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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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