT, Journal of Bone Marrow Transplantation and Cellular Therapy, which will certainly be a periodical to publicize the work of all those who believe that science , research and caring for patients, is the best way to improve our walking.

Fernando Barroso Duarte *Nelson Hamerschlak*

Summary

THE HISTORY OF THE SBTMO/SOBOPE PEDIATRIC GROUP

It is a great pleasure to introduce this special issue of our Journal of Bone Marrow Transplantation and Cellular Therapy (JBMTCT) with the 2021 Consensus of the Pediatric Group of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) and Brazilian Society of Pediatric Oncology (SOBOPE).

The Pediatric BMT Group has started its activity on July 2, 2001 at the Sobope Headquarters in São Paulo. Dr. Ricardo Pasquini, former SBTMO president, participated of this first meeting and requested the group to also represent Pediatric BMT at the SBTMO, with the Pediatric team from Curitiba being represented by Dr. Carmen Bonfim. Since then, the Pediatric Group has met at every Annual Meeting of the SBTMO and elected on alternate years a coordinator, vice-coordinator, and secretary among its participants.

The contact with Dr. Raul Ribeiro at the St Jude Research Hospital has allowed the group to meet regularly at the www.Cure4Kids.org platform for several years, with weekly meetings on every Tuesday morning since September 17, 2013. In 2021, the number of participants surpassed the capabilities of the Cure-4Kids website, and the group moved to the Zoom platform, coinciding with the Covid-19 pandemic. Today, we have 210 members registered at the platform and at least 40-50 participants every week.

The SBTMO held its First Meeting on Bone Marrow Transplant Guidelines in 2009.[1] A working group of hematologists and oncologists with experience in pediatrics was formed to review evidence-based indications for pediatric transplants. The recommendations include malignant and non-malignant hematological diseases, solid tumors, immunodeficiency, and storage diseases treated with hematopoietic stem cell transplants: either autologous or allogeneic from matched sibling donors or unrelated donors (adults or umbilical cord blood). Since then, the SBTMO has organized the Consensus meetings on alternate years and the final documents are available at the SBTMO2 and Cure4Kids[3,4] websites.

This is the first document we are so pleased to share with you with the recommendations from all disease-specific groups.

The Consensus Meetings and the Pediatric Group are open to participation of all associates and welcome everyone who would like to contribute for a better care to our children.

We dedicate this work to our children who thrive despite all adversities, to their families and all healthcare professionals taking care of these kids with so much love and dedication. Thank you so much. You are our heroes.

Enjoy the reading and see you in 2023!

Adriana Seber, past coordinator, for the Pediatric Group at SBTMO/SOBOPE

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3. Consenso 2009 - https://www.cure4kids.org/ums/home/files/file.php?id=7005

4. Consenso 2011/2012 - https://www.cure4kids.org/ums/home/files/file.php?id=5887

Fernando Barroso
President of SBTMO

Adriana Seber
Coordinator of the Pediatric Bone Marrow Transplant Group at SBTMO and SOBOPE

Carmem Bonfim
Coordinator of the scientific committee of the Pediatric Bone Marrow Transplant group at SBTMO

PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT ACTIVITY IN BRAZIL (2008 - 2019)

Brazilian Society of Bone Marrow Transplant and Cellular Therapy (SBTMO) - Data Managers Working Group - Pediatric Transplant Working Group

Hematopoietic stem cell transplants (HSCT) are performed in Brazil since the 70's, most of them in public centers. Transplant numbers are regularly reported by most centers to the Brazilian Transplant Registry/ Brazilian Solid Organ Association (ABTO/RBT), Latin American Bone Marrow Transplant Group/ Worldwide Network for Blood and Marrow Transplantation (LABMT/WBMT), but transplant outcomes are not available in our country. This is the first report on the outcomes of pediatric HSCT performed in Brazil between 2008 and 2019.

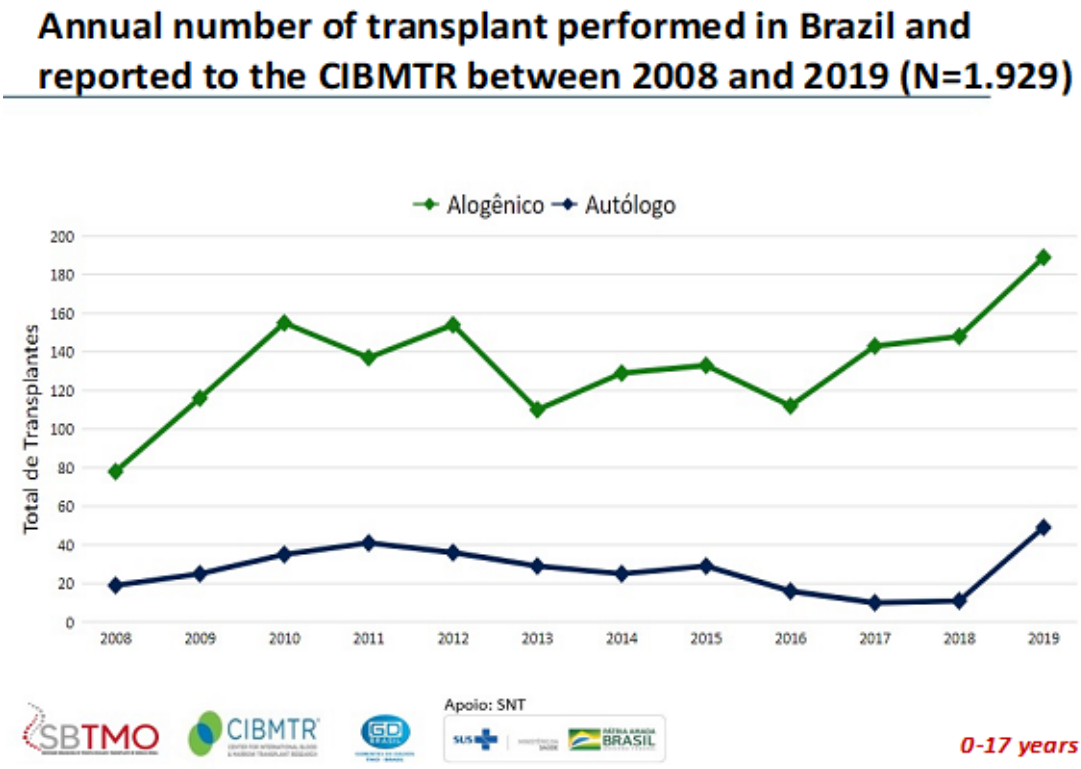
METHODS

The SBTMO has developed the initiative to collaborate with the Center for International Blood and Marrow Transplant Research (CIBMTR) to receive back deidentified aggregate nationwide data reported by Brazilian transplant centers. This was approved by our national central IRB (Conep CAAE: 65575317.5.1001.0071) in 2019 as a research project including data from 2008 through 2027. The SBTMO Data Managers Working Group prepared this report with the data reported to the CIBMTR and returned to the country as an enhanced Data Back to Center (eDBTC) file.

RESULTS

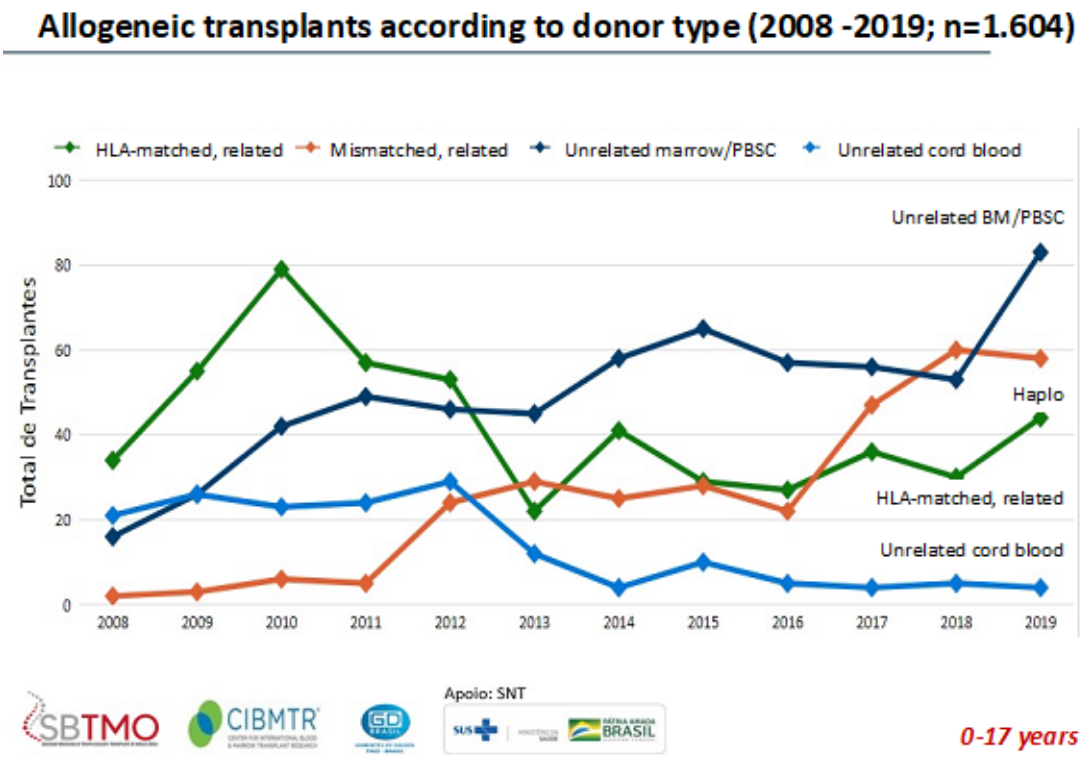
Between 2008 and 2019, 16 of the 19 institutions reporting to the CIBMTR also reported pediatric transplants. A total of 1,929 transplants were reported in children younger than 18 years of age and, different from the adult experience, most of them are allogeneic transplants (Figure 1).

FIGURE 1:



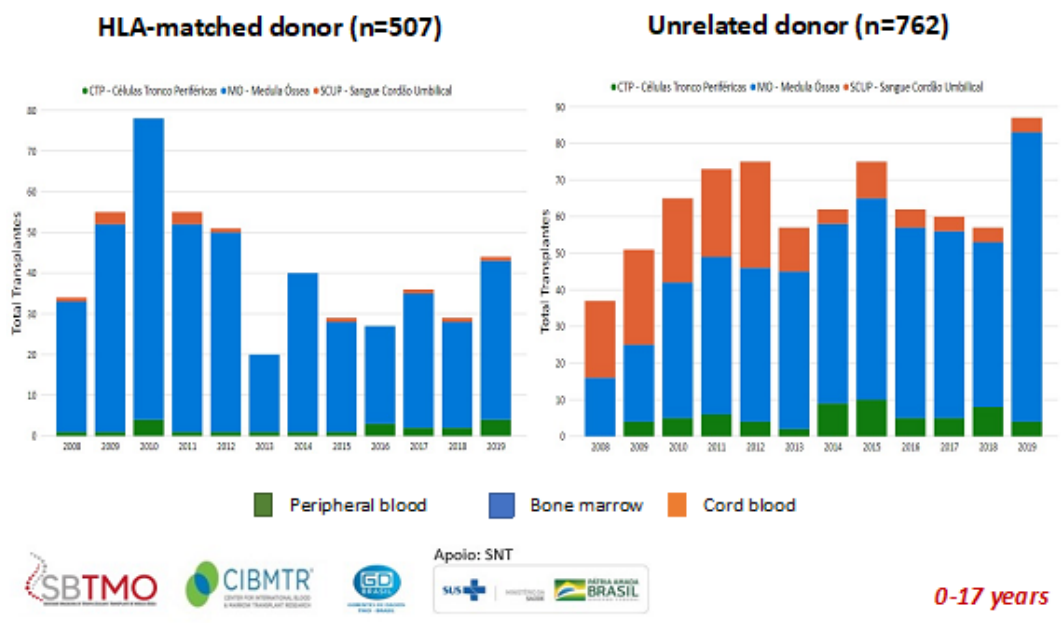
Within the past three years, the number of allogeneic transplants from unrelated and mismatched donors have increased and are now performed more often than transplants from matched sibling donors. Unrelated cord blood grafts are rarely used in the country (Figure 2).

FIGURE 2:



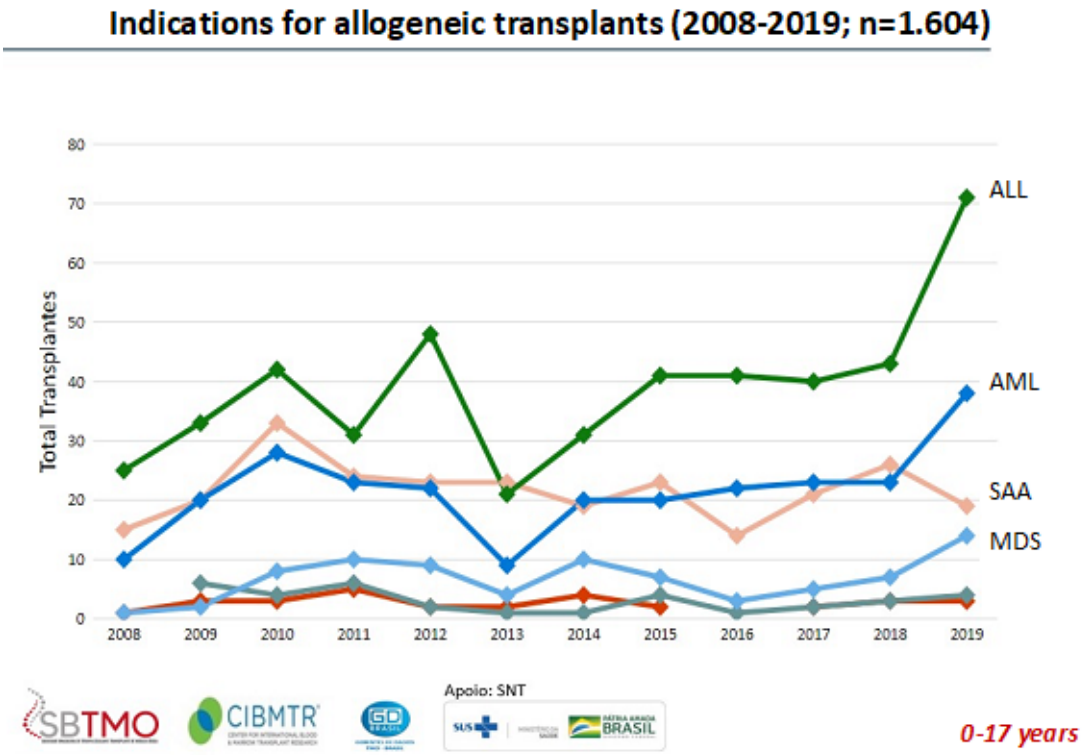
Marrow is the preferred graft source for all allogeneic transplants (Figure 3).

FIGURE 3:



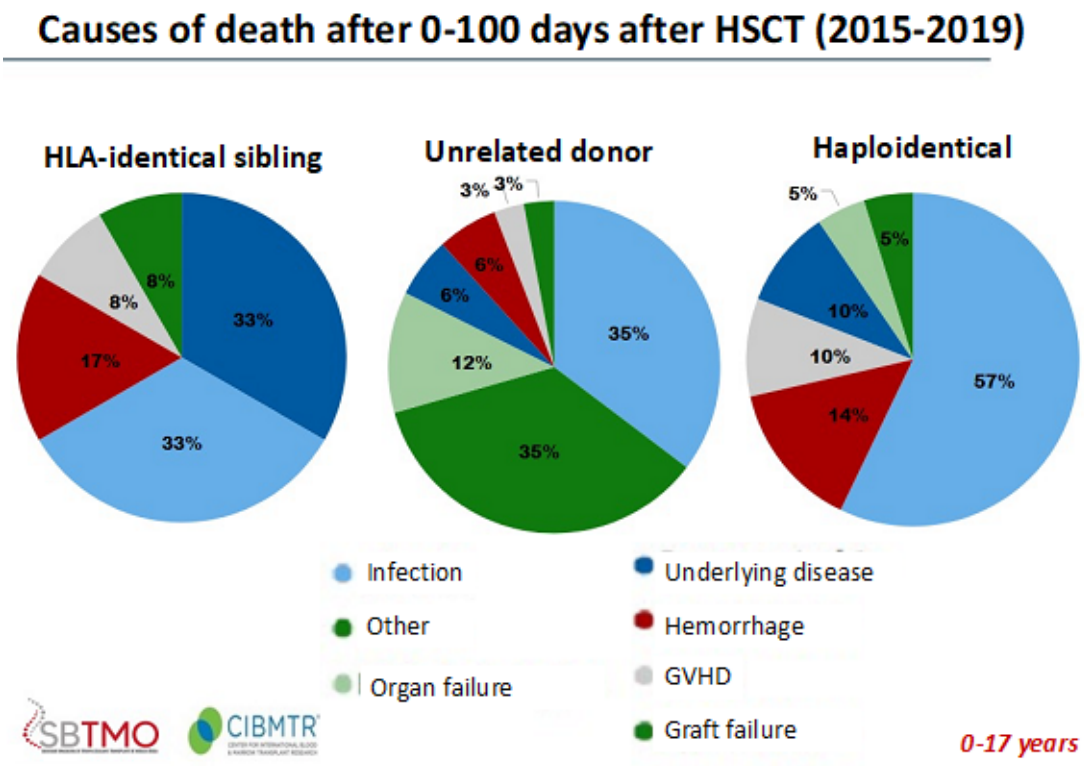
Acute leukemias and severe aplastic anemia are the most common indications for HSCT (Figure 4).

FIGURE 4:



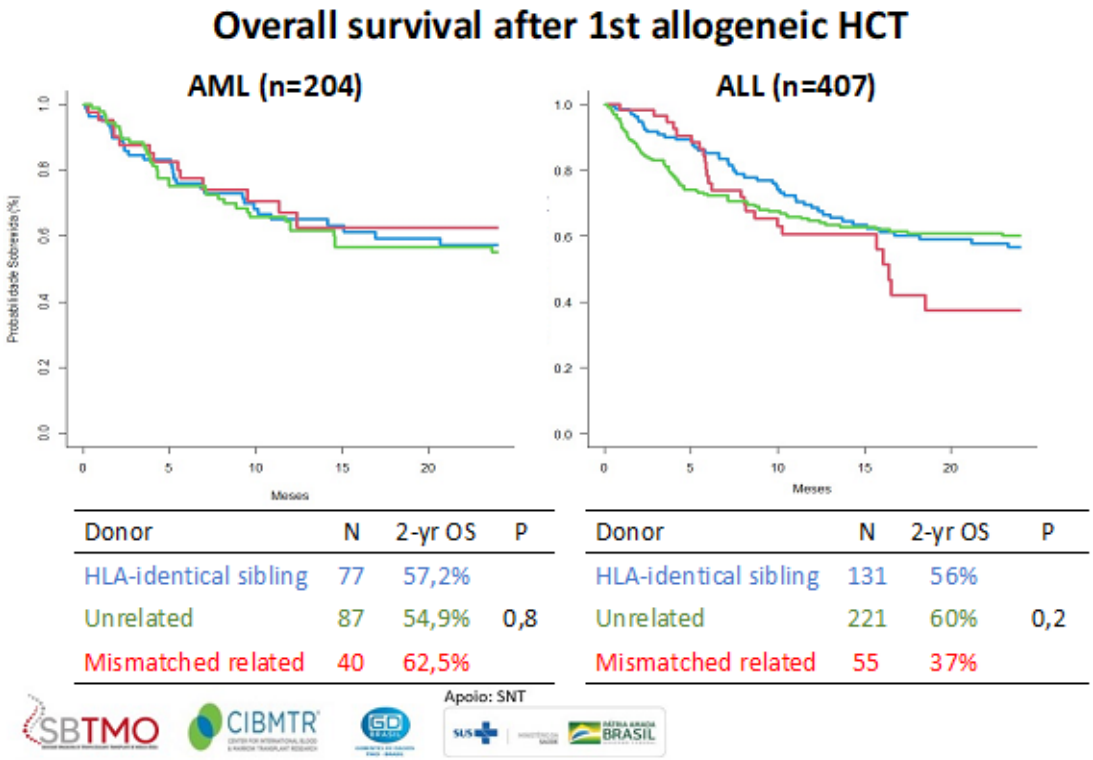
Infections cause 33% to 57% of the deaths within 100 days post HSCT (Figure 5).

FIGURE 5:



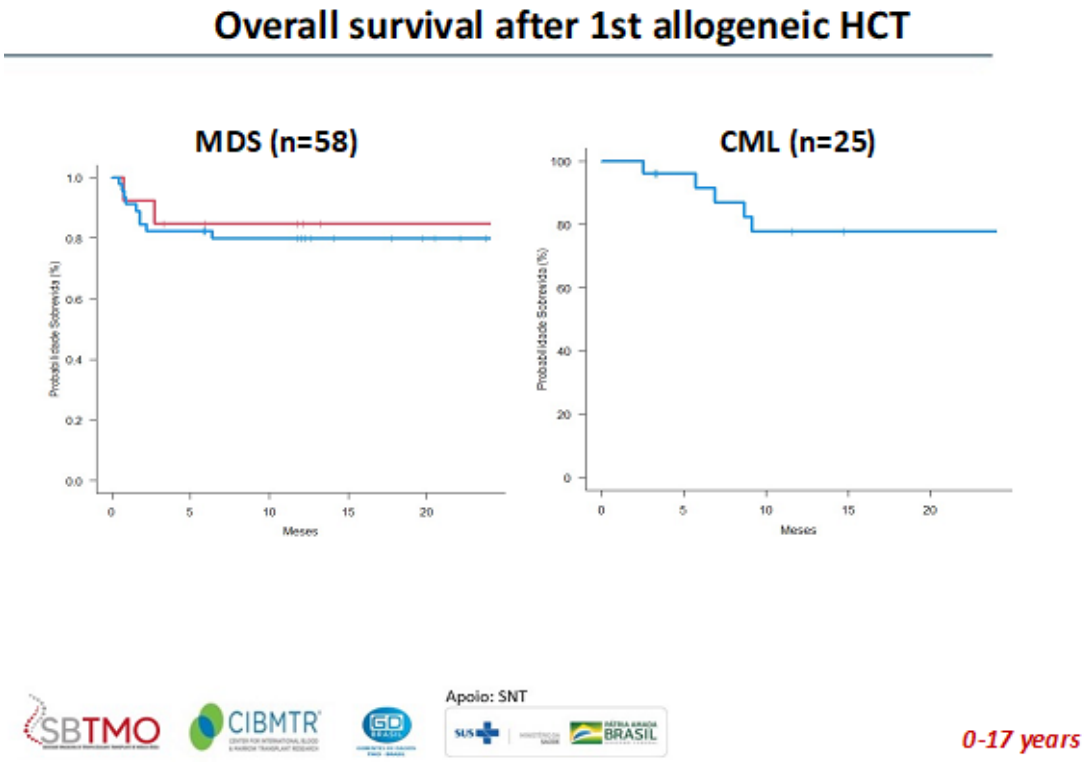
Overall survival after HSCT for acute leukemias is 37-62% without significant difference among different donor types (Figure 6).

FIGURE 6:



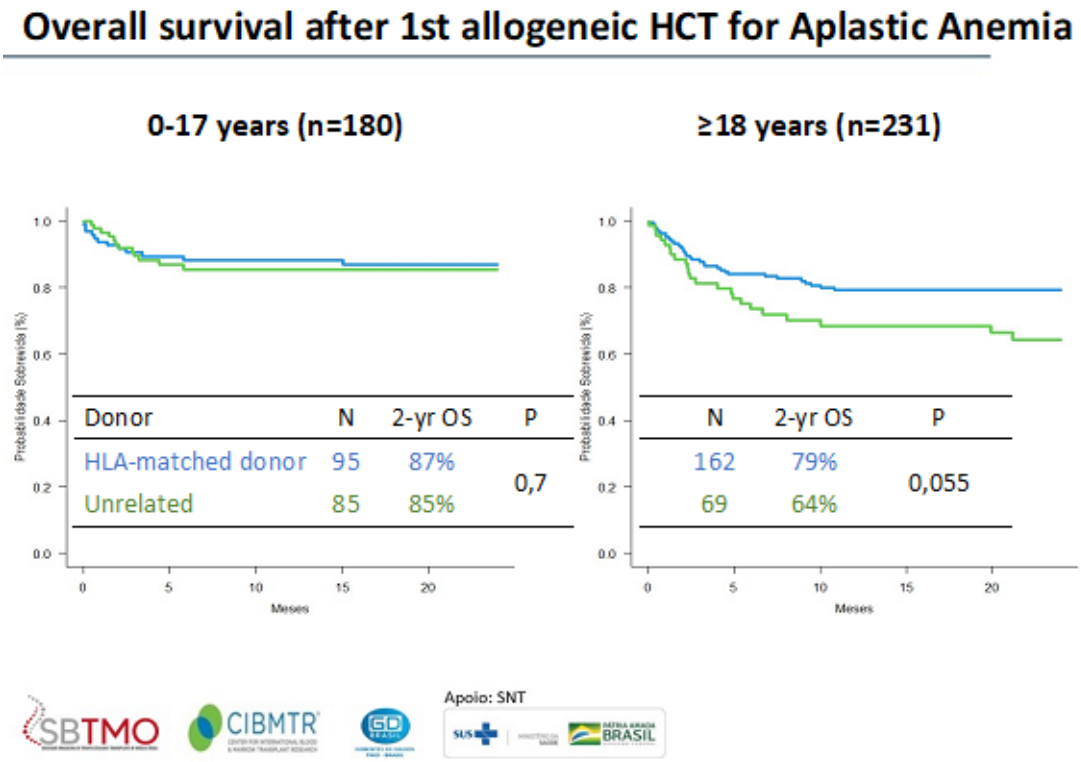
Pediatric myelodysplastic syndrome and chronic myelogenous leukemia have overall survival over 80% (Figure 7).

FIGURE 7:



Severe aplastic anemia is the most common non-malignant HSCT indication and the results with matched related and unrelated transplants are excellent, > 85% survival (Figure 8).

FIGURE 8:



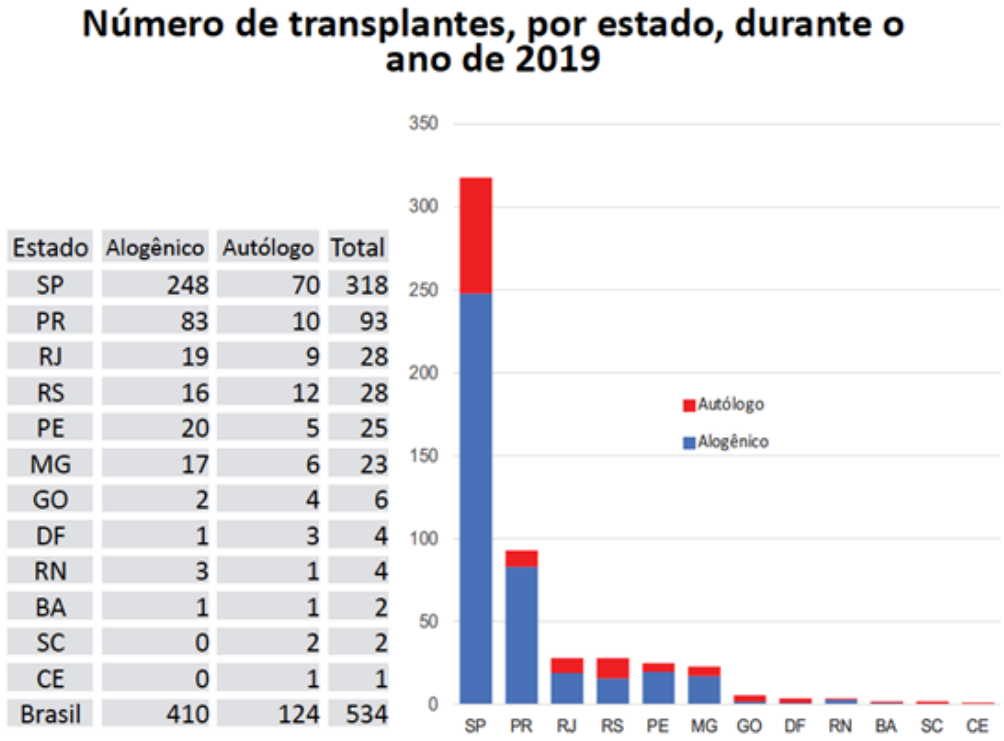
This is the first report on pediatric HSCT activity in Brazil and therefore, defines our national benchmark for future publications. The CIBMTR has reported on transplants performed for pediatric cancer,[1] that like ours, and acute leukemias are also the main transplant indication in the United States.

Since the SBTMO has partnered with the CIBMTR to organize the Brazilian HSCT Registry,[2] the first Summary Slide report, including all age groups, has already been published in our Journal.[3]

Two other available sources of Brazilian data on pediatric HSCT are the Brazilian Transplant Registry of the Brazilian Organ Transplant Association (RBT-ABTO)[4] and the Map of Transplants of the Bone Marrow Association (AMEO)[5,6]. In the latter, that also includes the transplants performed between August 2019 and 2020 reported to the CIBMTR, data can be filtered by most transplant characteristics, and children < 19 years were 32% of the patients undergoing HSCT in in Brazil.

The number of pediatric allogeneic HSCT vary according to data source, 190 reported to the CIBMTR, 410 to the ABTO (Figure 9), and 393 to AMEO (Figure 10).

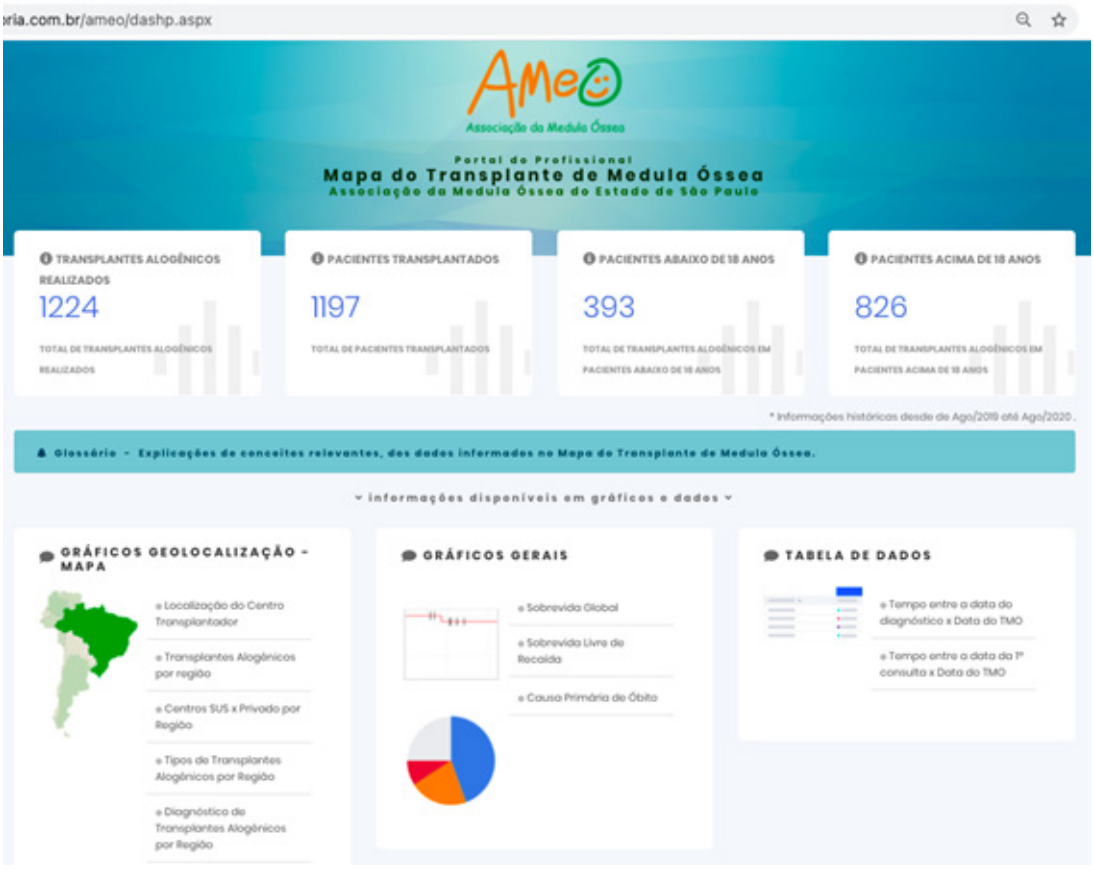
FIGURE 9: Number of Pediatric Bone Marrow Transplants (< 19 years of age), by State, performed in 2019 and reported to the Brazilian Organ Transplant Association



Estado	Alogênico	Autólogo	Total
SP	248	70	318
PR	83	10	93
RJ	19	9	28
RS	16	12	28
PE	20	5	25
MG	17	6	23
GO	2	4	6
DF	1	3	4
RN	3	1	4
BA	1	1	2
SC	0	2	2
CE	0	1	1
Brasil	410	124	534

https://site.abto.org.br/wp-content/uploads/2020/06/RBT-2019-completo.pdf

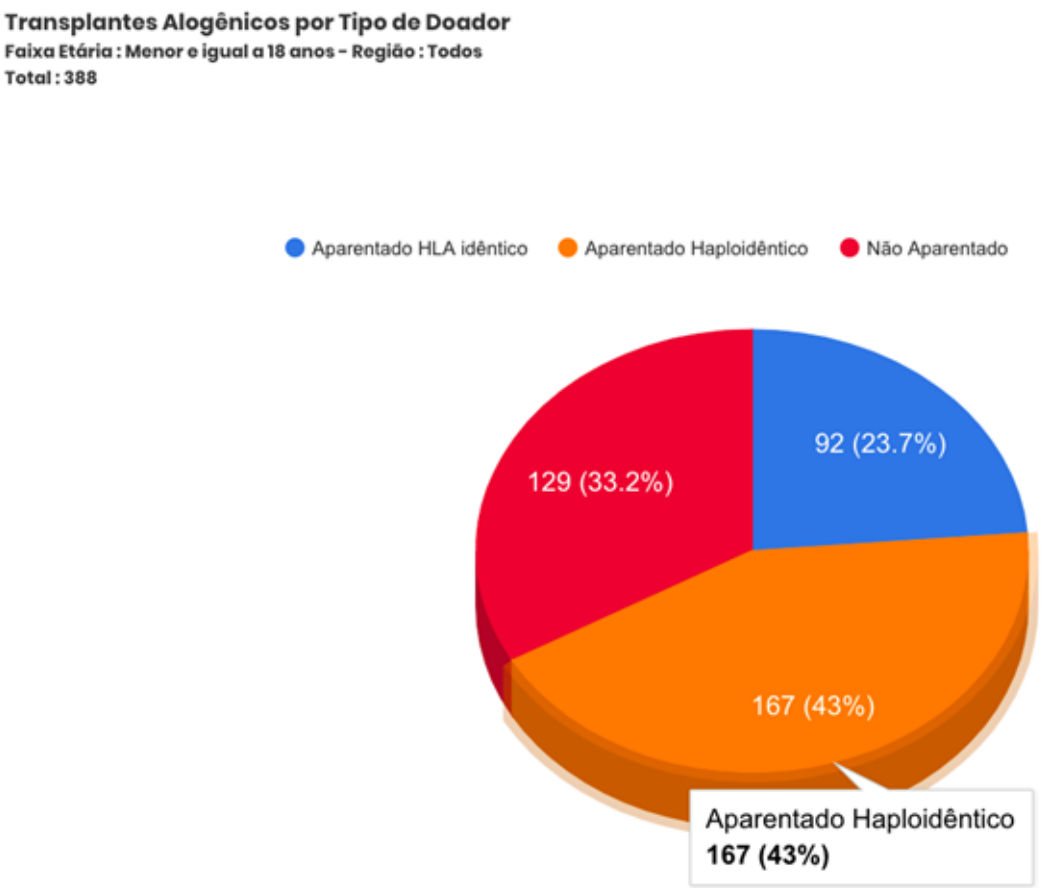
FIGURE 10: Pediatric allogeneic transplants (< 19 years of age), by State, reported to the Map of Transplant – Bone Marrow Association



https://rowconsultoria.com.br/ameo/dashp_ameo.aspx

In the Brazilian SBTMO-CIBMTR data, most pediatric transplants performed in 2019 were from unrelated donors (Figure 2), whereas in Map of Transplants, most (43%) pediatric HSCT were from haploidentical donors (Figure 11), although only centers performing unrelated transplants were included in this database. This may reflect a change in transplant practices during the Covid pandemic, since the timeframe included in the Map is August 2019 – August 2020, or different practices in centers reporting or not to the CIBMTR.

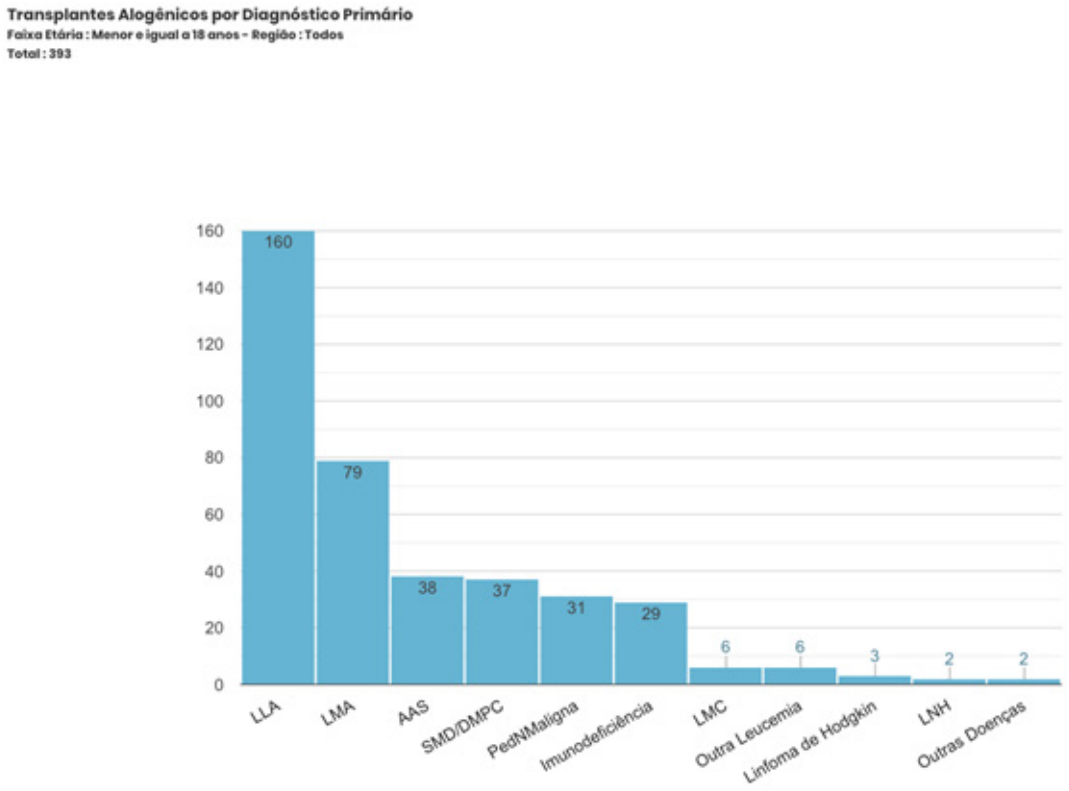
FIGURE 11: Pediatric allogeneic transplants (< 19 years of age), by State, reported to the Map of Transplant – Bone Marrow Association, by donor type



https://rowconsultoria.com.br/ameo/dashp_ameo.aspx

The transplant indications are similar in both data sources (Figures 4 and 12), with Acute Leukemias and Severe Aplastic Anemia being the most prevalent underlying diagnoses.

FIGURE 12: Pediatric allogeneic transplants (< 19 years of age), by State, reported to the Map of Transplant – Bone Marrow Association, by underlying disease



https://rowconsultoria.com.br/ameo/dashp_ameo.aspx

Infections are the most important causes of death reported in all data sources, followed by relapse of the underlying malignancy and graft rejection, indicating that much work is still to be done. But the first step was taken, and we must move forward together. Collaboration and continuous improvement are the most important objectives of our Society.

In conclusion, this is the first report on transplant outcomes in Brazilian children. The collaboration with the CIBMTR may be a feasible way for Latin American countries to know their transplant outcomes using a mature registry structure with several tools already in place to enhance the collaboration.

We would like to acknowledge Dr Nelson Hamerschlak, principal investigator of the National protocol, Dr. Marcelo Pasquini, for his help with the collaboration between CIBMTR and SBTMO, the Brazilian institutions reporting their data, the Data Manager Working Group and the Pediatric Working Group of the SBTMO and SOBOPE.

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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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BRAZILIAN CONSENSUS GUIDELINES FOR HEMATOPOIETC STEM CELL TRANSPLANTATION - INBORNS ERRORS OF METABOLISM

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For the past three decades, hematopoietic stem cell transplantation (HSCT) has been used as an effective therapy for selected inborn errors of metabolism (IEM), mainly lysosomal storage diseases and peroxisomal disorders. The main rationale for HSCT in IEM is based on correcting the decreases enzymes by the donor cells within and outside the intravascular compartment. Instead, the success of enzyme replacement therapy (ERT) in patients with a moderate/good clinical condition generated interest in employing ERT prior to or during HCT in patients with a poor clinical condition. The goal of HSCT is to achieve normal or near-normal quality of life by preventing further neurologic and development deterioration[1].

MUCOPOLYSACCHARIDOSIS

The mucopolysaccharidosis (MPS) diseases are a group of lysosomal storage disorders caused by deficiency of degradative enzymes of glycosaminoglycans (GAGs). These GAGs are usually excreted in urine and can be detected by initial diagnostic screening tests. Lysosomal enzymes are present at elevated levels in serum and body fluids of affected patients. Metabolic correction of lysosomal storage diseases is due to the mannose-6-phosphate receptor-mediated endocytosis of secreted enzymes, or by direct transfer of enzymes from adjacent cells. All the MPS disorders are autosomal recessive in their inheritance, except for Hunter syndrome (MPS- II X-linked)[2-5].

Mucopolysaccharidosis type I (MPS-IH, Hurler Syndrome) is caused by deficient enzyme activity of alpha-L-iduronidase (IDUA). The severe form of the disease is characterized by a progressive systemic dysfunction, affecting heart, liver, eyes, bones, joints, respiratory system, facial appearance, and often the central nervous system (CNS)[2-5].

In mucopolysaccharidosis type II (MPS-II, Hunter Syndrome) there is a deficiency of the enzyme iduronate-2-sulfatase (IDS). The severe neuropathic form of the disease presents before the age of 3 years with profound neurocognitive and developmental delay and shares clinical features with MPS-IH[2-5].

The mucopolysaccharidosis type VI (MPS-VI, Maroteaux-Lamy Syndrome) is caused by deficient enzyme activity arylsulfatase B (N-acetylgalactosamine 4-sulfatase). The patient with the rapidly progressive form often presents with short stature, several skeletal and joint abnormalities, compromised pulmonary and cardiovascular function, ocular alterations, including blindness in some cases, and early mortality[2-5].

HSCT is indicated for types I and II, whereas for type VI only for those who do not respond to enzyme replacement therapy. HSCT should preferably be performed in children under two years of age or in older children who have minimum cognitive deficit. The performance of HSCT in the pre-symptomatic phase offers the best results and the success of HSCT is associated with the level of enzyme production and the percentage of chimerism in the

donor. Despite successful HSCT, the benefits may be limited in skeletal deformities, in progression of corneal clouding and in the mitral and aortic valve deformities, in some, this may lead to progressive valvular dysfunction[6].

It can be performed with related non-carriers and unrelated donors (preferably hematopoietic cell source: bone marrow). In the literature, the use of umbilical cord blood has shown superiority in achieving complete chimerism and adequate enzyme production compared to other cell sources, but there is a higher rate of engraftment failure and these results have not been reproduced in Brazilian scenario. A recent study has shown that the use of a reduced toxicity regimen with the addition of thiotepa improves engraftment and is related to a low transplant mortality[7]. The use of heterozygous donors is NOT recommended. The use of haploidentical donors should also be avoided, except for X-linked forms or proved non-carrier relatives, parents are obligated heterozygotes. Myeloablative conditioning regimens are recommended, based on Busulfan (with pharmacokinetics), fludarabine, and thymoglobulini[8-12].

Intense international collaboration during the last decade has identified predictors of clinical outcomes, including myeloablative conditioning, early timing of transplantation, and probably enzyme activity level in blood after HSCT. This has resulted in optimized transplantation protocols and 5-year survival rates > 90%[6, 10,11]. The Brazilian government has approved HSCT with related and unrelated donors for patients with MPS I and II.

X-LINKED ADRENOLEUKODYSTROPHY

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder characterized by cerebral demyelination, adrenal insufficiency and progressive neurologic deterioration. The ALD gene encodes the ABCD1 protein which is involved in transport of fatty acyl coenzyme A substrates or their cofactors into peroxisomes. Its metabolic hallmark is the accumulation of very long chain fatty acids (VLCFA) in tissues and plasma, due to impaired transport and beta-oxidation of these fatty acids in peroxisomes. However, it has no effect in patients with established neurologic deficits, as brain levels of VLCFA are unchanged by the treatment[13].

Patients with X-Linked ADL may present with 6 forms of the disease. The cerebral form affects approximately 40-60% of patients and is characterized by cognitive deficits followed by progressive demyelination of the CNS and evolution to disability, dementia, neurovegetative state and death within a few months to several years from diagnosis. A complete evaluation of a boy with cerebral X-ALD includes a thorough neurologic examination, comprehensive neuropsychological assessment with IQ and an MRI of the brain with and without contrast (gadolinium) with MRI severity score determination, referred to as the Loes score. The predominant pattern of demyelination seen by brain MRI is posterior in 80-85% of cases. Although neurologic deterioration occurs in all boys with the cerebral form, 40% of female heterozygous carriers exhibit mild-to-moderate non-cerebral signs of the disease[13].

HSCT is indicated in the progressive cerebral form, at an early stage, aiming to prevent the progression of cerebral demyelination. The patient should undergo clinical assessment of neurological status (IQ >80) and MRI (Loes score >1 and <9) before the procedure. The neurologic benefits of HSCT in X-linked adrenoleukodystrophy are mediated by the replacement of brain microglial cells derived from donor bone marrow myeloid cells. HSCT can prevent the progression of neurological disease, but there is no improvement in other disease manifestations such as adrenal insufficiency and so far, there is no evidence that it prevents the development of adrenomyeloneuropathy[14-16].

HSCT can be performed with related non-carriers and unrelated donors (preferably hematopoietic cell source: bone marrow). The use of heterozygous carrier's donors is NOT recommended. There are case series using haploidentical (non-carrier) donors, but the experience is very limited and should be done in reference centers. Conditioning regimens are myeloablative and based on busulfan (recommended with pharmacokinetics), fludarabine, and thymoglobulin[14-16].

The Brazilian government has approved HSCT from related and unrelated donors for patients with X-linked ADL who have signs of cerebral disease (Loes score 1-9) and good performance.

GLOBOID CELL LEUKODYSTROPHY - KRABBE DISEASE

Krabbe Disease is a rare autosomal recessive lysosomal neurodegenerative disorder caused by deficiency of galactocerebrosidase (GALC). It is characterized by white matter degeneration in the CNS and peripheral nervous system, with large macrophages (globoid cells). There is progressive neurological deterioration, with loss of motor function, spasticity, cognitive deficit, auditory and visual deficit, seizures

are common, and the disease leads to early death[17,18]. There are 3 different presentations:

1. Classic or infantile form, with manifestations before 6 months and death before 2 years
2. Juvenile form, starting in childhood and dying in early adolescence.
3. Adult form, starting from late childhood to 5th. decade of life.

HSCT is indicated for patients with the infantile form if performed before the development of neurological symptoms, preferable in the first two months of life. In these cases, the diagnosis is usually made by family history or neonatal screening. It is also indicated for patients with juvenile and adult forms, with no or early neurologic symptoms. HSCT improves clinical outcomes in KD patients only if delivered pre-symptomatically or in oligosymptomatic. It can be performed with related non-carriers and unrelated donors (preferably hematopoietic cell source: bone marrow). The use of heterozygous carrier's donors is NOT recommended. Conditioning regimens are myeloablative and based on busulfan (with pharmacokinetics), fludarabine, and thymoglobulin[17,18].

METACHROMATIC LEUKODYSTROPHY

Metachromatic leukodystrophy is caused by arylsulfatase A (RSA) deficiency and is characterized by central and peripheral demyelination. Diagnosis is made by measuring the enzyme and urinary sulfatides[15,16]. The disease is classified according to the clinical presentation and age of symptom onset:

1. Late Infantile Form: The clinical presentation occurs before 30 months of life with rapid evolution and progressive motor dysfunction, walking difficulty, dysarthria, dysphagia, decerebration. Death occurs 2 to 4 years after the onset of manifestations.
2. Juvenile Form: Manifests between 2.5 and 16 years of age with postural abnormalities, behavioral changes, optic atrophy, spastic quadriparesis, language regression.
3. Adult form: It manifests after 16 years of age with psychiatric or intellectual symptoms, incontinence, spastic tetra paresis, cognitive regression. Progression tends to be slower than in other forms of the disease.

HSCT is not indicated in the late infantile form as it does not prevent the progression of the disease. In juvenile or adult forms, HSCT should be indicated in asymptomatic or mildly symptomatic patients. It can be performed with related non-carriers and unrelated donors (preferably hematopoietic cell source: bone marrow). The use of heterozygous carrier's donors is NOT recommended. Conditioning regimens are myeloablative and based on busulfan (with pharmacokinetics), fludarabine, and thymoglobulin[15,16].

GAUCHER DISEASE

Gaucher disease is the most common lysosomal storage disorder. It is autosomal recessive and characterized by deficient activity of the lysosomal enzyme glucocerebrosidase and as a result, the accumulation of glucocerebroside in the lysosomes. The pathophysiologic feature of Gaucher disease is the presence of Gaucher cells derived from the monocyte-macrophage system. Most Gaucher cells are found in the spleen, liver, bone marrow, and lymph nodes, causing enlargement and dysfunction of these organs and resulting in clinical manifestations. Bleeding due to thrombocytopenia, anemia, and hepatosplenomegaly are the common early features. Bone involvement is common, but it is not always associated with symptoms, when present, range from mild to severe bone pain crises.

The diagnosis can be made by measuring the glucocerebrosidase activity of peripheral blood leukocytes or by cultured skin.

There are three types of Gaucher disease:

Type 1: It is the most common form accounting for 90–95% of the cases, characterized by onset in adulthood and by the absence of primary CNS involvement.

Type 2: It is characterized by severe neurologic involvement, that include oculomotor apraxia, opisthotonos and bulbar signs, and an onset during infancy.

Type 3: It presents by the onset of neurologic disturbances later in the first decade of life.

Enzyme replacement therapy is the treatment of choice for type 1 Gaucher disease. However, since the pathophysiology of Gaucher disease is due to the accumulation of lipid-laden macrophages, HSCT is also considered a possible treatment choice, especially for those with matched unaffected related donors. The benefit of transplantation varies between organ systems. Hematologic and physical improvement is rapid and sustained. Reticuloendothelial organs, such as the liver and spleen, regress within a few months, and there is some evidence that the skeletal changes seen in Gaucher disease regress.

OSTEOPETROSIS

Osteopetrosis is a genetic disease characterized by skeletal sclerosis, resulting from the reduction or loss of osteoclasts function, consequently there is impairment of bone reabsorption. The severe form is an inherited autosomal recessive disease and is characterized by fractures, neurological symptoms and early spinal cord failure. These children rarely survive more than 2 years of life[19,20].

HSCT is indicated in the severe form (infantile malignancy), except in patients with neurodegeneration (OSTM1 mutation) and with mutations in RANKL. There is also a rare form of OP with CLCN7 mutation that presents with neurodegeneration, these cases may not be candidates for HSCT. HSCT can be performed with related or unrelated donors (preferably hematopoietic cell source: bone marrow) and, more recently, studies have shown satisfactory survival rates with haploidentical donors[21]. The use of unrelated umbilical cord is associated with a higher incidence of graft failure. Conditioning regimens should be myeloablative and based on busulfan (with pharmacokinetics), fludarabine, thymoglobulin and thiotepa. HSCT in osteopetrosis has high rates of engraftment failure (even with related sibling donors) and of a second transplant, in addition to a very high risk of sinusoidal obstruction syndrome[19,20,22].

GENERAL RECOMMENDATIONS FOR HSCT IN METABOLIC DISEASES

1. Do not use a carried donor.
2. Umbilical cord blood or bone marrow are the preferred stem cell source.
3. Most regimens are myeloablative and busulfan pharmacokinetics are strongly recommended.

MYELOABLATIVE CONDITIONING REGIMENS FOR METABOLIC DISEASES[23]:

Busulfan (weight based) mg/kg or recommended myeloablative AUC of 85-95 ng/ L x h.

TABLE 1 - Initial busulfan dose is based on weight:

Body weight	mg/kg/day
3 to 15kg	5,1
15 to 25kg	4,9
25 to 50kg	4,1
50 to 75kg	3,3
75 to 100kg	2,7

2. Fludarabine 160mg/m2
3. Rabbit ATG 7,5-10mg/kg

GVHD prophylaxis: with cyclosporine and mycophenolate mofetil or prednisone (1mg/Kg/day) for cord blood transplantations and cyclosporine and short course of methotrexate (Day +1, +3, +6, ± 11) for patients receiving bone marrow.

FINAL CONSIDERATIONS

HSCT corrects the enzymatic defect but does not modify the course of the disease in some organs. Due to the particularities of these diseases, it is recommended that these patients be transplanted in specialized centers. Even after the transplant, most patients will still need care from the multidisciplinary team (neurologists, cardiologists, orthopedists, ophthalmologists, endocrinologists, psychologists).

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MYELODYSPLASTIC SYNDROMES (MDS)

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MDS in children is a rare group of hematopoietic stem cell clonal disorder, with an annual incidence of 1 to 4 cases per million. Some peculiarities of MDS in childhood are associated with previous exposure to cytotoxic agents, hereditary bone marrow failure syndromes, or genetic predisposition syndromes.[1]

HLA typing and the search for a compatible donor must be carried out upon diagnosis, for all patients. When the potential donor belongs to the family, it is important that the same genetic changes present in the patient are ruled out, in addition to the complete hematological evaluation with complete blood count, myelogram, bone marrow biopsy and karyotype, to rule out incipient MDS.[2]

REFRACTORY CYTOPENIA OF CHILDHOOD

It is the most common subtype of MDS in the pediatric population. In contrast to adults, who usually have isolated anemia, hematological manifestations in children often include thrombocytopenia and/or neutropenia.[3]

Patients without an unfavorable karyotype can keep the disease stable for a long time. Thus, in the absence of transfusion dependence or severe neutropenia, a careful observation strategy without treatment is recommended.[1,4,5]

Allogeneic HSCT, with the best available donor, is indicated in the following situations:

a) Presence of monosomy of chromosome 7 or deletion of the long arm of chromosome 7, due to the high risk of progression to more advanced forms of the disease and acute myeloid leukemia (AML);1,4,6

b) Complex karyotype (3 or more chromosomal aberrations, at least one structural), despite the unfavorable prognosis even with HSCT;[1,4,7]

c) Sustained neutropenia (< 1000/mm3) or need for transfusion.[1,3]

Patients with hypocellular bone marrow and without an unfavorable karyotype can benefit from a reduced intensity conditioning regimen. For the others, a myeloablative regimen is indicated.[8,9]

In the absence of a suitable donor, immunosuppressive treatment with ATG and cyclosporine may be an option for patients with hypocellular bone marrow, without a bad prognosis karyotype. However, these patients remain at risk of relapse and clonal evolution and need careful surveillance.[10,11]

REFRACTORY ANEMIA WITH RING SIDEROBLASTS

In children with refractory anemia with ring sideroblasts and the presence of cell vacuolization, it is essential to investigate mitochondriopathies. If this diagnosis is confirmed, there is no indication for performing HSCT, as hematological changes regress spontaneously over time and transplantation does not change the sad natural history of the disease.[2]

ADVANCED MDS

The treatment of children diagnosed with MDS with excess blasts, with or without signs of transformation and with evolutionary AML of MDS remains a major challenge. Allogeneic HSCT is the only curative treatment, although the data published in the literature generally include a small number of patients, heterogeneously transplanted.[1,4]

In the largest cohort of children with advanced MDS reported to date, the European group (EWOG-MDS) demonstrated an overall 5-year survival of 63% in 97 patients undergoing allogeneic HSCT with the same myeloablative conditioning regimen (busulfan, cy-

clophosphamide and melphalan). Age over 12 years at HSCT, interval between diagnosis and HSCT over 4 months and occurrence of acute or chronic GvHD were associated with increased transplant-related mortality (TRM). Patients with evolutionary AML of MDS had high rates of relapse.[7]

A more recent update of the EWOG-MDS data, with the same conditioning regimen mentioned above, showed a decrease in TRM, particularly in the adolescent subgroup. The update also showed that event-free survival for patients who received a transplant from an identical HLA sibling or from an unrelated HLA donor in high resolution 9/10 or 10/10 was similar.[1,4] The presence of a complex karyotype is strongly associated with a poor prognosis.[12]

Pre-HSCT treatment remains a controversial issue. If, on the one hand, it would be desirable to reduce the percentage of blasts, on the other hand, the use of chemotherapy has been associated with significant toxicity. In addition, there is little data on the best scheme to be used. The European group suggests that intensive chemotherapy should not be used routinely, however, 1 cytoreductive chemotherapy cycle can be considered for children with[3] 20% of bone marrow blasts, in an attempt to reduce relapse after HSCT.[1] There is little data on the efficacy of hypomethylating agents in pediatric MDS, but 2 retrospective studies with a small number of patients have pointed to a possible role of azacitidine as a pre-HSCT bridge.[13-14]

MDS SECONDARY TO THERAPY

Specific reports of children with MDS and AML secondary to therapy generally include a limited number of patients. Allogeneic HSCT is indicated, but the evolution is generally unfavorable, with overall survival between 13 and 35%, despite HSCT. [1,4,15,16] A short time between diagnosis and HSCT was identified as an important factor for better survival of these patients.[17]

HSCT indication	Allogeneic HSCT	Autologous HSCT	Notes
Refractory cytopenia of childhood	C	N	For patients without unfavorable karyotype, without transfusion dependence or severe neutropenia, a careful observation strategy without treatment is recommended.
Advanced MDS	S	N	
MDS secondary to therapy	S	N	

S: Standard of care

C: Standard of care, clinical evidence available

R: Standard of care, rare indication

D: Developmental

N: Not generally recommended

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JUVENILE MYELOMONOCYTIC LEUKEMIA AND OTHER MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

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JUVENILE MYELOMONOCYTIC LEUKEMIA (JMML)

It is a clonal hematopoietic disorder that usually occurs in early childhood, characterized by hyperactivation of the RAS signaling pathway. About 90% of patients have mutations in 1 of 5 genes (PTPN11, NRAS, KRAS, NF1, CBL) that define genetically and clinically distinct subtypes of the disease, with a highly variable clinical course.[1,2]

Patients with somatic PTPN11 mutations generally have a rapidly fatal outcome if they are not submitted to allogeneic hematopoietic stem cell transplantation (HSCT). The relapse rate after HSCT is significantly higher in these patients, when compared to other genetic subtypes. Likewise, JMML is also fatal in the absence of HSCT in patients with neurofibromatosis type 1 (NF1). Patients with somatic mutation in KRAS generally present clinically very aggressive disease, promptly requiring HSCT, but the relapse rate after HSCT is relatively low. JMML associated with somatic NRAS mutation shows great clinical diversity, some patients have a disease that slowly regresses in the absence of HSCT, while others have an aggressive disease, with a high rate of relapse after HSCT (usually older children, with high levels HbF). Most children with CBL germline mutation have self-limiting disease and observation without therapy is generally recommended. In children with JMML phenotype without an identified mutation of the RAS pathway, HSCT is indicated, but it is necessary to exclude other rare myeloproliferative diseases, acute leukemia and non-malignant diseases. [1-3]

Patients with Noonan Syndrome (PTPN11 germline mutation or another gene in the RAS pathway) may have a transient myeloproliferative disorder, usually in the first months of life, with clinical characteristics indistinguishable from LMMJ. In these cases, HSCT is not indicated.[3,4]

The results of HSCT in patients with JMML have progressively improved over time. In the study including the largest number of JMML patients undergoing related and unrelated allogeneic HSCT, the probability of disease-free survival was 52%. Relapse was the main cause of treatment failure, with an incidence of 35%.[1,5] The use of umbilical cord blood proved to be a viable option.6 Although still experimental in the treatment of JMML, haploidentical HSCT can be considered for patients without a compatible donor.[1,7]

The classic conditioning regimen consists of busulfan, cyclophosphamide and melphalan.[5,8] The Japanese group uses busulfan, fludarabine and melphalan, with similar results.[9]

In order to optimize the effect of the graft against leukemia, a less intensive GvHD prophylaxis is recommended for patients with a higher risk of relapse (patients with NF1, somatic mutation of PTPN11 and NRAS, minimum 4 years of age or > 20% blasts in the bone marrow).[1]

Pre-transplant therapy is still a matter of controversy. Conventional chemotherapy is generally not associated with durable responses, but the use of low-dose 6-mercaptopurine and/or cytarabine can be effective in reducing leukocytosis and spleen size.1,10 Azacitidine as a bridge until transplantation has been shown to be a promising option.[11,12] The European group (EWOG-MDS) is currently conducting a multicenter phase II study that aims to prospectively assess the rate of complete or partial clinical remission after three cycles of pre-HSCT azacitidine in newly diagnosed JMML patients.[13]

A second HSCT can rescue more than a third of children who experience relapse after the first transplantation, while donor lymphocyte infusion (DLI) appears to be ineffective.[1]

Chronic Myelomonocytic Leukemia (CMML) and Atypical Chronic Myeloid Leukemia (negative Bcr-Abl aCML)

CMML is extremely rare in children. In the pediatric classification proposed by Hasle, in 2003, the term CMML was included only for cases secondary to previous chemotherapy. [14-16]

Atypical CML is even more rare in children than in adults. Of the few cases reported in childhood, some have failed to meet the diagnostic criteria. Due to its rarity and heterogeneity, there is no consensus on treatment, however, due to the unfavorable prognosis, HSCT is recommended.[14,17-19]

HSCT indication	Allogeneic HSCT	Autologous HSCT	Notes
JMML (patients with NF1, somatic PTPN11 mutation, KRAS, most patients with somatic NRAS mutation and patients with no identified mutation)	S	N	In some patients with germline mutation of NRAS, mainly with normal fetal hemoglobin and without significant thrombocytopenia, long-term survival without HSCT has been observed.
JMML (patients with CBL germline mutation)	N	N	Most patients have spontaneous resolution. Allogeneic HSCT should be assessed if chromosomal changes or disease progression occur.

S: Standard of care

C: Standard of care, clinical evidence available

R: Standard of care, rare indication

D: Developmental

N: Not generally recommended

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MYELOPROLIFERATIVE NEOPLASMS

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In addition to the chronic myeloid leukemia (CML) BCR-ABL1+, which will be discussed separately, classic myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). These have a very low incidence in the pediatric age group, with about 0.82 cases for every 100 thousand patients, about 100 times less than in adults.[1,2]

Pediatric patients generally have a lower incidence of mutations commonly found in adults, thrombotic events and transformation to myelofibrosis and acute leukemia. There is no consensus on treatment in children, with little data in the literature.1-2 Most children with PV and ET are treated with supportive care and sometimes cytoreductive therapies.[3,4] Although extremely rare, PMF has a very heterogeneous phenotype in children, with variable evolution, from occasional spontaneous resolution to a rapidly progressive disease, sometimes fatal, curable only by HSCT.[5-7]

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ANTINEOPLASTIC AGENTS USED IN PEDIATRIC HEMATOPOIETIC BONE MARROW TRANSPLANTATION: A REVIEW ABOUT PHARMACOLOGY AND PHARMACEUTICAL ISSUES

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ABSTRACT

This article proposes the characterization of the main chemotherapeutic agents used in hematopoietic stem cell transplantation in pediatric patients, carrying out a review of the main pharmacological and pharmacokinetic characteristics that are peculiar to children, as well as technical aspects for the handling, prescription, and administration of each one of these.

It is extremely important that all professionals know how to recognize the characteristics of each drug and how its peculiarities impact the quality of patient's treatment, being able to predict and propose necessary interventions for potential problems of therapy, which can be identified and measured.

Keywords: Chemotherapy. Chemotherapeutic agents. Bone Marrow Transplantation. Pediatrics.

1. INTRODUCTION

The indication for hematopoietic stem cell transplantation (HSCT) in pediatrics presents peculiarities, since there are a greater number of indications in non-malignant diseases and a greater chance of cure in hematological neoplasms, thus making it possible to carry out many combinations of chemotherapeutic agents for the elaboration of protocols. Moreover, the pharmacokinetics of chemotherapeutic agents may differ from the way they occur in adults.

In this scenario, studies reported and going on in the Pediatric Pharmacology using these drugs should be highlighted, since important differences are observed in comparison to adults in their pharmacodynamics and pharmacokinetics.[1] Important aspects of the pharmacology of these agents in children are related in pharmacokinetics aspects, which have a greater impact on distribution and metabolism phases than on absorption and excretion phases.

The absorption phase of the drug can suffer significative changes if administered per oral once the drug passes through the mouth, stomach or intestinal absorption, which can be affected by gastrointestinal motility, gastric pH and conveyors.[2] For instance, in oral absorption, we evaluate changes in development phase, mainly related to: acid secretion, gastrointestinal motility and biliary secretion. Usually, these changes are smaller at birth and after 6 or 8 months of life, thus, it may interfere in the reduction or delay of absorption.[2] In distribution phase, which the most of chemotherapeutic agents are already available, factors such as aqueous or lipid components, plasma proteins and carriers are essential for evaluation during developmental changes phase.[2]

The amount of extracellular fluid is greater at birth and with the arrival of youth, this factor is reduced, causing a greater distribution volume in children (smaller concentration peaks); the protein binding rate is also lower at birth but increases significantly up to 1-2 years of age; the permeability of the blood-brain barrier is much higher at birth, so that after 3 years of age, this barrier permeability is already similar to adults.[2]

After distribution there is a metabolism phase, usually in the liver, going through two enzyme phases. Phase I enzymes such as CYP450 (CYP3A4, 2D6, 2C8/9...) are in smaller quantities at birth and they increase to adult levels during childhood and youth, while phase II enzymes, such as glucuronides, glutathione, sulfates, and acetates reach levels compared to adults after 6 months of life.[2,3]

In the excretion phase, in which the kidney is the main drug excreting organ, the maturation of this organ begins in the embryo and is completed in childhood. Glomerular filtration rates reach adult values between 6 months to 1 year old. In general, it was observed expressive changes in children and youth with pre-existing comorbidity which can increase the risks of toxicity.[4]

Chemotherapy drugs often have a narrow therapeutic window and combined with a large variability between drug plasma concentrations observed in pediatric oncology patients, this can result in suboptimal therapy or increased toxicity.[5]

In clinical practice, physiologic characteristics, pharmacokinetics profile, and rational drug prescription are decisive for the success of the transplant.

To help physicians, pharmacists and nurses to perform the best therapy for the patient, it is described below the main chemotherapeutic agents used in mobilization and conditioning protocols. This discussion includes granulocyte colony-stimulating factor Filgrastim (G-CSF), with description of clinical, pharmacodynamic and pharmacokinetic aspects, emetogenic potential and recommended dose adjustments for renal or hepatic toxicity. In order to demonstrate clearly and objectively, technical aspects such as compatibilities, concentration, irritant potentials, needed care in administration, as well as guidance and drug characteristics for handling are compiled in a table (see Table 1), organized based on their alphabetical names.

2. ALKYLATING AGENTS

2.1 Busulfan

It is a bifunctional alkylating agent, that has a mechanism of action based on the release of methanesulfonate groups, producing carbon ions which can insert an alkyl group in the DNA strand. It is used in conditioning regimens in association with other drugs, such as melphalan, cyclophosphamide and fludarabine.[6,7]

The volume of distribution (Vd) ranges between 0.62 and 0.85 L/kg. It is mainly metabolized in the liver. About 30% of the administered dose is excreted in the urine over 48 hours with 1% of the drug in unchanged form.[6]

When administered orally, the bioavailability of busulfan is quite variable, so there is a preference for the intravenous route. Busulfan clearance is related to age (the higher the age, the lower the clearance) and weight (the higher the weight, the lower the clearance). For patients older than 18 years, clearance ranged from 2.64 to 2.9 mL/min/kg. For children aged from 2 to 14 years, it ranged from 4, 4 to 4.5 mL/min/kg and for children aged 3 years or less, clearance ranged from 6, 8 to 8.4 mL/min/kg.[6]

Busulfan has moderate to high emetogenic potential (>30-90% emesis frequency) at doses used in the conditioning regimen. They can cause epileptic seizures, which can occur up to 24 hours after the last dose of busulfan, due to their high lipid solubility and low level of protein binding. Thus, the prophylactic use of anticonvulsants is indicated for at least 12 hours before the first dose of busulfan, and for at least 24 hours after the last dose infusion. The most used drug for prophylaxis is phenytoin, but caution is needed in its administration because phenytoin increases busulfan clearance by ≥ 15%. If alternative anticonvulsants are used, busulfan clearance may be decreased and dosing should be monitored accordingly.[8]

For both intravenous and oral administration, it is recommended to monitor the serum level of busulfan to reach the desired levels (concentration between 200 to 600 ng/mL), thus avoiding possible toxicities. Busulfan doses can be adjusted according to serum level (according to protocol and disease).[6]

An adverse effect often associated with busulfan conditioning regimens is Sinusoidal Obstruction Syndrome (SOS). It usually occurs within the first 30

days of transplantation, with an incidence of 5 to 40% in pediatric patients.[9] For treatment, defibrotide is usually used in adults and children. The use of acetaminophen should be avoided due to the risk of SOS.[8,9]

There are no cases in literature about dose adjustment to renal or hepatic impairment.

2.2 Carmustine

Alkylating agent from nitrosourea family, their cytotoxic action is mediated by the inhibition of enzymatic processes involved in DNA formation. This drug also causes a break in DNA strands and, consequently, processes in the synthesis of DNA, RNA, and proteins were changed. It has a Vd of 3.25 L/kg and liver metabolism (not specified). Their excretion is mostly renal (60% to 70%), but it can also be excreted through the respiratory (6 to 10%) and fecal (1%) routes. Their elimination half-life is of 22 minutes (1.4 minutes in the primary phase and 17.8 minutes in the secondary phase), and the emetogenic potential ranges from high (when > 250mg/m2) to moderate (when < 250mg/m2). It is used in autologous HSCT in the conditioning phase in myeloablative schemes, such as BEAM and BEAC.[8]

2.3 Cyclophosphamide

Cyclophosphamide is an alkylating agent of the oxazaphosphorine class. With activation in the liver based on two cytotoxic metabolites: phosphoramide mustard and acrolein, knowing as a pro-drug. Their antineoplastic activity is linked only to phosphoramide, which binds to the DNA of the tumor cell, which in turn, does not interrupt the production of RNA and proteins. Therefore, an imbalance occurs, leading the tumor cell to death. Despite they have not an antineoplastic effect, acrolein is responsible for the urotoxic side effects of cyclophosphamide, treated prophylactically with mesna (65 to 100% of the cyclophosphamide dose) for uroprotection.[10,11,12]

Constant hydration is also essential, to help the stimulate bladder emptying at regular intervals, and their administration should be avoided at night to prevent urinary retention and increase the amount of toxic active metabolites that would remain in the bladder for longer. It is also important to monitor urinary sediments that may be signs of urotoxicity or nephrotoxicity.[13]

It has moderate emetogenic potential for doses less than or equal to 1500 mg/m2 and high emetogenic potential for doses greater than 1500 mg/m2, so the use of antiemetics is recommended. Stomatitis and mucositis can also be manifested with the use of protocols containing cyclophosphamide.8 Their plasma concentration varies according to the dose administered. The peak concentrations are 4, 50 and 500 nmol/mL after administration of 1 to 2 mg/kg (Peters et al, 1989), 6 to 15 mg/kg (Klein et al, 1980) and 60 mg/kg (Jardine et al, 1978), respectively.[10,11,12]

A delay in cyclophosphamide metabolization may occur in patients with liver failure. Importantly, it is a drug that crosses the placental barrier and is detectable in breast milk and cerebrospinal fluid. It is mainly excreted by the kidneys and it is indicated to change the dose in cases of renal failure. It has a half-life of approximately 7 hours in adults and 4 hours in children, with peak levels of alkylation occurring within about 2 to 3 hours of drug administration. For cases where creatinine clearance is less than 10 mL/minute, administer 100% of the dose, and if it is greater than or equal to 10 mL/minute, adjust to 75% of the initial dose.[8]

2.4 Melphalan

Alkylating agent that inhibits DNA and RNA synthesis via interstrand croos-liking with DNA, biding at the N7 position of guanine.[8]

It is a mechlorethamine derivative that stops the DNA replication process, leading to cell death. High dosage melphalan treatment is associated with side effects such as oral mucositis. To reduce the incidence of these side effects, it is recommended pre and post melphalan cryotherapy for patients who will receive high doses of the drug, which can also be performed with ice cubes. In addition, a high volume of hydration is recommended to avoid precipitation of melphalan in the renal tubules.[13]

Regarding pharmacokinetics, their Vd is 0.5 L/kg, and it binds to plasma proteins, mainly to albumin (55-60%). It has limited penetration of the blood-brain barrier and its excretion is fecal (20-50%) and renal (10%). Melphalan is not a dialyzable drug. Its elimination half-life is of 90 minutes, so the drug infusion should not pass this period. It has a high emetogenic potential (at doses > 140 mg/m2) and moderate (at doses < equal 140 mg/m2).[10]

At autologous stem cell transplant, if the serum creatinine was up then 2 mg/dL, a reduction of up to 30% of the programmed initial dose is recommended.[8]

2.5 Thiotepa

Thiotepa is a stable aziridinium compound that has activity in initial and metabolite forms, thiotepa (triethylenethiophosphoramide) triethylenephosphoramide (TEPA), respectively. it has activity against some solid tumors but, today it is reserved for some specific cases of conditioning with high doses of chemotherapy in HSCT. Their mechanism of action consists of the protonation of the nitrogen of the aziridinium group, leading to its instability and causing a consequent nucleophilic cross attack on the DNA strands.[14]

In pediatric HSCT doses vary between 125 mg/m2 and 350 mg/m2 in 2 to 3 subsequent days of infusion (autologous and allogeneic) and should not exceed the maximum cumulative dose of 1050 mg/m2 or 42 mg/kg.[15]

The plasma half-life varies between the two active forms, taking from 03 to 21 hours. Excretion is performed by both the kidneys and liver. It does not require dose adjustment in renal and hepatic dysfunctions (however, the risks must be less than the clinical benefits, and its use is contraindicated in severe insufficiencies) and these characteristics occur in the same way in adults and children.[14,16]

This drug can cause mucositis, SOS, hepatotoxicity, neurotoxicity and pneumonitis. It has a dose-dependent emetogenic potential (moderate at doses < 300 mg/m2; high at doses ≥ 300 mg/m2).[16]

The use of thiotepa may be contraindicated with existing renal or hepatic impairment and should be limited to cases where benefit outweighs risk.[8]

3. ANTIMETABOLITES

3.1 Methotrexate

It belongs to the class of folate antagonists, acting at three different sites: inhibiting of dihydrofolate reductase (DHFR) and thymidylate synthase and altering reduced folate transportation. At low doses, it is used as prophylaxis for graft versus host disease (GVHD) due to its immunosuppressive activity, probably because of to the inhibition of lymphocyte multiplication.[17]

The usual dose for children aged two years or older is of 8 to 15mg/m^2 intravenously on D1, followed by 8 to 10mg/m^2 intravenously on D3, D6 and D11 after HSCT.[18]

For the handling of small doses used in protocols for GVHD prophylaxis, it is recommended to use the commercial presentation of 25 mg/mL, thus obtaining a slightly larger volume for administration.[18]

The Vd is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). About 50% of the administered dose is bound to plasma proteins. The main route of elimination is renal, with 80% to 90% of the dose being excreted in the urine within 24 hours of administration. Biliary excretion is 10% or less. Half-life for low doses is of 0.7 to 5.8 hours.[18]

Methotrexate is metabolized by oxidation, its main drug interactions occur by reducing renal clearance, thus increasing exposure to the drug and its possible toxicities.[19] It has low emetogenic risk.[20]

3.2 Cytarabine

It is an antimetabolite, cytosine analogue, a pyrimidine nucleotide. Their main mechanism of action occurs through the inhibition of DNA polymerase by competition with deoxycytidine triphosphate, causing the inhibition of DNA synthesis. It is a cycle-specific drug that acts in the S phase, and it can also block the progression of the cell cycle from the G1 phase to S phase. Its toxicity is dependent on both the drug concentration and the time of exposure. Its main cytotoxic effects are due to drug incorporation into DNA and RNA chains.[21]

Cytarabine is used in myeloablative conditioning. Its emetogenic risk is dose-related, with a dose of 75mg/m^2 having moderate risk and doses above 3000mg/m^2 presenting high risk.[15]

The drug is 13% bounded to plasma protein. It is metabolized in the liver by deoxycytidine kinase and other nucleotide kinases to the active metabolite, aracytidine triphosphate. About 86% to 96% of the dose is metabolized as inactivated form, uracil arabinoside.[15] It is also metabolized, in a small proportion, in the kidneys, gastrointestinal mucosa, granulocytes, and other tissues that contain the enzyme cytidine deaminase.[21]

Initial elimination half-life is from 7 to 20 minutes and the final one is from 1 to 3 hours. About 80% of the administered dose is renally excreted, and 90% is converted in inactive form within 24 hours.[15]

Some guidelines have been used by clinicians, with dosing adjustment in renal impairment only in high-dose cytarabine (≥ 2000 mg/m2/dose) for serum creatinine 1.5 – 1.9 mg/dL or increase of 0.5 – 1.2 mg/dL, reducing dose to 1000 mg/m2/dose.[8]

Dosing adjustment for hepatic impairment is recommended to patients with liver failure since cytarabine

is partially detoxified in the liver. The recommendation of authors such as Floyd, 2006 is to reduce the dose by 50% for any increase in transaminases, and subsequent doses can be increased in the absence of toxicity.[8]

3.3 Fludarabine

It is a fluorinating nucleotide analogue to antiviral agent vidarabine. It is a water-soluble prodrug that is converted to the active 2-fluoro-ara-ATP by the enzyme deoxycytidine kinase. This metabolite competitively inhibits DNA synthesis through the inhibition of DNA polymerase, ribonucleotide reductase, DNA primase, and DNA ligase. Its action occurs mainly in the S phase of the cell cycle.[15,22]

It is used in conditioning regimen for reduced-intensity allogeneic transplantation with a dose limited to 30mg/m^2, once a day, for 6 doses. It can be used in combination with busulfan and thymoglobulin for hematologic malignancies or in association with busulfan and alemtuzumab in myeloid neoplasms and in non-malignant diseases. It has minimal emetogenic potential.[23]

Fludarabine Vd is of 83-98L/m^2. The active metabolite is quickly and totally dephosphorylated in plasma to the inactive metabolite, 2-fluoro-ara-A. The elimination half-life is of 10.5 to 19 hours. About 40 to 60% is excreted in the urine, with 23% as 2-fluoro-vidarabine within 24 hours. Renal elimination is dose dependent, being of 24% at doses of 25mg/m^2/day and reaching 40-60% at high doses. Drug clearance is 79mL/min/m^2.[15]

Adjustment of the dose for renal impairment in infants, children and youth is recommended if the glomerular filtration rate (GFR) is between 30-50 mL/minute/1.73m2, opting for the administration of 80% of the dose and if GFR <30 mL/minute/1.73m2 is not recommended.[8]

4. Epipodophyllotoxins - Etoposide

It is a semi-synthetic derivative from podophyllotoxin, a plant product with antimitotic action. It inhibits DNA topoisomerase II, thus interrupting DNA synthesis by binding to the DNA-enzyme complex, preventing enzyme repair and consequently propagating strand breaks. Through the action of p53, these strand breaks signal the interruption of the cell cycle and when there are many, induce apoptosis. It mainly affects the S and G2 phases of the cell cycle.[24,25]

Their Vd is of 5 to 10L/m^2 and its binding to plasma proteins is 94% to 98%. It is metabolized by liver, via CYP3A3 and 3A5, generating several metabolites. Its terminal half-life is of 6 to 8 hours, considering normal liver and kidney functions. About 55% is eliminated by urine as unchanged form within 24 hours.[26,27]

Adjustment of the dose for renal impairment in infants, children and adolescents is recommended if the glomerular filtration rate (GFR) is between 10 - 50 mL/minute/1.73m2, opting for the administration of 75% of the dose and if GFR < 10 mL/minute/1.73m2, opting for the administration of 50% of the dose.[8]

In hepatic impairment, administer 50% of dose if bilirubin between 1.5 – 3 mg/dL or AST > 3 times, and 25% of dose if bilirubin > 3 mg/d/L.[8]

In allogeneic conditioning protocol for acute lymphoid leukemia, it is used in association with fludarabine and busulfan from 6 months of age, at a dose of 20mg/Kg.18 It has low emetogenic potential.[26]

5. Biological products

Some agents from biological origin can be used both in HSCT conditioning regimens for the prevention of GVHD and in support of myelosuppression arising from therapy with cytotoxic drugs that induce myeloablation. In the specific case of alemtuzumab and antithymocyte immunoglobulin (rabbit), the main activity of these agents consists of inducing an immune response against tumor cells. Regarding supportive drugs from biological origin, they act by stimulating the production of progenitors of hematopoietic stem cells so that they can act in protection against microorganisms.

5.1 Alemtuzumab

Alemtuzumab is a humanized anti-CD52 monoclonal antibody developed for the treatment of lymphoproliferative disorders such as chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and prevention of GVHD. It binds to CD52, a glycoprotein contained in more than 95% of lymphocytes, macrophages, monocytes, among others (but not in granulocytes, red blood cells, platelets and hematopoietic stem cells), leading to the immune system response through ADCC-type effector mechanisms (antibody-dependent cellular cytotoxicity) and CDC (complement-dependent cytolysis).[31]

The elimination half-life varies according to administration periods and manufacturer (around 11 hours after the first dose of Campath®; 6 days after the last dose of Campath®; around 2 weeks for Lemtrada®). Clearance decreases after repeated doses due to

decreased CD52 receptors in peripheral blood. No need for adjustments due to kidney and liver failure. Furthermore, like most monoclonal antibodies, it has minimal emetogenic potential.[15]

5.2 Antithymocyte globulin (rabbit)

Antithymocyte globulin (ATG) is used in T lymphocyte depletion as a GVHD prevention strategy in both myeloablative conditioning regimens and reduced-intensity conditioning in allogeneic HSCT. It has several formulations based on the sensitization of horses, goats and rabbits, the latter being preferable for use in this scenario.[32]

Their mechanism of action consists mainly in the depletion of T lymphocytes but, it also decreases B lymphocytes, Natural Killer cells and dendritic cells when administered in high doses. The proposed mechanisms of action induce cell depletion through mechanisms of ADCC, CDC, B cell apoptosis and modulation of key surface molecules such as adhesion receptors and chemokines.[33]

It can lead to hypersensitivity and anaphylaxis reactions, requiring premedication with corticosteroids, paracetamol, and antihistamines.15 Besides that, it can induce cytomegalovirus (CMV) reactivation, requiring prophylaxis in HIV-positive patients. It can reactivate Epstein Barr virus as well and, in these cases, the physician should evaluate the use of rituximab for PTLD (post-transplantation lymphoproliferative disease) prevention.[32,15]

With regard of their pharmacokinetics, it can vary between adults and children. Seidel et al. demonstrated that the half-life of ATG can be constant and with a linear correlation between doses of 7.5 -20 mg/kg and Cmax, and that at high doses body accumulation of ATG may occur.[34]

Van Der Zilde et al. in turn, have demonstrated that ATG levels can be decreased in children due to development of anti-ATG antibodies, increasing the risk of acute GVHD.[35]

It does not need dose adjustment in renal or hepatic dysfunctions and has very low emetogenic potential.[15]

5.3 Filgrastim

Colony stimulating factors are used to mobilize hematopoietic stem cells from the bone marrow to the periphery, facilitating their collection for later transplantation. In addition, they are used in post-conditioning phase to promote bone marrow recovery. Among many agents in this class, we highlight filgrastim.[8]

Filgrastim (or G-CSF - granulocyte colony-stimulating factor) is an 18.8 kDa glycoprotein encoded by a single gene present on chromosome 17. It is produced by macrophages, monocytes, endothelial cells, among others, and generates a stimulus response from the activation of the JAK-STAT signaling pathway.[36] The pharmacokinetics of filgrastim indicates onset of action between 1 and 2 days after administration and normalization of neutrophil count within 4 days of use. It has a high Vd (150 mL/Kg), but no evidence of accumulation in intravenous administration. Bioavailability is around 60% and the elimination half-life in neonates is of 4.4 hours. It does not require adjustments in liver and renal failure, except in cases of filgrastim-induced glomerulonephritis, and has no emetogenic potential. The main adverse reactions of filgrastim are fever, thrombocytopenia, and bone pain.[15]

TABLE 1– Technical aspects (Drugs in alphabetical order) 8,15,17,18,21,22,23, 24,26, 27,28,29,30,37

Dosage form	Compatibility	Stability	Extravasation risk	Guidances
Antithymocyte globulin (rabbit) Ampoule vial 25 mg	NS or D5W	Used immediately	-	Required the use of 0.2-micron inline filter. Reconstitute with 5 mL of water for injection to a final concentration of 5mg/mL.
Alemtuzumab Ampoule vial 30 mg/1mL	Dilute for infusion in 100 mL NS or D5W	8 hours (15º-25ºC) or 8 hours (2º-8ºC)	-	Gently invert the bag to mix the solution. Do not shake the preparation prior to use.
Bussulfan Ampoule vial 6 mg + 10 mL of diluent - 10 mg/mL	NS or D5W to a final concentration of ≥ 0.5 mg/mL	8 hours (15º-25ºC) * or 12 hours (2º-8ºC) + 3 hours (15º-25ºC)*	May be an irritant	Diluent volume should be 10 times the volume of bussulfan. *including infusion time.
Carmustine Ampoule vial 100 mg + diluent (ethanol 3mL + 27 mL water for injection)	NS or D5W	24 hours (2º-8ºC) + 6 hours (15º-25ºC)* or 3 hours (15º-25ºC)*	May be an irritant	Incompatible with DEHP; protect from ligth; final concentration of 0,2-1 mg/mL; infusion over 1-2 hours. *including infusion time
Cyclophosphamide Ampoule vial of 200 mg or 1000 mg	NS or D5W	24 hours (15º-25ºC)	May be an irritant	Urotoxic agente, recommended prophylaxis with Mesna. Reconstitute with water for injections to a final concentration of 20 mg/mL.
Cytarabine Ampoule vial 100 mg/mL or 500 mg/mL	NS, D5W or Ringer lactato	48 hours (15º-25ºC)	-	-
Etoposide Ampoule vial 20 mg/mL	NS or D5W	0.2 mg/mL: 96 hours (2º-8ºC) or 0.4 mg/mL: 24 hours (2º-8ºC)	Irritant	Incidence of precipitation increases with final concentration > 0.4 mg/mL. Incompatible with DEHP material.
Filgrastim Ampoule vial 300 mcg/1mL or prefilled syringe of 300 mcg/1mL (in this latter the volume cannot be handled).	D5W	24 hours (15º-25ºC) or 48 hours (2º-8ºC)	-	It can be administered Subcutaneously or Intravenously, in this latter solution for administration should not exceed a final concentration of 15 mcg/mL, due to the risk of adsorption of the drug into the plastic syringe.
Fludarabine Ampoule vial 50 mg	NS or D5W	48 hours (15º-25ºC) or (2º-8ºC)	-	Reconstitute with 2 mL of water for injection to a final concentration of 25 mg/mL.

Melphalan Ampoule vial 6 mg + Diluent 10 mL - 6 mg/mL	NS or D5W	8 hours (15º-25ºC)*or 12 hours (2ºC a 8ºC) + 3 hours(20ºC ± 5ºC)*	May be an irritant	Concentration range ≥ 0,5 mg/mL; Infusion volume can be up 10 times the volume of Bussulfan. *including infusion time
Methotrexate Ampoule vial 25 mg/mL or 100 mg/mL	NS or D5W	24 hours (15º-25ºC)*	-	*including infusion time
Thiotepa Ampoule vial 15 mg or 100 mg, should be reconstituted with water for injection obtaining a final concentration of 10mg/mL	NS or D5W	8 hours (15º-25ºC)* or 24 hours (2º-8ºC) + 8 hours (15º-25ºC)*		In pediatrics, final dilution volume must allow finl concentration between 0,5 and 1 mg/mL; Infusion time over 2-4 hours; Mandatory the use of 0.2-micron inline filter. *including infusion time

NS: Normal saline; *D5W:* 5% dextrose in water; DEHP: Di-(2-ethylhexyl) phthalate (Used in plastic bags to provide malleability); Vd: Volume of distribution.

CONCLUSION

The pharmacologic profile of the drugs contributed to the elaboration of a safety recommendations list of each one. The safe use of drugs in HSCT will help in guide and systematize the main actions of the drugs in therapeutic process, helping minimize the risk of errors and ensure an effective treatment, increasing patient's safety.

Knowledge of pharmacological therapy is essential for clinical practice, as it provides support for possible drug-related reactions and presents necessary interventions for potential problems arising from the therapy, which can be identified and measured.

CONFLICTS OF INTEREST

There are no known conflicts of interest associated with this publication.

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HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH HEMOGLOBINOPATHIES: BRAZILIAN SOCIETY OF BONE MARROW TRANSPLANTATION CONSENSUS

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INTRODUCTION

Hemoglobinopathies are the most common monogenic diseases worldwide. There are approximately 300,000 to 400,000 newborns with hereditary hemoglobinopathies yearly. In Brazil it is estimated that there are around 70,000 – 100,000 people living with hemoglobinopathies, the most common being sickle cell disease[1].

Sickle cell disease (SCD) is a severe genetic disorder caused by a single point mutation in the adult β-globin (HBB) gene that causes a Glu > Val aminoacid substitution in the β-globin chain (βS-globin)[2]. The sickle hemoglobin (HbS, α2βS2) has the propensity to polymerize under deoxygenated conditions, resulting in the production of sickle-shaped red blood cells (RBCs). In your turn, sickle RBCs causes hemolytic anemia and occlusions of small blood vessels, leading to impaired oxygen delivery to tissues, multiple organ damage, severe pain, and early mortality[3]. Stand of care treatments, such as transfusions, hydroxyurea and L-glutamine still are associated to reduced life expectancy and quality of life[4]. More recently developed targeted therapies, voxelotor, and crizanlizumab, although able to reduce the number of VOC, have not been tested in the long term and are associated with high costs[4]. Currently, the only available curative treatment for SCD patients is allogeneic hematopoietic cells transplantation (allo-HCT), with overall survival superior to 90% and event-free survival higher than 85%[5]. Nevertheless, allo-HCT is limited by the availability of compatible donors and transplant-related mortality and long-term toxicities[4,5].

Thalassemias are a heterogeneous group of recessive hereditary diseases that present a decreased synthesis of the alpha or beta chains of hemoglobin (Hb). It is considered a quantitative defect of hemoglobin synthesis and is characterized by a hypochromic microcytic anemia[6]. The spectrum of disease severity is varied and depends not only on the subtype of thalassemia but also on the treatment provided such as splenectomy, transfusions, and iron chelation[6]. Similar to SCD, HSCT is considered the only curative option for patients with thalassemia[7].

In thalassemia, the main complications are due iron overload secondary to chronic blood transfusion while in sickle cell disease, the main complications arise from vaso-occlusion. Neurological events like seizures, stroke and silent ischemia and damage to several organs, reduces life expectancy by 20 years when compared to that of the normal population, according to a Brazilian study[1].

In Brazil, the treatment of hemoglobinopathies in the public health system (Sistema Unico de Saude – SUS) is regulated by the Joint Ordinance No. 05 of February 19, 2018. The protocol established by this ordinance regarding SCD, includes newborn screening, antibiotic prophylaxis, hydroxyurea and monitoring of neurological disease with transcranial Doppler. In 2015 hematopoietic stem cell transplantation (HSCT), the only curative option for hemoglobinopathies currently available, was incorporated as a procedure reimbursed by SUS. Reimbursement for allogeneic HSCT in thalassemia has been approved since 1999.

THALASSEMIA MAJOR

The greatest experience in HSCT for thalassemia is from the Pesaro group, which defined a risk stratification as early as 1994. The classification should be followed in patients under the age of 17 years (8) and basically involves the quality of iron chelation and its consequences (Table I).

TABLE 1. Pesaro Risk Classification

Risk factors	Class 1	Class 2	Class 3
Inadequate iron chelation	No	Yes/No	Yes
Hepatomegaly > 2 cm from RCM	No	Yes/No	Yes
Portal fibrosis	No	Yes/No	Yes

RCM, right costal margin

With this stratification thalassemia-free survival (TFS) was 90%, 80% and 65% for class 1, 2 and 3 patients, respectively. Transplant-related mortality (TRM), as expected, was also related to risk classification, being higher in class 3 patients[8].

RELATED HLA IDENTICAL DONORS (BONE MARROW OR CORD BLOOD)

Most of the data are from identical HLA related donors of Pesaro's group and two large retrospective analyses from the U.S. and Europe. The most used conditioning regimen in these studies, for patients under the age of 17 years and Pesaro classes 1 and 2, was myeloablative with Bussulfan (14 mg/kg), Cyclophosphamide (200 mg/kg) and anti-thymocyte globulin (ATG) (8). In patients with Pesaro class 3, due to high transplant-related mortality (TRM) and graft failureit appears to be better adopt a regimen with pre-HSCT immunosuppression with azathioprine, hydroxyurea, fludarabine and transfusion, with the objective of suppression of erythropoiesis, followed by reduced BuCy (cyclophosphamide of 120 mg/kg)[9]. With this new regimen, overall survival (OS) was 87% and thalassemia-free survival (TFS) was 82% in a group of 73 patients[10]. In patients over 16 years, this same regimen with pre-HSCT immunosuppression and reduced BuCY has been used[11].

The results with related HLA identical umbilical cord are similar to those of HLA identical bone marrow, both sources being currently recommended as standard of care for patients with transfusion-dependent thalassemia[12].

Some groups have associated Thiotepa with classic BuCY to reduce the rejection rate, especially in children under the age of 4 years[11]. A recent study compared data on BuCYATG versus BuCYThio and found no differences even in children under 4 years[13].

UNRELATED HLA IDENTICAL DONORS

Unrelated HSCT data in patients under 16 years and with HLA-identical donors (10/10) are similar to results with related HLA-identical donor (14). It is important to reinforce that, for hemoglobinopathies, typing should include HLA DPB1, considering that incompatibilities in this locus are associated with inferior outcome[15,16].

Data with unrelated umbilical cord blood, although restricted, resulted in high graft failure rates and, consequently, reduction in overall survival[17,18]. For this reason, we do not recommend the use of unrelated umbilical cord blood.

Haploidentical donors

Two strategies have been employed: *ex vivo* lymphocyte depletion and *in vivo* depletion. *Ex vivo* depletion comprises CD34 selection or CD3+/CD19+ depletion[19]. With overall survival of 100%, the data are encouraging, despite slow immune recovery and frequent viral infections[20].

Initial data on the use of post-transplant cyclophosphamide as T-cell depletion *in vivo* resulted in high rates of graft failure. Modifications such as increased TBI dose (200 cGy to 400 cGy) and inclusion of preconditioning immunosuppression, as that used in patients with Pesaro class 3, improved results significantly[21]. These transplants should be performed only in controlled clinical studies at this time.

SICKLE CELL DISEASE

Allogeneic Stem Cell Transplant indications

Currently, advances in conditioning regimens, graft-versus-host disease (GVHD) prophylaxis and better knowledge related to major complications of HSCT have made indications for HSCT broader, allowing both patients with severe disease and patients considered to be at higher risk for complications to be eligible for transplantation[22]. However, the decision to perform HSCT should be considered within a scenario in which each case should be individualized, since the clinical evolution is usually very variable

and the presence or absence of clinical symptoms in the first years of life does not predict how the patient will evolve in the future[23].

Thus, young patients with symptomatic sickle cell disease who have a compatible HLA sibling donor should be referred for evaluation at a transplant center, preferably at preschool age[5]. In adults, the risks and complications of HSCT have gradually decreased, so that symptomatic patients with an identical HLA sibling donor can also benefit from an evaluation at a transplant center[22].

Table 2 shows the main indications for HSCT for patients with SCD who are using hydroxyurea or under chronic transfusion and present at least one of the conditions described below. We highlight that in the recommendations of this consensus there is no contraindication associated with the patient's age.

TABLE 2. Indications for HSCT with HLA-identical sibling donors for sickle cell disease

Neurological alteration due to stroke, any neurological alteration persisting for more than 24 hours or altered imaging
Cerebrovascular disease associated with sickle cell disease
Two or more severe vaso-occlusive crises (including acute chest syndrome) in the last year
More than one episode of priapism
Presence of more than one antibody in patients on a hypertransfusion regimen
Osteonecrosis in more than one joint

PRE-TRANSPLANT CARE

Patients eligible for HSCT should be evaluated for their organic function and the presence of complications related to SCD (Table 3)24.

There is no contraindication for transplantation in patients with vascular alteration with Moyamoya's disease patter. Besides, we do not recommend pre-transplant surgical correction of this complication. In such cases, the decision to perform transplant shall be discussed and evaluated by the transplant center.

TABELA 3. Pre-TCTH evaluation

Organ/System	Exams
Lung	Pulmonary function test (PFT)
Heart	Echocardiogram with tricuspid valve evaluation
Central Nervous System	Brain MRI Transcranial Doppler ultrasound (Up to 16 years) Neuropsychiatric evaluation if possible
Liver	Liver MRI T2* (according to the number of transfusions and serum ferritin)
Kidney	Glomerular filtration rate Urinalysis Microalbuminuria-creatinine ratio
Hematological system	Anti-HLA antibody test (mismatch) Extended erythrocyte phenotype Number of transfusions received Ferritin Keep HbS% < 30% before transplantation with simple transfusion or erythrocytapheresis
Multidisciplinary evaluation	Social worker Psychology Hemotherapy Endocrinology (discussion on risk of infertility) Gynecology-obstetrics (if considering fertility preservation) Pain team - anesthesia (if chronic pain) Psychiatry (if pre-existing psychiatric disease)

CONDITIONING REGIMENS

The conditioning regimen currently recommended for HSCT-candidates with an HLA-identical sibling donor is myeloablative (MAC). This regimen is based on the use of busulfan (Bu) 14-16 mg/kg (total dose) and cyclophosphamide (Cy) 200 mg/kg (total dose) with ATG[7]. Studies published using BuCy have demonstrated an OS in the pediatric population of 95 to 97%, and EFS of 85%[25-27]. It is important to highlight the role of the addition of ATG in conditioning regimens, since its inclusion decreases the incidence of GVHD, in addition to reducing the rejection rate from 22.6% to 3% in one study[27]. Another recommended scheme is the use of fludarabine and busulfan, with results similar to those of BuCy[28]. There is a clear relationship between age at the moment of HSCT and the result obtained, which is superior in pediatric patients[29]. It is important to highlight that, despite the excellent results, myeloablative regimens are associated with higher morbidity and mortality due to the risk of infertility, secondary neoplasia, besides hindering transplantation in some cases in adults with important comorbidities and organic dysfunction[30]. The use of a less toxic myeloablative regimen with fludarabine (Flu), busulfan and ATG showed promising results with 95% EFS[31].

HSCT with reduced intensity conditioning (RIC) or non-myeloablative (NMA) in the pediatric population resulted in high graft failure rate, thus not being recommended for this age group[32]. In adults, conditioning containing alemtuzumab associated with low radiation dose (TBI 300 cGy) and sirolimus as prophylaxis for GVHD showed promising results[33]. However, the data are restricted, and we do not routinely recommend non-myeloablative regimens.

So, we recommend, for patients with a compatible sibling donor, myeloablative conditioning:

A) Cell source: Bone marrow or related umbilical cord

B) Busulfan 14 - 16 mg/kg IV + Fludarabin 150 mg/m^2 + rabbit ATG 4.5 – 7.5mg/kg

C) Busulfan 14-16 mg/kg IV + Cyclophosphamide 200 mg/kg + rabbit ATG 4,5 – 7,5 mg/kg

D) GVHD prophylaxis with cyclosporine and methotrexate. In the case of umbilical cord blood, methotrexate should be replaced by another immunosuppressive medication.

ALTERNATIVE DONORS

Although indications with alternative donors did not differ from indications with HLA-identical sibling donors, only the use of HLA-identical related umbilical cord blood showed results similar to those of bone marrow from HLA-identical siblings[12]. HSCT with matched unrelated donors are limited. A recent retrospective EBMT register study with 73 transplants showed that this is an important option for patients with severe complications (stroke) and non-responding to hydroxyurea[34]. The HSCT with haploidentical donors is an important option but with few cases published so far[19,35]. Haploidentical transplants should be performed only in the context of clinical trials at this time[19,36].

We emphasize that all patients (or their parents) diagnosed with sickle cell disease should receive information about all therapeutic options, including HSCT, as soon as possible. If they have siblings, they should be submitted to HLA typing. Patients with alterations indicating HSCT should be referred for evaluation as soon as possible at a transplant center.

TRANSFUSION SUPPORT

Patients with hemoglobinopathies usually arrive for transplant after a long period of exposure to red blood cell (RBC) transfusions. These patients have a higher rate of RBC alloimmunization than patients with cancer. Alloimmunization occurs in 10-20% of transfusion-dependent patients with thalassemia[17], while in patients with sickle cell disease, this rate varies between 20-50%[37]. Planning transfusion must involve the hemotherapy service. The number of previous transfusions, the history of transfusion reactions, information about the presence of acquired anti-erythrocyte antibodies (AEA) and red cell phenotyping data are essential for a good HSCT planning.

The tests to be performed pre-HSCT are, in addition to ABO and Rh typing, the search for AEA, antibody titration, in case of ABO incompatibility between donor and recipient, direct antiglobulin test and extended RBC phenotyping. This must include at least the following antigens: C (RH2), E (RH3), c (RH4), and (RH5), K (KEL1), k (KEL2), Jka (JK1), Jkb (JK2), Fya (FY1), Fyb (FY2), S (MNS3), s (MNS4). Genotyping is recommended to elucidate complex cases and to identify RHCE variants, common in patients with sickle cell disease[38].

All patients with hemoglobinopathies undergoing HSCT should receive leukocyte reduced and irradiated cellular blood products. It is advisable to initiate irradiation in the pre-conditioning period. Washed blood products are indicated for patients with previous severe allergic / anaphylactic reactions and may

be indicated in ABO-incompatible transplants to minimize the amount of antibodies infused[39] .

CHIMERISM EVALUATION

The evaluation of chimerism in the context of HSCT in hemoglobinopathies is of fundamental importance. The recommendation is that the evaluation starts on the D+30 post-HSCT and repeated on D+60, D+90, D+120 (if no complete chimera D+90), D+150, D+180 and D+365 post-HSCT. In sickle cell disease, Bernaudin et al. showed that 44% of patients submitted to an HLA-identical donor HSCT maintained mixed chimera one year after HSCT. This fact, however, did not result in graft failure or disease manifestations[27]. It is estimated that at least stable 25% donor mixed chimera is needed to prevent clinical manifestations of sickle cell disease after HLA identical sibling transplants[40]. Chimerism analysis should ideally be performed in specific cell populations (erythrocyte, myeloid and T cells) and not just in whole peripheral blood[40]. Mixed chimerism data in donors that are not HLA-identical siblings are scarce and cannot be extrapolated safely to these other scenarios. Approach to falling chimerism are not well established in the literature. Most authors recommend increasing immunosuppression, but no clear recommendation can be done.

IRON OVERLOAD

Patients with hemoglobinopathies usually present with iron overload for HSCT. We recommend, if possible, the best available iron chelation in the pre-HSCT period[41]. There are no prospective data in literature so far, if a period of intense iron chelation pre HSCT will improve long term outcome, since iron overload is a long-lasting process. Pre- and post-HSCT evaluation and approach of iron chelation are summarized in Table 5. Iron chelation options are phlebotomy 6-9 mg/kg each 2 weeks; if well tolerated, it can be done weekly (AIII); deferoxamine 40 mg/kg IV ou SC 5/7 days of the week (AII); deferasirox 10 mg/kg/day (AII).

TABLE 5. Recommendations regarding the evaluation and approach of iron overload.

	Iron overload evaluation	Toxicity evaluation of iron chelation
Before HSCT	Ferritin, Transferrin saturation Serum iron, MRI (LIC and T2*)	Kidney and hepatic function
6 months post-HSCT (from 6 months, if there is no GVHD or other complication that contraindicates it)	Ferritin Transferrin saturation MRI (T2* and LIC) (only if clinically indicated and in patients with pre-HSCT abnormalities)	Kidney and hepatic function every two weeks Most frequent assessments depending on clinical and laboratory assessment
12 months after the beginning of therapy and annually until normalization	Ferritin Transferrin saturation MRI (T2* and LIC)	

MRI, magnetic resonance imaging; LIC Liver iron concentration

LONG-TERM FOLLOW-UP

Long-term follow-up should be programmed according to the general recommendations for all HSCTs. However, some specific assessments, such as neurological, cardiac and hepatic, require special attention[31,42]. In relation to assessments of infections and immunizations, the recommendations of the corresponding chapters should be followed.

TABLE 6. Long-term follow-up after HSCT for hemoglobinopathies

Evaluation and Exams	Days		Months				Years	
	100	120	6	9	12	18	2 years	Annual
Disease evaluation	X	X	X	X	X	X	X	X
Chimera evaluation (VNTR or STR, ABO group if incompatibility, karyotype, Hb electrophoresis)	X	X	X	X	X	X	X	X
General exams (hepatic and kidney function, biochemistry exams)	X	X	X	X	X	X	X	X
Brain MRI (for SCD)					X		X*	X*
Transcranial Doppler (for SCD if abnormalities in previous exams)					X		X*	X*
Neurological and cognitive evaluation (if available)	X				X		X*	X*
Cardiac and hepatic MRI (if abnormalities in previous exams)					X		X*	X*
TSH					X		X	X
Ferritin and transferrin saturation			X		X		X*	X*
Echocardiogram					X			
PFT			X	X	X	X	X	
Lipidogram			X		X		X	X
Bone mineral density					X			
Vaccination (according to institutional protocol)								
Fertility evaluation (≥11 years): FSH, LH, Testosterone and sperm analysis (for men)					X			
Skin, mouth, eyes, gynecological evaluation					X		X	X
Screening for malignancy					X		X	X
Growth and hormonal evaluation (≥ 11 years)					X		X	X

HSCT, hematopoietic stem cell transplantation; VNTR, variable number tandem repeat; ST, short tandem repeat; Hb, hemoglobin; MRI, magnetic resonance imaging; SCD, sickle cell disease; TSH, thyroid-stimulating hormone; PFT, pulmonary function tests; FSH, follicular-stimulating hormone; LH, lutenizing hormone

TABLE 7. Recommendations

Transfusion-dependent talassemia	Recommendation
HLA-identical donor (bone marrow or umbilical cord) Age <16 years Pesaro classes 1 and 2	Standard
Unrelated donor 10/10 (preferably bone marrow), Age < 16 years, Pesaro classes 1 and 2 HLA DPB1 without mismatch or with permissive mismatch	Standard
Unrelated cord blood	Not recommended
Haploidentical	Experimental protocol
Sickle cell disease	Recommendation
HLA-identical sibling donor (bone marrow or cord blood)	Standard
Unrelated umbilical cord blood	Not recommended (NR)
Haploidentical	Experimental protocol (EP)

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CONSENSUS ON INDICATIONS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRICS. UPDATE 2020: GERM CELL TUMORS AND WILMS TUMORS

V Meeting of Brazilian Guidelines on Hematopoietic Stem Cell Transplantation of the Brazilian Society of Bone Marrow Transplantation – SBTMO

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SUMMARY

The indications for hematopoietic stem cell transplantation in solid tumors in children do not change a lot since our first Brazilian consensus publication in 2009. In this article, we are going to review indications to hematopoietic stem cell transplantation in pediatric germ cell tumors and wilms tumor.
For the consensus, a review was made using the most relevant articles, and a series of meetings was done to discuss the recommendations.

Keywords: Germ cell tumor; Wilms tumor; Hematopoietic Stem Cell Transplantation; Pediatrics

INTRODUCTION

Most studies of extracranial germ cell tumors are in adult patients. Transplantation appears to be beneficial in patients after the first or second relapse, with response to chemotherapy and with the least amount of residual disease.[1-2]

There is a tendency to use tandem transplantation[3]. Currently, an international prospective randomized study is in progress with HSCT as a rescue therapy for patients with first-line treatment failure.[4]

IN FIRST REMISSION

It may also be an option, as a first line, for some patients with unfavorable prognostic factors, especially for those with slow drop in markers after the first two cycles of chemotherapy.[5,6]

RELAPSED OR REFRACTORY PATIENTS

The standard rescue treatment for relapsed/refractory GCTs includes either conventional chemotherapy or high dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT).[3]

The use of high-dose chemotherapy with autologous HSCT seems to show better results in relation to progression-free survival.[3,7]

There is an international prospective randomized study is in progress with HSCT as a rescue therapy for patients with first-line treatment failure.[4]

SEQUENTIAL HSCT (TANDEM)

Randomized studies comparing a single transplantation with sequential HSCT do not show significant differences in relation to overall survival, progression-free survival and event-free survival.[8-9] However, they show a significant difference in terms of mortality related to transplantation.[8]

Thus, there is a tendency to increasingly use sequential HSCT with a preference for intervals between

transplants less than 28 days that show better results in relation to relapse and progression-free survival.[3]

PEDIATRIC PATIENTS

Studies in the pediatric population are scarce and mostly retrospective. They demonstrate beneficial results in the rescue treatments in children with extragonadal GCT, but there is a need for prospective studies[10], in addition to the importance of resection of the primary tumor for the results.[11]

WILMS TUMORS

Most patients with Wilms tumors WT have good overall survival outcomes. Despite the relatively small number of patients with relapsed Wilms' tumor, limiting the randomization of subgroups, there is relevant information extracted from literature reports favoring the use of HSCT. A meta-analysis study suggests that patients with initial stage III or IV and isolated pulmonary relapse within one year of diagnosis are the most benefited by HSCT [12,13].

A review of 234 transplanted children found similar findings, suggesting that HSCT has a positive impact on survival in patients with advanced early stage, unfavorable histology, previous exposure to more than 4 chemotherapeutic agents, in second relapse, or with disease progressing after first relapse[14].

Very high-risk patients can be transplanted in the first line, preferably within clinical trials[15]. There are no robust studies on better conditioning, but melphalan used alone seems to be an adequate regimen[15,16]. In all publications, only autologous transplantation is mentioned, with the allogeneic transplant out of context.

In the table 1 all indications are summarized.

TABLE 1- Indications for Hematopoietic Stem cell Transplantation in Pediatric Solid Tumors

TUMOR	AUTOLOGOUS	ALLOGENEIC
Germ Cell Tumor – First Line High Risk Features	CI	NR
Germ Cell Tumor – Relapse	CI	NR
Wilms Tumor – First Line - Very High Risk	CI	NR
Wilms Tumor Relapsed	CI	NR

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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC LYMPHOMAS

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INTRODUCTION

Lymphomas are the third most common cancer of childhood in Brazil, after leukemias and central nervous system tumors[1].

The diagnosis and staging are based on clinical presentation, pathology findings with immunohistochemistry, molecular biology and radiological imaging. The treatment with multiagent chemotherapy or radiotherapy is defined according to the lymphoma subtype and risk stratification[2].

The prognosis of children and adolescents with non-Hodgkin lymphomas (NHL) and Hodgkin's lymphoma (HL) has markedly improved in the last decades, however relapsed or refractory disease is still associated with an inferior outcome. Aggressive chemotherapy followed by either autologous or allogenic hematopoietic stem cell transplantation (HSCT) is a salvage treatment strategy described in the literature, with particularities according to lymphoma subtype and to the available source of stem cells.

NON-HODGKIN LYMPHOMA

Pediatric NHL have excellent prognosis with conventional chemotherapy. Current protocols can achieve overall survival rates exceeding 80% for the most common subtypes (Burkitt and Diffuse Large B cell, Anaplastic Large cell and Lymphoblastic lymphomas).

The optimal approach for relapsed/refractory (R/R) patients, including the incorporation of new therapies, is unclear. Given the excellent results of first-line treatment in children and adolescents with NHL, clinical trials for the treatment of relapses often include heterogeneous groups of patients. This fact makes it difficult to interpret and generalize the results that are obtained.

MATURE B-CELL LYMPHOMAS

Mature B-cell lymphomas (Burkitt lymphoma – BL, and diffuse large B-cell lymphoma – DLBCL) represent the largest NHL subtype with a 90% event-free survival rates according to contemporary approaches[3]. The R/R disease prognosis is dismal, and worse prognosis factors are the first line treatment intensity, including the addition of rituximab; elevated lactate dehydrogenase (LDH), early relapses and bone marrow involvement[4].

In addition, the mature B-cell lymphoma subtype also has an impact on survival, with the DLBCL having better results when compared to BL (52%±10% x 28±3%)[5].

HSCT is considered for chemo sensitive patients, with no survival benefit for those refractory to reinduction or to first line therapy, with few anecdotal cases alive in the literature[6-,9].

Several rescue schemes are proposed, usually associated with the anti-CD20, such as high-risk blocks of BFM, R-ICE (rituximab, ifosfamide, carboplatin and etoposide), R-ICI/ICN (rituximab, ifosfamide, carboplatin, idarubicin/mitoxantrone, paclitaxel) or R-VICI (rituximab, vincristine, idarubicin, ifosfamide, carboplatin and dexamethasone). Unfortunately, progressive disease occurs in about 50% of cases during reinduction,

with better results found with the R-VICI schema (up to 20 improvement in progression free survival)[9].

It is well known that those salvage regimens are associated with severe hematological toxicities and risk of failure in mobilization and stem cell harvest. The allogeneic HSCT is an alternative to the autologous HSCT with similar outcomes and, therefore, better results than conventional chemotherapy without HSCT[8,10-13]. Most of the retrospective studies include long periods and small number of patients, not allowing conclusions regarding the Graft versus Lymphoma (GVL) effect and the potential survival advantaged associated with the allogeneic HSCT.

Although there are no prospective randomized studies exploring the best HSCT modality, there is a tendency to perform autologous transplants in DLBCL, while in BL both modalities (allogeneic and autologous) overlap, with similar results (46±5% x 44±6%)[5].

Different conditioning regimens are described for autologous transplants, mainly containing carmustine (e.g. BEAM). Since carmustine is no longer available in Brazil, busulfan-based regimens are alternatives.

For allogeneic HSCT, myeloablative regimens with Total Body Irradiation (TBI) and busulfan and Burkitt's reduced intensity conditioning including rituximab, fludarabine, thiotepa, carboplatin, mitoxantrone and paclitaxel are suggested[5,3].

LYMPHOBLASTIC LYMPHOMAS

Lymphoblastic lymphomas (LL) are the second most frequent subtype of NHL in childhood and about 10% of patients experience relapses or progression on current protocols[14]. For those patients, long-term remissions are not sustained with chemotherapy alone and bone marrow transplantation is usually recommended in patients in complete remission[15,16]. Data from the CIBMTR showed better 5-year event-free survival in patients undergoing allogeneic HSCT (40%) when compared to autologous bone marrow transplantation (4%)[12]. Thus, allogeneic HSCT based on acute lymphoblastic leukemia (ALL) principles is the standard of care for R/R LL.

LARGE ANAPLASTIC CELL LYMPHOMAS

Childhood large anaplastic cell lymphomas (ALCL) represent 10 to 15% of pediatric NHL lymphomas with survival rates ranging from 70 to 85% in different cooperative trials[17-19].

Approximately 25 to 35% of patients progress to relapsed or refractory disease. In these cases, there is no consensus on the best treatment strategy. Unlike the other NHL subgroups, salvage therapy is effective on R/R ALCL and response rates around 80% are achieved[20,21].

Bone marrow transplantation is a curative alternative for those patients and both autologous and allogeneic HSCT are addressed in the literature. Risk factors such as early relapses (< 12 months from initial diagnosis), progression during first-line therapy, involvement of bone marrow and Central Nervous System at relapse and CD3 expression on the primary tumor are associated with unfavorable outcomes in retrospective series[21,22]. Results from the CIBMTR, the Berlin-Frankfurt-Muenster group (BFM) and the Japanese group report a 5-year event-free survival of 35%, 59% and 38%, respectively[12,21,23]. Patients in CR at the time of autologous transplantation had better results when compared to patients with active disease[23].

A recent prospective trial conducted by the European group showed that late relapses could be treated with vinblastine as a single agent and that high risk disease had 65% 5-year EFS following allogeneic HSCT. The autologous transplantation arm, initially planned for patients in the intermediate risk group (CD3 negative with relapse < 1 year and who had already received vinblastine) was held after inferior outcomes results were described when compared to the allogeneic HSCT group (EFS 44% ±9%), suggesting that early relapse disease should be consolidated with allogeneic transplantation[24].

Allogeneic HSCT with myeloablative conditionings (with TBI or busulfan) and reduced intensity are described in the literature with EFS ranging from 50 to 75%[23-26].

In the recent European prospective trial published by Knorr et al, the conditioning regimen adopted for 56 ALCL relapsed patients consisted of TBI 12Gy (substituted by bussulfan in patients younger than 24months), thiotepa and etoposide.

The incorporation of new drugs, such as brentuximab vedotin and crizotinib, are explored by some cooperative groups, however the optimal approach, whether associated or not with HSCT, has not been properly established so far.

POST-TRANSPLANT MAINTENANCE THERAPY

There are few studies regarding the use of post-HSCT maintenance in NHL in the pediatric group. Tavern JA

et al published a systematic review in patients older than 18 years and no benefit was observed with the addition of rituximab in DLBCL. Check point inhibitors are promising options for future trials[27,28]. The use of Brentuximab, Crizotinib (ALK inhibitor) and Nivolumab in R/R ALCL, both as a brige to HSCT and maintanance after high dose chemotherapy have been studied, however with no conclusive results so far[29].

SUMMARY OF TREATMENT RECOMMENDATIONS FOR NHL HISTOLOGICAL SUBTYPES

In R/R NHL it is important to maintain high dose-intense treatment, avoid treatment delays and consider treatment continuation prior to full hematological recovery, especially in mature B-cell lymphomas. There is limited or no role for irradiation and surgery in these scenarios. Achieve CR prior to HSCT is associated with better survival, and early taper of immunosuppression after allogeneic HSCT may allow lower relapse rates.

Specific recommendations for each NHL subtypes are described in table 1. There are unique clinical scenarios not covered by these recommendations that may require individualized decisions.

HODGKIN LYMPHOMA

Hodgkin's lymphomas in children and adolescents, likewise pediatric NHL, have excellent survival with conventional chemotherapy associated or not with radiotherapy. Even high-risk patients at diagnosis have a good chance of cure with standard treatment and, therefore, autologous HSCT (ASCT) is not recommended as frontline therapy in pediatric HL, but it is considered for relapsed or primarily refractory diseases (R/R)[30-32].

Some risk factors have been associated with inferior outcomes for R/R patients, such as bulky disease at diagnosis, B-symptoms, extra nodal disease, first-line chemo resistance, relapses within 12 months from diagnosis, advanced stage disease at relapsed and number of previous treatment regimens. The prognostic marker that seems to be more important is the result of the fluro-deoxy-glucose positron emission tomography (FDG PET) pre HSCT with a 10-year EFS of 31% (PET positive) versus 75% (PET negative)[33-35].

Recently, a guideline was published from the EuroNet Paediatric Hodgkin Lymphoma Group[36]. According to this guideline the risk stratification at the point of relapse identifies 3 groups: low, standard and high risk groups (table 2). The low and standard risk are based on assessment of pre-salvage risk factors, and the high risk is based on response of treatment i.e., the failure to achieve a negative FDG-PET after 2 lines of salvage standard dose chemotherapy (SDCT).

The European guideline proposed that the low-risk group could be treated with SDCT plus radiotherapy consolidation only, the standard risk group could be treated with SDCT plus high dose chemotherapy and autologous stem cell transplant (HDCT/ASCT) consolidation and the high-risk group is eligible for conventional HDCT/ ASCT plus additional treatments pre and/or post HDCT/ ASCT or experimental strategies. The aim of salvage chemotherapy is to achieve a complete metabolic remission (CMR) defined as Deauville 1–3 or qPET <1.3 (in the EuroNet group the semi-quantitative "qPET" method is widely used which is a quantitative extension of the Deauville scale; Deauville 4 and 5 are respectively equivalent to qPET values of 1.3 and 2.0 and a positive PET scan is a qPET value >1.3).

Myeloablative chemotherapy with ASCT is the recommended approach for patients who develop refractory disease during therapy or relapsed disease within 1 year after completing therapy. In addition, this approach is also recommended for those who recur with extensive disease after the first year of completing therapy or for those who recur after initial therapy that included intensive (alkylating agents and anthracyclines) multiagent chemotherapy and radiation therapy[2].

Most of the conditioning regimens for ASCT include carmustine, such as BEAM (carmustine, etoposide, cytarabine and melphalan) or CBV (carmustine, etoposide and cyclophosphamide). However, as carmustine was discontinued in Brazil and in several countries as previously mentioned, there was a need to explore different regimes such as: melphalan/ etoposide; busulfan/ melphalan; gemcitabine/ busulfan/ melphalan; and alternatives to the carmustine, including bendamustine (Benda-EAM), fotemustine, lomustine (LEAM), mitoxantrone and thiotepa. There are no studies comparing the efficacy among all different conditioning regimens and therefore, there is no standard conditioning in the pediatric literature. The optimal regimen should be based on clinical status, known efficacy of previous drugs utilized, tumor localization, financial cost and regulatory approval by local authorities.

Some strategies have been adopted to improve results for high-risk R/R candidates to bone marrow

transplantation, including better salvage treatment, alternative transplant modalities, e.g. TANDEM, and post transplantation maintanence therapy.

Radiation is a well-known effective therapy for HL, however the site of irradiation and potential toxicity should be considered when it is indicated. The ideal radiation timing is controversial, although many authors recommend radiotherapy after the autologous HSCT[36].

Brentuximab vedotin (BV) (anti-CD30) can be used for salvage treatment in R/R patients, as a bridge to transplantation[37], and as a post transplant maintenance therapy[38]. In a randomized study, a 1year post-transplant maintenance with BV was associated with better disease-free survival (DFS), although no impact on overall survival was observed. Similarly, checkpoint inhibitors (PD-1) are also explored for pediatric high-risk patients, with promising results[36,37,39].

Immunotherapy remains an experimental treatment in R/ R HL in children and young people and there are clinical trials in progress. It may be considered in high risk patients that were refractory to SDCT salvage regimens. Single agent Nivolumab achieves a low CR rate and combination of Brentuximab plus Nivolumab looks more promising[36]. Pembrolizumab was well tolerated in pediatric patients and showed encouraging antitumour activity in children with relapsed or refractory Hodgkin lymphoma, similar to the experience described in adult[40,41].

TANDEM transplantation is an alternative for patients considered at high-risk for relapses after autologous HSCT. This approach consists of a myeloablative autologous HSCT followed by a non myeloablative conditioning allogeneic transplant[42].

Allogeneic HSCT can be considered for post autologous HSCT relapses, as well as in cases of failure to harvest stem cells from the bone marrow or the peripheral blood and in cases of several relapses. The conditioning regimens are either myeloablative (MAC) or reduced intensity (RIC), with an expected graft versus lymphoma effect to reduce the risk of relapse. The overall survival is comparable in both MAC and RIC approaches, with relapses more like to occur after a RIC regimen, whereas toxicity is more common following MAC strategy. The choice between RIC and MAC should consider the patient clinical status, previous treatments and the perspective of adjuvant therapy[30].

As HLA identical related or unrelated donors are only available for a subset of patients, alternative donors often need to be found. Recently, the use of T-cell-replete haploidentical stem cell transplantation (haplo-HSCT) with post-infusion cyclophosphamide (PT-Cy) in advanced hematological malignancies showed a good toxicity profile. It has been observed that haplo- HSCT act effectively against HL cells (immunological effect) and is a good choice in the treatment of poor prognosis HL in patients who do not find a HLA compatible donor[43]. Comparative studies demonstrated that Allogeneic HSCT from full-matched and haploidentical donors have similar outcomes, there is a reduced relapse rate and better overall survival with post-Cyclophosphamide haplo-HSCT[44-46].

TABLE 1. Consensus recommendation for NHL

Subtype	2nd line treatment	HSCT	Conditioning regimen
BL	2-3 courses R-ICE or R-VICI	Autologous or allogeneic	Autologous - Busulfan based regimen Allogeneic – TBI or busulfan based, Burkitt-specific RIC
DLBCL	2-3 courses R-ICE	Autologous	Busulfan based regimen
LL	Intense treatment courses analogue to high-risk ALL or relapsed ALL protocols	Allogeneic	TBI based regimen
ALCL	Vinblastine, ICE	Allogeneic for high-risk patients Vinblastine if low risk, without HSCT	TBI or busulfan based regimen

Adapted from Burkhardt B, 2021[5]

TABLE 2. Risk Stratification for First Relapsed and Refractory Classical Hodgkin Lymphoma in Children and Young People

Low Risk Group	1.Early relapse after a maximum 4 cycles of first line chemotherapy. or 2. Late relapse after a maximum of 6 cycles of first line chemotherapy. And ALL of the following • Stage at relapse is I-III • No prior RT or relapse only outside prior RT field • No excessive RT fields required in salvage
Standard risk Group	1. Primary Progressive HL 2. Early Relapse after more than 4 cycles of first line chemotherapy 3. Stage IV relapse 4. Relapse in a prior RT field 5. Relapse requiring RT in salvage that is considered as having unacceptable toxicity
High Risk Group	High risk (HR) patients are those that fail to achieve a CMR after 2 lines of SDCT on PET4. Failure to achieve a CMR prior to HDCT is associated with an inferior prognosis compared to patients that achieve a negative FDG-PET scan pre-HDCT/ASCT.

Adapted from guidelines recommendations from Euronext pediatric Hodgkin lymphoma group

TABLE 3. Consensus recommendation for HL

Recommendation	Treatment options	Conditioning regimen
ASCT: Primary refractory disease Standard or high risk relapsed who respond to salvage therapy	Salvage therapy (chemo option pre ASCT) ICE ESAHP DHAP GDP GV	BEAM or CBV* Bu Mel – low risk patients Bu Mel Gen – high risk patients LEAM Be-EAM
Post-ASCT therapy	Radiotherapy Bulky disease (>5 cm) especially if not been previously irradiated) Primary refractory disease Persistent FDG-avid disease after salvage or after ASCT Brentuximab vedotin maintenance in high-risk patients	
Allo-HCT should be used for relapse after ASCT or failure to mobilization	Options for rescue: Chemo protocol Brentuximab	RIC: Fludarabin based regimens: - Flu Mel - Flu Bu MAC regimens: - TBI based - Bu Cy
Haplo option for patients with Allo-HCT indication, without MRD.		Cy Flu and TBI 2Gy Post-cy
Tandem SCT option for High Risk patients		ASCT: MAC Allo HCT: RIC

*BCNU is not available at this moment in Brazil

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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NEUROBLASTOMA

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Neuroblastoma (NB) is the most common extracranial solid tumor in childhood. Overall survival increased over time in this pathology from 34 to 68% for children aged 1 to 14 years. Much of this improvement is due to the implementation and adequate indication of high-dose chemotherapy with cell rescue[1]. Standard of care for patients with high-risk neuroblastoma includes multiagent chemotherapy induction, surgical tumor resection, consolidative high-dose chemotherapy with autologous stem cell transplant, posttransplant radiotherapy, and post-consolidation treatment with biological agents and immunotherapy[2]. Despite this multifaceted treatment, relapses still occur in 50% to 60% of patients in this risk group today3.

As mentioned above, the consolidation phase of high-risk regimens involves myeloablative chemotherapy and stem cell transplantation (SCT), which attempts to eradicate minimal residual disease using otherwise lethal doses of ablative chemotherapy rescued by autologous stem cells. Several large randomized controlled studies have shown an improvement in 3-year event free survival (EFS) for treatment with SCT versus conventional chemotherapy[4].

Current protocols use carboplatin/etoposide/melphalan (CEM) or busulfan/melphalan (BuMel) as conditioning regimen for SCT. Other myeloablative regimens, including CEM plus total body irradiation (CEM-TBI), cyclophosphamide-thiotepa (TC), single-agent melphalan, busulfan-melphalan-thiotepa (BuMelThio), and tandem transplantation with TC/CEM also have been used, with recent reports of improved outcomes with tandem transplantation[5-7].

The conditioning regimen for autologous transplantation should be determined based on the best result obtained within the crrent first-line treatment protocol. A prospective randomized study conducted by International Society Paediatric Oncologie Europe Neuroblastoma Group (SIOPEN) compared CEM versus BuMel conditioning regimen, after 8-10 induction cycles with high doses of platinum. Patients included in the BuMel regimen arm had improved disease-free survival and less toxicity. For this reason, BUMEL has become the standard conditioning regimen for children treated according to SIOPEN protocol[3].

Some recent data suggest that this regimen maintains its superiority when used in different treatment strategies, such as the COG group induction model that includes topoisomerase inhibitors, anthracyclines, high-dose cyclophosphamide and cisplatin.

A major concern is the accumulation of potential toxicities from these agents, including cardiotoxicity and hepatotoxicity. Recently, the results of a prospective multicenter pilot study (COG ANBL12P1) to examine the feasibility of BuMel and ASCT when administered after induction therapy according to the COG protocol were published. In it, acceptable pulmonary and hepatic toxicities were observed[7]. Within this context, additional consolidation regimen studies are underway to define the best ASCT conditioning regimen in high-risk neuroblastoma patients treated as per COG or similar protocols. Preliminary results today suggest the superiority of the BUMEL regime over the CEM also in these cases.

Regarding in tandem transplantation in neuroblastoma, several concerns regarding conditioning regimens and toxicity profile following different induction protocols still exist. Despite a trend towards improved response in some studies, the real benefit of in tandem transplantation is still being evaluated in international cooperative groups and is not routinely incorporated as a first-line treatment protocol.

Thus, it is suggested to use the conditioning regimen proposed by the patient's treatment protocol, avoiding extrapolation cases. Protocol variations must be careful and strict, not the rule.

Attention should be given to sinusoidal obstruction syndrome and thrombotic microangiopathy, conditions that may increase transplant-related mortality and are well- described complications of neuroblastoma stem cell transplantation.

While the role of autologous HSCT in neuroblastoma is well established, the use of allogeneic HSCT is controversial. Retrospective data analysis from the Center for International Blood & Marrow Transplant Research (CIBMTR) indicates that allogeneic HSCT may be useful in patients who have not previously undergone autologous HSCT. In those patients previously transplanted with autologous cells, the benefit of allogeneic HSCT after ASCT is dismal8. Recently, haploidentical stem cell transplantation is being evaluated in children with refractory/relapsing neuroblastoma[9], but the number of patients evaluated is still too small to assess the real benefit of this practice.

Postconsolidation therapy is designed to treat potential MRD after SCT, and consist of use of anti-GD2 therapy and isotretinoin. It is associated with improved 2-year event-free survival by 20% and overal survival by 11% in patients in high-risk neuroblastoma[10]. In 2021 Brazil has approved dinutuximab beta for use in this high risk patients, although the high costs of this medication will limit its routine use in near future.

Radiation therapy to consolidate local control after surgical resection of the primary tumor should be used. The optimal dose of radiation therapy has not been determined. Extensive lymph node irradiation, regardless of the extent of surgical resection preceding SCT did not provide a benefit to patients for local progression or OS[11].

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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC CHRONIC MYELOID LEUKEMIA

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ABSTRACT

Chronic myeloid leukemia (CML) accounts for approximately 2 to 3% of all pediatric leukemias. Compared to adults, children tend to present with more aggressive features, such as higher leukocyte counts and massive splenomegaly, and are more likely to be diagnosed with advanced stage disease. Before the advent of tyrosine kinase inhibitors, a couple of decades ago, allogeneic hematopoietic stem cell transplantation (allo-HSCT) was the mainstay of treatment for this disease. This, however, was associated with considerable treatment-related morbidity and mortality. Even so, despite its secondary and somewhat limited indication today, allo-HSCT remains an important alternative and the only curative treatment for CML. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society for Blood and Marrow Transplantation and Cellular Therapy (SBTMO) convened a task force to provide evidence-based guidance on the use of allo-HSCT for the appropriate management of childhood CML, the results of which are presented here.

Keywords: Hematopoietic Stem Cell Transplantation, Tyrosine Kinase Inhibitors, Chronic Myeloid Leukemia, Childhood, Pediatric, Consensus Guidelines.

Chronic myeloid leukemia (CML) accounts for approximately 2 to 3% of all childhood and adolescent (under 15 years old) leukemias[1]. These patients tend to present with more aggressive features, such as higher leukocyte counts and massive splenomegaly, and are more likely to be diagnosed with advanced stage disease[1]. Pediatric CML presents the same morphologic, cytogenetic and molecular features observed in adult CML. As such, it is characterized by the presence of the Philadelphia chromosome (Ph+), which results from a reciprocal translocation between the long arms of chromosomes 9 and 22 [t (9;22) (q34; q11)], which leads to the BCR-ABL fusion gene. This rearrangement encodes a new protein, with uncontrolled tyrosine kinase activity[2].

Despite their acknowledged applicability in the adult population, adult risk scores for CML cannot be applied to children, with the exception of the one defined by the European Treatment and Outcome Study, which is able to predict progression and long-term event free survival (EFS), but not overall survival (OS)[1,3,4]. Therefore, risk scores are not commonly used to guide treatment in pediatric patients with this disease.

Ever since the introduction of tyrosine kinase inhibitors (TKIs) in pediatric Ph+ CML, as in adults, notable changes have been observed in EFS and progression, as well as in the indication for hematopoietic stem cell transplantation (HSCT)4-6. Before the advent of TKIs, a couple of decades ago, allogeneic HSCT was the mainstay of treatment for this disease; even so, despite its secondary and somewhat limited indication today, it remains an important alternative and the only curative treatment for pediatric CML.

One of the major caveats of TKI-based therapy is that it should be used continuously, maybe lifelong, although this is still an unsolved issue. Moreover, TKIs are associated with a number of side effects, some of which are well known, such as growth delay and endocrine disorders, among others, not to mention potential long-term events[7,8]. Besides, the most appropriate approach to assessing treatment response remains unclear, and prospective studies are needed to better define the optimal timing for treatment discontinuation[1,5,6,9,10]. Allogeneic HSCT may thus help circumvent the long-term effects of indefinite TKI therapy in this population. One should, however, ponder the trade-off between its curative potential and its myriad acute and late toxicities when considering this treatment strategy.

Overall, outcomes of allogeneic HSCT tend to be superior in childhood CML as compared to those of adults with this disease, with an OS rate between 45 and 87%11-14. Some of the most favorable results may be explained by the improvement in supportive care measures and the use of reduced intensity conditioning regimens (RIC), adopted with a view to reducing the mortality risk associated with these procedures.

The choice of graft source might alter the results of HSCT for CML. A retrospective analysis of the Center for International Blood and Marrow Transplant (CIBMTR) showed worst EFS rates when peripheral blood stem cells (PBSC) were used when compared to bone marrow (BM) in children. Although the incidence of acute graft-versus-host disease (GVHD) was similar between children and adults, chronic GVHD rates were also higher in the group that used PBSC as stem cell source[15].

INDICATIONS FOR HSCT IN CML

In a study published in Leukemia in 2016, including 669 patients (among whom only 14 were younger than 20 years of age), 427 were eligible for transplant and randomized between drug therapy and HSCT, depending on related donor availability. The OS of the patients who underwent HSCT was 76% against 69% in the drug therapy arm. Additionally, superior rates of molecular remission were noted in the HSCT group (56% vs. 39%), and 56% of the HSCT patients were no longer in need of drug treatment, as compared to only 6% of those in the non-transplant group[16].

There are no robust studies to date in the pediatric population comparing TKIs and HSCT in the treatment of CML. As a rule, treatment is similar to the one applied in adults, where HSCT is indicated after failure of a second generation TKI or in advanced stage (accelerated and blast phase) disease17. In specific cases, HSCT may be indicated after failure of a first line TKI (imatinib mesylate), or when there is a T315I mutation[17]. As for third line TKIs (ponatinib), further studies are needed to better define their efficacy and safety in this population. As previously mentioned, the possibility of adverse events and of poor adherence to the long-term use of TKI, coupled with the potential for curing the disease with HSCT, should be carefully weighed and conditioned upon shared decision-making with the patient and his/her family, on a case-by-case basis, when choosing the best treatment approach for this population18-22.

In summary, the main indications for HSCT in children with CML are17:

1) Accelerated phase (AP) or blast phase (BP) at the time of diagnosis;

2) Progression to AP or BP. T315I mutation is associated with poor prognosis; children with this mutation may rapidly progress to BP; treatment failure with 1st (imatinib) and 2nd generation (dasatinib, nilotinib) TKI; benefits of the use of 3rd generation TKI are not well known in this population;

3) Poor adherence to TKI treatment (upon discussion of the possible benefit of HSCT in this situation);

4) Severe toxicities related to the use of TKIs.

CONDITIONING REGIMEN

A recent prospective, non-randomized study from a Japanese group compared results between RIC HSCT plus imatinib vs. imatinib alone in the treatment of young adults (including children) with CML in early (<12 months) chronic phase (CP) or late (≥12 months) CP, with a median age of 34 (11-49) years23. In this study, patients undergoing HSCT were conditioned with fludarabine 30mg/m2/day from D-10 to D-5, oral busulfan 4mg/kg/day or intravenous busulfan 3.2mg/kg/day from D-6 to D-5, and Thymoglobulin® – rabbit anti-thymocyte globulin (Fresenius®) 5mg/kg/day from D-4 to D-1. GVHD prophylaxis consisted of cyclosporine, mycophenolate mofetil (MMF), and methotrexate. In this group, imatinib was also used at a dose of 400mg/day, three to 12 months before HSCT, and, as a prophylactic drug, at a dose of 300mg to 400mg/day, from D+100 until 1 year after transplant. Prolonged treatment with a higher dose of imatinib was used for patients with

persistent residual disease or hematologic or cytogenetic relapse. In these cases, the drug was only discontinued 12 months after complete cytogenetic remission. Patients in the imatinib-only group took the usual 400mg/day dosage, with adjustments according to toxicity and response. The estimated 10-year OS and EFS were comparable between the groups. In the late CP CML group, although both treatments resulted in similar survival, a worse 10-year EFS was noted in the imatinib-alone group as compared to the HSCT + TKI group (40.8 vs. 66.7%, p = 0.047, respectively). Of note, HSCT patients with higher European Group for Blood and Marrow Transplantation (EBMT) risk scores had a worse OS than those with lower scores (69.2 vs. 92.9%, p = 0.04). The authors concluded that HSCT in combination with imatinib seems more cost-effective than imatinib alone and should be considered as an appropriate option, particularly for patients with low EBMT risk scores and for whom cure of CML is the ultimate goal.

Regarding haploidentical HSCT for pediatric CML, there are only a few studies available to date, all of which are limited to retrospective analyses of a small number of cases. Hence, further studies are needed to better define the role of this transplant modality in this population[24,25].

RECOMMENDATIONS:

1. Related donor HSCT: fludarabine + busulfan (RIC)23 or busulfan + cyclophosphamide (myeloablative)12. GVHD prophylaxis: cyclosporine + methotrexate.
2. Unrelated donor HSCT: fludarabine + busulfan + anti-thymocyte globulin (RIC)23 or busulfan + cyclophosphamide + anti-thymocyte globulin (myeloablative)12. GVHD prophylaxis: cyclosporine + methotrexate.

USE OF TYROSINE KINASE INHIBITORS AFTER HSCT

In the study by Zhao Y et al., 2017, imatinib was used prophylactically at a dose of 300mg to 400mg/day from D+100 until 1 year after HSCT. In patients with persistent residual disease, or with hematologic or cytogenetic relapse, a higher dose of imatinib (600mg/day) was used for at least 1 year after achieving complete cytogenetic remission[23].

In case of disease progression while using imatinib prior to transplant, one should switch to another generation TKI (dasatinib, nilotinib, or other), according to one's clinical history and mutational status.

STRATEGIES TO AVOID DISEASE RELAPSE

A few strategies can be used to avoid disease relapse after HSCT, as presented in the ASH Educational Program published in Hematology in 2018[17]:

1. Minimize pre-transplant disease burden;
2. Optimize conditioning regimen;
3. Optimize the graft-versus-leukemia (GVL) effect: minimize post-transplant immunosuppression and use prophylactic donor lymphocyte infusion (DLI).

Importantly, disease status should be regularly monitored in children with CML, with molecular and cytogenetic studies, following the National Comprehensive Cancer Network (NCCN), European Leukemia Net (ELN), or European Society of Medical Oncology (ESMO) guidelines, both pre- and post-transplant, since this will allow for appropriate and timely interventions according to optimal treatment response assessments[5].

Chronic myeloid leukemia	Allogeneic HSCT	Autologous HSCT
Chronic phase	Yes (standard of care, clinical evidence)	No
1st chronic phase refractory to TKIs	Yes (standard of care, clinical evidence)	No
1st chronic phase intolerant to TKIs	Yes (standard of care, clinical evidence)	No
Accelerated phase	Yes (standard of care, clinical evidence)	No
Blast phase	Yes (standard of care, clinical evidence)	No

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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC ACUTE MYELOID LEUKEMIA

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ABSTRACT

Acute myeloid leukemia (AML) represents 15%–20% of acute leukemias in children, and the risk of treatment failure is based on genetic risk and response to therapy1-4. Although the initial remission rate exceeds 90%, more than 30-40% of children with AML die of refractory/relapsed disease or treatment-related toxicity5. The best therapeutic results are achieved by integrating intensive chemotherapy, optimal supportive care, and hematopoietic stem cell transplant (HSCT) adapted to each patient's risk of relapse6–9. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) and the Brazilian Society for Pediatric Oncology (SOBOPE) convened a task force to provide general guidance on HSCT for childhood AML to provide evidence-based guidance for the appropriate management of this disease.

Keywords: Hematopoietic Stem Cell Transplantation. Pediatric Acute Myeloid. Leukemia. Clinical Guidelines

Acute myeloid leukemia (AML) represents 15%–20% of acute leukemias in children, and the risk of treatment failure is based on genetic risk and response to therapy[1-4]. Although the initial remission rate exceeds 90%, more than 30-40% of children with AML die of refractory/relapsed disease or treatment-related toxicity[5]. The best therapeutic results are achieved by integrating intensive chemotherapy, optimal supportive care, and hematopoietic stem cell transplant (HSCT) adapted to each patient's risk of relapse[6–9]. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) and the Brazilian Society for Pediatric Oncology (SOBOPE) convened a task force to review and update the main indications for HSCT for childhood AML based on previous guidelines, intending to provide evidence-based guidance for the appropriate management of this disease.

Currently, HSCT is not recommended for patients in first clinical remission (CR1) when they are classified as low or intermediate risk. Patients classified as high risk, either because of genetic/molecular factors or measurable disease after induction therapies, will be referred for HSCT in CR1.

With the evolution of methods for detecting genetic/molecular alterations, including the greater availability of gene sequencing techniques, novel genetic alterations have been correlated with different clinical

and prognostic characteristics. Recent studies have demonstrated new alterations and their clinical, morphological, immunophenotypic and prognostic correlates[10]. The implication of new genetic/molecular markers in AML is evolving. For example, AML with KMT2A rearrangements include AML subtypes with with disparate outcomesFor instance, AML cases with t (6; 11) (q27; q23), t (10; 11) (p12; q23) and t (10; 11) (p11.2; q23) have high relapse rates, while patients with t (1; 11) (q21; q23) have an excellent. outcomesThe t (9; 11) (p12; q23) is associated with intermediated risk when occurring in monoblastic or myelomonoblastic leukemia , but a high risk when associated with with acute megakaryoblastic.[6]. The table below show the abnormalities with a more consolidated prognostic impact.

TABLE 1 - Molecular genetic abnormalities with prognostic impact in Pediatric AML

FAVORABLE
t t(15;17)/PML-RARA
t(8;21)/RUNX1-RUNX1T1
inv(16)(p13.1;q22)/CBF β -MYH11
t(16;16)(p13.1;q22)/CBF β -MYH11
t(1;11) (q21;23)/ MLL AF1Q
NPM1 mutated without FLT3/ITD
Biallelic Mutation CEBPA
M6 or M7 with GATA-1 in Down Syndrome or mosaic for Down syndrome*1
UNFAVORABLE
-7
-5/del5q
t(6;11)(q27;q23)/MLLT4-KMT2A
t(10;11)(p12;q23)/MLLT10-KMT2A
t(10;11)(p11.2;q23)/ABI1-KMT2A
t(6;9)/DEK-CAN (NUP214)
t(8;16)(p11;p13)/MYST3-CREBBP
t(16;21)(q24;q22)/ RUNX1-CBFA2T3
t(5;11)(q35;p15.5)/NUP98-NSD1
t(9;22) (q34;q11)/ BCR/ABL
inv(16)(p13.3q24.3)/CBFA2T3-GLIS2 in megakaryoblastic LMA*2
t(11;15)(p15;q35)/NUP98-KDM5A
Complex karyotype (≥ 3 changes)
FLT3/ITD
FAB MO, M6 e M7 without t(1;22) or without GATA-1
Secondary AML (Myelodysplastic Syndrome or previous treatment)

*1 Mast KJ, et al. Pathologic Features of Down Syndrome Myelodysplastic Syndrome and Acute Myeloid Leukemia: A Report From the Children's Oncology Group Protocol AAML0431. Arch Pathol Lab Med. 2020 Apr;144(4):466-472.
*2 Gruber TA, et al. An inv(16)(p13.3q24.3)-encoded CBFA2T3-GLIS2 fusion protein defines an aggressive subtype of pediatric acute megakaryoblastic leukemia*Cancer Cell. (2012) 13; 22(5): 683–697.

In recent years, the measurement of residual disease (MRD) has been incorporated as an additional risk stratifier in the treatment of pediatric AML, usually after the induction cycles. Due to the different methodologies to assess residual disease, the clinical value of MRD is still evolving and should . interpreted within the context of specifictherapeutic protocols.

In countries with limited resources, there is great difficulty in reproducibility and standardization of the methodology used in flow cytometry to quantify low levels of residual disease in AML, which makes interpreting these results and determining their impact on clinical decisions very complex.

Considering the difficulties mentioned above, patients classified as low or intermediate risk, who are referred to HSCT only because they have detectable levels of residual disease after the induction phase, will be evaluated individually. If necessary, the review of MRD tests will be performed by immunophenotyping by the Brazilian Group of Flow Cytometry (GBCFlux) for further definition of the indication of HSCT by the Pediatric Group of SBTMO and by the Study Group on Acute Myeloid Leukemia (GELMAI) of the Brazilian Society of Pediatric Oncology (SOBOPE)5.

TABLE 2 - Risk classification based on diagnostic characteristics associated with MRD

Low Risk	Favorable genetic alterations and MRD ≤ 1% after the first cycle induction
Intermediate Risk	Patients who do not have criteria for low or high risk
High Risk	Unfavorable genetic alterations or MRD ≥ 0,1% after the second cycle of induction

In relapses, a second remission is attained in about two-thirds of patients with AML; however, lasting remissions in these cases are rare with chemotherapy regimens. Thus, in relapses, allogeneic bone marrow transplantation is always indicated, preferably soon after obtaining a new remission.[11,12]

A recent study reviewing the outcomes of 1940 pediatric AML patients treated with the BFM protocol, from 1987 to 2012, demonstrated that although EFS has remained similar since the 1990s, improvements in supportive care and HSCT have made patients who attained a second remission (CR2) potentially cured, and this resulted in an increase of approximately 20% in OS in the last 30 years.[11]

In a study with Brazilian HSCT centers for children, adolescents, and young adults, OS and EFS in 4 years were 47% and 40%, respectively.[12] Brazilian outcomes of HSCT in children with AML appear to be inferior to those reported in the United States and Europe. A report by Bitan et al. from the Center for International Blood and Marrow Transplant Research (CIBMTR) on 141 pediatric patients with AML who underwent the transplant in CR1 showed a 5-year PFS of 54% after myeloablative conditioning[13]. Data from the British MRC10 and MRC12 trials showed a 5-year OS of 68% in children who received marrow transplants from matched sibling donors[14]. The Nordic Society of Paediatric Haematology and Oncology (NOPHO) reported a 3-year EFS of 61% in children who underwent the transplant in CR[8]. Locatelli et al. analyzed the outcomes of 243 children with high-risk AML in CR1 who were enrolled in the AIEOP-2002/01 protocol and underwent either allogeneic (n =141) or autologous (n=102) HSCT. The 5-year probability of disease-free survival was 73%[15]. Finally, an AML SCT-BFM study aimed at standardizing pediatric HSCT for AML across centers in Germany and Austria reported 4-year EFS and OS of 61% and 70%, respectively[16].

The main prognostic factor for the success of HSCT in patients with AML remains the stage of the disease. CIBMTR data show 3-year OS of 70%, 65% and 31%, respectively, for patients under 18 years of age undergoing related HSCT in early (CR1), intermediate (CR2) and advanced stages (active disease or ≥ CR3) of LMA[17]. Patients with treatment-refractory AML or with more than one relapse still have a dismal prognosis[18].

The results of transplants using related, unrelated (matched or partially matched, with a greater than a 8/10 HLA-match) and haploidentical donors are very similar in AML, with no significant difference between type of donor, whether in overall survival, incidence of acute or chronic graft-versus-host disease (GVHD)[12,19]. In children, bone marrow is preferable in comparison to peripheral blood (PB) as stem-cell source, given the higher extensive chronic GVHD and transplant-related mortality with the use of peripheral blood stem cells[20,21]. The use of Umbilical Cord Blood is associated with higher transplant-related mortality in Brazil and should only be used by centers experienced with this stem cell source[22].

To date, the benefit of autologous marrow transplantation has not been proven when compared to isolated intensive chemotherapy and/or to allogeneic transplantation for non-promyelocytic AML in 1st CR. Thus, autologous transplantation as consolidation should be considered investigational. Conditioning with busulfan area under the curve (AUC) 4000-5000 µMol.min and melphalan total dose (TD) 140 mg/m2 is currently recommended[23-25].

As for conditioning in allogeneic transplants, there are better results (toxicity vs relapse) with the use of myeloablative protocols based on busulfan (BU) AUC 4000-5000 µMol.min or based on Total Body Irradiation (TBI) [16, 26-32].

Although transplantation for active disease (≥ 5% blasts in the bone marrow) is controversial, but in cases with adequate performance, benefit from the adapted FLAMSA conditioning scheme has been reported.[33-35]

FLAMSA regimen:

- Intrathecal chemotherapy D-14
- Etoposide: 150 mg/m2/day, D-13 to D-10
- Fludarabine: 30 mg/m^2/day, D-13 to D-10
- Cytarabine: 2000 mg/m2/day, D-13 to D-10 (4 h after fludarabine)
- Cyclophosphamide: 60 mg/kg/day, D-3 and D-2
- Mesna (1.4 x dose of cyclophosphamide, divided into 5 doses: 0, 3, 6, 9 and 12 hours of cyclophosphamide)
- Busulfan 4.8 mg/kg/day, D-6 and D-5
- If available AUC for busulfan (target 4000-5000 µMol.min), start busulfan one day earlier, then leave one day off the drug, to wait for the result and make necessary adjustments on the day after the break.
- Donor lymphocyte infusion (DLI): D+21 (106 CD3/kg), D+35 (5x106 CD3/kg), D+60 (5x106 CD3/kg), start DLI regardless of haematological engraftment, suspend in case of GVHD
- Azacitidine 75 mg/m2/day, for 5 consecutive days, with 1, 2, 3, 4 and 5 months after transplantation (total of 5 cycles)

Due to important differences in the transplant-related mortality rates (MRT) related to age and conditioning regimen, according to the risk/benefit and rates of Event-Free Survival (EFS) and Overall Survival (OS) for patients in pre-HSCT remission, investigators propose different conditioning for children over or under 6 years of age[36,37,38].

The preparatory regimen will consist of busulfan, cyclophosphamide and melphalan in those six years of age or older. The decision to adopt a preparative regimen containing a combination of three alkylating agents was based on several factors. First, the addition of a third alkylating agent was based on results of a preliminary study by Locatelli et al.[37], which demonstrated the safety of combining melphalan with busulfan in children, and in the fact that the analysis

A retrospective study of the EWOG-MDS group observed that a conditioning regimen containing a second alkylate was associated with a better EFS and a lower incidence of relapse when compared to regimens employing total body irradiation (TBI)[38]. Strahm published a TRM rate of 21% in a total cohort of children presenting a "BuCyMel" for advanced myelodysplastic syndromes[36]. Analyzing age groups separately, this MRT was considerably higher in those aged 12 years and over. With the increasing number of AML SCT-BFM 2007 recruitment, an identical MRT pattern has been reported for children and adolescents undergoing transplantation after "BuCyMel" for AML. An MRT of 32% in patients 12 years of age or older was considered unacceptable, while children under 12 have an excellent result after "BuCyMel," having an MRT rates below 10%. Therefore, we continue to recommend "BuCyMel" for younger children who are eligible for the treatment group.

Description of the "BuCyMel" scheme:

- Cyclophosphamide: 60 mg/kg/day, D-4 and D-3 (start 24 h after busulfan)
- Mesna (1.4 x dose of cyclophosphamide, divided into 5 doses: 0, 3, 6, 9 and 12 hours of cyclophosphamide)
- Melphalan 140 mg/m^2/day D-2
- Busulfan (per kg according to the table 3), D-8, D-7, D-6, D-5
- If available AUC for busulfan (target 4000-5000 µMol.min), start busulfan one day earlier, then leave a day without the drug, to wait for the result and make necessary adjustments the day after the break.

For children over 6 years old, the proposed scheme is the "BuFluMel":

- Fludarabine 30 mg/m2/day from D-7 to D-3
- Busulfan (per kg according to the table 3), D-7, D-6, D-5, D-4
- Melphalan 140 mg/m2/day D-2
- If available AUC for busulfan (target 4000-5000 µMol.min), start busulfan one day earlier, then leave a day without the drug, to wait for the result and make necessary adjustments the day after the break.

TABLE 3- Busulfan Dosage

Weight in kg	Busulfan dose (mg/kg/day)	Cumulative Dose of Busulfan (mg/kg)
≤9	4,0	16,0
> 9 - ≤16	4,8	19,2
>16 - ≤23	4,4	17,6
>23 - ≤34	3,8	14,2
> 34	3,2	12,8

The recent advent of haploidentical transplantation has made the search for a donor more agile, and as a consequence, has allowed transplants to be carried out for a larger number of patients. According to the exciting results presented by Jaiswal, for transplants with haploidentical donors, the suggested scheme is the one using busulfan AUC 4000-5000 µMol.min and melphalan (MEL) total dose (TD) 140 mg/m2, associated with fludarabine (FLU) TD 150 mg/m2. The infusion of donor lymphocytes on D+21, D+35 and D+60 had a positive impact on the outcome of patients with advanced disease/worse prognosis.

Depending on the experience of each Transplant Unit, there is the possibility of adopting other conditioning protocols.

About the Graft-versus-Host Disease (GVHD) prophylaxis regimen:

- In HLA-matched sibling donor (MSD) allo-HSCT, calcineurin inhibitors (Cyclosporine – CSP 2mg/kg or Tacrolimus – TAC 0.05mg/kg in two divided I.V. doses a day) as a single agent should be started on D-1, and switched to their corresponding P.O. formulations, with strict dose adjustment based on serum levels (100-200mcg/L for CSP and 5-15ng/ml for TAC), until 3 months after transplant, with subsequent tapering, in the absence of graft-versus-host disease (GVHD)[40-42].

- In HLA-matched unrelated donor (MUD) HSCT, calcineurin inhibitors (Cyclosporine – CSP 2mg/kg or Tacrolimus – TAC 0.05mg/kg in two divided I.V. doses a day) as a single agent should be started on D-1, and switched to their corresponding P.O. formulations, with strict dose adjustment based on serum levels (100-200mcg/L for CSP and 5-15ng/ml for TAC), until 3 months after transplant, with subsequent tapering, in the absence of graft-versus-host disease (GVHD)[40,42].

  **The use of single-agent, post-transplant cyclophosphamide (PTCy) at a dose of 50mg/kg two days between D+3 and D+4 has shown similar results regarding GVHD control, although further studies are awaited in order to define the optimal regimen in terms of long-term outcome for these patients* [43-45].

- In unrelated allo-HSCT, CSP (at the same dose as that for related donor transplants) combined with methotrexate (MTX) for a short period of time (i..e, on days +1, +3, +6 and +11) is the standard prophylactic regimen. MTX is used at an initial dose of 15mg/m^2, followed by three doses of 10mg/m^2, TAC at a total daily dose of 0.05mg/kg can also be used, with similar results[40,42]. In contrast, the combination of mycophenolate mofetil (MMF) with CSP was shown to be less effective [43-45].

- Although the use of anti-thymocyte globulin (ATG), primarily for the prevention of GVHD, has been consolidated in unrelated donor HSCT in adults, there is limited evidence as to its benefit in the pediatric population, even though it is used in most protocols. In a randomized study comparing different dose regimens of ATG, use of ATG at lower doses (4,5 – 6 mg/kg) could reduce the rate of infection while maintaining similar acute and chronic GVHD rates, as well as relapse rates. The investigators concluded that low-dose ATG should be the standard serotherapy regimen for URD HCST in children with hematologic malignancies[46], even though it should be borne in mind that the different ATG formulations available have variable immune responses, which may hinder any definitive conclusions as to its real benefit in this regard.

- In haploidentical HSCT, cyclophosphamide is generally used at a dose of 50mg/kg/day, in a 2-hour infusion, on D+3 and D+4, coupled with mesna (100-160% of the cyclophosphamide dose), in combination with a calcineurin inhibitor (CSP or TAC) and MMF (15mg/kg/dose q8h; maximum dose 2g/day), both starting on D+5. Both these immunosuppressants are usually kept for 3 months post-transplant[47,48].

As for UCB transplantation, the immunosuppressive regimen usually comprises the combination of a calcineurin inhibitor with MMF. Studies on the association of CSP with low-dose MTX or with corticosteroids have yielded worse results, as well as a greater graft failure rate[42].

Best time points for MRD assessment:

Pre-HSCT: MRD assessments should be made immediately before allo-HSCT.

Post-HSCT: MRD assessments by multiparameter flow cytometry (MFC) and/or reverse transcription quantitative polymerase chain reaction (RT-qPCR) are accurate in predicting relapse at days +30, +60, +90, and +180 post-HSCT.

Any detectable MRD level on days +180 and +365 post-HSCT is highly predictive of relapse and poor survival[49]. When decisions that may change patient management are based on low levels of MRD, we would recommend that the SBTMO – MRD Working Group GBFLUX may review the flow cytometric data to increase accuracy of the results.

Despite the immunological effect of the grafted cells against leukemia, the toxicity and mortality related to the procedure remain large barriers. The heterogeneity of data related to patient selection, type of conditioning for HSCT and donors makes data interpretation difficult in the pediatric population, particularly in developing countries, but procedure-related mortality is estimated to be between 10-25% in our country[12].

Another key point for better results is carrying out the transplant without delay, which is hampered by the scarcity of beds for patients dependent on the public health system. Patients in first and second remissions are potentially curable with HSCT, but from the second relapse and/or when the patient has active disease, there is a drastic reduction in the chances of cure. Delaying the procedure is harmful both due to the risk of losing the remission status as well as exposure to the toxicity of a new cycle of chemotherapy, which can worsen the child's performance for transplantation, or even be fatal[12].

We recommend in the AML the HLA typing of the patient, parents and siblings at diagnosis. If no related donor is identified, collect the patient's anti-HLA antibody test and start search for a donor at REDOME.

Once the indication for transplantation is confirmed, the interaction between the pediatric oncologist and the transplant center is essential for the prompt donor search and planning of the procedure.

Currently, advances have been achieved, in particular through the connection between the Brazilian Societies of Bone Marrow Transplant – SBTMO, of the Pediatric Oncology Society – SOBOPE, theFlow Cytometry – GBFlux and the Brazilian Association of Hematology, Hemotherapy and Cell Therapy -ABHH, in the challenging goal of improving the treatment of children and adolescents with AML. These efforts will also contribute to agreater knowledge of Brazilian experience.

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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative approach to children and adolescents with high-risk acute lymphoblastic leukemia (ALL) at diagnosis or relapsed disease. Nonetheless, despite the graft versus leukemia (GVL) effect, treatment-related morbidity and mortality remains a major challenge. Moreover, the significant heterogeneity of the available data on the selection of patients, type of conditioning regimen, and type of donor hampers any definitive conclusions in the pediatric population. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) and the Brazilian Society for Pediatric Oncology (SOBOPE) convened a task force to provide general guidance on HSCT for childhood ALL to providing evidence-based guidance for the appropriate management of this disease.

Keywords: Hematopoietic Stem Cell Transplantation;. Pediatric Acute Lymphoblastic Leukemia . Clinical Guidelines

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative approach to children and adolescents with high-risk acute lymphoblastic leukemia (ALL) at diagnosis or relapsed disease. Nonetheless, despite the graft versus leukemia (GVL) effect provided by this procedure, treatment-related morbidity and mortality remains a major challenge in this scenario. Moreover, the significant heterogeneity of the available data on the selection of patients, type of conditioning regimen, and type of donor hampers any definitive conclusions in the pediatric population (1).

In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) and the Brazilian Society for Pediatric Oncology (SOBOPE) convened a task force to review and update the main indications for HSCT for childhood ALL based on previous guidelines, with a view to providing evidence-based guidance for the appropriate management of this disease (Table 1).

TABLE 1: HSCT indications for pediatric ALL

HSCT indications for pediatric ALL in first remission:
ALL diagnosed before 6 months of age associated with MLL (KMT2A) rearrangement and with other risk factors, such as hyperleukocytosis (> 300,000/mm3) and non-response to corticosteroids.
Children who fail induction therapy (M2/M3 marrow), except if hyperdiploid ALL and age less than 6 years.
The current evidence does not support the use of HSCT in first remission for children with Ph+ (Bcr/Abl) ALL and hypodiploidy who have a good response to chemotherapy (CT).
HSCT is indicated for B- or T-cell ALL in first remission in patients with an MRD equal to or greater than 10-3, or 0.1%, by the end of the consolidation phase (i.e., after approximately 12 weeks of treatment)
HSCT indications for pediatric ALL in *second remission:*
Early bone marrow (BM) relapse of B-cell ALL (< 36 months after first remission). In late BM or extramedullary relapse of B-cell ALL, CT and HSCT exhibit similar results, so HSCT should be preferred, except in cases with persisting MRD positivity.
Early isolated extramedullary relapse of B-cell ALL (< 18 months of first remission).
Any, early or late, medullary, or extramedullary, relapse of T-cell ALL.

HSCT indications for pediatric ALL in *first remission*: Despite the different classification schemes and array of biologic and molecular risk factors recognized as highly relevant in the past, the advancements seen in the last few years have identified suboptimal response or persistence of minimal residual disease (MRD) after induction and consolidation therapy as the main risk factors indicating the benefit of HSCT [2,3], provided a minimal sensitivity of 10^{-4} (by analyzing a minimum of 1 million cells) technique and standardized protocol are used.

Of note, the choice, suitability, and definitions of the protocol to be used in the first-line treatment of childhood ALL are key when considering referral for transplantation in first remission. Indications not guided by defined protocols are:

HSCT is indicated for B- or T-cell ALL in first remission in patients with an MRD equal to or greater than 10^{-3}, or 0.1%, by the end of the consolidation phase (i.e., after approximately 12 weeks of treatment) [2,4,5,6].

HSCT in first remission for infants with ALL diagnosed before 6 months of age associated with *MLL (KMT2A) rearrangement* and with other risk factors, such as hyperleukocytosis (> 300,000/mm^3) and non-response to corticosteroids (7).

HSCT in first remission is indicated for children who fail induction therapy (M2/M3 marrow), except if hyperdiploid ALL and age less than 6 years (1,8,9).

The current evidence does *not* support the use of HSCT in first remission for children with Ph+ (*Bcr/Abl*) ALL and hypodiploidy who have a good response to chemotherapy (CT) [9, 10, 11].

HSCT indications for pediatric ALL in *second remission*: Early bone marrow (BM) relapse of B-cell ALL (< 36 months after first remission). In late BM or extramedullary relapse of B-cell ALL, CT and HSCT exhibit similar results, so CT should be preferred, except in cases with persisting MRD positivity [12, 13].

Early isolated extramedullary relapse of B-cell ALL (< 18 months of first remission).

Any, early or late, medullary, or extramedullary, relapse of T-cell ALL (13).

In third remission: From third remission onwards, survival at 5 years after HSCT varies between 26 and 33%, as compared to 15% after CT. Patients without morphological remission do *not* benefit from transplantation [14].

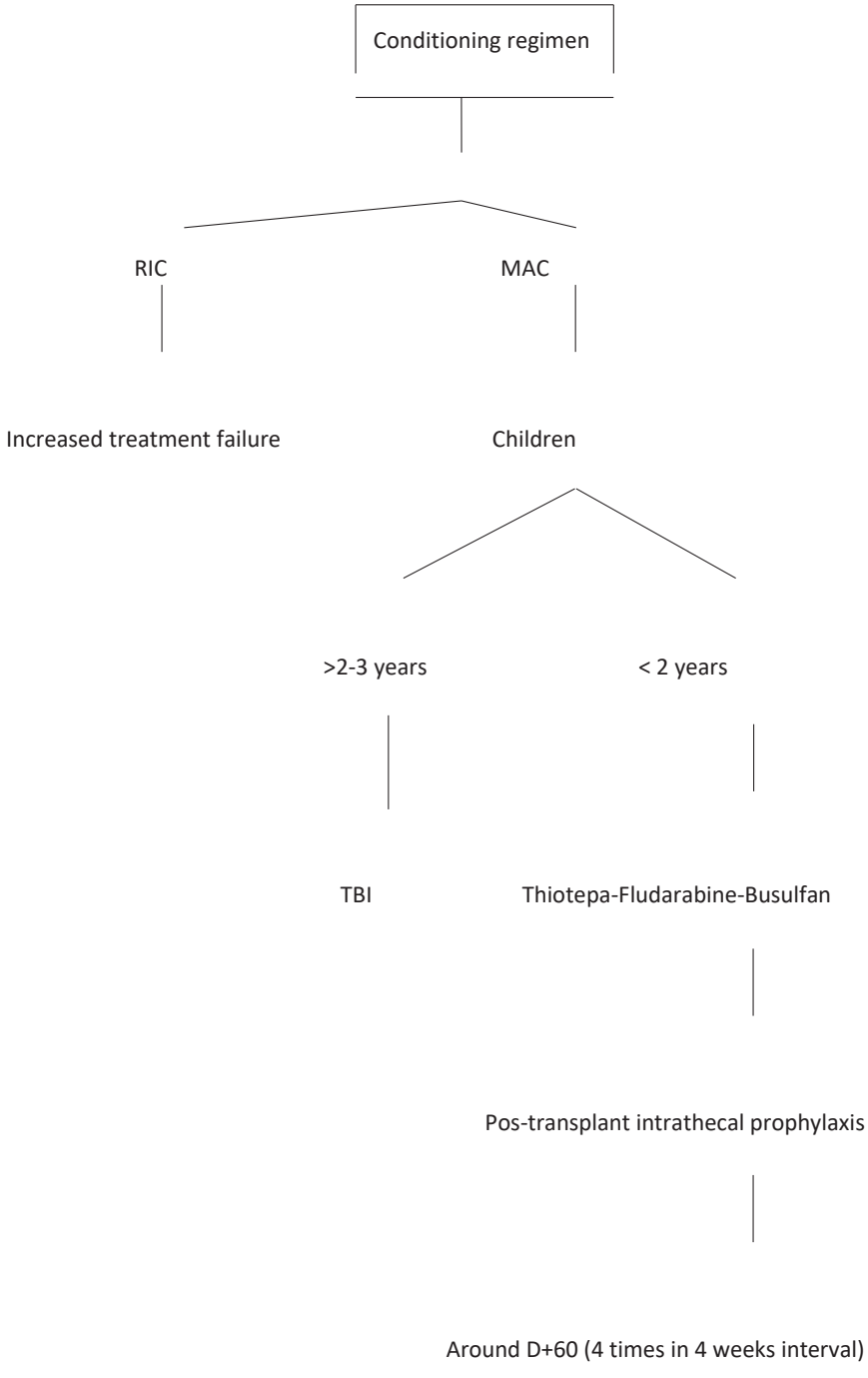
WHICH IS THE BEST DONOR AND STEM-CELL SOURCE?

Despite the better overall survival (OS) and mortality results seen with HLA-matched sibling donor transplants, there is current evidence that unrelated donors with a greater than 8/10 HLA-match and haploidentical donors provide fairly similar results [15, 16, 17]. In children, bone marrow is preferable in comparison to peripheral blood (PB) as stem-cell source, given the higher extensive chronic GVHD and transplant-related mortality (TRM) with the use of PB stem cells [8, 18]. The use of Umbilical Cord Blood (UCB) is associated with higher TRM in Brazil and should only be used by centers experienced with this stem cell source [19].

WHICH IS THE BEST CONDITIONING REGIMEN?

Myeloablative conditioning (MAC) regimens remain the standard of care for HSCT in childhood ALL. Reduced intensity conditioning (RIC) has not been shown to be of benefit in the treatment of ALL due to increased treatment failure (Figure 1) [20].

FIGURE 1. Flowchart of conditioning choice for Pediatric Acute Lymphoblastic Leukemia



Even though most children with ALL undergo HSCT with myeloablative conditioning regimens including total body irradiation (TBI), recent studies are trying different CT-based protocols to effectively replace TBI, particularly in children under 2 years of age. However, a retrospective study comparing TBI versus CT showed that TBI-based conditioning has better outcomes (OS and non-relapse mortality) and is the standard of care in the treatment of ALL in children older than 2-3 years old [21]. The only prospective trial randomizing children older than 4 years to conditioning therapy with TBI - Etoposide or Thiotepa - Fludarabine - Busulfan (or Treosulfan) demonstrated superiority of TBI in terms of lower relapse rate, TRM, and improved OS (91% vs. 75%, p<0.0001) [22].

Central nervous system (CNS) boost irradiation in the context of TBI is less commonly indicated but could be useful in certain scenarios (CNS involvement at diagnosis or at relapse) for treating and preventing CNS relapse after allo-HSCT [22,23].

The International "Forum" protocol also recommends post-transplant intrathecal prophylaxis whenever TBI is not part of the conditioning therapy. They suggest four weekly triple intrathecal administrations starting around D+60 if the patient is already stable and with greater than 50.000 platelets/mm3[22].

TBI has historically been used in combination with high doses of cyclophosphamide (120mg/kg), with favorable OS and event-free survival (EFS) results, yet considerable short- and long-term toxicity. Over the past few years, the association of TBI with etoposide (60mg/kg) has yielded somewhat better results in respect to OS, disease-free survival (DFS), and TRM [22]. The incorporation of other drugs to the preparative regimen, such as thiotepa, fludarabine, and melphalan would need further studies.

WHAT IS THE BEST GRAFT-VERSUS-HOST DISEASE (GVHD) PROPHYLAXIS REGIMEN IN CHILDHOOD ALL?

In HLA-matched sibling donor (MSD) allo-HSCT, calcineurin inhibitors (Cyclosporine – CSP 3 mg/kg or Tacrolimus – TAC 0.05mg/kg in two divided I.V. doses a day) as a single agent should be started on D-1, and switched to their corresponding oral formulations, with strict dose adjustment based on serum levels (100-200mcg/L for CSP - or 80 and 130 ng/mL if the methods measure CSP without its metabolites as fluorescence polarization immunoassay (FPIA) and enzyme-multiplied immunoassay technique (EMIT)- and 5-15ng/ml for TAC), until 3 months after transplant, with subsequent tapering, in the absence of graft-versus-host disease (GVHD)(24,25,26,27). In HLA-matched unrelated donor (MUD) HSCT, prophylaxis with short-term methotrexate (MTX) combined with either CSP or TAC showed similar results. The use of single-agent, post-transplant cyclophosphamide (PTCy) at a dose of 50mg/kg for two days on D+3 and D+4 (or D+5) has shown similar results regarding GVHD control, although further studies are awaited to define the optimal regimen in terms of long-term outcome for these patients (Table 2) [28,29, 30].

TABLE 2. GRAFT-VERSUS-HOST DISEASE (GVHD) PROPHYLAXIS REGIMEN IN CHILDHOOD ALL

MSD	CSP 2mg/kg or TAC 0.05mg/kg in two divided IV doses– started on D-1 (SL CSP: 100-200mcg/L or TAC: 5-15 ng/ml)
MUD	Short-term MTX (D+1, D+3, D+6)* + CSP or TAC
HAPLO	PTCy 50mg/kg (D+3 and D+4)** + CSP or TAC + MMF 15mg/kg/dose q8h; max 2g/day – started on D+5
UCB	Combination of CSP or TAC + MMF 15mg/kg/dose q8h; max 2g/day

*MTX is used at doses of 10mg/m2, all of which with leucovorin rescue after 24h
**coupled with mesna (100-160% of the Cy dose)
MSD, matched sibling donor; CSP, cyclosporin; TAC, tacrolimus; SL, serum levels; MTX, methotrexate; MUD, matched unrelated donor, HAPLO, haploidentical; PTCy, post-transplant cyclophosphamide; MMF, mycophenolate mofetil; UCB, umbilical cord blood

In unrelated allo-HSCT, CSP (at the same dose as that for related donor transplants) combined with MTX for a short period of time (i.e, on days +1, +3, +6 and +11) is the standard prophylactic regimen. MTX is used at an initial dose of 15mg/m^2 at most centers, followed by three doses of 10mg/m^2, all of which with leucovorin rescue after 24h of each dose for the prevention of oral mucositis. TAC at a total daily dose of 0.05mg/kg can also be used, with similar results. In contrast, the combination of mycophenolate mofetil (MMF) with CSP was shown to be less effective [31]. Although the use of anti-thymocyte globulin (ATG), primarily for the prevention of GVHD, has been consolidated in unrelated donor HSCT in adults, there is limited evidence as to its benefit in the pediatric population, even though it is used in most protocols. In a randomized study comparing different dose regimens of ATG, use of ATG at lower doses was associated with a reduction in the rate of infection while maintaining similar acute and chronic GVHD rates, as well as relapse rates. The investigators concluded that low-dose ATG should be the standard serotherapy regimen for URD HCST in children with hematologic malignancies [32], even though it should be borne in mind that the different ATG formulations available have variable immune responses, which may hinder any definitive conclusions as to its real benefit in this regard.

In haploidentical HSCT, cyclophosphamide is generally used at a dose of 50mg/kg/day, in a 2-hour infusion, on D+3 and D+4, coupled with mesna (100-160% of the cyclophosphamide dose), in combination with a calcineurin inhibitor (CSP or TAC) and MMF (15mg/kg/dose q8h; maximum dose 2g/day), both starting on D+5. Both these immunosuppressants are usually kept for 3 months post-transplant [33,34].

As for UCB transplantation, the immunosuppressive regimen usually comprises the combination of a calcineurin inhibitor with MMF. Studies on the association of CSP with low-dose MTX or with corticosteroids have yielded worse results, as well as a greater rate of graft failure [28].

CLINICAL SIGNIFICANCE OF MRD FOR HSCT IN ALL

Persistence of MRD positivity at the end of consolidation therapy has been associated with a high risk of relapse and the need for intensification of therapy [2, 6, 35, 36]. Patients with MRD ≥ 10-3 (0.1%) at this time point of treatment can benefit from allo-HSCT in first remission [2, 3].

Children and adolescents with high-risk relapsed ALL are eligible for allo-HSCT in second remission (CR2) or over [25]. In children with relapsed or high-risk ALL, MRD ≥10– 3 before HSCT indicates a highly resistant disease to conventional intensive CT. These patients are candidates for new therapeutic strategies, including targeted- or immunotherapy, to reduce the tumor burden and the risk of post-transplant relapse [3, 13].

Levels of MRD pre- and post-allo-HSCT have been shown to have a prognostic impact: patients with undetectable MRD before MAC allo-HSCT have a better outcome than those with any level of MRD positivity [3, 13, 35, 36,37,38,39]. In these series of patients, the discriminatory detection limits of MRD were defined as 10-3 and 10-4 [13, 36, 40]. Bader et al., 2009, showed that patients with pre-transplant MRD < 10-4 (0.01%) had a higher EFS and a lower cumulative incidence of relapse (CIR) than those having undergone allo-HSCT with MRD ≥ 10-4 [37].

Persistence of MRD positivity after transplantation is related to significantly worse outcomes compared to patients with undetectable MRD, regardless of the method used for MRD detection [3, 35,38-41]. On the other hand, conversion of an MRD-positive status into a negative one after transplant is associated with longer remission and lower relapse risk [3,35]. This has also been observed in the haploidentical HSCT scenario [43].

The prognostic utility of pre- and post-transplant MRD kinetics has been demonstrated as follows: (i) patients with detectable pre- and post-HSCT MRD, particularly those with higher MRD levels (≥ 0.1%), have significantly lower EFS and higher CIR; (ii) lower levels of pre-HSCT MRD (<10-4) converting into undetectable post-HSCT MRD do not have a negative impact on outcome; (iii) even low levels of post-HSCT MRD are invariably correlated with a higher risk of relapse ($p = 0.001$) [3]. In short, the risk of relapse is more strongly influenced by post-transplant MRD than by pre-transplant MRD [3]. Close surveillance and preemptive immunotherapy strategies post-transplant have been shown to effectively decrease the relapse rate in the high-risk population [44, 45].

BEST TIME POINTS FOR MRD ASSESSMENT:

Pre-HSCT: MRD assessments should be made immediately before allo-HSCT [13]. Berlin-Frankfurt-Munich (BFM) study protocols recommend an MRD assessment to be made at a median of 13 days before allo-HSCT to verify the prognostic significance of MRD prior to transplantation [37]

Post-HSCT: MRD assessments by multiparameter flow cytometry (MFC) and/or reverse transcription quantitative polymerase chain reaction (RT-qPCR)

are accurate in predicting relapse at days +30, +60, +90, and +180 post-HSCT. From D+60 onwards, the discriminatory power of MRD detection was shown to be greater in predicting the probability of relapse [39]. However, using a more sensitive method to detect MRD, such as next generation sequencing (NGS), even earlier time points after transplant (i.e., at D+30) are also predictive of relapse ($p < 0.0001$) [42].

Any detectable MRD level on days +180 and +365 post-HSCT is highly predictive of relapse and poor survival. On the other hand, negative MRD on D+365 is associated with long-term survival [3]. Several factors can impact the outcome of pediatric patients with ALL undergoing allo-HSCT, such as: peri-transplant MRD positivity, remission status (CR2, CR3), non-TBI conditioning regimen, and absence of acute GVHD by D+190 post-transplant. These factors can define subgroups of children who are at a higher risk of relapse and who may thus benefit from successive MRD assessments and early therapeutic interventions [3]

It is very important to note that most studies determine MRD with very specific real-time qPCR of immunoglobulin and TCR gene rearrangements because the flow cytometric analysis of a reactive pediatric marrow can be extremely challenging. When decisions that may potentially change patient management are based on low levels of MRD, we would recommend that the SBTMO – MRD Working Group review the flow cytometric data to increase accuracy of the results.

CONSIDERATIONS ON ALL SPECIFIC GENETIC SUBGROUPS

Several biologic characteristics in ALL patients are significantly associated with MRD status during treatment [46]. Patients with good-risk cytogenetics (ETV6-RUNX1, high hyperdiploidy) demonstrate faster clearance of leukemic cells (MRD < 1x10-5), while patients with high-risk features (iAMP21, KMT2A rearrangement, haploidy/ hypodiploidy) respond more slowly [47,48]. Intermediate-risk cytogenetics, such as TCF3-PBX1 or t(1;19), have variable MRD kinetics: even though they exhibit faster disease clearance, such patients need more intensive therapy to avoid relapse [48,49]. Children with B-cell precursor (BCP) ALL with other genetic abnormalities, including alterations in copy number, BCR-ABL1-like mutations, JAK-STAT abnormalities, IKZF1 deletion, and IKZF plus usually exhibit prolonged MRD persistence [48-51].

Intrachromosomal amplification of chromosome 21 (iAMP21) ALL is considered a high-risk disease which requires an intensive treatment approach [52,53]. The BFM group considers that MRD alone can identify iAMP21 as a high-risk cytogenetic feature in ALL patients [54].

Ph1 + ALL patients who reach an MRD level of ≤ 10-4 leukemic cells at the end of induction therapy have a lower risk of relapse and have been shown to achieve high survival rates without undergoing transplantation [55,56]. Conversely, persistence of MRD positivity at later time points of therapy in Ph1+ ALL patients is associated with a higher incidence of disease relapse [55].

T-cell ALL is also associated with MRD kinetics, with a slower blast clearance compared to BCP-ALL when delivered the same therapy. However, patients with MRD < 0.01% at the end of induction and consolidation therapy may harbor a favorable prognosis (57), whereas those with high MRD (≥ 0.1%) levels at the end of the consolidation phase tend to exhibit a high risk of relapse [57]. Early T-cell precursor (ETP)-ALL is also associated with high levels of MRD after induction therapy and lower long-term outcomes [58]. Intensification of therapy, based mainly on the high MRD status, has resulted in comparable outcomes in ETP-ALL and non-ETP-ALL in pediatric patients [59].

Although the risk of relapse is directly proportional to the level of MRD in each cytogenetic risk group, the absolute risk of relapse associated with a specific level of MRD varies according to the genetic subtype. Hence, the integration of genetic biomarkers and MRD testing may improve risk stratification algorithms for treatment decision in this population [47-49]. This seems particularly promising for peri-HSCT interventions, which may lead to a significant improvement in transplant outcomes for children with ALL [60].

In patients relapsing after first allogeneic transplant, therapeutic options may be a second allogeneic transplant in a subsequent remission, targeted immunotherapies, and palliative care [61]). In patients relapsing after haploidentical transplants, it is important to note that one third of the patients may have a patient haplotype loss in the leukemic cells, rendering the disease invisible to the patient's immune system but 100% incompatible with a graft from a family member with the other haplotype [62]. For these patients, a second haploidentical HSCT may be the ideal treatment strategy.

CONCLUSIONS

Allo-HSCT remains the treatment of choice for children with high-risk or relapsed ALL. Over the past few decades, the results seen with URD transplants

have progressively improved, with similar outcomes as those shown with matched sibling donors. The relatively recent advent of the PTCy platform in haploidentical transplantation has overcome the challenge of finding allogeneic compatible donors. Nonetheless, a number of factors ought to be taken into account to achieve a favorable outcome after allo-HSCT in childhood ALL, among which, the advantages and limitations of conditioning regimens containing TBI, the optimal GVHD prophylaxis regimen, and the long-term follow-up of this population.

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CONSENSUS ON INDICATIONS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRICS. UPDATE 2020: SARCOMAS, EWING FAMILY TUMOR, OSTEOSARCOMA AND HEPATOBLASTOMA

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SUMMARY

The indications for hematopoietic stem cell transplantation in solid tumors in children do not change a lot since our first Brazilian consensus publication in 2009. In this article, we are going to review indications to hematopoietic stem cell transplantation in solid tumors, including the ones that had no more virtual indications.
For the consensus, a review was made using the most relevant articles, and a series of meetings was done to discuss the recommendations.

Keywords: Sarcomas, Ewing Sarcoma, Rhabdomyosarcoma; Osteosarcoma; Hepatoblastoma; Hematopoietic Stem Cell Transplantation; Pediatrics

INTRODUCTION

The indications for hematopoietic stem cell transplantation in solid tumors in children do not change a lot since our first Brazilian consensus publication in 2009[1], In this article, we are going to review indications to hematopoietic stem cell transplantation in solid tumors, including the ones that had no more virtual indications.

For the consensus, a review was made using the most relevant articles, and a series of meetings was done to discuss the recommendations.

Also, there are virtually no studies using allogeneic transplantation, so most of the indication are related to autologous transplantation.

METHODS

The literature review for the elaboration of this consensus was based on indexed articles, preferably published in the last ten years, including what was published in the annals of national and international congresses. However, considering that many diseas-

es have few new publications, some diseases have older articles.

Personal experience of the service or of the country, even if not published, can be used to justify indications for transplantation, if the data are properly presented.

RECOMMENDATIONS

All recommendations are summarized in table one, and more details about each indication is in the following text

EWING FAMILY TUMORS

There are several studies including a small number of patients suggesting the benefit of using high doses in some subgroups[2]. Patients with relapse might have some benefit from this approach. However, the results of using autologous hematopoietic stem cell transplantation (HSCT) in patients with extrapulmonary metastases have been disappointing[3].

An article with patients with local and / or distance relapse, found a survival benefit among patients who had a favorable response in multivariate analysis of patients responsive to four to six cycles of conventional relapse chemotherapy shows a better outcome in patients who received additional using autologous hematopoietic stem cell transplantation[2].

Favorable results were seen in patients with isolated metastatic lung disease in first remission. When there is a good response to conventional initial chemotherapy, these patients seem to benefit from autologous HSCT[4].

Also in first remission a study showed that among the 61 patients with a disease considered to be at high risk (metastases, unresectable tumor or poor response to chemotherapy), there was a benefit to those who received consolidation with high doses (n = 35) when compared to patients who received only chemo (n = 26), with a relapse-free survival of 0.66 vs 0,27 (P = 0.008), respectively[5].

The Euro-Ewing conducted a randomized study comparing conventional chemotherapy and whole lung irradiation (WLI) versus HCST using Busulfan and melphalan (BuMel). Patients were randomly assigned to VAI plus WLI (n = 143) or BuMel (n = 144). For overall survival, the Hazard ratio was 1.00 (95% CI, 0.70 to 1.44; P = .99) The authors do not recommend high doses for this group of patients[6].

In the other hand, for patients with high-risk localized disease autologous HCST showed a benefit[7]. Randomization between busulfan and melphalan or standard chemotherapy (vincristine, dactinomycin, and ifosfamide, seven courses) was offered to patients if they were younger than 50 years of age with poor histologic response (≥ 10% viable cells) after receiving vincristine, ifosfamide, doxorubicin, and etoposide (six courses); or had a tumor volume at diagnosis ≥ 200 mL if unresected, or initially resected, or resected after radiotherapy.

Seventy-eight percent entered the trial because of poor histologic response. In an intent-to-treat analysis, the risk of event was significantly decreased by BuMel compared with VAI: HR, 0.64 (P = .026); 8-year EFS were 60.7% versus 47.1% . Overall survival (OS) also favored BuMel at 8-year OS were 64.5% versus 55.6%[7].

Conditioning using Bu-Mel has been associated with better survival and acceptable toxicity when compared to other regimens and is a recommendation in Ewing Sarcoma Family of tumors[6-10].

HSCT can be a therapeutic alternative for patients with localized disease and high-risk factors at first remission and should be analyzed on a case-by-case basis in patients with relapse disease. On the other hand, recent the data did not confirm the benefit of high doses for patients with isolated pulmonary metastasis at diagnosis or with metastasis.

OSTEOSARCOMA

Osteosarcoma, particularly metastatic, still has a limited prognosis. Attempts to intensify treatment with HCST have failed. A study included 71 patients with metastatic or axial osteosarcoma[11]. The patients received one or two cycles of high dose etoposide and carboplatin, the authors conclude that HDCT with carboplatin and etoposide should not be further explored as a treatment strategy in high-risk osteosarcoma.

A review analyzing multiple studies conclude that data regarding HCST in osteosarcoma are inconsistency[12].

Thus, for patients with osteosarcoma with localized or metastatic disease, there seems to be no significant benefit from transplantation as a rescue therapy.

RHABDOMYOSARCOMA AND NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMAS

For patients with high-risk or recurrent rhabdomyosarcoma, HCST's superiority over conventional chemotherapy is unclear.

A old study showed a 3-year event-free survival (EFS) and overall survival (OS) rates were 29.7% and 40%, respectively, for those receiving high-dose melphalan or other multiagent high-dose regimens and 19.2% and 27.7%, respectively, for those receiving standard chemotherapy. The difference was not statistically significant (P =.3 and P =.2 for EFS and OS, respectively)[13].

A more recent study showed a small advantage for patients submitted to HCST, but it was a case series with only 37 patients from 1982 and 2006. The 5-yr EFS for HCST group was 41.3% ± 17.8% and conventional multi-agent chemotherapy group 16.7% ± 7.6% for 5-yr EFS, respectively (P = 0.023). In this study there was not a multivariate analysis and to be in a partial or complete remission was also a good prognostic factor[14].

A retrospective study looking the results in 30 patients showed a three-year OS of 20% after allogeneic transplantation for relapsed or refractory rhabdomyosarcoma. Cumulative risk of progression was 67%. Eighteen patients died of disease and four of complications. Eight patients survived in complete remission (CR) (median: 44 months). No patients with residual disease before allo-SCT were converted to CR[15].

Data for other soft tissue sarcomas are scarse[16], published mainly more than 10 years ago and limited to case series.

There were no recent reports about transplantation in sarcomas and systematic reviews of rhabdomyosarcoma[17] or nonrhabdomyosarcoma soft tissue sarcoma[18] showed no benefit in using this approach.

For this diseases HCST should be considered only in case by case analysis or in clinical trials.

HEPATOBLASTOMA

Hepatoblastoma particularly those who relapse and those with metastases at diagnosis. Hepatoblastoma is also an uncommon pediatric cancer and all case series are small.

Anecdotic case reports showed a potential benefit for autologous transplantation, but more extensive reviews were not able to have any definitive conclusion[19,20].

The German HB99 trial (1999-2008) for hepatoblastoma (HB), was primarily to analyse the effect of high dose (HD) chemotherapy with carboplatin/etoposide (CE) in high risk (HR), Use of HD chemotherapy for HB did not improve patient outcomes, compared to contemporaneous and more recent trials like SIOPEL 4 [21].

Some reviews also showed that HSCT does not appear to be superior to the multimodal therapy currently used[22].

Hepatoblastoma is not a currently indication for HCST and this approach may only used in clinical trials or after case by case discussions.

TABLE 1- Indications for Hematopoietic Stem cell Transplantation in Pediatric Solid Tumors

Tumor	Autologous	Allogeneic
Ewing Sarcoma – First line High risk features	CI	NR
Ewing Sarcoma – Relapse	CI	NR
Osteosarcoma	NR	NR
Nonrhabdomyosarcoma soft tissue sarcoma	NR	NR
Rhabdomyosarcoma	NR	NR
Hepatoblastoma	NR	NR

Legend: Clinically indicated (CI) Clinical option (OC) - Generally not recommended (NR)

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CONSENSUS ON INDICATIONS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRICS. UPDATE 2020: CENTRAL NERVOUS SYSTEM TUMORS AND RETINOBLASTOMA

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SUMMARY

The indications for hematopoietic stem cell transplantation in solid tumors in children do not change a lot since our first Brazilian consensus publication in 2009. In this article, we are going to review indications to hematopoietic stem cell transplantation in solid tumors.
For the consensus, a review was made using the most relevant articles, and a series of meetings was done to discuss the recommendations.
In some indications, autologous transplantation is no longer used as a treatment option, however we chose to review these diseases and keep them as a non-recommendation.
In this article we are going to review CNS tumors and retinoblastoma

Keywords: Central nervous system; Medulloblastoma, Retinoblastoma; Stem Cell Transplantation

METHODS

The literature review for the elaboration of this consensus was based on indexed articles, preferably published in the last ten years, including what was published in the annals of national and international congresses. However, considering that many diseases have few new publications, some diseases have older articles.

Personal experience of the service or of the country, even if not published, can be used to justify indications for transplantation, if the data are properly presented.

RECOMMENDATIONS

All recommendations are summarized in table one, and more details about each indication is in the following text

TUMORS OF THE CENTRAL NERVOUS SYSTEM

Considering a significant proportion of embryonal tumors affecting young children, the High dose Chemotherapy are large explored in the literature in an attempt to avoid neurocognitive and endocrinological sequelae radiation induced.

Autologous transplantation was the most studied. Most conditioning schemes use Thiotepa (Triethylenethiophosphoramide) [1].

Medulloblastoma, in infants and children under four years are the most studied. Particularly tumors that present unfavorable histology and molecular changes may benefit from this approach. [1-3]

Patients with late recurrence, can also benefit from autologous transplantation, although not indicated in chemoresistant or bulky disease. [4,5].

The therapeutic option is Tandem (autologous stem cell transplant) transplantation: 2-3 courses, with Thiotepa being well tolerated (6) in combination or not with Carboplatin or single transplant with sequential use of Thiotepa, carboplatin and Etoposid. A retrospective analysis of recurrent primitive chemosensitive neuroectodermal tumors (PNET) also showed good cure rates in patients undergoing sequential Thiotepa courses [7].

Other tumors such as atypical rhabdoid teratoid, an embryonic tumor, can sometimes become difficult to classify and are commonly confused with medulloblastoma or a primitive neuroectodermal tumor. Standard treatment involves surgical resection followed by radiotherapy and systemic chemotherapy, but in children under 4 years old - most patients when considering a tumor of embryonic origin - high dose chemotherapy followed by rescue with stem cells becomes a reasonable option to avoid neurocognitive and endocrinological sequelae radiation induced [8-9]

Choroid plexus carcinoma has only small published series, the main publication being the Head Start sequential studies in which it showed benefit. Particularly TP53 and R337H mutations should be investigated before indicated TCTH [10].

High-grade gliomas in first remission have been the subject of studies, which have not been reproduced later. Patients undergoing surgeries with total or subtotal resection had better results [11].

Ependymomas seem not to have benefited from the use of autologous transplants [12, 13].

Brainstem gliomas are also tumors with poor results and autologous transplantation did not achieve the desired effect [14].

In the few CNS germinal tumors, autologous transplantation are explored in the management of patients with recurrent or refractory neoplasms and could be indicated in this population [15, 16]

RETINOBLASTOMA

Retinoblastoma (RB) is a rare embryonic tumor that originates in the neural retina, being the most frequent intraocular malignant tumor in children. More than 90% of cases are diagnosed before the age of five (median 2 years) [17].

The manifestation of the disease can be unilateral or bilateral, the latter being related to germline mutations. While intraocular RB has an excellent survival rate, patients with extraocular RB have historically a worse prognosis. [18].

Many groups have noted that intensified treatment in patients with advanced or metastatic disease with high doses of chemotherapy and autologous stem cell rescue (ASCT) has been associated with improved survival. (19,20,21) It is possible to achieve tumor control in those patients with trilateral, advanced bilateral disease, without CNS metastasis, and in those with tumor on the surgical margin of the optic nerve and / or extra-scleral extension. [17]

The prospective, multicenter and international study carried out by COG (ARET0321) evaluated the use of high-dose chemotherapy, using carboplatin, etoposide and thiotepa, with ASCT, in patients with advanced disease. Event-free survival (EFS) at 36 months was 87.7% (stages 2 and 3); 79.3% (4a); 8% (4b / trilateral disease). The observed results significantly improved EFS in each subgroup compared to historical results, especially for patients with extraocular and metastatic disease without CNS involvement [4].

TABLE 1 – Indications for transplantation in pediatric solid tumors

Disease	Autologous	Allogeneic	Comments
Retinoblastoma - extra ocular disease	CI	NR	
Retinoblastoma Relapse	CI	NR	
Pineoblastoma (trilateral retinoblastoma)	CI	NR	
Teratoid rhabdoid tumors	CI	NR	
Medulloblastoma younger than four years old (except low risk groups)	CI	NR	Unfavorable histology and molecular profile
Medulloblastoma relapse	CI	NR	Just special cases without previous radiotherapy
Central Nervous system Germ Cell tumor	CI	NR	
Glioblastoma multiforme	CO	NR	
Ependimoma	NR	NR	
High grade Gliomas	CO	NR	
Brainstem gliomas	NR	NR	
Choroid plexus carcinoma	CI	NR	Search for R337H and P53 mutations

Legends: Clinically indicated (CI) Clinical option (OC) - Generally not recommended (NR)

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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR INBORN ERRORS OF IMMUNITY

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Inborn errors of immunity (IEI) also referred to as primary immunodeficiencies, are a heterogeneous group of rare genetic disorders affecting the immune system. IEI may present as increased susceptibility to infectious diseases, autoimmunity, autoinflammatory and malignant diseases. There are currently more than 400 different genes identified that may cause IEI.[1] Hematopoietic Stem Cell Transplantation (HSCT) can correct the immune defect of several of these diseases and is currently considered the treatment of choice for some severe forms of IEI.[2] In Brazil, the first transplant performed for a patient with IEI was in 1990, at the National Cancer Institute in Rio de Janeiro. It was a patient with Chediak-Higashi Syndrome that was transplanted after diagnosing a Lymphoma. The first report of Brazilian experience of HSCT for PID was published in 2018 and included data from transplants in 221 patients transplanted from July 1990 to December 2015 in 11 centers which participated in the Brazilian collaborative group.[3]

Transplants in patients with IEI are highly complex and should be performed in centers with continuous and significant experience in these procedures and that participate in collaborative studies. In these rare disorders, single-center reports of small cohorts are of limited value. For that reason, both Europe (IEWP/EBMT (Inborn Errors Working Party/European Group for Blood and Marrow Transplantation) and USA (PIDTC (Primary Immune Deficiency Treatment Consortium) formed collaborative groups to study outcomes of HSCT in PID and elaborate protocols to standardize treatment in participating institutions. The Brazilian Pediatric study group on HSCT strongly recommends that centers transplanting patients with IEI should collaborate with international groups and follow the joint EBMT/ESID Inborn Errors Working Party guidelines.[4] We also recommend that international treatment protocols should be adapted taking into consideration patients' performance status and particularities found in our country (BCG vaccination, socio-demographic characteristics).

The main IEIs that can be treated with HSCT are described in the Table 1.

SEVERE COMBINED IMMUNODEFICIENCY (SCID):

Severe combined immunodeficiencies (SCID) are a group of rare, monogenic diseases that are characterized by a block in the development of T lymphocytes. Typical SCID are characterized by the absence of T lymphocytes and deficient T-lymphocyte proliferation. Lymphocyte immunophenotyping show different patterns considering the presence of B and/or NK cells, that are generally correlated with the causative genetic defect. There are currently more than 14 different genes that were described causing SCID, the most frequent being: IL2RG, JAK3 (T-B+NK-); RAG 1/2, DCLRE1C (T-B-NK+); ADA (T-B-NK-); IL7RA (T-B+NK+). HSCT is the only stablished curative therapy for patients with SCID. More recently, Gene therapy is appearing as a very promising alternative treatment and potentially may substitute HSCT as a standard of care for these patients, but as of today only one therapy has been commercially licensed by the European Medicines Agency (Strimvelis®) for ADA SCID. Clinical studies are ongoing for other genetic defects. [5-7]

Patients with SCID are considered a pediatric emergency. HSCT must be performed as soon as possible

with the more rapidly and best available donor. A matched related sibling that is not affected by the disease is the gold standard. If not available, alternative donors (matched unrelated bone marrow or umbilical cord blood donors) may be considered as long as they are readily available.[8] Haploidentical family donors have been used since the late 80s, but the larger experience with this type of donor comes from studies with in vitro T-cell depletion (former CD34+ selection and currently CD3alfa/beta/CD19 depletion). This techniques are very expensive and not easily available in our country. The use of haploidentical donors with post-transplant cyclophosphamide (haplo-PTCy) is a more accessible alternative and its use in patients with SCID have been done in series of case. The larger experience in haplo-PTCy was published by the Brazilian group. In this study there were 34 patients with SCID that received a haplo-PTCy. These transplants should preferably be performed in centers with experience due to their high complexity. [9]

Patients with SCID are profoundly susceptible to opportunistic infections and live vaccines are contraindicated. The Bacille Calmette Guerin (BCG) vaccine in these patients can promote disseminated infection by the vaccine strain and is associated with numerous complications, with increased rates of morbidity and mortality. If the patient has received BCG before diagnosis, prophylaxis with one or two drugs is recommended. For patients presenting with local or disseminated BCGosis, four or more drugs may be necessary for treatment.[10] Also the rotavirus vaccine may cause bloody diarrhea sometimes mimicking Cow's milk protein allergy. Patients with SCID present with life-threatening infections (viral, fungal, bacterial) within the first year of life. HSCT success rates are highly correlated to the early diagnosis and the presence of infections at the time of transplant.[11] For that reason, neonatal screening (measurement of T cell receptor excision circles levels) is encouraged and being implemented in different countries. In Brazil, a few pilot studies have been performed and currently the state of Minas Gerais and the city of São Paulo have started the screening program.[12] Reference to a specialized center as soon as the diagnosis have been made is crucial, immunoglobulin (IVIg) replacement therapy and PJP prophylaxis must be started promptly and active infections need to be aggressively treated. Blood products need to be irradiated and leukodepleted before transfusion to avoid GVHD and CMV infection. Breast-feeding from a CMV positive mother should be discouraged. Access to a specialist, although essential, should not delay the immediate start of IVIg replacement and antimicrobial prophylaxis.

SCID phenotype (presence of B and/or NK cells) and genetic defect (if available) are important in deciding which conditioning regimen to use. Although the most important outcome is developing a functional T-cell compartment, some degree of myeloid chimerism may help B-cell reconstitution and long-term thymic output. In addition, choice of the intensity of conditioning regimen may take into account the clinical and performance status of patients. In particular cases, HSCT can be performed without conditioning (T-B+NK- SCID, with matched sibling donor). In this situation only T cells from the donor will develop, while the myeloid compartment remains from the patient leading to a split chimerism. Some patients may not develop B-cell function, requiring lifelong IVIg replacement therapy. The majority of patients will need some conditioning and most indicated regimen include reduced dose of busulfan (pharmacokinetics is recommended – AUC 60–70 mg*h/L), associated with fludarabine +/- serotherapy (thymoglobulin or alemtuzumab) considering donor type. [4,13]

Patients with ADA-deficiency are a particular type of SCID. Internationally there are other options of treatment besides HSCT, including enzyme replacement therapy and Gene Therapy.[7] As these alternatives are not currently available in our country, HSCT remains the treatment of choice. For babies with SCID diagnosed by neonatal screening, as there is limited experience in newborns with regard to toxicity and tolerance of drugs used for conditioning, conditioned HSCT is not recommended before 6 to 8 weeks of age.[4]

WISKOTT-ALDRICH SYNDROME

HSCT is the main curative alternative, correcting the underlying immunodeficiency and thrombocytopenia. The outcome of transplantation in experienced centers is around 80-90% survival using related donors, voluntary bone marrow donors, umbilical cord blood or haploidentical donors. The most recommended conditioning regimen is myeloablative and the degree of donor chimerism, particular in the myeloid compartment, is associated with better results, especially related to correction of thrombocytopenia and autoimmunity. HSCT outcomes are more favorable in patients under 5 years of age and with fully matched donors.[14,15]

HEMOPHAGOCYTIC SYNDROMES

Familial Haemophagocytic lymphohistiocytosis (FHLH) is a clinical hyperinflammatory syndrome associated with an uncontrolled immune response, resulting in a cytokine storm caused by a primary im-

mune defect. Several mutations have been described as causes of FHLH (PRF1, UNC13D, STX11, STXBP2) and other genetic syndromes can also have a clinical presentation similar to HLH (Chediak-Higashi Syndrome, Griscelli type II, XLP). Up to 20% of primary HLH may have no known genetic mutation. Initial treatment includes chemotherapy and immunosuppressants (recommended protocol HLH-2004), or antibody-based therapy (thymoglobuline, alemtuzumab) until acute symptoms are controlled. HSCT is the treatment of choice for primary HLH and may be performed with the best available donor. Best results are reported when patients have no active HLH at the time of transplant. Choice of conditioning regimen may take into account the type of donor, clinical status of the patient and disease control. Reduced toxicity regimens are recommended including bussulfan (with pharmacokinetics), fludarabine and serotherapy; or fludarabine and melphalan. The high incidence of failure of engraftment and mixed chimerism requiring further intervention must be taken into consideration when using regimens with melphalan. Stable mixed chimerism (some reports say >30%) may be sufficient to protect against disease relapse.[4,16-20]

CHRONIC GRANULOMATOUS DISEASE

HSCT is the only established curative therapy for chronic granulomatous disease (CGD). Recent studies show excellent survival particular in younger patients, using reduced toxicity regimens, and matched donors. Preferred donors are matched sibling donor or a well matched unrelated donor. Carrier family donors should be avoided, but in the absence of other suitable donors, female carriers may be considered after functional analysis (DHR). The use of alternative donors is still associated with inferior results and HSCT should be performed in experienced centers. Reduced toxicity conditioning based on busulfan (with pharmacokinetics), fludarabine and serotherapy (thymoglobuline or alemtuzumab) is recommended. Also, conditionings based on treosulfan show excellent results, but this drug is not available in our country. Stable mixed chimerism may be sufficient to protect against infections. Patients with inflammatory symptoms (specially colitis) may need immunosuppressive treatment before HSCT to control symptoms, as inflammation may increase risk of graft failure and GVHD. [4,21,22]

PRIMARY IMMUNE REGULATORY DISORDERS (PIRD)

Primary Immune Regulatory Disorders (PIRD) are an expanding group of diseases caused by gene defects in several different immune pathways, such as regulatory T cell function. There is a growing number of recent reports showing that some PIRD may benefit from HSCT. These include diseases such as IPEX syndrome, CTLA4 deficiency, LRBA and immune dysregulation with colitis (very early onset inflammatory bowel disease with genetic defect – IL10, IL10R). Patients with PIRD develop clinical manifestations associated with diminished and exaggerated immune responses and disease symptoms control is important to HSCT success. Targeted biological agents such as abatacept are increasingly available and can result in significant reduction in disease activity. Except for IPEX syndrome, that a large multicenter study showed advantage in overall survival and quality of life in transplanted patients compared to those treated with immunosuppression, these diseases are rare and only few series of cases treated with HSCT have been reported in the literature. For this reason, no general recommendations may be done at this point regarding transplant indication and treatment regimens. Therefore, we recommend that these patients be referred to specialized reference centers and discussed in an expert panel. [23-25]

TABLE 1. Main indications of HSCT in IEI

Severe Combined immunodeficiency (SCID)	Standard of care
Hypomorphic SCID / leaky-SCID	HSCT Indication depends on history of infections or autoimmunity and patient performance status
Wiskott Aldrich Syndrome	Best results if performed before 5 years of age
Phagocyte disorders: Chronic Granulomatous Disease; Leucocyte Adhesion Deficiency (LAD)	Best results in younger age and well matched donors
HLH: Familial Hemophagocytic Lymphohistiocytosis (mutations in: PRF1, UNC13D, STX11, STXBP2); Chediak-Higashi Syndrome; Griscelli Syndrome type 2 (RAB27A mutation); X-linked Lymphoproliferative disease (XLP)	Standard of care Best results with controlled inflammatory symptoms
Combined Immune Deficiencies: HiperIgM syndrome (mutations in: CD40/CD40L); MHC class II deficiency; IFNGR deficiency; DOCK8	Control of infectious complications prior to SCT and performing HSCT prior to development of organ damage result in superior outcome
Primary Immune Regulation disorders: IPEX syndrome; CTLA4, LRBA, STAT3 GOF; Very Early Onset Inflammatory Bowel Diseases (IL10, IL10-R)	Few reports Cases should be discussed in reference centers

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BRAZILIAN CONSENSUS MEETING ON PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACQUIRED APLASTIC ANEMIA AND INHERITED BONE MARROW FAILURE SYNDROMES

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INTRODUCTION

Aplastic anemia (AA) is characterized by bone marrow failure associated with pancytopenia and bone marrow hypoplasia/aplasia, without excessive blasts, neoplastic infiltration, or fibrosis. AA can be hereditary or acquired, an important distinction given that hereditary presentations do not respond to immunosuppression[1]. Most cases are acquired where an etiologic trigger cannot be identified, in which autoimmune pathophysiology is inferred[2].

Acquired AA is a rare disease with an estimated incidence of 2 to 3 cases per million in the Western world and 1,64 cases per million in Latin America. This disease is even rarer in the population under ten years, with an incidence rate of 0,92 cases per million inhabitants/year. There are two incidence peaks, the highest around 20-30 years and the second after 60 years[3].

ETIOLOGY AND PATHOPHYSIOLOGY

The rarity of the disease is probably explained by the need for a combination of factors for its development. The etiology involves predisposing characteristics, exposure to specific events, and individual differences in the immune response. Unfortunately, the way each one of these factors contributes to disease mechanisms has not yet been completely clarified. Currently, about 70 to 80% of cases are considered idiopathic. However, exposure to certain drugs, infections, radiation, pregnancy, and rheumatologic diseases may be involved in its etiology, either by direct toxicity to the hematopoietic stem cell or by an immune mechanism[4].

In most cases, AA behaves like an immune-mediated disease. Initially, occurs an activation and expansion of oligoclonal cytotoxic T cells. Then, the release of hematopoiesis-suppressing cytokines: interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), which cause DNA damage and consequent apoptosis of bone marrow CD34+ stem cells. In vitro studies have already proven these mechanisms. However, it is still unknown what the initial trigger for T cell activation is, nor how the disruptive event that leads to loss of immune tolerance occurs[2,5].

The response to immunosuppressive therapy supports this immune hypothesis for the pathophysiology of AA. However, a small part of the cases may have other mechanisms involved. About a third of patients have shortened leukocyte telomeres, which may be due to mutations in the telomerase complex. These mutations reduce the enzyme activity, causing progressive erosion of telomeres and a deficiency in the proliferative capacity of hematopoietic progenitor cells[2,3].

Normal hematopoiesis also involves a complex relationship between progenitor cells and the bone marrow microenvironment, which is nec-

essary to regulate various stages of cell proliferation and differentiation. In AA, the microenvironment can also be affected, preventing the proliferation of stem cells, even if transplanted from a healthy donor[6,7].

The pathophysiology of AA, therefore, suggests two possibilities for treatment: Hematopoietic stem cell transplantation (HSCT), which replaces deficient hematopoietic stem cells (HSC) with normal progenitors; and suppression of the immune process that causes damage to hematopoiesis[1].

In face suspicion of aplastic anemia, the diagnosis of acquired AA must be differentiated from inherited bone marrow failure syndromes (IBMFS) since the management and treatment are different[8].

DIAGNOSIS AND CLASSIFICATION

Considering the need for proper investigation for the differential diagnosis, including personal and family history, exposure to toxins and infectious agents, physical examination focused on malformations and other somatic abnormalities characterizing constitutional marrow failure syndromes, in addition to careful clinical evaluation, the following tests are recommended (table1):

TABLE 1. Diagnostic tests

Mandatory tests for diagnosis	Ideal investigation for differential diagnosis with constitutional syndromes
- Complete blood count *- Reticulocyte count* *- Liver function tests* *- Testes de função hepática* *- Serology / PCR for viral hepatitis* *- Myelogram* *- Cytogenetics of bone marrow* *- Immunophenotyping of bone barrow* *- Bone marrow biopsy* *- Peripherical blood flow cytometry for paroxysmal nocturnal hemoglobinuria* *- Screening for autoantibodies* *- Dosage of vitamin B12 and folate*	*- Chromosomal fragility test (mitomycin or diepoxybutane)* *- Fecal elastase and pancreatic lipase* *- Fibrinogen and serum ferritin* *- Telomeric length* - Next-Generation Sequencing (NGS) panels to identify cryptic mutations: TERC and TERT mutation analysis TNF2, NHP2, NOP10, DKC1, and cMPL mutation analysis Shwachman-Diamond Syndrome mutation analysis Blackfan-Diamond Syndrome mutation analysis

After the diagnosis, the classification of disease must be made based on the abnormalities present in the bone marrow and peripheral blood, as demonstrated in table 2.

TABLE 2. Classification of AA based on the severity5

Moderate or Non-severe Aplastic Anemia (NSAA)	Severe Aplastic Anemia (SAA)	Very Severe Aplastic Anemia (VSAA)
- Hematopoietic marrow cellularity <30% - Neutrophil >500/µl but < 1000/µl - Lack of criteria for severe or very severe	- Hematopoietic marrow cellularity <30% - At least two of the following conditions: Neutrophil < 500/µl Platelets < 20.000/µl Reticulocytes < 20.000/µl	- Like severe but with neutrophils <200/µl

FIRST-LINE TREATMENT OF ACQUIRED SAA

Nowadays, HSCT and IST are considered acceptable treatment options for children with acquired AA. The current guidelines recommend that patients younger than 40 years with an HLA-identical related donor undergo HSCT as their first-line treatment[9]. Matched unrelated donor (MUD) HSCT is considered an option for first-line therapy if performed in less than 2-3 months. Otherwise, immunosuppression should be initiated[10]. Thus, HLA typing for the patient and family should be immediately performed for any patient with newly diagnosed SAA who is a candidate for HSCT. The source of HSC for HSCT in SAA should always be bone marrow. An EBMT registry study with 1886 patients with SAA who underwent HLA-identical related HSCT observed an overall survival (OS) advantage for patients who received bone marrow compared to peripheral blood in all age groups: 1-19 years (90% versus 76%, P<0.00001) [11]. Rabbit ATG should always be used in the conditioning regime for related HSCT. A CIBMTR registry study demonstrated a protective effect of rabbit ATG against acute and chronic GVHD in related HSCT: 17% versus 6% (P<0.001) and 20% versus 9% (P<0.001), respectivel[12]. In unrelated HSCT, rabbit ATG protected against acute GVHD (42% versus 23%, P<0.001) and was independently associated with better OS (83% versus 75%, P= 0.02)[12]. The conditioning regime in SAA must be non-myeloablative due to the absence of malignant cells, therefore preserving fertility in young patients and reducing the long-term sequelae after HSCT.

Currently, recommended conditioning regimens for related HSCT is CY 200 mg/kg + rabbit ATG 5 - 7.5 mg/kg while the recommended conditioning regimens for unrelated HSCT are Fludarabine 120mg/m^2 + CY 120 mg/kg + rabbit ATG 5 - 7.5 mg/kg $\pm$ total body irradiation (TBI) 200 cGy (10). The addition of TBI at a dose of 200 cGy reduces the incidence of primary failure, especially in adult and/or polytransfused patients[13]. The ideal immunosuppression regimen after HSCT in SAA consists of a combination of a calcineurin inhibitor (tacrolimus or cyclosporine A) with methotrexate[14]. The calcineurin inhibitor must be started on day -1 and must be maintained for at least one year after HSCT with a slow withdrawal afterward. Methotrexate should be used on the short-course regimen (15 mg/m^2 on day +1 and 10 mg/m^2 on day +3, day +6, and day +11).

Those not eligible for upfront transplant due to a lack of an HLA-matched donor should receive treatment with horse anti-thymocyte globulin (ATG) and cyclosporine (CSA) [9]. Due to the unavailability of horse ATG in Brazil, rabbit ATG is used for first-line treatment in association with CSA, despite the lower response rate observed with this ATG preparation compared with horse ATG[9,15]. A recent study showed that eltrombopag added to horse ATG-based IST did not improve outcomes in children with SAA[16]. The combination of rabbit ATG-based IST and eltrombopag for the first-line treatment of acquired SAA is still unknown.

SECOND-LINE TREATMENT OF ACQUIRED SAA

Patients who do not respond to first-line immunosuppressive treatment must undergo bone marrow reassessment to exclude clonal evolution. An HLA MUD should be preferred at this time using the conditioning regimen described before.

Although early studies on UCBT in patients with acquired AA showed limited success, new studies have shown promising results. Kudo et al, demonstrated the excellent OS in patients treated with the conditioning regimen comprising fludarabine, cyclophosphamide or melphalan, and low dose irradiation without anti-thymocyte globulin[17]. Similar results were demonstrated by the French group in a prospective study using conditioning with FLU, CY and 2 Gy of TBI with ATG; this group reported a 2-year OS rate of 81% and engraftment of 88%[18].but results from previous studies are not encouraging. We conducted a prospective nationwide phase 2 study to assess unrelated cord blood (CB Considering this data, we believe that UCB transplantation can be a treatment option for children who lack an MRD, MUD or emergency cases.

Haploidentical HSCT is another promising treatment option for patients with acquired AA who failed IST or even patients who failed a previous HSCT[19]. The choice between a mismatched unrelated donor or a haploidentical related donor must be made individually. This decision should be based upon the urgency of the transplant, neutrophil count, age of the recipient, the donor's characteristics (age, gender, and ABO/CMV agreement), and the presence of donor-specific antibodies against HLA (DSA).

Based on national experience, the recommended conditioning regimen for haploidentical HSCT consists in the association of:

Flu 150 mg/m^2 + CY 29 mg/kg + TBI 400 cGy single dose. The use of increased doses of TBI was associated with a reduction in the primary graft rejection rate, 27% versus 7% (P=0.02), and a higher 2-year event-free survival, 88% versus 60 % (P=0.01). The

role of rabbit ATG in conditioning for haploidentical HSCT remains controversial. It can be considered mainly for the treatment of naïve patients or those who have not received ATG during immunosuppressive treatment[20].

The source of HSC must be the bone marrow, and GVHD prophylaxis consists of the association of CY 50 mg/kg/day on days +3 and +4, mycophenolate mofetil 45mg/kg/day from day +5 to +35, and calcineurin inhibitor from day +5 to +365 with slow withdrawal after this period[20].

Although promising, haploidentical transplantation is still not recommended in the upfront treatment of AA until the results of prospective studies (NCT02833805). However, in some select cases in the pediatric setting, upfront haploidentical BMT may be considered for patients with zero neutrophils or very severe aplastic anemia and life-threatening infections in centers of expertise.

INHERITED BONE MARROW FAILURE SYNDROMES

Inherited Bone Marrow Failure Syndromes (IBMFS) constitute a heterogeneous group of genetic disorders characterized by the inadequate production of one or more hematopoietic lineages leading to the development of cytopenias[21,22]. Distinct biological mechanisms underlie the pathophysiology in IBMFS, such as repair pathways in Fanconi anemia (FA), telomere maintenance in dyskeratosis congenita (DKC), and ribosomopathy in Shwachman Diamond syndrome (SDS) and Diamond Blackfan anemia (DBA) [23]. These disorders are generally associated with the presence of congenital malformations and an increased risk of cancer, especially hematological and gynecological, as well as squamous cell carcinomas[24]. Although the diagnosis usually occurs in childhood, adults with a history suggestive of a hereditary bone marrow failure syndrome should be investigated[22]. It is essential to highlight that these patients must be monitored throughout their lives, given the risk of developing non-hematopoietic neoplasias, which have a better prognosis if detected early[25].

FANCONI ANEMIA

Fanconi Anemia (FA) is rare, with a prevalence of 1 in every 100,000 births, usually inherited as an autosomal recessive disease. It is characterized by progressive bone marrow failure, congenital malformations, and increased risk of myelodysplasia and acute myeloid leukemia, as well as solid tumors, particularly squamous or epithelial cell carcinomas. Although congenital abnormalities are frequent, up to 30% of FA patients may not present apparent somatic abnormalities. However, bone marrow failure will develop in approximately 90% up to 40 years of age, the majority at the end of the first decade[21,26].

The disease results from functional impairment of genes involved in the DNA repair pathway, making these patients highly susceptible to severe damage from ionizing radiation and chemotherapy, making HSCT particularly challenging. The diagnosis is based on the chromosomal breakage tests with diepoxybutane (DEB) and mitomycin. To date, 22 genes involved in the pathogenesis of the disease have been identified, with the FANCA mutation being the most prevalent[27].

For patients in the aplastic phase, treatment involves transfusions of blood components and androgens, while HSCT is considered the only curative treatment. Nevertheless, due to genomic instability, transplant strategies need to be modified to decrease transplant-related toxicity and mortality. The 5-year survival after a transplant from a compatible related donor is around 90%, and very similar for alternative donors[28,29].

BLACKFAN DIAMOND SYNDROME

Blackfan Diamond Anemia (BDA) is caused by a defect in erythropoietic progenitors, resulting in severe anemia with very early onset, most commonly before the first year of life. It has an incidence of 7 in every 1 million live births. It is caused by mutations in ribosomal protein genes, the most common being RPS19, or in non-ribosomal genes, such as GATA1, TSR2, ADA2, and EPO[30].

About 50% of patients have associated congenital abnormalities, the most common being craniofacial, skeletal, genitourinary, cardiac, and upper limbs. There is also a predisposition to hematologic malignancies, such as myelodysplasia and acute myeloid leukemia (AML), and solid tumors, such as colon carcinoma and osteosarcoma.

The first line of treatment is corticosteroid therapy, but although 80% have an initial response, only 20% of patients achieve complete and lasting remission without corticosteroid dependence. HSCT is potentially curative and is indicated for non-responders to corticosteroids, who need high doses to obtain a satisfactory response, or those who evolve with aplasia in other series or myelodysplasia/AML[31,32]. Best results are achieved when patients are transplanted young with a matched related or unrelated donor following a myeloablative regimen[32,33].

TELOMERE DISEASES / DYSKERATOSIS CONGENITAL (DC)

Telomere disease is a group of disorders with a broad spectrum of manifestations caused by a structural defect and repair of telomeres. Hematological manifestations are widespread and include bone marrow aplasia, cytopenia of at least one lineage, in addition to myelodysplasia and acute myeloid leukemia[34.]

The classic form of telomere disease is dyskeratosis congenita, which is characterized by a triad of manifestations that include reticular pigmentation of the skin, oral leukoplakia, and dystrophic nails. However, the range of manifestations associated with the mutations described in telomere disease is extensive, from patients with only hematological involvement to complex syndromes such as Hoyeraal-Hreidarsson Syndrome, Revesz Syndrome, and Coats plus Syndrome. The onset of manifestations can also occur from infancy to the fifth decade of life[34].

The pathophysiology of the disease is linked to mutations such as DKC1, TERC, TERT, NOP10, NHP2, TCAB1, NAF1, PARN, and TINF2, which affect the transcription of proteins linked to telomere maintenance. Failure in this maintenance leads to progressive telomere shortening, with consequent cessation of cell replication and senescence. The inheritance pattern can be X-linked or autosomal dominant, with variable penetrance[35]. Although results have improved in the past decade due to reduced-intensity regimens, long-term survival is still poor because of disease progression (pulmonary and liver fibrosis and hepatopulmonary syndrome) [36,37].

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIC

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare marrow failure syndrome, characterized by thrombocytopenia from birth, with progression to aplasia (91% at 13 years of age) or acute myeloid leukemia (55% at 17 years of age) [22]. Patients with this disease do not have typical physical characteristics, except for the signs of bleeding associated with thrombocytopenia.

In most cases, the disease is associated with an autosomal recessive mutation in the MPL gene, which encodes the thrombopoietin receptor[38]. Although there is a possibility of response to the use of androgens, a definitive cure can only be achieved with hematopoietic stem cell transplantation[39].

SHWACHMAN DIAMOND SYNDROME

Shwachman Diamond Syndrome accounts for up to a quarter of congenital neutropenia cases. It is characterized by bone marrow failure, exocrine pancreatic dysfunction, and predisposition to myelodysplasia and acute myeloid leukemia. The patient usually presents with moderate and intermittent neutropenia, mild to moderate thrombocytopenia and anemia and increased fetal hemoglobin. Diarrhea is expected, with increased fat and decreased fecal elastase[40]. The syndrome may be associated with malformations such as metaphyseal dysplasia and narrow thorax, cutaneous manifestations such as eczema and ichthyosis, in addition to psychomotor and growth retardation. The disease may go clinically unnoticed until malignant transformation, which occurs in up to 36% of patients[41].

Almost 90% of patients have an autosomal recessive mutation in the SBDS gene, which encodes a protein involved in ribosomal maturation. However, mutations in SRP54, DNAJC21, and EFL1 can have a similar clinical presentation[42]. HSCT is indicated for patients that develop severe cytopenias and clonal evolution. Two recent publications from Europe and the USA have shown a 5-year OS of 70% for pts with marrow failure (using reduced-intensity regimens) and a dismal outcome for those with MDS or AML [41,43].

GENERAL RECOMMENDATIONS

Donor selection: All siblings should be tested for IBMFS before being considered potential donors for HSCT[44].

HLA Compatibility: The ideal unrelated donor must be HLA identical in high resolution typing for the HLA-A, -B, -C, -DRB1, and -DQB1 locus, that is, 10:10 compatibility. Donors with one or more allelic incompatibility are at increased risk of primary graft failure, GVHD, and transplant-related mortality[45]. We recommend testing DP locus as incompatibilities in DPB1 are associated with an increased risk of GVHD and transplant-related mortality[46].

Cell source: Bone marrow is the preferred source of HSC. The use of cord blood is recommended only when matched unaffected siblings are available and outcomes are excellent[47,48]. Unrelated umbilical cord blood transplantation is usually associate with high rejection and GVHD rates and should be performed with caution[48,49].

INHERITED BONE MARROW FAILURE SYNDROMES

FANCONI ANEMIA

Recommendation:

Indications for transplant include marrow failure or clonal evolution (myelodysplastic syndrome - MDS or acute myeloid leukemia - AML). In an ideal scenario, HSCT should be performed before blood transfusions, serious infections, or the development of clonal disease[44,50,51].

Conditioning:

Patient in aplasia with an identical related donor[28]

- Cyclophosphamide (Cy) 60 mg/kg (divided into 4 days: D -6, -5, -4, -3);
- Mesna, 160% of the Cy dose, divided into five doses (0, 3, 6, 9, and 12 hours after Cy);
- Rabbit ATG at a dose of 5 mg/kg (divided into three days: D-3, D-2, and D-1), in patients aged 11 years and older, to reduce the incidence and severity of GVHD.

Patient in aplasia with unrelated matched donor [29,44,51]

- Cy 60 mg / kg (divided into four days: D -6, D-5, D-4, D-3);
- Mesna, 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);
- Fludarabine 150 mg/m^2 (divided into 5 days: D -6, D-5, D-4, D-3 D-2);
- Rabbit ATG 5 mg/kg (divided into three days: D -3, D-2 and D-1).

Patients progressing to MDS and/or AML with matched related or unrelated donors The preparatory regimen will depend on the clinical conditions and the disease stage. These patients may be referred for transplantation without prior chemotherapy. Patients with refractory cytopenia of MDS with less than 10% blasts (RAEB-1) should be treated according to the recommended protocol for Fanconi's anemia in the aplastic phase. In patients with 10% or more blasts in the bone marrow and good clinical condition, the FLAG protocol (fludarabine, cytarabine, and G-CSF) is recommended, followed by related or unrelated HSCT approximately two weeks after the beginning of the chemotherapy. This scheme should be performed only on patients with a related or unrelated donor and a confirmed transplant schedule[52].

GVHD prophylaxis for patients with matched related or unrelated donors should be performed with cyclosporine and a short course of methotrexate (D1 15mg/m2, D+3, +6 and D+11: 10mg/m2). If possible, methotrexate can be substituted by mycophenolate mofetil 45mg/kg/day divided into three doses. It is essential to have IV MMF available for patients unable to swallow oral MMF.

Patients in aplastic phase or with clonal evolution lacking a matched related or unrelated donor:

- It is recommended that the decision to proceed to transplant should be discussed with the experts to define the best time to perform this procedure and the best conditioning/prophylaxis regimen for GVHD.
- These patients can benefit from haploidentical transplantation using a modified dose of post-transplantation cyclophosphamide. However, we recommend that this transplant be performed only in centers with experience in this type of patient[53].

BLACKFAN-DIAMOND ANEMIA

Recommendation:[51,54]

- Non-response to steroids, steroid dependency at a dose of ≥ 0.3 mg/kg/day, unacceptable steroid toxicity.
- Dependence on transfusions and/or alloimmunization.
- Pancytopenia or with progression to MDS /AML.

Conditioning:

Patients with matched related or unrelated donors[55]

- Busulfan 16 - 20 mg/kg EV + Fludarabine 160 mg/m^2 + rabbit ATG 5 mg/kg;
- Rabbit ATG 5 mg/kg (divided into three days: D -3, D-2 and D-1).

Comments:

Transplantation should be performed in patients under ten years of age, preferably before five years of age[33,55]. The dose of busulfan should be myeloablative and based on the patient's weight and preferrable with pharmacokinetics.

GVHD prophylaxis for patients with matched related or unrelated donors (bone marrow) should be performed with cyclosporine and a short course of methotrexate (D1 15mg/m2, D+3, +6 and D+11: 10mg/m^2). For patients receiving related cord blood transplants, GVHD prophylaxis performed with cyclosporine with metilprednisolone or mycophenolate mofetil.

BODY WEIGHT	MG/KG/DAY56
3 to 15kg	5.1
15 to 25kg	4.9
25 to 50kg	4.1
50 to 75kg	3.3
75 to 100kg	2.7

TELOMERE BIOLOGY DISEASE OR DYSKERATOSIS CONGENITA (DC)

Recommendation:

The indication for transplant includes patients in the aplastic phase, myelodysplasia, or acute leukemia. In the ideal scenario, HSCT should be performed before transfusions, serious infections, or clonal evolution[51]**.** The prototype of telomeric biology disease (TBD) is DC; however, we recommend that transplants also be performed in patients with severe aplasia and very short telomeres (<1%), even in the absence of classic symptoms of DC.

Conditioning:

Patients with matched related or unrelated donors[36,51]

• Cy 60 mg/kg (divided into 4 days: D -6, D-5, D-4, D-3);

• Mesna 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);

• Fludarabine 150 mg/m^2 (divided into 5 days: D -6, D-5, D-4, D-3 D-2);

• Rabbit ATG 5 mg/kg (divided into three days: D -3, D-2 and D-1).

GVHD prophylaxis: same as in Fanconi anemia.

SHWACHMAN-DIAMOND SYNDROME

Recommendation[51,57] **:**

• Progressive cytopenias or pancytopenia.

• Dependence on blood transfusions.

• Progression to MDS / LMA.

Conditioning:

Patients with matched related or unrelated donors[41,43]

• Cy 120 mg/kg + Fludarabine 150 mg/m^2;

• Mesna 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);

• Rabbit ATG 5 mg/kg (divided into three days: D-3, D-2 and D-1).

Comments

Although there is no consensus regarding the best conditioning for SBDS patients, the best results were obtained in patients receiving a reduced-intensity conditioning regimen using a matched related or unrelated donor[41,43].

GVHD prophylaxis for patients with matched related or unrelated donors should be performed with cyclosporine and a short course of methotrexate (D1

15mg/m^2, D+3, +6 and D+11: 10mg/m^2). If possible, methotrexate can be substituted by mycophenolate mofetil 45mg/kg/day divided into three doses.

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIC PURPURA

Recommendation[58,59]

• Severe thrombocytopenia and transfusion-dependent patients.

• Pancytopenia or evolution to MDS / AML.

CONDITIONING:

Patients with matched related or unrelated donors:[59,60]

• Busulfan 16 - 20 mg/kg EV + Fludarabine 160 mg/m^2.

• Rabbit ATG 5 mg/kg (divided into three days: D -3, D -2 and D -1).

The busulfan dose should be myeloablative and based on the patient's weight and preferrable with pharmacokinetics, as mentioned before.

GVHD prophylaxis for patients with matched related or unrelated donors (bone marrow) should be performed with cyclosporine and a short course of methotrexate (D1 15mg/m^2, D+3, +6 and D+11: 10mg/m^2). For patients receiving related or unrelated cord blood transplants, GVHD prophylaxis performed with cyclosporine with metilprednisolone or mycophenolate mofetil

CONCLUSION

HSCT is currently the only curative option for the hematological complications related to the different IBMFS[21,47,61].

All family donors should be screened before considered potential donors.

Patients and their families should be informed that HSCT corrects only the hematological manifestations of the disease.

We advise that all transplant patients be followed up for a lifetime to prevent or detect early changes resulting not only from HSCT but also from the underlying genetic disorder[25].

Iron overload should be treated aggressively. Patients with DC/TBD may have progression of the disease with pulmonary and liver fibrosis and vascular complications. Particular attention should be paid to the increased risk of cancer in all IBMFS, especially in FA, DBA, and DC[25,26].

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PREVENTION AND MANAGEMENT OF RELAPSE OF ACUTE LEUKEMIA AND MYELODYSPLASTIC SYNDROME AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN PEDIATRIC PATIENTS

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SUMMARY

The best way to manage acute leukemia relapse after HCT is to prevent it, buying time for GVL with immunomodulation and, if no GVHD between days +60 and + 90, prophylactic DLI can be indicate for very high or high risk patients. Short-term low dose of cyclosporine or methotrexate can add safety to pro-DLI, particularly after mismatched or unrelated transplantation. Maintenance with imatinib or dastinib, recommended for Ph-positive ALL, with sorafenib, for FLT3-ITD AML, or azacitidine, for myelodysplastic syndrome patients, can be effective in reducing relapse rates. However, target agent maintenance can add toxicity, depends on patient adherence and demands physician experience to know when is safe to start, how adjust the dose according individual tolerance after transplant and to detect undesirable drug interactions. The second step to avoid hematological relapse is preemptive approach guided by measurable residual disease or mixed chimerism. In patients off immunosuppression, chemotherapy followed by DLI is a useful strategy, and if no response, interferon alpha can be associated to enhance GVL. Target-specific agents can be start at this point either. After relapse, antigen-directed therapy with blinatumumab for CD19 ALL, inotuzumab for CD22 ALL are excellent options to induce MRD negativity and facilitate HCT. Disadvantages of new immunotherapies are: high incidence of VOD with inotuzumab and gemtuzumab; lower response in patients with high leukemia burden or concurrent extramedullary relapse; necessity of consolidation with HCT after a bridging therapy with BiTE and probably with CAR-T cell therapy also. It is important to realize that if remission after chemotherapy is associated with the development of GVHD, then there may be limited benefit (and possibly harm) in consolidating with any kind of cellular therapy. However, for patients who achieved remission without GVHD, either DLI or second transplant can be recommend. Further studies are necessary to determine at which point each strategy might yield the best results.

Keywords: Acute leukemia, myelodysplastic syndrome, relapse, allogeneic hematopoietic cell transplantation

INTRODUCTION

Advances in leukemia biology knowledge, supportive care and combined treatment approaches added to the recent progress in haploidentical transplantation, which made possible a significant increase of donor availability for allogeneic hematopoietic cell transplantation (allo-HCT), had resulted in cures for approximately 85% of children with lymphoblastic acute leukemia (ALL) and 70% for those with myeloid acute leukemia (AML) or with myelodysplastic syndrome (MDS).[1-2] Allo-HCT is considered an established treatment for patients with high risk hematological malignancies.[3] The 3-year overall survival (OS) for children with ALL or AML varies, according disease phase, from 76-60% for early and intermediate to 50%-30% for advanced phase, respectively, with comparable outcomes after matched sibling (MSD) or matched unrelated (MUD) HCT.[4] Relapse incidence (RI) following transplantation varies from 13 to 47%, depending on patient, disease and transplant features, while the incidence of CNS relapse, the most common site of extramedullary relapse, varies from 3.9 to 9.4% for patients without or with prior CNS disease, respectively.[5,6]

In Brazil, two recent retrospective multicenter studies evaluated outcomes in pediatric patients and observed lower OS rates compared to higher-income countries. Tavares and cols.[7] reported acceptable 3-year relapse rates of 23% (30/130) for ALL and 18% (15/82) for AML/MDS patients transplanted with unrelated HCT, which were similar among donor type groups: matched (26%), mismatched (21%) and umbilical cord blood (13%) ($P = .18$). A higher relapse incidence (43%) was published by de Melo Rodrigues and cols.[8] when they analyzed 114 AML patients that received MSD (49), MUD (59) and haploidentical (6) HCT. The 4-year progression-free survival (PFS) for all cohort was 40%. Relapse occurred at a median of 122 days. After relapse, 12 patients received a second HCT, and four received donor lymphocyte infusion (DLI). Of the patients who experienced relapse, only six (12.2%) survived. The authors observed a significant association ($P < 0.0001$) for 4-year PFS, with worse outcomes recorded for patients in third or subsequent complete remission (CR) (HR 6.71) and for those with active disease (HR 3.08) at transplant.

The mainly risk factors for relapse in children with acute leukemia after HCT are advanced disease phase at transplantation, pre and post-HCT positive measureable residual disease (MRD) and absence of GVHD. Besides that, presence of high risk cytogenetics and molecular alterations at diagnosis, such as: BCR-ABL mutations; MLLT4-KMT2A; IKZF1 e 2; ETV6/RUNX1-like; iAMP21; TCF3/HFL; FLT3-ITD, monosomy 7, complex karyotype and TP53 mutations, among others, increase disease recurrence after HCT.

Graft-versus-leukemia effect (GVL) and myeloablative conditioning are crucial tools in prevention of leukemia relapse after allo-HCT. The GVL takes time to happen and, meanwhile, host leukemic cells persistence, which escaped the cytotoxicity of conditioning, can induce leukemia recurrence. Other mechanisms, such as: chemotherapy or graft insufficiency, inadequate responses by effector cells, immune mechanisms resistance induced by ALL blasts, migration of leukemic cells to sanctuaries protected from immune attack, inhibition of antitumor response by the tolerance conferred by immune microenvironment components (mesenchymal stem cells and T, B, NK regulatory cells), also contribute to relapse.[9,10] Standard recommendations to prevent relapse after transplant include: 1) improve disease control before HCT; 2) increase graft GVL potency by optimizing donor selection, conditioning, graft-versus-host disease (GVHD) prophylaxis; 3) keep disease under control until the GVL occurs, which can be achieved through target agents maintenance, immunosuppression (IS) modulation and/or prophylactic DLI; 4) monitor and act immediately if detect impending relapse. Advances in immunomodulatory interventions and maintenance approaches, with tyrosine kinase inhibitors (TKI) or hypomethylating agents (HMAs), have benefit selected patients.[8-13] Pulsipher et al reported[9], in a multicenter prospective study, risk factors and timing of relapse after allogeneic transplantation in a pediatric population diagnosed with ALL. They concluded that there is a window between day +55 and day +100 to 200 when most high-risk patients have not relapsed yet and that this population could benefit from measures to avoid relapse at that time.

TKI MAINTENANCE POST-HCT

Relapse after HCT for Philadelphia chromosome-positive (Ph+) ALL remains a significant challenge. Since the incorporation of TKI in first line treatment protocols, its maintenance post-HCT was indicate. Chen[14] and cols. compared outcomes in pediatric patients, 62 with imatinib versus 20 without maintenance post-HCT. Multivariate analysis identified maintenance therapy post-HCT with imatinib as an independent prognostic factor for DFS ($p = .0001$, HR =4.8) and OS ($p = .0001$, HR = 6.2). **According to E**sPhALL 2010 protocol, daily imatinib should start at 200 mg/m^2 by day +56, provided that satisfactory counts with stable neutrophil engraftment (plate-

let >50×10^{9} cells/L, WBC >1·5×10^{9} cells/L, and neutrophils >0·5×10^{9} cells/L for at least 15 days) were achieved. If well tolerated, daily dose should be increase to 300 mg/m^2 until 12 months.[15]

The Acute Leukemia Working Party of the EBMT[16] published a state position on the use of TKI to prevent relapse after allo-HCT for patients with Philadelphia (Ph) positive ALL. The authors made important recommendations to guide dose reductions according TKI toxicities, disease monitoring, maintenance duration and specific indications such as the choice of dasatinib maintenance for patients with previous CNS involvement. They advised that for patients transplanted in CR1 and continuous MRD negativity maintenance shoud last 12 months, but those transplanted in CR2 or a later remission should prolong TKI use indefinitely, unless precluded by poor tolerability or safety concerns. They concluded that the available data are insufficient to determine the better tolerated TKI in post-HCT setting. The choice has to be personalized according comorbidities and transplant complications. Moreover, patients with GVHD or transplant-related morbidities and undetectable MRD post-HCT may use TKI prophylactically or, alternatively, only after the detection of MRD (preemptive strategy). A recent systematic review performed by Warrich and cols.[17], analyzed comparatively survival outcomes with first and second-generation TKI maintenance on post-HCT setting in Ph+ ALL adult patients. They showed that the use of either imatinib or dastinib after transplant for patients in CR1 improved OS when given as a prophylactic or preemptive regimen. Limited data suggest that second-generation TKI (i.e., dasatinib) have a better OS, especially in patients with MRD-positive status. Imatinib did not improve OS in patients who were > CR1 at the time of HCT. The evaluation of survival benefit with newer generation TKI and their efficacy in patients transplanted in > CR1 needs further study in large randomized clinical trials. Evaluation of the use of dasatinib for maintenance post-HCT in Ph+ ALL children is an unmet need. Watanabe and cols.[18] reported prolonged molecular remission with dasatinib pre and post-HCT in a 10-year boy with imatinib resistant Ph+ ALL transplanted in molecular remission. Dasatinib use started on day +102 at 20 mg/m^2/day and gradually increased to 50 mg/m^2/day. After 2-year-lasting molecular remission, dasatinib was suspended, and the patient was still in remission at day +905 MRD analysis. Recently, Shen and cols.[19] conducted a phase 3 RCT study with 189 children to compare the efficacy of dasatinib versus imatinib in pre-HCT setting. Dasatinib (80 mg/m^2/day) was more effective than imatinib (300 mg/m^2/day) in the treatment of children with Ph+ ALL. Dasatinib therapy provided excellent control of CNS leukemia without the use of prophylactic cranial irradiation. These evidences justify the use of dasatinib as an option for maintenance post-HCT in pediatric patients, however routinely hematological counts and cytomegalovirus PCR screening are necessary for adequate dose adjustment and to prevent hemorrhagic colitis dasatinib induced, associated or not with CMV.[20]

FLT3-Internal Tandem duplication (ITD)-mutated AML is associated with poor outcomes. Allo-HCT can improve cure rates in children and adults, however around 35% of patients relapse. Maintenance post-HCT with sorafenib, an oral TKI with activity against FLT3, c-KIT, PDGF, VEGF and Raf, is a currently recommendation for FLT3-ITD-mutated AML patients, based on significant improvements in DFS, OS and a marked 65% reduced risk for relapse with two years of TKI therapy.[21] Tarlock and cols.[22] reported the response of 15 pediatric patients with FLT3-ITD-mutated AML to prophylactic (6) or therapeutic (9) sorafenib, which started around day +100 and was suspended at 18 months post-HCT. Initial median dose was 150 mg/m^2/day. Overall, 73% of patients experienced significant toxicities, although sorafenib did not appear to exacerbate graft versus host disease in this study. Among patients who experienced toxicity, 7/11 (64%) received doses ≥ 200 mg/m^2/day, which was later determined to be the maximum tolerated dose of sorafenib for pediatric leukemia. The authors observed a relevant efficacy of sorafenib in patients with MRD positive, since all patients treated for MRD immediately prior to transplant or with emergence of MRD after transplant were alive, in complete remission, at a median of 48 months post-HCT. Thus, for patients not receiving prophylaxis, administration of TKI at the first detection of MRD is recommend. Patients who achieve MRD-negative response by molecular detection methods may not require second HCT. More recently, Xuan and cols.[23] retrospectively evaluated sorafenib therapy (dose range, 200-800 mg daily) in 144 FLT3-ITD-mutated AML transplanted patients, with ages between 14 and 57 years. The study multivariate analysis showed that, compared with control group, the utilization of sorafenib before transplantation, as maintenance after HCT, and their combined application were significantly protective factors for a lower relapse rate (HRs: 0.44, 0.43 and 0.17, respectively) and for a longer LFS (HRs: 0.32, 0.34, and 0.19, respectively).

Sorafenib maintenance post-HCT (group A) was compared with prophylactic DLI (group B) and with patients without prophylactic intervention (group C) by Shi and cols.[24] in a retrospective study with 68

FLT3-ITD positive AML patients who received MSD (n = 21), MUD (n = 7) and haploidentical (n = 40) transplantation. The overall range of age was 12 – 62 years. When interventions started, all patients who received pDLI or sorafenib had complete chimerism, were negative for MRD and FLT3- ITD mutation and had no active GVHD. Sorafenib maintenance started at a median of 83 days post-HCT and last for a median of 238 days. Group B received DLI only once at a median of 102 days post-HCT. The median of $CD3^+$ cell dose was 3.4×10^7/kg. The 2-year OS, LFS, and CIR were 95.8%, 95.8%, and 4.2%, respectively, for group A; 75%, 66.7%, and 25.0%, respectively, for group B; and 67.0%, 60.9%, and 33.4%, respectively, for group C. Overall survival and LFS were significantly higher in sorafenib group. The grade II–IV aGVHD incidence was significantly higher after DLI than in sorafenib group (46.3 vs 8.7%, P < 0.001), but there was no significant difference between these groups in cGVHD incidence.

DNA HYPOMETHYLATING AGENTS (HMAS) POST-HCT

The most common non-targeted pharmacologic approach to treatment and prevention of relapse after HCT for AML and MDS has been HMAs (azacitidine and decitabine). Their mechanism of action post-HCT is uncertain, but they can induce allogeneic $CD8^+$T cell response by enhancing the expression of epigenetically silenced tumor-associated antigens. HMAs may also induce the GVL response through increased expression of tumor antigens.[25] Prophylactic azacitidine (Aza) post-HCT was first evaluated in a phase I study of 45 adults heavily treated previously, which established an optimal dosing schedule for maintenance to be 32 mg/m^2 IV × 4 cycles and resulted in a 1-year OS rate of 77%. Reversible thrombocytopenia was the dose limiting toxicity.[26] Unfortunately, this study extension to a phase III randomized controlled trial (RCT), failed to show significant differences for OS and DFS between Aza and control groups (p = .85 and p= .14), respectively.[27] However, pediatric case series[28-29] reported low incidence of relapse with prophylactic low-dose Aza (32 to 36 mg/m^2) as maintenance post-HCT. Despite the limitations of small numbers, a potential benefit in disease control of this approach warrants further investigation.

Recently, Hurchart and cols.[30] reported the results of a protocol combining Aza maintenance with prophylactic DLI (pro-DLI) performed in 10 high-risk AML pediatric patients. Aza started on Day +60 at 36 mg/m^2 for a 5-day monthly course from day +90, for 6 cycles. The dose was reduced to 24 mg/m2 if grade 3 or 4 of hematologic toxicity or increase of bilirubin >3x upper limit of normal persistent for > 2 weeks. Escalated pro-DLI started after Day +120 in patients off immunosuppression for at least 1 month, repeated every 6 weeks and limited to three doses. Patients with previous grades III-IV aGVHD were excluded. Initial CD3/kg doses were 10^6 for MSD, 0.5 x 10^6 for MUD and 0.5 x 10^5 for MMUD and haploidentical HCT. The increase of subsequent doses was by 0.5 log each. Nine patients (90%) remained in CR with median follow up of 17 months. These preliminary results suggest that post-HCT maintenance therapy with Aza and pro-DLI in pediatric setting is feasible, safe, and may contribute to improved event free survival.

PROPHYLACTIC DONOR LYMPHOCYTE INFUSION

Although the efficacy of therapeutic DLI in relapsed acute leukemia may be suboptimal, pre-emptive or, particularly, prophylactic DLI is effective approaches. However, the risk of severe acute GVHD (aGVHD) remains an obstacle to successful earlier use of DLI after HCT. To balance GVHD risk and GVL effect, the first pro-DLI $CD3^+$ cell dose should vary between 10^4 and 10^6/kg, according donor type, mainly if given before 6 months after HCT.[31] Some authors suggest that is safe and more effective to administer G-CSF-primed DLIs early after transplant, and this kind of manipulation can provide GVL effect without significant GVHD.[32-34] Yan and cols.[34], in a multicenter prospective study, evaluated the impact of G-CSF-mobilized peripheral blood stem cells (pro-G-DLI) followed by MRD and GVHD-guided multiple G-DLIs in preventing relapse after transplant in 100 patients (aged 6 – 60 yrs.) with refractory/relapsed acute leukemia. The pro-G-DLI was at 30 days after MSD or 45 to 60 days after MUD or haploidentical transplants. Patients in CR at day+30, without GVHD and uncontrolled infection were eligible. Subsequently G-DLIs were according GVHD occurrence and MRD results (at 1, 2, 3, 4.5, 6, 9, and 12 months and at 6-month intervals thereafter). Patients with positive MRD received chemotherapy and G-DLI. The median dose of mononuclear cells, CD3+ cells, and CD34+ cells for each G-DLI was 10^8/kg, 0.37 x 10^8/kg and 0.65 x 10^6/kg, respectively. Before pro-G-DLI, all patients received 2.5 mg/kg/day of cyclosporine (CsA) to prevent GVHD. After G-DLI, CsA dose and duration were adjusted according blood levels and MRD results, respectively. The 3-year CIR, DFS, and OS were 32.4%, 50.3%, and 51.4%, respectively. The authors suggested that this prophylactic and disease guided combined intervention reduced relapse and increased survival

post-transplant in patients with refractory/relapsed acute leukemia.

The risk of GVHD after unmanipulated DLI in the haplo-HCT/PTCy setting is comparable to DLI from an HLA-matched donor, following the recommended dose of $CD3^+$cell/kg according the indication: prophylactic or preemptive (10^5) and therapeutic (10^6). Patients with high-risk myeloid malignancies may benefit from a pro-DLI, which ideally should be performed in clinical trials. However, manipulated haplo-DLI, such as selectively depleted or gene-modified T cells, only should be used on clinical trial setting.[35] In a prospective study by Gilman et al. [36], reported 34 pediatric patients that received an unmanipulated prophylactic haplo-DLI after a T-cell depleted /CD34+ selected haplo-HCT, with GVHD prophylaxis with MTX between d+30 and d+42. The intervention was safe and 2-year NRM and OS were 25% and 63%, respectively. Similarly, Jaiswal et al. [37], in a prospective trial, evaluated the use of prophylactic G-CSF-primed peripheral blood progenitor cell (GBPC) in the T-cell replete haplo-HCT/PTCy setting. Twenty-one patients with AML (not in remission) received up to three doses of haplo-GPBC (d+21, d+35 and d+60). All patients received GVHD prophylaxis post-DLI. The control group consisted on 20 patients who received routine monitoring after haplo-HCT. In DLI cohort at 18 months, CIR, PFS, and OS were 21%; 62% and 71%, respectively and results were significantly superior compared with controls. Incidence of aGvHD was 31%, while incidence of chronic GvHD was 41% after GBPC infusions. NRM was equivalent between the groups.

MEASUREABLE RESIDUAL DISEASE CONSIDERATIONS

Improvements on relapse surveillance post-HCT became possible due to advances in monitoring MRD. The recommended methods for MRD surveillance are: multicolor (six to ten colors) flow cytometry (MFC); real-time PCR (for Ig and TCR rearrangements and fusion gene transcripts) and, more recently, next-generation sequencing of Ig or TCR genes (NGS - MRD).[12] For ALL patients, the adequate time to access MRD is between 12 a 30 days before HCT, and those with MRD positive should receive additional treatment pre-HCT.[38] This approach is not well defined for AML patients, and, unless in cases where target agent can be apply, a positive MRD must not delay the transplant, since allo-HCT provides acceptable survival rates in AML, even in patients with very high risk disease.[11]

MRD post-HCT is more important than pre HCT[6], and screening at days +30, +60, +90, +180 and + 365 is the routine adopted by most Brazilian centers. However, recent US National survey[5] revealed a higher frequency of relapse detection at day +270 (11.9%) compared to day +365 (0%). MRD for ALL patients are classified according quantitative PCR or MFC results, respectively, as following: MRD negative (if undetectable); MRD low positive if $< 10^{-4}$ or 0.01%; MRD high positive if $> 10^{-4}$ to $< 10^{-3}$ or > 0.01 to 0.1%; and MRD very high positive if $\geq 10^{-3}$ or >0.1%. Bader and cols.[6] derived a risk score with an MRD cohort from Europe, North America, and Australia, using negative predictive characteristics (advanced disease status, non–total body irradiation regimen, and MRD [high, very high]) defining good, intermediate, and poor risk groups for relapse. They validated the score in a second cohort, more recent, and the 2-year CIR were 13%, 26%, and 47% ($p < .001$) for the defined risk groups.

Ph-positive ALL patients should be evaluate also for the presence of BCR-ABL transcripts and ABL kinase domain mutations before HCT and after engraftment. The PCR monitoring of BCR-ABL rearrangement should start 4 weeks after transplant, be repeated every 6 to 8 weeks in bone marrow (BM) and monthly in peripheral blood (PB), during the first year post-HCT.[16] After that, we recommend monitoring as follows: every 3 months in PB during the second year post-HCT, besides the 18-month BM analysis, every 6 months in PB until five years from transplant and annually afterwards. The detection of MRD should prompt rapid confirmatory testing in BM.

MRD sensitivity limit by MFC for AML is around 10^{-4} to 10^{-5}. Adequate sample cellularity and standardized protocols to detect leukemia-associated immunophenotypes (LAIPs) is mandatory for accurate MRD results. However, reliable analysis of post-transplant MRD for AML patients requires also a high level of expertise, knowledge of regenerative bone marrow marker expression patterns, and an integrated approach of LAIP-based Different from Normal (DfN), which is crucial to identify new LAIPs due to clonal evolution and occurrence of immunophenotypic shifts in regenerative marrow after therapy. Despite that, MFC is currently the most commonly used method to determine MRD in AML patients. Molecular PCR based techniques have higher sensitivity than MFC MRD, depending on the specific gene and the used molecular technique. The chosen genes for the MRD assay are NPM1, RUNX1-RUNX1, CBF-MYH11, FLT3 and WT1. Although FLT3 harbors frequent recurring mutations, the internal tandem duplication (FLT3/ITD) is highly unstable and can be gained or lost during therapy. However, *FLT3*/ITD negativity does

not imply that residual leukemia cells are absent, and therefore highly sensitive techniques will be required to ensure *FLT3*/ITD negativity. The detection of Wilms' tumor 1 *(WT1)* by mutation and expression, has also been used by several centers for disease monitoring but the ELN 2018 MRD guidelines stated that *WT1* expression should only be used when there is no other MRD marker available.[39]

A more sensitive method of MRD detection, NGS, is improving the predictive value of MRD for relapse and survival in ALL and AML patients after HCT. Thus, as soon become more widely available, NGS MRD should be incorporate into ALL and AML studies to identify patients who are at high risk for post-HCT relapse to allow timely interventions in order to improve patient outcomes.

DONOR CHIMERISM CONSIDERATIONS

Monitoring the post-HSCT dynamics or kinetics of chimerism status by serial bone marrow analysis at same points of MRD (listed above), as well as on suspicion of relapse or graft failure, is needed to monitor engraftment, disease control and to predict relapse. Intervals ranging from weekly to monthly chimerism analysis have been used in clinical trials. Particularly for pediatric leukemia patients, is recommended to follow chimerism closely, alternating blood samples with the scheduled marrow analysis, every 2 weeks until day +100, at monthly basis until one year and yearly afterwards, to a minimum of 5 years post-HSCT to monitor for secondary graft failure and as a marker of possible minimal residual disease and relapse. Analyses can be limited if complete chimerism has been reached and sustained, if not, serial analyses should be performed at short time intervals when a decreasing donor chimerism or persistent MC is detected.[40]

Chimerism analysis shows the donor origin hematopoietic cells percentage thus, complete chimerism (CC) is when 100% of hematopoietic cells are of donor origin; mixed chimerism (MC) when both donor and recipient hematopoietic cells are present and split chimerism when CC has been achieved in one or more cell lineages while other cell lineages still shows a mixed pattern. Low-level chimerism is when host cells are detect in a proportion < 1% of hematopoietic cells. Mixed chimerism can be classified as decreasing MC (reduction of host cells) and increasing MC (host cells increasing). The cell lineages generally used are mononuclear and granulocytic, but CD34+cells and specific-leukemia lineage (marrow sample) chimerism analysis can predict relapse more accurately. Chimerism is preferentially evaluated by amplification of short-tandem-repeats markers (STR-PCR), due to its high sensitivity (nearly 100%). It can be performed also by X/Y FISH (only applicable in sex mismatched HCT) and RT-qPCR, with 50 % and 90% of sensitivity, respectively.[40-41]

Relapse prediction using chimerism relies on the interpretation of chimerism kinetics. A sustained MC or drop on donor chimerism early after HSCT has shown to be an independent risk factor for relapse and impaired survival after MAC, RIC or NMA conditioning, in both adults and children, independent of the underlying hematological malignancy. Chen and cols.[42] showed that early achievement of CC in pediatric ALL patients after MAC transplant was associated with a longer PFS. Brolie and cols[43] evaluated chimerism trends in 63 children who underwent HCT for AML or MDS. Mixed T-cell chimerism at engraftment and absence of cGVHD were associated with relapse ($P = 0.04$ and $P = 0.02$, respectively). Mixed T-cell chimerism at engraftment was predictive of relapse in patients without cGVHD ($P = 0.03$).

Preemptive post-HSCT interventions based on MRD and chimerism kinetics

Reduction or cessation of immunosuppression (IS) and/or DLI single or on escalonated doses can convert a MC to CC, thereby boosting the GVL effect. The efficacy of these strategies combined or not for mixed chimerism conversion has been confirmed in retrospective and cohort studies[44-46] and by pediatric prospective trials[47-49] also. Horn[49] and cols. evaluated prospectively 71 pediatric AML patients and found that the rapid IS tapering with or without DLIs in patients presenting with MC on 2 consecutive blood or bone marrow samples until achievement of CC could significantly improve DFS. The DLI CD3+ cells dose/kg schedule was according donor type, with first doses of 10^5 to 10^6, increased by 0.5 log for each subsequent dose until limits of 10^7 and 10^8 for MUD and MSD, respectively.

Fresh whole blood DLI, obtained by collection of small aliquots from donors, seems to be a very cost effective technique and an attractive form of immunotherapy for children. Swaminathan and cols.[50] reported their experience with early withdrawal of IS and the use of fresh whole blood DLI to mitigate relapse of leukemia and prevent graft rejection after HCT in children with mixed chimerism, transplanted for benign diseases or leukemia. In total, 58 patients received DLI, in an escalating dose regimen with $CD3^+$cell/kg as follow: $1x10^5$ (or 10^4 for haploidentical recipients), 5×10^5 and $1x10^6$, depending on the graft kinetics and the clinical status of the children.

The 2-year OS and DFS were 81.1% and 67.2%, respectively. The collection by phlebotomy is safe for the donors, particularly for the younger pediatric donors, who otherwise, to donate lymphocytes through apheresis machine, would need a venous catheter and volume expansion or a red blood cell pack to tolerate the procedure. This preemptive DLI escalating regimen works well for patients who requires repeated lower doses of T cells.

Since monitoring MRD in Ph-positive leukemia by qRT-PCR for BCR-ABL rearrangements in marrow and blood is easy, some investigators have advocated for a MRD-triggered approach instead prophylactic. The first choice can be imatinib or dasatinib in cases with previous resistance to imatinib or presence of ABL kinase domain mutations before or after HCT, since the use of ponatinib is not approved for children yet. Patients with early molecular recurrence, within first three months after HCT, or those with more than 10^4 transcripts at any time after HCT, appear to have little benefit with imatinib, and should be started on dasatinib at 50-100 mg/day or, if intolerance, on nilotinib at 200 mg every 12 hours, with close monitoring for toxicities.[16] In one prospective evaluation of 27 patients undergoing allo-HCT for Ph^+ALL, preemptive imatinib at MRD detection post-HCT was associated with prolonged disease-free survival in approximately half of patients, which could be anticipated by rapid achievement of molecular remission in response to therapy.[51] A phase II study, compared maintenance or preemptive MRD-triggered imatinib in 55 Ph-positive ALL patients and showed low rates of hematological relapse in both arms. Although, molecular recurrence was lower for maintenance compared with preemptive strategy.[52]

Some cytokines have been evaluated on their capacity to improve the efficacy of donor cells. An older approach with new interest is the combination of GM-CSF and/or interferon alpha (IFN-α) and DLI. Both cytokines increased the capacity of dendritic cells and leukemia cells to present target antigens, and improved donor T-cell stimulation by providing co-stimulatory signals and adhesion molecules.[53] Cooper and cols.[54] showed better disease control with the use of IFN-α to augment GVL responses, with or without DLI, in high-risk leukemia, not cured with standard transplant measures. However, they observed a high rate of GVHD (59%) and morbidity, probably due the high dose and prolonged exposition of IFN used. They suggested that earlier IFN-α use, prompted by detection of MRD, coupled with its rapid cessation at onset of GVHD, may potentiate GVL effect and reduce mortality from GVHD in this high-risk group of children. The Chinese group put it into practice, and in consecutives, prospective clinical studies[55-57], showed the safety and the efficacy of preemptive IFN-α-2b in acute leukemia and MDS pediatric and adult patients with MRD positive post-HCT. The IFN schema was 3 million units 2–3 times per week subcutaneous, for median treatment duration of 35 days (range, 4 to 180 days). The first study[55] compared the preemptive use of IFN-α alone to G-DLI preceded by chemotherapy and showed similar 1-year cumulative incidence of relapse, NRM and DFS (27.3% versus 35.6%; p=.514), (4.5% versus 4.4%; p=.985) and (68.2% versus 60.0%; p=.517), respectively. Both approaches were significantly better than those of the MRD-positive patients with IS tapering or without preemptive interventions. All patients treated with G-DLI received IS (CsA or MTX) for 2 to 6 weeks after infusion. The authors observed that, even when IFN-α treatment was discontinued, due to active GVHD, MRD remained significantly decreased and MRD-negative status was achieved, and discussed that IFN-α indeed might promote the GVL effect and clear tumor cells, through enhancement of NK cell cytolytic activity as well as up-regulation of interleukin-2 (IL-2) production by T cells. In a subsequent study[56], they investigated the efficacy of salvage IFN-α in 24 patients who persisted MRD-positive at 1 month after G-DLI (unsatisfactory response). IFN-α-2b started within 3 months after G-DLI, before hematological relapse, with the same schema described above, except for a reduction to 3 million units/m^2 for patients ≤ 16 years (maximum of 3 million units) and longer treatment duration (median 80 days, range, 19–187). Most patients (75%) achieved molecular remission, the majority of them within two months and 12.5% at > 2 months after the start of IFN-α treatment. The 2-year DFS, OS, severe aGVHD (G-III/IV), chronic and severe cGVHD were 54.3%, 68.0%, 8.3%, 37.5% and 16.7%, respectively.

More recently, the same group, extended the cohort of preemptive IFN-α treatment to 68 Ph-negative ALL patients who had MRD positive after allo-HCT, half of them in a single bone marrow analysis (MRD sin+) and half with consecutives MRD positive (MRD-co+), and compared the outcomes with 18 non-IFN controls. They found that patients with MRD sin+ benefit more from preemptive IFN-α after allo-HCT. They stated that would be premature to derive conclusions regarding the superiority of IFN-α treatment over chemo-G-DLI for MRD positive patients. However, the outcomes were encouraging, with low incidences of NRM (6%), severe acute (2.9%) and cGVHD (7.5%) and significantly higher 4-year probabilities of DFS (62%) and OS (71%) for IFN-α group compared

to controls. Thus, preemptive IFN-α treatment could protect against relapse and improve long-term survival for ALL patients who had MRD after allo-HCT.[57]

TREATMENTS OPTIONS FOR HEMATOLOGIC AND EXTRAMEDULLARY RELAPSE

For many decades, treatment options for hematologic or extramedullary relapse (EMR) include chemotherapy, DLI, radiotherapy, second allo-HCT and often a combination between them. The landscape of strategies for relapsed/refractory leukemia has advanced a lot with the availability of molecular targeted therapies and new immunotherapies including antibody-drug conjugates, bi-specific t-cell engagers (BiTEs) and chimeric antigen receptor T (CAR-T) cells. Unfortunately, low and middle in-come countries have very limited access to these new therapies due to cost issues. For all interventions, their benefits and potential risks, particularly occurrence of severe GVHD, must be evaluate in each patient.[9]

The approach to post-HCT relapse has to be personalized. No simple algorithm can be adopted to address relapse after transplantation, mainly in pediatric patients. The choice of salvage therapy has to be guide by several factors, such as disease histology, donor availability, presence of targetable mutations, tumor burden, post-transplant interval, patient clinical condition, presence of active GVHD, concurrent immune suppression medications and previous treatments (response and toxicities). Standard chemotherapy can be used, combined or not with DLI or molecular target agents (bone marrow relapses) or local therapy (radiotherapy, surgery for combined or isolated extramedullary relapses). However, response rates are between 30 to 50% and toxicity can be high. If success in inducing complete or near CRs with any of the cited approaches, the question is which would be the best option: ongoing chemotherapy, DLI or inhibitor maintenance, observation, second HCT or CAR-T cell. For ALL patients with hematological relapse prophylactic intrathecal therapy (IT), usually with methotrexate, cytarabine and steroids, is recommend during chemotherapy or immunotherapy treatments.

The salvage chemotherapy for leukemia relapse before and after HCT have been change for less extended and toxic protocols. Recent comparison between FLAG and FLAG-IDA, in 76 adults and pediatric patients with relapsed and refractory acute leukemia, showed a significant higher CR rate, OS and subsequent transplant rate for FLAG regimen (p= 0.033).[58] Bertaina and cols.[59] evaluated bortezomib in combination with dexamethasone, doxorubicin, vincristine and pegylated asparaginase (VXLD) in 30 and 7 children with B-cell precursor (BCP) and T-cell ALL, respectively. Fifteen (40%) had previous HCT and the median interval for relapse was 218 days. The CR or CR with incomplete platelet recovery (CRp) rate of patients with previous allo-HCT was 60%. Among the 27 patients who achieved CR/CRp, 18 underwent allo-HCT. Moreover, 12/16 patients who had failed blinatumomab responded to this combination, with 5 of them achieving MRD <0.1%. The overall 2-year OS and DFS were 31·3%, but CR/CRp patients with an MRD response had a remarkable 2-year OS of 68·4%. Similarly, a multicenter European study[60], explored the efficacy of re-induction including bortezomib in pediatric relapsed/refractory acute lymphoblastic leukemia. Patients were randomized 1:1 to bortezomib (1.3 mg/m2 /dose) administered early or late to a dexamethasone and vincristine backbone, with MTX intrathecal; both timing led to same results. The overall response rate (CR+ PR) was 60% with a low intensity schedule, in a heavily pretreated cohort of patients.

Chemotherapy combined with DLI is a useful strategy to treat leukemia relapse following HCT. In hematological relapse, the efficacy of DLI alone varies according type and burden of the disease. Since higher doses of $CD3^{+}$cell would be necessary, substantial risk of severe GVHD is a limitation, mainly after unrelated or haploidentical HCT. Most patients receiving single therapeutic DLI relapse and succumb to their disease. Close monitoring of MRD and chimerism after a successful therapeutic DLI is important to identify the patients who are at high-risk of subsequent relapses. Yan and cols.[61] confirmed these observations in a prospective study, including adults and pediatric patients, 66% of them underwent haplo-HCT. They concluded that MRD-guided repeated administration of chemo-G-primed-DLI protocol was effective in reducing the risk of subsequent relapse after achieving initial disease response and the utilization of short-term IS, with CsA after haplo-DLI and CsA or MTX after matched- DLI, could preserve GVL effect and either reduce the incidence of severe aGvHD.

The Acute Leukemia Working Party of European Society for Blood and Marrow Transplantation (EBMT) consensus[35] recommend cytoreductive therapy prior to haploidentical DLI for patients with a hematologic relapse after T-replete with PTCy transplants and that $1x10^{6}$ CD3+cells/kg is a reasonable starting dose, followed by dose escalation every 6 weeks depends on disease response and GVHD. They stated also that long-term immune tolerance after PTCy may be enough to overcome the immunological barrier of haplo-DLI and G-CSF priming may be

not required in this setting. Besides that, since mismatched-HLA allele loss occurs in one-third of leukemia relapses after a haplo-HCT and such patients are unlikely to benefit from DLI or second HCT from original donor, this possibility must be investigate. If HLA loss confirmed, a second transplant from a related donor with a different mismatched haplotype or a mismatched unrelated donor may be considered.

Several transplant groups have been evaluated the combined chemo-DLI and chemo-second HCT strategies.[61-71] Tables 1 and 2 summarizes the main ones of them.

Willasch and cols.[62] reported the Frankfurt experience in a retrospective study which compared the results of 23 ALL patients relapsed post-HCT and treated with high-dose chemotherapy or specific immunotherapy (HDCHT/SIT) followed by a second HCT (transplant approach) or low-dose chemotherapy and repeated DLI (LDCHT+DLI) (non-transplant approach). The time point of relapse (until or after day +200) guided the decision how to treat. Eight patients received HDCHT/SIT, followed by haploidentical HCT in 7/8. Ten received LDCHT+DLI and five palliative care. The transplant approach and non-transplant approach groups had comparable 4-year OS of 56% and 40%, respectively (p=0.232). Prerequisites related with successful treatment of post-transplant relapse by either approaches were donor availability, good clinical condition and the capacity to achieve hematological remission by the induction treatment element. In a larger cohort study, Roux and cols.[63] aimed to compare treatment strategies in 334 consecutive children with acute leukemia relapse or progression after HCT in a 10-year period. Data of 288 evaluable patients showed that the median OS duration after relapse differed according to therapy: chemo-DLI (385 days), second allograft (391 days), chemotherapy (174 days), isolated DLI (140 days) and palliative care (43 days). A second HCT or a combination of chemotherapy and DLI yielded similar outcome (HR = 0.85, p=0.53), unlike chemotherapy alone (HR=1.43 P=0.04), isolated DLI (HR=1.94, p <0.04) or palliative care (HR=4.24, p<0.0001). Despite limitations of this retrospective analysis, strategies including immuno-intervention appear superior to other approaches, mostly in AML.

A multicenter Spanish study [64] also reported comparable outcomes for acute leukemia (AL) relapsed patients treated with debulking therapy followed by DLI or second allo-HCT. The time interval from HCT to relapse was the only statistically significant factor with impact on outcomes, a shorter time associated lower OS and DFS. Within the DLI cohort, previous T-cell-depleted HCT was associated with higher OS (p = 0.003) and DFS (p < 0.001) and lower CI of relapse (p = 0.002) than T-cell-replete HCT.

Dahlberg and cols. [65] helped to define subsets of pediatric patients that may have a realistic chance for long term OS with current therapies. They stated that, in contrast to ALL, it was possible to achieve DFS in patients with early AML/MDS relapse, likely due in part to better response to DLI, which was able to bridge some AML/MDS patients to second HCT. Patients with AML/MDS also were less likely to have received a TBI-containing regimen as conditioning for the first HCT allowing a myeloablative TBI-based second HCT regimen, which was associated with increased OS. Factors associated with improved survival included late relapse (greater than 12 months), ALL in first CR at the time of first transplant and chemotherapy-based first conditioning regimens.

The EBMT Paediatric Diseases Working Party analyzed registry data of 373 children from 120 centers with relapsed leukemia who underwent second allo-HCT between 2004 and 2013. The 2-year OS and DFS rates were 38% and 30%, while at 5 years were 29% and 25%, respectively. Favorable prognostic factors for OS and LFS included >12 months between transplantations and occurrence of cGVHD after the first HCT (in both groups), achieve CR before the second HCT (ALL group only), and age >12 years (AML group only). Results were more consistent over time in the ALL group, with no significant differences between 2-year and 5-year rates of relapse, NRM, and LFS. The authors stated that relapsed acute leukemia pediatric patients have a substantial likelihood of long-term survival following second HCT.[66] Similarly, Lund and cols.[67] reported a 2-year LFS of 33% after second HCT in remission compared to 19% for children and young adults with acute leukemia not in remission (p=0.02). The corresponding 8-year probabilities were 24% and 10% (p=0.003). Late relapse led to a 10% decrement in LFS beyond the second year after second HCT. This differs from first HCT were most relapses occur within 2 years after HCT. Given the many novel targeted and immunomodulation therapies currently under development, these extended analyzes reinforce the importance of stratifying specific subgroups of patients that may benefit from a second HCT compared with those better suited to new approaches.

Despite extramedullary relapse of acute leukemia is relatively rare, with incidence ranging from 6 to 20% in single-center reports, it confers a poor prognosis, mainly if occur early post-transplant. There are no standardized therapeutic strategies for EMR af-

ter HCT. Combination of systemic and local therapy should be considered, given that local therapy alone often results in subsequent systemic relapse. Local therapy includes surgery (mainly for gonads and soft tissues), intrathecal injection, and/or radiotherapy, and systemic therapy involves chemotherapy combined or not with target agents (e.g., dasatinib, sorafenib), immunotherapy, and, when indicated, second allo-HCT. The optimal treatment remains controversial. Responses have been reported with some monoclonal antibodies, including rituximab for B-ALL and gemtuzumab ozogamicin for AML EMR. Azacitidine and decitabine can be successfully used in the salvage treatment of AML patients who experienced EMR after allo-HCT also. It was hypothesized that HMAs are directly cytotoxic and also might increase the GVL effect by inducing leukemic cell differentiation and expression of HLA-DR to enhance the effects of DLI given concomitantly, since EMR usually do not respond well to DLI alone.[72]

Central nervous system (CNS) relapse in post-transplant setting, particularly for ALL patients, with prior CNS disease, pre-HCT craniospinal radiation and conditioned with ≥ 12 GY dose of TBI plus cranial boost, is considered a challenge. Intrathecal therapy, usually with methotrexate, cytarabine and steroids, is mandatory for cerebrospinal fluid blasts clearance and maintenance, if response. However, refractory disease can happen and IT or intraventricular administration of rituximab is an option for this group of patients. Ceppi and cols. [100] reported, in a multicenter intercontinental case series, 25 children with CNS involvement of CD20+ B lymphoid malignancies who received in total 163 IT/intraventricular rituximab doses. The median number of doses received by each patient was 6, with a median dose of 25 mg. The most common adverse events were Grades 1 and 2 peripheral neuropathies in five patients (20%), allergy in two patients, and headache in two patients. These events were self-limited, occurring in the 48 hours after treatment and resolving within 24 hr. Three patients had more severe though transient side effects, one a grade III neuropathy and two with seizures. Eighteen patients (72%) of those treated with IT/intraventricular rituximab, with or without other CNS directed treatment, achieved a CNS remission. The authors suggest that IT/intraventricular rituximab has therapeutic efficacy and relatively limited toxicity. Prospective trial of IT rituximab for these patients, with CNS involvement of CD20 + B lymphoid malignancies, is warranted.[73] CNS relapse is less frequent in AML than in ALL patients. Patients with myeloid malignancies, who usually receive a myeloablative chemo-based regimen conditioning for HCT, may benefit of multimodal therapy that include IT therapy, chemotherapy, curative radiotherapy, sometimes DLI and maintenance with target agent if indicated. For some cases this strategy can be sufficient and second HCT can be reserved to be performed only in case of new recurrence.

IMMUNOTHERAPIES AND FUTURE DIRECTIONS

The use of immunotherapy for leukemia has been successful in providing durable remissions for heavily treated, relapsed and refractory patients who otherwise had little chance of cure. The new immunotherapies like antibody-drug conjugates, BiTEs and chimeric antigen receptor T-cells (CAR-T) cells share adverse effects such as: cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which coincide with T cell activation; hypogammaglobulinemia, which can be managed by immunoglobulin administration; invasive fungal infections and venooclusive disease (VOD), particularly with inotuzumab. The BiTEs contain two antibodies, one targeting the CD3 domain of T cells and the other targeting a surface antigen on the tumor, when antibodies are bound to both targets they signal the T cell to degranulate, resulting in cytotoxicity. Blinatumomab was the first BiTe, a CD3/CD19-bispecific T-cell engager, produced for B-ALL. The results of the phase I/II study and several single-institution or national retrospective evaluations showed response rates to blinatumomab ranging from 34–38% to around 60% for children with relapsed or refractory (R/R) ALL.[74] Sheleghel and cols.[75] reported the use of blinatumomab in nine post-transplant relapsed pediatric patients with B-precursor ALL. The protocol used was a 4-week continuous IV infusion at a dosage of 5 or 15 μg/m^2/day, all patients received 18 cycles. Complete remissions were achieved by four patients after the first cycle and by 2 patients after the second cycle (with previous cytoreduction by chemotherapy), while three patients did not respond. Four patients were successfully bridge to second haplo-HCT in molecular remission. The 1-year probability of EFS was 30%. They observed that blinatumomab could induce molecular remission and facilitate subsequent allo-HCT in post-transplant relapsed B-ALL patients with subsequent long-term LFS. The results of both phase III RCTs[76-77] in children with first relapse of ALL confirm the superiority of blinatumomab in achieving MRD-negativity before HSCT and even show evidence for an advantage in OS, with less severe adverse events, mainly infections, compared to conventional chemotherapy. These results warrant the inclusion of blinatumomab into pre B-ALL relapse protocols before or after allo-HCT. Extramedullary escape and CD19 antigen loss

are patterns of relapse following blinatumomab therapy. Interestingly, MLL1 ALL can switch to a myeloid lineage under the pressure of ALL-targeted therapies as a mechanism of resistance.[78]

Blinatumomab and DLI combination is a promising therapy, since blinatumomab might achieve a reduction in disease burden, and after its clearance, DLI can potentially induce GVL, which can provide longer lasting remission. Ueda and cols.[79] reported four adult cases of relapsed pre-B ALL after HCT treated with concurrent blinatumomab and DLI, administered with no acute adverse effects. They kept low-dose of cyclosporine during this treatment in three patients, who achieved CR. Two of them remained in remission at 13 and 7 months of follow up after relapse, probably because they had low disease burden when the therapy started. The patient with extramedullary relapse did not respond. We found also, two case reports of concomitant use of DLI with blinatumomab following a MUD and a haploidentical HCT for mixed lineage acute leukemia[80] and primary mediastinal large B-cell lymphoma[81] relapsed patients, respectively.

Ongoing trials will show if blinatumomab is capable of inducing lasting remissions without a subsequent HCT and if it can be a suitable maintenance post-HCT therapy for high risk patients. Combination therapies with inotuzumab ozogamicin (InO), DLI, checkpoint inhibitors, such as PD-1- or CTLA-4-inhibitors, could enhance the efficacy of blinatumomab and are currently being test.[82] Besides that, the efficacy of antibody-based immunotherapies in relapsed and refractory BCP-ALL is evident, but knowledge on their effect on CNS disease is limited. Limited efficacy in the CNS is probably due to their poor penetration into the CNS, which can, however, be overcome by IT or intraventricular application.

Inotuzumab ozogamicin, an antibody-drug conjugate designed using a monoclonal antibody directed against CD22 bound to the cytotoxic antibiotic calicheamicin.[74] Data from pediatrics studies with InO for R/R-ALL, including post-HCT patients, showed that it was well tolerated and has an antileukemic effect, similarly to what observed in adults. Bhojwani and cols.[83] reported a 67% CR rate in 51 pediatric patients with R/R-ALL treated with InO in a phase I study. The patients were heavily treated and 43% of them had previous HCT. However, among 21 bridged to HCT, 11 (52%) developed sinusoidal obstructive syndrome (SOS), a higher expected rate than was previously observed in adults (11%). The preliminary outcomes of the COG AALL1621 phase 2 trial [84], which tested the efficacy of InO in 48 pediatric patients and young adults in second or greater relapse of B-ALL, showed CR rates > 50%, nearly 33% of whom achieved MRD negativity. A more recent phase 1 study investigated the recommended phase 2 dose of InO in pediatric patients with multiple R/R CD22+ ALL. The dose taken forward to the ongoing phase 2 cohort of this study was 1.8 mg/m^2 (fractionated schedule) during course 1, as recommended in adults; the dose for subsequent courses remains at 1.5 mg/m^2 per course up to a maximum of 6 courses, and limit of 2 cycles if HCT is planned. Additionally, to reduce the incidence of SOS it is recommend a longer interval between InO administration and HCT (i.e., 2 months or more), ursodiol prophylaxis and to avoid conditioning regimens with dual alkylating agents (e.g., busulfan and melphalan) and concomitant hepatotoxic drugs (e.g., azoles).[85]

In comparison with CAR T-cell immunotherapy, blinatumomab and InO are "off-the-shelf" and less expensive products that are easily available for use, in private health services, have been associated with a lower incidence of CRS and a quick reduction is possible in the case of adverse events, such as ICANS or CRS. Blinatumomab or InO can be effectively used to induce often-deep MRD negativity and facilitate HCT, which has been shown to improve outcomes for many patients. Disadvantages are higher incidence of SOS with InO and lower response with blinatumomab in patients with high leukemia burden, concurrent extramedullary relapse, and the fact of all available data in R/R-ALL suggest a necessity for HCT after a bridging therapy. Further studies are necessary to help to determine at which point each therapeutic option might yield the best results.[74]

Several BiTEs targeting some AML-associated surface proteins (CD33, CD123, and CD371) that have shown potent experimental activities are currently undergoing clinical trials. Gemtuzumab ozogamicin (GO), a humanized anti-CD33 monoclonal antibody conjugated to the cytotoxic antibiotic agent calicheamicin, is approved for the treatment of relapsed or refractory CD33-positive AML in adults and children ≥ 2 years old. However, GO treatment has been associated with an increased risk of hepatotoxicity and severe SOS, especially following HCT. Other non-specific serious adverse events associated with GO use are myelosuppression, bleeding/thrombocytopenia, infusion-related reaction, and tumor lysis syndrome. Fractionated dosing using 3 mg/m2 were associated with less toxicity, myelosuppression and VOD with equal efficacy. In a recent review, Cortes and cols. recommended to avoid GO in previously transplanted AML patients.[86]

The revolution in immunotherapy for hematologic neoplasms is the development of CAR-T, a targeted immunotherapy, which utilizes autologous T cells to attack malignant cells. T cells are collected through apheresis from the patient or donor and modified ex vivo, by introducing a gene that codes for an antigen recognition receptor, often a single chain variable fragment (scFv) from an antibody, which is fused to T-cell costimulatory domains. These genetically modified T-cells are transfused to the patient and the cytotoxic killing of the leukemic cells starts.[74]

The safety and efficacy of Tisagenlecleucel (CTL019), an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, was investigated by Maude and cols.[87] in a single-center phase I/II study involving 60 children and young adults with R/R B-cell ALL, conducted at the Children's Hospital of Philadelphia and the University of Pennsylvania showed a rate of complete remission of 93%. The CRS occurred in 88% of patients and were managed with supportive measures and anti-cytokine therapy, including the interleukin-6 receptor antagonist tocilizumab. Long-term disease control without additional therapy and with persistence of tisagenlecleucel for up to 4 years were observed in this cohort.[88] Seattle Children's Hospital group published a phase I/II study[89], which evaluated the efficacy of a CAR-T-cell product, transduced to express a 4-1BB costimulatory domain, in targeting CD19-positive leukemic cells, in 43 relapsed/refractory B-ALL heavily treated patients, with previous HCT in 62%. The maximum tolerated dose was 10^6 CAR T cells/kg. They showed a 93% MRD-negative remission rate within 21 days, and this rate was 100% in the subset of patients who received fludarabine and cyclophosphamide lymphodepletion. The 1-year EFS of 50% and OS of 66%. Reversible severe CRS and/or reversible severe neurotoxicity occurred in 23% of patients. Based on these studies, a global phase 2 pivotal, nonrandomized, trial (ELIANA) of tisagenlecleucel, sponsored and designed by Novartis, was performed to analyze the efficacy, safety and cellular kinetics of tisagenlecleucel. The outcomes of 75 children and young adults with R/R B-cell ALL (61% of whom had a relapse after HCT), who received an infusion of Tisacel, were published by Maude and cols.[90]. Within three months, the ORR was 81%, with all responded patients became also MRD negative. The 6-months and 1-year EFS and OS rates were 73% and 90%, 50% and 76%, respectively. Tisacel persistence in the blood was observed for more than one year after infusion in patients with response to treatment. CRS occurred in 77% of patients, 48% of whom received tocilizumab. Neurologic events occurred in 40% of patients, all managed with supportive care. Nineteen deaths occurred after tisagenlecleucel infusion, 13 (68%) due to B-cell ALL relapse or progression; others causes were: cerebral hemorrhage due to coagulopathy and CRS (1), HHV-6–positive encephalitis due to prolonged lymphopenia (1), systemic mycosis due to prolonged neutropenia (1), unknown cause (1) and 2 deaths due to pneumonia and hepatobiliary disease each (after new therapies for ALL). The authors concluded that Tisacel produced high remission rates and durable remissions without additional therapy. The study was updated by same group[91] and ORR was 82%, and 62% of patients had a CR. Among patients who had CR previously, 66% were still in remission at 18 months, and the ORR was 70% at 18 months post-infusion, with a median OS not reached.

Recently, two studies analyzed the real-world clinical outcomes after Tisacel treatment. Schultz and cols.[92] reported the results from Pediatric Real World CAR Consortium (PRWCC). Retrospective data collected from 15 institutions, included 185 patients infused with Tisacel. At the time of CAR T cell infusion, the median age was 12 years (range 0–26). Early responses at one month and OS and EFS at 6 and 12 months are comparable to reported in ELIANA trial. The rate or CRS and ICANS was low. Comparative analysis of outcomes in patient cohorts with varying disease burden demonstrates decreasing CR, EFS, and OS in patients with high disease burden compared to patients with lower disease burden or no detectable disease at last evaluation before CAR infusion. Pasquini and cols.[93] published the largest set of safety and efficacy data for tisagenlecleucel in a real-world setting, collected from a cellular therapy registry, shared to CIBMTR. This non-interventional prospective study includes 410 patients treated at 73 US centers, who had follow-up data reported (255 pediatric ALL; 155 adults NHL). Among pediatric patients with ALL, the initial CR rate was 85.5% and the 1-year duration of response (DOR), EFS, and OS rates were 60.9%, 52.4%, and 77.2%, respectively; all rates statistically comparable to results observed in the Eliana trial. Grade ≥ 3 CRS and ICANS were reported in 16.1% and 9.0% of patients, respectively, compared with 48.1% and 12.7% of the ELIANA study. Pivotal Tisacel trial did not include children <3 years of age; while 6% of the ALL real-world cohort were age <3 years. Prior allo-HCT was less frequent among patients in this study than the Eliana trial (28% vs. 61%). Primary refractory patients were more common in the registry than in the pivotal trial (15% vs. 8%). The authors concluded that in the real-world setting tisagenlecleucel demonstrates outcomes with similar

efficacy and improved safety compared with those seen in the pivotal trials.

The utilization of allogeneic CAR-T cells is under experimental clinical evaluation. Zhang and cols.[94] presented at the 2020 ASH Annual Meeting the results of the use of CAR-T cells derived from related donors in 37 patients (range of age: 3–61), with R/R B-ALL. Among the 37 patients, 28 relapsed following allo-HCT. For them, the lymphocytes were collected from their transplant donors (3 MSD and 25 haploidentical). For the remaining nine patients without a prior transplant, the lymphocytes were collected from a MSD (n = 5) or haploidentical donors (n = 4). The authors showed that manufacturing CD19+ CAR-T cells derived from donors were feasible. For patients who relapse after allo-HCT, the transplant donor-derived CAR-T cells were safe and effective with a CR rate as high as 96.4%, but they observed inferior efficacy of CAR T-cells derived from haploidentical donors.

Despite second generation of CD19-CAR-T have shown, in real world setting, impressive molecular responses and acceptable toxicity profile, more than half of patients will experience a relapse. Therefore, rather than using CAR-T cell therapy as a stand-alone option, consolidation with allo-HCT might increase long-term outcome. Several other targets, such as CD20 and CD22, dual-targeting CARs, combination therapy and development of allogeneic "off the shelf" therapy are under evaluation.[95]

Immunotherapy for T-ALL with daratumumab, a monoclonal antibody anti-CD38, and with CAR T cells targeting CD1a, CD5, and CD7 are under investigation.[96] Similarly, CARs targeting CD33 and CD123 for treat AML have been tested in preclinical models[97-98], however, these antigens are also expressed on normal bone marrow progenitors, raising concerns about potential bone marrow ablation.[72] Clinical trials with immune-based therapeutic modalities for AML, such as: monoclonal antibodies; T cell engager antibodies; allo-reactive natural killer (NK) cells and CART cell; immune checkpoint blockade via blockade of PD1 (programmed cell death protein 1) and its ligand PD-L1, CTLA4 (cytotoxic T-lymphocyte associated protein 4), TIM3 (T-cell immunoglobulin and mucin domain 3) and macrophage checkpoint blockade, via CD47 with signal-regulatory protein α (CD47/SIRPa) signaling complex, are underway in adults and are expected to move to pediatric AML once safety has been well established. The ongoing clinical research continues to advance our understanding of these immune-based therapies and will help to provide guidelines for more precise clinical indications for leukemia relapsed patients.[99,100]

Table 3 summarizes the preventive and therapeutic interventions reviewed here according to the type of post-HCT relapse.

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TABLE 1. Donor lymphocyte infusion studies including pediatric patients

Study	N. patients	Diagnosis	Indication of DLI ± others	CD3+ cell dose	N. DLI	Disease response	GVHD	LFS	OS	Notes
Willasch et al (2017)	10 8	ALL	[illegible] relapse < day 200 or 2nd HCT not feasible: LD-chemo + [illegible] – 52 weeks + 6 x DLI – each 6 weeks HD-chemo (5) / Blina (3) → ? → Haplo PB – CD3/CD19 depleted (2nd HCT)	Initial: MSD: 1 x 10^6/kg; MUD: 1 x 10^5/kg; MMFD: 2.5 x 10^4/kg; Increase dose by 0.5 log if no GVHD occurred	6 (in 5 pts)	Non-HCT: 4/10 (40%) pts remained CR; HD/Blina group/HCT: [illegible] remained CR	1 death	50% all	4-y OS 40%; 4-y OS 56% (P = 0.23)	4 pts EM relapse [illegible]; NS due to small numbers?; MAC [illegible] HCT-NRM: 1 [illegible], 2 MOF; Chemo-DLI: NRM (GVHD)
Yan et al (2016)	LLA: 32 LMA: 25	LLA LMA	Relapse: consolidation chemo-G-DLI	Median: [illegible]/kg	1 a 4	67% in CR – 1st DLI	a [illegible]; c [illegible]	3-y: [illegible]	3-y: [illegible]	The group with 1–4 consolidations after CR with chemo-G-DLI had < rate of 2nd relapse [illegible] vs [illegible] for pts with only 1 chemo-G-DLI after 1st relapse (p < 0.0001)
[illegible] et al (2017)	288	AML: 123 ALL: 157 Biphenotypic: 8	Chemo-DLI [illegible]; DLI [illegible]; 2nd HCT [illegible]; Chemo only [illegible] x palliative [illegible]	Not reported	Not reported	> B-ALL and late REL	aGVHD [illegible]	F.up [illegible] days: [illegible] for whole cohort	1-y: chemo-DLI: [illegible]; 1-y [illegible]: chemo [illegible], DLI [illegible], Palliative [illegible]	Chemo-DLI and 2nd HCT showed similar outcomes. Pts with B-ALL, GVHD and relapse > 1y after 1st HCT fared better than others.

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, chemo-DLI: chemotherapy + Donor Lymphocyte Infusions; 2nd HCT: second Hematopoietic Cell Transplantation; LD-chemo: low-dose chemotherapy; HD-chemo: high-dose chemotherapy; MSD: matched sibling donor; MUD: matched unrelated donor; MMFD: mismatched familiar donor; PB: peripheral blood; MAC: Myeloablative conditioning; RIC: Reduced Intensity Conditioning, CR: Complete Remission,; OS: Overall Survival, LFS: leukemia free survival; aGVHD: acute graft-versus-host disease; REL: relapse; F.up: follow up; w/o IS: without immunosuppression

TABLE 2. Second allogeneic HCT studies including pediatric patients

TABLE 3- Summary of preventive and therapeutic interventions for relapse post-HCT

Interventions	Prophylactic	Preemptive	Therapeutic	Extramedullary relapse
Immunosuppression withdrawal	yes	yes	yes	yes
Donor lymphocyte infusion (DLI)	yes	yes	yes	no
Chemotherapy + DLI	no	yes	yes	no
Interferon-alpha	no	yes	yes	no
Blinatumomab (CD19 pos ALL)	no	clinical option	yes	no
Inotuzumab (CD22 pos ALL)	no	clinical option	yes	no
CAR-T cell therapy	no	no	yes	no
Local therapy Surgery and/or radiotherapy intrathecal therapy	no no	no no	no yes	yes yes
Hypomethylating agents (AML/MDS)	clinical option	yes	clinical option	no
Tyrosine kinase inhibitors (Ph-positive acute leukemia* or FLT3-ITD AML	yes	yes	yes	yes
Chemotherapy	no	yes	yes	yes
Second-HCT	no	no	yes	yes

*according mutacional status; only without active GVHD; chimeric antigen receptor T cell

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EARLY COMPLICATIONS IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has the potential to cure a significant proportion of patients with malignant and nonmalignant diseases. The high doses of chemotherapy and/or radiotherapy included in conditioning regimens affect all organs and tissues, producing several early and late complications.

The most common early effects are nausea, vomiting and mucositis. Other early complications, less frequent, but cause of morbidity and mortality are hemorrhagic cystitis, sinusoidal obstruction syndrome, thrombotic microangiopathy, capillary leak syndrome, engraftment syndrome, diffuse alveolar hemorrhage, idiopathic pneumonia syndrome.

NAUSEA/VOMITING

The conditioning regimens used in HSCT are known to have a high emetogenic risk. Nausea and vomiting are some of the most feared adverse effects of chemotherapy and radiotherapy. Studies show that administering prophylactic regimens concordant with published guidelines significantly reduces and controls symptoms for patients receiving moderately or highly emetogenic treatment. Focused on the prevention, guidelines recommend a combination of aprepitant, dexamethasone and a serotonin antagonist in pediatric patients.[2,4]

Emetogenic potential of intravenous antineoplastic agents

Probability of vomiting	Agent
High	Busulfan IV ≥0,8mg/kg/dose Cyclophosphamide IV (≥ 1200mg/m²/dose) Melphalan IV Carmustine Carboplatin IV ≥175mg/m²/dose Cisplatin IV ≥12mg/m²/dose Cytarabine IV ≥3g/m²/day Methotrexate IV ≥12g/m²/dose Thiotepa ≥300mg/m²
Moderate	Cyclophosphamide IV (1000mg/m²/dose) Cytarabine IV 75mg/m²/dose Methotrexate IV 5g/m²/dose Ifosfamide
Low	Cyclophsphamide IV 500mg/m²/dose Mitoxantrone IV ≤33mg/m²/dose Etoposide Methotrexate IV ≤90mg/m2/dose Procarbazine PO
Minimal	Fludarabine Vincristine IV ≤1,5mg/m²/dose

*Adapted from Sing EPC et al4 and EBMT Handbook[2]

MUCOSITIS

Mucositis is characterized by mucosal damage ranging from mild inflammation to extensive ulceration, which may affect the oral cavity and other parts of the gastrointestinal tract. It is seen in 75-99% of patients who had combined total body irradiation and chemotherapy. It peaks between day 6 and 12 and resolution coincides with engraftment. Oral mucositis causes disturbances in feeding, swallowing, and speaking, along with the possibility of secondary severe infection. Basic oral care consists of a pre-transplant oral/dental examination aimed at decreasing the oral infectious and inflammatory burden, and routine mouth care with bland rinses and soft toothbrush. Cryotherapy prevents oral mucositis in protocols containing high dose melphalan. Oral mucositis is often so severe that patients require parenteral narcotics for relief of pain and total parenteral nutrition.[2,5,6] Oral mucositis grading scales are below:

WHO SCORE	
GRADE 0	No objective findings, function irrelevante
GRADE 1	Erythema plus pain, function irrelevante
GRADE 2	Ulceration, ability to eat solids
GRADE 3	Ulceration, ability to eat liquids
GRADE 4	Ulceration, nothing by mouth

WHO ORAL MUCOSITIS SCALE	
0	None
1	Soreness +/- erythema
No ulceration	
2	Erythema, ulcers
Patients can swallow solid diet	
3	Ulcers, extensive erythema
Patients cannot swallow solid diet	
4	Mucositis to the extent that alimentation is not possible

*Adapted from WHO classification

HEMORRHAGIC CYSTITIS

Hemorrhagic cystitis is characterized by diffuse bladder inflammation and bleeding, with sustained hematuria and lower urinary tract symptoms, in the abscence of other conditions such as vaginal bleeding, bleeding diathesis, or urinary tract infection. It has significant morbidity, prolonged hospitalization and occasional mortality. Symptoms vary from microscopic to macroscopic hematuria with clots, urinary obstruction, and renal and/or bladder damage, and dysuria.[1,3,7,8]

GRADING SYSTEM FOR HEMORRHAGIC CYSTITIS	
GRADE I	Microscopic hematúria
GRADE II	Macroscopic hematúria
GRADE III	Macroscopic hematuria with small clots
GRADE IV	Gross hematúria with clots causing urinary tract obstruction requiring instrumentation for clot evacuation

*Adapted from Decker DB et al[7]

Etiology:

1) Chemotherapy: alkylating agentes (especially cyclophosphamide and ifosfamide): the main metabolite, acrolein, can precipitate in the bladder, causing mucosal edema, ulceration, epithelial necrosis and submucosal fibrosis;

2) Infectious: adenovírus, cytomegalovirus, BK vírus – cytopathic effect on bladder mucosa, causing inflammation;

3) Radiotherapy: causes chronic fibrosis, endarteritis and mucosal desquamation.

Prevention:

The three main approaches for prophylaxis of cyclophosphamide-induced hemorrhagic cystitis include mesna, hyperhydration with forced diuresis, and continuous bladder irrigation.

Treatment:

Intensive intravenous hydration, forced diuresis, analgesia, spasmolytic drugs, treatment of infections. Progression of hematuria and possibly clot retention often necessitate bladder irrigation. In more aggressive cases, it is possible to use cystoscopy, clot evacuation, and fulguration1,3,7,8.

Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome (SOS), also called hepatic veno-occlusive disease (VOD), remains a complication after HSCT and belongs to a group of systemic endothelial diseases. Toxic metabolites generated by the conditioning regimen damage the sinusoidal endothelial cells and hapatocytes in zone 3 of the hepatic acinus. The first events are loss of fenestrae in endothelial cells, formation of gaps, and rouding up or swelling. Red blood cell, leukocytes and debris penetrate into the space of Disse and dissect off the sinusoidal lining. The venous lumen narrows and sinusoidal venous outflow is reduced, resulting in post-sinusoidal hypertension9-11. Risk factors are below:

Transplant-related factors	Unrelated donor HLA-mismatched donor Non T-cell-depleted transplant Myeloablative-conditioning regimen Oral or high-dose busulfan-based regimen High-dose TBI-based regimen Second HSCT
Patient and disease-related general factors	Older age Karnofsky score below 90% Metabolic syndrome Female receiving norethisterone Advanced disease (beyond second CR or relapse/refractory) Thalassemia Genetic factors (GSTM1 polymorphism, C282Y allele, MTHFR 677CC/1298CC haplotype)
Hepatic-related	Transaminases >2.5 upper limit of normal Serum bilirubin >1.5 upper limit of normal Cirrhosis Active viral hepatites Abdominal or hepatic irradiation Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin Hepatotoxic drugs Iron overload
Specific pediatric risk factors	Osteopetrosis Hemophagocytic lymphohistiocitosis Griscelli syndrome X-linked lymphoproliferative disease Neuroblastoma Hemoglobinopathies Infants (age <1-2 years)

*Adapted from Mohty M et al10 and Corbacioglu S et al[11]

Clinical manifestations are weight gain, fluid retention with ascites and anasarca, painful hepatomegaly, jaundice, consumption of platelets (it is usually one of the earliest signs in children) and multi-organ dysfunction in severe cases with pleural effusion, renal failure and encephalopathy9-11. Differences between children and adults are below:

CRITERIA	CHILDREN	ADULTS
INCIDENCE	Approximately 20% Up to 60% in high-risk patients	Approximately 10%
RISK FACTORS	Additional pediatric factors: -Infants - Pediatric/genetic diseases with incidences above average	Established risk factors
CLINICAL PRESENTATION	Late-onset in 20% Anicteric in 30% Hyperbilirubinemia, if present: -Is frequently pre-existent -Occurs late during SOS -Is typical of severe SOS	Late-onset is rare Anicteric is rare
NEED FOR PROPER ASSESSMENT OF ASCITES AND HEPATOMEGALY	High incidence of disease-related hepatomegaly and ascites pre-HSCT	
TREATMENT	Defibrotide for severe SOS with multi-organ dysfunction/failure was associated with better results in children	
PREVENTION	Defibrotide demonstrated efficacy for prevention in children in a randomized prospective trial	

*Adapted from Corbacioglu S et al[11]

The diagnostic criteria recently published by European Society for Blood and Marrow Transplantation (EBMT) are below:

EBTM diagnostic criteria for hepatic SOS in children
-No limitation for time onset of SOS
The presence of two or more of the following:
-Unexplained consumptive and transfusion-refractory thrombocytopenia
-Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain >5% above baseline value
-Hepatomegaly (best if confirmed by imaging) above baseline value
-Ascites (best if confirmed by imaging) above baseline value
-Rising bilirubin from a baseline value on 3 consecutive days or bilirubin >2mg/dL within 72h

*Adapted from Corbacioglu S et al[11]

Diagnostic imaging is complementary. Ultrasonography (US) is more available, and as a bedside tool. Computed tomography and magnetic resonance imaging can substitute for or complement US. The most common findings are hepatomegaly, ascites, hepatic artery resistive index, velocity of portal venous flow, increased periportal echogenicity and increased hepatic echotexture, and gallbladder wall thickening. Doppler US assesses hepatic and portal vascular flow, pressure abnormalities and hepatic arterial early acceleration indices. Portal venous flow reversal (hepatofugal flow) are not consistently present or are a late finding, and might therefore be useful for the assessment of severity rather than early diagnosis.[11]

Severe SOS resulting in multi-organ dysfunciton/failure, EBMT criteria for grading the severity is below:

CRITERIA	MILD (1)	MODERATE (2)	SEVERE (3)	VERY SEVERE (4)
Liver function test	<2x normal	>2 and <5x normal	>5	>5
Persistent refractory thrombocytopenia	<3 days	3-7 days	>7 days	>7 days
Bilirubin (mg/dL)	<2	<2	>2	>2
Ascites	Minimal	Moderate	Necessity for paracentesis	Necessity for paracentesis
Bilirubin kinetics				Doubling within 48h
Coagulation	Normal	Normal	Impaired coagulation	Impaired coagulation
Renal function (mL/min)	89-60	59-30	29-15	<15 (renal failure)
Pulmonary function (oxygen requirement)	<2L/min	>2L/min	Invasive pulmonar ventilation (including CPAP)	
Central nervous system	Normal	Normal	Normal	New onset cognitive impairment

*Adapted from Corbacioglu S et al[11]

Prophylaxis for SOS includes reducing iron overload, use reduced intensity conditioning regimen if possible, busulfan pharmacokinetic monitoring, avoid acute fluid overload. For those patients receiving a busulfan(Bu)-cyclophosphamide(Cy) regimen, studies show that the order of application of Cy and Bu as impact on lower incidence of SOS. Ursodeoxycholic acid reduces hydrophobic bile acids, which can be toxic to hepatic parenchymal cells, and randomized trials demonstrate a reduced risk of SOS in transplant patients. Heparin is not suggested for prophylaxis in adults, but some studies showed a significant reduction in SOS in children.[12-15]

The treatment includes supportive care (restriction of fluids, diuretics, and renal replacement in severe cases) and use of Defibrotide (6.25mg/kg/dose, 4 times a day). Corticosteroids can be used in some cases where Defibrotide is not available or in combination with Defibrotide in severe cases. The initial dose is 500mg/m2/dose every 12 hours for six doses and gradual reduction.[12,16]

Implementation of the new criteria for diagnosis and assessment of the severity of SOS allowed earlier identification of patients in need of intervention for the better treatment of SOS.

Transplant-Related Thrombotic Microangiopathy

Transplant-related thrombotic microangiopathy (TA-TAM) is a side effect that usually occurs in the first

100 days after hematopoietic stem cell transplantation (HSCT), with undetermined incidence and more frequently reported in allogeneic bone marrow transplantation.[17] TA-TAM corresponds to a clinical syndrome resulting from endothelial injury, with platelet activation and microthrombi deposition at the capillary level, which may lead to consequent ischemic injury of several organs and microangiopathic hemolytic anemia. It presents a wide variety of severity levels, and there may be mild self-limited conditions up to multiple organ dysfunction with mortality up to 80%.

The pathogenesis of TA-TAM is not fully understood yet, however, it is known that endothelial injury plays a central role in its origin. During an early period of HSCT, several factors may lead to a hypercoagulable states in the endothelium due to collagen exposure and tissue factor activation, such as, conditioning regimen, use of colony growth factors, HLA incompatibility, long period of immobility and infections. This scenario leads to a second phase, which causes further endothelial injury and starts platelet aggregation, abnormal activation of the complement and thrombus formation in microvessels. At this time, the use of calcineurin inhibitors, especially when associated with mTOR inhibitors, in addition to GVHD and infectious conditions are the main responsible for the endothelial injury[17]. Abnormal activation of the classical and alternative complement pathway causes endothelial damage, propagating its dysfunction.[18,19]

The kidney is the main target organ, also accompanied by gastrointestinal tract, heart, lungs and central nervous system. The main signs include increased creatinine serum level, proteinuria and hypertension, nonspecific conditions that also can happen in patients without TA-TAM. Impaired renal function may not be present, but its absence should not exclude the diagnosis. Signs of pulmonary hypertension, headache, diarrhea, vomiting, abdominal pain, gastrointestinal bleeding and pericardial effusions may be the predominant symptoms, and therefore they should be highly suspicious18.

The most common and early clinical manifestations seen in TA-TAM are hypertension, thrombocytopenia, and increased lactate dehydrogenase serum level (LDH). Proteinuria may be also present about 10-14 days before the diagnosis of microangiopathy. Thus, patients who present risk factors should be routinely screened twice weekly LDH dosage, weekly urinalysis, and a careful follow-up of blood pressure assessment, especially in the first 100 days post- HSCT. [20,21,22]

Hypertension is a common post- HSCT side effect, however, when its levels are upper than expected while using calcineurin or steroid therapy, usually requiring >2 antihypertensive medications, it should increase clinical suspicion for TA-TMA and be further investigated.

The diagnosis is confirmed by biopsy of the target organ, but due to the complexity and performing risks, such evidence is hardly feasible.[1] Therefore, TA-TAM is confirmed by using diagnostic criteria. There is a wide variety, according to the authors, in the parameters to be evaluated, which makes it difficult to evaluate its incidence. The four most used currently are described below:

	BMT-CTN	IWG	Cho et al	Jodele et al
Schistocytes	>2 Per field	> 4%	>2 Per field	Present
Elevated LDH	+	+	+	+
Thrombocytopenia	-	+	+	+
Decreased Hb or increased red cell transfusion	-	+	+	+
Negative coombs test	+	-	+	-
Decreased haptoglobin	-	+	+	-
Renal and/or neurologic dysfunction	+	-	-	Hypertension or proteinuria
Normal coagulation studies	-	-	+	-
Elevated soluble C5b-9	-	-	-	+
Abbreviations: BMT-CTN =Bone Marrow Transplant Clinical Trials Network; Hb =hemoglobin; IWG =International Working Group; LDH =lactate dehydrogenase; TA-TMA = transplant-associated thrombotic microangiopathy; '+'= required; ' – ' =not specified				

*Adapted from Khosla J et al[18]

It is important to rule out others conditions that can be similar to TA-TAM, as sinusoidal obstruction syndrome, autoimmune hemolytic anemia and other types of microangiopathy, like thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)[20].

The factors associated with worst severity in TA-TAM are the presence of proteinuria and evidence of activation of the complement terminal pathway (increased dosage of C5b-9) showing survival rates under 20% when two factors are present, however, the last mentioned is not performed in Brazil[21,23]. Another easy to be performed parameter, which can help predict prognosis, is the TAM index based on the relation of LDH (in U/L) by platelet count (in x109/L), which when ≥ 100 is associated with lower survival[20,24].

Since fast start of therapy leads to better survival rates and long-term outcomes, regular screening and early diagnosis are important. Initial treatment is based on reducing the factors that can induce TA-TAM, and should be promptly performed by treating infections and GVHD, in addition to discontinuation of calcineurin inhibitors. However, the change of immunosuppressors in the presence of GVHD should be done with precaution, since its reactivation can lead to worsening of the microangiopathy scenario. In addition, hypertension should be strictly controlled by the risk of posterior reversible encephalopathy syndrome (PRES).

The benefit of plasmapheresis is controversial, being described only in small cohorts[25]. Most studies describe low survival rates despite the initial response to it26. If performed, its early onset seems to be associated with better survival, especially when there is still no target organ injury[25,27]. Initially, daily sessions should be performed for at least 2 weeks, with subsequent gradual pause according to clinical and laboratory response. Rituximab can be used alone or in association with plasmapheresis and is especially effective in the presence of antibodies.

The use of eculizumab, an inhibitor of the complement terminal pathway, is associated with better results and survival[28,29] and should by choice be used in all high-risk cases (proteinuria >2mg/mg or target organ injury – C5b-9 dosage not performed in Brazil). In the disease displayed by gastrointestinal bleeding, doses of eculizumab with shorter pauses (up to alternate days vs weekly) should be used29. Attention should be given to a higher risk of encapsulated bacteria infections related to its use, and antimicrobial prophylaxis should be established. In general, the discontinuation of eculizumab use after induction and maintenance phases is not associated with reactivation of the disease.

Several reports have been made regarding the benefit of the use of defibrotide in the treatment of TA-TAM20.

Currently, prophylaxis with N-acetylcysteine and omega[3] has been described as effective in reducing the incidence of TA-TAM with the rates in the pediatric high-risk population falling from 28.2% to 4.5%30.

CAPILLARY LEAK SYNDROME

Capillary leak syndrome is characterized by the loss of intravascular fluids into interstitial spaces and is triggered by a combination of inflammation and endothelial damage. Patients presents sudden weight gain, generalized edemas (ascites, pleural effusion, pericarditis) unresponsive to diuretic treatment, and hypotension eventually leading to cardiovascular shock with respiratory and pre-renal insufficiency. It is mainly observed in children, although true incidence is unknown (some series: 5%)[1,3,31].

Diagnostic criteria include: early after HSCT (days +10 to 11), unexplained weight gain >3% in 24h, positive intake balance despite furosemide evaluated 24h after its administration. (livro EBMT)

Treatment: withdraw growth factors and supportive care (colloids, catecholamines, plasma). Corticosteroids can be used. Intravenous immunoglobulin (IVIG) and Bevacizumab (anti-VEGF) have been used in some cases with good response[1,3,31].

ENGRAFTMENT SYNDROME

Engraftment syndrome (ES) includes a range of signs and symptoms occurring close to granulocyte recovery after stem cell transplantation is performed. ES is classically observed after autologous HSCT, although it has also been described after allo-transplantation. Several names can be given to this syndrome, as capillary leak syndrome, autoaggression syndrome (after autotransplants), aseptic shock syndrome and autologous GVHD. There is not a consent regarding the definition of ES, which makes it difficult to dictate the incidence and risk factors. There are also conflicting data regarding an association between ES, NRM and survival32-34.

The pathophysiology of ES is poorly understood although it probably involves release of pro-inflammatory cytokines, consequence of degranulation and oxidative metabolism, and systemic endothelial damage that may ultimately result in multi-organ failure[35]. In some cases, the concomitant administration of G-CSF, which is highly toxic to endothelial tissue, contributes to its development[1].

Diagnosis criteria for ES typically includes fever from non-infectious etiologies and features of systemic vascular leak. The two most used diagnostic criteria were described according to Spitzer and Maiolino and are listed below.

	Spitzer	Maiolino
Requirements	3 major or 2 major + 1 minor within 4 days of the engraftment	major + 1 minor within 1 day from presence of neutrophils
Major criteria	- Temperature ≥ 38.3 °C with undefined infectious etiology - Erythrodermatous rash compromising 25% of body surface area and not caused by a medication - Non-cardigenic pulmonary edema, expressed by diffuse pulmonary infiltrate, expected with this diagnosis, and hypoxia	- Non-infectious fever
Minor criteria	- Hepatic impairment with either bilirubin 2 mg/dL or transaminase serum levels twice baseline - Renal insufficiency (serum creatinine twice baseline - Weight gain 2.5% of baseline body weight - Transient encephalopathy unexplainable by other causes	- Skin rash - Pulmonary infiltrates - Diarrhea starting 24 hours before or at any time after the first rise of neutrophils

Regardless of the criteria used to diagnose ES, it is important to distinguish ES from other complications including acute GVHD, and radiation and drug-related toxicities and infections. Whether the ES cytokine cascade contributes to the initiation of GVHD after allotransplantation or is an early manifestation of ES is unclear[36].

ES may be self-limited and require no therapy. In several cases with clinically significant manifestations of vascular leak, in the absence of other etiology, treatment with corticosteroid 1 mg/kg/day as a starting dose is usually enough. ES is highly responsive to corticosteroid and treatment is given only as long as symptoms persist, which typically occurs within 2 to 3 days, followed by progressive lowering[36,37].

DIFFUSE ALVEOLAR HEMORRHAGE

Diffuse alveolar hemorrhage (DAH) is probably a consequence of damage to the alveolar capillary basement membrane[3]. It is a non-infectious complication that occurs in up to 5% of patients post-HSCT and carries a high mortality (60-100%). Clinical presentation is hypoxemia, dyspnea, diffuse opacities on chest radiography, and progressively bloodier bronchoalveolar lavage on bronchoscopy. Alveolar hemorrhage results from loss of integrity in the alveolar-capillary basement membrane, and accumulation of red blood cells in the alveolar space. Lung injury from conditioning regimens, total body irradiation, occult infections, and other comorbidities such as graft versus host disease, TMA, and cytokine

release and inflammation are risk factors. Management includes supportive measures (intensive care, ventilation, optimization of fluid and electrolyte balance, correction of coagulation and prophylactic antibiotics), transfusion of blood products, corticoids. Some studies demonstrate benefits with aminocaproic acid, nebulized tranexamic acid, recombinant activated fator VII[3,38].

IDIOPATHIC PNEUMONIA SYNDROME

Idiopathic pneumonia syndrome (IPS) is a rare complication following HSCT, defined by diffuse alveolar injury in the abscence of active lower respiratory tract infection, cardiac or renal dysfunction, and iatrogenic fluid overload. The incidence ranges from 2% to 15% in the first 120 days after HSCT. Some risk factors are full intensity conditioning, TBI, older age at transplant, acute GVHD, diagnosis of acute leukemia or myelodysplastic syndrome. Clinical presentation is variable but includes fever, non-productive cough, dyspnea, tachypnea and hypoxemia. X-rays or CT scans demonstrates diffuse alveolar or interstitial infiltrates. The pathogenesis is multifactorial, with endothelial cell activation and injury for toxic effect of conditioning regimens, leading to release of inflammatory cytokines, specifically TNF-alfa. The treatment includes supportive measures: oxygen therapy, ventilation (invasive or not – high-flow nasal, CPAP), empiric antimicrobials and control of fluids. Specific treatment options are corticosteroids, and Etanercept (an TNF-alfa binding protein). Despite the advances, the mortality from IPS remains high at 59-80% at 2 weeks of evoluition[3,39].

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ACUTE AND CHRONIC GRAFT-VERSUS-HOST-DISEASE – A FOCUS ON PEDIATRIC PATIENTS

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ABSTRACT

Graft-versus-host disease (GVHD), either in its acute or chronic form, is the main contributory factor for morbidity and non-relapse mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Recent advancements in the classification of this disease, with better applicability and reproducibility of standardized criteria, coupled with improvements in the management of steroid-refractory or resistant cases, have led to promising results. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society for Blood and Marrow Transplantation and Cellular Therapy (SBTMO) convened a task force to provide updated, evidence-based guidance for the diagnosis, classification, staging, prophylaxis, and treatment of GVHD, with a focus on the pediatric population, the results of which are presented here.

Keywords: Graft-Versus-Host Disease, Diagnosis, Classification, Grading, Staging, Prophylaxis, Treatment, Hematopoietic Stem Cell Transplantation, Pediatric, Consensus Guidelines.

DEFINITION AND RISK FACTORS FOR ACUTE AND CHRONIC GRAFT-VERSUS-HOST DISEASE

The original classification of acute graft-versus-host disease (GVHD) was published in 1974 and was based on time of onset as the sole criterion. From 2005 onwards, patients presenting with typical acute GVHD (aGVHD) symptoms before D+100 were categorized as having "classical aGVHD", whereas those with such manifestations starting after D+100 were classified as having "late onset or recurrent aGVHD"[1].

In 2005, the *National Institutes of Health* (NIH) published a new set of consensus guidelines harboring both the diagnostic and the grading criteria for chronic GVHD (cGVHD), including various aspects pertaining to the diagnosis, classification, and treatment of this post-hematopoietic stem cell transplant (HSCT) complication[1,2].

Roughly a decade later, in 2014, the NIH updated these guidelines, which kept the original structure, but added more robust evidence-based guidance for the diagnosis and management of cGVHD[3]. These guidelines focused on controversial aspects, including, but not limited to, the distinction between active disease and prior tissue injury. Additionally, the diagnostic criteria for target-organ involvement, such as mouth, eyes, genitalia, and lungs, were thoroughly revised, and cGVHD-related organ impairment was specifically addressed. In short, this update aimed at a comprehensive diagnostic and prognostic assessment of cGVHD, as well as at better guidance toward appropriate treatment and defining eligibility for clinical trials, with greater specificity and precision.[3].

A number of risk factors have been widely recognized as related to an increased incidence of

aGVHD[4,5,6]. These factors may be directly related to the recipient, the donor, the graft, or the HSCT itself. Age, baseline disease, sex (particularly female donor to male recipient combinations), Human Leukocyte Antigen (HLA) mismatch, conditioning regimen intensity, GVHD prophylaxis used, stem cell source (peripheral blood > bone marrow > umbilical cord blood), CD34+ count, T-lymphocyte depletion, and infection risk are among the main risk factors in this regard.

During the last few years, several biomarkers have been investigated as potential surrogates for a greater occurrence of aGVHD or a worse response to therapy[7]. In this respect, a panel of four biomarkers has been more widely investigated: suppressor of tumorigenesis 2 (ST2), regenerating islet-derived 3-alpha (REG3α), tumor necrosis factor (TNF) alpha receptor type 1(TNFR1α) and interleukin-2 receptor alpha (IL-2Rα orCD25)[7]. ST2, for instance, has been shown to be an important biomarker of treatment-resistant aGVHD[7]. Nonetheless, these biomarkers are not yet available for use in clinical practice in Brazil.

The Endothelial Activation and Stress Index (EASIX) serves as a practical tool for identifying patients with high-risk GVHD, since it is based on readily available laboratory markers, namely: lactate dehydrogenase (LDH), serum creatinine, and platelet count[8]. The EASIX score may be useful for identifying patients, including children, with aGVHD who are at greater risk of death, particularly in the reduced-intensity conditioning (RIC) setting, where a statistically significant difference was shown[8]. The EASIX score may thus become an important clinical tool for the development of a risk-adapted strategy toward the treatment of GVHD[8].

As for cGVHD, the main underlying risk factor is a prior history of aGVHD.

ACUTE GVHD DIAGNOSIS AND CLINICAL DESCRIPTION

Acute GVHD is a reaction of donor immune cells against host tissues which can occur after allogeneic HSCT (allo-HSCT). The three main tissues affected by acute GVHD are skin, liver, and gastrointestinal (GI) tract. Its onset normally correlates with engraftment of donor cells.

Acute GVHD is commonly suspected based on the clinical presentation that represents the organs involved. The earliest and most common manifestation is skin GVHD. This is essentially a maculopapular rash that can begin anywhere in the body but often starts in palm and sole, with or without pruritus or tenderness in affected areas. If the rash progresses, it may become confluent. In severe cases, blisters may occur. The GI manifestations include diarrhea, which may become bloody, cramping, nausea, and vomiting. Furthermore, jaundice from hyperbilirubinemia is the hallmark of liver GVHD[9], although a hepatitic variant of GVHD with elevated liver enzymes, as in an acute viral hepatitis, has been recognized[10]).

The diagnosis of aGVHD is a clinical one but, as many of the symptoms of aGVHD are non-specific, histologic confirmation, whenever possible, may be extremely useful. Tissue biopsy is recommended to confirm a histological diagnosis of aGVHD and, most importantly, to exclude opportunistic infection or drug toxicity. However, the combination of rash, nausea, and diarrhea, occurring after neutrophil engraftment renders the diagnosis very likely. The histologic hallmark of cellular injury by GVHD is apoptosis, which is observed in basal epidermal keratinocytes, bile ducts, and/or intestinal crypt epithelial cells and is frequently associated with lymphocyte infiltration[11].

GRADING OF AGVHD

As mentioned above, the skin, GI tract and liver are the main target organs affected in aGVHD. The first organ affected is most often the skin, which is clinically manifested as a maculopapular rash in the nape, cheeks, ears, shoulder (head end), palms and soles. It can disseminate throughout the body surface (BS) and become confluent and, sometimes, itchy. In severe forms, bullous wounds secondary to epidermal necrosis occur. The degree of cutaneous involvement is quantified by the extent and severity of lesions, as described in tables 1 and 2.

Regarding the GI tract, it often affects both its upper and lower portions. It may clinically present with anorexia, nausea, vomiting, diarrhea, and abdominal pain. The diagnosis can be confirmed by histopathological examination of biopsies obtained through upper digestive tract endoscopy, rectal biopsy or, in some cases, colonoscopy, depending on the risk of bleeding. Several studies, including a recent prospective one, suggest that most GI tract GVHD diagnoses can be made through rectal biopsies[12].

It is important to note that a negative rectal biopsy does not rule out aGVHD, for which further endoscopy is required to confirm the diagnosis and differentiate it from other common pathologies, mainly infections, of the early post-HSCT period.

The degree of GI tract involvement is classified by the severity of the diarrhea, as described in tables 1 and 2.

GVHD of the *lower* GI tract is usually severe, with or without hematochezia and abdominal cramps. The diarrhea is often watery and abundant (up to several liters per day) and may become bloody. In such cases, it is of utmost importance that blood transfusion support is assured, along with hydroelectrolytic replacement, use of opiates to control pain, and close monitoring due to the risk of hemodynamic instability.

As diarrhea is a common presentation in the immediate post-HSCT period and can be caused by organic toxicity due to the conditioning regimen or by broad-spectrum antibiotics, histopathological examination may serve as a useful diagnostic tool to exclude bacterial toxins or concomitant cytomegalovirus (CMV) infection.

GVHD of the *upper* GI tract must also be differentiated from herpes simplex virus infection, candida esophagitis, peptic ulcer, and secondary toxicity, which can be achieved by endoscopy.

The liver injury caused by GVHD generally occurs in patients with concurrent signs of skin and / or GI tract GVHD and is only rarely seen in its isolated form. It often presents itself with abnormal liver function tests, with a characteristic rise in total bilirubin (predominantly in its conjugated form) and alkaline phosphatase. It can progress to painful hepatomegaly, fluid retention, and pruritus. In a few cases, coagulopathy may be present.

These laboratory abnormalities reflect biliary canaliculi destruction, leading to cholestasis. However, these changes are non-specific and should be differentiated from those of other disorders, such as sinusoidal obstruction syndrome (SOS), viral hepatitis, and drug toxicities (from conditioning, antimicrobial therapy, or GVHD prophylaxis). Liver biopsy may play an important role in the diagnosis, but it is generally not feasible due to the high risk of bleeding.

The graduation of hepatic GVHD is based on bilirubin serum levels and is also summarized in tables 1 and 2, below.

The most popular systems for graduating GVHD are those of Glucksberg (grades I-IV) and the *International Bone Marrow Transplant Registry* (IBMTR)(A-D)[13,14]. The severity of aGVHD is determined by assessment of the degree and extent of each organ involved, as summarized in tables 1 and 2. The stages of individual organ involvement are combined using the Glucksberg with or without the *IBMTR criteria*. Grade I(A) aGVHD is characterized as mild disease, grade II(B) as moderate, grade III(C) as severe, and grade IV(D), as life-threatening[14,15].) The IBMTR grading system defines the severity of aGVHD as follows (adapted for children from Rowlings PA, 1997 and Carpenter PA, 2010)[13,11,16]:

- Grade A – Stage 1 skin involvement alone (rash of <25% of BSA with no liver or GI involvement);
- Grade B – Stage 2 skin involvement; Stage 1 to 2 gut or liver involvement (rash of 25-50% of BSA; diarrhea 10-19.9ml/kg/day – stage 1; diarrhea 20-30ml/kg/day - stage 2; bilirubin 2.1 to 3.0 mg/dL – stage 1; bilirubin 3.1 to 6.0mg/dL – stage 2);
- Grade C – Stage 3 involvement of any organ system (generalized erythroderma; bilirubin 6.1 to 15.0mg/dL; diarrhea > 30ml/kg/day);
- Grade D – Stage 4 involvement of any organ system (generalized erythroderma with bullous formation; bilirubin >15mg/dL; frank blood or melena **or** pain **or** ileus).

TABLE 1: Grading of Acute Graft-Versus-Host Disease

Glucksberg Grade
I – Stage 1 or 2 skin involvement; no liver or gut involvement; Lansky PS 90-100
II – Stage 1 to 3 skin involvement; Stage 1 liver or gut involvement; Lansky PS 70-80
III – Stage 2 or 3 skin, liver, or gut involvement; Lansky PS 50-60
IV – Stage 1 to 4 skin involvement; Stage 2 to 4 liver or gut involvement; Lansky PS 30-40
International Bone Marrow Transplant Registry Severity Index
A – Stage 1 skin involvement; no liver or gut involvement
B – Stage 2 skin involvement; Stage 1 to 2 gut or liver involvement
C – Stage 3 skin, liver, or gut involvement
D – Stage 4 skin, liver, or gut involvement

Legend: PS: performance status. Adapted for children from Rowlings PA, 1997 and Cahn JY, 200511,13

TABLE 2: MAGIC target organ acute GVHD staging in children

Stage	Skin (erythema)	Liver (bilirubin)	Upper GI tract	Lower GI tract (stool output per day)
0	No active rash	<2mg/dL	No or intermittent nauseaa, vomiting, anorexia	< 10ml/kg/day or <4 episodes/dayb
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexiaa	10–19.9ml/kg/day or 4–6 episodes/day
2	Maculopapular rash 25 – 50% BSA	3.1-6 mg/dL		20 – 30ml/kg/day or 7–10 episodes/day
3	Maculopapular rash > 50% BSA	6.1-15 mg/dL		> 30ml/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation > 5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

Legend: a. Acute GVHD is suspected if anorexia is associated with weight loss, nausea ≥ 3 days, and/or vomiting ≥ 2 episodes/day for at least 2 days; b. one episode of diarrhea corresponds to approximately 3ml/kg of stool volume in children (< 50 kg). If >50kg, consider an approximate stool volume of 200ml as in adults.

MAGIC: *Mount Sinai Acute GVHD International Consortium*; GI: gastrointestinal tract; BSA: body surface area. Adapted from Harris AC, 2016[16].

PROPHYLAXIS AND BIOMARKERS OF GVHD IN PEDIATRIC PATIENTS

Allo-HSCT practices in children differ from those applied to adults mainly because of the following factors inherent in the pediatric population: lower incidence of acute and chronic GVHD, differences in transplant baseline variables (non-malignant diseases, comorbidities, previous treatments, graft sources) and better thymic function. Since HSCT can treat a wide range of non-malignant diseases in children and GVHD is usually less severe and responds better to treatment in this population, GVHD prophylaxis strategies vary more between pediatric than adult transplant centers, particularly among recipients with malignant diseases[17].

Although several pediatric studies were (or are being) conducted to test new strategies, such as ultralow-dose IL-2[18], sirolimus[19-21], maraviroc[22], individualized mycophenolate mofetil (MMF)[23] and anti-thymocyte globulin (ATG) dosing[24-25], abatacept[26], *ex-vivo* T-cell depletion (CD34 positive selection and/or T-cell subset depletion)[27-29], calcineurin inhibitors (CNI) remain the standard for GVHD prophylaxis in adults and children[30]. Few yet important options have been consolidated in the past decade, the most important of which are: cyclosporine A (CsA) as a single agent for matched sibling donor (MSD) transplants[31] or with rabbit ATG (rATG) for matched unrelated donor (MUD)[32] ones as safe options for children under 12 years old[33]; and post-transplantation cyclophosphamide (PTCy)[34-36] or alpha-beta+ T-cell receptor (TCR) and CD19+ depletion for mismatched related or unrelated donor (haploidentical or MMUD) HSCT[37-38].

Lawitschka and cols.[39] performed a survey capturing different real-life approaches for pediatric GVHD prophylaxis. Single-agent CsA was used for MSD myeloablative HSCT in 47% of the 75 included EBMT centers; most of them used a dose of 1.5 mg/kg twice a day and reported lower CsA blood levels (100-150ng/ml in 37% and 160-200ng/ml in 34%). According to the conditioning regimen, CsA target levels < 200ng/ml were reported for myeloablative conditioning (MAC) by 85% and for RIC by 68% of the responding centers, without a higher target lev-

el during the first weeks. The relapse risk in malignant diseases induced early CsA withdrawal, whereas longer CsA maintenance and higher target levels (> 200 ng/ml) was the policy for non-malignant diseases. Most centers (95%) used CsA with methotrexate (MTX), and 81% used additional ATG for MUD and 96% for mismatched donor (MMD) transplants, while only 21% used this approach for MSD HSCT. Scheduling of MTX and leucovorin rescue varied as follows: 10 mg/m^2 (days +1, +3 and +6) in 37%, 15 mg/m^2 (day +1) + 10 mg/m^2 (days +3, +6 and +11) in 28%, and 25% of the centers used the latter option omitting the day +11 dose. Ex-vivo T-cell depletion was used by 50 centers (positive CD34+ selection in 78% and negative selection in 44%), usually for MMD transplants. Prophylaxis for RIC HSCT, mainly for non-malignant diseases, varied widely; the combination of CsA and MTX was the most frequently used regimen (92%), and 90% used additional ATG. Other agents, such as tacrolimus, MMF and alemtuzumab, were used by 19%, 43% and 23% of the centers, respectively, for aGVHD prophylaxis.

In Brazil, three recent retrospective multicenter studies performed by the *Brazil-Seattle GEDECO Consortium* evaluating outcomes in pediatric HSCT patients observed a low incidence of severe acute and cGVHD. Darrigo Jr and cols.[40] reported an incidence of 11% of grade III-IV aGVHD and of 19% of cGVHD in 37 patients treated with bone marrow transplantation from a MUD for severe aplastic anemia (SAA). GVHD prophylaxis comprised CsA and MTX in 97% plus *in-vivo* T-depletion in 100% of cases. Tavares and cols[41], in turn, showed incidences of grade III-IV aGVHD of 18%, 13% and 17% and of moderate/severe cGVHD of 8%, 22% and 4% after MUD (n = 95), MMUD (n = 47) and umbilical cord blood (UCB) (n= 70) transplants, respectively, in patients undergoing HSCT for acute leukemia and myelodysplastic syndrome. In this study, GVHD prophylaxis consisted of a calcineurin inhibitor (CNI) + MMF or steroids in 90% of UCB transplants and of a CNI + MTX in 80% and 89% of MUD and MMUD transplants, respectively. ATG was used in 57% of UCB, 66% of MUD, and 83% of MMUD recipients. In their haploidentical HSCT study, Fernandes and cols[42] reported incidences of 14% and 16% of grade III-IV acute and chronic GVHD, respectively, in 73 patients with primary immunodeficiency diseases. These patients received PTCy, MMF and a CNI as GVHD prophylaxis, coupled with ATG or alemtuzumab in half of the patients.

As an effective and widely available strategy, PTCy induces functional impairment of alloreactive T-cells supported by highly active suppressive mechanisms, including rapid preferential recovery of regulatory T cells (Tregs), thus preventing donor cells from causing GVHD. Haploidentical HSCT with PTCy has been associated with low rates of GVHD and non-relapse mortality (NRM). Efficacy and overall survival (OS) seem comparable to MUD transplants in a number of published studies, though more robust head-to-head comparisons are still underway. Delayed immune reconstitution after PTCy has been shown to lead to a higher incidence of infectious complications, including CMV infection. Furthermore, decreasing relapse in malignant and graft failure in non-malignant diseases without additional toxicity remains an important challenge. GVHD prophylaxis in this setting consist of PTCY (50 mg/kg on days +3 and +4) plus tacrolimus or CsA (target levels between 5 to 15 ng/mL and 200 to 400 ng/mL, respectively) and MMF (30 to 45 mg/kg divided in 3 daily doses), both from day +5, until 1 year and day+35 post-HSCT, respectively. The addition of rATG (0.5mg/kg on day -9 and 2mg/kg/day on days -8 and -7) may be necessary to overcome engraftment failure in non-malignant diseases, particularly in immunosuppression-naive SAA patients[43].

Prophylactic *in vivo* T-cell depletion with ATG has been associated with decreased GVHD rates in many allo-HSCT settings. Walker and cols.[44] tested the benefit of adding rATG to standard GVHD prophylaxis in a recent randomized, multicenter, phase 3 trial. Included patients (196) had a hematologic malignancy (leukemia, myelodysplastic syndrome, or lymphoma), were between 16 and 70 years of age, and received a MUD or a one-locus mismatched graft at HLA-A, HLA-B, HLA-C, or DRB1 following MAC or RIC. In patients receiving rATG (0.5mg/kg on day -2, and 2mg/kg on days -1 and +1) plus CNI + MTX or MMF, they observed a significant improvement in the incidence of cGVHD (26.3%) as compared to that of the standard GVHD prophylaxis group(41.3%),p=0.032, and in the OS rate (70.6% *vs.* 53.3%); adjusted hazard ratio (HR) 0.56 (95% Confidence Interval - CI: 0.35–0.90, p=0.017) at 24 months. Moreover, cGVHD-free, relapse-free survival (GRFS) at 12 months was 57.6% in the rATG combined group *vs*. 40.2% in the standard GVHD prophylaxis group (p=0.010). Despite decades of clinical study, optimal ATG dosing is yet to be determined. Increasing evidence shows that the current weight-based dosing is suboptimal and that the absolute lymphocyte count (ALC) before the first dose of rATG can determine its clearance and thus drug exposure. Depending on the conditioning regimen (mainly total body irradiation *vs.* busulfan-based conditioning), the ALC before rATG was highly variable. Adult patients with low ALCs

had worse OS compared with those with a higher ALC when receiving rATG. Currently, a historically controlled clinical trial in children (the PARACHUTE study; NTR4960) investigating a fully personalized dosing regimen for rATG is at the analysis stage. The proposed dosing regimen varied from 2 mg/kg to 10 mg/kg, depending on body weight and ALC, starting 9 days before HSCT. A preliminary analysis has indicated an apparent improvement in survival and that early CD4+ T-cell recovery is significantly faster and more robust with individualized dosing[45].

Table 3 summarizes the recommendations for GVHD prophylaxis for MAC, non-myeloablative (NMA), and RIC allo-HSCT in pediatric patients, including peripheral blood stem cell (PBSC) and haploidentical transplants, along with their corresponding levels of evidence and grades of recommendation.

TABLE 3- Recommendations for graft-versus-host disease prophylaxis in pediatric patients

Type of HSCT	Disease/ Graft Source	Prophylaxis Regimen	Level of Evidence
MAC allo-HSCT from HLA-matched related donors	. Malignant - BM	CNI ± short MTX 10mg/m2 (D+1,3,6)*	1b, GR-A
	. Malignant - PB	CNI + short MTX ± rATG	2b, GR- B
	. Non-malignant (BM or PB)	CNI + MTX standard - 15mg /m2 D+1 and 10mg/m2 (D+3,6,11)	1a, GR- A
		(if PB, rATG 2,5 - 5mg/kg can be added)	2b, GR- B
MAC allo-HSCT from HLA-matched or 9/10 unrelated donors	. Malignant - BM	CNI + rATG (4.5mg/kg) ± short MTX*	2b, GR- B
	. Malignant - PB	CNI + rATG (< 6mg/kg) + short MTX	2b, GR- B
	. Non-malignant (BM or PB)	CNI + rATG (< 6mg/kg) +MTX standard	1a, GR- A
		(if UCB: CNI + rATG + MMF)	2b, GR- B
MAC allo-HSCT from related or unrelated donors	. Malignant or non-malignant (BM, avoid PB)	HD PTCy (50mg/kg/day on D+3, D+4) If PB, unrelated, or mismatched donors: add CNI + MMF or MTX	2b, GR -C
RIC or NMA allo-HSCT from related or unrelated donors	. Malignant or non-malignant (BM or PB)	CNI + MTX (as for MAC) or MMF (15mg/kg in 3 daily doses) ± rATG (4-6mg/kg) if PB or unrelated	2b, GR- C
Haploidentical allo-HSCT – Baltimore regimen	. Malignant	HD PTCy (50mg/kg/day on D+3, D+4) plus CNI + MMF	2b, GR- B
	. Non-malignant (avoid PB or mother as donor)	Same as above + rATG (0.5mg/kg on D-9, 2mg/kg/day on D-8, D-7)	3b, GR- C

HSCT: hematopoietic stem cell transplantation; allo-HSCT: allogeneic HSCT; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; NMA: non-myeloablative conditioning; HLA: human leukocyte antigen; BM: bone marrow; PB: peripheral blood; UCB: umbilical cord blood; CNI: calcineurin inhibitor (cyclosporine or tacrolimus); MTX: methotrexate; GR: grade of recommendation; r-ATG: rabbit anti-thymocyte globulin; MMF: mycophenolate mofetil; HD PTCy: high dose post-transplant-cyclophosphamide. *CNI alone or with MTX can be the choice in children < 12 years old after bone marrow transplantation for malignant diseases from HLA-matched donors; δ Since UCB transplantation is rarely used nowadays, the dose and use of rATG should be determined on a case-by-case basis, and mini-MTX can possibly replace MMF.

BIOMARKERS FOR ACUTE AND CHRONIC GVHD

Despite several advances in allo-HSCT over the past few decades, GVHD remains the leading cause of NRM after transplant. Therefore, identifying valid and useful GVHD biomarkers for clinical use is still an unmet need.

GI tract GVHD triggers a systemic inflammatory reaction and is thus the main driver of mortality. Recently, the *Mount Sinai Acute GVHD International Consortium* (MAGIC) validated an algorithm probability (MAP) tool derived from the combination of serum levels of two biomarkers of GI GVHD: ST2 and REG3α. When measured at the time of aGVHD diagnosis, the MAP separates patients into three distinct groups, known as Ann Arbor scores, each carrying a significantly different risk of 6-month NRM. Hence, the MAP can be considered as a "liquid biopsy" of the GI tract damaged by the inflammation caused by GVHD and represents a more accurate quantitation of disease burden than clinical symptoms alone. Moreover, the threshold of probability value ($p \leq 0.291$) calculated from these biomarker blood concentrations, taken 1 week after systemic treatment with steroids, was able to separate patients into groups with low and high probability of 12-month NRM, OS and resistance to steroid treatment at week 4. The MAP can also be calculated at day +7, prior to the onset of aGVHD symptoms in any patient, and can predict NRM better than GVHD-related pre-transplant characteristics, such as HLA mismatch, unrelated donor, recipient age, and intensity of conditioning regimen[46].

Giaccone and cols.[47] summarized the recent evidence on the different types of biomarkers linked to acute and chronic GVHD. The authors highlighted the main markers and their types of interaction, as follows: genetic (minor histocompatibility antigens; association between single-nucleotide polymorphisms and genes involved in innate or adaptive immunity); plasmatic (reduced IL-15; increased: sIL-2R alpha, soluble B-cell activating factor [sBAFF], REG3α, ST2, TNFR1, Elafin, IL-8, CXCL9, CXCL10, CXCL11); cellular (reduced: Tregs, $CD56^{bright}$ Natural Killer [NK] cells, CD27+ memory B cells, follicular helper T cells, invariant NK T cells; increased: CD4/CD8 ratio, Th17 lymphocytes, recent thymic emigrant or RTE CD4+CD45RA+CD31+ T cells, BAFF/B-cell ratio, $CD19+CD21^{low}$ B cells) and others associated with disruption of the microbiota (loss of bacterial diversity; expansion of a single taxon, as that of Enterococci, oral Actinobacteria and oral Firmicutes; and reduced levels of protective intestinal metabolites, such as urinary-3-indoxyl sulfate and butyrate).

Research efforts have been done to better understand the exact mechanism by which ATG prevents cGVHD. In a randomized, multicenter trial conducted by *the Canadian Bone Marrow Transplant Group* (CBMTG), ATG prophylaxis significantly impacted cGVHD cellular markers at day +100 in 40 patients (aged ≥16 years). The ATG-treated group had a significant >10-fold decrease in both naive T helper (Th) cells and RTE Th cells, which has been previously associated with moderate/severe cGVHD, and a 10-fold increase in $CD56^{bright}$ NK_{reg} cells ($p<.0001$). Evaluation of Tregs, conventional Th cells, $CD21^{low}$ B cells, and plasma markers (ST2, OSP, sBAFF, IL2Ra - sCD25, TIM-3, MMP-3, ICAM-1, CXCL10, and soluble aminopeptidase N) revealed no impact of ATG on their concentration at day +100. This analysis suggests that ATG primarily prevents cGVHD through suppression of naive Th cells (CD45RA+ CD4+ T cells), with a concomitant expansion of noncytolytic $CD56^{bright}$ NK_{reg} cells after transplantation[48].

Bronchiolitis obliterans syndrome (BOS) is a pulmonary manifestation of cGVHD associated with high morbidity and mortality due to fibrosis of small airways and respiratory insufficiency. Pulmonary function tests have shown limited value for the diagnosis of BOS, particularly in children, since they are able to identify only the most severe cases. Therefore, plasma proteins correlated with BOS would be extremely valuable to enable early diagnosis, guide treatment choices, and monitor responses. A few cellular and plasmatic markers that correlate with BOS after HSCT, such as lung epithelial proteins, are being proposed for their diagnostic potential: matrix metalloproteinase-3 (MMP-3), Krebs Von Den Lungen-6 (KL-6), BAFF levels, and CD19+CD21low B cells[49].

KL-6 is a glycoprotein expressed on pulmonary epithelial cells that is undetectable in the serum of healthy individuals or only present in very small amounts. However, there is emerging evidence that epithelial cells of the proximal and distal air spaces of sick patients release host defence mediators that can facilitate the initiation of inflammatory airway changes; therefore, KL-6 has been shown to be a useful serum marker for BOS after lung transplantation. Gassas and cols.[50] conducted a prospective study to test KL-6 and other plasma markers in allo-HCT recipients. Thirty-nine pediatric patients (≤ 18 years old) were included. They found that KL-6 serum levels, measured before transplant or at 1 month post-HSCT, were significantly higher in surviving patients who developed BOS *vs.* in those who did not (pre-HSCT: mean, 32.6 U/mL *vs.* 5.8 U/mL, $P < .03$; at 1 month: mean, 52.5 U/mL *vs.* 11.4 U/mL, $p < .04$). KL-6 levels at 3 and 6 months after HSCT remained higher

in the BOS group but were not statistically significant ($p < .12$). The high pre-HSCT levels of KL-6 in patients who later on developed BOS indicate that these patients are predisposed to develop this complication. The authors emphasized the importance of performing serum KL-6 level measurements before transplant and at 1 month post-HSCT with a view to a timely identification of patients at a high-risk for BOS. Such patients may benefit from more frequent pulmonary surveillance and early therapy.

The *Applied Biomarker in Late Effects of Childhood Cancer* study (ABLE/PBMTC 1202)[51] evaluated the immune profiles related to cGVHD and to late aGVHD (L-aGVHD). A peripheral blood immune cell panel and a set of plasma markers analyzed at day +100 correlated well with cGVHD diagnosed according to the NIH consensus criteria (NIH-CC). A total of 241 children were evaluable and categorized as L-aGVHD, cGVHD, active L-aGVHD or cGVHD, and no cGVHD/L-aGVHD. Patients with only distinctive features but defined as having cGVHD by the adjudication committee (non-NIH-CC) had immune profiles similar to those of the NIH-CC. Both cGVHD and L-aGVHD had decreased transitional B cells and increased cytolytic NK cells. Additional abnormalities were observed in cGVHD, such as: increased activated T cells, naive Th and cytotoxic T cells, loss of $CD56^{bright}$ NK_{reg} cells, and increased ST2 and soluble CD13. Active L-aGVHD before day +114 had additional abnormalities in naive Th cells, naive Tregs, and in certain cytokines. On the other hand, active cGVHD had an increase in programmed cell death protein 1 (PD-1)-negative memory Th cells and a decrease in PD-1-positive memory Tregs. An exploratory analysis appeared to show a progression of immune alterations from no cGVHD/L-aGVHD to active L-aGVHD, with the most complex pattern seen in cGVHD. Comprehensive immune profiling might thus allow for the development of more specific strategies to minimize L-aGVHD and cGVHD. The same study group performed an additional analysis to compare T cell populations across age groups and to evaluate the impact of the estimated pubertal status at the time of HSCT. In children, the authors observed a broad suppression of newly formed B (NF-B) cells, whereas adults exhibited an increase in T1-$CD21^{lo}$ B cells and a decrease in T1-$CD24^{hi}CD38^{hi}$ B cells. Pre-pubertal children had elevations of aminopeptidase N (sCD13) and ICAM-1. Treg abnormalities in children appeared to occur primarily in memory Tregs, whereas in adults these abnormalities were seen in naive Tregs. It is probable that abnormalities in sex hormone levels post-transplant have an impact on immune reconstitution, since the onset of puberty seems to be the trigger for the decrease in thymic function. These findings support the role of pre-HSCT age and pubertal stage on the occurrence of cGVHD, and both may explain why pre-pubertal children have lower cGVHD rates, less aggressive disease, and biological differences in the pathways involved in the development of this complication[52]. Table 4 (modified from Cuvelier *et al.*, 2020[52]) summarizes the differences in statistical correlation between cellular and plasmatic biomarkers and cGHVD according to pre-pubertal and pubertal stages at the time of transplant.

TABLE 4 - Cellular and Plasma Markers Significantly Associated with cGVHD According to Pubertal Status

	Pre-pubertal	**Pubertal1**
Naïve T cells		
. Naïve Th cells	Increased	Increased (NS)
. RTE naïve Th cells	Decreased	NS
Newly formed B cells		
. CD21lo B cells	Decreased	NS
. T2 transitional	Decreased	NS
. T3 transitional	Decreased	NS
Peripheral B cells		
. Mature Naïve	Decreased	NS
. Unswitched memory/Marginal-zone like	Increased	Increased (NS)2
. Classical switched memory	NS	Increased (NS)
Regulatory T cells		
. PD1- memory Tregs	Increased	Decreased (NS)
. PD1+ memory Tregs	NS	Increased

. RTE memory Tregs	Decreased	NS
. RTE naïve Tregs	NS	Increased (NS)
Regulatory NK cells	Decreased	Decreased
Cytokines and Chemokines		
. ST23	Increased	Increased
. Aminopeptidase N (sCD13)	Increased	Increased (NS)
. ICAM-14	Increased	NS

[1] Prepubertal was defined as a girl aged <10.9 years or boy <12.4 years and pubertal as a girl ≥ 10.9 years or boy ≥ 12.4 years at the time of HSCT. 2 NS = Not statistically significant due to small number of patients. 3 Supressor of tumorigenicity-2. 4 Intracellular adhesion molecule 1.

FIRST-LINE TREATMENT OF AGVHD

The therapeutic approach toward a patient with aGVHD will depend on the organs and sites involved, GVHD grade, prophylactic regimen used, relative importance of the graft-versus-leukemia (GVL) effect (depending on the baseline disease), as well as on patient-related factors (e.g., renal impairment, coexisting infections, center expertise, and access to therapeutic alternatives)[16].

PEDIATRIC CONSIDERATIONS

Even though the incidence of GVHD in children is generally lower than that in adults, roughly 50% of allogeneic transplants in the pediatric population are for the treatment of non-malignant diseases. In some of these disorders, such as in Fanconi anemia, repair systems are highly dysfunctional, which may impact the occurrence of GVHD. Moreover, specific recommendations both for the diagnosis and treatment of GVHD in children should be taken into account in the approach to these patients, such as the need for: adapting the BSA so as to allow for an accurate assessment of the cutaneous GVHD score; ruling out cases of transient macular rash due to viral infection (most common in children); quantifying diarrhea per episode[53]; and combining, whenever possible and indicated, non-pharmacological therapy (e.g., ultraviolet B phototherapy) and oral, non-absorbable corticosteroids (oral budesonide and beclomethasone), with the aim of reducing both the exposure time to and cumulative dose of systemic corticosteroids[11].

Treatment of grade I aGVHD: the first approach is to optimize the prophylaxis regimen used, by adjusting CNI trough levels and adding topical agents (corticosteroids or tacrolimus) accordingly. Adjuvant supportive therapy with anti-hystaminics for controlling pruritus, for instance, may be helpful. No systemic immunosuppression is recommended[54].

Treatment of grade II-IV aGVHD: the initial treatment does not differ between adults and children. Systemic treatment with methylprednisolone (MP) at a dose of 2mg/kg/day or its prednisone equivalent should be promptly initiated upon diagnosis[55]. Concomitant CNI (CsA or tacrolimus) prophylaxis should not be withdrawn, and trough levels should be checked for. For less severe forms (i.e., grade IIa aGVHD), starting MP at a dose of 0.5-1mg/kg/day is acceptable, with close monitoring and possible escalation up to 2 mg/kg if worsening occurs after 72h[56,57]. Non-absorbable glucocorticoids (beclomethasone and budesonide) have also been used in the treatment of mild upper or lower GI aGVHD (10.0–19.9ml/kg/day or 4–6 episodes/stool output/day in children) as an adjuvant to systemic corticosteroids[58,59] . Unfortunately, only around 60% of patients favorably respond to first-line treatment, and many of such responses are not durable[60]. These patients are considered steroid-refractory and should then undergo second-line therapy.

SECOND-LINE TREATMENT OF GRADE II-IV AGVHD

Second-line treatment is recommended in case of aGVHD progression within the first three days (72h) or of lack of improvement after 5-7 days after initial therapy with MP 2mg/kg/day, in combination with an optimized-level CNI, as mentioned above[30]. Studies on the second-line treatment of aGVHD in children are scarce, predominantly retrospective, with poor historical controls, and, as in adults, highly heterogeneous, with great variability across institutions. Since no superiority of one agent over another has been proven to date in this population, the choice of the most appropriate approach should be individualized and dependent upon the following factors: comorbidities, previous therapy, drug interaction, availability, accessibility, and center expertise[30]. Steroid-refractory aGVHD has typically a poor progno-

sis, both in adults and in children, given the high treatment-failure rates in this scenario. Overall, the average response to second-line agents is around 50%, with a median OS of ~60% at 6-months, with or without active disease[61,62]. The 1-year OS in this population is approximately 20-30%[61]. The main results seen with these agents are depicted below.

MMF: this drug acts by inhibiting the synthesis of guanosine triphosphate, a key enzyme involved in T-cell proliferation. MMF was one of the four drugs tested in the phase II, randomized-controlled *BMT CTN* 0302 trial, while assessing its possible role in first-line therapy in combination with MP.[63] In a subsequent phase III study, *BMT CTN* 0802, no significant benefit was seen in GVHD-free survival, nor in the cumulative incidence of cGVHD at 12 months[61]. Retrospective studies showed complete and partial response (PR) rates of up to 77% at 6-months. MMF may hence be considered in select cases as a second-line approach[64,65].

Extracorporeal photopheresis (ECP): this treatment modality uses ultraviolet A rays to irradiate circulating lymphocytes during leukapheresis after *ex vivo* incubation with 8-methoxypsoralen (8-MOP). This leads to lymphocyte apoptosis (including that of alloreactive T-cells) within 24 hours after reinfusion due to subsequent phagocytosis by antigen-presenting cells (APCs), which produce immunomodulatory effects through cytokine regulation and immune-tolerance induction via Treg expansion, as seen in murine models[66,67]. Of note, there are no solid data pointing to an increase in the risk of opportunistic infections, nor of loss of the GVL effect, with ECP, given its immunomodulatory, as opposed to immunosuppressant, properties[68,69]. Several retrospective studies to date have shown the favorable results of ECP in the management of steroid-refractory aGVHD, with complete response (CR) rates varying between 54 to 75%[67,70]. This is particularly true for cases with skin involvement, in which CR rates reach up to 90%[71]. In a retrospective, multicenter study including 98 patients with steroid-refractory aGVHD receiving either ECP or anti-cytokine therapy, ECP was shown to be superior, with a CR rate of 54% *vs.* 20%, respectively[72]. Another study which included 21 patients undergoing ECP therapy, a CR of 100% and 67%, respectively, was observed for those with grade II/III aGVHD.[73]. In a prospective, phase II study published in 2006, which included 59 patients with steroid-refractory or steroid-dependent aGVHD, a CR was observed in 82% of patients with skin involvement and in 61% of those with hepatic or GI tract involvement[68]. A fairly recent meta-analysis including nine prospective studies and a total of 323 patients showed favorable results, particularly for the treatment of GVHD of the skin (84%) and GI tract (65%)[74]. As for the time to observed response, the Spanish group showed early ECP responses, of which 80% occurred within the first 6 months of therapy. This was further corroborated by Greinix and cols., with a significant response being noted after an average of 4 cycles of ECP[68]. Nonetheless, studies specifically addressing the pediatric population are still lacking. Overall, the current evidence, for both adults and children, support the fact that the clinical response to ECP depends mainly on the grade and extent of aGVHD and on the time until initiation of therapy after diagnosis of refractoriness to first-line steroid therapy[75].

ATG: polyclonal and monoclonal antibody-based therapies are among the most widely used second-line agents for GVHD and with which considerable experience has been gained over the past three decades or so. Nonetheless, response rates seldom reach more than 50%, given that most studies exhibit response rates between 20% and 50%, with slightly better results for cutaneous acute GVHD[76,77].

Anti- IL-2Rα antibody therapy: the potential role of IL-2Rα antibody therapy for aGVHD is based on the molecular structure of this antibody in that its alpha subunit (CD25) is found predominantly in activated (alloreactive) T-cells. Basiliximab, as a chimeric IL-2Rα antagonist, has shown some promising results, with CR rates of up to 71% in a phase I study with a small number of patients[78]. Funke *et al*. observed an overall response rate (ORR) of 80% and a 5-year OS of 30% among 34 patients with refractory grade III-IV aGVHD[79].

TNF antagonists (Infliximab, Etarnecept): TNF antagonists seem particularly useful for the management of steroid-refractory GVHD involving the GI tract, with a number of case series, one of which showed an ORR of 70% in 37 patients[80].

Ruxolitinib: this *Janus kinase* (JAK) inhibitor has been shown fairly recently to be efficacious and safe in the treatment of refractory cases of both acute and chronic GVHD[81,82,83]. It was also shown to exert an inhibitory effect over interferon-gamma (IFN- γ) receptor (IFNGR) signalling pathways, which are known to be implicated in the effect of alloreactive T-cells in the pathogenesis of aGVHD. Similarly, *Janus kinases* (JAKs) are involved in all three pathophysiological phases of aGVHD, since they interfere with common cytokine production and signalling pathways, as well as with the development and function of non-T-cell immune effectors, such as APCs[84]. Importantly, JAK-STAT (*signal transducer and activator of transcrip-*

tion) inhibition in preclinical models showed an improvement in aGVHD, while the GVL effect seemed to remain unaltered, with its obvious advantages[85]. Over the past decade, two pivotal studies – REACH 1 and REACH 2 - enabled ruxolitinib to become, in 2019, the first second-line treatment approved by the *Food and Drug Administration* (FDA) as an alternative to the management of steroid-refractory grade II-IV aGVHD[86,87,88]. *REACH1* was a prospective, phase I, single-arm study which reported an ORR (CR and PR) of 54.9% on D+28 and an OS at 6 months of 73%. Cytopenia and viral reactivation were the most common adverse events observed.[86] *REACH2*, in turn, was a much larger, multicenter, phase III, randomized-controlled study, which compared the efficacy of ruxolitinib (20mg/day) with nine commonly used salvage therapies for steroid-refractory aGVHD (at physicians' discretion). A total of 309 patients were randomized, with a statistically significantly higher ORR at D+28 (62% vs. 39%, OR: 2,64, 95%CI 1.65-4.22, p< 0.0001) and at D+56 (40% vs. 22%; p<0.05) as compared to controls. After a 6-month follow-up period, 10% of patients in the ruxolitinib arm lost their response to therapy, as opposed to 39% in the control group[88]. More recently, ruxolitinib was assessed in a study of 29 pediatric patients with steroid-refractory grade II, III-IV aGVHD or cGVHD and showed rather astonishing results, with response rates of 80%, 82% and 100%, respectively, with initial doses of 5mg or 10mg/day, according to body weight (<15kg or ≥ 15kg), and possible dose escalation to 20mg/day, if tolerable, regardless of weight. Data on the pharmacokinetics of ruxolitinib in this population, however, are still pending in order to better define the optimal dosing of this inhibitor and the most appropriate schedule for immunoglobulin G (IgG) serum level monitoring[89]. Of note, children under ruxolitinib therapy should receive appropriate antimicrobial prophylaxis and be closely monitored and followed up for possible intervening infections.

DIFFERENTIAL DIAGNOSIS BETWEEN ACUTE AND CHRONIC GVHD

The classification of GVHD in classic and late or recurrent forms proposed by the 2005 NIH Consensus[1] was not changed in the 2014 Consensus[3]. It includes: (1) classic GVHD (erythema, maculopapular lesions, nausea, vomiting, anorexia, diarrhea, paralytic ileus, or cholestatic liver disease) that appears before 100 days after HSCT or after donor lymphocyte infusion (DLI), without distinct signs or diagnosed cGVHD; (2) Late, persistent or recurrent GVHD: classical GVHD presentation, which occurs after 100 days of HSCT or DLI (often after decrease or withdrawal of immunosuppression) without distinct signs or diagnosed cGVHD. Overlap GVHD occurs when both acute and chronic GVHD features are present. It is generally correlated with a worse prognosis and an adverse impact on OS. There is no time limit for its onset.

TABLE 5 - Acute and Chronic GVHD Categories

Category		Time of onset	aGVHD	cGVHD
aGVHD	Classic	<100 days	Yes	No
	Persistent/Recurrent/Late Acute	> 100 days	Yes	No
cGVHD	Classic (De Novo/ Quiescent/Progressive)	No limit	No	Yes
	Overlap	No limit	Yes	Yes

Legend: aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host disease; persistent (previously unresolved aGVHD); recurrent (previously resolved aGVHD); late acute (without prior aGVHD); classic and overlap cGVHD: de Novo (without prior aGVHD); quiescent (previously resolved aGVHD); progressive (previously unresolved aGVHD)

DIAGNOSIS AND INDIVIDUAL ORGAN PRESENTATION OF CGVHD

As a rule, distinguishing between acute and chronic GVHD basically depends on the clinical manifestations rather than the time point at which they present after HSCT[1]. Presenting signs and symptoms may be termed "diagnostic", when they allow for a prompt diagnosis of cGVHD, regardless of any additional testing or organ involvement; "distinctive", which are commonly present in cGVHD and not in aGVHD but are not enough for a definitive diagnosis of cGVHD; and "common", when features of both chronic and acute GVHD are present at the same time[3,90]. A diagnosis of cGVHD is obtained when at least one of such diagnostic manifestations is observed or at least one distinctive manifestation is confirmed with a histopathological examination or with laboratory tests, or, yet, upon specialized evaluation (e.g., with a gynecologist or ophthalmologist) or radiological examination of the same or of different sites[3,90].

From the pathophysiological standpoint, cGVHD involves an array of phenomena comprising inflammation, cellular and humoral responses, and fibrosis. This way, it closely resembles autoimmune diseases of the collagen vascular type. Disease onset is more commonly seen during the first year post-transplant but may also be noted several years after HSCT[9].

Clinical manifestations of cGVHD may be limited to a single organ or site, or may be widespread, with disseminated disease potentially leading to a severe quality of life (QoL) burden for the patient[91,92].

Of note, cGVHD must be clearly differentiated from post-transplant infectious complications, such as those due to fungal or viral infections, or yet from other causes, such as those related to drug toxicity, disease relapse, or secondary malignancy.

It may involve virtually any organ or site, the most common of which being the skin, mouth, hair/scalp, nails, eyes, GI tract, genitalia, liver, lungs, muscles, fasciae, and joints, hematopoietic and immune system, among others[1,3,90]. As mentioned previously, the NIH consensus statements from 2005 and 2014 offer a comprehensive guide for the appropriate identification of the diagnostic, distinctive, and common features of c GVHD, as well as for the grading process based on the specific organ/site involvement observed [1,3].

An accurate diagnosis and grading of cGVHD may be quite challenging, given the uncertainties related to the pathophysiology of this disease and the common coexistence of aGVHD manifestations. This is further aggravated by the lack of a robust validation of the current grading tools and biomarkers for the diagnosis and risk assessment of this post-transplant complication[3].

GLOBAL SEVERITY SCORE OF CGVHD

The NIH global severity score for cGVHD was first proposed in 2005 and later revised and updated in 2014[1,3]. In this grading system, the score varies from 0 to 3 at each organ or site involved, comprising a total of eight sites (skin, eyes, gut, liver, lungs, joints, fasciae, and genitourinary tract) The global score takes into account both the number of organs or sites involved and the severity of involvement at each organ/site[1,3].

According to the total score obtained, the cGVHD observed may be classified as mild, moderate, or severe, which will reflect the degree of impact and functional impairment at each organ or site involved.[3,90]. Importantly, cGVHD should be graded at diagnosis and during follow-up, hence allowing for clinical severity and prognostic re-evaluation in a timely manner[3,90]. Table 6 depicts the global severity scoring system of cGVHD.

TABLE 6: NIH global severity score of cGVHD

Mild cGVHD 1 or 2 organs involved and Individual organ score of no more than 1 and Lung score of 0
Moderate cGV 3 or more organs involved and Individual organ score of no more than 1 OR At least 1 organ (except lung) with a score of 2 OR Lung score of 1
Severe cGVHD At least 1 organ with a score of 3 OR Lung score of 2 or 3
Key points: Skin: the highest of the two scores should be used for calculating global severity. Lung: FEV1 should be used instead of the clinical score for calculating global severity. If the abnormality in an organ is considered to be unequivocally explained by a non-GVHD cause, its corresponding score will be zero and thus not included for calculating global severity. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes), its corresponding score will be used for calculating global severity regardless of the contributing causes (without any downgrading of organ severity score).

Legend: NIH: National Institutes of Health; cGVHD: chronic graft-versus-host disease; FEV1: forced expiratory volume in the first second.
Adapted from: Jagasia MH et al., 20153.

TREATMENT OF CGVHD

No systemic treatment is needed for cases of asymptomatic, mild cGVHD. In such cases, topical steroids, for instance, for skin, mouth, or genital involvement, may be applied, with close monitoring for possible signs of disease progression at other sites so as to avoid clinical deterioration due to suboptimal treatment[3,90]. A prompt intervention might thus help prevent cGVHD progression[3,90].

In patients with three or more organs/sites involved, or with a global NIH score of 2 or more, at whatever site, systemic immunosuppression should be promptly initiated[3,90].

For patients with a diagnosis of *de novo* cGVHD, possible alternatives are to increase the dose of the immunosuppressant being used and/or to add another immunosuppressant[3,90].

To date, chronic GVHD remains one of the main drivers of late post-allogeneic transplant morbidity and mortality. Some of the main risk factors for a higher transplant-related mortality are: multiple organ involvement, low performance status, low platelet count at diagnosis of GVHD (< 100.000/µL), hyperbilirubinemia, cGVHD progressing from prior aGVHD, extensive skin involvement at diagnosis of GVHD, among others[6,90,93,94,95,96].

Patients presenting with cGVHD are more prone to infectious complications due to the intense immunosuppression they are submitted to, as well as the functional asplenia and hypogammaglobulinemia that typically accompany the post-transplant period[90,92]. This results in infections being the predominant cause of mortality in these patients. Therefore, all patients with a diagnosis of cGVHD should receive appropriate *Pneumocystis jirovecii* pneumonia prophylaxis, as well as vaccines against encapsulated bacteria, namely *Meningococcus* sp., *Haemophilus* sp., and *Pneumococcus* sp, coupled with human immunoglobulin replacement at regular monthly intervals, as needed[90,92]. When presenting with fever, patients with cGVHD need to be promptly evaluated and treated, due to the risk of sepsis and of rapid clinical deterioration[90,92].

The main goal of the treatment of cGVHD is to reduce its corresponding symptoms, control disease progression, and prevent harm or disability[3,90]. Treatment intensity will depend on both the extension and severity of the disease. The 2014 NIH Consensus Guidelines addresses the severity criteria and grading of the disease, thus aiding in the decision-making process as to whether topical or systemic treatment should be applied[3]. In patients presenting with only mild symptoms, limited to a single organ or site, it is acceptable to adopt a conservative, watch and wait approach, or to use topical therapy alone, whereas, for patients with a worse clinical picture or multiple organ involvement, systemic treatment is warranted.[3,90]. The management of cGVHD may be quite challenging, and caution should be taken to keep systemic immunosuppression to the least degree possible, with the aim of controlling the disease until immunological tolerance is established between donor and recipient[3]; less immunosuppression allows for a lower rate of severe infections.

Some key points ought to be emphasized when managing cGVHD in the pediatric population, one of which is the potential long-term effects of high-dose steroid therapy. Another aspect is that of children who undergo HSCT for non-malignant diseases, wherein the GVL effect coexisting with GVHD is unnecessary[97,90].

Since cGVHD often involves several organ systems, a multidisciplinary approach to the management of this disease is of at most importance and should generally include physical therapy, psychological, nutritional, dental, social and occupational therapy support[98].

TABLE 7. Indications for systemic therapy of chronic GVHD[3,90,99]

Global severity	High mortality risk *	Systemic therapy
Mild	No	No
Mild	Yes	Yes≠
Moderate	No/Yes	Yes
Severe	No/Yes	Yes

Legend: GVHD: graft-versus-host disease.
* Platelets < 100,000/µL or under steroid therapy at the time of diagnosis of GVHD
≠ A balance between the potential benefit of graft-versus-leukemia effects and the risk of GVHD should be sought

FIRST-LINE TREATMENT

According to the 2014 NIH Consensus criteria, systemic treatment of cGVHD should be administered for cases with: score >2 in any organ, involvement of three or more organs, and mild cGVHD with high-risk features (platelet count <100,000/mm3 and use of immunosuppression at the time of the diagnosis of cGVHD)[94].

First-line systemic treatment consists of 1mg/kg/day prednisone (or its equivalent) and CsA (or tacrolimus), with dose adjustment for serum level[100]. There is no solid evidence that the addition of another immunosuppressant (MMF, azathioprine, or thalidomide) to first-line therapy improves the results, in which case this should not be done[20]. After a two-week period, if there is a response to therapy or the condition is stable, one should start tapering the dose of steroids every other day, with a weekly reduction of 25%, for 6 to 8 weeks, until a dose of 0.1mg/kg/day is reached. According to the *Fred Hutchinson Cancer Research Center* (FHCRC), this dose should be maintained for 2 to 3 months, in case of incomplete response, severe presentation, or GVHD-related risk factors.[99] This should then be followed by a second period of dose tapering, with a dose reduction of 10 to 20% a month, until total withdrawal after 9 to 12 months[99]. When other immunosuppressants are being used concomitantly, these should be sequentially tapered, after steroid withdrawal, for a period of 2 to 4 weeks, until complete withdrawal[90].

Steroid-refractory cGVHD is defined as progression of disease after a two-week period under 1mg/kg/day of steroids, whereas stable disease is considered when a dose of > 0.5mg/kg/day is used for 4 to 8 weeks or when one does not tolerate a prednisone dose < 0.5mg/kg/day[101].

Second-line therapy for cGVHD is indicated when at least one of the following criteria are met: worsening of cGVHD at a primarily involved organ or site, lack of response to therapy after a 1-month period, or inability to reduce the dose of prednisone to levels below 1mg/kg/day for a period of 2 months[97].

SECOND-LINE THERAPY AND NOVEL TREATMENTS FOR CGVHD

There is currently no optimal treatment choice for second-line therapy for cGVHD. Choice of treatment will depend on several factors, such as: organ or site involved, toxicity profile, center expertise, treatment availability, and patient preference. One should not start a third treatment (e.g., immunosuppressant) before an observation period of two to three months so as to better assess response to each therapy[90,99]. The main second-line treatment options for cGVHD are:

- ECP: ECP constitutes an effective treatment modality for refractory or steroid-dependent cGVHD, both in adults andchildren[102]. It is considered a good option for the second-line approach to patients who are dependent upon, intolerant to, or, yet, resistant to corticosteroids. It may also be considered for cases with recurrent infections or at a high risk of relapse of their baseline disease. ECP has been shown to be particularly effective in mucocutaneous cGVHD, with CR rates of up to 80%, as well as a good response in sclerotic forms of this disease[103,73]. Response rates also tend to be high in cGVHD with mouth, eye, and liver involvement, with a response rate of 70%, 60%, and 68%, respectively[104,105]. Moreover, ECP has been shown to enable dose reduction of chronic steroid therapy in select cases[73,106,107,108]. On the other hand, ECP should not be performed in patients with a total white blood cell count of <1000/mm^3, intolerance to 8-MOP, heparin, or citrate, and/or in those who are hemodynamically unstable[109]. ECP has been shown to be well tolerated in children, with a low rate of, typically mild, side-effects, even in low- or underweight patients[110]. Most often, treatment is interrupted due to a lack of an appropriate vascular access, which can usually be managed by insertion of a large-caliber and rigid-type central venous catheter[30]. Hence, ECP is a both feasible and safe treatment option for cGVHD in children, with favorable results. Some studies have suggested the use of ECP as a possible first-line therapy option for refractory or moderate/severe cGVHD in specific clinical situations[111,112].

- Mammalian target of rapamycin (mTOR) receptor inhibitors: the most commonly used agent within this class is sirolimus (rapamycin). It is generally used in combination with a CNI, with response rates varying from 56% to 81% [113]. However, since it is used in association with a CNI, its serum level should be closely monitored, given the increased risk of thrombotic microangiopathy with this combination[113]. Other relatively common side-effects of this medication include dyslipidemia, renal dysfunction, and cytopenia[90]. Caution should be taken regarding potential drug-drug interactions with sirolimus, for which close serum level monitoring and dose-adjustment should be performed accordingly.

- Low-dose MTX: MTX has long been used in a number of autoimmune disorders, with favorable results. This led several investigators to assess its potential role, at low doses, in the management of cGVHD,

both in adults and children[114,115]. Recommended doses vary from 5 to 10mg/m^2 of BSA at weekly intervals or every 3 to 4 days, with partial or complete responses achieved[115,116]. Some authors reported favorable results with a dose of 7.5mg/m^2/week for refractory cGVHD, with a low toxicity profile and allowing for dose tapering of steroids.[114]. These results have also been reproduced in children[115]. MTX was well tolerated and exhibited a low rate of grade III-IV hematologic toxicity and grade II hepatotoxicity[115]. Current studies have shown that the best response rates tend to be obtained in the treatment of skin and mouth cGVHD, with no apparent increase in the risk of relapse of baseline disease[114,115,116].

- Tacrolimus: CNIs are generally used in association with corticosteroids as first-line treatment of cGVHD. Their use as second-line therapy is fairly limited and has provided somewhat modest results[117]. Switching from CsA to tacrolimus has not significantly improved these results, except for a single study which showed a 20% improvement in overall response[118].

- MMF: the ORR in cGVHD with this immunosuppressant has varied between 23 and 79% in several case series[90,119,120,121]. The most often observed side-effects of MMF comprise both hematologic and GI toxicity, including the development of ulcers of the intestinal mucosa[90]. Infection rates also tend to increase with this medication, particularly viral infections[122,65].

- Rituximab: as a chimeric, humanized anti-CD20 monoclonal antibody (MoAb), it exerts its anti-GVHD effect by depleting autoreactive B-cells. A prospective study by Cutler *et al*., 2006, showed favorable response rates of rituximab at a dose of 375mg/m^2 in patients with refractory cGVHD, with the additional benefit of allowing for significant steroid tapering[123]. The best responses were observed for GVHD of the skin, particularly in its lichenoid form, and for musculoskeletal GVHD[123]. Most studies recommend a weekly dose of 375mg/m^2 for 4 to 8 weeks[124,125]. The most common side-effects relate to infusion reactions and infectious complications[123].

- Imatinib: this tyrosine-kinase inhibitor has been used as a potential alternative for the treatment of cGVHD, given its anti-platelet derived growth factor receptor (PDGFR) and anti-transforming growth factor receptor beta (TGFB) effect and, thus, its antifibrotic effect[90]. The current evidence has shown favorable results with the use of imatinib for sclerotic-type cGVHD of the skin[126,127]. The recommended dose varies between 100mg and 400mg/day, which is equivalent to a dose of 65mg/m2 to 260mg/m^2/day in pediatric patients.[90,128] Some of the most common side-effects of this medication include hematologic toxicity, fluid retention, and dyspnea[90].

- Low-dose (100-150cGy) thoracoabdominal irradiation (TAI): given its immunosuppressive and immunomodulatory effects, this therapeutic modality can be used in patients with refractory cGVHD[129,130]. The best responses are seen for mucocutaneous cGVHD, particularly for fasciitis and GVHD of the mouth. TAI has also been shown to allow for systemic steroid tapering[90,130].

- **Ruxolitinib**: this *Janus kinase* (JAK) inhibitor has more recently been shown to be efficacious and safe in the treatment of refractory cases of both acute and chronic GVHD[81,82,83]. In a muticenter study by Gomez *et al*., 2020, ruxolitinib showed an ORR of 57% inr the treatment of cGVHD, but only a 4% CR rate was achieved after a median of 4 weeks follow-up[81]. Steroid tapering was possible among 57% of cases[81]. The OS rate at 1 year was 81%. Of note, this comprised a heavily pre-treated population, with several lines of therapy for GVHD. In a recent study by Yang *et al.,* 2021, which included a total of 53 pediatric patients with acute or chronic GVHD who had had a poor response to prior therapy, ruxolitinib had an ORR of 75.5%, which reached 80.6% in those with cGVHD. Among these, 10 were complete responses and 19 were partial responses[82]. Additionally, a total of 39% of cases were able to have their steroids withdrawn[82]. A possible drawback of ruxolitinib is the potential increase in the rate of opportunistic infections due to its anti-T-cell effect. In a study assessing children with acute or chronic GVHD receiving ruxolitinib, an ORR of 77% and 89% was observed, respectively[83]. In these children, ruxolitinib was shown to increase CD4+-memory B-cells, decrease CD4+-Tregs, decrease CD8+-T-cells, and reduce NK cells, with a resulting increase in the occurrence of infections, with a rate of 54%, 18%, and 13% of viral, bacterial, and fungal infections, respectively[83]. Therefore, children under ruxolitinib therapy for GVHD should receive appropriate antimicrobial prophylaxis and be closely monitored and followed up for possible intervening infections. In a recent publication from Brazil, Ferreira *et al.* reported the experience of ruxolitinib in a cohort of 35 adult patients with corticosteroid-refractory cGVHD from two transplantation centers, with the longest follow-up described to date[131]. The patients had a median of 3 organs affected (range, 1 to 7 organs), with most (64%) having moderate cGVHD. The median number of previous therapy lines was 2 (range, 1 to 6). The ORR was 89% (CR, 26%) after a median of 4 weeks of therapy. The median follow-up was 43 months (range, 11 to 59

months). At follow-up, of the 27 patients still alive, 18 (67%) were free of any immunosuppression, and 6 (22%) were receiving ruxolitinib as their sole immunosuppressive drug. Failure-free survival (FFS) was 77% at 6 months, 68% at 12 months, 54% at 24 months, and 51% at 36 months. Toxicities were mostly hematologic and resolved after dose reduction in most cases, supporting the use of this drug as a safe and effective option for refractory cGVHD[131].

- Ibrutinib: this *Bruton-tyrosine kinase* inhibitor has been extensively studied in the past several years and has been shown to be of benefit in adult patients harboring refractory or steroid-dependent cGVHD. Currently, it is the only *FDA*-approved therapy for adults failing at least one prior line of systemic therapy for cGVHD[132,133,134]. In a study by Waller *et al*., 2019, which evaluated 42 patients with refractory or steroid-dependent cGVHD receiving ibrutinib at a dose of 420mg/day over a follow-up period of 26 months, an ORR of 69% was noted, of which 31% were complete responses and 38% were partial ones[132]. Moreover, a sustained response was observed after 44 weeks of treatment in 55% of these patients. Patients with two or three organs involved had a response rate of 73% and 60%, respectively. Of note, in this study, ibrutinib enabled a dose reduction of steroids to < 0.15mg/kg/day in 64% of patients, and complete withdrawal was possible in 19% of cases[132]. As for the side-effects of ibrutinib, pneumonia, fatigue, diarrhea, nausea and vomiting, muscle cramps, and hematomas were among the most commonly reported ones[132,133]. After a mean follow-up of over 2 years, patients with cGVHD who had failed a prior line of therapy continued to show durable responses while on ibrutinib[132,133]. There are no robust data as yet, however, as to the ideal dose and safety of this medication in the pediatric population. In a retrospective study published in 2020, where 22 children with predominantly moderate or severe cGVHD received ibrutinib at a daily dose of 250mg/m^2 per day, a total of eight (36%) children had their medication withdrawn due to adverse events or died. Among the 14 evaluable patients, 12 (86%) achieved a PR after a follow-up of 6 months. Notably, Epstein-Barr virus (EBV) reactivation occurred in one of these patients and pneumococcal sepsis in another, despite appropriate antimicrobial prophylaxis. The authors concluded that, although the results of ibrutinib for the treatment of cGVHD in children are seemingly promising, further studies addressing the pharmacokinetics of this tyrosine-kinase inhibitor are warranted so as to better define its efficacy and optimal dosing in this population[135].

- Mesenchymal stem cells (MSCs): given their potent immunomodulatory properties, especially for their effector function inhibition, MSCs have risen as a promising alternative for the management of immune-mediated disorders, including GVHD[136]. These cells provide the necessary support for stem cell growth and differentiation within the bone marrow milieu, and they are also able to suppress the proliferation of reactive lymphocytes without Major Histocompatibility Complex (MHC)/HLA restriction[90,137,138]. There have been a number of publications reporting successful responses with MSC infusion for the treatment of cGVHD, with an ORR of around 70% and the additional advantage of enabling dose reduction or complete withdrawal of the prior immunosuppressants being used[139,140]. These results have been particularly encouraging in patients with cutaneous, pulmonary, liver, mouth, and eye involvement[140,141]. Durable response rates have also been reported[142]. In a study by Krasowska-Kwieciena *et al*., 2019, nine children with severe acute or chronic GHVD who were resistant to corticosteroids and second-line immunosuppressants were assessed for their response to MSC infusion[143]. In this study, children received between one and six MSC infusions, with no infusion-related adverse events and an ORR rate of 56% after the first infusion and of 44% after the end of treatment[143] Patients presenting with cGVHD of the skin, GI tract, and liver had a CR rate of 50%, 38%, and 33%, respectively[143].

- Belumosudil: this is a selective oral inhibitor of *Rho-associated coiled-coil kinase-2* (ROCK2), a signaling pathway that modulates inflammatory response by regulating Th17/Treg balance and fibrotic processes, which led to its investigation for the management of cGVHD. Belumosudil reduces type 17 and follicular Th cells via downregulation of STAT3 and enhances Treg function via upregulation of STAT5[144,145]. Jagasia *et al*., 2021, published the results of a phase IIa, open-label, dose-finding study of belumosudil, which enrolled 54 patients with cGVHD who had received one to three prior lines of therapy[144]. The primary endpoint was ORR. The median time from cGVHD diagnosis to enrollment was 20 months. Seventy-eight percent of patients had severe cGVHD, 50% had ≥ 4 organs involved, 73% had cGVHD refractory to their last therapies, and 50% had received ≥ 3 prior lines of therapy. With an overall median follow-up of 29 months, the ORR with belumosudil 200 mg once daily, 200 mg twice daily, and 400 mg once daily was 65%, 69%, and 62%, respectively. Responses were clinically meaningful, with a median duration of response of 35 weeks, and were associated with QoL improvements and corticosteroid dose re-

ductions. Corticosteroid treatment was discontinued in 19% of patients[144]. The FFS rate was 76% and 47% at 6 and 12 months, respectively. The 2-year OS rate was 82%[144]. Belumosudil was well-tolerated, with low rates of cytopenia. There were no unexpected adverse events and no apparent increased risk of infection, including CMV infection and reactivation[144]. Another phase II, randomized, multicenter registration study, published in the same year, evaluated belumosudil 200mg once daily and 200mg twice daily in 66 patients in each group with cGVHD who had received 2 to 5 prior lines of therapy[145]. Overall, median follow-up was 14 months. The best ORR of belumosudil 200mg once daily and 200mg twice daily was 74% and 77%, respectively, with high response rates observed in all subgroups. All affected organs demonstrated complete responses, with a median duration of response of 54 weeks[145]. Adverse events were consistent with those expected in patients with cGVHD receiving corticosteroids and other immunosuppressants[145]. Therefore, selective ROCK2 inhibition with belumosudil was found to be a promising therapy for refractory cGVHD, with a high ORR and OS rate, limited toxicity, and improvement in QoL, by allowing for steroid dose reduction in these patients[144,145]. Belumosudil was thus recently approved by the FDA for the treatment of cGVHD in adult and pediatric patients aged 12 years or older after failure of at least two prior lines of systemic therapy.

OTHER DRUGS

- Baracitinib: this is an inhibitor of *Janus kinase* 1 and 2 (JAK1/JAK2) which was shown to inhibit both the IFNGR and IL-6 receptor (IL6R), resulting in elimination of GVHD in a fully MHC-mismatched allo-HSCT model[146]. Baracitinib can also expand Tregs, by preserving JAK3-STAT5 signaling (thus providing a potential preventive role), and downregulate CXCR3 and Th1 and Th2 cells, while preserving allogeneic APC-stimulated T-cell proliferation[146]. Moreover, baracitinib may also be of benefit in the treatment of established GVHD by promoting intestinal tissue repair via epidermal growth factor receptor (EGFR) effects[147]. Nonetheless, thus far, it has not been approved for the management of GVHD, and further studies are pending.

- Pomalidomide: thalidomide is active in mouse models of cGVHD and has been tested for the prevention and therapy of cGVHD in humans[148]. However, doses expected to be effective were poorly tolerated because of somnolence, neuropathy, and constipation. Pomalidomide is a new immune-modulating drug, with a 4000-fold greater inhibition of TNFα relative to thalidomide, and is well tolerated, without the adverse effects commonly seen with the latter[149]. Several features of pomalidomide suggest it may be useful in treating cGVHD[149]. In a phase II, open label, randomized study, patients with moderate/severe unresponsive or progressive cGVHD exhibited an ORR of 47% at 6 months, with a greater response rate in joint/fascia, followed by skin, GVHD[149]. Further studies may help elucidate its potential role in this setting.

ORGAN-SPECIFIC MANAGEMENT AS AN ADJUVANT THERAPY FOR CGVHD

Specific treatment and supportive care measures directed at individual target organs, such as the skin, genitalia, eyes, and mouth, have been thoroughly addressed in a previous issue of this journal, within the *Consensus Guidelines for hematopoietic stem cell transplantation from the Brazilian Society for Blood and Marrow Transplantation and Cellular Therapy* – SBTMO, which we kindly encourage the reader to access for a deeper look into this matter[150].

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LONG-TERM FOLLOW-UP OF PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) offers the opportunity for cure to patients with malignant and non-malignant diseases. Given the myriad advances in the past few decades, coupled with the rising numbers of transplants worldwide, the number of long-term survivors, many of whom are free of the disease for which they were transplanted, is constantly increasing. Despite the improved prognosis observed overall, long-term outcome may be undermined by transplant-associated morbidity and mortality. Long-term survivors may present a variety of complications, comprising physical, psychological, social, and economic arenas, with a deep impact on quality of life. Therefore, drawing greater attention to and raising awareness of the potential long-term effects of HSCT is key to providing a tailored approach to pretransplant counseling and to devising appropriate recommendations for post-transplant screening, prevention, and timely treatment of secondary events. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society for Blood and Marrow Transplantation and Cellular Therapy (SBTMO) convened a task force to provide updated, evidence-based guidance for the long- term follow-up of pediatric patients undergoing HSCT, the results of which are presented here.

Keywords: Hematopoietic Stem Cell Transplantation. Counseling. Long-Term Follow-Up. Quality of Life. Pediatric. Consensus Guidelines.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) offers the opportunity for cure to patients with malignant and non-malignant diseases. The number of long-term survivors, many of whom are free of the disease for which they were transplanted, is continuously increasing. Despite the improved prognosis of HSCT, long-term outcome may be undermined by transplant associated morbidity and mortality. Long-term survivors can present a variety of complications, impairing physical and psychological performance, normal integration into family and social life, and quality of life. Raising awareness of the potential long-term effects of HSCT is key to providing a tailored approach to pretransplant counseling and to devising appropriate recommendations for post-transplant screening, prevention, and timely treatment.

In this chapter we will be discussing some of the main topics related to the long-term follow-up of patients undergoing HSCT.

OCULAR COMPLICATIONS

Post-HSCT ocular complications are considered common, especially after allogeneic HSCT (allo-HSCT) and can be classified as referring to the posterior or anterior segments[1].

Risk factors, early diagnosis, prevention, and treatment: Whenever possible, an ophthalmological evaluation should be carried out before HSCT, with the objective of identifying changes, and serve as a basis for future evaluations. In young children, there is also the difficulty of verifying the reduction in visual acuity, reinforcing the importance of regular follow-up with the ophthalmologist[2].
The anterior segment presents complications more frequently, reaching 33% of the cases, represented by cataract and keratoconjunctivitis sicca[1].

Cataract: Posterior subcapsular cataract is the most common, with an incidence of up to 19% in 4 years after HSCT in patients who do not receive total body irradiation (TBI). The incidence is even higher in patients undergoing TBI, especially in a single dose (non-hyperfractionated), the highest dose rate (> 0.04 Gy/min) was also identified as a risk factor[2]. In addition, patients who have used corticosteroids, especially for a prolonged period of time, are also at risk of this complication[2].

Surgery is standard treatment, and early diagnosis and setting of the appropriate time for surgery are important in children, especially those under 7 years of age, in order to prevent irreversible amblyopia[3].

Keratoconjunctivitis sicca: It is commonly diagnosed in the post-transplant period and may resemble Sjogren's syndrome, with tear hyposecretion, thinning of the superficial epithelium, and keratinization of the cornea and conjunctiva, which may progress to ulceration and perforation of the cornea[4]. It is a complication more related to ocular graft-versus-host disease (GVHD), although it is not exclusively associated with it. TBI and drugs used in conditioning, immunoprophylaxis (such as methotrexate), or GVHD treatment may be responsible for its development.

The posterior segment refers to microvascular retinopathy, optic disc edema, hemorrhages, and infections, such as cytomegalovirus (CMV) retinitis, varicella, or toxoplasma. These complications have an estimated incidence of 10%and occur most frequently in the first year after HSCT[1].

Ischemic microvascular retinopathy: Its clinical presentation can occur from an asymptomatic form to complaints of blurred vision and change in color vision. This complication may have an abrupt, gradual, or progressive onset, and may affect one or both eyes. May occur in patients who have undergone an autologous or allogeneic transplant, and the risk factors associated with it are TBI conditioning, carmustine, busulfan, and cyclosporine prophylaxis[2]. Spontaneous regression may occur, and permanent loss of visual acuity is rare. The removal or reduction of immunosuppression may lead to resolution of retinal lesions in many cases[5].

Retinal hemorrhage and retinal detachment: Retinal hemorrhage and detachment usually occur as a consequence of other pathologies, such as CMV retinitis and neovascularization due to ischemic retinopathy. The best way to treat it is to keep platelet levels above 50.000/ul and correct possible coagulopathies. Retinal detachment is a rare posterior segment complication and is responsible for <1% of ocular complications after HSCT. Treatment depends on the underlying disease and includes laser photocoagulation, cryotherapy and various surgical techniques[6].

Recurrence of the underlying disease: Ocular involvement related to recurrence of the disease is a rare event, but that can happen[7]. In view of the suspicion, the patient should be evaluated by an experienced ophthalmologist, and imaging and biopsy may be required to confirm the diagnosis[8].

Glaucoma: Classically, glaucoma is known as a late complication of irradiation used in conditioning regimens, with an average interval of 22 months for the onset of this complication. Prolonged corticosteroid use is also a risk factor[9].

Other late complications involving the eyes are related to chronic GVHD, as described in the accompanying chapter on GVHD.

ORAL COMPLICATIONS

The main acute oral complications occur due to chemotherapy used in conditioning regimens, or due to the presence of GVHD with involvement of the oral cavity. Therefore, it is important that these patients are regularly followed up by dentists.

Developmental disorders: Dental changes caused by myeloablative conditioning usually occur after six months of the procedure[10]. Dental development in children undergoing chemotherapy and TBI for HSCT can be significantly compromised. Radiotherapy is an important risk factor for craniofacial development changes, especially when performed before 5 years of age may lead to a reduction in mandible

growth[11]. Regarding dental disorders, the most frequent findings are dental agenesis, microdontia, teeth with root shortening and alteration in the corona-root ratio.

Fungal and viral infections: Oral fungal infections have been observed in 15% to 56% of patients in HSCT, with Candida infections being the most common, and the oropharynx is a site prone to colonization[13]. *Candida albicans* is the commonest species, usually associated with oral candidiasis. Risk factors for this infection are mucositis, severe and persistent neutropenia, use of broad-spectrum antibiotics and corticosteroids, as well as GVHD and xerostomia[12].

Infections caused by the herpesvirus family may be common in patients undergoing HSCT, especially recrudescent lesions of human herpes virus type 1 (HHV-1) and human herpesvirus type 6 (HHV-6). CMV may also cause lesions in the oropharynx, without any characteristic clinical presentation[13].

Later after HSCT, patients may have decreased saliva production, which increases the chance of developing severe cavities and gum disorders. Repeated trauma to the oral mucosa, especially in patients with oral chronic GVHD also increases the chance of developing secondary oropharyngeal carcinoma. Patients and families must be educated to report any new oral lesions and the team following them must always have a high suspicion to promptly diagnose a new cancer.

GVHD: about 30% to 80% of patients with post-HSCT GVHD have oral cavity lesions associated with significant symptoms[14]. For further information, please refer to the GVHD chapter.

BONE COMPLICATIONS - OSTEOPENIA AND OSTEOPOROSIS

Risk factors, early diagnosis, prevention, and treatment: Osteopenia and osteoporosis are common complications after HSCT. The most common risk factors are prolonged corticosteroid use, hypogonadism, vitamin D deficiency, lack of sun exposure, use of immunosuppressive medications, sedentary lifestyle, family history, conditioning regimen used in HSCT, TBI, among others[15]. Bone mineral density reduction has an incidence of up to 26% in patients without GVHD and up to 94% in patients with chronic GVHD[14].

Diagnosis:
Bone mass reduction in children is defined as z > 2 standard deviations below population norms of age and gender in densitometry[16]. Osteoporosis in children is defined as the reduction of bone mass associated with a history of fractures (2 or more up to 10 years or more from 3 to 19 years). If the patient presents with a compressive fracture in the spine with no history of trauma that justifies it, it also indicates the establishment of osteoporosis[17]. Several studies have highlighted that fractures are important, despite being an underrecognized manifestation of osteoporosis in children. This usually occurs for two reasons: the first because they are usually asymptomatic, and second, because monitoring with lumbar spine radiography is not routinely performed[18].

Patients who have used corticosteroids for more than 3 months should perform an x-ray of the spine at the time of initiation of treatment and repeat the examination after 3-4 months to avoid the first incident of vertebral fracture. It is also suggested to repeat the test again after 12 months, and from then on, only if the patient maintains exposure to risk factors such as corticosteroids[18,19].

Treatment: The first line of treatment for bone health maintenance is based on three points: nutrition, physical activity, and treatment of the underlying disease and associated comorbidities[20]. The best nutritional factors for bone health are vitamin D and calcium. However, several other nutrients are also relevant for bone metabolism, such as proteins, potassium, magnesium, copper, iron, zinc and vitamins A, C and K. Post-HSCT patients are at particularly high risk of vitamin D deficiency due to limited sun exposure, malabsorption and dietary restrictions. The investigation and treatment of possible endocrine changes is also important for these patients[21].

The initial therapeutic approach is usually conservative. Not all children with symptomatic osteoporotic fractures and chronic diseases require therapy for osteoporosis due to the potential for spontaneous recovery (without specific medications) if risk factors are transient[18]. But children with vertebral fracture(s) and/or low bone density and two or more long bone fractures should be considered for intravenous bisphosphonate therapy[22]. A retrospective study from Seattle suggested that the use of bisphosphonates associated with vitamin D and calcium supplementation may reverse osteopenia and post-HSCT osteoporosis[23]. However, these cases should be discussed and followed up together with a pediatric endocrinologist. The use of bisphosphonates may cause some important adverse effects, such as mandible necrosis.

BONE COMPLICATIONS - AVASCULAR NECROSIS

Avascular necrosis (AVN) is an important bone post-HSCT complication. Risk factors include age ≥ 5 years at HSCT, female gender, myeloablative conditioning regimens, and exposure to corticosteroids (especially dexamethasone). AVN typically affects the femoral head and can cause severe pain and bone destruction, resulting in significant impairment in quality of life, and eventually requiring joint replacement in many patients[24]. In children, the knees (31%-40%) are the most frequently affected site, followed by hips (19%-24%), shoulders (9%), and other locations. Although not so well described, AVN findings on magnetic resonance imaging (MRI) do not always have clinically significant symptoms in children[25]. Performing MRI, referring to physical therapy and evaluating the need for surgery in early strategies should be considered in patients at higher risk for developing AVN, especially with prolonged steroid use due to chronic GVHD, which can mitigate the morbidity associated with this complication[26]. However, the indication of surgery should be discussed with an experienced orthopedist and multidisciplinary team[24].

INFECTIONS

Infection prophylaxis and preemptive therapies

All post-HSCT patients have some degree of immunodeficiency, especially during the first 6 to 12 months after transplantation. Bacterial, fungal and viral infections occur more frequently during this time interval. In the absence of GVHD, most patients have adequate immunological reconstitution one year after transplantation. Patients with chronic GVHD remain immunodeficient for longer and have a high risk of infections[27].

Pneumocystis jirovecii pneumonia (PCP or PJP)

Patients undergoing an allo-HSCT should receive prophylaxis against PCP for at least 6 months after transplantation or until all immunosuppressive drugs have been discontinued, which may subsequently occur[28]. The preferred drug is sulfamethoxazole and trimethoprim, and patients allergic to sulfa should be desensitized whenever possible. If desensitization is not feasible, dapsone can be administered at a dose of 2 mg/kg once daily (maximum 100 mg/day). Before starting treatment with dapsone, patients should be tested to rule out G6PD deficiency[27].

VARICELLA ZOSTER

After primary infection with the varicella zoster virus (VZV), it establishes latency in the dorsal ganglia and can be reactivated over time as herpes zoster in immunocompetent individuals or as a severe episode of chickenpox in immunocompromised patients. The use of corticosteroids, immunosuppressive drugs, chronic GVHD, transplants from alternative donors and cord blood are risk factors for VZV reactivation after HSCT[29].

There is a recommendation for all VZV seropositive patients (by vaccine or disease) to receive prophylaxis with acyclovir or valacyclovir during the first year after transplantation or up to 8 months after the end of systemic immunosuppression, whichever is longer[28].

Patients exposed to chickenpox or zoster during the first year after transplantation or during the use of immunosuppressive drugs should be clinically evaluated. Those seronegative to VZV and who do not receive prophylactic acyclovir should be treated with valacyclovir on days 3 to 22 after exposure, unless treatment with ganciclovir, foscarnet or cidofovir is being administered for another reason. In seronegative patients, administration of varicella zoster immunoglobulin (VZIG) within 96 hours of exposure should also be used, if available, in addition to valacyclovir, as described above[27].

ENCAPSULATED BACTERIA

Patients with chronic GVHD are highly susceptible to recurrent bacterial infections, especially from encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophylus influenzae* and *Neisseria meningitidis*[28].

Long-term prophylaxis is recommended in this scenario and, due to the emergence of penicillin resistance (and the concomitant need for prophylaxis for PCP in these patients), sulfamethoxazole and trimethoprim is recommended as a first-line drug for chemoprophylaxis for infections by encapsulated bacteria. Patients receiving systemic immunosuppressive therapy for chronic GVHD should receive antibiotic prophylaxis against encapsulated bacterial infections for at least 6 months after discontinuation of all immunosuppressive drugs[27].

Antimicrobial prophylaxis for asplenic patients

Patient education is essential to prevent fatal infections in asplenic patients. Patients who have had splenic irradiation, sickle cell disease and chronic GVHD may also have completely lost their splenic function. Studies have shown that 11% to 50% of post-splenectomy patients remain unaware of their increased risk of severe infection or the appropriate health precautions that should be taken[27]. Antimi-

crobial prophylactic regimens are the same as for the prevention of encapsulated bacteria in patients with chronic GVHD and include daily sulfamethoxazole and trimethoprim or twice daily Penicillin V. As penicillin V does not offer PCP protection, another prophylaxis for PCP shall be performed[27].

The duration of prophylaxis for patients without GVHD is up to 6 months after immunosuppression or up to 6 years or 2 years after splenectomy (which happens later). Patients with GVHD should be on prophylaxis for up to 1 year of HSCT or 6 years or 2 years after splenectomy (which happens later).

Sickle cell anemia: all patients with sickle cell anemia should receive penicillin prophylaxis daily for two years after transplantation or until the tenth anniversary, whichever takes longer to happen[27].

These patients should have the anti-pneumococcal, anti-meningoccocal and anti-haemophylus titers checked after they get the post-transplant revaccination. Despite prophylaxis or after it is discontinued, invasive fulminant infections still do occur. Education must be over emphasized for patients in all routine visits to seek medical attention should they develop fever or feel sick, to tell the healthcare provider that they do not have a functional spleen, and that they do need to receive antibiotics.

CYTOMEGALOVIRUS (CMV)

CMV infection is a potentially serious complication after HSCT.

Risk factors for CMV infection: these are related to the CMV serological status of the recipient and the donor, the degree of Human Leukocyte Antigen (HLA) compatibility between recipient and donor, characteristics of the conditioning regimen, T-cell depletion, the development of GVHD, and immune reconstitution after transplant[30].

Patients with a positive immunoglobulin G (IgG) serological status who receive the stem cells from an IgG-negative donor have the worst outcomes in allogeneic transplants. On the other hand, IgG-negative patients receiving the graft from donors also IgG-negative, rarely develop any CMV-related complication[31]. Thus, if possible, a CMV-negative seronegative donor should be selected for a seronegative recipient and a CMV-positive donor for a CMV-positive patient ("CMV matched donor").

CMV reactivation: it is defined as the detection of the virus DNA in the blood or a new episode of antigenemia in patients who had IgG+ serology prior to HSCT.

CMV disease: this requires detection of CMV in tissues by molecular or virological methods in patients with CMV-related symptoms[32]. May include variable clinical manifestations such as interstitial pneumonia, enteritis, hepatitis, retinitis, encephalitis, and a CMV syndrome that includes cytopenia and fevers.

CMV disease-related mortality is on average 40-50% but can reach 86% in cases of severe pneumonia. In the case of CMV pneumonitis, the use of immunoglobulin should be considered.

Febrile CMV syndrome: it is diagnosed when patients have fever (>38oC) lasting more than two days and CMV is detected in their blood samples, but not in their tissues[32].

Diagnosis: The diagnostic methods for CMV infection are pp65 antigenemia - Agpp65 (sensitivity 89%, specificity 100%) or polymerase chain reaction - PCR (sensitivity from 95 to 100%) for the early detection of CMV replication. There is a current trend of antigenemia to be substituted by molecular methods, particularly in post-transplant monitoring of CMV viral replication[33].

PCR should be normalized for quantification according to the World Health Organization (WHO) standard as UI/ml results, and each center should establish its cut-off for preemptive therapy.

Weekly follow-up by PCR or antigenemia is suggested in patients transplanted up to D+100, but in high-risk patients (related mismatched HSCT, unrelated donors, cord blood, persistent immunodeficiency in haploidentical transplants), monitoring should be extended until D+180.

Treatment: The current best strategy to decrease morbidity and mortality is the early initiation of preventive therapy against CMV[28]. First-line preemptive treatment should be performed with ganciclovir 5mg/kg/dose every 12 hours[32]. In early post-HSCT reactivation, for which this medication cannot yet be used due to its myelotoxicity, the use of foscarnet 60mg/kg/dose every 8 hours or 90mg/kg/dose every 12 hours can be evaluated. Unfortunately, however, there is a huge difficulty in accessing foscarnet for patients in the Brazilian unique health system (SUS), which limits the therapeutic options for these patients.

Treatment should be maintained for at least 14 days until the patient has at least one negative test. Increased CMV-DNAemia (or Agpp65) in the first two weeks of preemptive therapy does not require a change in therapy. However, if this is sustained for

more than two weeks, a ganciclovir dose increase (7.5 to 10mg/kg/dose) and immunosuppression reduction (when possible) can be evaluated.

Monitoring during treatment:
Complete blood count with leukocyte count and differential should be performed before the beginning of the treatment and then tart of treatment, 2-3 times a week during treatment with valganciclovir or ganciclovir.

If the neutrophil count is < <1.500/ mm^3, a blood count should be performed daily.

If leukocytes <1.000/mm^3 before the start of treatment or during treatment, the use of foscarnet should be considered[27].

Renal function should always be followed (at least once a week) and adjustments should be made as needed.

Other therapeutic options:
- Cidofovir (5mg/kg once a week) is a second line of treatment and can be considered on occasion. However, it is also a medication that is difficult to access for patients in the Brazilian unique health system.

- Valgancyclovir: Some randomized trials have already used it for patients after a HSCT, although it has not yet been officially approved for these patients[28]. Its use should be considered for patients with good oral intake, no active intestinal GVHD, no significant liver disease and no severe diarrhea. However, it is expensive and not widely available.

Valgancyclovir dose[27]:

≥ 40 a <50kg: 675 mg, oral every 12 hours

≥ 30 a <40kg: 450 mg, oral every 12 hours

≥20 a <30 kg: 450 mg, oral every 12/12 hours ou 14 mg/kg every 12 hours

≥ 15 a <20 kg: 225mg, oral 12/12 hours (= ½ tablet) ou 14 mg/kg every 12 hours

≥10 a <15 kg: 14 mg/kg, oral, every 12 hours

Prophylaxis:
The use of CMV prophylaxis with letermovir has encouraging results in adult patients but requires further studies in the pediatric population[34]. Some randomized studies have shown that high doses of acyclovir or valacyclovir may reduce the risk of CMV infection, but not CMV disease[35,36].

FUNGAL INFECTIONS

Invasive fungal infection (IFI) is an important cause of morbidity and mortality in patients after HSCT. Pathogens can usually be divided into three groups: Candida, Aspergillus and other fungi (Zygomycetes, Fusarium species, and Scedosporium species). Over time, and with the introduction of prophylaxis, there has been a change in the infectious profile of these patients: Candida species were previously more common, but currently, Aspergillus, has emerged with a relevant prevalence[29].

Risk factors: age at transplant, diagnosis, type of transplant, stem cell source, prolonged neutropenia, the use of high doses of corticosteroids, severe acute and chronic GVHD, and fungal infection before transplantation[37].

Prophylaxis: Options include fluconazole, voriconazole, micafungin and liposomal amphotericin B. In children over 13 years of age, posaconazole is also an option[38].

Fluconazole can be used[29] up to D+75 after HSCT; this strategy has been shown to reduce the incidence of candidemia and candidiasis-related mortality[27]. However, risk factors and patient history should always be evaluated to define the best prophylactic option.

In the presence of GVHD treated with increased immunosuppression (including the use of corticosteroids at a therapeutic dose ≥0.3mg/kg per day of prednisone or equivalent), prophylaxis against fungal infections is recommended[38].

TABLE 1: Doses of antifungals[38]:

	Dose	Comments
Fluconazole	8 to 12mg/kg (maximum 400mg)	Active only against yeasts
Voriconazole	2 to <12 years or 12–14 years and <50 kg: 8 mg/kg every 12 hours (on the first day 9mg/kg) IV or 9 mg/kg oral every 12 hours ≥15 years or 12-14 years and ≥50 kg: 4 mg/kg every 12 hours (on the first day 6mg/kg) IV or 200 mg oral every 12 hours	Important to perform serum monitoring (Target dosage: minimum concentration 1–5mg L)
Micafungin	1 mg/kg/day (or in children ≥50 kg, 50 mg) IV	The spectrum includes Candida spp and Aspergillus spp; approved for prophylaxis of invasive Candida infections in neutropenic patients
Liposomal amphotericin	1 mg/kg IV every day or 2.5 mg/kg IV 3 times a week	Alternative option for patients who do not tolerate triazoles or have contraindications
Posaconazole	600mg/day oral every 8 hours in teenagers over 13 years of age	Serum monitoring is desired. Minimum concentration ≥0.5 mg /L

Diagnosis:

- Draw blood cultures for fungi

-Neutropenic patients with >96h without focus fever, may undergo imaging (e.g., chest CT scan for possible fungal infection)[38].

- Galactomannan: is a component of the cell wall released by Aspergillus spp. Twice-weekly monitoring in children at high risk of IFI can be considered for early diagnosis of invasive aspergillosis[38]

Empirical treatment:
Neutropenic patients with persistent fever (>4 days) of undefined cause and unresponsive to broad-spectrum antibiotics may receive empirical treatment for fungal infections and should maintain the medication until neutropenia is resolved[38].

Endocrine disorders, gonadal insufficiency, and fertility
The organs involved in endocrine functions are known to be sensitive to cytotoxic drugs and radiation. Consequently, endocrine complications are among the most important in post-transplant patients, with a potential risk of reducing their survival and quality of life[39]. Previous treatments, type of conditioning, use of TBI and patient age are the factors that most influence late effects.

Gonadal dysfunction
Puberty disorders post-HSCT are caused by central damage to the hypothalamic-pituitary axisby TBI, or by direct damage to gonads by irradiation or alkylating agents, such as busulfan (BU), cyclophosphamide (CY) and melphalan (MEL)[39,40,41].

Boys:
Conditioning with cyclophosphamide only or associated with TBI seems to preserve the normal function of Leydig cells, maintaining normal serum testosterone levels. However, these patients usually have evidence of germ cell dysfunction, with increased follicle-stimulating *hormone (*FSH), volumetric reduction of the testicles, and reduction of spermatogenesis. There seems to be greater harm to post pubertal patients than in pre pubertal patients[39,41]. These patients may require treatment with gradually increased doses of testosterone to promote sexual maturity, but it should be done in collaboration with a pediatric endocrinologist. Those who have passed puberty at the time of transplant may develop primary gonadal insufficiency[27].

From the age of 10 on, all children should have Tanner's development scores determined as part of an annual physical examination. Children with Tanner stage I or II at age 12 should be referred to a pediatric endocrinologist to assess the need for hormone supplementation[27].

Girls:
The use of busulfan represents a high risk of persistent ovarian failure in about 50% of the patients[39,42]. As in men, the highest risk of dysfunction occurs in post-pubertal girls at the time of transplant. The protective effect of younger age seems to be due to the large number of primordial follicles in girls under 10 years[43]. Ovarian function recovery was observed after transplantation in 54% of younger patients (under 26 years of age) conditioned only with cyclophosphamide. The probability of recovery of ovarian function after fractional TBI is 10% at 6 years after transplant[27].

Prepubertal girls should be closely monitored for the onset of puberty and, if not occurring around 12 to 13 years, should be referred for complete endocrine evaluation and consideration of hormone supplementation[44]. Estrogen replacement therapy is often critical for the development of secondary sexual characteristics during the transition from adolescence to adulthood and for obtaining peak bone mass in early adulthood. Hormone replacement in prepubertal girls should be performed in collaboration with a pediatric endocrinologist[27].

Fertility:
Fertility rates in patients undergoing HSCT in adolescence remain low. It is important that this be reported to patients and family members, and that forms of fertility preservation, such as cryopreservation and gonadal shield, are offered during radiotherapy[42,45,46]

Thyroid Dysfunction
Thyroid dysfunctions are described as common after HSCT, especially when TBI is used. Clinically, the most common manifestations are compensated subclinical hypothyroidism in 7 to 15% of patients in the first year of HSCT. Clinical hypothyroidism depends on other factors that determine its incidence: single ablative dose of TBI have a 50% incidence; those receiving fractionated doses of TBI have an incidence of around 15%; and patients after conditioning with BU+CY have an 11% of incidence[40,44]. The mean time to diagnosis of hypothyroidism is 4 years after HSCT or exposure to TBI. When thyroid-stimulating hormone (TSH) is elevated with normal thyroxine (T4) levels, evaluation should be repeated in 2 months or therapy should be initiated at the discretion of the treating physician. Patients who initiate thyroid hormone replacement should be reassessed about 6 weeks after initiation of therapy[44]. In addition, thyroiditis and thyroid neoplasms may develop in patients who have received radiation. Patients should be evaluated annually with physical examination and thyroid function tests[27].

Growth impairment
The growth process can be affected by a chronic disease or by toxic treatments such as HSCT. Decreased growth rate in these patients is due to the interaction of different factors, such as growth plate lesions, gonadal damage, precocious or delayed puberty, hypothyroidism and growth hormone (GH) deficiency[45].

GH deficiency and growth failure (decreased growth rate/year) occur in 70-80% of children who received total body irradiation or cranial irradiation ≥ 1800 cGy[27,39]. TBI with a single fraction dose of 10 Gy or a fractional dose of 12 Gy may lead to GH deficiency[47]. The onset of GH deficiency and insufficient growth varies with the age of the child at the time of irradiation. The onset of these problems seems to occur later in younger children than in peri pubertal children. All children should be monitored at least once a year, and those under 14 years of age should have an annual GH test until they develop GH deficiency or are older than 14 years of age, whichever occurs first[27].

Adrenal insufficiency
The incidence of adrenal insufficiency is low in patients post-HSCT. It usually occurs by prolonged corticosteroid use, suppressing the pituitary-adrenal axis, but its function tends to gradually recover after corticosteroid suspension. When long-term corticosteroid use occurs, it is necessary to test the pituitary-adrenal axis during corticosteroid discontinuation due to the risk of acute adrenal insufficiency[44]. In addition, it is important to leave those responsible for the patient with a letter that guides the family and other health care professionals about the need to increase the dose of corticosteroids in stressful situations, such as febrile episodes with temperatures ≥ 38.5ºC, major trauma and surgeries. On these occasions, it is advised to double the corticosteroids dose in use for the period in which the fever lasts. When the patient cannot receive oral doses of the medication, intramuscular or intravenous hydrocortisone is indicated. For surgeries, an attack dose in the preanesthetic phase of hydrocortisone 100 mg/m^2, IV, followed by infusion during surgery of over 100 mg/m^2 of hydrocortisone. Of note, patients with pre-HSCT adrenal insufficiency (e.g., adrenoleukodystrophy) are also at higher risk during stress situations.

Metabolic syndrome
Metabolic syndrome, including insulin resistance, glucose intolerance, hypertension, obesity and dyslipidemia, is an important risk factor for cardiovascular disease in individuals after HSCT[39]. TBI can induce metabolic syndrome through effects on the hypothalamic integrity or attenuating the ability to

develop adipose tissue to accommodate caloric excessive intake[48].

Post-HSCT patients have a high risk of developing abdominal adiposity, insulin resistance (52%), glucose intolerance (26%), type II diabetes mellitus (17%), dyslipidemia (26.9%), and systemic arterial hypertension. All these items are important risk factors for the development of life-threatening cardiovascular diseases[44,42].

The risk of developing type II diabetes mellitus is three times higher in transplanted patients when compared to a control group. This risk is associated with exposure to TBI, due to changes in mitochondrial function of muscles, liver, and pancreas, resulting in insulin resistance and diabetes. The prolonged use of corticosteroids may also be implicated in this mechanism[42,44]. Post-HSCT patients should undergo an annual assessment of glucose and lipid metabolism, especially if there is a family history of metabolic syndrome[39].

Post-Transplant Lymphoproliferative Disorders

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoproliferative diseases in the setting of transplantation resulted from proliferation of neoplastic lymphoid or plasmacytic cells in the context of extrinsic immunosuppression after transplantation[49,50]

PTLDs in the hematopoietic stem cell transplantation (HSCT) setting are almost exclusively related to Epstein-Barr virus (EBV) infection.

The pathogenesis of PTLDs is a result of EBV-induced transformation of B cells in the context of impaired anti-EBV cellular immunity due to iatrogenic IS and resulting in an outgrowth of EBV-infected B cells.

PTLDs occur usually between 3- and 6-months post-transplant, when virus-specific T cell immunity has not yet reconstituted and are generally of donor origin. Recipient-derived PTLDs have been described, but they occur mainly in patients with poor graft reconstitution.

T-PTLD after HSCT are quite rare. The frequency of T-PTLDs ranges 4–15% of all PTLD cases. EBV is present in approximately one-third of T-PTLDs. EBV-negative PTLD occurs after 5 and 10 years after SOT essentially, but it can occur after HSCT as well. These cases must be characterized as malignant lymphoma rather than PTLD and treated with appropriate chemotherapy protocols[51].

The main risk factors to develop EBV-PTLD after HSCT are described in the table below.

TABLE 2: Risk Factors for the development of PTLD

Pre-transplant risk factors
EBV serology donor/recipient mismatch
Cord blood transplantation
HLA mismatch Splenectomy Second HSCT
Post-transplant risk factors
Severe acute (especially steroid-refractory) or chronic GvHD requiring intensive immunosuppressive therapy
High or rising EBV viral load
Treatment with mesenchymal stem cells

Legend: PTLD: post-transplant lymphoproliferative disorder; EBV: Epstein-Barr virus; HLA: Human Leukocyte Antigen; HSCT: hematopoietic stem cell transplantation; GvHD: graft-versus-host disease.

Primary EBV infection is defined when EBV is detected (nucleic acid or serologically) in an EBV-naïve individual (most often asymptomatic acquisition, or occasionally presenting as infectious mononucleosis). Recurrent EBV DNAemia is diagnosed by detection of EBV deoxyribonucleic acid (DNA) in the blood of a previously infected individual, as defined by detection of EBV-specific IgG-antibodies[52].

Fever and lymphadenopathy are the most common clinical presentation of EBV-PTLD and rare, if not treated, are associated with rapidly progressive multi-organ failure and death[49].

EBV-associated disease following transplantation can be categorized as EBV-PTLD or EBV end-organ disease, according to its clinical presentation.

The clinical staging of EBV-PTLD includes: nodal versus extranodal, limited (unifocal) versus advanced (multifocal) disease. The Ann Arbor classification, established for staging of lymphoma, can also be recommended. EBV-PTLD can also be staged according to the Lugano classification by PET-CT in children and adults[53].

Diagnosis

The diagnostic work-up of EBV-PTLD includes[49]:

- physical examination, including an examination for fever, tonsillitis, adenopathy and organomegaly.
- Positron emission tomography (*PET*) - computed tomography (*CT*) (PET-CT) imaging.
- Endoscopy in case of gastro-intestinal symptoms
- Tissue biopsy with histological examination, including immunohistochemistry for viral antigens.

The WHO classification is most commonly used, with four types of morphological lesions being recognized: polyclonal early lesions, polymorphic, monomorphic (B-cell or T/Natural Killer [NK]-cell) and classical Hodgkin lymphoma-type PTLD[53].

- Peripheral blood EBV viral load by PCR.

EBV-PTLD can be diagnosed as probable or proven. Probable EBV disease: significant lymphadenopathy, hepatosplenomegaly or other end-organ manifestations (without tissue biopsy, but in the absence of other documented cause), together with significant EBV DNAemia. Proven EBV disease: detection of EBV nucleic acids or EBV-encoded proteins in a tissue specimen, together with symptoms and/or signs from the affected organ. Detection of EBV nucleic acid in blood is not sufficient for the diagnosis of EBV PTLD.

The diagnostic approach to EBV-PTLD should, whenever is possible, be based on biopsies of lymph nodes and other sites of suspected EBV disease[49,51,54]

Monitoring EBV DNA in blood

Prospective monitoring of EBV DNA performed by quantitative PCR is recommended. The whole blood, plasma or serum are appropriate specimens for monitoring EBV DNAemia. Screening for EBV DNAemia should start within the first month after allo-HSCT. However, the incidence of EBV PTLD during the first month after HSCT is estimated to be below 0.2%[50]. Monitoring should continue for at least 4 months after HSCT or while the patient is immunosuppressed, with a frequency of at least once a week

Management strategies

Due to the involvement of lymphoid tissue localized throughout the whole body, PTLD needs to be seen as a disseminated disease at diagnosis. Therapeutic approaches applied in the prevention and treatment of EBV-PTLD include administration of rituximab (RTX), reduction of immunosuppression, use of EBV-specific cytotoxic T-lymphocytes (CTLs), donor lymphocyte infusion (DLI), and chemotherapy. There is no antiviral drug effective against EBV so far[49].

Prophylaxis: it is defined as drug or cellular therapy given to an asymptomatic EBV- seropositive patient to prevent EBV-DNAemia. The rationale for prophylactic use of RTX before or early after allo-HSCT is B-cell depletion. This strategy is only rarely administered and despite the fact that post-transplant RTX reduces the risk of EBV-DNAemia, it has not been shown to have an impact on the incidence of PTLD, transplant-related mortality (TRM), or overall survival (OS) in comparison to preemptive therapy. Therefore, this strategy should be evaluated on an individual basis, depending on transplant center expertise (European Conference on Infections in Leukemia – ECIL-6 - guidelines).

Preemptive Treatment: There is a correlation between rising or high EBV-DNAemia in blood and the development of EBV-PTLD, but it is not a rule. Usually, EBV-DNAemia occurs prior to the beginning of symptoms[52,55].

The available data does not allow the determination of a cut-off for EBV-DNA value for the diagnosis of EBV-PTLD or other end-organ EBV disease in HSCT patients. The kinetics of a rising EBV-DNAemia, together with the evaluation of the patient's immune function are very important to determine the need for preemptive therapy[52]. Local experience based on correlation of clinical and laboratory might be a rationale for each center.

The primary method for preemptive therapy includes Rituximab, once weekly until blood EBV negativity. Usually, 1–2 doses of Rituximab are sufficient. If possible, Rituximab should be combined with reduction of the immunosuppression. Donor or third-party EBV-CTL is another option but it is not yet available in our country.

T**herapy for EBV-PTLD**: therapeutic interventions for patients with probable or proven EBV disease. The therapy should be implemented as soon as possible to prevent the risk of multi organ failure. The first line therapy in EBV-PTLD is Rituximab, 375 mg/m^2, once weekly for 1 to 4 doses. Reduce the immunosuppressive therapy combined with rituximab must always be considered, if possible[56,57]. Cellular therapy as adoptive immunotherapy with in vitro generated donor or third-party EBV-specific CTL, if available[59].

Second line therapy in EBV-PTLD includes: cellular therapy (EBV-specific-CTLs or DLI)[49,54]. Chemotherapy ± RTX is a potential option after failure of other methods.The treatment goal is resolution of all signs and symptoms of PTLD, including a negative viral load. Response to rituximab therapy can be identified by a decrease in EBV DNAemia of at least 1 log10 in the first week of treatment.

Administration of RTX results in a positive outcome for over 90% of patients treated preemptively and over 65% when it is used as targeted therapy for EBV-PTLD. The use of EBV-CTLs achieves >90% of patients treated preemptively and approximately 75% in therapy of established EBV-PTLD[59].

Central Nervous System (CNS) PTLD

CNS PTLD is a particular presentation of the disease because it implicates risk of serious neurological consequences even in case of successful treatment. The current recommendations for treatment of CNS PTLD are extrapolated from the experience with Primary Central System Lymphoma[54].

Possible therapeutic options include RTX, systemic and/or intrathecal (IT) dose of RTX: 10–30 mg in 3–10 mL saline administered weekly). T-cell therapy with EBV-CTLs. Radiotherapy. Chemotherapy ± RTX according to primary CNS lymphoma protocols51

IRON OVERLOAD AFTER TRANSPLANT - DIAGNOSIS, EVALUATION AND MANAGEMENT

Iron overload/toxicity is an inevitable effect in several diseases characterized by anemia and red blood cell transfusion requirement.

After transplant has reestablished normal hematopoiesis and red cell transfusions are no longer necessary, body iron stores decline over several years[60]. Some patients will be affected by the already acquired iron overload that cannot be eliminated without active intervention even if they're free from transfusions. In this condition the acquired intracellular iron overload continues to disrupt the delicate labile cellular iron (LCI) equilibrium and promotes *reactive oxygen species (*ROS) generation.

Elevated ferritin estimates 32-58% of HSCT survivors may be overloaded with iron[61]. It has been also demonstrated in transplanted thalassemia patients that elevated transferrin saturation persists indefinitely without treatment and liver disease progresses even in the absence of other comorbidities[62].

High liver iron content (above 7mg/g) and ferritin above 1,000ng/mL has been associated with decreased survival (Extreme tissue iron overload (> 15 mg/g dry weight) has been associated with extensive organ toxicity in the post-transplant survivors of thalassemia[62].

Evaluation of iron overload post-HSCT

Although ferritin measurement is recommended as part of long-term follow-up post-HSCT, it also changes with inflammation and cell injury. Assessment of body iron by MRI is noninvasive and has been calibrated with liver biopsies and ex vivo heart tissue iron measurements, allowing accurate and more frequent assessment of iron overload than liver biopsy[63]. Liver or marrow iron content correlates poorly with the number of transfused red blood cell units.

We recommend iron studies - ferritin, iron, total iron-binding capacity and transferrin saturation at the following timepoints: 100 days, 6 months and 1 year post HSCT and at least yearly if still receiving red blood cell transfusions.

We highlight that biochemical laboratory tests are non-specific and can be very affected by inflammation, infection (elevated ferritin and decreased transferrin saturation) and graft versus host disease (increased iron absorption). So, they should not be used as sole criteria to consider the presence of iron overload that will be confirmed by *T2**-weighted MRI (MRI-T2*)[63].

Assessment of tissue iron

MRI-T2* is highly accurate in measuring tissue iron. It's mainly used to determine iron in the heart and liver but can also evaluate the spleen and pancreas[64].

MRI-T2* is the preferred method of evaluation and requires orders for both cardiac and abdominal MRI, specifying the exam is for iron evaluation. All patients should undergo MRI-T2* when being evaluated for iron overload, because of lack of correlations between liver iron concentration (LIC) and laboratory tests.

If the MRI-T2* is not available for all patients, is very recommend for patients that will meet one or more classic criteria used to indicate evaluation of iron overload, listed below:

- Lifetime history of receiving 10 red blood cell (RBC) units or more;
- Transferrin saturation >45%;
- Ferritin >1000ng/mL;
- Prior iron chelation therapy.

Patients that will need to undergo MRI-T2* to rule out cardiac iron overload during their long term follow up are those with risk factors such as lifetime history of receiving 75 RBC units or more; diagnosis of thalassemia, sickle cell disease and other congenital anemias (Diamond-Blackfan anemia; hereditary sideroblastic anemia).

Endocrine screen - patients with detectable cardiac iron (T2*<20ms) may benefit from earlier endocrine gland abnormalities screen with fasting glucose, TSH, free thyroxine (FT4), parathyroid hormone (PTH), FSH, and luteinizing hormone (LH).

Transient elastography – can be ordered if liver fibrosis or cirrhosis is a concern.

Liver biopsy – procedure very risky and should be an exception to be discussed case-by- case.

MANAGEMENT OF IRON OVERLOAD POST-HSCT

Phlebotomy is the preferred mechanism to remove excess iron after HSCT because normal erythropoiesis is achieved by transplantation. Phlebotomy can be started once engraftment is sustained. The general phlebotomy protocol consists of 6 mL/kg of blood removed every 14 days for thalassemic patients, as tolerated. This procedure should not be performed in patients younger than 11 years if hemoglobin is < 9.5 g/dL[65].

For other patients, 5ml/Kg, as tolerated, can be withdrawn every 3 or 4 weeks. Do not perform phlebotomy if hematocrit < 35%. It can be discontinued if ferritin below 500ng/ml or ferritin below 100ng/mL for hemoglobinopathy patients. No maintenance therapy is required. The duration of treatment ranges from a few months to several years[65].

Table 3 depicts the established indications for removal of excess tissue iron.

TABLE 3: Indications for Iron Excess Therapy by Tissue Iron Content

Cardiac T2* (ms)	LIC (mg/g dry weight)	Marrow Iron Content	Mobilization of Iron
>20ms	>15	Very high	Phlebotomy ± Single iron chelator
	7-15	Moderately high	1st choice: Phlebotomy 2nd choice: Single iron chelator
< 20ms	Any	Any	Phlebotomy + combination iron chelation; Consider admission if symptomatic or T2*<8ms Erythrocytapheresis for faster removal

Legend: LIC: liver iron concentration: ***T2*: T2***-weighted magnetic resonance imaging.

CHELATION THERAPY FOR IRON OVERLOAD AFTER HSCT

If phlebotomy cannot be performed in patients with high iron levels who cannot be treated with phlebotomies, daily subcutaneous administration of deferoxamine can successfully reduce iron stores [66,67]. Two oral iron chelators, deferiprone and deferasirox, have been used in iron-overload patients, but only deferasirox has been tested after transplantation[65].

Desferal or deferasirox (DFX) starting dose is 20mg/kg/day. The dose modification is 5-10mg/kg/day increments every 3-6 months if necessary, depending on serum ferritin (maximum 40mg/kg/day).

In table 4, we summarize the pros and cons of each therapeutic modality[68].

Table 4: Selecting the appropriate post-HSCT iron removal modality

	Phlebotomy	Oral Chelation
Strengths	– Efficient – Safe – Inexpensive – Permits complete iron removal and normalizes iron body content	– Efficient – Safe -Expensive – Immediate effect on cellular injury – Hospital access not required
Weaknesses	– Requires sustained engraftment – Immediate effect on cellular injury still remains to be verified – Hospital access required - Venous access is required	– Warning of renal toxicity in the case of concomitant use of cyclosporine A – Possible increase in toxicity for low level of iron burden

Considering the results of epidemiologic studies in thalassemia and in the normal population in the post-transplant setting, we must consider our goal for iron overload treatment a normal iron level and a normal transferrin saturation[62].

HEPATOBILIARY AND GASTROINTESTINAL COMPLICATIONS

Hepatobiliary Complications

Elevations of serum alanine aminotransferase (ALT), alkaline phosphatase, or bilirubin may occur after day 100, even in children who had signs of liver problems earlier.

The possible presentations drive to four clinical categories[69]:

-Acute hepatitis: Elevations of serum ALT after day 100 are most caused by drug-induced liver injury (antifungal azoles and sulfamethoxazole/trimethoprim are the most common causes of drug induced liver injury after HSCT in both children or adults), chronic GVHD, an exacerbation of hepatitis B or C, or a herpesvirus hepatitis (VZV, herpes virus simplex - HSV).

It's important to note that some clinical situations demand immediate diagnosis and treatment, such as rapidly rising ALT accompanied by anorexia, abdominal distension, or pain in the abdomen or back, which can suggest visceral VZV infection.

Patients who have indications of hepatitis B before transplant (HBsAg-positive or anti-HBc-positive) or who had a donor who was infected with hepatitis B are at risk of fulminant hepatitis B after the transplant if they did not receive antiviral prophylaxis.

Chronic GVHD can present as an acute hepatitis, usually after tapering or discontinuation of immunosuppressive medications, particularly cyclosporine or tacrolimus, or after DLI [70].

It's recommended to give IV acyclovir until VZV hepatitis is excluded for patients with a rapidly rising ALT and those with ALT values >500 u/L. A PCR for VZV DNA in serum is needed to establish the diagnosis.

-Chronic hepatitis: chronic fluctuations in serum ALT levels without a discrete episode of acute hepatitis may represent drug induced liver injury, hepatitis B or C virus infection, iron overload or chronic GVHD.

-Jaundice / cholestasis: elevated serum bilirubin and elevated alkaline phosphatase can be caused by chronic GVHD, drug-induced cholestasis, acute hepatitis, or biliary obstruction. An ultrasound can evaluate whether the common bile duct is dilated. Some patients have liver involvement as the dominant manifestation of chronic GVHD, and liver biopsy might be needed in order to establish the diagnosis when other manifestations of chronic GVHD are absent, otherwise liver biopsy is not recommended.

- Hepatomegaly or right upper quadrant pain: The sudden beginning of hepatomegaly suggests acute hepatitis, EBV-induced PTLD involving the liver, or in a few cases, Budd-Chiari syndrome.

For indolent hepatomegaly, the differential diagnosis includes metastatic tumor, leukemia infiltration and even constrictive pericarditis or mycobacterial infection (very rare).

Right upper quadrant pain can be caused by acute cholecystitis, biliary obstruction with cholangitis, or fungal liver abscess in rare cases.

For these signs / symptoms a liver imaging with helical CT X-ray or ultrasound would resolve the diagnosis. Liver biopsy and its technique depend on the clinical situation (diffuse process vs. focal lesion) and the platelet count.

An additional, much less common, late effect is the development of focal nodular hyperplasia. MRI is diagnostic and usually no surgical intervention is required. Routine surveillance is necessary because the risk of malignant transformation is unknown.

Gastrointestinal complications:
Gastrointestinal complications including graft-versus-host disease (GVHD) can cause high morbidity and mortality in HSCT recipients.

Late posttransplant complications appear after day 100. By this time, recovery of cellular immunity is, generally, complete. The most common complications during this period are chronic GVHD, PTLD, and secondary tumors and tumor recurrence. Late effects can also include toxicity from the treatment regimen, infections resulting from immunodeficiency, endocrine disturbances, growth impairment, and psychosocial adjustment disorders [71].

GVHD is the most common cause of anorexia, nausea, vomiting and diarrhea after an allogeneic transplant. However, each of these symptoms has a precise differential diagnosis that requires accurate evaluation before concluding that GVHD is the exclusive cause.

Anorexia, nausea and vomiting can be caused by HSV, VZV, and CMV infections and by certain medications such as trimethoprim-sulfamethoxazole, voriconazole, itraconazole, mycophenolate mofetil, cyclosporine or tacrolimus.

Abdominal pain can be caused by visceral VZV infection, biliary sludge syndrome, acute cholecystitis, or rarely, EBV-induced PTLD. Diarrhea occurring more than 3 months after transplant is commonly caused by magnesium – containing medications, unresolved GVHD, or less commonly by an infection (giardiasis, cryptosporidiosis, *Clostridium difficile*, and others)[72].

Clinically, chronic GVHD resembles autoimmune collagen disorders, with esophageal, and salivary gland changes, as well as anorexia and weight loss. Nowadays, chronic GVHD is defined as the presence of these features regardless of the time of onset [73]. Gastrointestinal GVHD often runs its course without demonstrating imaging findings, but strictures of the esophagus or small or large bowel are observed in some cases.

Long-term gastrointestinal complications have not been very reported outside of the chronic GVHD context. There are no known long-term effects on the gastrointestinal lumen or mucosa after acute GVHD has been successfully treated.

Neurological complications
Neurological complications are serious and significantly contribute to morbidity and mortality in children and adults experiencing allogeneic or autologous HSCT.

Approximately 11–59% of patients who undergo HSCT suffer from neurologic complications[74] and more than 90% of the cases who die after HSCT show neuropathological abnormalities in autopsy studies[75].

Various factors, including underlying disease, the pre-transplant conditioning regimen with high-dose chemotherapy, radiation therapy, vascular complications generated by thrombocytopenia and/or coagulopathy, immunosuppressive therapy, GVHD, infection and disease recurrences, are associated with neurotoxicity[76].

In many previous studies, GVHD has been identified as a risk factor for neurologic sequelae[77,78,79,80,81] and the prognosis of CNS GVHD is alleged to be very poor[82]. In addition to CNS GVHD, CNS infections and thrombotic microangiopathy (TMA)-associated neurological events can be frequent following the increased use of calcineurin inhibitors (CNIs) and corticosteroids in patients with GVHD[82]

Regarding infectious complications, cerebral aspergillosis and toxoplasmosis after unrelated allo-HSCT are a major challenge associated with a high mortality. Infection caused by varicella zoster is also reported after 1 year of transplant and can lead to a fatal outcome. If the patient presents progressive neurological symptoms after HSCT, the situation requires prompt diagnostic procedures and initiation of antimicrobial therapy if any findings suggestive of CNS infection were seen.

In the late phase (≥6 months) after HSCT the possible neurologic complications are CNS relapses of the original disease, neurologic complications of GVHD and second neoplasms.

Neurological manifestations of chronic GVHD are rare and can affect both peripheral and central nervous system. They usually occur several months to years after HSCT after administration of multiple

potentially neurotoxic drugs, when often infectious and metabolic complications have occurred.

Manifestations of peripheral nervous system, neuromuscular junction and muscle involvement in GVHD include polymyositis, myasthenia gravis (MG) and chronic inflammatory demyelinating polyneuropathy (CIDP) often developing late after HSCT at a time of reduction in immunosuppressive therapy[82].

MG is rarely reported post-HSCT in children and has a severe clinical presentation[83,84] which could be controlled only after several lines of treatment including plasma exchange and RTX.

Recent studies analyzing cohorts with a high number of pediatric recipients of HSCT showed increased risk of second neoplasms (SN) among all primary childhood cancer cases[85]. When compared to the general population, the overall standardized incidence ratio of developing SNs was 6.4 with an estimated 30-year cumulative incidence of 9.3%. Radiation has been shown to increase the risk of SNs. Allogeneic hematopoietic stem cell transplantation also increases the risk for SNs in children [85]. The types of tumors reported were neuroblastoma (39%), lymphoma (26%), sarcoma (18%), CNS tumors (14%) and Wilms tumor (2%) after a median follow-up of 8 years.

There is also an important concern about cognitive impairment due to total body irradiation, GVHD treatments, and cytotoxic agents[86]. Some children, especially those given cranial irradiation before the transplant, may have learning disabilities. These abnormalities typically begin to appear 24-42 months after the transplant and if it is recognized as a problem, we must refer for psychological testing and special educational instruction should be considered for these children.

TBI can delay the onset of developmental landmarks in very young children. These effects are most severe throughout the first year after transplant, and affected children benefit from occupational therapy to assist their normal development. After they have achieved appropriate developmental landmarks, further development appears to proceed normally. Intelligence quotient (IQ) and ability to succeed in school do not appear to be affected by TBI. However, the issue of cognitive impairment after HCT was not so much studied in pediatric patients.

Neurologic complications commonly occur in pediatric HSCT recipients. Major significant risk factors for mortality in pediatric recipients with neurologic complication were the existence of neurologic sequelae and extensive chronic GVHD.

In generally, clinical symptomatology is highly unspecific, and does not allow for any prediction on the later clinical course. So, a comprehensive diagnostic work-up is recommended in any patient presenting with neurological symptoms. Cerebral imaging and lumbar puncture have a great diagnostic value. In many cases, imaging studies are only able to provide useful information at advanced disease stages. Hence, early presumptive treatment is clearly warranted in order to prevent a fatal outcome.

Chronic pulmonary complications:

Late pulmonary complications in patients who have undergone bone marrow transplantation may involve both the airways and the pulmonary parenchyma. These complications can be infectious and non-infectious. The most common late noninfectious complications are obliterating bronchiolitis, or bronchiolitis obliterans (BO), obliterating bronchiolitis with organizing pneumonia (BOOP), and idiopathic pneumonia syndrome (IPS)[87,88,89]. BOOP/COP was also called cryptogenic organizing pneumonia (COP) in order to avoid confusion with airway diseases, such as BO[90]. These late pulmonary complications usually appear within 3 months to 2 years after HSCT. However, the functional consequences often persist for years after HSCT[88]. Patients undergoing allogeneic bone marrow transplants have higher risks than those who underwent autologous HSCT[88]. It is also uncommon for these complications to appear after 3 months of HSCT, in recipients of autologous bone marrow transplants[88]. Predisposing factors may include infections, extent and type of chemotherapy and radiation pre-transplant and in the conditioning regimen and GVHD[91]. Patients with chronic GVHD have a higher incidence of late pulmonary complications[88]. Overall survival is worse in patients with pulmonary complications, with significantly higher mortality and morbidity when compared to patients without pulmonary complications[88]. Table 5 illustrates some clinical manifestations, risk factors and interventions to be considered in patients with late pulmonary complications after bone marrow transplantation[88].

TABLE 5. Clinical manifestations, risk factors and interventions of late pulmonary complications after HSCT[88]

Organ	Clinical manifestation	Risk factors	Intervention
Respiratory tract	Bronchiolitis obliterans Bronchiolitis obliterans organizing pneumonia Restrictive lung disease	Graft-vs-host disease (GVHD) Infection Smoking Radiotherapy Chemotherapy Infection	Treatment of infection GVHD treatment Fractionated radiotherapy Steroids Consider lung transplantation

Adapted from: Tichelli A, 2008.

Abnormalities in gas transfer, such as restrictive and obstructive ventilatory defects are common in patients after HSCT. A decrease in forced expiratory volume in 1 second (FEV1) and the FEV1/ forced vital capacity (FVC) ratio is the hallmark of airflow obstruction[88]. Restrictive defects are measured by the total lung capacity and may be associated with impaired diffusing capacity for carbon monoxide (DLCO)[88]. Having evidence of abnormal pulmonary function pre HSCT and chronic GVHD are independent factors of worsening of pulmonary function in the period after HSCT[88].

A significant proportion of children have abnormal pulmonary function tests (PFTs) after HSCT[92]. These alterations are mainly DLCO and total lung capacity, implying restrictive lung disease and diffusion abnormalities; obstructive abnormalities are less frequent in children[92]. In a prospective study of the Late Effects Working Party of the *European Society for Blood and Marrow Transplantation* (EBMT), the cumulative incidence of PFT alteration in 162 children was 35% in 5 years, and in most cases pulmonary function deterioration was asymptomatic. The presence of chronic GVHD was the risk factor most involved in this context[93].

IPS, also known as interstitial pneumonitis, is more common in the early post-transplant period. However, it can occur in long-term survivors and may lead to delayed respiratory failure. Predisposing factors include allogeneic HSCT, exposure to high doses of TBI and GVHD. Patients with extensive chronic GVHD, especially sclerodermoid skin GVHD, have a higher risk of presenting to IPS[94]. Immune compromise delays recovery from infection, allowing greater damage to the lung interstitium[91]. Certain chemotherapy agents (e.g., carmustine, bleomycin, BU, methotrexate) can cause lung toxicity directly or may increase the damaging effects of radiation[91]. Fractionation of irradiation and protection of the lung may decrease irradiation toxicity[91]. Prophylaxis strategies focus on decreasing the risks of infections post-HSCT, especially in patients with chronic GVHD. The clinical presentation and radiological findings of IPS are nonspecific and do not differ from infectious pneumonia. PFTs show a restrictive pattern, such as decreased total lung capacity and DLCO, with normal FEV1[88].

BO is a severe pulmonary manifestation characterized by a nonspecific inflammatory lesion affecting mainly the small airways. In the initial phase it is typically an obstructive disease, but at a more advanced stage, due to progressive peribronchiolar fibrosis, often presents obstructive and restrictive functional changes[88].

BO occurs in 2-14% of allo-HSCT recipients and is almost exclusively seen in patients with chronic GVHD, for which it is classified by several authors as pulmonary GVHD[73,95,96,97]. However, BO may arise in patients without any other GVHD manifestation[91]. In such cases, it may be characterized by a new obstructive pulmonary defect, manifested clinically as stress dyspnea, cough or wheezing. Patients may be asymptomatic at the beginning of the disease process. BO is clinically diagnosed when all of the following criteria described above present together with active GVHD in at least one organ other than the lung: (1) relationship between FEV1 and FVC - FEV1/FVC < 0.7 and FEV1 < 75% of predicted FEV1, (2) evidence of air trapping or small airway thickening or bronchiectasis on high-resolution chest CT, residual volume >120%, or pathological confirmation of constrictive bronchiolitis and (3) absence of infection in the respiratory tract, documented with investigations (e.g., bronchoalveolar lavage) directed by clinical symptoms. Some experts consider a decrease in FEV1 of 10% or more over the baseline pre-transplant as a diagnostic criterion for obliterating bronchiolitis or an indication to perform a PFT more frequently[73,95]. Treatment of BO includes immunosuppressive agents, such as corticosteroids, CNIs, sirolimus, among others (see chronic GVHD section)[98,99]. Early diagnosis and prompt immunosuppressant treat-

ment may contribute to a more favorable response. Inhaled corticosteroids with bronchodilator showed benefits in the treatment of BO[100-101]. A prospective, multicenter study showed that the addition of FAM (inhaled fluticasone propionate, azithromycin and montelucaste) together with prednisone stabilized pulmonary function in 70% of newly diagnosed patients with BO and also allowed the reduction of systemic corticosteroids[102]. Prevention of *Pneumocystis jirovecii* pneumonia and the early treatment of superinfection is an important treatment strategy[88]. However, prognosis of patients with BO remains poor and 5-year survival rates are <20% if patients do not respond to initial treatment[96,97]. In most cases, death is attributed to progressive respiratory failure or opportunistic infections[88].

It is important to emphasize that infants and young children are not able to perform pulmonary function tests. In these cases, the evaluation of BO will have to be done exclusively by a CT of the chest without contrast to evaluate the areas of air trapping during the expiratory phase of the examination. Depending on the age the children will not be able to coordinate the expiration during the CT scan and in these cases, images can be performed in right and left lateral decubitus, being possible to evaluate the lung that is below, which will be expired. Pulmonary lobules with normal airways increase their density during expiration, while areas with obstructed airways and air trapping remain radiolucent. This provides a characteristic mosaic image that is highly suggestive of obliterating bronchiolitis[103-105]. When no air trapping is seen on expiratory chest tomography, the diagnosis of BO is very unlikely.

COP, previously known as BOOP, is a clinicopathological syndrome that involves the bronchioles, alveolar ducts and the alveoli and is the result of a variety of toxic, immunological or inflammatory injuries to the lungs. COP presents typically in the first 6 to 12 months after transplantation, although a late onset may occur, mainly in patients with chronic GVHD[91]. Clinical presentation includes nonproductive cough, low grade fever, and dyspnea. Radiological imaging may reveal areas of consolidation with ground glass or nodular infiltrates. In contrast to BO, the pulmonary function tests typically show a restrictive pattern, with decreased total lung capacity and normal DLCO and FEV1[103,106]. Bronchoscopy with bronchoalveolar washes is useful to rule out pulmonary infection. Biopsy may be required to confirm the diagnosis of COP. The mainstay of treatment is based on corticosteroids, and recovery is expected in 80% of patients, but relapses are common if steroids are rapidly tapered[88,91]. This complication is rare after transplantation and no specific screening tests are available for early diagnosis and prevention[91].

Recurrent sino-pulmonary infections may occur in patients with delayed immune reconstitution and chronic GVHD. Appropriate vaccination is recommended, and in patients with ongoing immune deficiency and infections, monitoring of immune globulin levels and replacement therapy should be considered according to indication[91]. Given the high risk of pulmonary infections in patients with a history of toxic lung therapy, especially in patients who have received mediastinal radiotherapy, it is very important to carry out the vaccination schedule with three doses of the pneumococcal conjugated vaccine and a dose of the *pneumococcal* polysaccharide *vaccine 23 (*Pneumo 23)[107]. It is also worth mentioning that the influenza vaccine should be applied annually[107].

Other rare late complications involving the lungs include diffuse alveolar hemorrhage, pulmonary thromboembolism, pulmonary hypertension, pulmonary veno-occlusive disease (VOD), and pleural effusions[91]. The most common causes of pulmonary hypertension are pulmonary arterial hypertension and pulmonary VOD, which is sometimes related to thrombotic microangiopathy associated with bone marrow transplantation[108,109].

Children who receive total body irradiation are at risk of having restrictive lung disease 5 to 20 years after bone marrow transplantation[91]. Therefore, all patients who underwent transplantation in the pediatric age group should perform pulmonary function tests annually, regardless of whether or not they have respiratory symptoms.

Changes in the values of pulmonary function tests usually precede symptomatology, which makes periodic evaluation with spirometry and/or chest tomography an indispensable monitoring for the follow-up of these patients. The earlier the diagnosis, the lower the impairment of pulmonary function and the better is the prognosis[110]. Childrenin particular may not report initial and frustrated respiratory symptoms, hence the importance of performing the tests in search of possible incipient chronic pulmonary complications.

One study showed a significant decline in FEV1 during the six months prior to the diagnosis of BO, with a lower FEV1 at diagnosis associated with worse survival[111]. Some centers perform pulmonary function tests every three months in patients with active chronic GVHD[111]. When the test shows a significant new obstruction of airflow, it can repeat pulmonary function tests monthly until a stabilization of the patient[112,113].

Recommendations[91]
Routine clinical evaluation by history and physical exam for pulmonary complications is recommended for all patients in D+100, at six months, one year and, yearly thereafter.

Perform clinical evaluations with earlier and more frequent clinic assessments including pulmonary function tests in patients with chronic GVHD. Perform every three months in the first year of diagnosis of chronic GVHD; every six months in the second year and then space according to the evolution of the patient.

Advise and encourage adolescents not to smoke.

In patients with signs or symptoms of lung compromise pulmonary function test and specific radiological assessment should be performed as clinically indicated. Follow-up evaluations should be guided according to the patient's clinical evolution.

Long-term cardiovascular complications:
Compared to other post-HSCT complications, the incidence of late cardiovascular effects is lower. However, as cure rates and follow-up times increase, their incidence tends to increase[114], reaching up to 17% of patients 15 years after HSCT[115]. Early complications are related to the disease and its treatment before HSCT, age, type of transplantation and comorbidities. Late complications, up to decades after HSCT, are associated with cardiotoxic chemotherapy used, mainly with the use of cyclophosphamide in the conditioning regimen, mediastinal irradiation, gender, age at HSCT, presence of GVHD and classical cardiovascular risk factors[114]. Late cardiovascular complications occur most commonly after allogeneic HSCT, suggesting an immunological role in the development of atherosclerosis[114]. Endothelial injury may result from persistent vascular inflammation and death of endothelial cells caused by GVHD, leading to atherosclerosis and cardiovascular complications[114]. Cardiac GVHD is very rare and may have pericardial effusion, dysrhythmia (mainly bradycardia), coronary heart disease, and cardiomyolysis[116,117].

Cardiovascular events after HSCT occur in patients younger than in the general population and are mainly cerebrovascular diseases (stroke, transient ischemic attack, carotid occlusion, and symptomatic lacunar infarctions) and coronary diseases (myocardial infarction, cardiac arteriosclerotic disease, and angina)[118].

In addition to the usual risk factors (smoking, hypertension, obesity, diabetes, dyslipidemia, and sedentary lifestyle), HSCT recipients have additional risks such as total body irradiation, endothelial damage caused by chemotherapy, GVHD, infectious complications, prolonged use of corticosteroids and other immunosuppressive medications[119,120].

The prevalence of endocrine factors that increase the chance of cardiovascular complications, such as insulin resistance, glucose intolerance, type 2 diabetes, hypertriglyceridemia and central obesity, are increased in HSCT recipients, even in young people with adequate weight, as a result of prolonged immunosuppressive therapies, exposure to radiotherapy or other frequent complications such as growth hormone deficiency and hypothyroidism[114,118,121].

In HSCT recipients, the risk of developing cardiovascular complications is five times higher and of dying from cardiac causes is two to four times higher than in the general population[118]. Cardiovascular events are the second cause of late death in some series, second only to recurrence of neoplastic disease[118].

It is worth mentioning the importance of recognizing that metabolic syndrome, including systemic arterial hypertension, dyslipidemia and diabetes has a high prevalence in patients who have undergone HSCT and this condition is associated with a higher incidence of premature coronary heart disease[122].

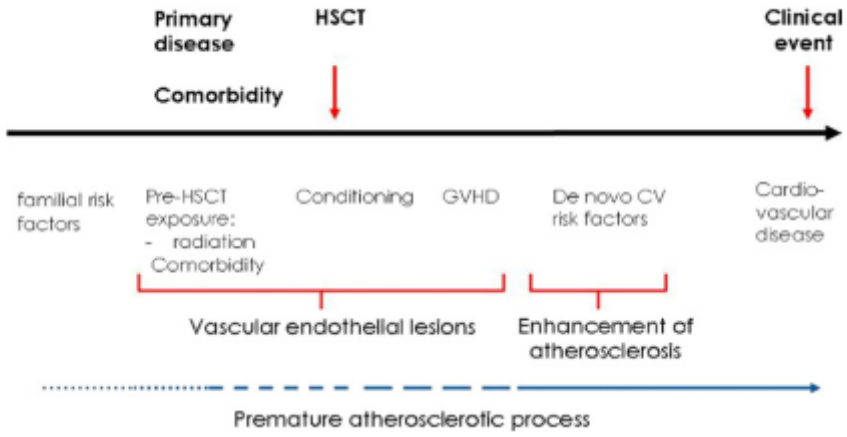
Iron deposition in the myocardium, due to multiple transfusions, may persist for years after HSCT[114,123]. Therefore, it is essential that patients with elevated ferritin undergo therapy to remove excess iron from the body through regular phlebotomy (therapeutic bleeding) or iron chelators.

Publications of late cardiac complications in transplanted children are rare[124]. In a prospective European multicenter study, the incidence of cardiac damage at five years was 26% in 119 children undergoing allogeneic HSCT. The use of total body irradiation and anthracycline in chemotherapy before HSCT significantly worsened cardiac function[125]. Another study showed that the children/adolescents most susceptible to cardiac complications were those submitted to unrelated allogeneic HSCT, total body irradiation and chronic GVHD in activity[119].

As endothelial injury caused by atherosclerosis occurs years before cardiovascular disease[118], the identification of indirect signs of atherosclerosis after HSCT is extremely important, with the potential to benefit children, improving their survival and quality of life[126]. The increased incidence of cardiovascular events after allogeneic HSCT supports the hypothesis that GVHD may be involved in the process, since in GVHD there is endothelium injury that may be re-

sponsible for atherosclerotic changes and lead to post-HSCT cardiovascular events. Because of the long latency period between the initial vascular lesion and the cardiovascular clinical manifestation, complications appear only decades after bone marrow transplantation, emerging as a very late event[127].

FIGURE 1: Diagram of the hypothetical atherosclerotic process occurring in long-term HSCT survivors leading eventually to a therapy-related cardiovascular event[128]

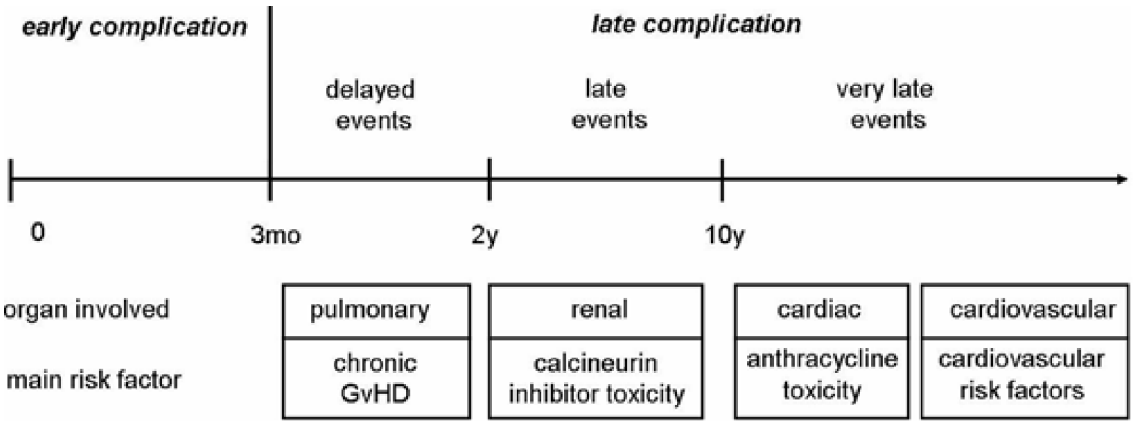


Legend: HSCT: hematopoietic stem cell transplantation. GVDH: graft-versus-host disease; CV: cardiovascular.
Adapted from: Rovó A, 2012[128].

Figure 2 illustrates pulmonary, renal, and cardiac complications according to the time elapsed after HSCT, such as delayed events when they occur 3 months to 2 years after transplantation; late events, which occur from 2 years to 10 years after HSCT and very late events when they occur after 10 years of transplantation[127]. Cardiac complications will occur decades after treatment as very late events and many patients may develop asymptomatic cardiac dysfunction. Therefore, the real magnitude of the risk of cardiac events after HSCT will actually only be measured over the course of years[127].

Thus, as cardiovascular complications can occur after several years of bone marrow transplantation, cardiovascular follow-up should be performed throughout the patient's life, with the involvement of multidisciplinary teams (cardiologist, endocrinologist, pediatric oncologist, nutritionist, among others), in an attempt to detect early and intervene in the lifestyle of these patients to prevent cardiovascular effects.

FIGURE 2. Sequence of appearance of pulmonary, cardiac, cardiovascular, and renal complications after HSCT and main corresponding risk factors. Late complications are subdivided into delayed events (between 3 months and 2 years), late events (between 2 and 10 years), and very late events (> 10 years)[127]



Legend: Legend: HSCT: hematopoietic stem cell transplantation. GVHD: graft-versus-host disease.
Adapted from: Tichelli A, 2008[127].

Early intervention in patients with cardiovascular risk factors may delay the onset of late cardiovascular disease. Therefore, a targeted and regular approach is needed to identify patients at risk. As children and adolescents will have a prolonged life expectancy, a thorough screening of modifiable cardiovascular risk factors and possible early interventions are of paramount importance to prevent premature death and for a better quality of life of these patients[128]. In addition, counseling for a healthy, tobacco-free lifestyle, with regular exercise, healthy eating and maintaining adequate weight became fundamental as part of the long-term management of transplanted patients[129].

The recommendations regarding the evaluation and monitoring of cardiovascular function and metabolic profile before, during and after autologous and allogeneic bone marrow transplantation are described in Table 6.

TABLE 6. Recommendations for evaluation and follow-up of cardiovascular function in children and adolescents undergoing bone marrow transplantation

Class	Level of evidence	Indication
I	C	Clinically evaluate for signs and symptoms of heart disease
I	B	Analyze accumulated dose of anthracyclines and use of pre-HSCT mediastinal radiotherapy
I	B	Assess whether there are a history of thromboembolic events in the family
IIA	C	Analyze risk-benefit before HSCT in patients with risk factors and perform HSCT in patients with left ventricular ejection fraction <55% if there is significant benefit
I	C	Perform ECG pre-HSCT, before the use of cyclophosphamide in conditioning, in the infusion of stem cells and periodically after HSCT (3 months, 6 months, 12 months and then annually)
I	C	Periodically evaluate patients undergoing HSCT for signs and symptoms of congestive heart failure
I	B	Evaluate ventricular function by transthoracic echocardiogram before HSCT
I	D	Perform transthoracic echocardiography periodically after HSCT: 3 months, 6 months, 12 months and then annually or at any time if there are changes in the symptoms
IIA	D	Perform three-dimensional echocardiography or cardiac magnetic resonance imaging in cases of transthoracic echocardiogram limitation
IIA	D	Perform stress tests on patients with echocardiogram changes or symptoms suggestive of cardiac dysfunction or who have risk factors

IIA	C	Echocardiogram and ECG every 3 months in patients with chronic GVHD due to increased risk of arrhythmias, endothelial injury and pericardial effusion
I	C	Pre- and annual endocrine control after HSCT: body mass index, glycemia, triglycerides, cholesterol, thyroid hormones, insulin
I	C	Ferritin control before and after HSCT (6 months, 1 year post HSCT and then annually until normal values are reached) and perform therapeutic bleeding or use of iron chelators if necessary
IIA	C	Perform cardiac MRI after HSCT in patients who are undergoing or wil undergoing treatment to reduce iron deposition in the heart

Legend: HSCT: hematopoietic stem cell transplantation; GVHD: graft-versus-host disease; ECG: electrocardiogram; MRI: magnetic resonance imaging. Note: Class I – Consensus; Class IIA – Conflicting evidence, but which favors the procedure; B – Non-randomized studies; C – Case series; D – Expert opinion.

Renal complications:

Renal dysfunction may occur in patients who underwent bone marrow transplantation in the pre, peri, and post-bone marrow transplantation period. Exposure to nephrotoxic drugs plays an important role in this renal dysfunction. The incidence of chronic kidney disease, defined as a sustained decrease in glomerular filtration rate below 60 ml/min/1.73m^2 for at least three or more months can range from 5 to 65%[130,131,134,135,136]. Chronic kidney disease usually becomes apparent 6 to 12 months after transplantation, although it can occur earlier as well as much later post-transplantation. Renal failure may present as TMA, glomerulonephritis, nephrotic syndrome, or nephritis by irradiation after exposure to TBI[91]. Other etiologies include persistent acute kidney injury and BK virus nephropathy[137]. Most patients have an idiopathic form of chronic kidney disease, which is not associated with thrombotic microangiopathy or nephrotic syndrome and has a multifactorial etiology[91].

Risk factors for chronic kidney disease in bone marrow transplant recipients include advanced age at HSCT, renal function and pre-transplant therapy (e.g., platinum compounds), acute and chronic GVHD, use of TBI in the conditioning regimen, exposure to medications to prevent or treat GVHD (e.g., CNIs), and certain antimicrobial agents (e.g., acyclovir, amphotericin B, aminoglycoside antibiotics)[131.132,133]. Antibiotics and antifungals cause tubular damage rather than glomerular damage. CNIs can cause glomerular thrombosis and tubular injury. A late syndrome of renal damage secondary to calcineurin inhibitors may affect renal arterioles and tubules and can be accompanied by interstitial fibrosis. CMV infection has also been associated with glomerular injury and the use of foscarnet for the treatment of CMV infection may induce even more tubule-interstitial nephritis and irreversible damage due to its crystallization within the renal tubules. Radiation exposure (e.g., TBI) can lead to degeneration and sclerosis of arterioles and secondary destruction of glomeruli and tubules[91].

Patients with substantial hemorrhagic cystitis in the early post-transplant period have a higher risk of scarring and late contracture of the bladder wall. In patients with hemorrhagic cystitis, research and treatment of polyomavirus and adenovirus is of vital importance, especially in patients using prolonged immunosuppressive therapy. Patients receiving immunosuppressive therapy for chronic GVHD, particularly women with GVHD of the vulva and vagina, are at risk of recurrent urinary tract infections[91].

The incidence of TMA is 2 to 21% in patients after HSCT and is characterized by renal dysfunction, thrombocytopenia, neurological dysfunction, hemolytic anemia with schistocytes, elevated lactate dehydrogenase and decreased haptoglobin[138,139]. Risk factors for TMA include TBI, use of calcineurin inhibitors, acute or chronic renal injury associated with GVHD[140]. TMA often improves with tapering or interruption of calcineurin inhibitors, but full renal function is often not completely restored[141]. In some cases, TMA did not improve until GVHD was treated[142].

Nephrotic syndrome occurs in 6-8% of patients after allogeneic HSCT, with membranous nephropathy in 61% of cases and minimal change disease comprised 22% of cases, with a median onset of approximately 14 months and eight months after HSCT, respectively[143,144,145]. Nephrotic syndrome after HSCT is usually related to chronic GVHD and tapering of immunosuppressive medications[145].

Idiopathic chronic kidney disease comprises most cases of renal dysfunction. The main risk factors involved are acute GVHD, chronic GVHD, acute kidney injury, prolonged use of calcineurin inhibitors and previous autologous HSCT[132,146]. Whenever possible renal biopsy should be considered with the objective of appropriate diagnostic and therapeutic elucidation of chronic kidney disease[147].

Systemic arterial hypertension is a frequent complication in patients who have undergone bone marrow transplantation. The main cause of this hypertension is medication, with corticosteroids, cyclosporine, and tacrolimus being the main culprits[148]. In most cases, systemic arterial hypertension is transient during the use of these medications, with blood pressure normalization after their suspension. However, it is essential to perform the diagnosis and appropriate treatment of systemic arterial hypertension in HSCT recipients to minimize damage to target organs, especially in the brain, heart and kidneys[148].

By performing the proper control and treatment of hypertension, there will be a lower incidence of heart failure, coronary heart disease and strokes. If the patient has a difficult to control systemic arterial hypertension or with any target organ injury it is important to refer him to follow-up with a specialist (pediatric nephrologist).

In the pediatric population, no class of drugs has emerged as a standard for the treatment of systemic arterial hypertension in patients receiving calcineurin inhibitors. The choice of antihypertensive will depend on the experience of each center. Among the drug options, thiazide diuretics can be used, but caution is needed when the patient is on calcineurin inhibitors, as it has a higher risk of metabolic side effects. Calcium channel blockers are also at the top of the list of options; however, it is important to monitor serum levels of cyclosporine and tacrolimus because they may interact with calcineurin inhibitors and can also worsen proteinuria in patients with proteinuria or microalbuminuria. Beta-blockers may decrease sympathetic activity and cause headaches/migraines induced by calcineurin inhibitors, in addition to tachyarrhythmias. Angiotensin converting enzyme (ACE) inhibitors may be a good choice in patients with chronic kidney disease, proteinuria, or even in diabetic patients. In patients with heart failure, diuretics, ACE inhibitors and angiotensin 2 receptor blockers may be used, but it is necessary to carefully monitor renal function to avoid renal azotemia with loop diuretics. If the patient does not have hyperkalemia, spironolactone may be used. Carvedilol and metoprolol are the beta-blockers of choice for patients with cardiac dysfunction[148].

In uncomplicated hypertension, without diabetes mellitus, renal dysfunction or cardiac dysfunction, it is recommended to follow blood pressure targets according to table 7[149,150].

TABLE 7: Updated definitions of blood pressure categories and stages in children and adolescents[150]

For Children Aged 1–13 y	For Children Aged ≥13 y
Normal BP: <90th percentile	Normal BP: <120/<80 mm Hg
Elevated BP: ≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mm Hg
Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg
Stage 2 HTN: ≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg (whichever is lower)	Stage 2 HTN: ≥140/90 mm Hg

Adapted from: Flynn JT, 2017[150].

Recommendations[91]**:**
Blood pressure should be checked at every clinical visit and hypertension should be investigated and treated appropriately in all HSCT recipients

Renal function should be evaluated periodically in all HSCT recipients. Screening tests should include assessment of blood urea nitrogen (BUN), creatinine, and urine protein. Additional evaluations (e.g., renal ultrasound, renal biopsy) should be performed if clinically indicated in patients with late onset acute renal failure or chronic kidney disease post-transplantation. More frequent assessments may be required based on the patient's medical status (e.g., ongoing therapy with calcineurin inhibitors).

In patients with progressive chronic kidney disease, avoid nephrotoxic drugs and consider early referral to a nephrologist for evaluation and treatment.

SECONDARY MALIGNANCIES FOLLOWING HSCT

As mentioned before, allo-HSCT is a curative option for several malignant and non-malignant disorders of childhood[151-157]. Nonetheless, the high exposure to chemo- and/or radiotherapy at a young age increases the risk of cumulative organ compromise, thus leading to late morbidity and mortality[158,159]. Earlier studies in adults undergoing allo-HSCT, as well as studies among cohorts of both children and adults, have shown an increased risk of late mortality, mainly due to recurrence of baseline disease, subsequent malignant neoplasm, chronic GVHD, infectious complications, and cardiovascular and pulmonary disease[160-166]. Of note, HSCT does not abrogate the inherent risk of malignancy in some disorders, such as Fanconi anemia (FA), dyskeratosis congenita, and other immunodeficiency syndromes[156,165,166]. Extra caution should therefore be taken toward defining the role and optimal timing of HSCT for these patients, given the relatively young age at HSCT, the expected longevity, and the potential for late treatment-related morbidity and mortality[167].

There are only a handful of studies, with relatively small cohorts, assessing late mortality after allo-HSCT specifically in the pediatric population[156,157,168-171], with most of the available studies combing adult and pediatric outcomes[172]. Moreover, it remains unclear whether late mortality rates have changed over the past three decades as a consequence of changes in transplant practice (e.g., conditioning platforms and supportive care). The incidence of secondary neoplasms may vary depending on the primary diagnosis (e.g., Fanconi anemia, myelodysplasia), disease status at transplantation, preparative regimens used (e.g., etoposide, high-dose TBI), HLA-mismatch, chronic GVHD, agents used for GVHD prophylaxis or treatment, as well as on certain demographic characteristics (e.g., age, sex, race/ethnicity, smoking status, and transplant time period)[162,165-6,168,173]. Neoplasms at less common sites, such as the oral cavity, liver, central nervous system, connective tissue, bone, thyroid and salivary glands are most frequently diagnosed after HSCT[173]. The main risk factors associated with individual solid cancers after HSCT are depicted in Table 8[174].

TABLE 8. Main risk factors reported for individual secondary cancers in the HSCT population.

Site	Risk Factor
Skin	cGVHD
Squamous cell carcinoma	aGVHD, cGVHD, male, age <18y at HSCT
Basal cell carcinoma	Age <18y at HSCT, MAC-TBI, white, cGVHD, attained age
Melanoma	MAC-TBI, T-cell depletion, female
Thyroid	Radiation conditioning, female, age $^{\delta}$20y at HSCT, cGVHD
Oral	Persistent cGVHD, cumulative duration of IST, including prophylaxis >24 mo, history of localized field irradiation, age <10y at HSCT, male
Esophagus	Persistent cGVHD, prolonged IST >24mo
Stomach None reported	NR

Colorectal	NR
Liver	TBI-based conditioning, younger age (<34y) at HSCT, liver cirrhosis, chronic hepatitis C infection
Lung	Lung Tobacco use prior to transplantation
Breast	MAC-TBI or Hx of radiation treatment, longer time since HSCT, age <18y at HSCT, use of growth factors, ATG
Cervix	cGVHD with systemic IST >3y, age >34y
Endometrial	NR
Ovary	NR
Prostate	NR
Testis	NR
Brain/CNS	NR (prior Hx of CNS irradiation may increase risk)
Sarcoma	NR

Legend: cGVHD: chronic graft-versus-host disease; aGVHD: acute GVHD; y = years; HSCT =hematopoietic stem cell transplant; MAC-TBI = myeloablative total body irradiation conditioning; IST = immunosuppressive therapy; mo: months; Hx = history; ATG: antithymocyte globulin; CNS=central nervous system; NR = none reported.

Adapted from: Inamoto, 2015[174].

FA patients are particularly prone to developing squamous cell carcinoma of the head and neck, with a corresponding poor prognosis in this patient group[165-6]. TBI, for instance, has long been known to be an established risk factor for both cancer and late mortality in HSCT recipients[158-9]. This has supported the fairly recent move toward reduced intensity non-TBI- or low-dose TBI-based regimens. Likewise, T-cell depletion has decreased toxicity with less GVHD, which, in turn, may potentially contribute to a lower risk of late cancer, morbidity and mortality[175]. Of note, in a study by Eapen *et al*., 2012, including pediatric patients with primary immunodeficiencies and inborn errors of metabolism, late mortality (7%) was found to plateau after a significant period of time post-transplant. In this cohort, as in other studies, chronic GVHD was found to be an important risk factor for these late complications[176,177].

Overall, the available literature shows an invariable excess risk of both cancer and late mortality in children undergoing allogeneic HSCT for either malignant or non-malignant diseases.[158-9,172,178-180] Nonetheless, since some secondary cancers are quite rare and most studies available are mostly retrospective analyses based on registry data, study populations are highly heterogeneous and details regarding chemotherapy and radiation therapy exposures prior to transplant are not always clear, larger studies are required to provide a better understanding of the incidence and risks of secondary cancers in post-HSCT patients.

In a large registry study by the *Center for International Blood and Marrow Transplant Research* (CIBMTR)[181], Kahn JM *et al*., 2020 examined the risk of SNs and late mortality in 6028 children and adolescents undergoing allo-HSCT for non-malignant diseases (NMDs) between 1995-2012. Median age was 6 years (interquartile range, 1-11; range, 1 to 20). Standardized mortality ratios (SMRs) in 2-year survivors and standardized incidence ratios (SIRs) were calculated to compare mortality and SN rates with expected rates in the general population. Median follow-up of survivors was 7.8 years. Diagnoses included severe aplastic anemia (SAA; 24%), FA (10%), other marrow failure syndromes (6%), hemoglobinopathy (15%), immunodeficiencies (23%), and metabolic/ leukodystrophy syndrome (22%). The 10-year survival was 93% (95%CI, 92% to 94%; SMR, 4.2; 95% CI, 3.7-4.8). A total of 71 patients developed SNs (1.2%), with the highest rates in FA (5.5%), SAA (1.1%), and other marrow failure syndromes (1.7%); for other NMDs, incidence was <1%. SNs were predominantly hematologic (27%), oropharyngeal (25%), and skin cancers (13%). Leukemia risk was highest within the first 5

years post-transplant, as opposed to oropharyngeal, skin, liver, and thyroid tumors, which primarily occurred after 5 years. Despite the relatively low number of SNs, patients presented an 11-fold increased risk of SN (SIR, 11; 95% CI, 8.9-13.9) when compared to the general population. This study emphasized the excellent survival after transplantation for NMDs observed in a large cohort of children and adolescents after the first 2 years post-transplant and the fact that the cumulative incidence of SNs is low. Even so, as mentioned previously, it underscored the increased risk for SN development in those with FA and other bone marrow failure syndromes, highlighting the need for long-term post-transplantation surveillance in this population.

It has long been known that patients undergoing a myeloablative conditioning (MAC) regimen prior to allo-HSCT are at increased lifelong risk for second solid cancers[158,174,182-84]. There is typically a latency period of 3 to 5 years before second solid cancers start appearing after transplant, with the most recent and robust studies reporting cumulative incidence rates of 1–2% at 10 years and 3–5% at 20 years after HSCT[157,158,172,177,182].

In a retrospective multicenter study by Kolb *et al*, 1999, 1036 consecutive patients who underwent transplantation for leukemia, lymphoma, inborn diseases of the hematopoietic and immune systems, or severe aplastic anemia and survived for more than 5 years were assessed for the incidence of malignant neoplasms and compared to the general population[159]. Median age was 21 years. Median follow-up since allo-HSCT was 10.7 years (range, 5 to 22.1 years), and malignant neoplasms were seen in 53 patients, with an actuarial incidence of 3.5% at 10 years and 12.8% at 15 years. This rate was 3.8-fold higher than that in an age-matched control population ($P < 0.001$). The most incident neoplasms were that of the skin (14 patients), oral cavity (7 patients), uterus (including cervix) (5 patients), thyroid gland (5 patients), breast (4 patients), and glial tissue (3 patients). These were more frequent in older patients and in patients with chronic GVHD under immunosuppression with cyclosporine.

In the MAC allo-HSCT scenario, important risk factors for these cancers include exposure to high dose TBI, younger age at transplantation, use of an HLA-mismatched donor, and chronic GVHD[158,175,182,183]. As for the risk factors related to reduced intensity conditioning (RIC) transplants, age at the time of HSCT, gender, Karnofsky performance score at transplant, diagnosis/disease status, time from diagnosis to HSCT, TBI dose (e.g., high dose and greater risk of breast cancer in women, donor/graft source, history of prior autologous transplant, GVHD prophylaxis regimen used, duration of immunosuppression, year of HSCT, and occurrence of acute (grade 2–4) or chronic GVHD are all potentially meaningful factors[184-85]. Given the increased survival rates observed in transplantation over the last few decades, in all such cases the incidence of secondary cancers continues to rise, for which lifelong surveillance is strongly recommended[91,158,172,175,181-82,186,187]. As a rule, RIC/NMA recipients should receive screening for solid cancers in a similar manner to what is typically recommended for MAC recipients, with extra awareness toward long-term survivors after RIC/NMA at an increased risk of cancers of the lip, tonsil, oropharynx, bone, soft tissue, vulva, and skin melanoma.

In the *Blood or Marrow Transplant Survivor Study–2*, a multicenter collaborative effort by Holmkvist *et al*., 2014, including a large cohort of children who had undergone an allo-HSCT between 1974 and 2010 and had lived for at least 2 years, investigators assessed the long-term outcome (all-cause mortality, relapse-related mortality - RRM, and non-RRM) of such patients[188]. In this study, individuals were stratified between three time periods: before 1990, 1990-1999, and 2000-2010. The SMR, a ratio of observed to expected number of deaths, was used to compare the mortality experienced by this cohort with the age-specific (5-year interval), sex-specific, and calendar specific (5-year interval) mortality of the US general population. Person-years at risk were computed from > 2 years after all-HSCT to either the date of death or the date of censoring, whichever occurred first. In this cohort study of 1388 children, individuals living for >/=2 years after undergoing allo-HSCT during childhood, transplant recipients were at an elevated risk of early death compared with the general population. Overall, the cohort had a 14.4-fold increased risk for premature death (95% CI, 12.8-16.1) compared with the general population (292 deaths observed; 20.3 deaths expected). High relative mortality was noted across all primary diagnoses, with SMRs ranging from 4.6 for SAA to 28.2 for inborn errors of metabolism and was highest for patients who had undergone transplantation at age 5 to 9 years (SMR, 22.8; 95% CI, 17.9- 28.4) and in the first 2- to 5 years after allo-HSCT (SMR, 522.0; 95% CI, 439.9-613.6), decreasing sharply thereafter. Nonetheless, it remained significantly elevated even >/= 25 years after transplantation (SMR, 2.9; 95% CI, 2.0-4.1). As for the specific causes of death, subsequent malignant neoplasms accounted for 18.4% of cases, with a 10-year cumulative incidence of 1.6% (95% CI, 1.0%-2.4%) for the occurrence of this event. The cumulative incidence of non-RRM was higher than that

of RRM (13.2% vs. 4.5% at 20 years after allo-HSCT). These findings underscore the need for close follow-up in respect to chronic GVHD and infections, as well as relapse, particularly during the first 10 years after transplantation. Additionally, given the significant proportion of deaths due to subsequent malignant neoplasms in this study, although the rate of late mortality was shown to decrease in the past three decades, lifelong proactive follow-up care of children (and adults) who live 2 or more years after transplant, including screening, preventive interventions, and counselling is strongly encouraged.

In a large, Brazilian, single-center, nested, case-control study by Tavares *et al.,* 2016, aiming at determining the cumulative incidence of secondary neoplasms in HSCT recipients and the possibly associated risk factors for this complication, 520 patients who had undergone a related or unrelated donor transplant between 2000 and 2010 were assessed[173]. All patients having a histopathological confirmation of neoplastic disease within this cohort were selected as cases and matched in a 2:1 ratio to transplant period-matched controls Among these, 19 recipients were found to have developed a post-HSCT neoplasm and were considered as cases, with the following neoplasms being identified: melanoma (3), basocellular carcinoma of the skin (3), squamous cell carcinoma of the esophagus (3), adenocarcinoma of the prostate (2), intraepithelial cervical carcinoma (2), squamous cell carcinoma of the uterus, breast cancer, diffuse-large B-cell non-Hodgkin lymphoma, choroidal carcinoma, squamous cell carcinoma of the tongue, and rectosigmoid adenocarcinoma (1 case each), Table 9. In the second malignancy group, the mean age at transplant was 39 (15-63) years, with a predominance of males (12). All cases were transplanted for a hematologic malignancy, most of which with advanced disease at HSCT. Two patients had received radiotherapy prior to conditioning. Conditioning regimens were as follows: BU-CY (9), CY-TBI (5), Fludarabine (FLU)-CY (3) and FLU-MEL (2). Moderate to severe chronic GVHD was diagnosed in 13 cases. In the control group, the mean age at transplant was 26 (5- 58) years, with a predominance of males (24). Among these, 31 were transplanted for a hematologic malignancy (five of whom had received prior radiotherapy) and seven for bone marrow failure or immunodeficiency. Conditioning regimens comprised: BUCY (18), CY TBI ≥ 10Gy (11), FLUCY (4), FLUMEL (1), BUMEL (1) and CY + TBI 600cGy (1). Moderate to severe chronic GVHD was diagnosed in 24 of the controls. Multivariate analysis showed a direct and significant association between older age at transplant and diagnosis of moderate to severe chronic GVHD with the occurrence of secondary neoplasm, with a relative risk (RR) of 1.12 and 3.66, respectively ($p<0.01$), Table 10. In contrast, type and status of the underlying disease, prior radiotherapy, conditioning intensity, use of TBI, type of donor, and graft source were not significantly associated with this complication. The cumulative incidence of secondary neoplasms in survivors at 14 years was 6.3%, with a gradual increase over time, as seen in other studies. Tavares *et al.,* 2016, concluded that, although it is clear that there has been in the incidence of secondary neoplasms after transplant due most probably to the improvement in post-HSCT survival rates in the last few decades, the heterogeneity of the study sample, with varying incidence and conflicting results preclude any definitive conclusions regarding the risk factors for secondary neoplasms, especially in respect to age (since some studies state younger age as a possible risk factor) and the use of TBI in this population. Further studies in this regard are hence warranted.

TABLE 9 – Histological types of second neoplasms in children undergoing HSCT (INCA, 2016) 173

Melanoma	3
Non-melanoma skin cancer	3
Esophagous carcinoma	3
Prostate dancer	2
Cervical in situ neoplasia	2
Uterine carcinoma	1
Breast cancer	1
Non-Hodgkin lymphoma	1
Choroidal carcinoma	1
Tongue carcinoma	1
Rectosigmoid adenocarcinoma	1

Legend: HSCT: hematopoietic stem cell transplantation; INCA: Instituto Nacional de Câncer.
Adapted from: Tavares et al., 2016[173] (with permission).

TABLE 10- Univariate and multivariate analyses of risk factors for second neoplasms in children undergoing HSCT (INCA, 2016) [173]

Table 3. Univariate and multivariate analysis

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age				
Each 10-year increase	2,1 (1,2 – 3,9)	**0,01**	3,2 (1,1 – 8,9)	**0,03**
Chronic GVHD				
None or not severe	Ref			
Severe	5,6 (1,1 – 28)	**0,03**	3,7 (0,54 – 24)	0,18
Donor				
Sibling	Ref			
Unrelated Donor	0,7 (0,2 – 2,9)	NS	7,5 (0,5 – 120)	0,16

Legend: HSCT: hematopoietic stem cell transplantation; INCA: Instituto Nacional de Câncer.

Adapted from: Tavares et al., 2016 (with permission)173

In a more recent retrospective study by Freycon *et al.,* 2019, which included 71 childhood leukemia survivors (of whom 36 were females) undergoing allo-HSCT with 12Gy fractionated TBI (fTBI), the number of severe late-effects was specified for each patient, with a median of 14.8 years since transplantation and a median age of 25.0 years at the time of follow-up[189]. Subsequent cancers (n=14) were reported in 11 patients (8 women), as follows: 7 with thyroid carcinomas, 3 with multiple squamous cell carcinomas, 2 with tongue or lip carcinomas, 1 with bone sarcoma, and 1 with carcinoma of the breast). In this study, the average overall number of severe late effects was 2.3, with a positive correlation with time since fTBI ($p < 0.0002$). Two-thirds of all patients had at least 2 late-effects (comprising neoplastic and non-neoplastic complications). These results suggest the need for a cautious reconsideration of the use of TBI in this population[189].

Ringden *et al*., 2014, examined the risk of second solid cancers after allo-HSCT using RIC/non-myeloablative conditioning (NMA) regimens in recipients with leukemia/myelodysplastic syndrome (MDS) (n=2833) and lymphoma (n=1436) from 1995 to 2006 They also compared the results among, RIC/NMA recipients of 40–60 years of age (n=2138) with those of the same age receiving MAC (n=6428)[185]. The cumulative incidence of solid cancers was 3.35% at 10-years. Interestingly, there was no increase in overall cancer risk compared to the general population. However, risks were significantly increased in leukemia/MDS patients for cancers of the lip (SIR 14.28), tonsil (SIR 8.66), oropharynx (SIR 46.70), bone (SIR 23.53), soft tissue (SIR 12.92), vulva (SIR 18.55), and skin melanoma (SIR 3.04), whereas lymphoma patients had significantly higher risks of oropharyngeal cancer (SIR 67.35) and skin melanoma (SIR 3.52). Higher risks than the general population have also been reported at these sites in MAC recipients[158,172,183]. Among the RIC/NMA recipients, age >50 years was the only independent risk factor for solid cancers (hazard ratio [HR] 3.02, $P<0.001$. Among patients aged 40–60 years, when adjusted for patient, disease, and transplant variables, no difference in cancer risk between RIC/NMA and MAC in leukemia/MDS patients (HR 0.98, 95% CI: 0.64–1.45;P=0.905) was noted, while, in lymphoma patients, risks were marginally lower after RIC/NMA (HR 0.51, 95% CI: 0.26–0.99; P=0.047). The authors concluded that the overall risk of a second solid cancer in RIC/NMA recipients is similar to that in general population controls matched for age, gender, and region, although there is an increased risk of cancer at some sites and a longer follow-up is needed to better clarify these findings. In MAC recipients, second solid cancer risks do not start increasing until 5–10 years after-transplant[172,158,159,190].

In a large, population-based cohort of 318 Australian children who underwent allo-HSCT for non-malignant disease, cancer occurrence and late mortality was assessed using SIRs and SMRs compared with matched population controls[191]. During follow-up (range, 0.0–25.4 years) six (1.9%) cancers were identified at a median of 9.2 years (range, 0.4–14.5 years) post-HSCT, which represented a 15-fold increase in the occurrence of cancer as compared to the age and sex-matched general population (SIR 15.4, 95% CI = 6.9–34.2), with a progressively higher cumulative incidence of cancer of up to 5.4% at the end of follow-up, quite similar to that observed in a US cohort of HSCT children and adults, in which 5%–6% of

patients undergoing transplant for a non-malignant condition developed a secondary cancer[187]. In the Australian cohort, the cumulative incidence of second malignancy at 10 years was 15.9 ± 10.1% for patients with FA and 1.1 ± 0.8% for those without this disease. In this study, all malignancies developed in males, and one third of such patients were conditioned with the use of radiation. Among the 198 patients surviving at least 2 years post-HSCT, 11 (5.6%) died at a median of 7.5 years after transplant, a mortality rate 17 times higher than that in the general population (SMR 17.5, 95% CI = 9.7–31.2). In both the US and the Australian cohort, the malignancies did not develop until a relatively late follow-up time, hence underscoring the need for evidence-based survivorship programs, with continued and vigilant long-term follow-up of patients, so as to reduce the excess morbidity and mortality observed in children transplanted for non-malignant conditions[192].

According to Nelson *et al*., 2015, this follow-up should include, at a minimum, regular clinical review and monitoring for complications of treatment and risk of malignancy related to underlying disease, patient, and transplant covariates[191]. Careful counseling regarding potentially modifiable risk factors, including diet, exercise, and alcohol and tobacco avoidance, must be provided and worked upon at each clinical visit[193].

Besides the overall findings reported above, a seemingly important association has been repeatedly shown between prior exposure of young women to TBI and higher risk of breast cancer after HSCT for hematologic malignancies[189,184,194]. Friedman *et al*., 2008, in a report from the *Fred Hutchinson Cancer Research Center* (FHCRC) and the EBMT-Late Effects Working Party, had already shown an increase in the risk of breast among survivors of allo-HSCT in 2008. In this study, which included 3337 female 5-year survivors who had undergone an allo-HSCT at one of 83 centers, 52 survivors developed breast cancer at a median of 12.5 (range: 5.7-24.8) years from transplant (SIR=2.2). The 25-year cumulative incidence of breast cancer was 11.0%, higher among those receiving TBI (17%) compared to those who did not receive TBI (3%). The following factors were found to be associated with increased risk of cancer in multivariable analysis: longer time since transplantation (HR for ≥20 years HSCT=10.8), use of TBI (HR=4.0), and younger age at transplantation (HR=9.5 for <18 years), with a 2.5-fold increase in the hazard for death associated with breast cancer (HR=2.5; 95%CI: 1.1-5.8). This highlighted the need for female HSCT-survivors to be educated about the importance of regular breast cancer screening during long-term follow-up[184].

In the *Blood or Marrow Transplantation Survivor Study* (BMTSS), a retrospective cohort study which included a total of 1,464 (allogeneic: n = 788; autologous: n = 676) female survivors transplanted between 1974 and 2014 and surviving for over 2 years post-HSCT, with the aim to assess the excess risk of subsequent breast cancer compared with that in the general population, 37 women (2.5%) developed subsequent breast cancer (allogeneic: n = 19; autologous: n = 18), with a median follow-up of 9.3 years from transplant[194]. TBI was used in 660 patients (46%) and was shown to be associated with an increased risk of breast cancer among both allogeneic (HR, 3.7 [95% CI, 1.2 to 11.8]; p = .03) and autologous (HR, 2.6 [95% CI, 1.0 to 6.8]; p = .048) HSCT survivors. Moreover, pre-transplant exposure to alkylating agents was also associated with an increased risk of breast cancer among autologous HSCT recipients (HR, 3.3 [95% CI, 1.0 to 9.0]; p = .05). Of note, compared with that in the general population, exposure to TBI at age < 30 years was associated with a 4.4-fold and a 4.6-fold higher risk of subsequent breast cancer in allogeneic and autologous HSCT survivors, respectively, which corresponds to a roughly 13.9% risk of being diagnosed with breast cancer by age 50, as compared to a 2.38% risk in the average American population[194,195]. These findings suggest that women exposed to TBI, particularly at a young age (< 30 years), should be strongly considered for enhanced breast cancer screening strategies, with mammography and breast MRI for the early detection of this disease.

In summary, although indications for allo-HSCT and conditioning regimens have largely changed over time, the risk of secondary malignancy and late mortality continues to affect the pediatric population for a significant period of time after transplant. This emphasizes the need for evidence-based screening and lifelong follow-up care of these patients, focusing on the need for surveillance and early management of infections, chronic GVHD, and disease recurrence during the first decade after transplantation, as well as screening for early detection of subsequent malignant neoplasms and other complications to reduce the risk of late effects throughout life. In this regard, Inamoto *et al*., 2015, propose a consensus-based guideline applicable for screening and prevention of individual secondary solid cancers among HSCT recipients, as summarized in Table 11[174]. As a general rule, all HSCT recipients should be counselled in respect to the risks of secondary cancers on an annual basis and encouraged to undergo recommended screening based on their predisposition.

TABLE 11 – Consensus guidelines for post-HSCT screening for secondary cancers (Inamoto, 2015)[174]

Site	Consensus panel recommendations
Skin TBI	Routine skin examination in all HSCT survivors, particularly for patients who had myeloablative HSCT at ages <18 years or GVHD
Thyroid	Annual physical examination. Heightened awareness for patients aged 20 years at HSCT, female patients, those receiving TBI-conditioning regimens and those who develop chronic GVHD
Oropharyngeal	Screening every 6 months may be considered for patients with risk factors (summarized in Table 8)
Esophagus	Upper GI endoscopy for patients who have persistent GERD symptoms or dysphagia. Endoscopic screening may be considered for patients with prolonged IST (>24 months) for chronic GVHD
Stomach	Follow guidelines for the general population
Colorectal	Follow guidelines for the general population
Liver	Follow guidelines for the general population. Consider liver ultrasound every 6 months in HBV seropositive recipients or in patients with a history of cirrhosis
Lung	Follow guidelines for the general population. Encourage smoking cessation. Consider screening if there are additional risk factors (e.g., smoking history)
Breast	Breast awareness for all patients. Average risk: •age 20–40 years: clinical breast exam every 1–3 years; •age >40 years: annual clinical breast exam; annual mammogram; Prior radiation therapy or TBI: •age 25 years or 8 years after radiation therapy/TBI, whichever comes first, but no later than age 40 years: annual clinical breast exam; annual mammogram; annual breast MRI
Cervix	Annual Pap test and HPV DNA test
Endometrial	Follow guidelines for the general population
Ovary	Follow guidelines for the general population
Prostate	Follow guidelines for the general population
Testis	Follow guidelines for the general population
Brain/CNS	No specific guidelines
Sarcoma	No specific guidelines

Legend: HSCT = hematopoietic stem cell transplant; TBI = total body irradiation; GVHD = graft-versus-host disease; GI = gastrointestinal; GERD= gastroesophageal reflux disease; IST = immunosuppressive treatment; HBV =hepatitis B virus; MRI = magnetic resonance imaging; HPV =human papillomavirus; Pap test = Papanicolaou test; Central Nervous System.

Adapted from: Inamoto, 2015[174].

VITAMIN AND MINERAL SUPPLEMENTATION IN PEDIATRIC PATIENTS AFTER HSCT

A good diet, including adequate levels of vitamins and minerals, plays a major role in the recovery and well-being of patients undergoing bone marrow transplantation.

Post-HSCT patients have a higher risk of food-related infections. The recommendation is to maintain a diet directed to immunosuppressed patients in allo-HSCT recipients while using immunosuppressive drugs or until they show signs of immune system reconstitution; and in autologous bone marrow transplant recipients the recommendation is to follow the diet for immunosuppressed patients up to one month after discontinuation of corticosteroids (if they are using) or three months after the HSCT[148].

Patients who have had severe graft versus host disease of the gastrointestinal tract usually present some degree of malnutrition, enteropathy with loss of proteins and needy changes; deficiencies of vitamins D, B12 and zinc. Therefore, it is important to dose vitamins and zinc in these patients for diagnosis of a possible deficit and adequate replacement.

Deficiency of some vitamins may culminate in severe conditions, such as in patients with neurological symptoms and who are not receiving adequate nutrition may have vitamin B1 deficiency (Wernicke's encephalopathy). The low level of vitamin B1 along with the clinical improvement of the patient after vitamin B1 replacement will give the diagnosis of this condition. The replacement of vitamin B1 (thiamine) should be done intravenously until improvement of the condition, which is usually fast. After improvement, oral vitamin B1 replacement is maintained at a dose of 300mg/day for approximately 2 to 3 months. The oral dose has to be higher due to lower intestinal absorption[149].

Vitamin D is a liposoluble vitamin necessary for bone and calcium homeostasis. Vitamin D receptors are found in almost every cell in the body, including immune system cells. Immunomodulatory effects resulting from vitamin D reduce inflammation and mediate activation and damage of endothelial cells[196,197]. Inflammation due to activation of endothelial cells during HSCT is related to serious complications such as GVHD, hepatic VOD, and TMA. Immunological dysregulation in the setting of vitamin D deficiency during HSCT may therefore predispose patients to these complications associated with bone marrow transplantation[198].

Vitamin D deficiency is a well-described phenomenon in pediatric patients undergoing bone marrow transplantation. Some factors that are associated with this deficiency are: lower sun exposure, use of various medications that potentially affect vitamin D absorption, compromised intestinal epithelium and mucositis. Up to 70% of pediatric patients have vitamin D (< 30ng/mL) deficiency before HSCT and over D+100; many, including, despite being in replacement therapy[192]. Vitamin D modulates inflammation, and deficiency in pre-HSCT and in D+100 have already been associated with graft-versus-host disease and worse survival[198]. There are reports of an association between vitamin D deficiency and immune-mediated complications, including GVHD and VOD. In addition, there is also little data to guide the recommendations for monitoring and supplementing vitamin D during bone marrow transplantation. In an article published in 2020, the association between vitamin D and post-HSCT complications in pediatric patients was evaluated and the routine use and efficacy of vitamin D monitoring and supplementation practices were also evaluated[199]. Vitamin D level was correlated with overall survival and each increase of 10ng/mL was associated with a 28% reduction in the risk of death[199]. This same study showed that the vitamin D supplementation regimens currently accepted for children who have had bone marrow transplantation do not reach sufficient vitamin D values in most cases. Vitamin D status was associated with all causes of mortality, but not with individual comorbidities[199]. Prospective studies are needed to establish the connection between vitamin D status, immune-mediated HSCT complications, and the potential benefit of vitamin D supplementation before and after HSCT. These studies are necessary so that we can have evidence of how to adequately monitor and supplement vitamin D during bone marrow transplantation.

Other publications have shown the association between vitamin D deficiency with a higher incidence of acute[200-01] and chronic[202-03] GVHD, as well as cytomegalovirus reactivation[207]. However, the impact of vitamin D on the survival is more controversial; some studies have shown that vitamin D deficiency is associated with a decrease in overall survival after HSCT[202,204], while others have not been able to reproduce these findings[205,203,205]. This inconsistency could have been caused by small cohorts in existing studies and differences in population characteristics; thus, further research with a larger and more homogeneous number of patients is clearly necessary.

There is a recommendation in the FHCRC Guideline to dose the level of vitamin D (25-hydroxy) in the blood between 80-100 days after bone marrow transplantation for all patients[148]. As it is a popula-

tion at risk, it is recommended that this group of patients maintain a target serum level between 30-60 ng/mL. Vitamin D levels are usually checked again 2 to 3 months after the start of replacement therapy[148].

Vitamin D deficiency is a risk factor that can be modified in patients after HSCT, with low cost and negligible side effects[206,207] and has the great potential to restore immune tolerance and prevent some complications after HSCT[208].

Therefore, it is important to perform routine evaluation and nutritional follow-up of all patients submitted to bone marrow transplantation, since they are patients at risk for vitamin and mineral deficiencies.

Biochemical tests (biomarkers) can help in risk assessment, diagnosis and nutritional follow-up of children and adolescents, including patients with associated morbidities, such as overweight, dyslipidemia, changes in glucose metabolism, among others. It is important to emphasize that the child's clinical condition may interfere in the interpretation of biochemical test results. In addition, previous nutritional status and the presence of inflammatory response, in addition to water balance, are factors that may interfere in the interpretation of these tests[196]. Table 12 describes the most common nutritional deficiencies according to clinical signs and symptoms[196].

Specific micronutrient dosages can help assess nutritional status. With the early identification of possible deficiencies, it is possible to perform an adequate treatment, contributing undeniably to the nutritional recovery of the patient.

TABLE 12: Most frequent signs of nutritional deficiencies[196]

Areas	Clinical signs	Diagnosis
Hair	Natural brightness loss: dry and ugly Thin and sparse brittle Depigmented Easy to boot Flag sign	Kwashiorkor and, less often, marasmus
Face	Nasolabial seborrhea (dry skin around the nostrils) Swollen face ("full moon") / Pallor	riboflavin Kwashiorkor iron
Eyes	Pale conjunctiva Red membranes Bitot's spots Conjunctival xerosis Corneal xerosis Keratomalacia Redness and fissure of epicanthi Corneal arch (white ring around the eyes) Xantelasma (small yellowish bags around the eyes)	iron vitamin C vitamin A riboflavin, hyperlipidemia
Lips	Angular stomatitis (rosy or white lesions in the corners of the mouth) Queilose (redder or lip edema)	riboflavin
Tongue	Scarlet and inflamed tongue Magenta language (purple) Edematous tongue Filiform papillae, atrophy and hypertrophy	nicotinic acid riboflavin niacin folic acid and vitamin B12

Teeth	Stained enamel	fluorine
Gums	Spongy: bleeding and leaking	vitamin C
Glands	Thyroid enlargement Increased parathyroid	iodine starvation
Skin	Xerosis Follicular hyperkeratosis (skin on sandpaper)	vitamin A
	Petechiae (minor bleeding on the skin)	vitamin C
	Dermatosis, pelagra (reddish edematous pigmentation in sun exposure areas)	niacin
	Excess bruises	vitamin K, vitamin C
	Desquamative cosmetic dermatosis	Kwashiorkor
	Vulvar and scrotal dermatosis	riboflavin, vitamin B2
	Xantomas (fat deposit under the skin and around the joints)	hyperlipidemia
Nails	Koilonychia (spoon shape), brittle and rough.	iron
	With small white spots	zinc
Skeletal muscle system	Muscle wear	starvation, marasmus
	Epifisaria enlargement (increased extremities)	rickets
	Front-parietal boss (front edema / lateral head) Persistence of the opening of the anterior fontanel	vitamin D
	X leg or pie	vitamin C
	Musculoskeletal hemorrhages	thiamin
	Calf laxity Rickety rosary	vitamin D

	Scurvy rosary	vitamin C
Cardiovascular system	Heart augmentate	thiamin
Digestive system	Hepatosplenomegaly	Kwashiorkor
	Psychomotor changes	Kwashiorkor
	depression Sensory loss	pyridoxine, vitamin B12
Nervous system	Motor weakness Loss of sense of position Loss of vibratory sensitivity Loss of wrist and ankle contraction Paraesthesia (Tingling of hands and feet)	thiamin

Therefore, biochemical tests in association with clinical examination enrich the diagnosis of the nutritional status of patients after bone marrow transplantation. The analysis of these data should always take into account the clinical condition of the patient, the use of medications, mainly corticosteroids and other immunosuppressive agents, among other factors that can influence the results and guide the treatment.

There is data in the literature that recommend the use of supplements with vitamins and amino acids in order to increase immunity and reduce inflammation and oxidative stress[209]. It has a meta-analysis published in 2016 that assesses the impact of this supplementation on the incidence of GVHD and infections associated with HSCT[210]. There were ten randomized clinical studies involving 681 HSCT recipients, 332 of whom received supplementation with vitamins and minerals with glutamine, n-acetylcysteine, selenium, and eicosapentaenoic acid (which is a fatty acid in the omega 3 family) and 349 received standard nutrition. Most of the studies included in this meta-analysis used parenteral nutrition; only two studies used enteral administration. Patients receiving vitamin supplementation had a 19% decrease in the incidence of GVHD and there was no significant difference in the incidence of infections. The conclusion of the study was that the use of these supplements is associated with a reduced risk of GVHD probably as a result of better immune support and elimination of free radicals[209]. However, although the results of this meta-analysis are significant, there are limitations to this study, including the fact that the patient sample is relatively small. Therefore, further studies will be necessary to better evaluate the route, efficacy and duration of treatment[209].

VACCINATION IN HSCT RECIPIENTS

In HSCT, patients reconstitute the immune system from new hematopoietic stem cells. Thus, the entire pre-transplant immune memory is lost. Memory T and B-cells acquired by vaccination have thus to be reestablished, with the downside of a less favorable thymic and splenic environment due to the toxicity derived from the chemotherapy and/or radiotherapy used in the preparative regimen[211].

Neutrophils are the first to recover within the first 15 to 20 days after transplantation. Next, there is an increase in the number of natural killer lymphocytes, but the production of T lymphocytes and B lymphocytes from the new bone marrow takes months, even years to normalize. It is therefore necessary to restart the entire basic vaccination schedule so that specific antibodies are produced from the new mature plasmocytes.

Three months after transplantation it is already possible to start vaccination schedule, detailed in the *Manual of Reference Centers for Special Immunobiologicals* (CRIEs)[212], spread throughout Brazil. It is important to note that vaccines against oral poliomyelitis (Sabin), Bacillus *Calmette-Guérin* (BCG), cholera, Oral typhoid fever and rotavirus are permanently **contraindicated**[211,212], and we should always be cautious with regard to the yellow fever vaccine, as it can cause severe encephalitis if the patient is still immunosuppressed, being hence **contraindicated** in the first two years after transplantation or in the

presence of immunosuppressive treatment, even in epidemic situations. Immunosuppressed patients should be removed for 45 days from home contacts receiving oral polio vaccine to prevent vaccine virus disease. All donors can update their vaccination card, except with live viruses, before donation. Patients and home contacts should be immunized annually against influenza.

It is important to emphasize that pneumococcus 23 vaccine should be used only as reinforcement, as it is less immunogenic than other pneumococcal vaccines. Although the triple viral vaccine is usually offered from two years after transplantation, it can be started earlier, safely, in epidemic situations. There is an international recommendation for seasonal administration of palivizumab, monoclonal antibody against respiratory syncytial virus, devastating and fatal disease in young children after transplantation, although we have not yet obtained its approval in the public system of Brazil.[212]

Tables 13 and 14 illustrate the proposed vaccination schedules for patients who have undergone HSCT[212].

TABLE 13: Recommendations of the Brazilian Society of Immunizations (SBIm) for children after hematopoietic stem cell transplantation (HSCT)212

For children over 1 year and under 7 years of age			
Inactivated vaccines	Time to start revaccination after HSCT	Dose scheme Considering months after HSCT	Comments
Influenzae	Ideal: six months Minimum: three months	Prefer 4V vaccine Two doses: 6 - 7 months	-Prefer 4V (if available) for providing greater coverage of circulating strains -Vaccinate contacts in the same household
Hexa acellular (DTaP, polio inactivated, H. Influenzae type B, Hepatitis B) DTaP: acelular Pertussis-Tetanus-Diphtheria	Six months	Three doses: 6 – 8 – 10 months	-In case the Hexa vaccine is unavailable, administer each of the components separately. -The use of polio vaccine (OPV) is contraindicated -Contactors should receive the IPV (if indicated)
Pneumococcal conjugate 13 (PCV13) or Pneumococcal conjugate 10 (PCV10)	Six months	Three doses: 6 - 8 - 10 months	Preferential use of PCV13 in order to extend protection for the three additional serotypes -PCV10: for children under 5 years old
Pneumococcal polysaccharide vaccine 23 (PPSV 23)	Two months after last dose of PCV10 or PCV13	For > 2 years of age: 2 doses. The first dose is from 12 months after HSCT. The second dose, five years after the first	The first dose should be applied at least two months after the last dose of PCV10 or PCV13
Meningococcal ACWY or Meningococcal C	Six months	Two doses: 7 - 9 months Apply a booster five years later and follow the scheme recommended for age	Whenever possible, prefer the MenACWY vaccine for extended protection
Meningococcal B	Six months	Two doses: 7 - 9 months	-
Hepatitis A	Six months	Two doses: 7 and 13 months	-

Attenuated vaccines	Time to start revaccination after HSCT	Dose scheme Considering months after HSCT	Comments
Measles/Mumps/Rubella (MMR)	12-24 months	Two doses: 24 - 25 months	-If epidemiological risk and immune status permits, it can be applied from 12 months. Otherwise, wait 24 months or evidence of immune system reconstitution -Vaccinate contacts in the same household
Varicella-Zoster	24 months	Two doses: 24 - 27 months	-Vaccinate ifseronegative status -Vaccinate contacts in the same household
Yellow fever	24 months	One dose: 24 months	If first dose applied before 5 years of age, take two doses, with a minimum of 30 days interval between them

TABLE 14: Recommendations of the Brazilian Society of Immunizations (SBIm) for children, adolescents, and adults after hematopoietic stem cell transplantation (HSCT)212

Children aged 7 >, adolescents, adults, and the elderly

Inactivated vaccines	Time to start revaccination after HSCT	Dose scheme Considering months after HSCT	Comments
Influenzae	Ideal: six months Minimum: three months	-Prefer 4V vaccine Children from 7 to 8 years: two doses with 30-day interval -From 9 years: single dose	-Prefer 4V (if available) for providing greater coverage of circulating strains -Vaccinate contacts in the same household
DTaP/Polio inactivated Polio inactivated: IPV	Six months	Three doses: 6 - 8 - 10 months	-If the DTaP vaccine is not available, administer dTpa and IPV separately -Use of the polio vaccine (VOP) is contraindicated -Contactors should receive the IPV (where indicated)
Pneumococcal conjugate 13 (PCV13)	Six months	Three doses: 6 - 8 - 10 months	-
H. Influenza B (Hib)	Six months	Three doses: 6 - 8 - 10 months	-
Pneumococcal polysaccharide vaccine 23 (PPSV 23)	Two months after last dose of PCV13	Two doses. The first dose is from 12 months of HSCT. The second dose five years after the first	The first dose should be applied at least two months after the last dose of PCV13

Meningococcal ACWY or Meningococcal C	Six months	Two doses: 7 - 9 months Apply reinforcement five years later and follow the recommended scheme for age for children and adolescents	Whenever possible, prefer the MenACWY vaccine for extended protection
Meningococcal B	Six months	Two doses: 7 - 9 months	-
Hepatitis A	Six months	Two doses: 11 and 17 months	-
Hepatitis B	Six months	Three doses: 11 - 12 - 17 months	-
HPV	Six months	Three doses: 11 - 12 - 17 months	From 9 years of age
Attenuated vaccines	Time to start revaccination after HSCT	Dose scheme Considering months after HSCT	Comments
Measles/Mumps/Rubella (MMR)	12-24 months	Two doses: 24 - 25 months	-If epidemiological risk and immune status permits, it can be applied from 12 months. Otherwise, wait 24 months or evidence of immune system reconstitution -Vaccinate contacts in the same household
Varicella Zoster	24 months	Two doses: 24 - 25 months	-Vaccinate seronegative patients < 50 years old -Vaccinate contacts in the same household
Yellow fever	24 months	Single dose	-
Herpes Zoster	24 months	Single dose	For > 50 year-olds

Key messages related to post-HSCT vaccination:[148,213]

- Some centers start vaccination with inactivated vaccines six months after HSCT; however, it may be started three months after HSCT (depending on the risk-benefit ratio).

- Check titers for Streptococcus pneumoniae (IgG, 23 serotypes). If titer not checked at 12 months, check it at 24 months.

- In patients with chronic GVHD who are unlikely to respond to the Pneumococcal polysaccharide vaccine (Pneumo23), it is preferable to administer a 4th dose of the Pneumococcal-conjugate vaccine (Pneumo13).

- Check anti-tetanus toxoid titer.

- Hepatitis B: titer at the 24-month visit if not done at 20 months. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the 3rd dose to ensure protection. Patients who do not respond to the primary vaccine series should receive a second three-dose series.

- For inactivated ("dead") virus vaccines, vaccination should be at least 2 months after the last dose of IVIG.

- The Meningococcal B vaccine is recommended for patients with anatomic or functional asplenia conditions (i.e., chronic GVHD) or increased environmental risk.

- For live virus vaccines, vaccination should be at least 5 months after the last dose of IVIG.

- To receive live virus vaccines: not until 2 years post-HSCT and > 1 year off all immunosuppressive therapy and at least 5 months since the last dose of IVIG/VZIG (if possible).

- Check varicella serology at least 1-2 months after the second dose of the vaccine to ensure seroconversion of the VZV seronegative patient.

- For patients receiving immunotherapy, consider the vaccines after immunotherapy is completed. Counsel patients regarding risks/benefits

- Factors that might influence a decision to delay a series of vaccinations include:

- Delay of T cell recovery: CD4 T cells < 200/µL, active GVHD, IVIG therapy < 2 months before, and patients receiving chemotherapy comprising therapeutic biological agents.

- Delay of B cell recovery: CD19 ou CD20 B cells < 20/µL, anti CD20 antibody < 6 months, moderate to severe GVHD and patients receiving chemotherapy comprising therapeutic biological agents.

- If a patient is on disease-associated maintenance therapy that can affect T or B cell numbers, then before beginning vaccination: check CD19 or CD20 B cells to determine > 20/µL and check CD4 T cells to determine > 200/µL.

- Inactivated vaccine injections should be used for family members who need vaccinations against polio. Isolation is necessary if live (oral) polio vaccine is administered to family members or other persons in close contact with the patient during the first year after the transplant or at any time during treatment with immunosuppressive medications. The virus can be shed for 8 to 12 weeks after vaccination.

- The smallpox vaccine is comprised of live vaccinia virus. Smallpox vaccination is contraindicated in HSCT recipients because it may result in the development of generalized vaccinia or inadvertent inoculation at other sites, such as the face, eyelid, nose, mouth, genitalia, and rectum. The smallpox vaccine should not be administered to any family members or other persons who share living space with the patient during the first year after transplant and beyond one year if the patient continues on treatment with immunosuppressive medications. If smallpox vaccination is administered to these close contacts, then these individuals should be prevented from having close contact with the immunocompromised HSCT recipient.

- All patients exposed to chickenpox or zoster during the first year after the transplant or during treatment with immunosuppressive medications should be evaluated. VZV seronegative patients and those not receiving prophylactic acyclovir should be treated with valacyclovir or acyclovir from days 3 to 22 after exposure unless treatment with ganciclovir, foscarnet or cidofovir is being given for another reason. In seronegative recipients, administrations of VZIG within 96 hours of exposure should also be used, if available, in addition to valacyclovir.

PSYCHOLOGIC ASPECTS AND QUALITY OF LIFE IN PEDIATRIC PATIENTS UNDERGOING HSCT

HSCT has become the only curative option for a myriad of life-threatening disorders in pediatric patients. Advances in this procedure (medical, technological, and pharmacological) over the past few decades have allowed for an increased[214] number of transplants each year, with a dramatic improvement of pediatric HSCT survival rates. Even so, the literature is scarce as to the psychological and psychosocial effects HSCT on patients (and also on their siblings and parents)[215]. Children and adolescents experience a number of acute and long-term emotional, cognitive, social and familial reactions throughout the whole transplant process, from the pre-HSCT period, through hospitalization and the procedure itself, and during and after the recovery process[216,217]. Anxiety, depression, behavioral and social problems, and post-traumatic stress reactions are among the most commonly witnessed ones[214,216]. Of note, since a significant proportion of transplants depend on the patients' siblings as the best stem cell donor candidates or HLA-match for these patients, sibling donors, as well as parents, are also at risk of developing psychological distress, such as post-traumatic stress reactions, anxiety, and low self-esteem[214,215]. Parents of children undergoing allo-HSCT are also prone to psychological disturbances, with increased levels of anxiety and depression, particularly for those whose healthy child is also involved in the HSCT process as a stem cell donor.

This has raised the need for developing interventions for both pediatric patients and their families, with a view to devising interventions capable of decreasing distress and improving emotional and psychosocial functioning for children undergoing HSCT, siblings and parents. In this regard, a number of strategies have been proposed:

Cognitive behavioral interventions: the bulk of experience already gained with this strategy in caring

for children with cancer and chronic illness has set a promising arena for furthering this approach to the HSCT pediatric population, with the aim of improving emotional distress, compliance with treatment, and behavioral issues related to transplant, thus improving social skills and overall emotional well-being.

Familial interventions: these aim at fostering protective factors, improving communication skills, and decreasing parental anxiety and depression.

Cancer-specific interventions: these may serve as a template for the development of HSCT-specific interventions.

PSYCHOLOGICAL REACTIONS TO HSCT

As mentioned previously, escalating anxiety tends to appear days to weeks before the actual transplant period in ~40% of children, peaking around a week post-transplant[218]. According to Meyers et al., such levels of distress decrease sharply during the hospitalization period and remains at low levels eight months post-HSCT[217]. Another study assessing the psychosocial effects in HSCT survivors indicated that, at 3 months post-transplant, over 80% of children displayed moderate emotional distress symptoms[219] Pot Mees *et al.*, 1989, in turn, observed that around 40% of children undergoing HSCT exhibited significant increases in anxiety, depression, peer isolation, and behavioral problems, including aggression, during the first 6 months after transplant, compared with only 15% pre-HSCT. These authors point out that the numberless behavioral symptoms found in patients 6-months after transplant suggests an "after-stress reaction", similar to what is denoted "post-traumatic stress disorder[219] Importantly, this post-traumatic stress reaction persisted for over a third (35%) of these patients at 1-year post-transplant, thus underscoring the potential for long-term persistence of such distressful effects.[219]

There is ample evidence that depression heightens during hospitalization, worsens with prolonged hospital stay, and may endure for months after HSCT.[216,217,219,221]

PSYCHOSOCIAL PREDICTORS OF PSYCHOSOCIAL OUTCOMES AND ADJUSTMENT AFTER HSCT

Identifying possible psychosocial factors present in children before HSCT as possible predictors of psychological outcomes in the post-transplant period may be of particular help in the post-HSCT management of this complication, by providing physicians and the multidisciplinary team with the necessary tools to better assess this vulnerable population as to the need for a more intensive or specialized strategies in the post-transplant period[222]. Adopting a more holistic approach may help in the post-traumatic adjustment process of both the patients and their families. In a study of 103 HCST patients from 3 to 17 years of age suggested that age at the time of transplant influences educational and cognitive outcomes, with older age being seemingly associated with better outcomes[223]. Patients who are at increased emotional distress, with extreme worrying and poor communication prior to HSCT, exhibit worse health-related quality of life (HRQL) after transplant[225]. On the other hand, certain patients and parent characteristics seem to help minimize the psychosocial impact of HSCT. Children who show greater optimism and resilience, for instance, tend to have better HRQL outcomes[224] Barrera et al., 2008, showed that specific maternal factors, such as older maternal age and fewer maternal depression symptoms, are also associated with more favorable outcomes. Some familial attributes, such as the quality of family communication, may even affect HRQL to a greater degree than disease-specific factors[224]. Maternal anxiety after transplant is also associated with poorer HRQL in this population[226]. These findings highlight the need for an attentive approach to both patients and families to better identify potential pre-transplant factors that can be amenable to a timely and more focused approach in the post-HSCT period[217].

EFFECT OF HSCT ON QUALITY OF LIFE

HRQL is potentially affected during all stages of HSCT, starting at the pre-transplant phase, escalating in the acute post-HSCT phase (where rejection rates are high), persisting in the longer-term hospitalization period (with prolonged social isolation), and extending in the reintegration phase to life outside the hospital [220].

Children undergoing HSCT tend to report low baseline levels of HRQL during hospitalization, with some studies showing that improvement ensues as early as 4 months post-transplant and that HRQL returns to baseline within 1 year of HSCT[214] However, this behavior may be modulated by certain factors, as follows:

1) Younger children (aged 5–12 years) experience higher HRQL than older children (aged 13–21 years). In one study, overall emotional functioning scores declined by 1.3 points on the emotional functioning domain for every 1-year increase in age[229];

2) Children with lower socioeconomic (SE) status report lower HRQL between 3 and 6 months post-HSCT[230];

3) Lower intelligence quotient (IQ) and social competence have also been associated with a worse HRQL at 1-year post-transplant[231];

4) Children undergoing an unrelated allo-HSCT were shown to report lower HRQL 3 months post-HSCT; nonetheless, no difference between allo-HSCT and autologous HSCT was observed 3 years post-HSCT; the effects on the HRQL of children undergoing HSCT may thus be short lived[229,232];

Of note, factors such as gender, age at time of HSCT or pre-transplant disease symptoms were not consistently related to HRQL[233].

EFFECT OF HSCT ON PSYCHOSOCIAL FUNCTIONING AND COGNITIVE ABILITIES

As in other chronic illnesses affecting children, both the baseline disease (e.g., relapse) and the potential post-transplant complications related to HSCT (e.g., chronic graft-versus-disease) may hinder a child's development by limiting the opportunities to participate in developmental and psychosocial behaviors[234]. These children are particularly subject to cumbersome emotional and psychosocial adjustment processes. Absence from school after a prolonged period of time may diminish their social competence and self-esteem[222]. Even though most pediatric HSCT survivors return to school within 1-year of transplant, these children tend to exhibit increased behavioral problems, as well as social isolation and lower academic level functioning compared to their same age counterparts[219]. This may either be due to actual cognitive effects or to the prolonged period of absence from school itself[219,235].

The presence of neurological and cognitive sequelae of the HSCT process, including that resulting from the preparative regimens, is critical for the reintegration of both patients and families to the outside world[236]. The extent of such deficits is intrinsically related to the ability of pediatric survivors to transition back to school and society as a whole[235].

The current evidence is inconsistent in regard to the topic of neurological deterioration after HSCT. Although earlier studies suggested that significant, global declines in pre- and post-cognitive functioning did occur after transplant, more research findings suggest that the impact of HSCT on pediatric patients' cognitive abilities may actually be more modest, based on baseline to post-HSCT measurements[229-242]. This may vary depending on certain patient and HSCT-related factors, such as age at the time of HSCT and use of total body irradiation (TBI) in the condition regimen or not[236]. Younger age (i.e., <2 years) at transplantation has been related to a worse cognitive outcome, with a higher risk for deficits in IQ scores, academic achievement, fine motor skills, and memory [238,243]. It is noteworthy, though, that children who are more fully developed at the time of HSCT are less likely to exhibit significant deterioration in their cognitive and functioning skills after transplant[236,244].

In summary, HSCT affects virtually all aspects of a child's life, with long-term effects on the psychosocial arena and on overall quality of life. This highlights the need for a systematic assessment of pre-HSCT psychosocial factors that may allow for timely, targeted interventions to undermine the effects of such factors on overall, post-transplant functioning. Unfortunately, almost all of the known protective or unfavorable characteristics that affect HSCT outcomes in the pediatric population are constitutional and, hence, cannot be modified by specific interventions. Nonetheless, identifying non-constitutional characteristics in these children may help modulate the deleterious impact of HCST and enable a better plan for the future of these patients.

CONCLUSIONS

HSCT offers a curative approach for otherwise lethal diseases. Today, the long-term prognosis has greatly improved. Nevertheless, there are still a number of malignant and non-malignant late effects that can cause substantial morbidity, with considerable impact on the health status and quality of life of long-term survivors. A broad expertise is mandatory to manage long-term survivors. Aftercare of long-term survivors includes a standardized screening, counselling of the patients as well as prevention and treatment of late effects.

Beyond immediate survival, HSCT is a lifelong commitment between long-term survivors and the transplant team, involving the recipient's family and the general healthcare providers.

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CONDITIONING REGIMEN FOR LANGERHANS HISTIOCYTOSIS

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Langerhans cell histiocytosis (LCH) is a rare disease, with an estimated incidence of 0.5 per 100,000 children in the United States of America[1]. HCL occurs due to differentiation of myeloid precursors into CD1a+ / CD207+ cells and is characterized by constitutional activation of the MAPK2 signaling pathway, leading to a spectrum of organ involvement and dysfunction. Treatment of HCL is risk-adjusted: single lesions may respond to local treatment whereas multisystem disease requires systemic therapy. Although survival for patients without organ dysfunction is excellent[3], mortality in those with compromised organs at risk (hematopoietic system, liver, and/or spleen) reaches 20%[2,4]. Despite the progress made in the treatment of HCL, disease reactivation rates remain above 30% and the best second-line treatment has not yet been established. Treatment failure is associated with increased morbidity and mortality, including an association with neurodegeneration[2].

As it is a rare disease and generally has a good prognosis, few scientific studies are evaluating the role of allogeneic hematopoietic stem cell transplantation (HSCT) in the treatment of this disease.

In 2015 Veys et al[5] published retrospective results of 87 high-risk patients transplanted between 1990 and 2013. Myeloablative conditioning regimens (MAC) based on total body irradiation or busulfan[6] were the most used until the 2000s, and reduced-intensity conditioning regimens (RIC) – predominantly a combination of Melphalan and Fludarabine – were most used between 2000 and 2013. Transplant-associated mortality rates in 3 years were similar between RIC and MAC conditioning regimens (21% versus 15%, respectively). Recurrence was higher in the RIC group compared to the MAC group (28% versus 8%, respectively), however, the 3-year overall survival (OS) was similar (77% versus 71%, respectively), since the patients who relapsed after RIC transplantation could be rescued with chemotherapy.

More recently, Kudo et al7 published a retrospective study with 30 patients with refractory LCH who underwent HSCT between 1996 and 2014. Eleven patients received myeloablative conditioning regimen based on total body radiotherapy (RCT) with a dose equal to or greater than 8 Gy or busulfan, and 19 of reduced intensity based on Fludarabine and Melphalan, associated or not with low dose of RCT. There was no significant difference between the conditioning regimen modalities, with OS of 56.8% for the RIC group and 63.6% for the MAC group. Disease status was the main prognostic factor, with a 5-year OS of 100% for patients who arrived at HSCT with disease in remission or with partial remission, versus 54.5% for those who had active disease at the time of the procedure.

Regarding the type of donor used and the source of stem cells, there is great variation, with greater frequency for unrelated and extensive use of bone marrow and umbilical cord, and apparently, there is no impact on survival rates.[5,6]

There are few case reports and extremely restricted performance of autologous HSCT in HCL.

	Autologous	**MRD**	**MUD**
Localized Disease	Not indicated	Not indicated	Not indicated
Multisystem involvement			
≥ 1ª CCR*	Not indicated	Standard	Standard
(if previously refractory)			

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