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JBMTCT

IN THIS EDITION

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

VOLUME FOUR

SBTMO
Sociedade Brasileira de Transplante de Medula Óssea

JOURNAL OF BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY

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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, 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

V MEETING FOR BRAZILIAN GUIDELINES ON HEMATOPOIETIC STEM CELL TRANSPLANTATION – BRAZILIAN BONE MARROW TRANSPLANT SOCIETY (SBTMO)

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The BRAZILIAN SOCIETY OF BONE MARROW TRANSPLANTATION (SBTMO), founded in 1996, has always been guided by the qualification of its members and related professionals, constantly developing mechanisms and activities capable of prioritizing education and science, above all. Based on these principles and with the participation of more than one hundred renowned members and guests of this scientific community, it was in May 2009, with the initiative of the former Board member prof. Dr Julio Cesar Voltarelli (in memorian), that we organized the first SBTMO Guidelines meeting[1,2].

Those were different times, but the Guidelines reached such importance that new editions have been published every 2 years, updating and improving its content and the pattern of the activity. The published material provides a basis for the education and improvement of Transplant Units professionals, for the establishment of national norms and protocols, to be consulted by public and private agencies, related publications, among other purposes. It is also an important compilation of data and a guidance to programs already in progress in different countries.

This has been the method adopted in different countries and continents. SBTMO follows as an example the EBMT – European Group for Blood and Marrow Transplantation and the ASTCT – American Society for Transplantation and Cellular Therapy. [1,2,4]

Levels of evidence for the main recommendations have been included and corroborated by extensive updating of published and selected bibliographic references.

The previously used pattern model has been modified to adapt to the circumstances imposed by the Pandemic SARS COVID19, establishing a historic milestone for SBTMO and its future activities. The groups and their respective coordinators received the norms and schedule for the guidelines presentation and met in a totally virtual meeting space provided by the platform. The texts of each chapter, the video lessons and the references that served as the basis for this document were presented. The coordinators were also invited to the final presentation, which took place on October 26th, 2020, subsequent to the SBTMO 2020 Congress. This virtual reunion replaced the former plenary model, permitted the participation of all group members and included the online possibility of discussion and suggestions about the themes. This model of presentation proved to be efficient and enabled the fulfillment of the proposed schedule.

Dr. Luis Fernando Bouzas chaired the meeting with the collaboration of Drs. Leonardo Javier Arcuri and Abrahão Elias Haallack Neto, in addition to the precious support of Dr. Adriana S14eber and the entire SBTMO Board of Directors.

Despite all the difficulties that arose, the schedule started in March and ended in October 2020, composed by more than 120 collaborators, was fulfilled, originating the guidelines for publication.

It is also worth mentioning the participation of members of other societies such as ABHH - Brazilian Association of Hematology and Hemotherapy, SOBOPE - Brazilian Society of Pediatric Oncology, Brazilian Association of Histocompatibility and specialists who, with their knowledge, contributed to enhance this content.

The chapters were divided into large groups such as:

- **Selection of patients and donors**
- **Indications**
  - Adults
  - Pediatrics
- **Complications**
  - GVHD
  - Infectious
  - OS/VOD
- **Hemotherapy and Cell therapy**
- **COVID 19**

In this edition, topics relevant to medical practice and consistent with the current moment were included.

Undoubtedly, the recommendations inherent to the Covid 19 pandemic will guide the management of patients' cases and donors. The pre-transplantation care significantly changed its logistics, affecting directly the HSCT Units and the data management of voluntary donors. The management of intra and extra-hospital procedures, of how it affects caregivers, of social isolation and infection prevention required extensive effort by specialists in presenting recommendations. Therapy must be administered to patients with the disease conforming to its evolution and their individualization in phases, and needs uniformity, so we can benefit them with well-established protocols and algorithms.

The Guidelines in all editions addressed Indications and complications related to HSCT, however, complex has been the task of choosing the best time, the criteria for electing the type of transplant, the donor, the conditioning regimen – always focused on the least toxicity possible, greater efficacy and prognosis with survival and quality of life. This edition, by the quality and depth of the work presented, will be of great use to those who must decide or understand the reasons of the choices make by the specialists.

Still, in this new phase and rescuing the pioneering and prominent role of SBTMO and its members, in establishing the practice of cell therapy, we have included the specific chapter to guide the application of these procedures. Immunomodulation with infusion of cells (lymphocytes) from the donor, extracorporeal photopheresis, use of mesenchymal cells (MSC) and NK cells in addition to CAR T are some of these therapies. These are techniques and procedures that depend on experienced and trained teams, with well-established protocols and uniformization for both administration and control of possible complications, practice which is historically associated to the HSCT centers and the SBTMO.

This fifth edition of the SBTMO Guidelines will be of great use to assist Services specialized in HSCT and related specialties, not only in its referral to patients but also in consideration to the brazilian public (SUS / SNT) and private Health Services (ANS) and current health regulatory agencies (ANVISA) aiming their constant updating and adaptation.

Finally, we understand that providing the country with another instrument developed by scientific bases, stimulating and undertaking controlled, registered and uniform techniques and procedures, will only bring benefits to our main audience – patients and family members who depend on an HSCT.

We finalize by thanking all collaborators and calling for full disclosure the SBTMO's commitment to provide regularly this important instrument to the scientific community.

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PRESENTATION

Fernando Barroso Duarte

In the past few years, we have learned a lot about Hematopoietic Stem Cell Transplantation in patients with more than 60 years of age. These patients have been more often transplanted as a result of the use of reduced intensity – or even of non-myeloablative – conditioning regimens. The understanding and adjustment of therapy directed to this age group have been important factors to achieve this knowledge. If, by one hand, we were able to be more inclusive and liberal in the management of this type of HSCT, on the other hand, issues – such as prognostic scores not exclusive to this age group and physiological age – prevailed over the decisions, to indicate a bone marrow transplant in this age group.

Other relevant considerations – such as the incidence of relapse, the need for post-transplant therapies and the management of MRD monitorization based on immunological and genetic-molecular criteria – also took place in the discussions. It became almost mandatory to implement a comprehensive geriatric assessment before HSCT for patients over 60 years of age. In fact, some European groups already perform it to individuals over the age of 50 or 55.

We believe that the individualization of the treatment to this group of patients is necessary, and that the age is not the only eligibility criteria to be considered for indicating or choosing the type of conditioning regimen on HSCT. For this reason, we added this unprecedented chapter to the Brazilian Society of Bone Marrow Transplant 2020 Consensus, organized by Dr Morgani Rodrigues, Dr Nelson Hamerschlak, Dr Polianna Souza, Dr Natália Costa and Dr Fernando Barroso.

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LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATIONS IN HSCT AND CELLULAR THERAPY

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In this issue of the Journal of Bone Marrow Transplantation and Cellular Therapy, we present results of the 2020 update of the 2017 Bone Marrow Transplantation Consensus of the Brazilian Society of Bone Marrow Transplantation (Sociedade Brasileira de Transplante de Medula Óssea, SBTMO) for bone marrow transplantation indications.

Like earlier editions, we used the 2009 Levels of Evidence from the Oxford Centre for Evidence-Based Medicine for evidence and strength of recommendation grading1.

The process of these reviews involves the classification of the evidence (Levels of Evidence) and grading the strength of recommendation (Grades of Recommendation).

In brief, levels of evidence are classified 1 to 5, in which class 1 represents the highest level of evidence (usually randomized controlled trials) and class 5 represents the lowest one (expert opinion or based on physiology). Each 1 to 3 level of evidence is subdivided in 'a', 'b' and 'c' or 'a' and 'b', in lower case letters.

The analysis of the Levels of Evidence leads to a Grade of Recommendation, which are graded in A to D, in capital letters, in which grade A is the highest grade of recommendation, and D the lowest one.

Please note that the word 'levels' is reserved for evidence, while 'grades' is for recommendation. Also, do not mistake lower case letters of levels of evidence by capital letters of grades of recommendation.

Here, we present a summary of the 2009 Oxford Levels of Evidence.

LEVELS OF EVIDENCE (TABLE 1)

LEVEL 1 – MAINLY RANDOMIZED CONTROLLED TRIALS

Systematic reviews with meta-analysis of randomized controlled trials (RCT) are classified as 1a, as long as there is homogeneity, or the heterogeneity is not worrisome. Worrisome heterogeneity should be classified as Level 1a- (1a minus). Level 1b is for individual RCT with narrow confidence interval (just like in meta-analysis, wide confidence interval should be marked with a 'minus' sign). Low quality RCT should be classified as Level 2, not 1. All or none case series should be graded as Level 1c. All or none studies is met when all patients died before the treatment became available, but some survive on it, or when some patients died before, and all survived on it.

LEVEL 2 – MAINLY COHORT STUDIES

Level 2a is reserved for systematic review with meta-analysis of cohort studies (again, worrisome heterogeneity should be marked with a 'minus' sign). Individual cohort studies (except poor quality cohort studies, which should be labelled Leve 4) and low quality RCT should be classified as Level 2b. Outcomes research and ecological studies (which are seldom available in the hematopoietic cell transplantation field) should be classified as Level 2c.

LEVEL 3 – CASE-CONTROL STUDIES

Systematic reviews with meta-analysis of case-control studies without worrisome heterogeneity should be labelled as Level 3a; worrisome heterogeneity should be marked with a 'minus' sign. Individual case-control studies should be labelled as Level 3b.

LEVEL 4

Level 4 is reserved for case-series and poor-quality cohort and case-control studies. According to the Oxford Levels of Evidence, "poor quality cohort study means one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of pa-

tients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders".

LEVEL 5

Level 5 is evidence based on expert opinion or physiology.

GRADES OF RECOMMENDATION

The next step involves the classification of the Grade of Recommendation. Usually, evidence level 1 leads to Grade of Recommendation A, evidence level 2-3 to Grade of Recommendation B, 4 to C and 5 to D. Note that inconsistent results or extrapolations may downgrade the Grade of Recommendation (table 2).

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TABLE 1 - Levels of Evidence

Level	Therapy / Prevention, Aetiology / Harm
1a	Systematic review (with homogeneity) of Randomized Controlled Trials (RCT)
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c	"Outcomes" Research or Ecological studies (seldom available in hematopoietic cell transplantation)
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Adapted from 1	

TABLE 2 - Grades of Recommendation

Grade of Recommendation	Level of Evidence
A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level
Extracted from 1	

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DONOR SELECTION: GENERAL ASPECTS

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Hematopoietic stem cell transplantation (HSCT) provides potential curative treatment for a wide range of potentially fatal hematological diseases. The number of patients treated with HSCT has greatly increased in the past four decades, accompanied by steady improvement in results. Ideally, HSCT is performed with stem cells collected from an HLA compatible sibling, but this is not always possible, as only about 30% of patients will have this donor. The expansion in alternative sources of donor stem cells, together with the advent of reduced intensity conditioning regimes (RIC), contributed to the increase in the number of HSCT in general and in transplantation with unrelated donors in particular. Advances in HLA typification have facilitated improved donor selection, which, in turn, has improved the outcome of HSCT with unrelated donors, so that survival is now approaching transplantation with related donor.

In addition, the improved safety of haploidentical transplantation with modern approaches, such as post-transplantation cyclophosphamide (PTCy), has led to an increase in the use of haploid donors.

The selection of a donor is a critical element that contributes to the success of HSCT. Considering HLA compatibility as the most important criterion in this choice, other factors can influence the outcome of the transplant, such as age and sex of the donor, parity in the case of female donors, ABO compatibility and CMV serological status.

AGE

As older patients are eligible for HSCT, older siblings are increasingly being proposed as related donors. This data has been extensively studied because it is known that older donors are more likely to exhibit indeterminate potential clonal hematopoiesis (CHIP), and this has been associated with an increased risk of hematological malignancies [1,2,3].

In 2015, Andrew R et al demonstrated that there was no difference in transplant-related toxicity and concluded that graft from donors older than 60 years did not adversely affect the results of the allogeneic BMT when compared with graft from younger donors. No significant difference was observed in neutrophil and platelet recovery time, except for an average delay of 1.3 days in neutrophil recovery between patients undergoing myeloablative transplantation with older donors (P = 0.04). Myeloablative and non-myeloablative transplant recipients with older sibling donors had significantly lower grade II-IV GVHD than recipients with younger unrelated donor grafts. The rates of grade III-IV acute GVHD, chronic GVHD and TRM for recipients with older donors were not significantly different from recipients with younger donors. [4]

These data have been controversial in the literature. In a study by Kollman et al, donor age under 30 years was associated with a 30% incidence of acute GVHD compared to 34% in patients with donors over 30 years (p = 0.005). The improvement in survival was also observed in younger donors aged 18-30, 31-45 and 45 years old, being associated with an overall survival (OS) in 5 years of 33%, 29% and 25%, respectively (p = 0, 0002). [5]

In a 2015 study with HLA-compatible donors, sibling donors over 50 were associated with a 3 years OS of 54% compared to 72% in URDdonors under 50 (p <0.0001). TRM and relapse occurred in 20% and 39% of transplants from donors over 50 years-old, compared with 8% and 28%, respectively, after the younger donor transplant (p = 0.03). [6]

However, these data were not confirmed by Shaw B et al. analysing a cohort of URD transplantation. Donor age was not associated with recurrence and when tested as a continuous variable, it was also not associated with risk of relapse (HR, 1.004; 95% CI, 0.99-1.01; P = 0.20). The only donor characteristic associated with a lower risk of recurrence was the transplantation of female multiparous donors compared to male donors. [7] However, In the same study, donor younger age was associated with better survival, with 2 year-survival 3% better when a donor 10 years younger is selected. These results support previous studies that suggest prioritizing a younger 8/8 HLA compatible donor. [7]

The use of younger donors was also associated with higher doses of cells in the graft, better immunological reconstitution and easier collection. [8]

The donor's older age was also associated with an increase in acute GVHD, but not in chronic GVHD. The higher rates of grade 2 to 4 acute GVHD observed after transplantation of grafts from older donors can be explained by the replacement of naive T cells with memory T cells as the immune system ages in older donors.[9]

In the context of Haplo-HSCT, the main criterion continues to be the absence of anti-HLA antibodies directed against the donor present in the recipient serum (DSA - Donor Specific Antibodies). In the case of positive DSA research and in the absence of an alternative donor, there are desensitization protocols. The other criteria are impossible to prioritize: age, sex, CMV and blood type. [10]

SEX

The impact of the difference between the sex of the donor and the sex of the recipient is still controversial. The selection of a male donor has been reported in some studies to be a factor with a positive impact on overall survival, regardless of the recipient's gender [11,12] and many studies show worse prognosis when the donor is female and the recipient is male [13–20]; however, new studies have shown that there are many other factors that influence these outcomes such as female donor parity [5], the type of conditioning used [13) and the number of cells collected [21].

Several authors credit the higher incidence of chronic GVHD in transplants performed with female donors to male donors to the immune response against minor histocompatibility antigens present on the Y chromosome of male recipients (HY antigens) [19,22–25], and other authors believe that this effect it is even more intense in the case of donors who have been pregnant with male fetuses or received transfusions from male donors and therefore have already been exposed to HY antigens [26–28]. Copelan et al, on the other hand, reported that the higher incidence of chronic GVHD in male patients who received cells from female donors was protective due to a lower incidence of relapse of the underlying disease [29]. Studies with a small number of individuals included suggest that, in the pediatric setting, the donor's gender has less influence on outcomes, especially if the donor is under the age of 12, and therefore this criterion should be taken into account in the donor for the pediatric population [30,31].

As for the type of conditioning proposed, a study that evaluated more than 1,000 adult patients demonstrated that among patients who received myeloablative conditioning regimen, male recipients of female donors had a higher incidence of chronic graft versus host disease ($p = 0.01$), higher mortality not related to recurrence ($p = 0.022$) and a lower overall survival ($p = 0.018$). Among patients who received reduced intensity conditioning, male recipients of female donors had a higher incidence of acute graft versus host disease ($p = 0.01$), but there was no statistical difference in terms of mortality rate, unrelated to recurrence. Among patients who received conditioning based on total lymphoid irradiation and anti-thymocytic globulin, there was no influence of donor's gender on the incidence of acute or chronic GVHD or mortality not related to recurrence; however, only in this group a statistically significant reduction in recurrence was noted ($p = 0.01$) and the anti HY alloantibodies titers were predictors of protection against recurrence. Also in this group of patients, the gender difference between donor and recipient resulted in a longer overall survival ($p = 0.037$), probably related to a greater graft against leukemia effect [13].

Kollman led a study that included almost 7,000 transplants and found no effect of donor sex on overall survival, acute graft versus host disease (GVHD) or engraftment, however, when only bone marrow recipients were analyzed, female donors were associated to a greater risk of developing chronic graft versus host disease (GVHD), but this effect was restricted to donors with previous pregnancies ($p = 0.0001$) and nulliparous donors had no statistical difference.The same analysis was not performed for peripheral blood source.[18]

Considering the use of umbilical cord blood, small studies suggest a higher incidence of chronic graft versus host disease when male recipients receive cord blood cells from a female donor ($p = 0.02$), while female recipients of male cord blood cells showed higher platelet engraftment failure ($p = 0.02$) [34], suggesting this scenario needs further studies.

An important aspect in the case of bone marrow collection is the size and weight of donors and in general, male donors offer a greater volume of bone marrow [21]. Data from the National Marrow Donor Program (NMDP) reveal that the average bone marrow volume donated by male donors is 1.1 L, with 25% of men able to donate more than 1.35 L. Female donors are able to donate, on average, 1L. [21] In addition, when the requested source is peripheral blood cells, men have a higher average CD34 +

pre-apheresis cell count, which leads to differences of more than 30% in the total of CD34 + cells collected, even when adjusted by the donor weight besides the fact male donors more often have adequate peripheral venous access for collection by apheresis.[21]

ABO INCOMPATIBILITY

ABO incompatibility is not a barrier to the success of hematopoietic progenitor cell transplantation because ABO group antigens are not expressed in pluripotent cells or in the early stages of differentiation [33], even though, each type of incompatibility presents specific potential adverse events as well as preventive measures to be taken and all patients and their respective possible donors should be tested for ABO group, preferably before collection [34].

There are three types of ABO incompatibility:

- Major: occurs when the recipient has isohemagglutinins directed against the donor's erythrocyte antigens. About 20 to 25% of transplants performed worldwide have this type of incompatibility. [35]

- Minor: occurs when the donor has isohemagglutinins against the recipient. About 20% of transplants have this type of incompatibility. [35]

- Bidirectional: occurs when major and minor incompatibilities are present, as, for example, in the case of a donor A to a recipient B. This type of incompatibility occurs in up to 5% of transplants.[35] A study conducted by Rowley et al showed that the infusion of 10 to 30mL of incompatible red blood cells infused with cells from a donor with in a setting of major ABO incompatibility can be well tolerated by adults and when this volume is less than 15mL there are no signs of clinical hemolysis [36] while Bolan et al showed that late hemolysis resulting from the infusion of progenitor cells from a donor with minor incompatibility can be severe and difficult to diagnose.[37]

The medium and long-term clinical impact of ABO incompatibility is still controversial, while large studies have shown that greater or lesser incompatibility does not lead to significant impacts on overall survival and does not constitute a contraindication for donor selection [38], many smaller studies , mostly unicentric, show decreased overall survival rates, higher treatment-related mortality and even a higher incidence of graft-versus-host disease, in addition to greater and more prolonged red cell transfusion dependence. [39,40]

A study involving more than 5,000 unrelated allogeneic transplants performed in Japan for malignant and non-malignant diseases showed that in the period from 1993 to 2005, patients undergoing transplantation with an unrelated ABO incompatible donor had worse overall survival and higher rates of treatment related mortality. Subsequently, the same group analyzed the transplants performed between 2000 and 2006 and again showed that the greater ABO incompatibility was associated with worse overall survival ($p = 0.004$) and higher treatment-related mortality ($p = 0.001$), however, when the same analyzes were carried out with transplants performed between 2007 and 2015, the greater incompatibility had no effect on overall survival ($p = 0.79$). Thus, these authors concluded that the clinical significance of ABO incompatibility has decreased over time. [38]

On the other hand, Watz et al studied 310 patients who underwent transplants with reduced intensity conditioning and showed that both patients with greater incompatibility and those with lesser incompatibility required red blood cell transfusions for a longer period than patients without incompatibility. [39]

Brazilian studies by Soares Júnior et al [41] in the southeastern region and by Paz et al [42] in the south, show similar results and do not show an impact on overall survival, the development of graft-versus-host disease or transplant related mortality in patients who received cells from donors with ABO incompatibility. The study conducted by De Santis et al [43] showed that in the case of greater ABO incompatibility, patients who had antibody titers ≥32 of IgG, but not IgM, needed a greater number of red blood cell transfusions than those who had lower titers.

CMV STATUS

Cytomegalovirus (CMV) diseases are the main causes of significant morbidity and mortality in HSCT recipients. [44] The risk of CMV recurrence depends on the level of immunological competence, manifested as impaired T-cell immunity, including the presence and function of CMV-specific cytotoxic T lymphocytes [45].

Most events of CMV recurrence occur between 2 and 4 months, with a median of 44 days after HSCT [62-64]. The greatest risk of CMV reactivation and CMV disease is reported for HIV-positive recipients regardless of the donor's serological status. [45]

Other risk factors associated with a higher risk of recurrence are: transplantation with unrelated donor or HLA disparity [46-47-48], acute GVHD [48,49,50,51], bone marrow as stem cell source [46], reduced intensity conditioning [49], conditioning based on TBI [48.51] and steroid use [51]. A protective effect of sirolimus use on GVHD prophylaxis was demonstrated in one study[46]. Sirolimus possibly has a protective effect against CMV infection due to the inhibition of cell signaling pathways that are triggered during CMV infection for the synthesis of viral proteinsThese antiproliferative properties probably inhibit CMV replication kinetics[52,53].

The importance of donor serological status is controversial. A large European registry study showed that seronegative patients who received grafts from unrelated seropositive donors had a decreased overall survival (HR 1.13 [1.06-1.21]; p <0.01) compared to seronegative donors, while no difference was observed in patients who received grafts from compatible siblings. In contrast, seropositive patients who received grafts from non-seropositive donors improved overall survival (HR 0.92 [0.86-0.98]; p <0.01) compared to seronegative donors, if they had received myeloablative conditioning this effect was absent in the context of reduced intensity conditioning. These data are not confirmed when the donor is related. Although no study has validated the role of CMV in haplo transplant, the available data suggest that there is an increase in the rate of CMV reactivation after haplo compared to related and unrelated donors BMT [55,56] Therefore, reducing the risk of CMV can be particularly important for patients submitted to haplo transplant platforms.

DONOR SAFETY DURING HSCT

The hematopoietic stem cell donation is a voluntary and altruistic act, and the initial medical donor evaluation must consider aspects related to donor safety.

In general, the recommendations related to unrelated donors are more restrictive than the ones for related donors. In terms of age limit, for instance, NMDP unrelated donors are allowed to donate until 60 years-old while older related donors are accepted in USA and donors younger than 18 years-old are eligible exclusively for related donation. Considering the eventual risks, the American Pediatric Society published in 2010, a list of minimum criteria for children donation: 1) Absence of equivalent adult donor, in terms of compatibility; 2) A relevant relation between donor and receptor; 3) The clinical and emotional risks for donor are acceptable when compared to receptor benefits; 4) A formal authorization from parents or other legal representative is required.

Related and unrelated donors´ medical evaluation should include a physical examination, a medical interview with emphasis on previous diseases, illegal drugs abuse, surgeries, blood transfusions, pregnancy and travels; and testing for infectious disease or other conditions that require additional data.

The laboratory tests performed during work up are: Complete blood count, biochemistry tests including liver function tests; Infectious disease markers for HIV, HTLV-1 and HTLV-II, hepatitis (HAV, HBV and HCV), Chagas disease, syphilis, CMV and EBV.

In the case of a positive test for an infectious disease marker like B hepatitis the risks for receptor must be considered and the patient should be informed. However, an HIV positive test is a definitive exclusion criterium for related and unrelated donors. Pregnancy test is recommended for female donors younger than 55 years old. Hemoglobin electrophoresis can be requested for donors who report familial history of hemoglobinopathies but falcemic trait or minor talassemia do not represent risk for receptor. X-ray test and electrocardiogram can be requested for specific cases.

Related and unrelated donors should be oriented about the donation risks as well as eventual benefits for patient, and an informed consent form should be obtained during the work up process. The professionals responsible for donor evaluation should not be related to patient treatment for the purpose of reducing any conflict of interests.

In order to assure the donor safety during bone marrow harvest, donors with hemoglobin level lower than 13g/dl have the recommendation for collection of autologous blood and the prescription of iron supplements is also indicated as strategies to avoid symptomatic anaemia.

After bone marrow collection, serious complications are rare but donors can complaint of local pain and the use of analgesic drugs is also recommended. In the case of mobilized peripheral blood apheresis, donors can require analgesia to treat symptoms associated to filgrastim use. Complications associated to apheresis include the use of central venous catheter while splenic rupture is a rare but serious event.

Finally, some donors can be requested for a subsequent donation. The interval between the first and the second procedure should be evaluated on an

individual basis but, as a general recommendation, donors submitted to apheresis as the first stem cell source should wait at least 30 days before a second donation while after a bone marrow donation the recommended interval is 90 days.

CONSIDERATIONS FOR COVID-19

The COVID-19 pandemic represented an additional challenge on the complex process related to hematopoietic stem cell donation.

According to the World Marrow Donor Association (WMDA), the main recommendations should balance additional donor risks, the benefits of (59)

• Clinical evaluation for related and unrelated donors should include epidemiological aspects and risk factors associated to COVID-19

• Swabbing all donors for SARS-CoV-2 prior to donation (e.g.at work-up or before G-CSF) has some potential value.

• Swabbing all donors for SARS-CoV-2 on the day of donation has no value, because it does not prevent harm to the donor or to the recipient, because there is no evidence for pre-symptomatic viraemia.

• In case of diagnosis of COVID-19, donor must be excluded from donation for at least 28 days after full recovery of symptoms but this time can be reviewed on specific cases.

• In case of close contact with a person diagnosed with SARS-CoV-2, the donor shall be excluded from donation for at least 28 days but this time can be reviewed.

• Quarantine of product is NOT recommended considering the lack of evidence of SARS-Cov-2 transmission.

The recommendations from Brazilian authorities are described on NOTA TÉCNICA Nº 36/2020-CGSNT/DAET/SAES/MS (60) which establishes the RT-PCR testing 24h prior the donation for all donors

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DONOR SELECTION: IMMUNOGENETICS AND HISTOCOMPATIBILITY

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INTRODUCTION

The selection of donors with adequate HLA compatibility is essential for the success of hematopoietic stem cell transplantation (HSCT) [1, 2]. HLA genotypically identical donors are the first choice, but only about 30% of patients have this possibility. Unrelated donors, umbilical cord blood, or haploidentical donors are alternatives for the remaining 70%. (Level of evidence 2a; Grade of recommendation B).

RECOMMENDATIONS FOR PATIENT HLA TYPING

It is recommended high-resolution HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 typing for patients in search of related and unrelated donors.

CONFIRMATION OF HLA TYPING (CT)

- All patients referred to HSCT and their respective donors (related, unrelated, and umbilical cord blood) must have HLA typing confirmed with a second (new) sample before transplant.

- The purpose of the CT is to exclude possible errors related to the identification of samples after collection or laboratory errors in any of the pre-analytical, analytical, or post-analytical steps.

- It is mandatory that this verification be done before the patient starts pre-HSCT conditioning. CT can be done in medium resolution if the previous HLA typing was performed in high resolution.

- The transplanted patient may eventually need a second transplant. Therefore, complete HLA genotyping of the patient is required to search for a new donor as well as a cryopreserved DNA sample for further examination.

SAMPLE COLLECTION RECOMMENDATIONS FOR HLA TYPING

- Peripheral blood collected in EDTA (5 to 10 mL).

- Saliva is an alternative in leukopenic patients post-chemotherapy,

- Patients with leukemia: if there are many immature cells in peripheral blood, the initial or confirmatory HLA typing should be performed on DNA isolated from oral mucosa cells or other tissue in order to avoid false homozygous results.

- Patients with Fanconi anemia: if the initial HLA typing is done with blood in EDTA, the confirmatory typing should be done on DNA isolated from oral mucosa cells, as these patients are prone to chromosomal breakages.

- Patients with Severe Combined Immunodeficiency Syndrome (SCID): collection of oral mucosa cells with the aid of swabs should preferably be utilized to avoid interference of possible maternal cells in the peripheral blood of these patients.

- Patient post-allogeneic HSCT: collection of oral mucosa cells with the aid of swabs.

Recommendations for related donor selection

- Request medium resolution HLA-A, -B, and -DRB1 typing of siblings, parents and/or children.

- Confirmatory Typing (CT): it is mandatory that HLA confirmatory typing of the selected donor be done in a second/new sample before the transplant is performed.

- CT resolution level: request the medium resolution typing of the pre-selected donor if the four paren-

tal haplotypes were identified. Otherwise, request high-resolution typing including HLA-C, -DQB1, and -DPB1 loci.

- In the absence of a fully HLA matched sibling, request high resolution HLA typing if an HLA 11/12 related donor is selected. This kind of donor can be found among siblings

as a consequence of crossing-over process that results in recombinant haplotypes, i.e., new allelic combinations that differ from those in the parental haplotypes.

- Regarding **haploidentical related donors**, it is essential to choose a donor with **one shared haplotype with the patient** (minimum compatibility of 6/12 for HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1). It is possible to occur additional compatibility in one or more loci of the non-shared HLA haplotype, although there is currently no evidence of a beneficial effect of this extra compatibility on HSCT [3, 4]. Therefore, the selection criteria for haploidentical donors should be based on the presence or absence of antibodies against incompatible HLA antigens expressed by the donor (DSA) and other non-HLA factors [5, 6]. (Level of evidence 2b; Grade of recommendation B)

RECOMMENDATIONS FOR UNRELATED DONOR SELECTION

- Choose preferably HLA 8/8 donors considering HLA-A, -B, -C and -DRB1[7-9] loci to proceed to REDOME phase 3, which consists of confirmatory typing (CT) of HLA-A, - B, -C, -DRB1, -DQB1, and -DPB1 genes. It is mandatory that CT be performed with a new sample. (Level of evidence 2b; Grade of recommendation B)

- Prioritize donors with **permissive HLA-DPB1 mismatches**, according to the **T-Cell Epitope** (TCE) algorithm, when several HLA 8/8 matched donors are available. HLA-DPB1 alleles may also be assessed by the **Expression model**, which is based on the single nucleotide polymorphism (SNP) rs9277534 in the 3' untranslated region. In this model, the HLA-DPB1 alleles associated with rs9277534 G and A variants are classified as high and low-expression, respectively. The concomitant use of the TCE and Expression models may optimize the selection of permissive HLA-DPB1 mismatches. [9-11]. (Level of evidence 2b; Grade of recommendation B)

- Prioritize **HLA-DQB1 and -DRB3, -DRB4, -DRB5** matched donors (12, 13) when several HLA 8/8 compatible donors are available. (Level of evidence 2b; Grade of recommendation B)

- When 8/8 (HLA-A, -B, -C, -DRB1) allele compatible donors are not available, then HLA 7/8 donors with the permissible HLA-C*03:03 vs. C*03:04 incompatibility should be prioritized [14]. (Level of evidence 2b; Grade of recommendation B)

- In the HSCT for malignant diseases setting, when HLA 8/8 (HLA-A, -B, -C, -DRB1) allele compatible donors are not available, choose preferably **HLA 7/8 donors** whose incompatibility vector is the Host versus Graft (HvG) instead of bidirectional or Graft versus Host (GvH) [15, 16]. When it comes to non-malignant diseases, there is evidence that unidirectional incompatibilities in the HvG vector can increase the risk of rejection, and as precaution, they should be avoided [17]. (Level of evidence 2b; Grade of recommendation B)

- The presence of HLA mismatches also adversely affect the outcomes of unrelated donor HSCT for **non-malignant diseases**. In a previous CIBMTR study, HLA mismatches were associated with increased risks of graft failure [17]. (Level of evidence 2b; Grade of recommendation B)

- In the selection of **umbilical cord blood**, it is recommended that a segment of the cord blood bag be utilized for HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 high resolution typing. It is suggested that the allelic compatibility be at least 5/8, considering HLA-A, -B, -C and -DRB1 loci [18, 19]. (Level of evidence 2b; Grade of recommendation B)

ANTI-HLA ANTIBODIES: IDENTIFICATION AND DSA ASSESSMENT

- In selecting alternative donors, the search for anti-HLA antibodies and the analysis to identify **donor-specific antibodies (DSA)** is recommended to minimize the risk of graft failure [20-25], except when a donor is HLA genotypically identical including HLA-DPB1 locus (HLA 12/12). (Level of evidence 2b; Grade of recommendation B)

- The test is performed by solid-phase assays on the Luminex platform, using panels of HLA isolated antigens (Single Antigen Beads - SAB). It is recommended the utilization of complementary technical resources for accurate designation of DSA whenever SAB results leave doubts about the veracity of positive or negative reactions. These resources may include CDC cross-match, flow cytometric cross-match, HLA phenotype panel, and others. The integration of the results revealed by SAB and by complementary tests, in addition to the information on patient's sensitizing events, is essential for greater precision in the estimation of post-transplant immunological risk.

- In general, the probability of graft failure increases as the strength (MFI) of the DSA do so. In addition, some studies have shown that DSAs with MFI > 5000 are associated with an increased risk of rejection [25, 26]; therefore, they should be avoided. In the absence of a donor without DSA, it is recommended to carry out a desensitization protocol and respective monitoring. (Level of evidence 2b; Grade of recommendation C)

TECHNICAL RECOMMENDATIONS FOR THE IDENTIFICATION OF ANTI-HLA ANTIBODIES

- **Sample Collection:** the test for anti-HLA antibody identification is performed with the recipient's serum. The peripheral blood sample from the recipient should be collected in a dry tube or a gel serum separator tube followed by centrifugation to separate the serum.

- **Transport:** whenever possible separate the serum before shipment and transport preferably at a temperature between 2º and 8ºC (artificial ice). If this is not possible, ship the whole blood sample at room temperature (avoid extreme temperatures) to the laboratory where the serum will be separated. The serum sample should preferably be kept in a -70ºC freezer until the time of testing.

- **Identification of anti-HLA antibodies:** each clinical laboratory should choose the solid phase assays for detection (screening) and characterization (SAB = isolated HLA molecules) of anti-HLA antibodies. All of the selected tests must be validated before their utilization in the clinical routine.

- **Complementation of HLA typing for DSA analysis:** receptor and donor HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 matched, may or may not be identical at HLA-DRB3, -DRB4, -DRB5, -DQA1 and -DPA1. Thus, when patient has antibodies specific to allelic products of these genes, it is necessary to type them in the donor. It is also suggested to type the recipient for HLA-DRB3, -DRB4, -DRB5, -DQA1, and -DPA1 loci because the knowledge of self HLA can contribute to the interpretation of SAB test results.

- **Frequency of testing:** the identification of anti-HLA antibodies should be done when the patient starts the donor search process and reassessed with his recent serum after his donor has been selected, even in the absence of DSA in the initial test. This is due to the fact that the patient's immunological profile is dynamic and can be altered by several factors, being the transfusion of blood components one of the main factors. In addition, inflammatory processes resulting from infections or tissue damage can induce reactivation of memory B cells resulting in the production of DSAs regardless of re-exposure to alloantigen.

- **Desensitization and post-transplant monitoring:** when the patient is submitted to a desensitization protocol to remove DSA against the alternative donor (haploidentical, unrelated, umbilical cord blood or related with HLA incompatibility), it is recommended that the effectiveness of the procedure be monitored by determining the DSA strength after each of the steps [27-29]. In some cases, it is necessary to monitor DSA post-HSCT because a rebound effect may occur after the infusion of the allograft, and therapeutic intervention can be done in a timely manner to avoid graft failure [27]. The frequency of sample collection for post-desensitization and post-transplant monitoring should be customized for each patient according to the understanding between the transplant physician and the HLA Laboratory. (Level of evicence 2b; Grade of recommendation C)

CHIMERISM TESTING FOR POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION MONITORING

- The evolution of HSCT is assessed by hematological recovery and chimerism analysis, as these parameters provide information on the hematopoietic reconstitution of the patients, which can be autologous, allogeneic, or chimeric. Chimerism testing must be performed because it is essential to assess engraftment, to diagnose graft rejection, graft dysfunction, and disease relapse [30-35]. (Level of evidence 2b; Grade of recommendation B)

- The post-HSCT chimerism monitoring has been assessed by the analysis of genetic markers distributed throughout the human genome that have variable numbers of tandem repeats (STRs).

- The identification of these markers must be done on the pre-transplant peripheral blood sample of the patient, and on a peripheral blood sample of the donor in order to define their respective genetic profiles based on the utilized STRs. Chimerism testing can be performed on total nucleated cells, but the test sensitivity can be increased by analyzing cell subpopulations in blood or bone marrow samples in the post-transplant.

TECHNICAL RECOMMENDATIONS FOR CHIMERISM TESTING COLLECTION

samples should preferably be collected in EDTA. The determination of the post-transplant chimerism level requires the identification of STR markers in the following samples:

- **Pre-transplant peripheral blood of the patient** to define his/her pattern of allelic variants in the STR loci;

- **Peripheral blood of the donor** to define his/her pattern of allelic variants in the STR loci;

- **Post-transplant peripheral blood or bone marrow of the patient** to define if the alleles identified in the STR loci are only those of the patient or both patient and donor or only donor's.

TRANSPORTATION:

samples must be stored and transported at room temperature (15º - 25ºC), mainly when the analysis of cell subpopulations is necessary. Refrigeration can compromise cell viability, and consequently the determination of sub-populations' purity by flow cytometric immunophenotyping.

- Time elapsed between collection and delivery of patient and donor samples to the laboratory should not exceed 24 hours, when destined for chimerism testing in cell sub-populations.

- The purity must be assessed in all cell fractions. Insufficiency of cells to evaluate the purity must be informed in the chimerism testing report.

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HAPLOIDENTICAL STEM CELL TRANSPLANTATION

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DEFINITION

A haploidentical donor is one who divides, by common genetic inheritance, exactly one haplotype with the recipient and presents mismatch in a variable number of genes in the non-shared haplotype. Potential haploidentical donors include biological parents, children, siblings, uncles, aunts, cousins, nephews, or grandchildren.

INTRODUCTION

As matched related donors can be found in only 30% of cases, alternative donors such as unrelated matched transplants, cord transplantation, partially compatible transplantation, and haploidentical transplantation are important alternatives. Due to important improvements in techniques for performing haploidentical transplantation and as first-degree haploidentical donors can be found in more than 95% of patients, this type of transplantation has been growing in recent years [1-3].

The advantages of using this type of transplant are the immediate availability of the donor, the immediate access to the donor for cell therapy in the post-BMT, and the possibility of selecting several family members according to clinical characteristics and NK alloreactivity. The biggest challenge is the intense bidirectional alloreactivity with increased risk of graft-versus-host disease (GVHD) and rejection, leading to the need for depletion of T cells in vivo or ex vivo and a greater incidence of infection by slow immuno-reconstitution and high incidence of relapse [4].

HISTORICAL ASPECTS

The haploidentical stem cell transplant initiatives in the 1970s were catastrophic and prohibitive, with graft vs host disease incidence above 70% and grafting failure of 20% (5). In the 1980s, with the use of depletion of T cells with sheep red blood cells, the methodology started to be accepted [5].

In 1994, the Italian group demonstrated a reduction in the risk of rejection using high doses of cells ("mega dose": 13.8x 106 CD34 with 1x 104 CD3) with CD34 cell selection(6).In 2007, the Duke University group, led by Nelson Chao, presented a protocol with depletion "in vivo" with Campath in the conditioning regime, without selecting CD34 cells "in vitro" [7]. But a breakthrough was in 2008 when the Baltimore group led by Efraim Fuchs consolidated the use of cyclophosphamide on days +3 and +4 post-transplant, also with depletion "in vivo"[8]. From that moment on, what is seen is a constant search for methodologies that further improve the results of haploidentical transplants [4, 9].

Post-transplantation cyclophosphamide is the most frequently used immunosuppression to perform haploidentical transplants. The reasons are the high cost of a column to select CD34+ cells and the encouraging results with the use of post-transplant cyclophosphamide [2, 3, 8].

TRANSPLANTATION STRATEGIES

The main haploidentical transplant strategies are:

a) "In vitro" T cell depletion: in this methodology, it is used mega doses of CD34 and is most used by the Perugia group [5, 6, 10, 11]

b) GIAC: in this protocol, it is used GCSF (G) to stimulate the donor, an intensified immunosuppression after transplantation (I), ATG in the conditioning (A), and combined (C) use of bone marrow and peripheral blood. This methodology is used almost exclusively in China, where there is extensive experience in haploidentical transplants [11]

c) Post-transplant cyclophosphamide: this is the main strategy of T cell depletion used worldwide. It was first described with a non-myeloablative protocol using Fludarabine, low-dose total body irradi-

ation (200 Gy), and cyclophosphamide. Cyclophosphamide 50 mg/kg is used on days + 3 and +4 and the graft vs host disease prophylaxis is done with mycophenolate mofetil and tacrolimus [8, 12, 13].

CHOOSING THE DONOR:

The studies comparing haploidentical transplantation with post-transplantation cyclophosphamide to unrelated matched transplant did not demonstrate great superiority for one or other donors. Registry studies have shown that overall survival (OS) was not significantly different between patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) receiving haploidentical or unrelated grafts (reduced intensity or myeloablative conditioning) [12, 14]. Similarly, in recipients with lymphoma, OS, non-relapse-related mortality and progression-free survival were comparable between these two types of donors, although the incidence of acute GVHD grades III-IV and chronic GVHD was lower in haploidentical transplantation [15]. In aplastic anemia, haploidentical transplantation has also been associated with satisfactory experiences [16].

Registry studies comparing haploidentical transplant and umbilical cord transplantation have shown superior outcomes with haploidentical transplantation compared to cord transplantation [17-19]. The BMT CTN 1101 phase 3 randomized trial recently demonstrated superior OS in haploidentical transplant recipients compared to cord transplantation [20]. In the future, studies may compare better-selected cord transplantations (eg, higher cell dose, grafts with fewer HLA mismatches, and others) to haploidentical transplantation [6, 10, 11, 21, 22].

CHOOSING THE BEST HAPLOIDENTICAL DONOR:

The main factor in the donor choice is the presence of donor-specific antibodies (DSA), which is present, more frequently, in women with children, but can also occur due to a history of transfusions. The donor chosen should be preferably the one for whom the patient does not have antibodies. Besides, the specific antibody titer is also an important factor, since mean fluorescence intensity (MFI)> 1500 (23) may be associated with graft dysfunction, MFI> 5000 with graft failure, and> 10,000 (24) with a high incidence of graft failure [23]. MFI values may vary between laboratories and each institution must establish its cut-off value for graft failure risk. As high MFI values are usually more frequent in family donors, the search for an unrelated donor should be done. If another donor cannot be identified, desensitization to reduce antibody concentration can be considered in centers with expertise. Desensitization schemes generally include immunosuppressants, plasmapheresis, "buffy coat", among others, and the protocol must be established at the institution.

Another important factor to be considered is donor age, with preference for the younger donor. Donors who are the recipient's children or siblings are preferred over parents [25]. Blood group, donor gender, serology for cytomegalovirus, non-inherited maternal HLA antigen (NIMA), the disparity in specific HLA alleles, and mismatching KIR are still controversial factors that need further study at this time.

GRAFT SOURCE

Bone marrow and peripheral blood are possible stem cell sources for haploidentical transplantation, and the choice is generally based on the institution's expertise and preferences. Studies comparing both graft sources have shown no difference in overall survival, but there may be a difference in transplant-related mortality, relapse, GVHD, and cytokine release syndrome.

In a multicenter study, bone marrow was associated with a lower risk of acute GVHD grades II to IV and chronic GVHD and a higher risk of relapse in patients with acute leukemia, but not in lymphomas, with no difference in overall survival and transplant-related mortality [26]. In another study, bone marrow was associated with a lower risk of acute GVHD, but the source did not affect the risk of chronic GVHD, relapse, and non-relapse mortality [27]. Some studies have shown a higher incidence of ≥ grade 2 cytokine release syndrome using a peripheral source [28, 29]. If bone marrow source is used in haploidentical transplantation with post-transplant cyclophosphamide, the higher nucleated cell count is associated with increased progression-free survival and overall survival [30].

CYTOKINE RELEASE SYNDROME

Fever of noninfectious origin occurs in 80-90% of the cases after haploidentical transplantation, usually between days 0 and 6, with resolution after post-transplant cyclophosphamide. This fever is related to a mismatch in HLA class II and high doses of CD3 + lymphocytes in the infused product. In most cases, there is no need for steroid treatment. Treatment is based on supportive measures that include blood culture collection, antipyretics, and

broad-spectrum antibiotic therapy according to institutional protocol due to the difficulty of differentiating with septic conditions. Grade III and IV cytokine release syndrome may be related to increased transplant-related mortality. Some authors have shown benefit of using tocilizumab in this situation or, if not available, steroids. Routine administration of steroids before post-transplant cyclophosphamide is generally avoided until 24 hours after the last dose of cyclophosphamide since the mechanism of action of cyclophosphamide involves the proliferation of alloreactive lymphocytes [31].

CONDITIONING REGIMEN

Most of the data on conditioning regimen in haploidentical transplantation came from non-myeloablative or reduced-intensity conditioning, especially the protocol with cyclophosphamide, fludarabine, and a low dose of TBI. A study that compared myeloablative regimen with reduced intensity, showed a lower incidence of relapse with myeloablative regimens, but at the expense of increased transplant-related mortality, with no difference in overall survival or disease-free survival [32]. In patients over 60 years of age, a retrospective study demonstrated that there was no difference between myeloablative regimens or reduced-intensity regarding non-relapse mortality, relapse, overall survival, and progression-free survival [33]. A recent CIBMTR study comparing myeloablative and reduced-intensity regimens demonstrated greater disease-free survival with the myeloablative regimen in young patients, but not in patients aged 55 to 70 years [34].

POST-TRANSPLANT RELAPSE

In the case of post haploidentical transplant relapse, it is important to evaluate if the incompatible HLA haplotype is maintained or lost (HLA lost). Donor lymphocyte infusions (initial dose of 1 million CD3 + T cells/kg of recipient weight) are capable of inducing sustained remissions if the incompatible HLA haplotype is maintained. Cases that have lost expression of the incompatible HLA haplotype are candidates for a second haploidentical transplant from a relative who has HLA incompatibility with the original donor [35-37].

RECOMMENDATIONS:

- Haploidentical and unrelated transplants show comparable results in recent studies (2B). Haploidentical transplantation has been associated with superior overall survival compared to cord transplantation (1B). In malignant diseases, particularly in acute myeloid leukemias and lymphomas, haploidentical transplantation presents results comparable to unrelated matched transplants (2B). In patients with severe aplastic anemia previously immunosuppressed, haploidentical transplantation is an alternative (2C) and randomized studies will show the real role of this type of transplantation.

Thus, haploidentical transplantation can be used in patients without a matched related donor readily available or when there is a delay in unrelated donors search (grade of recommendation B; level of evidence 2B)

- Post-transplant cyclophosphamide (50mg/Kg days +3 and +4) is the main strategy for T cell depletion, associated with mycophenolate mofetil and tacrolimus or cyclosporine (grade of recommendation B; level of evidence 2B)

- The main factor in the donor choice is the presence of donor antibodies (DSA), with preference to the donor for whom the patient does not have antibodies. Besides, young donors (siblings and children) are preferable (grade of recommendation B, level of evidence 2C)

- Bone marrow and peripheral blood are possible graft sources. The choice should be based on the institution's expertise and preferences (grade of recommendation B; level of evidence 2B)

- Cytokine release syndrome in haploidentical transplantation must be treated with supportive measures that include blood culture collection, antipyretics, and broad-spectrum antibiotic therapy according to the institutional protocol (grade of recommendation B; a level of evidence 2B). Grade III and IV cytokine release syndrome can be treated with corticosteroids or tocilizumab (grade of recommendation C; level of evidence 4)

- Non-myeloablative, reduced intensity, and myeloablative conditioning schemes can be used, however, there is a lack of randomized studies comparing the types of conditioning (grade of recommendation B; level of evidence 2C)

- Donor lymphocyte infusions (initial dose of 1 million CD3 + T cells/kg of recipient weight) can be used in relapses after haploidentical transplantation if the incompatible HLA haplotype is maintained. Cases that have lost expression of the incompatible HLA haplotype are candidates for a second haploidentical transplant from a relative who has HLA incompatibility with the original donor (grade of recommendation B; level of evidence 2C).

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THE USE OF COMPREHENSIVE GERIATRIC ASSESSMENT: A TOOL FOR DONOR SELECTION

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Allogeneic hematopoietic stem cell transplantation (allo- HSCT) is an effective therapy for a variety of malignant and nonmalignant diseases. It provides a life-prolonging or potentially curative treatment option for these patients when clinically indicated.

Several factors interfere with the risk for transplantation-related mortality (TRM), including patient age, donor type, and conditioning regimen intensity. Given the high transplant-related morbidity, these treatment strategies were initially restricted to younger patients, but are increasingly used in older adults [1–3]. The advent of reduced intensity and nonmyeloablative preparative regimens, coupled with substantial improvements in supportive care, have resulted in increasing numbers of older adults referred for allogeneic transplant [4,3,5]; indeed, approximately 40% of transplant recipients in the last decades were over 50 years [3]. Yet, the overall survival (OS) in older patients have not yet been fully elucidated regarding who will have the best benefit for such therapy, since not all older patients are referred to transplant evaluation.

In Brazil until the last year, only young patients were allowed to received allogeneic HSCT in the public health system (SUS – Sistema Único de Saude). The new regulation (PORTARIA número 1813 de 22 de Julho de 2020) of HSCT in Brazil make it possible. Now patients aged 75 years old or younger get a HSCT. For instance the choice of patients who will best have benefit with transplant is necessary.

The standard pre-transplant evaluation provides a detailed assessment of the many health-related factors that predict clinical outcomes; however, older adults are predisposed to a unique set of medical and social characteristics that may not be prevalent in young individuals, but may impact outcomes in elderly patients. Changes in cognitive function, hearing problems, falls, urinary incontinence are rare in young transplant patients, but much more frequent in older adults. The age alone is not the best predictor of HSCTrelated toxicity, while the comorbidities and functional status of the older patients are likely better predictors of toxicity than the chronologic age

The use of comprehensive geriatric assessment (CGA) in older adults who are candidates to hematopoietic stem cell transplantation HSCT) may improve the detection of potential risks in pre-transplant assessment in addition to the traditionally used comorbidity scores, such as Hematopoietic stem cell comorbidity index (HCT-CI), enabling the detection of vulnerabilities commonly found in this population.

The CGA can also, when recognizing vulnerabilities, intervene for patient's clinical improvement before, during and after transplant.

The standard domains commonly assessed by the CGA are: functionality, mental health, cognition, nutrition, polypharmacy, comorbidities and social support (Table 1).

CGA AND HSCT

Muffly *et al*. (6) reported a high prevalence of vulnerabilities through CGA among older adults' recipients of allo- HSCT. They showed that deficiencies were present in 40% according to the assessment of the IADL (Instrumental activities of daily living). Self-reported physical and mental functions were significantly worse than expected for each related age group; 58% were considered pre-frail and 25% frail. Lin et al also found changes in ADL (activities of daily living) and IADL (Instrumental activities of daily living) in almost half of the patients, of which 81% had more than one ADL / IADL impairment and deficit and one third had cognitive changes [8].

Cognition impairments were found in 5 to 47% of patients and can be seen as early as 6 months after myeloablative allo- HSCT and up to 3 years in reduced intensity regimes. In autologous HCT 19–26%

of adults (age ≥ 18) had cognitive impairment compared with 9–20% of healthy controls. The recovery and persistence of neurocognitive dysfunction is highly variable after transplantation and can impact the quality of life of these patients [7]

The presence of Nutritional Risk is another important domain. It was found in 36% to 76% of transplanted patients [9]. Around 58% aged ≥50 have significant weight loss; 15% of patients with hypoalbuminemia. [10] It is important to identify the nutritional risk early, as they can benefit from referral to a nutritionist before HCT being in a better condition for transplantation

Physical functionality has been the most well-established domain of CGA as a predictor of survival and treatment toxicities in allo- HSCT. In a multicenter study without restricting the age of adult patients who were candidates for HSCT, the presence of better physical functionality was related to better survival and unrelated mortality [11]. Recently Olin *et al* [12] showed that in older allo- HSCT recipients, cognitive impairment is associated with worse survival (HR 1.94; P = .01) and increased mortality (HR: 2.36; P = .01); being a new risk factor to be considered in older adults candidates for HCT.

One of the first studies in prognostication was carried out by Muffly *et al* [10] who prospectively evaluated, in a single institution, the prognostic role of CGA in 203 patients who received an allogeneic transplant, The patients were aged 50-73 years (average of 58 years). In the multivariate analysis, some factors associated with worsening overall survival were identified: the IADL score, the slow gait speed, high HCT-CI scores and impaired mental health, evaluated by SF-36 (Short Form) questionnaire. [36], The limitations in IADL were the greatest predictor for worsening of overal survival (OS) (HR of 2.28; p <0.001). The impact was even greater in patients over 60 years of age (HR 3.25; p <0.001). In this study, IADL with HCT-CI were also combined in a single 3-point model: an HCT-CI score greater than or equal to 3 or IADL with a score <14 would lead to a combined score of 1. Both abnormalities would point a score of 2. Patients with a score of 0 (without scoring HCT-CI and IADL score) have a OS of 62%, and those with a score of 1 (one of the two scores) and 2 (the two scores) have a OS of 44 and 13% respectively. None of the patients aged 60 years or over with the combined score of 2 survived more than 2 years.

More recently, Polverelli *et al* [13] evaluated the feasibility and efficacy of a multidimensional geriatric evaluation, used by the Fondazione Italiana Linfomi (FIL), in a cohort of 228 patients over 60 years old who underwent allo- HSCT in Italy and France from 2008 to 2018. A total of 228 patients were evaluated. The score consisted of 4 domains: 1- CIRS-G, (geriatric specific comorbidity score); 2- ADL; 3-IADL and 4- age over 80 years. The patients were then classified as robust, frail and vulnerable. The FIL score was considered a predictor of survival: patients in the vulnerable and frail group had excess mortality unrelated to relapse.

The importance of CGA in the bone marrow transplant scenario is being increasingly analyzed and recent studies reinforce its importance in the prognosis and intervention to improve the health condition of patients before the transplant and even in the post-transplant period (8,10,14-18). The CGA tools studied in bone marrow transplantation are summarized in Table 1.

SCREENING TOOLS X CGA

The CGA is considered a very complete tool but it takes some time to complete it and requires a geriatrician to analyzed it. For this reason Homes et al tried to evaluate other two screening tools compared to CGA: The Elderly Vulnerability Survey (VES-13) and the G8 screening tool, for abnormal CGA or frailty criteria. It was analyzed Fifty patients who were candidates for allo-HST aged 60 years or older were included. The CGA variables included: medical history, physical, functionality and social health. Frailty was defined as three or more abnormalities in the criterion of physical strength, gait speed, weight loss, tiredness and activity level. Thirty-three patients (66%) with a mean age of 65.4 years had abnormal CGA and 11 patients (22%) were considered frail. The G8 screening tool showed greater sensitivity in detecting abnormality in the CGA (69.7%), and VES-13 had a higher specificity (100%). Both tools had a similar discriminatory capacity. The authors concluded that elderly patients who are candidates for HCT had a significant number of deficits in the CGA domains, and a high prevalence of frailty and the existing screening tools cannot be able to replace the complete performance of CGA.

A new scale developed especially for hematological patients by the Spanish group, the GHA (Geriatric Hematologic assessment) [20] has managed to discern groups of toxicity and is also sensitive to clinical changes in the patients' health status [21]. GHA has 30 items divided into 8 categories that include CGA to categorize patients into healthy, or vulnerable to standard treatments based on clinical, functionality and mental status. It takes about 11 minutes to do and does not

need to be applied by a doctor. Unfortunately, we don't have still data in the use of HSCT scenario.

In October 2020 during de the Annual Brazilian Society of Bone Marrow transplant congress (SBTMO) a consensus meeting rouse this discussion on the agenda since the increased number of older adults transplanted coupled with the new regulation (Portaria No 1813) is a reality.

The application of CGA before HSCT has become practically mandatory for patients over 60 years old, some European groups have already applied it over 50 or 55 years old. We believe that the most important is the individualization of treatment, and that in fact the age group is not the only criterion in the eligibility for HSCT nor in the choice of the type of conditioning. For this reason, we have added this new chapter to the 2020 consensus of SBTMO in an unprecedented way. The committee also propose a development a study group in the field of HSCT in older adults with the aim in improving outcomes and quality of life of these patients.

Due the lack of robust data in witch are the best CGA tools and how to better select patients for transplants; our suggestion, based on our experience and literature [10],[19], is to use the routine recommended for the evaluation of older adults with cancer (as suggested in table 1) At a minimum, the tools should cover physical functionality to complement the comorbidity scores: For example: the use of IADL together with HCT-CI has already been shown to be a predictor of overall survival [10]. The use of screening tools is open for validations in the HSCT. Some trials are underway as the BMT CTN Protoco l1704 CHARM and can, in the future, bring more information.

Patients with no Will in get a transplant; Cognitive disability, Falls and postural instability, Immobility, Family / social support failure and high HCT-CI score are non-candidates for HSCT and alternatives treatment should be offered.

Members of committee: Dra Morgani Rodrigues, Dr Nelson Hamesrclak, Dra Polianna Mara Rodrigues de Souza, Dra Natália Costa and Dr Fernando Barroso.

TABLE 1 - CGA Domains and CGA domains in HCT. Adaptad from R. Jayani, *et al*. (19)

CGA Domains	CGA – Tools in HCT	Others impairments/tools
Comorbidity Number Type Gravidity Risk of worsening during Cancer treatment	HCT-CI (Hematopoietic stem cell transplant comorbidity index.)	Urinary, vision, hearing impairments; Diastolic dysfunction; Osteoporosis; Previous renal impairment
Physical Function ADL IADL Status performance Falls Gait speed	IADL Timed up and Go test Gait speed Number of falls Grip strength	Arthritis Exercises balance
Cognition -decision-making ability - Dementia - Depression - delirium	Mini-mental test MOOCA Orientation- memory- concentration tests	Previous History of mental confusion Loss of memory and duration Information retation
Psychologic Depression Anxiety Distress	GDS (Geriatric Depression Scale) Mental healthy inventory	Sleep disorders Motivationto get a Transplant Resources for dealing with adversity Expectations in life
Social Support Emotional support Financial support Assistance for ADL	MOS (medical outcomes survey) Social support survey (ISSS)	Presence of caregiver Use of alcohol Presence of stairs at home Person preparing food at home
Nutritional status Unintentional loss of weight Low BMI Access to food	Loss of weigth BMI Albumin	Last dentist evaluation Use of dentures Food supplements Effects of previous therapies on nutrition and weight gain
Polipharmacy	More than 5 medication	over the counter medication Previously side effects

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HSCT FOR INHERITED BONE MARROW FAILURE SYNDROMES

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ABSTRACT

The inherited bone marrow failure syndromes (IBMFS) are a heterogeneous group of genetic disorders characterized by the inadequate production of one or more hematopoietic lineages, leading to cytopenias' development. Allogeneic hematopoietic stem cell transplantation (HSCT) offers the potential to cure patients with an IBMFS. However, the procedure corrects only the hematological manifestations of the disease, and long-term follow-up should be provided for all patients. Recently a consensus document was established on behalf of the Brazilian Society of Bone Marrow Transplantation (SBTMO) to discuss HSCT in the setting of IBMFS. Recommendations from this expert panel are presented in this report.

Keywords: Anemia, Diamond-Blackfan, Fanconi Anemia, Shwachman, Telomere Diamond Syndrome, Bone Marrow Transplantation and Hematopoietic Stem Cells

INTRODUCTION

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 [1,2]. Distinct biological mechanisms underly the pathophysiology in IBMFS, such as repair pathways in Fanconi anemia (FA), telomere maintenance in dyskeratosis congenita (DKC), and ribossomopathy in Shwachman Diamond syndrome (SDS) and Diamond Blackfan anemia (DBA) [3]. 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 [4]. Although the diagnosis usually occurs in childhood, adults with a history suggestive of a hereditary bone marrow failure syndrome should be investigated [2]. Currently, hematopoietic stem cell transplantation (HSCT) is the only curative option for hematological complications related to IBMFS [1,2]. 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 [5].

GENERAL RECOMMENDATIONS

Donor selection: All siblings should be tested for IBMFS before being considered as potential donors for HSCT [6]

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, HSCT complications, and mortality [7]. We recommend testing DP locus as incompatibilities in DPB1 are associated with an increased risk of GVHD and transplant-related mortality [8].

Cell source: Bone marrow is the preferred source of stem cells. The use of cord blood is recommended only when matched unaffected siblings are available, and outcomes are excellent [9,10]. Unrelated umbilical cord blood transplantation is usually associate with high rejection and GVHD rates and should be performed with caution in this group of patients [9,11].

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 [6,12,13].

Conditioning:

Patient in aplasia with an identical related donor (14)
• 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 (6,13,15)
• 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 or 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 available and a confirmed transplant schedule [12].

Patients in the aplastic phase or 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 should be performed only in centers with experience in this type of patient [16].

TELOMERE BIOLOGY DISEASE

Recommendation:
The indication for transplant includes patients in aplastic phase, myelodysplasia, or acute leukemia. In the ideal scenario, HSCT should be performed before transfusions, serious infections, or clonal evolution [13]. The prototype of telomeric biology disease (TBD) is DKC; however, we recommend that transplant also be performed in patients with severe aplasia and very short telomeres (<1%), even in the absence of classic symptoms of DKC.

Conditioning:
Patients with matched related or unrelated donors [13,17]

• 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).

BLACKFAN-DIAMOND ANEMIA

Recommendation [13,18]:
• 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 (19)

• 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 [19,20]. The dose of busulfan should be myeloablative and based on the patient's weight and preferrable with pharmacokinetics.

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

Adaptado de (21)

SHWACHMAN-DIAMOND SYNDROME

Recommendation [13,22]:
• Progressive cytopenias or pancytopenia.
• Dependence on blood transfusions.
• Progression to MDS / LMA.

Conditioning:
Patients with matched related or unrelated donors [13,22]
• 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:
The best results are obtained in patients receiving a reduced-intensity conditioning regimen using a matched related or unrelated donor [13,22]

Congenital Amegakaryocytic Thrombocytopenic Purpura

Recommendation [23,24]
• Severe thrombocytopenia and transfusion-dependent patients.
• Pancytopenia or evolution to MDS / AML.

Conditioning:
Patients with matched related or unrelated donors [24,25]:
• 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.

CONCLUSION

• HSCT is currently the only curative option for the hematological complications related to the different IBMFS [1,10,26]

• All family donors should be screened before considered as 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 with the aim of preventing or detecting early changes resulting not only from HSCT but also from the underlying genetic disorder [5]

• Particular attention should be paid to the appearance of hematological and non-hematological malignancies [4,5]

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HSCT FOR HEMOGLOBINOPATHIES

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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. (Lobo et al., 2018) 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 sickle cell disease, 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. In thalassemia, the main complications are due iron overload secondary to chronic blood transfusion. In sickle cell disease, the main complications arise from recurrent vaso-occlusive crises. 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. (Lobo et al., 2018)

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 (Lucarelli et al., 1998) and basically involves the quality of iron chelation and its consequences (Table I).

TABLE I - 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. (Lucarelli et al., 1998)

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). (Lucarelli et al., 1998) 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) (Sodani et al., 2004). With this new regimen, overall survival (OS) was 87% and thalassemia-free survival (TFS) was 82% in a group of 73 patients. (Gaziev et al., 2016) In patients over 16 years, this same regimen with pre-HSCT immunosuppression and reduced BuCY has been used. (Lucarelli et al., 2012)

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. (Locatelli et al., 2013)

Some groups have associated Thiotepa with classic BuCY to reduce the rejection rate, especially in children under the age of 4 years (Lucarelli et al., 2012). A recent study compared data on BuCYATG versus BuCYThio and found no differences even in children under 4 years. (Faulkner et al., 2017)

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. (La Nasa et al., 2005) It is important to reinforce that, for hemoglobinopathies, typing should include HLA DPB1, considering that incompatibilities in this locus are associated with inferior outcome. (Fleischhauer et al., 2006) (Ramprakash et al., 2017).

Data with unrelated umbilical cord blood, although restricted, resulted in high graft failure rates and, consequently, reduction in overall survival. (Ruggeri et al., 2011) (Shah et al., 2015). 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. (Foell et al., 2017) With overall survival of 100%, the data are encouraging, despite slow immune recovery and frequent viral infections. (Oevermann et al., 2019)

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. (Bolaños-Meade et al., 2019). 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. (Stenger et al., 2019). 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 (Saraf & Rondelli, 2019).

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. (Gluckman E. et al., 2017) 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. (Stenger et al., 2019)Table 2 shows the main indications for HSCT for patients with sickle cell disease who are using hydroxyurea and/or 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 sickle cell disease (Table 3). (King et al., 2019) (Allen et al., 2018)

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. (Angelucci et al., 2014) Studies published using BuCy have demonstrated an OS in the pediatric population of 95 to 97%, and EFS of 85%. (Walters et al., 1996) (Panepinto et al., 2007) Bernaudin et al., 2020) 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. (Bernaudin et al., 2020) Another recommended scheme is the use of fludarabine and busulfan, with results similar to those of BuCy. (Krishnamurti, L et al., 2019) There is a clear relationship between age at the moment of HSCT and the result obtained, which is superior in pediatric patients. (Cappelli et al., 2019) 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. (Lukusa et al., 2009) The use of a less toxic myeloablative regimen with fludarabine (Flu), busulfan and ATG showed promising results with 95% EFS. (Bhatia et al., 2014)

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. (Iannone et al., 2003) In adults, conditioning containing alemtuzumab associated with low radiation dose (TBI 300 cGy) and sirolimus as prophylaxis for GVHD showed promising results. (Hsieh et al., 2014) 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. (Locatelli et al., 2013) 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. (Gluckman et al., 2020) The HSCT with haploidentical donors is an important option but with few cases published so far. (Foell 2018, de la Fuente 2019 , Oevermann 2019) Haploidentical transplants should be performed only in the context of clinical trials at this time. (Foell et al., 2017) (Oevermann et al., 2019) (Patel et al., 2020)

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 (Shas et al., 2015), while in patients with sickle cell disease, this rate varies between 20-50%. (Yazdanbakhsh et al., 2012) 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. (Allen et al., 2018) (Chou et al., 2020)

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. (De Santis et al., 2020)

CHIMERIS 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. (Bernaudin et al., 2020) It is estimated that at least stable 25% donor mixed chimera is needed to prevent clinical manifestations of sickle cell disease. (Abraham et al., 2017) Chimerism analysis should ideally be performed in specific cell populations (erythrocyte, myeloid and T cells) and not just in whole peripheral blood. (Abraham et al., 2017) 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. (Hoffbrand et al., 2012) (Navneet S. Majhail et al., 2010) (Kontoghiorghes, 2020) 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 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. (Dallas et al., 2013) (Majhail et al., 2012) (Mishkin et al., 2020) (Bhatia, 2011) 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

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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HSCT FOR MONOCLONAL GAMMOPATHIES: MULTIPLE MYELOMA AND AMYLOIDOSIS

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MULTIPLE MYELOMA

1.INTRODUCTION

Multiple myeloma (MM) is part of a spectrum of pathological conditions known as monoclonal gammopathies. In recent years, significant progress has been made in treating this disease, with the approval of new agents and new combinations for relapsed and newly diagnosed patients. The options must be individualized according to the patient's condition. Autologous Stem Cell Transplantation (ASCT) upfront is the standard of care for patients with good clinical conditions, and usually under the age of 75. In Brazil and three other Latin American countries, the median age for patients eligible for ASCT was 54.7 years, and the procedure is being effectively performed in 58.6% of the patients for whom they were planned at start treatment. [1]

2. INITIAL TREATMENT OF PATIENTS ELIGIBLE FOR ASCT

The combination of bortezomib and dexamethasone and a third drug such as cyclophosphamide, thalidomide, or lenalidomide is the primary basis in pre-ASCT induction therapy. The pre - ASCT induction is performed for a period of 4 to 6 cycles. The pre-ASCT combinations based on bortezomib comparing with schemes without bortezomib were evaluated in a meta-analysis. Post-transplant complete remission (CR) rate, time to progression (TTP), and progression-free survival (PFS) were higher in bortezomib-based induction, with a tendency to improve overall survival (OS). [2]

The combination of bortezomib, thalidomide, and dexamethasone (VTD) was compared to bortezomib, cyclophosphamide, and dexamethasone (VCD) in a randomized study from the Intergroupe Francophone du Myélome (IFM). After four cycles, in an intention-to-treat analysis, 66.3% of patients in the VTD arm achieved at least a very good partial response (VGPR) vs. 56.2% in the VCD arm (P = 0.05). The overall response rate was significantly higher in the VTD arm than in the VCD arm (92.3% vs. 83.4%, P = 0.01). [3]

Thalidomide was replaced by lenalidomide in the bortezomib, lenalidomide and dexamethasone (VRD) regimen, with higher response rates and less neuropathy.

The Spanish Group PETHEMA showed excellent results with VRD in a different dose and number of cycles than those applied by the French group. VRD was used in 458 patients at induction (6 cycles) and post-ASCT consolidation (2 cycles). The responses deepened during the treatment, reaching 70.4% of VGPR or better after the sixth induction cycle. After induction, the CR rate of 33.4% was similar in the 92 patients with high-risk cytogenetics (34.8%), also deepened after ASCT and consolidation (44.1% and 50.2%, respectively). Rates of minimal residual disease (MRD) also increased from induction (28.8%) to transplantation (42.1%) and to consolidation (45.2%). [4]

Combinations of four drugs, including anti-CD38 monoclonal antibodies, can further improve results. The CASSIOPEIA phase 3 study was conducted in patients eligible for ASCT with newly diagnosed MM. Patients were randomized to receive four cycles of

pre-transplantation induction and two cycles of post-transplantation consolidation of VTd alone or in combination with daratumumab (Dara-VTd). The Dara-VTD arm increased PFS and MRD response rates compared to VTD alone (34.6% in the VTD-daratumumab vs. arm. 23.1% in the VTD arm (p, .0001). [5]

3. WHEN IS THE BEST TIME TO PERFORM THE TRANSPLANT?

To evaluate the benefits of ASCT in first line compared to new drugs combinations, the EMN02 / HO95 MM Trial compare four cycles of bortezomib-melphalan-prednisone (VMP) versus melphalan 200 mg / m2 (HDM) followed by a single or double ASCT. In intention to treat analysis, the median PFS was 41.9 months in the VMP arm and 56.7 months in the HDM arm (HR = 0 · 73, 0.62-0.85; p = 0.0001). [6]

Another study, conducted by the IFM, evaluated lenalidomide, bortezomib, and dexamethasone (RVD) in 700 patients up to 65 years old who were randomized to receive induction therapy with three cycles of RVD and then consolidation therapy with five additional cycles (350 patients) or high doses of melphalan and ASCT followed by two other cycles of RVD (350 patients). ASCT arm patients obtain a higher CR rate, PFS (50 months versus 36 months) and MRD negative rate compared to the group without transplant [7].

4. HIGH DOSE CHEMOTHERAPY REGIMENS

The vast majority of high-dose chemotherapy regimens used in MM are based on high doses of melphalan (140 to 200 mg / m2). Combinations, including other alkylating agents, have already been used, but none has shown significant advantages than melphalan. The use of oral busulfan and melphalan (BU-MEL) when compared to MEL200, did not offer benefits for OS (77 versus 70 months, P = 0.4) [8]. The association of venous busulfan (9.6mg / kg) and melphalan (140mg / m2) is still a subject of studies [4] and can be used for high-risk patients (9).

5. POST-TRANSPLANT STRATEGIES

Although high doses of melphalan deepen response rates, most patients inevitably relapse. Post-transplant consolidation and maintenance are two strategies that have been used to improve responses and increase the duration of remission; however, there is still much controversy regarding the best strategies.

5.1 CONSOLIDATION / DOUBLE TRANSPLANTATION

The StaMINA Study was designed to assess the role of double ASCT and consolidation post-ASCT. Patients eligible for ASCT were included within 12 months after starting treatment and were randomly assigned to ASCT plus consolidation (arm 1) or double ASCT (arm 2) or a single ASCT (arm 3). All arms included maintenance with lenalidomide until progression. The results demonstrated comparable PFS and OS, suggesting that consolidation with RVD or a second ASCT was not superior to a single ASCT, followed by maintenance with lenalidomide in MM's initial treatment. [10]

The EMN02 / HO95 Study evaluated 1499 MM patients aged ≤ 65 years eligible for ASCT. Of these, 1121 patients underwent VCD induction and then a first randomization (R1) that compared four cycles of VMP (505) versus high doses of melphalan (HDM) and single or double ASCT (n = 706). 877 patients underwent a second randomization (R2) for consolidation therapy with two cycles of VRD (n = 449) versus non-consolidation (n = 428), and all patients received maintenance with lenalidomide at a dose of 10 mg continuously until progression or toxicity in both arms. The primary endpoints were PFS after R1 and R2. The PFS of R1 was favorable to ASCT vs VMP with a median of 56.7 vs 41.9 months respectively, (HR = 0.73; p = 0.0001). PFS after R2 with adjustment for R1 was significantly prolonged in patients randomized to VRD (HR = 0.77; 95% CI = 0.63-0.95; P = 0.014). The benefit of consolidation was seen in patients with low-risk cytogenetics (HR = 0.68; P = 0.03), but not in patients with high-risk cytogenetics (del (17p) and / or t (4; 14) and / or t (14; 16); HR = 1.03; P = 0.91). Another data emerged from this study, was the advantage in PFS and OS in favor of performing a double ASCT [6].

5.2 MAINTENANCE

The IFM 2005-02 study compared lenalidomide versus placebo after ASCT, with 307 patients in each arm. This trial demonstrated a clear advantage in PFS for the lenalidomide group (p <0.001). However, there was no difference regarding OS. The CALGB study, on the other hand, demonstrated an advantage of lenalidomide maintenance in both PFS (p <0.001) and OS (p = 0.03). [11.12].

A meta-analysis confirmed a significant improvement in PFS and OS of lenalidomide mainte-

nance versus placebo or observation. PFS was 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group. The median OS was not achieved in the lenalidomide maintenance group and was 86 months in the placebo or observation group (HR, 0.75; 95% CI, 0.63 to 0.90; P = 0.001), representing a reduction of 25% in the risk of death with maintenance, benefiting all subgroups, except patients with high cytogenetic risk and ISS stage III. [13]

6. ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

The role of allogeneic bone marrow transplantation (BMT) in MM's treatment remains controversial, mainly due to a high transplant-related mortality (TRM). [14] Non-myeloablative (NMA) and reduced intensity (RIC) conditioning brought the prospect of lowering TRM. Although the TRM rate reduction was achieved, there was no increase in the overall survival for patients submitted to the allogeneic BMT RIC due to the increased frequency of relapse. [14]

Several studies have evaluated the strategy of combining an autologous BMT followed by a reduced intensity allogeneic BMT (Tandem auto / RIC alo). However, a meta-analysis demonstrated that despite the high CR rates in the tandem auto / RIC alo, there was no increase in OS compared to the auto-auto tandem BMT. It occurs mainly due to a high mortality rate not related to relapse, primarily attributed to acute and chronic graft versus host disease. [15]

RECOMMENDATIONS:

• First-line treatment for patients under the age of 75, with good PS and preserved organic functions. (Grade A of recommendation; level Ib of evidence)

• Recommended conditioning: Melphalan 200mg / m2 (Grade A of recommendation; level Ib of evidence)

• Best moment of ASCT: upfront, after 4 to 6 cycles of induction with a combination of 3/4 drugs, including new agents, bortezomib, thalidomide, lenalidomide, daratumumab – VTD, VRD, Dara-VTD (Grade A of recommendation; level Ib of evidence)

• Double transplantation as an initial strategy: Not recommended (Grade A recommendation; level Ia of evidence). Consider for patients with high-risk cytogenetic.

• Mobilization of PBSC: Patients responding to induction treatment should be mobilized with GCSF alone. Collect a minimum cell dose of 3 x 106 CD34 cells / kg. It is desirable to store cells for an eventual second ASCT; in this case, collect at least 6 x106 CD34 cells / kg. Plerixafor is recommended for patients with GCSF mobilization failure (Grade C of recommendation; level IV of evidence)

• Patients with renal failure: ASCT can be recommended, with a reduced dose in conditioning. Use melphalan 100 to 140mg / m2 (Grade C of recommendation; level IV of evidence).

• Consolidation strategies after ASCT: Two to four consolidation cycles, repeating the initial treatment (VTD or VRD or Dara-VTD), particularly for patients with no complete response after ASCT. (Grade B of recommendation; level IIb of evidence)

• Maintenance strategies after ASCT: Lenalidomide until progression. (Grade A of recommendation; Ib level of evidence).

• Myeloablative allogeneic BMT or RIC can be considered for younger patients with good PS and adequate organic function who present high-risk MM (primarily refractory or less than a year of response after ASCT or with deletion of chromosome 17p). The procedure should preferably perform at a Center of Excellence. (Grade B of recommendation; level IIb of evidence).

• RIC after auto-ASCT did not show favorable results in most clinical studies and is not recommended (Grade A of recommendation; level Ib of evidence).

Clinical significance of the measurable residual disease (MRD) in multiple myeloma patients

Minimal / measurable residual disease (MRD) assessment has been considered the most important independent prognostic factor in multiple myeloma (MM), used to assess drug efficacy and in selecting further therapeutic options in MM[16-20]. Depth response based MRD emerged as a criterion for better results in MM [21-23]. Patients who remain with detectable MRD after front-line therapy have inferior outcomes [17,24-30] whereas those who achieve undetectable MRD in bone marrow (BM) have significantly improve survival [31-33]. In the context of autologous stem cell transplantation (ASCT), MRD status also provides a powerful prognostic information in MM [26-27,34], including stratification of risk relapse after HDT/ASCT (day +100)[16].

However, MM often recurs due to residual MM cells, drug resistance and/or persistence of resistant dor-

mant subclones [32,35]. Therefore, more sensitive and standardized methods, such as next-generation sequencing (NGS) and next-generation flow cytometry (NGF) [16,33,36-37] are needed to fulfil the MRD criteria response accordingly with the International Myeloma Working Group (IMWG) [33,38] (Figure 1). Moreover, MM patients present high frequency of extramedullary relapses, not detected by BM-MRD assessment. Thus, sensitive imaging techniques such as PET-CT have become relevant in assessing low levels of disease outside BM [36-37]. Therefore, both BM-MRD and imaging techniques must be complementary to assess the response to MM treatment. In conclusion, considering the patchy pattern of BM infiltration observed in MM that leads to a degree of ambiguity regarding MRD negative results, it would be safer to make clinical decisions based on MRD positivity rather than on MRD negativity [37].

Time-points of BM-MRD assessment: MRD kinetics are more informative than single time point assessments and may be useful to address specific clinical decisions, such as early versus delayed ASCT for complete response (CR) patients after induction [33,37]. It allows the identification of chemosensitive (MRD-negative cases at 2 time points), intermediate, and chemoresistant patients (MRD-positive patients at 2 time points) [37].

Recommendations (not consensual): 1) at time of most optimal response (e.g. immunofixation-negative CR) ; 2) before ASCT ; 3) at D+100 post-ACST; 4) after post-transplant consolidation therapy; 5) before the start of maintenance therapy and in subsequent time points (e.g. every 6 months), to assess the maintenance of MRD negativity achieved [16,20,33].

Methods for BM-MRD assessment: flow cytometry methods do not require patient-specific diagnostic phenotypic profiles [37] as a reference, but molecular methods are based on the patient's initial specific sequences of IgH-VJ/DJ and IgK DNA regions [39]. NGF or NGS have similar sensitivity (10-5 to 10-6 neoplastic cells), high applicability, specificity and reproducibility, but their performance depends on strict rigor in the execution of the methodology [20]. NGS is a labor intensive and expensive technology, and it is yet not commonly available for clinical practice [16]

Recommendations for ensuring high quality samples for MRD detection: 1) first pull of BM aspirates [19], 2) maximum volume of 2-5mL to avoid hemodilution[15,25-26]. In clinical practice, BM hemodilution needs to be recognized and reported, due to its impact on the distribution of cell populations including cPC.

Note: the true prognostic value of the detection of MM cells in the circulation of MM patients who achieve a CR should be confirmed in prospective studies [33].

Method for disease monitoring in serum: Mass spectrometry is able to identify the M protein molecular mass with high precision and accuracy, allowing single clone tracking with very high sensitivity, slightly higher than NGF. It is a promising method for measuring disease activity, but it needs prospective studies to validate its applicability in clinical trials of MM [42,43].

MRD assessment reports: to allow a correct interpretation of the MRD results, the MRD report must provide clear information about the MRD result and the MRD technique used, including the limits of detection and quantification achieved by the specific assay used, which are parameters of the sensitivity of the method [44,45].

Status of MRD in MM and clinical practice currently: The association of MRD negativity and outcome improvement has been evidenced in both the newly diagnosed and relapsed/refractory MM patients and thus is currently considered a prognostic biomarker. However, at this time, MRD has been established as a surrogate endpoint only in clinical trials. A surrogate endpoint does not directly measure the clinical benefit of primary interest but rather is expected to predict the clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. Therefore, the use of MRD to make treatment decisions outside of the context of a clinical trial is not recommended [46].

LIGHT CHAIN (AL) AMYLOIDOSIS

High dose melphalan followed by rescue with autologous hematopoietic stem cells (ASCT) was introduced as a promising treatment option for light chain (AL) amyloidosis patients, but with a high mortality rate. To reduce mortality, the Mayo Clinic Group suggest a risk stratification for ASCT that is widely used and includes the following criteria: Age ≤ 70 years, Troponin t <0.06 ng / dl, NT pro-BNP <5000 ng / L, Creatinine Clearance ≥ 30 mL / min, Performance Status (ECOG) ≤ 2, Functional Cardiac Status (New York Heart Association) classes I or II, maximum of two organic impairments (liver, kidney, heart or autonomic neurological) , absence of significant pleural effusion and lack of oxygen support. Only patients who meet all these criteria are considered potentially eligible for ASCT. [47]

Although any recommendation in AL amyloidosis is controversial by the rarity and heterogeneity of the disease [48], for which randomized studies are lacking, the Andromeda Phase 3 study, for patients with no intention of transplantation, points out the Dara-CyBorD as a potential therapeutic regimen of choice for this group of patients. In this Study, 388 patients were randomized to receive CYBorD (cyclophosphamide, bortezomib and dexamethasone) or Daratumumab- CyBorD. The CR haematological rate, Major Organ Deterioration - PFS and the organ response was in favor to Dara – CyBorD. The safety profile was consistent with that previously observed for Dara SC and CyBorD. [49]

GROUP RECOMMENDATIONS:

• ASCT is the first-line treatment for patients with low-risk light chain (AL) amyloidosis. Use risk stratification criteria for this purpose (Grade B of recommendation; level IIa of evidence)

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HSCT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a hematological neoplasia characterized by the proliferation, accumulation and infiltration of immature lymphoid cells in the bone marrow, blood and extramedullary sites, associated with several molecular rearrangements, cytogenetic alterations, conferring clinical and biological diversity and the existence of groups of patients with different prognosis. In childhood, ALL represents 80% of acute leukemias, with a prospect of cure around 80 to 90%, with intensive chemotherapy treatment. In adults, it is responsible for 20% of acute leukemias, with a survival rate of around 20-30% in 5 years1,2. Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for adult patients and children with ALL, being an effective method in preventing relapses. Depending on the risk factors for recurrence, the prognosis must be analyzed in two moments: at diagnosis and after induction3

II. ALO SCT RECOMMENDATIONS

A) Indication of ALO TCTH in First Remission:

A1) PATIENTS WITH RISK FACTORS RELATED TO THE DIAGNOSIS

Risk factors at diagnosis

Age> 40 years

Leukocyte count:> 30x109 / L in B cell ALL and > 100 x 109 T cell ALL (except CD1a +)

Cytogenetic changes:

- Complex karyotype (5 or more chromosomal abnormalities).
- t (9; 22) (q34: q11.2)
- t (4; 11) (q21: q23)
- t (8; 14) (q24.1q32)
- Low hypoploidy (30-39 chromosomes)
- Molecular rearrangements involving KMT2A, BCR / ABL,
- Ph-like ALL;
- intra chromosomal amplification of chromosome 21 (iAMP21)

At the diagnosis, the most important parameters are: age, number of leukocytes, immunophenotyping, cytogenetics and molecular genetics.

In adults, there is a progressive and significant unfavorable change in biological behavior and clinical outcome in patients with ALL compared to children. The large concentration of negative prognostic factors observed in the adult population contributes significantly to this scenario3.

All patients with high cytogenetic risk generally have poor results, even achieving a good response with undetectable MRD at any time during treatment4.

Adult patients with Philadelphia-like ALL, rearrangement of the KMT2A-MLL gene and initial T-cell precursor ALL are also more likely to have persistent MRD and a higher risk of relapse, despite intensive therapy5.

Other LLA-B of high genetic risk, with normal or abnormal cytogenetics and also changes in the number of copies, such as ABL class fusions, IKZF1 deletion, IKZF plus generally have a slower elimination of the disease with prolonged persistence of MRD4.

A.2- PATIENTS WITH RESPONSE RELATED RISK FACTORS:

Risk factors after induction

Induction failure – period of more than 3 to 4 weeks to obtain remission

Presence of MDR >1x10-3 (0,1%) when using pediatric protocols or >1x10-4 (0,01%) after two courses of therapy

3- Some considerations regarding indication of Allo SCT in First Remission in young higher risk patients (20 to 40 y), who had been submitted to pediatric asparaginases containing ALL protocols (table 1)

TABLE 1 - factors to consider for SCT consolidation

Favors consolidation without SCT	Favors Allo SCT as consolidation
Age closer to 20 years	Age closer to 40 years
HLA mismatched donor	HLA donor 10x10
DRM evaluated consistently	No consistent DRM assessment
ECOG 2 e 3	ECOG 0 e 1
History of high toxicity to treatment*	Treatment without significant toxicity
Completed QT cycles without delays*	Treatment with frequent delays
Access to good salvage options	Limited Salvage options
Patient/family prefers to avoid SCT	Patient-family prefers SCT

*in the case patient suffers drug specific toxicities and consequent treatment delays (methotrexate, cytarabine), that hampers correct maintenance and in case of a good donor (HLA id sibling, MUD 10x10), stem cell transplantation can be considered also in this situation.

The use of pediatric-inspired protocols increased the cure rates of young adults with ALL, especially for patients with a higher molecular response. Allogeneic SCT is an option for consolidating high-risk patients in first remission, however the procedure-related mortality rate and overall survival remain a barrier.[7] Factors such as comorbidities[8], access to adequate treatment, performance status, and type of donor help to reflect on this decision.

In an age-adjusted retrospective study that compared allogeneic SCT with pediatric-inspired chemotherapy and associated transplantation with lower overall survival (45% vs 73%, p <.0001) and higher unrelated mortality (37% vs 6 %, p <.0001) in adolescent and adult patients up to 40 years old and in first ALL remission[7].
Thus, the risk related to the procedure must be incorporated into the decision when indicating SCT in first complete remission for patients aged 20 to 40 years . Factors such as comorbidities[6], access to adequate treatment, performance status, and type of donor, are necessary to ponder this decision.

B) Allo SCT indication in second remission:

SCT is indicate for ALL patients who achieve a second remission and have an adequate clinical status.

C)Indication of Allo SCT in special situations:

c.1) Active disease: transplant usually not indicated outside Clinical trial.

c.2) When the MRD reached is $> 10^{-3}$ (0,1%)immediately after first line treatment, one should consider the risk/benefit of further treatment to deepen pre-SCT response. Ideally MRD < 0,1% pre SCT should be persuit, using 1 or 2 cycles of therapeutics of high efficacy and low toxicity strategies like bi-specific Monoclonal Antibodies (Blinatumumab). In the context of impossibility of accessing or using these drugs, and an exclusively high toxicity (FLAG IDA- MEC) conventional chemotherapy is available, consider (ponder risk vs benefit) following direct to ALLO SCT, with myeloab- lative conditionings.

c.3) Patient with a history of CNS infiltration: it is necessary to be without blasts inclear the CNS at the time of the SCT. The prophylactic use of MADIT is contraindicated in case of TBI. If radiation free conditioning is chosen, intrathecal therapy along with conditioning and as a maintenance after SCT is controversial.9

c.4) Adult patients with Ph1 + ALL, rearrangement of the KMT2A-MLL gene and early T cell precursor (ALL-ETP) are immediately eligible for allo SCT 10

III) Type of donor:
Without No restrictions regarding the type of donor, whether it is completely compatible related or unrelated or , haploidentical or unrelated. Use the best available.

IV) Conditioning
IV.1) Suggested myeloablative conditionings

a) TBI-based: Recommended primarily for patients between 03 and 40 years

b) Other options: BuFlu, BuMel, BuCy

IV.2) Reduced intensity conditioning: recommended in patients at higher risk of SCT- related mortality, speciallyespecially after age >40 -45yearsras-old.

V) Stem Cell Source 63,64:

PBSC, BMSC and UCBSC are all good source of graft options. The decision process has several variables to be considered: disease status and relapse risk, center experience, local policies, pandemia, donor availbility: The SBTMO 2020 ALL Consensum Comitte has create a table with factors that can discreetly suggest one source or another(regarding BM and PSC) (table 2) See also special considerations of stem cell source in the Haplo Transplant setting session.

TABLE 2 - choice of stem cell source

Favors BMSC source	Favours PBSC Source
ALL in First Complete Remission and Low risk of relapse	Higher Relapse Risk ALL. Second Remission. No complete remission special situations.
No known Graft Failure Factors present	Known Graft Failure Factors present
Local policies- Center Experience-Logistic Situations	Local Policies- Center Experience-Logistic Situations
Special Infection Risk Situation absent (COVID 19, others)	Special Infection Risk Situation present (COVID 19, others)

VI. SPECIAL PARTICULARITIES:

VI. Positive Ph ALL (Ph+ ALL)

VI.1- Positive Ph ALL (Ph + ALL): The Philadelphia (Ph) chromosome resulting from the balanced translocation between chromosomes 9 and 22 leads to the fusion of the BCR/ABL gene (p190), responsible for the irregular and exacerbated production of proteins with tyrosine kinase activity that interferes in the cellular proliferation and apoptosis process. It is considered an unfavorable prognostic factor for three decades[2,23].

VI.2 Ph like ALL: A new subtype of ALL identified by the expression of genes that cluster with BCR-ABL1. This new entity is called "Ph-like" and represents 15 to 20% of adolescents and young adults. These patients show unfavorable results and 25.8% disease-free survival in 5 years. This group of patients with "Ph-like" has kinase activation favoring an increase in lymphoblast proliferation. Breaks in the "Ph-like" ALL affect only ABL with genes other than BCR. Some of these fusions are sensitive to tyrosine kinase inhibitors in vitro18

VI.3-Autologous transplantation in Ph ALL

Autologous transplantation should not be indicated in patients with Philadelphia negative ALL and is also contraindicated in patients with Ph + ALL with positive MRD. But retrospective data from the EBMT suggest that this can be a valid option if patients obtain at least 3 log reduction (major molecular response) before transplant. Recent meta-analysis, including the data from EBMT and others, showed no difference in terms of overall survival or relapse free survival even when autologous stem cell transplant was compared to HLA identical sibling transplants.

There are few studies examining the use of autologous transplantation in patients with positive Philadelphia ALL who achieve negative MRD. One study to mention is that of the EBMT Leukemia Study Group published in 2018, which compared 67 patients with Ph + ALL who underwent autologous (auto) transplantation with 255 patients with a related HLA compatible donor (AP) and in 247 with unrelated HLA compatible donor (NAP), carried out from 2007 to 2014. All patients were in complete molecular remission and without data on minimal residual disease. The probability of overall 2-year survival found in autologous myeloablative transplants was similar to that of allogeneic transplants: 70%. The incidence of relapse in 2 years was 47% in autologous transplantation: 28% in allo-related transplantation and 19% in transplantation with unrelated donor, p = 0.0002. The probability of relapse-free survival was similar: 52% (self); 55% (AP) and 60% (NAP), p = 0.69. In this EBMT study, conditioning using TBI showed the best results, regardless of the type of donor.

Although few data are available, in the era of TKIs, autologous transplantation may be an reasonable option for consolidation in those who achieve negative MRD and are not candidates for allogeneic transplantation.[19]

VI.4) Haploidentical transplantation (*)in ALL:
Only about 45% of ALL patients with an indication for transplantation are able to perform the procedure, either due to difficulty in finding a donor or due to early relapse 20.

The probability of a patient finding an HLA compatible donor depends on ethnicity and the frequency of his haplotype. The possibility of performing the transplant depends also on the status of the disease at the time of donor search. Therefore, donor search should be started as early as possible.

Retrospective studies suggest that the results of haploidentical transplants using post-transplant cyclophosphamide have results comparable to those of transplants with unrelated HLA-compatible donors. Two recent studies with a significant number of patients are worth mentioning. The European Bone Marrow Transplantation Society (EBMT) recently published data comparing 136 adult patients with ALL in first complete remission (CR1) who underwent haploidentical transplantation (Haplo-SCT) with 1198 transplanted patients with unrelated donors, 809 of whom are HLA-compatible 10/10 (MUD) and 289 with 9/10 mismatch MMUD)21. The post-transplant cyclophosphamide (PTCy) platform was used in 85% of Haplo-SCT and in 15% ATG was included with PTCy. The results of haploidentical transplant in relation to overall survival, leukemia-free survival, rate of relapse, transplant-related mortality and GVHD, were statistically similar to those of unrelated donors, both HLA 10/10 and 9/1021.

Overall survival (OS) and leukemia-free survival (LFS) in the group undergoing haploidentical transplantation and unrelated stem cell transplantation was 54% + 11% and 49% + 11%, respectively. Emphasizing that the average age of this group was 38.5 years, and all were in CR1. In multivariate analysis age impacted negatively on OS and LFS; b) that there was fewer relapses and, therefore, greater leukemia-free survival in patients who received total body irradiation in myeloablative regimes ($p = 0.006$) and also less relapse in those whose source of progenitor cells was peripheral blood and not bone marrow ($p = 0.044$) . In conclusion, the use of total body irradiation in myeloablative regimens in haploidentical transplants seems to result in better relapse-free survival compared to myeloablative regimens with chemotherapy only. In this study, the type of cell source also did not impact global survival, but it resulted in a higher incidence of acute GVHD grade III-IV ($p = 0.008$).

Another study analyzed European and American data of 1461 adult ALL patients transplanted from 2005 to 2018, with 487 undergoing haploidentical transplantation (Haplo), all using PTCy and 974 to HLA-compatible non-parenting transplants (NAP). In this study, 32% of patients were in CR and 15% had active disease. The patients were compared, in the ratio 1: 2, in relation to sex, conditioning regime, cytogenetic risk. The overall 3-year survival was similar in the 2 groups, both in those undergoing myeloablative regimen (44% -Haplo and 51% NAP) and in the group that received non-myeloablative regimen (43% - Haplo and 42% NAP). The grafting rate was also similar in the 2 groups of transplants: 87-88%. The incidence of acute grade II-IV GVHD in 3 months was similar: 33% in Haplo and 34% in NAP (group with myeloablative conditioning) and 31% Haplo and 30% NAP in the group of reduced intensity. However, patients who underwent haploidentical transplantation were less likely to die from GVHD than those with unrelated donors. In this study, the cell source did not impact the risk of relapse[22].

The use of ATG as prophylaxis of GVHD in unmanipulated haploidentical transplantation seems to have inferior results to the use of post-transplantation cyclophosphamide, with less progression-free survival.[23]

The choice of the best source of progenitor cells in haploidentical transplants is still a controversial topic, several publications show a higher incidence of GVHD[8–10] with the use of peripheral blood progenitor cells, in addition, some works have associated this source with lower incidence of relapse8, while other studies have not seen this association[910]. The preferential use of the peripheral blood source to allow the freezing of cells and ensure the infusion of transplants in the year 2020 during the pandemic, may allow one to bring more information on this subject.

Therefore, haploidentical transplantation using post-transplantation cyclophosphamide can be considered a valid option for adult patients with high-risk ALL without an identical HLA donor, preferably in the initial phase of leukemia.

- GVHD prophylaxis: Recommended use of post-transplant cyclophosphamide- PTCy- over ATG

- Graft: Bone marrow seems to result in better survival after haplo-HCT, although the best source of progenitor cells is still controversial

- Conditioning: TBI in myeloablative regimens seems to result in better relapse-free survival

VII.Post-Transplant follow-up

Recommendation:

Measurable/Minimal Residual Disease- MRD- at D + 30, + 60, +90, +180 and +360

Chimerism at D + 30, +90, +180 and +360

The follow-up of post-BMT chimerism is an important tool in risk assessment for relapse, and is usually performed at D+30, +90, +180 and +360. However, MRD has been shown to be more sensitive and specific for this purpose24, and should be performed in D+30, +60, +90, +180 and +36025. This measure should be maintained every 03 months for another year by clinical decision. It is still questionable whether, in cases where MRD is available, the association of chimerism remains useful.

Patients with CSF involvement pre-BMT are at increased risk of CNS relapse[26]. For them, monitoring with post-transplant serial punctures can be an interesting strategy, especially when performed by flow cytometry, which is capable of increasing the sensitivity of the exam27. However, there is no consensus on the frequency of this analysis or the management if a relapse is detected.

VIII-Post-SCT relapse: use of DLI, Chemotherapy, Immunotherapy and second SCT should be defined on a case-by-case basis

Post-transplant recurrence is always a serious event, and the severity is proportional to the time of recurrence. The earlier the recurrence, the worse the prognosis. The treatment used the longest is chemotherapy followed by infusion of donor lymphocytes, with the possibility of a second transplant[28,29].

More recently, blinatumomab has become an option that can be used to rescue patients with post-transplant recurrence, including reports of its use in conjunction with DLI[30,31] .There are also case reports with the use of inotuzumab, which is particularly effective in extra-medullary disease[32].

Car T Cell therapy is also an alternative in rescuing these patients, with patients surviving for more than five years. Access to this therapy is still quite limited in our country, but there is a significant advance happening with commercial and non-commercial presentations, being an interesting alternative for patients who relapse after BMT[33].

The choice of the best treatment must be made on a case-by-case basis taking into account the time since the transplant and the recurrence, the availability of donor for DLI and a second transplant, the patient's clinical condition and access to other treatments.

SUPPLEMENT: MINIMAL RESIDUAL DISEASE (MRD) IN ACUTE LYMPHOBLASTIC LEUKEMIA

MRD status associated with other relevant prognostic factors for SCT

a. Flow Cytometry

b. PCR

The early achievement of MRD negativity in both pediatric and adult patients with ALL has prognostic impact regardless the presence of conventional risk factors, therapies, methods, time of MRD assessment, cutoff levels and leukemia subtypes[34]. Children and adult Ph1 negative ALL patients with persistent MRD after consolidation therapy are indicated for alloSCT in CR1[35,36,37,38–45]. In patients undergoing non-pediatric inspired regimens (eg.hyperCVAD), MDR ≥10-4 after 1 -3 cycles of chemotherapy is an indication of alloSCT42. In patients with ALL MRD ≥10−3 (0.1%) before alloSCT, treatments to reduce tumor burden should be considered46,47 when possible, but this does not exclude alloSCT. The risk of increased toxicity must also be considered. Levels of 10-3 and 10-4 MRD post-allo SCT were always highly predictive of relapse[37,46,48].

Adult patients with Ph1+ ALL, KMT2A -MLL gene rearrangement, and early T-cell precursor ALL(ETP-ALL) are immediately eligible for alloHSCT[48,42]. Ph like / IKZF1 and IKZF1 plus deletion, iAMP21, will be recommended for transplantation if they do not achieve a complete remission by the end of induction therapy[48,49–51]. Adult Ph1+ ALL patients, who achieved MRD <0.1% within 3 months of treatment, with access to blinatumomab and ponatinib may decline from alloSCT in CR150. AlloSCT has no impact on the outcome in hypodiploid B-ALL in CR1, mainly for patients with MRD ≥ 0.01% at the end of induction[53]. Time points for MRD assessment are < 30 days pre-alloSCT and D+30,+60, +90, + 180 and +360 post-SCT by flow cytometry (MFC) and/or RTqPCR and eventually by NGS54–57. RTqPCR for BCR-ABL1 should be the eligible method for monitoring MRD in Ph1+ALL48,58. MFC is widely available, so laboratories must have complete standardization of pre, post and analytical processes, including the evaluation of not less than 1 million cells per tube, to obtain a reliable MRD detection result[55,57,59–61]. In addition, it should be emphasized that MRD assays should be performed by analysts experienced in this type of evaluation, due to the impact of the results on clinical practice[62].

TABLE 1 - Summary: Allo SCT Recommendations in Adult ALL:

Indication	Recommendation	Degree of recommendation
ALL Ph negative Adult (>40 y)		
Standard risk 1st CR	Standard	A
High risk 1st CR	Standard	A
2 RCC	Standard	D
Refractory	Generally Not Recommended	D
ALL Ph Positive Adult (> 40 y)		
1 CR with previous TKS	Standard	B
2 CR com TKS previous	Standard	B
Refractory	Clinical Option	D
ALL Ph Negative Young Adult (20-40y)		
Basic risk 1st CR (*table 1)	Clinical Option	A
High risk 1st CR (*table 1)	Clinical Option	A
2 RC	Standard	D
Refractory	Generally Not Recommended	D
LLA Ph Positive Young Adult (18-40)		
1st CR with previous TKS (see table 1)	Clinical Option	B
2nd CR with previous TKS	Standard	B
Refractory	Clinical Option	D

Recommendation of Autologous SCT in Adult ALL:

Indication	Recommendation	Degree of Recommendation
LLA Ph negative in 1st RCC	No	A
LLA Ph positive in 1st RCC	Clinical Option	C

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HSCT FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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INTRODUCTION

Chronic Lymphocytic Leukemia (CLL), the most common leukemia in adults, is characterized by a clonal expansion of mature B cells that express CD5. It is probably one of the onco-hematological disease that has advanced the most in recent years[1]. As usual, therapeutic advancement occurs as a result of progressive biological knowledge of the disease. In this regard, in the last decade, we have learned a lot about its pathogenesis, including the identification of recurrent mutations and the clarification of clonal architectures, analysis of transcriptomes and the several stages of the leukemogenic process. These biological characteristics make it possible to classify a CLL into different risk groups and make the therapy more "intelligent"[2]. Rapidly, we evolved from conventional chemotherapy to most effective treatments, such as monoclonal antibodies, especially anti-CD20 of the first and second generations, target drugs that interfere with the signaling pathways of B cell receptors (BTK[3–6] and PI3K inhibitors7) and drugs that inhibit anti-apoptotic protein BCL-2[8,9].

Current treatment strategies include the combination of chemotherapy (chlorambucil, fludarabine and cyclophosphamide, or bendamustine), with anti-CD20 monoclonal antibodies (rituximab or obinutuzumab), BTK inhibitors (ibrutinib and acalabrutinib), the PI3K inhibitor idelalisib, and the anti BCL2 inhibitor, venetoclax. Worldwide, chemoimmunotherapy has progressively lost space for new therapies that show improved response duration and progression-free survival (PFS), in addition to the better profile of adverse events[10]. B-cell receptors inhibitors achieve high response rates but are used as a continuous treatment (until progression or intolerance), while BCL-2 inhibitors strategies induce deeper responses and are usually part of finite therapies.

Despite the progress with a significant improvement in progression-free survival with the new agents, CLL remains an incurable disease in most cases. The disease often relapse relatively early and progressively becomes refractory. Besides, in some cases, Richter's transformation occurs and outcome of this serious complication is usually dismal.

Allogeneic hematopoietic stem cell transplant (allo-HSCT) has been used less and less, but it is still an alternative to be discussed, especially in countries where the availability of new drugs is limited. Previous series have demonstrated encouraging results with a progression-free survival (PFS) of around 40-50% and overall survival (OS) of around 50-60% at 5 years. [11,12]

New alternatives of treatment, such as CAR-T cells, are also being tested for refractory patients after several previous treatment lines, and will be further discussed in this chapter.

WHEN TO PERFORM ALLOGENEIC STEM CELL TRANSPLANT FOR CLL

In 2007, an EBMT consensus of allo-HSCT for the treatment of high-risk CLL patients was proposed[13]. At that time, allo-HSCT became the treatment of choice for this group of patients. However, the treatment of CLL has changed over the last decade due to the development of new and very active agents8,[14,15]. However, there are no randomized clinical trials that compare the outcomes of allo-HSCT with conventional chemoimmunotherapy, or novel non-chemotherapy-containing regimens so far.

In this setting, there has being a great paradigm change on who, and especially when, a patient would

be a suitable candidate to an allo-HSCT. The approval of novel agents has had an impact on the role of allo-HSCT in CLL and, since the approval of ibrutinib, idelalisib, and venetoclax in the United States and Europe, the number of transplants continues to decrease (Figure 1). This trend is likely to continue as other new agents are approved and the existing approved agents are used earlier in the course of the disease 12. The same pattern seems to occur in Brazil, although slower, considering the delay on the approval of the new agents. It is important to note the great heterogeneity of the availability of the new agents in different treatment centers in Brazil, leading to a great variability on the time of transplant indication

FIGURE 1 - Allogeneic hematopoietic stem cell transplant for CLL by year

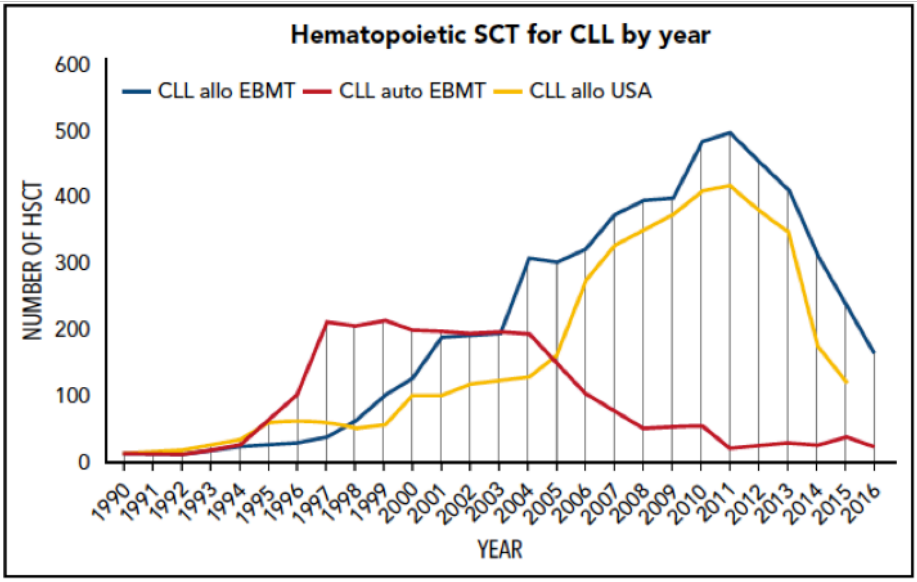


Figure 1. Changing patterns over time of HSCT in CLL in the US and Europe

The Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia of the American Society for Blood and Marrow Transplantation[16] is one of the most comprehensive guidelines on HSCT for CLL. In order to define recommendations regarding the most appropriate time for HSCT for CLL, it is mandatory to describe when in the disease therapy timeline should the HSCT be proposed.

RECOMMENDATIONS

Patients to be considered for allo-HSCT:

A.Standard Risk CLL (patients **without** del[17]p and/or TP53 mutations and/or complex karyotype): when there is lack of response or disease progression after BCR inhibitors or BCL-2 inhibitors.

B.For High Risk CLL (patients with del17p and/or TP53 mutations and/or complex karyotype):

1.Patients that experienced objective response to after BCR inhibitors or BCL-2 inhibitors after 2nd line treatment

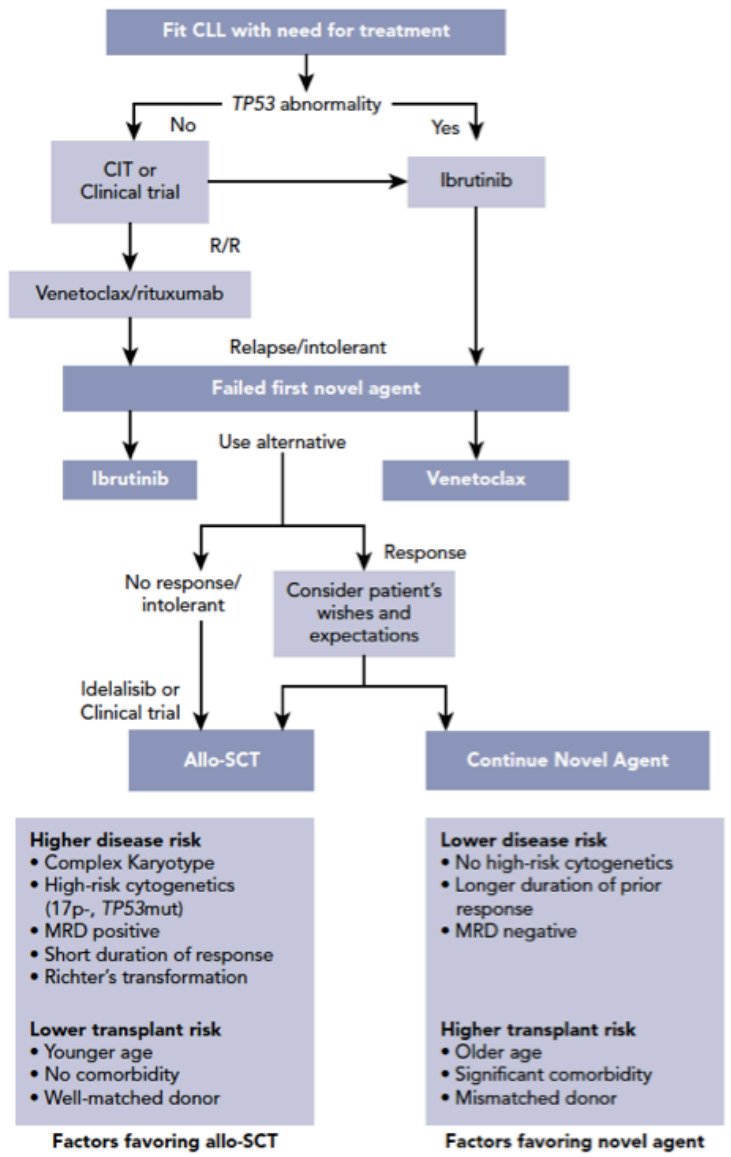
2.Patients with relapsed / refractory disease after treatment with BCR inhibitors or BCL-2 inhibitors after 2nd line treatment

3.Patients experiencing Richter transformation after achieving an objective response to therapy.

The considerations above may depend on the availability of new agents at different Brazilian treatment centers.

In 2018, Dr. John Gribben published recommendations on how and when an allo-HSCT should be performed considering the novel agents including ibrutinib, acalabrutinib, idelalisib, and venetoclax[12]. His approach led to the algorithm shown in Figure 2. Patients that require treatment and do not have TP53 mutation are candidates for chemoimmunotherapy or a clinical trial. Those patients with TP53 mutation are candidates for non-chemotherapy regimens with new agents in front line. Patients who are relapsed or refractory can be treated with BCR inhibitors or venetoclax plus rituximab. Patients who relapse or are intolerant to ibrutinib are candidates for venetoclax and those who have failed venetoclax plus rituximab are candidates for ibrutinib. Patients responding to second novel agents can either proceed to allo-HSCT or continue with the novel agent[17].

FIGURE 2 - Allogeneic hematopoietic stem cell transplant for CLL algorithm



CONDITIONING REGIMEN

There is no randomized trial comparing different conditioning regimens intensity, although myeloablative conditioning (MAC) proved to be toxic for CLL patients with high rates of transplant-related mortality since most of patients are elderly presenting great toxicity to MAC[18,19].

The reduced intensity conditioning (RIC) appears to be a more adequate regimen intensity for the CLL population. With matched sibling donors (MSD) and matched unrelated donors (MUD) the non-relapsed mortality (NRM), relapse, progression-free survival (PFS) and OS at 5 years was 23%, 38%, 39%, and 50%, respectively. The cumulative incidence of chronic extensive graft versus host disease (GVHD) was 49% for MSD and 53% for MUD. Lymphadenopathy ≥ 5cm was associated with a higher risk of relapse at 5 years (71% vs. 27%), when compared with patients without[20,21]. Allo-HSCT may overcome the poor prognosis of these high-risk genetic aberrations, including 17p deletion[22–26].

There is a great variety of conditioning regimens. The most common are: FluBu, FluTBI 200cGy[20,21], FluCy[24–26], FCR[27], and BFR[28], nevertheless, there is no comparative trial between these conditioning regimens.

RECOMMENDATIONS FOR MSD AND MUD:

A.BFR: rituximab 375mg/m^2 on day -13, and 100mg/m2 on days -6, +1 and +8, fludarabine 30mg/m^2 on days -5, -4 and -3, and bendamustine 130mg/m^2 on days -5, -4 and -3. GVHD prophylaxis with oral cyc-

losporine (CSP) starting on day -2, and intravenous methotrexate (MTX) 5mg/m^2 on days +1, +3, and +6. In MUD will receive an additional MTX 5mg/m2 on day +11, and rabbit antithymocyte globulin 1mg/kg on days -2 and -1[28].

B.FluTBI 200cGy*: fludarabine 30mg/m^2 on days -4, -3 and -2, and TBI 200cGy on day -1. Immunosuppressive therapy starts with CSP on day -3 and oral mycophenolate mofetil (MMF) 15mg/kg tid on day +120,21. **When rituximab or bendamustine is not available,*

Allo-HSCT alternative donors are also good options for CLL. For the haploidentical donors, 2 years PFS and OS were 38 and 48% respectively[29]. Cord blood transplant is also feasible in CLL when sibling ou matched unrelated donors are absent, in a retrospective study the PFS and OS at 3 years were 54% and 45%, respectively[30].

RECOMMENDATIONS FOR ALTERNATIVES DONORS:

A.Haploidentical donors. FluCyTBI 400cGy: cyclophosphamide 14.5mg/kg on days -7 and -6, fludarabine 30mg/m2 on days -7 to -3, ant TBI 200cGy on days -2 and -1. GVHD prophylaxis: cyclophosphamide 50mg/kg on days +3 and +4, CSP starting on day +5 until, and oral MMF 15mg/kg tid starting on day +5 [31,32]. Granulocyte-colony stimulating factor (G-CSF) 5mcg/kg from day +5 until neutrophil engraftment.

B.Cord blood transplant. FluCyTBI 200cGy: cyclophosphamide 50mg/kg on day -6, fludarabine 40mg/m2 on days -6 to -2, and TBI 200cGy on day -1. For GVHD prophylaxis, we recommend CSP starting on day -3, and oral MMF 1000mg twice daily from day -3 to day +30. G-CSF 5 mcg/kg per day from day 0 until the absolute neutrophil count (ANC) was greater than 2500/mcL for 2 consecutive measurements[33].

AUTOLOGOUS STEM CELL TRANSPLANTATION

In trials comparing autologous stem cell transplantation (auto-SCT) with observation, auto-SCT improved event free survival, without benefit in overall survival, and autologous did not overcome the poor prognostic markers, in addition to worse the quality of life[34–36]. Currently, with access to targeted therapies and the small benefit of auto-SCT, this therapy is not routinely indicated in CLL.

MANAGEMENT OF RELAPSE AFTER ALLOGENEIC TRANSPLANTATION FOR CLL

Treatment of patients with relapsed CLL after allo-HSCT is a challenging unmet clinical need, particularly because patients are often refractory to chemoimmunotherapy before transplantation and, more recently, they might also be also refractory to BTK inhibitors and venetoclax. However, even in this group of high-risk patients, opportunities to achieve long-term survival remain, and the prognosis is not as bad as observed in acute leukemias or aggressive lymphomas, for example. In a retrospective analysis of 52 patients with CLL who relapsed after allo-HSCT, median OS from relapse was 35 months; and the median OS from the time of re-treatment was 21 months[37].

Relapse of CLL after allo-HSCT can be sometimes rescued by immunotherapeutic approaches, such as immunosuppression withdrawal or donor lymphocyte infusion (DLI), not all patients are responsive to these strategies. Such cases could benefit from combinations of monoclonal anti-CD20 antibodies, standard chemotherapy, and especially from targeted agents such as ibrutinib, lenalidomide, and venetoclax[37–43] In addition, promising data have emerged from several studies evaluating the effect of CAR-T cells and, more recently, CAR-NK cells for high-risk and very advanced CL[44–46]

DONOR LYMPHOCYTE INFUSION (DLI) - MRD-DRIVEN STRATEGIES

A retrospective analysis of the German Group[42] analyzed 77 consecutive allografted CLL patients for CLL in which immunosuppression tapering and rituximab-augmented donor lymphocyte infusions (DLI) were guided by MRD monitoring. Interventions started at a median of 91 (22–273) days after allo-HSCT, resulting in a probability of being event-free and MRD-negative 1 year after transplant of 57%. Patients who were event-free and MRD-negative at 12 months had a 4-year PFS of 77%. Relapse incidence post allo-HSCT was 26% at 3 years and patients who experienced relapse had a survival of 56% 2 years after relapse.

Recently, a joint French Innovative Leukemia Organization (FILO) and Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) multicenter phase II trial[47] evaluated prospectively an approach of post-transplantation MRD-driven immune-intervention for CLL that included early CsA tapering (day+90) potentially followed by DLI in case of a post-transplantation MRD positive status or keeping cyclosporine for a longer period for those with a MRD negative status. They observed relatively low rates of chronic GVHD and NRM and a very high rate of overall survival at 3 years (close to 90%). MRD negative at 12 months was achieved in 79% of evalu-

able patients. In this context of early preemptive immune-intervention, the study failed to show a benefit of DLI to convert MRD from positive to negative, although 3 out of 5 patients who received DLI were already in clinical progression at the time of infusion.

IBRUTINIB

In 2016, Ryan et al. published results of 27 patients with relapsed CLL following allo-HSCT who subsequently received ibrutinib salvage therapy and achieved an overall response rate of 87.5%, PFS rate at 2 years was 77%40.

More recently, an EBMT registry-based retrospective multicenter study included patients who underwent allo-HSCT for CLL between September 2002 and December 2015[48], and who received ibrutinib after transplantation for disease relapse. Patients in this study received a range of treatments including anti-CD20 monoclonal antibodies, DLIs, lenalidomide, standard chemotherapy and, in a small number of patients, ibrutinib. This study demonstrated that, notwithstanding high-risk disease and multiple lines of prior therapy before allo-HSCT (median 3 lines, range: 1–10), ibrutinib was an effective and tolerable salvage therapy for CLL relapse following allo-HSCT, with an OS rate at 2 years of 72% and 2-year PFS rate of 50%. Patients with late relapse after allo-HSCT (≥24 months) tended to had a superior outcome as compared to those with earlier relapses. Only 30% of patients achieved CR, as expected for a BTK-inhibitor strategy. However, among 11 patients in CR tested for MRD, 5 were negative, showing a possible ibrutinib-mediated GVL effect40,[49,50]. At the time of ibrutinib initiation, ten patients had still an active chronic GVHD, all these patients had their GVHD resolved after receiving ibrutinib and only one patient had limited de novo chronic GVHD while on Ibrutinib, with a quick resolution. Ibrutinib is indeed a therapeutic option for steroid-refractory chronic GVHD, being approved for this indication by the FDA[51–53]. Ibrutinib was well tolerated with a safety profile similar to the one observed in the overall population of patients with relapsed/refractory CLL treated with ibrutinib3. Based on this analysis, ibrutinib seems to be efficient and safe for CLL relapse after allo-HSCT, and combinations including this agent should be evaluated in larger prospective trials in this scenario.

SECOND ALLO-HSCT

The availability of new alternative therapies, including both BCR and BCL2 inhibitors have taken the place of a 2nd allo-HSCT in the relapse/refractory setting, either obviating the need for transplant or delaying this strategy until later in the management of the disease. Consequently, the number of 2nd allo-HSCT for CLL has considerably decreased, both in the United States[16] and Europe[47].

CAR-T CELLS

The first description of CAR-T cells for CLL was a clinical trial of a single infusion of allogeneic anti-CD19-CAR T cells for 10 patients with B-cell malignancies (4 with CLL) that persisted after allo-HSCT and standard DLIs. Three patients achieved durable CRs, including 2 patients with CLL. This approach is associated with significant acute toxicity, especially due to the cytokine release syndrome, but does not represent a risk for GVHD[54].

However, as more patients with CLL were included in trials with CAR-T cells, results became more disappointing. In the 134 highly pre-treated CLL patients treated with CAR-T cells reported to date, the CR rate remains of 20 to 30%, with a median PFS of 18% at 18 months55, and a proportion of the patients have a subsequent relapse at follow-up[44,56,57]

More recently, a pilot study evaluated the safety and feasibility of administering ibrutinib concurrently with CD19 CAR T-cell in 19 CLL patients. CD19 CAR T-cell therapy with concurrent ibrutinib was well tolerated; 13 patients (68%) received ibrutinib as planned without dose reduction. The 4-week overall response rate was 83%, and 61% achieved a MRD-negative marrow. In this subset, the 1-year OS and PFS were 86% and 59%, respectively, with lower CRS severity and lower serum concentrations of CRS-associated cytokines, despite equivalent in vivo CAR T-cell expansion[58].

CAR-NK CELLS

More recently, the early results of a phase 1 and 2 study of NK cells that were derived from cord blood and engineered to express anti-CD19 CAR, interleukin-15, and an inducible caspase 9 safety switch were published46. This therapy was tested in heavily pretreated patients with multiply relapsed or refractory CLL. At a median follow-up of 13.8 months, 4 of 5 patients with CLL had an objective response and 3 (67%) had a complete response. Response durations cannot be assessed because of the administration of other therapies (immunomodulatory agent, chemo-immunotherapy, or allo-HSCT), starting as early as 30 days after the infusion of CAR-NK cells. The infused CAR-NK cells persisted at low levels for at least 12 months, despite the substantial HLA mismatch between the infused NK cells and the recipient. The

inclusion of interleukin-15 in the construct may have played an important role in the persistence and anti-tumor activity of these CAR-NK cells. Allogeneic CAR-NK cells can be delivered in adoptive transfer without the serious cytokine release syndrome, GVHD, or neurologic toxic effects that have been associated with CAR T-cell therapy[59,60] Besides, this technique may become accessible to many patients with R/R CLL due to the minimal HLA-matching requirements between the donor of CAR-NK cells and the patient and the possibility to produce more than 100 doses of CAR-NK cells from a single cord-blood unit[61] .

CONCLUSIONS

Although allo-HSCT in CLL is decreasing in developing countries, in Brazil we may still consider allo-HSCT as an option in lower transplant risk patients, mainly due to inaccessibility of new agents in the public system in patients with relapse/ refractory disease. However, if new agents are available, allo-HSCT should be reserved for high-risk patients and/or relapsed / refractory disease after treatment failure with BCL-2 inhibitor and/or BTK inhibitors. Besides, clinicians should always consider including their patients in this scenario in clinical trials.

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HSCT FOR ACUTE MYELOID LEUKEMIA

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In the last few years, there were several developments in the field of hematopoietic stem cell transplantation (HSCT) for acute myeloid leukemia (AML). The approval of new target drugs and the mounting clinical experience also with the epigenetics agents, leaded to an increase in response rates for the mainly elderly population of patients. These drugs have a safer profile than high dose chemotherapy; aggressive infections treated with an array of toxic medicines and its related side effects are less frequently observed with these drugs, enabling the patient to be forwarded to HSCT in a better clinical condition. On the other hand, less toxic conditioning regimens designed for this fragile population of patients, and donor availability have changed for the better HSCT outcomes. Utilizing an haploidentical donors makes it easier to find a donor – frequently among a younger progeny. Pos transplant cyclophosphamide (Cy) as a major graft versus host disease (GVHD) prophylaxis is effective and have been successfully tested in other HLA donor-recipient combinations, in particular, in the mismatch unrelated HSCT scenario. Finally, the increasingly robust data about the impact of the presence of minimal residual disease (MRD) after remission induction that can predict HSCT outcome, is improving patient selection.

In the US and some of the Brazilian Transplantation Centers, AML is the leading indication for Allogeneic HSCT. HSCT still is the gold standard for intermediate and adverse risk AML. In addition to the new developments outlined above, the widespread utilization of disease's and patient's risk categorization as well as the above-mentioned increased utilization of less toxic conditioning regimens, both myeloablative and reduced intensity (RIC), have improved SCT outcomes over the years. [1-3]

Finally, the indication for HSCT should be at AML diagnosis, taking into consideration disease risk, patient risk (such as age and possible comorbidities), as well as donor type (related, unrelated, age and gender). It is never too much to outline that HSCT is indicated when the risk of relapse is higher than the risk of transplant related mortality (TRM).

SCT FOR AML IN FIRST COMPLETE REMISSION

European Leukemia Net (ELN)4 recommendations based in karyotypic and molecular abnormalities are widely accepted and validated for AML risk stratification. (Table 1)

Intermediate and adverse risk AML should be transplanted at first complete remission (CR) provided that factors such as patient's risk or TRM chances are weighted.[5-7]

TABLE 1 - ELN AML risk stratification

Risk Category	Genetic Abnormality
Favourable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD or with FLT3-ITDlow
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITDhigh
	Wild-type NPM1 without FLT3-ITD or with FLT3-ITDlow (without adverse risk genetic lesions)
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favourable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
	–5 or del(5q); –7; –17/abn(17p)
	Complex karyotype, monossomal karyotype
	Wild-type NPM1 and FLT3-ITDhigh
	Mutated RUNX1
	Mutated ASXL1
	Mutated TP53

RISK OF TRANSPLANT RELATED MORTALITY (TRM)

It is accepted three different score systems for risk of TRM. These are HCT-CI that utilizes 17 comorbidities with diverse weights[8] and also adapted for reduced intensity conditioning regimens[9]; EBMT[10], and the combined HCT-CI/EBMT[11-13], all validated and accepted in this guideline. First CR favorable risk AML should not be submitted to HSCT when MRD is negative, however, if positive a SCT should be considered.

HSCT SHOULD BE OFFERED TO AML PATIENTS IN SECOND CR.

Conditioning Regimens

Myeloablative conditioning (MAC) regimens that combine a higher chance for engraftment with higher antileukemic activity, are ideal for AML patients younger than 55 years of age. Older age or the presence of comorbidities usually is an increased risk factor for TRM.[14] Several studies including meta-analysis comparing Bu4/Cy with Bu4/Flu concluded that both MAC regimens have equivalent antileukemia effect with Bu4/Flu been less toxic.[15,16] TBI (Cy/TBI) should be restricted for those patients with extramedullary disease.[17] Fludarabine based RIC with alkylating agents should be chosen for elderly or those with comorbidities. When compared with MAC, RIC regimens are less toxic although a higher relapse rate is observed.[18-20]

SOURCE OF STEM CELLS: BONE MARROW (BMSC) OR PERIPHERAL BLOOD (PBSC)

Although in the matched related donor (MRD) scenario studies comparing BMSC and PBSC as a source for stem cells are inconclusive, chronic graft versus

host disease (cGVHD) is higher and leads to worse quality of life for MAC MUR HSCT of PBSC; the latter should be utilized for patients with high risk disease receiving a MRD transplant.[21,22] With faster neutrophils and platelets engraftment, and because inconclusive studies, PBSC is indicated for RIC transplants.[23] It should be noted that in the Brazilian experience, PBSC for myeloablative MRD transplants have been associated with significant higher incidence of cGVHD[24] leading to the Brazilian GVHD Study Group to recommend that the choice of SC source should be individualize according cGVHD risk.

UNRELATED TRANSPLANTS

Albeit retrospective, both CIBMTR and EBMT registries studies on MRD and MUD 10/10 HLA identical HSCT showed similar results.[25,26] Although MUD transplants leads to a higher incidence of II-IV acute GVHD, TRM and OS are apparently similar to MRD transplants. Comparing MRD to MUD 8/8 or 7/8 HLA identical, although TRM is higher in the latter an increase in DFS at 3 years follow up, leaded to a similar OS.[27] In the absence of a MUR 10/10 HLA identical, an 8/8 donor is recommended and an 7/8 can be acceptable. Pos transplant Cy (PTCy) associated to two immunosuppressors as GVHD prophylaxis either for MRD or MUD transplants looks promising.[28]

HAPLOIDENTICAL SCT

Haploidentical HSCT with PTCy GVHD prophylaxis[29] is a good alternative for patients without an HLA matched donor since its related RR is similar to the TRM of an HLA 8/8 identical MUD transplant, leading to a comparable OS.[30] On the other hand, a retrospective EBMT registry study including 10.679 patients submitted to either haplo or MRD transplant was not able to show a difference in RR probability.[31] It is necessary to be aware that after PTCy haplotransplants, relapse can occur with leukemic cell losing its HLA molecules[32], in which case DLI will be ineffective and if a second transplant is considered it should be from a different haploidentical donor.[33]

HSCT FOR THE ELDERLY

Overall, elderly AML patients have a worse prognosis. In addition to the frequent presence of comorbidities, high risk cytogenetic and molecular abnormalities are frequent in this patient population. The latter frequently contribute for remission induction failure, presence of MRD at best hematopoietic CR, and/or shorter CR duration.[34] It should be pointed out that the increasing population of healthy elderlies associated with the new target drugs and epigenetic agents for remission induction, when combined with TRM risk stratification and less toxic conditioning regimens are changing this scenario.[35-37] In a recent CIBMTR study comparing MAC to RIC, OS was similar since the TRM of the first was comparable to the higher RR observed in the latter, in particular for Flu/Mel RIC.[38]

HSCT FOR REFRACTORY/RELAPSED AML (R/R AML)

HSCT in active AML disease patients is usually ineffective. In an EBMT registry study including 852 with R/R AML, OS and DFS in **two years** was 30% and 25%, respectively.[39] In a smaller number of patients, the early utilization of sequential high dose chemotherapy and RIC regimen (FLAMSA-RIC)[40] which rational is to avoid the utilization of several remission inductions schemes in the pursue of CR might be an alternative. In a recent metanalysis, FLAMSA-RIC **tree years** OS and DFS was 40,2% and 39,3%, respectively, suggesting this treatment strategy might be a good option for these patients.[41]

AUTOLOGOUS HSCT

Although autologous HSCT for AML remission consolidation is a moderately effective strategy, since RR is higher than allogeneic HSCT RR,[42,43] however, it was shown in a recent metanalysis for intermediate risk AML patients without a related donor that autologous HSCT could be an option.[44] Analyzing data from Brazilian HSCT Centers, Hamerschlak et al.[45] found no difference in OS between allogeneic or autologous HSCT for AML. For low risk AML patients, autologous HSCT as a first CR remission consolidation might also be an option since when compared to chemotherapy consolidation only, results are not statistically different from allogeneic HSCT.[46] For second CR in acute progranulocyte leukemia (APL) consolidation, autologous HSCT is superior to arsenic trioxide.[47]

MINIMAL RESIDUAL OR MEASURABLE DISEASE (MRD)

Quantifying MRD became a key element in AML treatment strategy. The presence of MRD before allogeneic HSCT predicts pos transplant relapse, irrespective of AML risk category.[48,49] Multiparametric flow cytometry (MPF) MRD measurement is widely accepted and increasingly validated, provided laboratory expertise is available.[50] RT-PCR, a method highly sensitive is only available for APL, Core Bind-

ing Factors (CBF) or NPM1 AML mutations.[51] According to ELN's recommendation, MDR measurement should be done before, (4 or less weeks before HSCT), and at three months thereafter for MPF, or at 4 to 6 months period for RT-PCR. The first should be done in bone marrow, and the latter in peripheral blood samples.[52]

POST HSCT CR MAINTENANCE

With the availability of target and epigenetic drugs, pos transplant maintenance is been studied actively. There are however several unanswered questions beyond efficacy. Pos HSCT period is very complex. The patient comes out from a profound neutropenia, transfusions, proper prophylaxis including GVHD's, and is frequently receiving antimicrobial and antiviral drugs. To determine the time to start maintenance without affecting engraftment, GVHD, or infection, and for how long maintenance should be administered are the main questions to be answered. Clinical trial results are just coming out of phase I or II with very few phase III studies.

Among the drugs been tested, sorafenib appears to be associated with favorable results when compared with historic controls[53-56] and in some prospective randomized trials including a rather small number of patients, RR appears lower than the control arm without an impact in OS.[57] As for midostaurin (RADIUS study) a randomized study comparing with no maintenance, did not showed a significant difference in RFS.[58] In phase I/II non-randomized studies on azacytidine results appears favorable,[59,60] on the other hand, one prospective randomize study including 187 patients comparing azacytidine with no maintenance, no difference in RFS was observed.[61] While we await for results of several studies testing maintenance pos HSCT for AML, patients should receive it in the context of a clinical trial.

NOTES ABOUT DONOR SELECTION

The immunogenetic donor selection strategies for AML HSCT are described elsewhere in a specific chapter of this Brazilian Guideline for HSCT. In haploidentical transplants it should be stressed that at relapse, myeloblasts can have lost their HLA identity (HLA loss), in which case DLI or a new HSCT utilizing the same donor will be ineffective. Crucitti et al. described HLA loss in 33% of relapses.[62] HLA loss can be detected by various methods such as myeloblast directed HLA typing, HLA-KMR or next generation sequencing (NGS).[63-66] HLA loss tests should be done at relapse.

All donors with HLA mismatch should be screened for the presence of donor specific antibody (DSA). If positive and the only possible donor, the patient should be desensitized.

Finally, myeloid neoplasms with germ line predisposition was included in the new WHO AML classification, and Hereditary Myeloid Malignancies Syndromes (HMMS) should be ruled out when there is previous history of cytopenia or family history of cytopenia or hematologic malignancies. Donors diagnosed with a pathogenic or likely pathogenic mutation in a HMMS related gene, even if asymptomatic, should be avoided.[67,68]

RECOMMENDATIONS

HSCT Allogeneic (related or unrelated)

1)HSCT allogeneic is indicated to AML high risk (A1).

2)HSCT allogeneic is indicated to AML in second completed remission (RC2) (A1).

3)HSCT allogeneic is indicated to AML intermediate risk, particularly in patients with MRD positive on RC1 (A1)

4)HSCT allogeneic is indicated to AML refractory/relapsed (C4).

Conditioning Regimens

1)Myeloablative conditioning is indicated to young patients, without significant diseases (younger than 55 years of age with HCT-CI equal or under than 2) (A1).

2)Older patients or with another disease should prefer reduced intensity conditioning (B2).

Haploidentical SCT

Level of evidence A2
Category recommendation: B

Autologous HSCT

1)Indicated to AML low risk after 1 consolidation (C4)

2)Indicated to AML RC1 (according to the Brazilian experience) (C4)

3)Accept to APL second molecular remission (B2)

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HSCT FOR CHRONIC MYELOPROLIFERATIVE DISEASES

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INTRODUCTION

According to the World Health Organization, myeloproliferative neoplasms (MPN) are defined as clonal diseases caused by proliferating hematopoietic progenitor cells. They can be divided into Philadelphia-positive - chronic myeloid leukemia (CML) – and Philadelphia-negative disorders - primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET).[1] This document is a summary of the recommendations of the Brazilian Society of Bone Marrow Transplantation Consensus Panel in 2020 for these areas.

PHILADELPHIA-POSITIVE MYELOPROLIFERATIVE DISEASE

CHRONIC MYELOID LEUKEMIA: SUMMARY OF RECOMMENDATIONS

1. Imatinib mesylate, nilotinib, or dasatinib are the treatment of choice for newly diagnosed chronic phase (CP) chronic myeloid leukemia (CML) (level 1b).[2-9]

2. Main indications for hematopoietic stem cell transplantation (HSCT) for CML patients in the tyrosine kinase inhibitor (TKI) era:

a. Children: there are no currently available studies comparing TKI and HSCT in this population. The therapeutic approach is similar to that in adults and is based on the use of first or second generation TKIs. Hematopoietic Stem Cell Transplantation (HSCT) should be considered after failure of a second generation TKI or in advanced phase (AP and BC) CML. Data on the primary efficacy and safety of ponatinib are still lacking in children, for which further studies are awaited. Likewise, ongoing studies are still assessing the adverse effects of the long-term use of TKIs in this population. Adherence to TKI therapy should also be taken into account when deciding upon the best treatment

strategy in children and adolescents (level 2b). [10-15]

b. Advanced phase disease: in AP, HSCT should be indicated if the response to second generation TKI therapy (dasatinib or nilotinib) is suboptimal, or in case of a T315I mutation when ponatinib is unavailable.[16-20] In BC, it should always be considered, preferably after a preliminary course of TKI therapy with or without chemotherapy (level 2b). [21,22]

c. In case of failure of imatinib, in accordance with the European LeukemiaNet 2020 recently updated criteria, in the absence of a T315I mutation, a second generation TKI should be started. In case of TKI failure, consider third generation TKI therapy (ponatinib) or HSCT, if the former is unavailable (level 2b). [20, 23]

d. T315I mutation, if ponatinib is unavailable (level 2b). [18,19]

3. For young patients with an HLA-identical related or unrelated donor, myeloablative conditioning should be used. Reduced intensity or non-myeloablative conditioning should be reserved for patients over 60 years of age and/or with significant comorbidities (level 1b). [24-27]

4. Graft-versus-host disease (GVHD) prophylaxis should be based on a calcineurin inhibitor (cyclosporin, tacrolimus) plus methotrexate. In a long-term follow-up analysis, triple immunosuppressant-based prophylaxis with methylprednisolone resulted in better overall survival, but these results are yet to be confirmed in larger, prospective studies (level 1b). [28,29]

5. Bone marrow, if available, is the preferred stem cell source in patients with CP CML. Patients with advanced disease should receive peripheral blood stem cells (PBSC). Alternative stem cell sources, such as umbilical blood cord (UBC), or haploidentical transplants are acceptable in the absence of an HLA-identical BM (or PBSC) donor (level 1a). [30-33]

6. Post-transplant monitoring of BCR-ABL using real time quantitative polymerase chain reaction (RT-qPCR) should be performed every three months, during the first two years, and every six months, up to five years post-transplant. This should be followed by yearly monitoring from then onwards (level 2b). [34-37]

7. Molecular relapse is defined as progressively increasing BCR-ABL/ABL1 gene transcripts in at least two consecutive results (level 2b). [36,37]

8. Use of imatinib mesylate and of second generation TKIs (dasatinib and nilotinib) does not seem to affect the occurrence of early transplant-related toxicity, nor to delay engraftment. Similarly, it does not seem to affect survival, relapse, or non- relapse mortality (level 2b). [38-40]

9. In case of molecular relapse, consider donor lymphocyte infusions (DLI) at escalated doses (1 x 10 6 , 5 x 10 6 , 1 x 10 7 , 5 x 10 7 , 1 x 10 8 CD3+ cells/kg) at three-month intervals. In case of cytogenetic or hematologic relapse, consider DLI at escalated doses at three-month intervals, starting at 1 x 10 7 CD3+ cells/kg, or consider use of imatinib mesylate. Subsequent DLI doses should not be administered if a satisfactory response is obtained or in case chronic GVHD ensues. In case of unrelated or haploidentical related donors, start at a DLI dose 1 log lower than that depicted above (1b). In case of hematologic relapse in CP or cytogenetic relapse, consider DLI, starting at higher escalated doses (1 x 10 7 , 5 x 10 7 , 1 x 10 8 CD3+ cells/kg), or imatinib mesylate, at a dose of 400mg per day, or a combination of these. In case of hematologic relapse in AP or BC, consider the use of a TKI plus DLI (level 1b). [41-46]

10. Imatinib mesylate, nilotinib, or dasatinib are currently acceptable alternatives to DLI for the treatment of post-transplant relapse of CML, or in cases where relapse occurs in the setting of chronic GVHD (level 2b). TKIs may also be combined with DLI in the management of such cases, with better overall responses (level 2b). Prompt and long-lasting responses are usually seen under TKI therapy for CML relapsing in CP (level 2b). Response tends to be worse and less durable in AP or BC relapse (level 2b). [47,48]

11. In patients previously resistant or intolerant to imatinib mesylate, consider using a second generation TKI (nilotinib or dasatinib), when deciding upon use of a TKI alone or in combination with DLI (level 2b). In patients previously resistant or intolerant to more than one TKI, consider using a previously unused TKI, or opt for DLI without a TKI, in the absence of chronic GVHD (level 2b). [47,48]

12. Consider using post-transplant TKI prophylaxis in patients at a high risk for relapse (>1 st CP and AP/BC) (level 2b). [49-53]

13. In case a post-transplant BCR-ABL fusion gene mutation is detected, the mutational profile should be taken into account when choosing the most appropriate TKI for prophylaxis or preemptive therapy in this setting (level 2b). [54]

14. A second allogeneic HSCT may be considered in case of TKI- and/or DLI- resistant relapse following a first transplant, if a suitable donor is available, in the absence of contraindications to transplant (level 2b). [55]

TABLE 1– Response to TKI definitions.[31]

Time	Optimal Response	Failure	Warning
Diagnosis	-	-	High risk (ELTS)* additional clonal abnormalities in Ph+ cells (ACA)
3 months	RTQPCR (EI) ≤10%	>10%, confirmed in-3 months	RQPCR>10%
6 months	RTQPCR (EI) ≤1%	RQPCR>10%	RQPCR 1 a 10%
12 months	RTQPCR(EI) ≤0,1%	RQPCR>1%	RQPCR 0,1 a 1%
Any moment	MMR sustained RTQPCR (EI) ≤0,1%	RQPCR>1%, resistant mutation, additional clonal abnormalities in Ph+ cells (ACA) **	RQPCR 0,1 a 1%; loss of MMR

* ELTS: *EUTOS long term survival score*
Adapted from: Hochaus, A, et al. Leukemia 2020;34(4):966-984 [23].
** Two results exhibiting the same abnormality in at least two Ph+ cells are necessary to fulfill this criterion: TKI: tyrosine kinase inhibitor; MMR: major molecular response; ACA: additional chromosome abnormalities in Ph+ cells; RTPCR: real-time quantitative polymerase chain reaction; IS: International Scale (BCR-ABL/ABL1 control gene ratio).
*** Risk scores can be calculated directly by accessing the following site: http:/leukemia- et.org/content/leukemias/cml/cml_score/index_eng.html.

TABLE 2 - European LeukemiaNet 2020 chronic myeloid leukemia treatment recommendations31

Prevention by elimination of BCR-ABL1	Assurance of effective TKI treatment
Early: emergence of high-risk ACA	Observe closely, consider intensification of treatment (ponatinib, early allo-SCT)
Blast Crisis at diagnosis	Start with imatinib, change to a 2nd generation TKI according to mutation profile
Resistance to second generation TKI	Ponatinib or clinical trial , consider HSCT, donor search
Ponatinib failure	High risk of progression, early allo-HSCT recommended
Accelerated phase	Treat as high-risk patients; proceed to allo- HSCT if response to TKI is not optimal.
Progression to blast phase	Poor outcome with currently available TKIs. Add chemotherapy based on AML regimens for myeloid BC (such as dasatinib or ponatinib + FLAG-IDA) or ALL regimens for lymphoid BCP (such as imatinib or dasatinib + hyperCVAD). Choice of TKI based on prior therapy and mutational status. Proceed to allo-HSCT soon after CP2 is achieved

Adapted from: Hochaus, A, et al. Leukemia 2020;34(4):966-984 22.
TKI: tyrosine kinase inhibitor; ACA: additional chromosomal aberrations: 2CP: second chronic phase; BC: blast crisis; allo- HSCT: allogeneic hematopoietic stem cell transplant; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; FLAG-IDA: fludarabin + cytarabin + granulocyte-colony stimulating factor + idarubicin; HiperCVAD: hyperfractionated CVAD: cyclophosphamide + vincristin + doxorubicin + dexamethasone.
Figure 1: Treatment algorithm for chronic phase (CP), accelerated phase (AP), and blasts crisis (BC) chronic myeloid leukemia (CML).31

FIGURE 1 - Treatment algorithm for chronic phase (CP), accelerated phase (AP), and blasts crisis (BC) chronic myeloid leukemia (CML).31

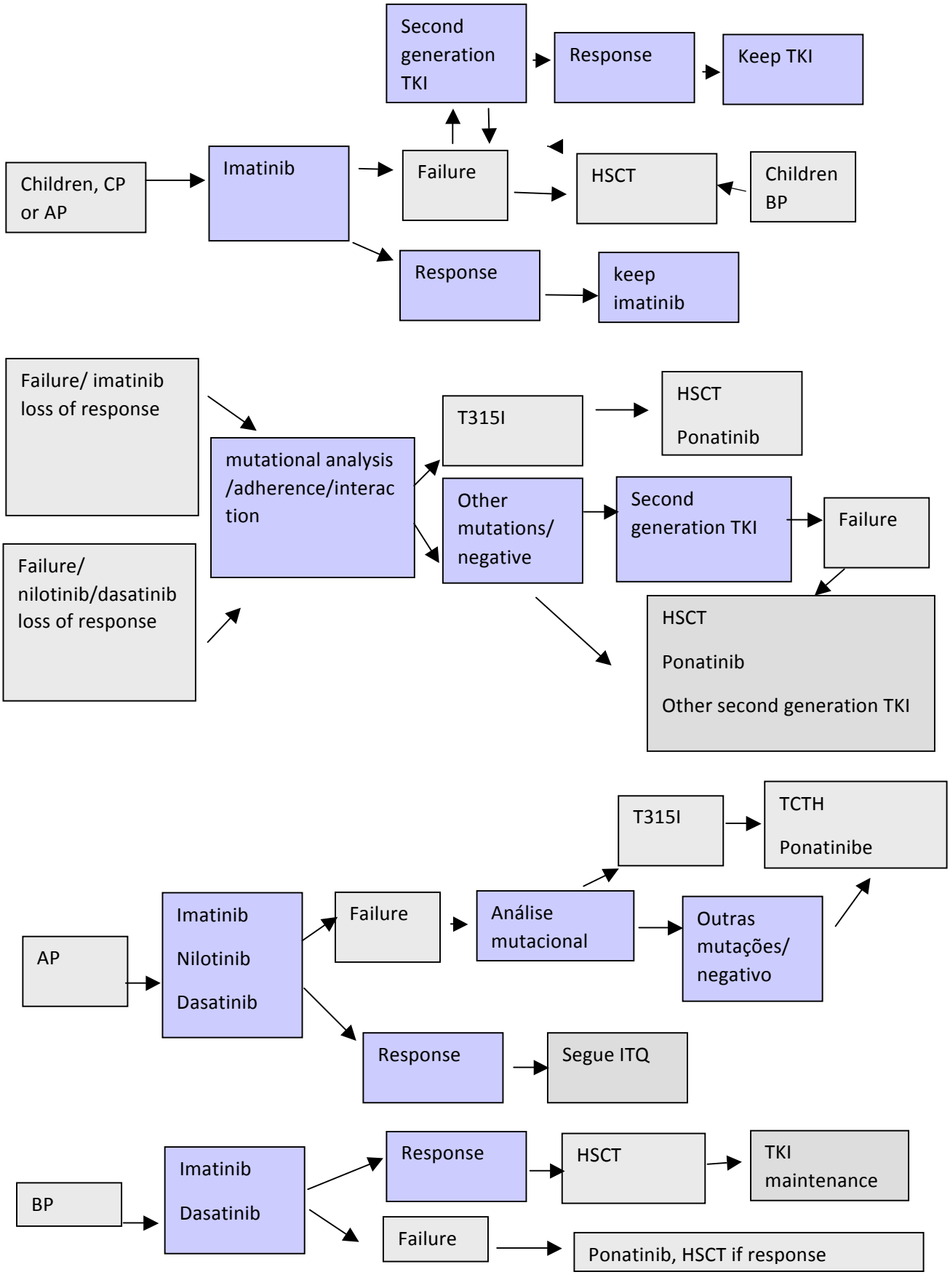

TABLE 3 - Recommendations for post HSCT monitoring and relapse therapy in CML patients 41-46

Time after HSCT	MONITORIZATION	RESULT	INTERVENTION
Two years	Quantitative RT-PCR every 3 months (level 2b)	Molecular relapse: increasing BCR-ABL/ABL ratio in two measures: relapse cutoff defined by local lab (2B)	Consider escalated dose DLI. For related transplants: CD3+/Kg: 10 6®5 x 10 6 ®10 7® 5 X 107 ® 108 every 3 months. For unrelated transplants: 1 log less: 105 ® 5 X 105 ®106 ® 5 X 106 ® 107 Hold dose if chronic GVHD signs or symptoms (1B)
3-5 years	Quantitative RT-PCR every 6 months (level 2b)		
After 5 years	Quantitative RT-PCR every year (level 2b)		
Any time	Cytogenetics if positive PCR (level 2b)	Cytogenetic relapse	Consider DLI as above (1B) and imatinib (2B)
Any time	Complete Blood Count	Hematologic relapse	Consider DLI as above (1B) and imatinib (2B)

DLI = donor lymphocyte infusions; RT-PCR = real time polymerase chain reaction

PRIMARY MYELOFIBROSIS, POLYCYTHEMIA VERA, ESSENTIAL THROMBOCYTHEMIA

INTRODUCTION

According to the World Health Organization, myeloproliferative neoplasms (MPN) are defined as clonal diseases caused by proliferating hematopoietic progenitor cells and most common Philadelphia-negative disorders are primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET). [1]

STRATIFICATION

Patients with PMF often have a dismal prognosis, with a mean overall survival of only 6 years after diagnosis. 56 Even so, the clinical course is highly heterogeneous, and survival may vary from a few months to more than 10 years. 57 Therefore, prognosis may be better estimated by a number of scoring systems, among which the Dynamic International Prognostic Scoring System plus (DIPSS plus)58 is one of the most commonly applied. According to this prognostic model, patients stratified as low risk present a median survival of 185 months, which decreases to 78 months in intermediate 1-risk patients, 35 months in the intermediate 2 subgroup, and 16 months in the high-risk category.58 Polycythemia vera and essential thrombocythemia, in turn, have a more favorable prognosis, and patients should only be referred for allogeneic HSCT in case myelofibrosis or leukemic transformation has developed (level 2b).

MUTATIONS

Mutational profiling, including CALR, MPL, JAK2, ASXL1, EXH2, SRSF2, IDH1/2 and U2AF1 mutations, should be performed whenever possible, to allow for the Mutation Enhanced International Prognostic Scoring System 70+ v2.0 (MIPSS70+ v2.0) 59 and the Clinical-Molecular Myelofibrosis Transplant Scoring System (MTSS) 60 to be applied, given their ability to estimate post-transplant outcomes based on disease-, patient-, and transplant-related factors. This may aid in the clinical decision-making process when assessing eligibility for transplantation. Such prognostic models should not, however, replace the DIPSS plus score when assessing these patients (level 2b).

INDICATION

No therapeutic agents have thus far been shown to improve the overall survival of patients with PMF; allogeneic HSCT remains the only curative option for such patients to date. Not all patients, however, benefit from this procedure. Hence, we recommend that transplant indication be based on the DIPPS plus score, whereby allogeneic HSCT should be performed in intermediate-2 and high- risk patients.61 HSCT may sometimes be indicated for patients classified as intemediate-1 risk 62 , particularly in younger patients and those with high transfusion dependency, more than 2% blasts in peripheral blood, or with an unfavorable karyotype. Other scoring systems, namely the MIPSS70+ v2.0 and the MTSS, may further assist in the clinical decision-making process (level 2b).

CONDITIONING REGIMEN INTENSITY

It is not defined what is the ideal conditioning regimen in transplantation for myelofibrosis patients, given the patients' average age of diagnosis, most regimens will be of reduced intensity, however the ideal dose is not established. For patients under the age of 50, we recommend myeloablative conditioning; for those over 50 years old, reduced intensity conditioning 63, which is usually fludarabine associated with busulfan or melphalan. There is no superiority between conditioning regimens, the melphalan regimen seems to obtain greater control of the disease, but with higher mortality unrelated to relapse than the regimen with busulfan, resulting in similar overall survival 64.

The MD Anderson group recently published a non-randomized, phase II study comparing 2 different levels of intravenous busulfan associated with fludarabine: 15 patients using low busulfan (130 mg / m2 for 2 days) and 31 patients with high busulfan (100mg / m2 for 4 days), with 27 patients with a serum level adjusted to AUC of 4000. In an average follow-up of 3 years, patients using busulfan with a higher dose had an event-free survival of 58% against 27% of those who used low doses. In conclu-

sion, the use of fludarabine regimen with busulfan with serum level control seems to reduce relapse without increasing transplant-related mortality.65 Non-myeloablative conditions have a higher rate of grafting failure 66 (level 2b).

DONOR

HLA-matched unrelated donors are an acceptable alternative for patients without an HLA-identical sibling donor. 67 HLA-mismatched related donors may also be acceptable, but further studies are needed to better address this issue (level 2b). [68]

STEM CELL SOURCE

Both BM and PBSCs are acceptable stem cell sources in this scenario (level 2b).[69]

SPLENECTOMY

Routine splenectomy prior to transplant is not recommended in patients with splenomegaly, except in cases with a spleen size greater than 22cm 70. Splenic radiation, in turn, may be considered within the context of clinical trials (level 2b).

RUXOLITINIB

Ruxolutinib is a Janus kinase (JAK) 1/2 inhibitor known to be involved in the pathophysiology of PMF. Despite its effectiveness in controlling many of the symptoms presented by PMF patients, it should not be regarded as an alternative to HSCT, since it does not affect the natural history of the disease. Hence, though we do recommend it for symptomatic control, it should not delay referral for transplantation.

The use of ruxolitinib in most patients with myelofibrosis (MF) results in a reduction in the size of the spleen, which could decrease the time of grafting in the transplant, in improving constitutional symptoms and therefore in performance status, which could result in improvement of survival, and given the immunomodulatory action on T lymphocytes, it could decrease the incidence and severity of graft disease against the host. There are some concerns regarding the use of ruxolitinib in pre-transplantation: cytopenias, increased incidence of viral infections such as CMV, increased immunosuppression could interfere with the graft versus disease effect, the withdrawal syndrome: fever, recurrence of symptoms, splenomegaly of rebound, cytokine release syndrome, the latter being more common when the interruption is made abruptly and / or long before the conditioning regime starts.

A prospective study that studied the use of ruxolitinib for 56 days, started 60 days before conditioning, gradually decreased in 4 days and interruption 1 day before conditioning, showed that its use was safe. However, in this group of 21 patients, no significant reduction was seen in the rate of graft failure or in the incidence of GVHD 71. Another prospective study, phase II, this one using ruxolitinib for at least 8 weeks, with a gradual reduction of 5 mg every 4 days and interruption 4 days before the infusion also showed that the use of pre-HSCT ruxolitinib is safe: none patient had cytokine release syndrome and the overall 2-year survival was 86%, suggesting a benefit in overall survival 72. Level of evidence 2b. In addition studies have shown that ruxolitinib use is well tolerated during conditioning and others investigate its use in low doses until grafting: in a study with a small number of patients maintained low dose ruxolitinib until D + 28: 2 out of 12 patients had to cease on medication, the average grafting time was 12 days, no grafting failure, low incidence of acute GVHD and about 40% reactivation of CMV. [73]

We recommend it be used at the highest tolerated dose, with gradual tapering every four days and complete withdrawal by one to two days prior to transplant. 70 According to a recent phase II study published this year, its use prior to HSCT seems to be safe and to improve overall survival in patients who are referred for transplantation (level 2b) [71]

HAPLOIDENTICAL TRANSPLANTATION IN MYELOFIBROSIS

The results of haploidentical transplantation in myelofibrosis still lack published data. One of the first reports was published in 2016 analyzing the use of alternative donors from 2000 to 2014, unrelated and haploidentical, with related donors compatible in myelofibrosis 74. Although it was an analysis of a few patients: 23 haploidentical transplants, without which 20 in the last 5 years, the study showed a significant improvement in the survival of transplanted patients with myelofibrosis who used alternative donors: when analyzed the period of 2011 to 2014 the transplant survival curve with compatible related donor and haploidentical donors are comparable.

In 2019, the EBMT group published the retrospective report of 56 patients, median age of 57 years 75. Myeloablative conditioning was chosen in 70% of the cases and 59% of the cases used thiotepa + fludarabine + busulfan with cyclophosphamide in PT; 2/3 used bone marrow as a source of progenitor cells. The grafting rate was 82%. The cumulative incidence of acute GVHD up to D + 100 was 28% (grade II-IV)

and 9% (grade III / IV) and chronic GVHD in 1 year was 45%. In 2 years, overall survival was 56%, the incidence of relapse 19% and unrelated mortality 38%. This study showed that haploidentical transplantation is feasible, with good rates of grafting and overall survival and relapse not unlike unrelated transplants, however approaches must be instituted to decrease the considerable transplant-related mortality rate.

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HSCT FOR HODGKIN LYMPHOMA

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ABSTRACT

Over the past few decades, advances in combination of chemotherapy and radiotherapy have significantly improved treatment for patients with classic Hodgkin's lymphoma (cHL). Currently, more than 80% of patients aged <60 years, and mainly with localized disease, have an enormous chance of cure. However, the prognosis of patients with primary refractory disease or those who reach a complete remission (CR) and eventually relapse remains poor. Autologous stem cell transplantation (ASCT) is the standard treatment for most patients with relapsed or refractory HLc (R/R) when compared to conventional chemotherapy with a significant proportion of cured patients but 50% of them still relapse. Allogeneic transplantation is potencially the only curative therapy and since new agents such as brentuximab vedotin, nivolumab and more recently, pembrolizumab have been used before allogeneic transplant, we noticed an improved response to the procedure.

INITIAL APPROACH

After staging with the Lugano Classification, disease is, in general, classified into 3 groups: favorable localized (stages I and II, without risk factor), unfavorable localized (stages I and II with one or more risk factors) and advanced disease (stages III and IV, and some specific cases IIBX) [1,2,3,4,5,6.7,8,9] The risk factors, based on characteristics of subgroups of patients with a worse prognosis in clinical trials are: (A) bulky mediastinal mass, (B) extranodal disease, (C) eritrocyte sedimentation rate and (D) ≥3 nodal sites. The IPS, which stands for International Prognostic System, defines advanced disease as a risk; patients over the age of 45 years; male; stage IV; hemoglobin < 10.5g / L; albumin < 4g / L; leukocytes > $15x10^9$ /L and lymphocytes < $600x10^9$ / L . [8,9,10]

PET-CT with FDG is recommended both at the initial evaluation and end of treatment, its result should always be reported using the Deauville score. If possible, it can be performed after 2 or 3 cycles of chemotherapy as an interim PET for early prognosis definition. Bone marrow biopsy is useful in patients without access to PET-CT at diagnosis, or special cases (such as in presence of cytopenias, for example).[7,9] Response Assessment: PET-CT [8,9,10] Deauville scores 1 and 2 are considered negative and scores 4 and 5 are positive (active lymphoproliferative disease). Although patients with score 3 may have a good prognosis, it is recommended that if there is a plan to reduce treatment intensity, it is considered an inadequate response for safety.[7,9,10]

We will not address first-line treatment in this article as this is not the focus of this SBTMO consensus.

AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) - IA

Management of R/R cHL includes a mandatory new biopsy if relapse occurs >12 months from the end of first-line treatment and it is highly recommended if relapse is suspected <12 months or in primary refractory disease.[11]

The two immediate and simultaneous measures for R/R cHL consist of enrolling patient in a transplant center and initiating salvage chemotherapy. Chemo sensitive patients are those who achieve a response rate greater than 50%, with different drug-based protocols. Patients with primary refractoriness or recurrence in less than 1 year after first-line treatment have a worse prognosis.[12] Linch and colleagues demonstrate a clear improvement in disease-free survival (DFS) for the BEAM scheme associated with ASCT.[13,14,15,16,17,18] PET-CT is an important prognostic factor and when negative in pre-HSCT it is associated with a higher event-free survival rate.[19.20] The Chemo rescue more frequently used are DHAP, ESHAP,ICE with Overall Response(OR) 89%,67%,88% respectively. Gencitabine schemas are GDP,CVD e IGV with OR 62%,70 and 88%.

Anti CD30 Brentuximabe Vedotim isolated for patients that have used 2 or more

chemo schemas have been 50% OR. Combinations with Brentuximab Vedotina (BV), monoclonal antibody anti cd30 associated with several chemotherapy schemes such as: BV-DHAP has been emerging as possibilities of rescue with very encouraging results in substitution to conventional chemotherapy thanks to high rates of complete metabolic response before transplantation[20,21,23,24].

MOBILIZATION

Different methods for mobilization are employed and there is no uniformity or significant divergences between the techniques used: a) isolated application of G-CSF in standardized doses of 10 mg and 20 mg/kg/day.[25, 26,27] b) Cyclophosphamide + Growth Factor. Cyclophosphamide in a single dose, 1 to 2 g/m2 7 days before starting the application of G-CSF in the standard dose of 10 mg/Kg/day for 5 days.[28,29,32,33] c) Plerixafor: Fixed dose of 20 mg or 0.24 mg/Kg of body weight for patients weighing ≤ 83 Kg, or 0.24 mg/Kg for patients over 83 kg. It should be applied after 4 days of G-CSF at a dose of 10 mg/Kg/day 6 to 11 hours before apheresis, for 1 to 4 consecutive days.[30,31,34]

CONDITIONING SCHEMES

There are few studies to evaluate different conditioning schemes for ASCT in cHL. The BEAM scheme, Carmustine based, has always been the most used and many European groups emphasized its high antitumor response with acceptable toxicity.[27]However, in 2015 Carmustine left the international market due to the limited availability of the alcoholic solvent necessary for its preparation. The transitory scarcity of Melphalan must also always be considered when choosing the best scheme. Table 1 show schemes that can be used with acceptable toxicity and acceptable relapse rates.

SCHEME	DRUGS
LACE35	Lomustine/Cytarabin/Cyclophofamide/Etoposide
LEAM36	Lomustine/Etoposide/Cytarabin/Melphalan
TEAM37	Thiotepa/Etoposide/Cytarabin/Melphalan
BUEM37	Busulfan/Etoposide/Melphlan
GEMBUMEL37	Gemcitabine/Busulfan/Melphalan
BUCYE37	Bussulfan/Cyclophosfamide/Etoposide
Benda-EAM37	Bendamustin/Etoposide/Cytarabin/Melphalan

POST-AUTOLOGOUS CONSOLIDATION OR MAINTENANCE

Recent studies validated the risk factors for post-autologous relapse and which patients may benefit from post-transplant irradiation. [21,22] These prognostic factors may characterize patients at higher risk of relapse after ASCT: primary refractory disease, relapse in the first 12 months after first-line treatment or after 12 months with extranodal disease or B symptoms, need for > 2 rescue lines or PR/SD before transplantation. Patients with 2 or more factors have high risk replased.[20,22,23] The AETHERA study, a randomized phase III study, evaluated post-autologous consolidation therapy by comparing Brentuximab vedotin versus placebo in patients at high risk of relapse or primarily refractory and after a 5 year median follow up confirmed the DFS benefit of this strategy..[23]

ALLOGENIC TRANSPLANTATION

Reduced intensity conditioning (RIC) - III C

Allogeneic hematopoietic stem cell transplantation remains the only potentially curative strategy for patients with cHL who relapse after ASCT due to graft versus lymphoma effect. However, quality of life and mortality unrelated to relapse is still significant for patients who develop acute or chronic graft versus host disease (GVHD) and severe opportunistic infections. But role and timing for an allogeneic transplantation has been questioned in recent years with the availability of new agents.[38,39,40]

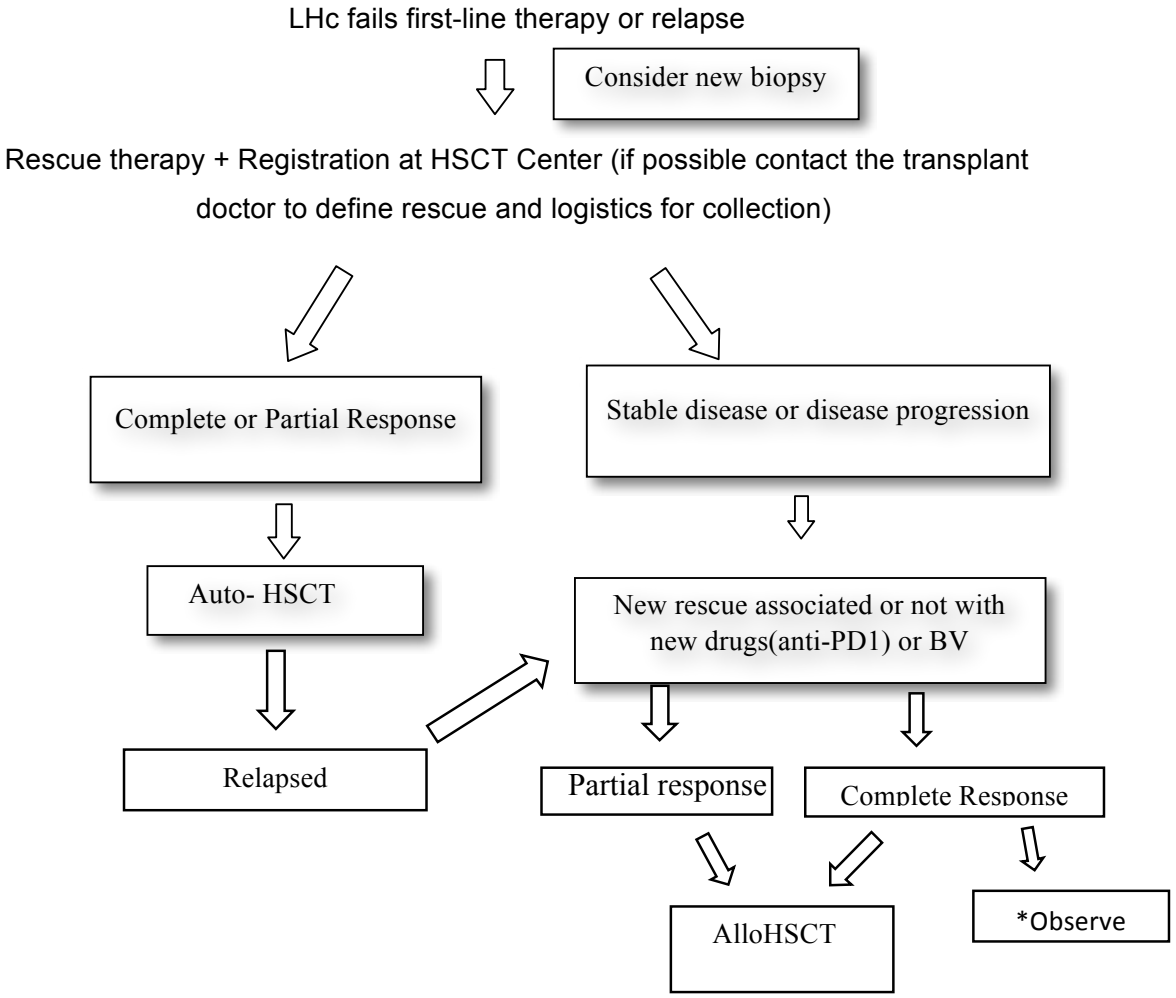
Despite the absence of randomized clinical trials, allogenic HSCT with reduced intensity conditioning (RIC) with an HLA match or haploidentical related donor, and with an unrelated donor has been a therapeutic option for the treatment of patients with relapsed post-autologous LH or with no response to rescue therapies.[41] RIC HSCT is considered the best choice by the American society because it allows a drastic reduction in mortality related to the procedure, however, the relapse rates still remain high. [42.43] The complete response before HSCT was an important differential for the increase in lymphoma-free and global survival, emphasized in the publication by Sarina and collaborators. [44]

In 2018, Gaudio et al. demonstrated through a multicenter retrospective study, no difference in OS (35%) and DFS (34%) between related and unrelated donors. Main risk factor for relapse was disease activity at time of HSCT.[45] The only prospective phase 2 study that evaluated low intensity allogeneic HSCT with 92 patients with LHc showed a TRM of 15% in 1 year and DFS and OS in 4 years completely different in the global population, 18% and 41 % respectively, and in transplant patients with a disease classified as chemossensivel was 40% and 60%.[46]

Currently, the use of monoclonal anti-CD30 antibody, Brentuximab vedotin (BV) has achieved remission rates of around 50% in patients, including those considered refractory to other rescue schemes.[47] BV and anti-PD1 inhibitors are increasingly used before allogeneic HSCT in order to achieve deeper responses before the procedure.[47,48,49].Anti -PD1 inhibitors can be a alternative to relapsed patients after alo HSCT, but the used must be caution because GVHD risk.[50]

There is no consensus regarding the ideal conditioning regimen for RIC HSCT. Fludarabine with alkylating agents are the most used ones. In unrelated HSCT, the association of thymoglobulin is recommended for in vivo depletion of T lymphocytes. The vast majority of patients do not have a full match sibling or unrelated donor and, therefore, haploidentical transplantation has gained strength, especially after the use of cyclophosphamide 50mg/Kg/day (D +3 and D +4) post-transplant for depletion of allo T cells in vivo. Several retrospective studies have shown no significant differences in OS or PFS between transplant modalities with haploidentical donors when compared with matched sibling or unrelated donors.[51,52,53,54]. In some studies, haploidentical HSCT has also been associated with a lower rate of chronic GVHD. Main advantages of haploidentical donor are a faster search, good tolerability and a lower rate of chronic GVHD, but there are considerable disadvantages such as graft failure, acute GVHD and also a delayed immune reconstitution or risk of recurrence.In conclusion, the available evidence of haploidentical transplantation for recurrent / refractory Hodgkin's lymphoma after autologous HSCT is encouraging and this may, in fact, be an excellent option for patients without an available HLA donor.[55]

Algorithm for early referral of LH patients to the HSCT center



*Checkpoints inhibitors seem very effective with promising survival results, however the follow up still too short, to final decision of whether to allograft a patient relapse after auto-HSCT might rely on the risk profile of the underlying disease as well a transplant-related risk.

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HSCT FOR NON-HODGKIN LYMPHOMA

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DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL):

The addition of rituximab to the CHOP chemotherapy protocol (cyclophosphamide, doxorubicin, vincristine and prednisone) significantly improved the results for patients with DLBCL, the most frequent subtype of non-Hodgkin's lymphomas (NHL) [1]. However, there is a subgroup of patients with a worse prognosis [2] identified by the international prognostic index (IPI), where survival rates remain around 50%. Efforts have been made to improve R-CHOP including increasing dose density with 14-day cycles, the use of obinutuzumab, or intensifying therapy such as the DA-EPOCH protocol, but with no definitive clinical benefits [3]. Biological agents such as ibrutinib, lenalidomide and bortezomib have also been incorporated in an attempt to improve results [4] without success. Since the pre-rituximab era studies have incorporated high-dose therapy and autologous HSCT as part of the treatment of these lymphomas in various stages of treatment: remission induction [5-7] with results favoring the therapeutic arm of conventional chemotherapy, consolidation of remission and rescue in disease recurrence [8]. Studies and recent meta-analysis incorporating autologous HSCT as consolidation, after achieving remission in intermediate and high-risk IPI patients have not yet demonstrated evidence of benefit [9-11]. Sub-analyzes within these studies showed that in high-risk patients early intensification could be beneficial. In addition to IPI adverse biological characteristics such as tumor cell of origin (CGB x ABC), presence of MYC rearrangement, BCL-2 and BCL-6 (double / triple-hit) have been studied in this context with no benefit proven [12]. Aggressive NHL relapses, after initial therapy, have a poor prognosis. Rescue regimes with conventional QT, give survival rates, in two years, below 25%. The PARMA TRIAL [13] randomized study demonstrated that autologous HSCT is the treatment of choice for chemosensitive recurrence. SLE rates, over 8 years, were 36% for the transplant arm and 11% for DHAP rescue. In the CORAL trial [14], less than 25% of patients who relapsed within 1 year of diagnosis achieved long-term disease-free survival with autologous HSCT. Final analysis of this study [15] confirmed the previous findings, in addition to demonstrating no benefit of maintenance with rituximab after autologous HSCT. In patients with DLBCL, the data on the results of allogeneic HSCT come from retrospective case series studies and record analyzes [16]. These studies included patients with very advanced disease, with several previous therapeutic lines, in addition to grouping diversified histologies, making it difficult to interpret the findings and take conclusions. Myeloblative conditioning promoted lower rates of recurrence compared to autologous HSCT, but with unacceptably high mortality rates. Reduced intensity conditioning (RIC) have promoted the immune control of the tumor with increased survival rates and reduced transplanted-mortality related [17,18].

DLBCL RECOMMENDATIONS

1.Autologous HSCT is not recommended as consolidation of remission for patients with diffuse large B-cell lymphoma, regardless of the IPI subgroup (1A)

a.Patients with partial response to R-CHOP can be considered for consolidation with ASCT

b.Patients with Double-Hit lymphomas can be considered for consolidation with ASCT if:

i.They have not received non-intensified regimens as initial therapy

ii.They have not achieved Complete Response after intensified schemes

c.DLBCL patients with secondary infiltration in the CNS can be considered for consolidation with ASCT

with schemes targeted for central nervous central primary NHL

2.Autologous HSCT is recommended as the therapy of choice for chemosensitive recurrence (1A); regardless of the time of recurrence.

a.There is no preferred recovery scheme, it is recommended that each center uses the scheme that is most familiar with

b.There is no maintenance benefit with post-transplant rituximab (1B)

3.Allogeneic HSCT is indicated in young patients with post-autologous recurrence using reduced intensity conditioning

FOLLICULAR LYMPHOMA (FL)

Currently, for most patients with FL without early disease-related events, survival is similar to the general population. The prognostic impact of early progression within 24 months of chemotherapy treatment (POD24), with 50% of OS in 5 years compared to 90% in patients without early progression [1-4].

The indication of early intensification in patients with FL in first remission was a matter of debate in the pre-rituximab era [5-8]. In the rituximab era, a randomized study comparing autologous HSCT and conventional chemotherapy and rituximab as the first line showed no difference in OS [9]. A meta-analysis published by Shaaf et al [10] confirmed the absence of benefit in OS rates, when comparing autologous HSCT to conventional chemotherapy with rituximab in previously untreated patients, as first-line therapy for FL.

The management of recurrence should be based on the time of recurrence, if early (POD24) or late. For young patients with POD24, consolidation with high-dose chemotherapy and autologous HSCT should be considered [11]. In the pre-rituximab era, a randomized study (CUP Trial) demonstrated superior results for autologous HSCT compared to conventional rescue in FL [12]. Data from the CIBMTR and the National LymphoCare Study (NLCS), showed that patients who relapse less than 1 year after transplant had a higher OS at five years than those who did not undergo autologous HSCT (73% versus 60%, P = 0.05). In the multivariate analysis, the early use of autologous HSCT was associated with significantly reduced mortality (RR: 0.63; 95% CI: 0.42 to, 94; P = 0.02). [13]

Studies envolving patients with transformed FL (TFL) before the incorporation of immunotherapy demonstrate the efficacy of autologous HSCT [2,14-18]. A study by the Canadian bone marrow transplant group demonstrated a modest improvement in OS and PFS for patients undergoing HSCT compared to the group of patients who had received rituximab and chemotherapy [19]. In CIBMTR analysis, the OS rate was 50% in 5 years and although a small number of patients had previously used pre-transplant rituximab, it did not impact survival rates [20]. In the PRIMA study, patients with TFL who had previously used rituximab appeared to do better when undergoing autologous HSCT. A recent study with untreated TFL patients revealed a tendency towards worse OS in the group submitted to autologous HSCT. [21, 22]

Data from retrospective studies [23], indicate a significantly lower risk of relapse for allogeneic HSCT when compared to autologous, but the benefit is suppressed by the high mortality rates related to the procedure with myeloablative conditioning. For allogeneic HSCT with reduced intensity conditioning (RIC), the recurrence rate is generally below 30%, whether or not preceded by an autologous HSCT, with a 5-year PFS ranging from 50 to 85% [24-28]. The results of match related donors (MSD) and unrelated (MUD) in FL are similar. For patients who do not have MSD or MUD, the use of cord blood or haploidentical family donor may be considered [29-32].

FL RECOMMENDATIONS

1. Autologous HSCT is not indicated in the first line treatment of FL (1A).

2. Autologous HSCT can be considered therapy of choice in young patients with FL with early recurrence (POD24) and chemosensitive (1B).

3. Autologous HSCT should be considered in patients with TFL with chemosensitive disease, who have received therapy initially for FL (1B).

4. Allogeneic HSCT, with conditioning at reduced intensity, should be offered to patients with post-autologous recurrence and HLA-compatible donor (2C), preferably in chemosensitive disease.

MANTLE CELL LYMPHOMA (MCL):

Symptomatic patients or patients with a large tumor load, who have treatment indication, good performance status and permissive comorbidity profile benefit from a more intensive induction regimen with immuno-polychemotherapy through protocols that include rituximab and cytarabine. After induc-

tion treatment, consolidation in first remission with high dose chemotherapy and autologous HSCT is recommended. This recommendation is based on restrospective case series and a prospective study from the pre-rituximab era [1-7]. Progression-free survival ranged from 48 to 68% in 4 years in these studies and overall survival from 61 to 80%. The subpopulations of patients that can benefit the most are those with blastoid / pleomorphic morphology and with a high MIPI risk score. TP53 mutation carriers do not appear to benefit.

The most frequently used conditioning regime is BEAM. Alternatively, CBV, BEAC, BuCyVP [8] and BendamustinaEAM [9] have also been employed. Maintenance treatment with rituximab for 3 years after transplantation is recommended from a prospective randomized study that showed a PFS of 83% in 4 years in the Rituximab arm versus 64% in the control arm [10].

First-line regimens that include new drugs (BTK inhibitors, bortezomib, venetoclax, lenalidomide) may, in the future, replace consolidation with high doses of chemotherapy and autologous HSCT [11-13], depending on the results of prospective studies in progress.

Autologous HSCT can also be offered as a rescue treatment for chemosensitive relapses of fit patients who have not received this treatment modality as consolidation in the first line.

Evidence of an immunological effect of the graft against mantle cell lymphoma supports the indication of allogeneic HSCT in post-autologous recurrence or in first remission for selected cases [14]. Retrospective studies describe progression-free survival of 49 to 56% and overall survival of 54 to 75% in 5 years, with an incidence of 40% relapse reported in the largest series of cases, recorded by the EMBT [15-17]. The conditioning regimes most frequently used were of reduced intensity.

Mostly proposed as a rescue treatment in post-autologous recurrence [18], allogeneic HSCT can be indicated in the first line for fit patients with subtypes of poor prognosis, such as those with mutated TP53 [19], blastoid or pleomorphic variants[20].

MCL RECOMMENDATIONS

1. Autologous HSCT is indicated as consolidation in the treatment of MCL that reached at least PR after the 1st line of treatment in eligible patients (2B).

2. Autologous HSCT can be considered as rescue therapy in patients with MCL with chemosensitive relapses who did not receive ASCT in the first line (2B).

3. Allogeneic HSCT may be indicated for the first-line treatment of MCL in fit patients with poor prognosis disease, such as those with mutated TP53 or blastoid (2C) variants.

B. Allogeneic HSCT can be indicated as a rescue treatment in patients who relapse after autologous HSCT (2C).

PERIPHERAL T-CELL LYMPHOMAS (PTCL)

The 2016 World Health Organization (WHO) classification recognizes up to 29 different types of PTCL [1]. The most common PTCL include peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL, ALK-positive and ALK-negative), extranodal NK/T-cell lymphoma and other rares subtypes. Most of them have an aggressive clinical course and historically dismal results [2]. Treatment in the front-line setting is most often done with anthracycline-based chemotherapy, which is associated with a high failure rate and frequent relapses [3]. The addition of etoposide to CHOP results in an advantage in terms of event-free survival (EFS) but the greatest benefit was observed in young patients and ALK-positive ALCL subtype [4]. Aggressive approaches have failed to bring consistent improvements in long-term survival [5]. Currently, the better understanding of the biology of these diseases and prognostic models [6] has translated into the development of novel treatment options as brentuximab-vedotin (BV) upfront chemotherapy regimen for the PTCL CD30+, histone deacetylase inhibitor (epigenetics therapies), Janus Kinase inhibitor, phosphoinositide-3-kinase inhibitors, lenalidomide, bortezomib as therapeutics strategies [7,8]. Despite the availability of newer active single agents, relapsed and refractory patients are less likely to receive these therapies and continue to have inferior outcomes and improvements in front-line therapies are needed [9,10]. The recent publication of the ECHELON-2 trial [11] has significantly changed front-line treatment paradigms for CD30+ histologies, incorporing BV in front-line therapy, which includes ALK+ and ALK– ALCL, and some AITL and PTCL-NOS, demonstrated by a statistically significant improvement in PFS and OS with a manageable safety profile.

Prospective studies have demonstrated the feasibility and benefit of autologous HSCT as part of the frontline strategy in nodal PTCLs [12,13,14]. In the

final analysis of the largest conducted prospective phase II trial including autologous HSCT in first remission, the Nordic study (NLG-T-01) [13], evaluated the outcomes of 166 patients, of which 62 were classified as having PTCL-NOS. This study demonstrated that 71% of patients completed the therapeutic sequence and 90 patients were in CR 3 months after transplantation. The overall response rate was 78%; and at a median of 60 months, although 82% of patients had advanced disease at diagnosis. The TRM was 4%. The best results were achieved for the ALK- subtype, with OS and PFS rates, in 5 years, of 70 and 61%, respectively. An EBMT registry study, with a median follow-up of 65.8 months, showed a PFS rate for patients transplanted in CR/ PR was 75% compared to 32% for those transplanted with relapsed or refractory disease [15]. The COMPLETE data registry [16] was a prospective multicenter analysis of 499 patients with PTCL. Among the patients in CR following frontline therapy who underwent autologous HSCT, in of nodal types, the median OS was not reached for the autologous HSCT group, versus 57.6 weeks for the non-HSCT group, with a trend of significance ($p = 0.06$). By subgroup, there was superior survival in patients with advanced-stage and intermediate to high-risk IPI in favor of transplant. There was improved PFS and OS specifically for AITL (2-year PFS of 68.8 vs. 41.2) and a trend for improvement in ALK– ALCL (100 vs. 83.8), but not in PTCL NOS. This study demonstrated a trend toward improvement with autologous transplantation in PTCL. High-dose chemotherapy followed by autologous HSCT may improve the outcome in PTCL, and the achievement of a first complete remission before HSCT has proven to be a strong predictor of improved outcome [17,18]. High-dose therapy followed by autologous HSCT is widely recommended for consolidation after a complete or partial remission is achieved. With regard to allogeneic versus autologous transplant, a European trial randomized patients with PTCL to allogeneic versus autologous transplant and found no difference in EFS or OS. There was increased treatment-related mortality in the allogeneic group (31%) but increased relapses (36%) in the autologous group. At this time, there is insufficient evidence to broadly support allogeneic HSCT as part of the frontline strategy, however, reduced toxicity of allogeneic HSCT with recent advances, may alter the risk to benefit risk- benefit ratio [18]. Allogeneic HSCT is not recommended frontline other than for very rare subtypes with extremely poor outcome, such as hepatosplenic T-cell lymphoma (HSTCL) [19].

Most patients with PTCL will eventually relapse. A phase 2, open-label, multicenter study evaluated the efficacy and safety of brentuximab vedotin, for relapsed/refractory CD30+ non-Hodgkin lymphomas, and objective responses were observed in 41% of patients with relapsed T-cell lymphomas, including 54% of AITL patients [20]. There have been no prospective trials evaluating high-dose regimens of chemotherapy followed by autologous HSCT in patients with relapsed PTCL. Treatment with salvage chemotherapy and autologous HSCT may be recommended in those who are transplant eligible and did not receive a transplant in the first remission. Report of the International T-cell project demonstrated that autologous HSCT at the time of relapse was associated with a 3-year survival of 48% compared with only 18% in those without transplantation [21]. However, long-term remission rates to autologous HSCT in this setting are unsatisfactory. For the approximately 30% of patients without relapse in 2 years, the survival is significantly better (5-year OS, 78%) [22].

Allogeneic HSCT for patients with chemo-resistant relapsed/refractory PTCL, and for those who relapse following autologous HSCT, is the only potentially curative therapy. Numerous retrospective studies have been published on this topic, relapse rates ranging range from 17% at 3 years to 49% at 5 years; NRM rates range from 12% at 5 years to 46% at 5 years; and OS rates range from 38% at 3 years to 57% at 5 years [23]. Recent studies have addressed this therapy [24-26]. As novel therapies for relapsed PTCL become available, it will be critical to combine them with allogeneic HSCT (as conditioning and/or maintenance therapies) to improve outcomes in patients with relapsed/refractory disease [27].

PTCL RECOMMENDATIONS

1.Patients with nodal PTCL, in CR/PR, should receive consolidation of remission with autologous HSCT, except ALCL ALK+ subtype (1B)

a.The remission treatment induction therapy must contain etoposide; and brentuximab-vedotin in ALCL CD30+ (2B)

b.Autologous HSCT can be considered in second chemo-sensitive remission in ALCL ALK+ (2C)

c.Primarily refractory patients should not be transplanted with autologous HSCT (2B)

d.PET positivity found at the end of induction treatment and in patients who have received autologous HSCT is a strong predictor of reduced survival

2.ATLL: Allogeneic transplantation is the only chance to cure ATLL and is recommended for aggressive

subtypes (acute, lymphoma type and chronic high risk) upfront for transplant-elegible patients (2B) [28]

3.HSTCL: For patients eligible, allogeneic transplantation is recommended as consolidation after induction therapy reaching CR or PR. Autologous transplant can be considered if a suitable donor is not available or the patient is not elegible for allogeneic transplant (2B) [29]

4.Allogeneic transplantation is the therapy of choice for patients with post-autologous recurrence disease (2C)

a.Myeloablative or non-myeloablative conditioning regimens can be used

b.Allogeneic HSCT is recommended frontline in hepatosplenic T-cell lymphoma due to its refractoriness to conventional chemotherapy regimens, aggressive clinical course and poor outcomes.

AUTOLOGOUS CONDITIONING:

The most commonly used protocols in autologous HSCT, for patients with lymphoma, include carmustine but in the current Brazilian reality, this medication is not marketed. Therefore, substitutes such as lomustine, bendamustine, busulfan or mitoxantrone are some of the alternatives to be associated with alkylating agents and topoisomerase inhibitors.[1-9]. The combination of gemcitabine with other drugs has also been used for lymphomas.[10-12]

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HSCT FOR MYELODYSPLASTIC SYNDROMES (MDS)

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MYELODYSPLASTIC SYNDROMES (MDS)

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal disorder that is characterized by cytopenias, dysplasia in one or more cell lines, ineffective hematopoiesis and, depending on its subtype, may have presence of blasts, being frequently associated with genetic alterations. In approximately 30% of cases it can progress to acute myeloid leukemia.

CLASSIFICATION AND PROGNOSTIC STRATIFICATION

Detailing in the classification is very important, as it is decisive in defining the initial conduct and in the prognosis of the disease. Currently, we use the WHO classification 2016.[10-14,34] A very relevant aspect are the situations in which we have cytopenias, sometimes severe, with transfusion dependence or even complex karyotypes with large numbers of mutations, and even so the diagnosis of MDS cannot be concluded, being defined as Clonal Cytopenia of Undetermined Meaning (CCUS) NCCN Guidelines version 2.2020[35], where there is already a discussion of HSCT, in selected cases.

Risk stratification in MDS can be performed using different scores, such as R-IPSS, IPSS, WPSS and MD Anderson Score.[15-17] This first is the most used and is divided into five prognostic groups (Very Good, Good, Intermediate, Poor and Very poor), in which cytogenetics is crucial for classification. Despite being revised and being more refined in cytogenetic changes, it still does not fully cover the complexity of stratification of this pathology, as it does not consider marrow fibrosis and the presence of prognostic mutations, among the most relevant we have TP53, RUNX1, ASXL1 , EZH2, ETV6, TET2 and DNMT3.[18-21]

We know that some patients classified as low risk (LR) could have a poor evolution, due to severe neutropenia, recurrent infections and a high transfusion need[22], which, if not resolved, can lead to lethal outcome.

TREATMENT

The rationale for treatment is based on the risk stratification of the patient at low risk (LR) or high risk (HR). In patients classified as LR in the R-IPSS, who are not transfusion dependent, management should be conservative. Clinical treatment, if necessary, is the best option, based on the use of erythropoietin and oral iron chelators in case of ferritin> 1000 ng / mL or more than 20 transfusions.[35]

INDICATION OF ALLOGENEIC HSCT IN MDS

Allogeneic HSCT is still the only curative procedure, but some questions are imposed in the face of this statement: who and when?. Since most of these patients are elderly and have comorbidities, many are ineligible for HSCT. We can use the HCT-CI comorbidity index[24-26] and prognostic stratification to assist in this difficult decision. Cutler et al. through Markov's analysis, it was determined that patients classified as high risk should be considered eligible for early allogeneic HSCT if the IPSS was used as a prognostic instrument.[26]

Comprehensive geriatric evaluation (CGA) is currently considered a fundamental criterion for defining eligibility and type of conditioning.

With the use of R-IPSS, some patients previously considered LR by IPSS, were reclassified as HR. This modification, added to the presence of factors of bad prognosis, such as marrow fibrosis, CD34 positivity in immunohistochemistry or presence of mutations

of poor prognosis, can be considered, at the moment of clinical decision, for the implementation of a more aggressive therapy such as use of hypomethylating agents and allogeneic HSCT.[36]

Myeloablative allogeneic HSCT should be considered for patients under 60 years of age who have an identical HLA related donor. In elderly patients over the age of 60 years, allogeneic HSCT with reduced intensity conditioning (RIC) becomes an alternative, as studies show that age alone should not be considered a contraindication. Some European groups have proposed the 55-year limit for defining the type of conditioning, but this conduct is not a consensus. We believe that the individual characteristics, associated with HCT-I and CGA, can be reliable parameters in defining the type of conditioning. With the possibility of RIC and the inability to cure with chemotherapy drugs despite increased survival,[27] more and more, we are faced with the dilemma of the indication of allogeneic HSCT in the elderly. The growth of haploidentical transplantation, made the chance of an alternative family donor and the intensity was more reduced.

In HR patients, hypomethylating therapy should be considered in the first approach, with azacitidine being the drug of choice with level of evidence 1A according to the NCCN Guidelines version 2.2020. [35] This drug can be used in pre-HSCT while looking for a compatible donor. The need for compulsory cytoreduction prior to HSCT has been questioned, since retrospective studies of the German (Schroeder, BMT)[39] and Latin American (Duarte, BBMT)[40] groups have not shown significant differences in the results of transplants. Perhaps the reduction of the time between donor preparation and the time of transplantation, is more relevant.

In patients with no doubt in the indication of allogeneic HSCT and the absence of a related donor, we must start the search for unrelated donors. According to retrospective data from the CIBMTR,[28,29] corroborated by the EBMT data,[30] this procedure should not be disregarded, since the analysis of 4-year survival is similar to that of patients undergoing HSCT with a related donor.

The possibility of using umbilical cord cells should be considered mainly in pediatric patients. In addition to disease recurrence, the high rate of graft failure should be considered, and more recently an early monitoring of chimerism has been proposed as a way to better monitor this complication.[31]

STRATEGIES AFTER ALLOGENEIC HSCT

The relapse of MDS after allogeneic HSCT is a concern, especially in patients undergoing HSCT with

RIC. It has been associated with reduced survival in two years, with prognostic factors being the presence of acute GVHD and relapse in the first six months after HSCT. Donor lymphocyte infusion and a second allogeneic HSCT are options in this context, when possible.[32]

Azacitidine started to play an important role in post-HSCT[32] due to its immunomodulatory action and the ability to raise T-reg Lymphocytes,[33] in order to maintain remission. Some studies propose that when there is evidence of loss of chimerism, azacitidine can be started early, being able to prevent disease relapse. The use of azacitidine after HSCT can be an alternative to increase the action of the graft versus leukemia, without increasing GVHD.[33-38]However, in a prospective and randomized study (Oran B et all),[41] the role of isolated maintenance with azacitidine was questioned, with no significant survival difference between the groups using or not using azacitidine. Numerous studies with new drugs have been conducted, among them, the associations of venetoclax, check point inhibitors and APR-246 associated with the hypomethylating agent, showing at first an improvement in maintenance results, but still without randomized studies. The role of the association of DLI (donor lymphocyte infusion) cannot be forgotten.

CONCLUSION

The chronic course of some patients with MDS and transplant-related mortality (TRM) lead to a reluctance to offer such a procedure earlier, but this delay can compromise the chances of success. We must surround ourselves with criteria for this decision, remembering the use of the specific comorbidity index for HSCT, CGA and risk stratification. The possibility of using reduced intensity conditioning decreased the TRM, allowing one to envision this procedure for patients previously considered ineligible. The IPSS and the R-IPSS are useful parameters to guide the clinical decision to decide the allogeneic HSCT, especially in patients with a HLA compatible donor. According to data from the NCCN, survival in HR patients is better if the transplant is performed early.

Already classified as LR, we must surround ourselves with the greatest possible prognostic refinement to

make this decision. The valuation of mutations, especially p53, TET2, DNMT3, ASXL1, has been increasingly relevant as a prognostic factor for treatment, indication for transplantation and sometimes follow-up of minimal residual disease. The p53 mutation specifically confers an independent prognostic factor, is associated with a complex karyotype and when present together with the 5q deletion, it has been related to the loss of response to lenalidomide and confers a poor prognosis even with transplantation.

With the knowledge we have today, allogeneic HSCT for MDS is an option, which can be performed in elderly patients, with acceptable levels of mortality and morbidity related to transplantation. The decision of when to perform the HSCT should be based on the patient's comorbidities and on the predictive factors of the disease, always evaluating the benefit-risk between the transplant and the other treatment options.

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HSCT FOR AUTOIMMUNE DISEASES

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Autologous hematopoietic stem cell transplantation (AHSCT) has been used worldwide as treatment for autoimmune disease patients, and although different centers have slightly different approaches, the main strategy remains similar[1]. Briefly, the procedure consists of a first phase, when autologous hematopoietic stem cells are harvested (mobilized) and cryopreserved, and a second phase, including conditioning regimen and infusion of stem cells. The aim of AHSCT is to promote immune depletion, eliminate autoreactive lymphocytes and reprogram the immune system, restoring long-lasting immune tolerance. As result, patients maintain long-term clinical remission in absence of further immunosuppression.

Three of the most important and current indications for AHSCT are multiple sclerosis (MS), systemic sclerosis (ES) and Crohn's disease (CD)[1]. The American Society for Cellular Transplantation and Therapy (ASTCT), the European Society for Blood and Marrow Transplantation (EBMT) and the Brazilian Society of Bone Marrow Transplantation (SBTMO) currently consider AHSCT as part of the already established therapeutic strategies for these three autoimmune disorders, apart from the research setting.

MULTIPLE SCLEROSIS

In addition to numerous studies published since 1993, two randomized clinical trials are available in the literature. In the ASTIMS study, AHSCT was compared to mitoxantrone; 9 of 21 MS patients were randomized to AHSCT, conditioned with BEAM and rabbit antithymocyte globulin (ATG)[2]. In this study, patients with an average disease duration of 10 years were included, most of them already in the secondarily progressive phase of the disease. Over 4 years, the average number of new T2-weighted magnetic resonance imaging (MRI) lesions was 2.5 in the AHSCT group versus 8 in the mitoxantrone group (p=0.00016). None of the transplanted patients presented new MS lesions at MRI with gadolinium. The progression of the Expanded Disability Status Score (EDSS) was similar in both groups, worsening in 57% of the patients in the AHSCT group, versus 48% in the mitoxantrone group (p=0.50). More recently, a multicenter study compared AHSCT with the best available treatment chosen by the neurologists at each center[3]. One hundred and ten patients with highly inflammatory MS (relapsing-remitting subset and inflammation on MRI) were randomized. The AHSCT group was conditioned with 200 mg/kg cyclophosphamide plus rabbit ATG. In the first year of follow-up, the EDSS decreased (neurological improvement) in the transplanted patients, while increased in the non-transplanted patients (p <0.01). In 5-year follow-up, the EDSS worsened in 3/52 (5.8%) patients in the AHSCT group, against 34/51 (66.7%) in the non-transplanted group, and there were relapses in 15.4% of patients in the AHSCT group versus 85.2% in the non-transplanted group. There were no deaths or grade 4 toxicities related to transplant.

In 2019, the American Society for Transplantation and Cell Therapy (ASTCT) published a comprehensive review of the literature and recommended AH-

SCT as "standard of care, available clinical evidence" for relapsing-remitting, treatment-refractory MS[4].

Patients to be considered for transplantation should have inflammatory phenotypes of MS, which include patients with the relapsing-remitting form having presented well-defined relapses in the last 12 months, or patients with the secondary progressive form showing inflammatory lesions (gadolinium enhancement or new T2 lesions) on MRI images in the last 12 months.

SYSTEMIC SCLEROSIS

Case reports and phase I/II studies have been published since 1996, demonstrating safety and efficacy of autologous transplantation for SSc. In the last decade, three randomized studies have shown that AHSCT is superior to conventional treatment in patients with SSc, promoting greater overall survival, progression-free survival and quality of life.

The first study included 19 SSc patients, who were randomized either to non-myeloablative AHSCT with 200 mg/kg cyclophosphamide plus rabbit ATG or to conventional treatment with cyclophosphamide monthly pulses[5]. In a two-year follow-up, AHSCT was more effective in controlling skin involvement, lung function and improving quality of life than conventional treatment. No deaths were reported. The second study, led by the EBMT, compared 79 transplanted SSc patients with 77 others, treated with cyclophosphamide monthly pulses, showing superiority of AHSCT in terms of overall survival, progression-free survival and quality of life[6]. Although the final outcomes were positive, this study showed a transplant-related mortality of approximately 10%, mainly due to cardiac causes[7]. As result of this and other studies, the EBMT and partners now recommend careful cardiac evaluation before enrolling a patient for AHSCT, aiming to improve patient selection and reduce treatment-related mortality[8,9]. Cardiac evaluation should include electrocardiogram, echocardiogram, 24h-Holter, cardiac resonance and right-side cardiac catheterization with volume overload8.

The third study, multicenter randomized, compared 36 SSc patients undergoing myeloablative AHSCT, with 39 treated with cyclophosphamide pulses[10]. The transplant-conditioning regimen included low-dose cyclophosphamide plus total body irradiation and horse ATG. The study demonstrated greater overall survival and progression-free survival in transplanted patients compared to the non-transplanted group. A transplant-related mortality of 3% was observed.

Since 2017, the European League Against Rheumatism (EULAR) has recommended AHSCT for patients with rapidly progressive SSc at risk of organ failure[11]. Since 2018, the ASTCT has also recommended autologous transplantation as standard treatment for severe cases of SSc[12]. Treatment protocols have been refined and incorporated into the routine of several transplant centers.

AHSCT is indicated for patients with diffuse SSc with worsening of skin involvement, or patients with interstitial lung disease with worsening of lung function, in the last 6 months, refractory to immunosuppressive treatment.

CROHN'S DISEASE

AHSCT has emerged as a potential treatment for CD due to the chronicity of the disease and lack of therapeutic options in refractory patients. Since 1993, there have been reports of patients with CD who had concomitant leukemias or lymphomas, with complete remission of both diseases after hematopoietic stem cell transplantation. In 2010, researchers from the Northwestern University (Chicago, USA) described the long-term follow-up of 24 patients with severe, active and refractory CD who underwent AHSCT with 200 mg/kg cyclophosphamide and rabbit ATG[13]. The study showed an excellent remission rate after AHSCT, but with high incidence of disease reactivation in the long-term follow-up. The progression-free survival of CD patients was 91% in the first year, 63% in the second, 57% in the third, 39% in the fourth and 19% in the fifth year after AHSCT. Nevertheless, when compared to conventional treatment, AHSCT outcomes are quite encouraging. The Crohn's Disease Activity Index (CDAI), used in the routine assessment of CD patients, must be less than 150 to indicate remission[14]. Conventional medications (synthetic and biological immunosuppressants) induce clinical remission in 40 to 50% of patients in one year, and this percentage also decreases over time. Thus, when studies show that AHSCT induces clinical remission (CDAI <150) in more than 80% of patients in the first year, these results can be interpreted as favoring AHSCT.

In 2017, the EBMT published a study that included 45 patients with active CD and who were refractory to conventional treatment[15]. Patients were randomized to either only mobilization with 4 g/m2 of cyclophosphamide or to mobilization followed by AHSCT with 200mg/kg of cyclophosphamide plus rabbit ATG. The primary endpoint of this study, however, was excessively stringent, as complete clinical, radiological and endoscopic remission (a sustained dis-

ease remission composite score) should be achieved at the end of the first year. As consequence, there were no differences in the number of patients who met the sustained disease remission target, between transplanted and non-transplanted patients. For secondary endpoints of disease activity, endoscopic activity and use of medical therapy, results favored the group of transplanted patients.

A subsequent reassessment of the results from the same study, using more traditional evaluating tools, led to conclusions that AHSCT promotes clinical and endoscopic benefits, despite the high number of adverse events[16]. Other transplant centers, including from Brazil, have shown beneficial results from non-myeloablative AHSCT[17]. The studies demonstrate acceptable toxicity of the procedure with reduced doses (2 g/m2) of cyclophosphamide in the mobilization phase, and improvement of the immediate and long-term quality of life in patients undergoing AHSCT. The mortality rate was zero in most studies. In a large number of cases, there were endoscopic remissions with healing of lesions and remissions in imaging studies.

Allogeneic HSCT may be a future option. A recent pilot study with 9 patients undergoing allogeneic transplantation showed that the procedure was effective in controlling the disease in the short and long term[18]. However, there was high transplant-related toxicity and one patient died due to infection by adenovirus three months after transplantation.

To date, the EBMT, the Center for International Blood and Marrow Transplant Research (CIBMTR), and communications from the United States and Brazil report a total of 334 transplants for CD, 318 of which are autologous, characterizing this autoimmune disease as the third most frequently transplanted in the world. These data reflect the severity of the disease and the demand for more effective therapeutic resources. Patients with clinically and endoscopically active CD, refractory to conventional treatment including at least two biological drugs, should be indicated for autologous transplantation.

In conclusion, data from national and international studies provide scientific support to recommend AHSCT as treatment for multiple sclerosis, systemic sclerosis and Crohn's disease (Table 1). Allogeneic transplantation, however, should still be further evaluated in the experimental setting.

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TABLE 1 – SBTMO recommendations for AHSCT in autoimmune diseases

Disease	Autologous transplantation	Allogeneic transplantation		
		MSD	MUD	MMAD
Multiple sclerosis	Recommended/I	Experimental/III	Not recommended/III	Not recommended/III
Systemic sclerosis	Recommended/I	Experimental/III	Not recommended/III	Not recommended/III
Crohn's disease	Recommended/II	Experimental/III	Not recommended/III	Not recommended/III

SBTMO: Brazilian Society of Bone and Marrow Transplantation; AHSCT: autologous hematopoietic stem cell transplantation. MSD: matched sibling donor; MUD: matched unrelated donor; MMAD: mismatched alternative donor. Table created by the authors.

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HSCT FOR SOLID TUMORS

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INTRODUCTION

High-dose chemotherapy (HDCT) with stem-cell support is a procedure that allows the administration of high doses of chemotherapy that would be lethal otherwise. In HDCT, extra-medullary toxicity is the dose-limiting factor. Use of peripheral blood stem cells and improvement in patient management has reduced non-relapse mortality to less than 5%. Over the last decades, knowledge about HDCT in solid tumors has increased, particularly in breast, ovary, lung, and germ cell tumors (GCT)[1–3]. Allogeneic hematopoietic stem-cell transplantation (HSCT) has also been explored, especially in advanced kidney cancer[3].

HIGH-DOSE CHEMOTHERAPY (HDCT) FOR GERM CELL TUMOR (GCT)

Recommendation: HDCT should not be offered for frontline therapy in germ cell tumors (Level of Evidence 1b, Grade of Recommendation A).

Recommendation: HDCT should be offered as second or third-line therapy of germ cell tumor, even in patients with mediastinal, platinum-refractory, or non-seminomatous GCT (Level of Evidence 2b, Grade of Recommendation B).

Recommendation: Conditioning regimen should be carboplatin and etoposide (Level of Evidence 1b, Grade of Recommendation A).

Recommendation: Two or three cycles of HDCT should be offered instead of one (Level of Evidence 1b, Grade of Recommendation B).

Recommendation: For patients with residual disease following HDCT, surgical resection should be performed (Level of Evidence 4, Grade of Recommendation C).

Testicular malignant tumors are the most frequent solid tumor of the young male, and 95% of these are germ cell tumors (GCT)[4]. They are unique tumors in which they represent a malignant transformation of a totipotent germ cell. They are divided, histologically, in seminoma and nonseminoma. Both secrete beta-human chorionic gonadotropin (beta-HCG), while only the latter produces alpha-fetoprotein (AFP). Approximately 75% of the patients are cured with conventional5. Follow-up includes serial image exams and of the serum markers HCG e AFP.

FRONTLINE HIGH-DOSE CHEMOTHERAPY

Frontline HDCT is not recommended. There are four randomized trials (an Italian[6], a French[7], an American phase III[8], and a European phase III[9]) that have not shown a benefit of HDCT in high-risk patients. In the American trial, however, there was a trend towards better response in patients with unsatisfactory tumor marker response (61% CR with 1-y duration, against 34%, p=0.03). A systematic review that included phase III and phase II trials showed no overall survival benefit in patients with unsatisfactory serum marker response[10].

RELAPSE AND REFRACTORY DISEASE

A unique characteristic of germ cell tumor management is that conventional chemotherapy can cure relapsed patients. A large series is frequently cited for comparison[11]. In this series, relapsed and refractory patients were treated with vinblastine, ifosfamide, and cisplatin (VeIP). Fifty percent reached a complete response, and 24% were long-term disease-free.

Diagnosis of relapsed/refractory disease is not always straightforward. Patients with residual disease and persistently high AFP or HCG markers frequently have irresectable viable cancer and should undergo chemotherapy instead of surgery. On the other hand, radiologic progression paradoxically associated with adequate decline of serum markers can occur with teratoma growth syndrome, which should not be interpreted as progression[12]. Teratoma is insensitive to chemotherapy, and residual lesions should be resected. Likewise, lung nodular lesions, especially subpleural, can be induced by bleomycin. Moreover,

marijuana can lead to a rise in HCG, and a rise in luteinizing hormone secondary to hypogonadal status may interfere with the HCG test.

Patients whose diseases progress during frontline therapy or within 4 weeks of the last dose of chemotherapy (platinum-refractory) are a poor-prognosis group of patients. Patients with seminoma have a better prognosis, as well as those with testicular or retroperitoneum relapse. Patients with mediastinal disease are another group of poor prognosis. Patients with an incomplete response, who are platinum-refractory, or primary mediastinal site have less than 10% overall survival in 10 years[13,14].

HIGH-DOSE CHEMOTHERAPY IN RELAPSED/ REFRACTORY PATIENTS

High-dose chemotherapy is the second-line treatment of choice in many institutions, despite the lack of positive randomized trials. The chemosensitivity of GCT, the marked dose-response effect, the extremally low incidence of bone marrow metastasis, and the young age of these patients make HCT very attractive.

First phase I and II studies, from Indiana University[15] and the Eastern Cooperative Oncology Group[16], have shown that 15-20% of patients with multiple relapses can be cured. In the Indiana series, all long-term surviving patients received two cycles of HDCT, and 75% of the patients with partial remission achieved complete remission after the second cycle. These studies underline the importance of surgery in patients with residual disease following HDCT.

Subsequent studies focused on drug-dose escalation[17], establishing the maximal tolerated dose Carboplatin 2,100 mg/m2 and Etoposide 2,250 mg/m2. Marked reduction of non-relapse mortality was achieved with peripheral blood stem-cells.

There is only one phase III trial of HDCT in relapsed GCT[18]. In this study, 280 patients were randomized to receive 4 cycles of conventional chemotherapy or 3 cycles followed by HDCT. There was no difference in disease-free or overall survival. This study has been criticized by the low power, the toxic conditioning regimen, and the one-HDCT cycle. A systematic review supports the need for at least 2 cycles of HDCT10.

The greatest evidence of benefit of HDCT comes from a registry study[19], which included more than 1,500 patients and showed a lower risk of death in first-relapse patients who received HDCT (HR=0.65, 95%CI 0.56-0.75). In subgroup analyses, nonseminoma and low-risk patients seemed to not benefit. These results were confirmed in a retrospective analysis of the German Testicular Cancer Study Group[20]. Moreover, this study shows that more than 70% of relapsed patients undergo HDCT in second-line therapy, making comparisons more difficult.

Currently, the best reported results are from the Indiana University[21] and the Sloan-Kettering Cancer Center[14].

The Indiana University [21,22] performs two HDCT cycles with Carboplatin 2,100 mg/m2 and Etoposide 2,250 mg/m2 followed by oral etoposide maintenance. With a median follow-up of 40 months, progression-free survival was 40%. Interestingly, half of the patients with platinum-refractory or third-line patients had an excellent response.

The Memorial Sloan-Kettering Cancer Center[14] performs three cycles of HDCT with Carboplatin and Etoposide. 5-y overall survival was 52%. Most patients were platinum-refractory. Long-term overall survival for patients with mediastinal disease was 24%.

CONDITIONING REGIMEN AND SEQUENTIAL THERAPY

The role of sequential HDCT and the addition of a third drug have been studied.

The German Testicular Study Group[17,23] compared one cycle of HDCT with three cycles. A third drug was added to the group that received one cycle, but the mortality was significantly higher (16 versus 4%), and the study was halted.

Grossi et al[24], in a prospective study that included all patients treated in Switzerland, have not found differences in outcomes between 2 or 3 cycles of HDCT, while 1 cycle seemed to yield inferior results. In subgroup analysis, the third cycle of HDCT seemed to benefit patients who achieved a complete response after the first cycle. DeFilipp[25] also found no difference between 2 or 3 cycles of HDCT.

In a large registry study[19], 5-y overall survival was significantly higher in patients who received sequential HDCT (61% versus 46%, $p<0.001$) and in those who received Carboplatin and Etoposide conditioning (62%, against 35% with +Ifosfamide, 44% +Thiothepa, 56% +Cyclophosphamide, $p<0.001$).

An EBMT registry study[26] suggested that non-relapse mortality is lower with Carboplatin and

Etoposide conditioning regimen for patients older than 40 years.

A systematic review[10] suggests that at least two cycles of HDCT should be offered, and a single cycle should not be used.

An EBMT study[27] showed that the rates of secondary malignancies are 4.2% (solid tumor) and 1.4% (hematologic malignancy).

POST-HDCT RESIDUAL MASS

Surgical resection of residual masses plays an important role, contributing to the cure. In a German retrospective analysis[28], viable tumor cells were found in 46% of the patients, and event-free survival in 5 years was 38%. In patients with viable cancer, there is no benefit in chemotherapy. Progression and relapse following HDCT have a dismal prognosis, and in the Indiana series[29] only patients who received surgical treatment were alive.

Graft product contamination

Tumor cells can be identified in up to half of the apheresis-collected grafts, but its importance is unknown. Results are contradictory. In one of them, there was no difference between the groups[30], in another all patients with detectable tumor cell relapsed[31], and in the third no patients with undetectable tumor relapsed[32].

HIGH-DOSE CHEMOTHERAPY FOR OTHER SOLID TUMORS

Recommendation: HDCT should be offered for ovarian germ tumor or gestational trophoblastic tumor, chemorefractory (Level of Evidence 4, Grade of Recommendation C).

Recommendation: HDCT should not be offered to any kind of breast cancer (Level of Evidence 1a, Grade of Recommendation A).

Recommendation: HDCT should not be offered for ovary or lung cancer (Level of Evidence 2b, Grade of Recommendation B).

Recommendation: HDCT should be offered to patients with high-risk localized Ewing sarcoma (Level of Evidence 1b, Grade of Recommendation A). HDCT can be offered for relapsed Ewing sarcoma (Level of Evidence 2a, Grade of Recommendation B)

High-dose chemotherapy in ovarian cancer

HDCT was tested in refractory and chemosensitive ovarian cancer[33–38]. Despite initial response, short remission was documented, and no benefit was observed[36–39]. For patients with relapsed ovarian germ cell tumors, HDCT can be curative [40,41].

High-dose chemotherapy in lung cancer

Small cell lung cancer is an extremally chemo- and radio-sensitive disease, with response rates of 80%. Few patients are cured however2. Results with HDCT were disappointing, and the procedure was abandoned[42,43].

High-dose chemotherapy in breast cancer

The role of HDCT in breast cancer remains controversial despite more than 20 years of experience. Two meta-analyses of randomized trials[44,45] have not found survival benefit in HDCT. Recently, in a subgroup analysis, Steenbruggen et al[46] suggest there might be a benefit for patients with 10+ positive lymph nodes or with triple-negative breast cancer. These results, however, must be confirmed in appropriately designed clinical trials.

High-dose chemotherapy for gestational trophoblastic neoplasia

Gestational trophoblastic disease is a heterogeneous group of diseases that arise from the abnormal proliferation of the placental trophoblast, i.e., of the fetal tissue. It includes, among others, choriocarcinoma, trophoblastic tumor, and invasive mole. Beta-HCG may be high. Case reports and case series reported cure with HDCT[47–50].

High-dose chemotherapy for Ewing sarcoma

Overall survival of Ewing sarcoma patients with conventional therapy ranges between 9 and 41%. Patients with high-risk localized disease benefited from frontline HDCT[51]. High-risk disease was defined as poor histologic response (≥10% viable cells), large tumor volume at diagnosis (≥200 mL), or small tumors with poor radiologic response (<50% reduction). In patients with pulmonary metastases, no benefit was seen[52]. A systematic review of observational studies suggests that relapsed patients might benefit from HDCT[53].

Allogeneic stem cell transplantation in solid tumors

Recommendation: There is no data to recommend allogeneic stem-cell transplantation in solid tumors in any setting.

TABLE 1 - Selected conditioning regimens

Institution	Carboplatin	Etoposide	Cyclophosphamide	# Transplants
MSKCC14,54dose-intense chemotherapy with paclitaxel and ifosfamide followed by carboplatin and etoposide (TICE	AUC=24	1,200mg/m2	x	3
Indiana16 *	2,100mg/m2	2,250mg/m2	x	2
MSKCC55	1,500mg/m2	1,200mg/m2	150mg/kg	2
Germany56	1,500mg/m2	1,500mg/m2	x	3
	Cisplatin	Etoposide	Ifosfamide	# Transplants
EORTC9etoposide, and ifosfamide (VIP	100mg/m2	1,500mg/m2	12,000mg/m2	3

*etoposide oral maintenance 50mg/day x 21 days every 4 weeks for 3 cycles

TABLE 2 - High-dose chemotherapy in relapsed/refractory GCT patients

Institution	#Patients	%CR	%Alive and disease-free	Follow-up	TRM
MSKCC55	58	40	21	28 months	12%
Indiana15	40	30	15	> 24 months	18%
Germany57230 patients were planned to be recruited in a prospective, randomized, multicenter trial comparing one cycle of cisplatin 100 mg/m2, etoposide 375 mg/m2, and ifosfamide 6 g/m2 (VIP	74	50	38	48 months	3%
MSKCC58which had been identified previously as favorable prognostic factors to conventional-dose salvage chemotherapy.\nRESULTS: Thirty-two (70%	84	56	50	58 months	NA
Indiana21	184	NA	63	48 months	3%
ECOG16	38	24	13	> 18 months	13%
Europe18	109	26	31	45 months	7%
Germany59	176	15*	34	> 60 months	NA
Germany28postchemotherapy resections of residual tumors were performed in 57 patients who had been treated with HDCT for relapsed or refractory GCT and who had achieved a partial remission to this treatment.\nRESULTS: Complete resections of residual masses were achieved in 52 (91%	211	22**	43	36 months	9%
MSKCC14	107	42***	53	> 60 months	2%

CR: complete remission; TRM: Transplant-related mortality. NA: Not available
* 38% in total, when included patients who underwent posttransplant surgical resection
** 37% in total, when included patients who underwent posttransplant surgical resection
*** 50% in total, when included patients who underwent posttransplant surgical resection

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HSCT FOR PEDIATRIC DISEASES

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The Brazilian Society of Bone Marrow Transplantation (SBTMO) started in 2009[1] its Consensus Meetings to discuss the indications for Hematopoietic Stem Cell Transplantation (HCT), and the resulting consensus guidelines have ever since remained freely available at the SBTMO website (www.sbtmo.org.br/consenso).[2] Now, in its 5th edition, the Consensus material will, for the first time, be published in the Journal of Bone Marrow Transplantation and Cellular Therapy (JBMTCT - www.jbmtct.com.br) recently launched by SBTMO, the first scientific journal in Latin America focused on HCT.[3] The recommendations will remain in Portuguese at the SBTMO website, and in English at the Journal website.

All prior meetings have been presential except for this one, on October 26, 2020, initially planned to be hosted in the city of São Paulo, immediately before the XXIV SBTMO Annual Meeting, and modified to a digital platform (www.congressosbtmo.org.br) due to the SARS-Cov2 pandemic, as has been the case with so many other national and international meetings in the field.

Although a significant impact of COVID-19 on the activity of solid organ transplantation has been witnessed in the country over the past few months, when comparing the first half of 2019 to that of 2020, an overall reduction of only 10% in allogeneic HCT was observed,[4] which highlights the critical relevance of this procedure and the boundless commitment of both donors and healthcare professionals to the treatment of an array of life-threatening diseases that may be effectively treated with a timely transplant. Hence, the annual number of transplants has been growing continuously worldwide,[5] as well as in our country.[4]

The addition of post-transplant cyclophosphamide to haploidentical transplantation for graft-versus-host disease (GVHD) prophylaxis, initially developed within experimental platforms[,6] has been used in clinical trials since 2002[7] with an astounding impact on donor selection and transplantation practices worldwide. As a result, hundreds of publications on haploidentical HCT have shown very similar outcomes to those obtained with unrelated HCT[8,9] To date, the only randomized-controlled trial available comparing double unrelated cord blood with haploidentical marrow transplantation (BMT-CTN 1101) showed a lower transplant-related mortality and better overall survival with the use of haploidentical donors.[10]

Allogeneic HCT, traditionally a therapeutic option restricted to patients with an HLA-compatible donor, is now available to virtually all who need it, since parents and children invariably share a common haplotype, in addition to half of the siblings. The worldwide and Brazilian experience acquired during the past several years with the various types of donors and grafts has enabled us to change our rationale for recommending HCT.

Many current consensuses for HCT indications no longer differentiate between indications for transplants using grafts from HLA-identical related and haploidentical donors, adult unrelated donors, and umbilical cord blood units.[11] Nonetheless, each transplant strategy has its own particularities, risks and benefits. When performing any HCT with HLA incompatibility, it is essential to look for donor-specific antibodies (DSA) and to have strategies to desensitize the patient if antibodies against the donor are found.

Patients with an indication for allogeneic HCT should be transplanted with the best available donor as soon as the procedure is indicated, before disease progression or deterioration of the patient's clinical status. These are the most important prognostic factors for treatment outcome.

Pediatric diseases requiring HCT have a much lower prevalence in the population than diseases affecting adults. The discovery of a myriad of specific genetic abnormalities has changed our understanding of many malignant and non-malignant pediatric diseases. When all these specificities are combined to the various types of donor and transplant strategies now available, we understand that the classical model used to define HCT indications in adults, with meta-analyses and randomized trials, are not applicable in pediatrics. In addition, many pediatric diseases do not have therapeutic alternatives with curative potential that can be compared to HCT results. Thus, in this 2020 Consensus, we chose to follow international guidelines[11] and make recommendations for indications of autologous and allogeneic HCT, regardless of the type of graft or donor.

Members of the Pediatric Working Group participated in several meetings to discuss the specific consensuses on bone marrow failure syndromes, hemoglobinopathies, autoimmune diseases, and sinusoidal obstruction syndrome (Supplementary Table 1). These topics were not included in this document.

Six groups were formed to review the indications for non-malignant diseases and fifteen groups for the review of malignant diseases (Supplementary Table 2). All reviews were discussed during the group's weekly meetings on the www.Cure4Kids.org website, kindly offered by St. Jude Children's Research Hospital.

The main changes in relation to the previous consensus are presented in this article and were orally presented at the SBTMO – Consensus Plenary Session on October 26, 2020 for comments. A supplement of the JBMTCT will follow, discussing all Pediatric HCT indications in depth. The indications are summarized in Tables 1 to 3 and the recommendations of essential medications used to perform allogeneic HCT are listed in Table 4.

For each disease, we have defined whether autologous and/or allogeneic HCT are recommended or not and have added a few important notes on the implications regarding specific indications and the approach to performing the transplants. In the tables, the letter Y means Yes, HCT is indicated", and N means "No, it is not indicated".

Of note, we have only included the most common pediatric indications in this guideline. Diseases that have not been previously discussed as treated with HCT are not included in the tables, which does not mean that HCT may not be performed as an exemption or under compassionate use, as far as it is based on a strong rationale, or on documented previous HCT successes. A rare indication does not imply that a transplant is experimental; it means that that there are not enough patients under that indication to perform a formal clinical trial. Therefore, sound clinical judgment is advised at all times when faced with the challenge of an indication for transplant.

We thank all of those who have dedicated their time and effort toward updating these guidelines and hope that this 2020 Consensus succeeds in providing solid evidence-based guidance to all healthcare workers involved in the continuous care of HCT patients in Brazil and developing countries alike.

TABLE 1- Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Non-Malignant Diseases in Pediatrics

	Observations/indications	Allo	Auto
Inherited inborn errors of metabolism			
Osteopetrosis	Urgent HCT due to the risk of blindness and hearing loss, except in the presence of neurodegeneration (OSTM1 mutation) and with RANKL mutations	Y	N
Mucopolysaccharidosis type I - MPS-IH, Hurler syndrome		Y	N
Mucopolysaccharidosis type II, Hunter syndrome		Y	N
Mucopolysaccharidosis type VI, Maroteaux-Lamy Syndrome	ONLY if unresponsive to enzyme replacement therapy	Y	N
X-linked adrenoleukodystrophy	ONLY progressive cerebral form, early stage	Y	N
Leukodystrophy of globoid cells – Krabbe disease	Warning: family donors should not be used if healthy carriers of the disease	Y	N
Metachromatic leukodystrophy		Y	N
Immunodeficiencies	We strongly suggest following ESID recommendations for conditioning therapies https://esid.org		
Severe combined immunodeficiency		Y	N
Severe combined immunodeficiency due to ADA deficiency	Alternative: enzyme replacement and gene therapy	Y	N
Wiskott Aldrich syndrome		Y	N
Familial hemophagocytic lymphohistiocytosis	HCT with active disease has worse results	Y	N
Chediak-Higashi syndrome		Y	N
Griscelli syndrome - type II		Y	N
X-linked lymphoproliferative disease		Y	N
Chronic granulomatous disease	HCT from mismatched unrelated donors or cord blood have inferior results	Y	N
HyperIgM Syndrome (CD40/CD40L)		Y	N
Leaky- Severe combined immunodeficiency		Y	N
Leukocyte adhesion deficiency		Y	N
Class II MHC deficiency		Y	N
Purine nucleoside phosphorylase (PNP) deficiency		Y	N
Complete gamma-interferon receptor deficiency	Attention to higher graft failure rate	Y	N
Severe congenital neutropenia	Patients refractory to GCSF, with a history of major infections	Y	N
Early-onset inflammatory bowel disease (IL10, IL10-R, XIAP)		Y	N
Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome		Y	N
Other immunoregulation defects (CTLA4, LRBA, STAT3 GOF)	Some may have good response to immunobiologicals	Y	N
Langerhans cell histiocytosis	Multisystemic involvement beyond first remission or 1st remission of refractory disease	Y	N

TABLE 2 - Indications for Hematopoietic Stem Cell Transplantation for Malignant Hematological Pediatric Diseases

		Allo	Auto
Acute myeloid leukemia			
1st remission	Only if minimal residual disease > 0.1% after second induction or unfavorable genetics (karyotype or molecular findings)	Y	N
> 2nd remission, persistent disease after 2nd induction/ refractory disease		Y	N
Acute promyelocytic leukemia			
1st remission		N	N
> 2nd remission or persistently positive PML-RARA	If PML-RARA negative, autologous HCT. If PML-RARA positive, allogeneic HCT	Y	Y
Acute lymphoblastic leukemia			
1st remission			
Ph+ Acute Lymphoblastic Leukemia (Bcr/ Abl)	Only if there is not a good response to treatment	Y	N
Hypodiploid	Only if there is not a good response to treatment	Y	N
Age <6 months and KMT2A (MLL) positive	Only if >300,000 leukocytes /mm3 or poor response to corticosteroid	Y	N
Inductive failure (M2/M3 marrow) after 4 weeks of treatment	Except if hyperdiploid and age < 6 years	Y	N
Minimal Residual Disease (MRD) ≥10-3 (0.1%) at the end of consolidation		Y	N
2nd remission			
T-lineage	Any relapse	Y	N
B-lineage			
Isolated or combined medullary relapse	Early: 1st remission < 36 months	Y	N
	Late: 1st remission > 36 months only if positive minimal residual disease	Y	N
Isolated extramedullary relapse	Early: 1st remission < 18 months	Y	N
	Late: 1st remission > 18 months	N	N
3rd remission (B or T lineages)		Y	N
Refractory disease	Absence of morphological remission	N	N
Chronic myeloid leukemia			
1st chronic phase	Only if therapeutic failure (lack of response or intolerance) is the tyrosine kinase inhibitor	Y	N
	Mutation T315I	Y	N
Accelerated phase		Y	N
Blast crisis	In 2nd chronic phase	Y	N
Myelodysplastic syndrome			
Refractory cytopenia	Only if unfavorable karyotype, transfusion dependence or severe neutropenia	Y	N
Advanced stages		Y	N
Any MDS secondary to chemotherapy		Y	N
Juvenile myelomonocytic leukemia	Except Noonan syndrome or germline CBL with spontaneous remission.	Y	N
Lymphomas Burkitt, diffuse large B cell, anaplastic large cell, Hodgkin lymphoma	Only if poor response to treatment or 2nd remission If relapsed after autologous transplantation or failure to mobilize autologous stem cells	Y N	N Y

TABLE 3 - Indications for Autologous Hematopoietic Transplantation for Pediatric Solid Tumors

Disease	Stage of the disease with indication for autologous transplantation	Auto	Allo
Neuroblastoma	All patients with high-risk disease in 1st complete or partial remission	Y	N
	> 2nd remission	Y	Y
Germ cell tumors: gonadal, extra-gonadal and central nervous system	In 1st remission only patients with unfavorable risk factors	Y	N
	> 2nd complete or partial remission	Y	N
Wilms tumor	> 2nd complete or partial remission	Y	N
Clear Cell Sarcoma	> 1st complete or partial remission. Extremely aggressive tumor	Y	N
Ewing's sarcoma	1st remission if unfavorable risk factors	Y	N
	> 2nd complete or partial remission	Y	N
Alveolar soft part sarcoma	> 1st complete or partial remission	Y	N
Retinoblastoma	> 1st remission of extra-ocular disease	Y	N
	> 1st trilateral disease remission	Y	N
Pinealoblastoma	> 1st complete or partial remission	Y	N
Rhabdoid teratoid tumor	> 1st complete or partial remission of central or extracranial nervous system disease	Y	N
Medulloblastoma	1st complete or partial remission in young children as an option for radiotherapy, except for low-risk disease	Y	N
	> 2nd complete or partial remission	Y	N
Choroid Plexus Carcinoma	> 2nd complete or partial remission	Y	N

TABLE 4 - High-cost drugs that are fundamental to transplant and unavailable in the domestic market or for specific indications in bone marrow transplantation

Medicine/ Procedure	Use
Thiotepa	Single chemotherapy that achieves optimal concentration in the cerebrospinal fluid and brain parenchyma
Treosulfan	Similar to busulfan, but significantly less toxic
Defibrotide	Sinusoidal obstruction syndrome
Eculizumab	Single effective treatment for post-HCT thrombotic microangiopathy, extremely serious complication
Graft versus host disease	
Mycophenolate mofetil	Prevention and treatment of graft-versus-host disease, IV presentation is unavailable
Tacrolimus	Prevention and treatment of graft-versus-host disease
Ruxolitinib	Treatment of refractory graft-versus-host disease
Ibrutinib	Treatment of refractory graft-versus-host disease
Extracorporeal photopheresis	Treatment of refractory graft-versus-host disease
Antivirals	
Cidofovir	Single antiviral with activity against poliomavirus and adenovirus
Probenecid	Combination with cidofovir, increase bioavailability and decrease renal toxicity
Foscarnet	Ganciclovir-resistant cytomegalovirus (CMV) infection
Ribavirin (IV and inhaled)	Single antiviral with spectrum against respiratory syncytial virus, unavailable in our country
Palivizumab	Specific immunoglobulin anti- respiratory syncytial respiratory virus
Pentamidine	Prevention and treatment of Pneumocystis jirovecii pneumonia in patients with G6PD deficiency

SUPPLEMENTARY TABLE 1 - Participation of pediatricians in other groups:

Pathology	Participants
Acquired and Hereditary Bone Marrow Failure Syndromes	Carmem Bonfim, Luiz Guilherme Darrigo Jr
Hemoglobinopathies	Luiz Guilherme Darrigo Jr, Julia Lopes Garcia, Ana Karine Vieira, Laila Rigolin
Autoimmune diseases	Luiz Guilherme Darrigo Jr
High-cost medications	Luiz Guilherme Darrigo Jr, Antonio Vaz de Macedo
Acute lymphoblastic leukemia	Liane Daudt, Claudio Galvão
Acute myeloid leukemia	Ana Luiza Melo Rodrigues
Graft-versus-host disease	Rita Barbosa Tavares
SOS/VOD	Gabriele Zamperlini, Natalia Borges

SUPPLEMENTARY TABLE 2 - Participation of the Pediatric Groups:

Non-malignant diseases		
Coordinator	**Diagnosis**	**Participants**
Carmem Bonfim Juliana Folloni	**Immunodeficiencies**	
	Severe combined immunodeficiency	Samantha Nichele
	Other	Samantha Nichele
	Hmephphagocytic lympho	Gabriele Zamperlini, Samantha Nichele
Carmem Bonfim Juliana Folloni	**INBORN ERRORS**	
	Osteopetrosis	Alessandra Gomes
	Mucopolysaccharidoses	Alessandra Gomes
	Adrenoleukodystrophy and other leukodystrophies	Alessandra Gomes
Malignant diseases		
Coordinator	**Diagnosis**	**Participants**
Liane Daudt	ALL	Adriana Seber, Antônio Vaz de Macedo, Claudio Galvão, Cinthya Rocha, Renata Guimaraes, Luciana Domingues, Maria Gabriela Matos, Maura Ikoma, Virginio Fernandes
Ana Luiza Melo	AML	Antonella Zanette, Victor Zecchin, GELMAI - Ana Maria Marinho da Silva, Maria Lucia Lee, Raul Ribeiro
Roseane Gouveia	CML	Antonio Vaz de Macedo, Luciana Domingues, Paola Soriano
Neysimelia Villela	JMML	Patricia Ikeuti Simone Franco
Neysimelia Villela	MDS, JMML, and other MPS	Carla Zanchetta, Gustavo Zamperlini, Roseane Gouveia, Simone Franco, Patricia Ikeuti, Carla Zanchetta, Pediatric SMD Group
Carla Nolasco	Lymphomas	Cilmara Kuwahara, Gabriele Zamperlini, Mariana Michalowsky, Valeria Ginani
Monica Cypriano Victor Zecchin	Histiocytosis	Gustavo Zamperlini, Monica Cypriano
Solid tumors		
Coordinator	**Diagnosis**	**Participants**
Claudio Galvão - SOBOPE	Neuroblastoma, Ewing, Soft tissue sarcoma, Rhabdomyosarcoma, Osteosarcoma, Hepatoblastoma, Extra ocular retinoblastoma, Germ cell tumors, Brain tumors, GCT	Carla Nolasco, Fernanda Lima, Gabriele Zamperlini, Karoline Helena da Silva, Lauro Gregianin (guest), Mariana Michalowski (guest), Natalia Borges, Patricia Ikeuti, Paulo Klinger, Simone Franco
High cost medications	Antonio Vaz de Macedo, Luiz Guilherme Darrigo Jr	

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GUIDELINES ON CELL THERAPY

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INTRODUCTION

Advanced therapy products, among the ex vivo gene (ex. CAR-T cell category) and cell therapy products (ex. NK and mesenchymal cells), cannot be used without the authorization of Anvisa, according to the laws 6360/77, 6367/77, 9782/99 and 9677/98. In this sense, places that want to use this technology must be fully regularized with the official standards and techniques. For clinical research purposes, guidelines from CEP-CONEP and Anvisa related to ethical evaluations and security and quality systems must be followed. It is also recommended that the procedures described here should be done with a multi-professional and multidisciplinary stem cell transplantation team with ability to manage complications related to these therapies.

AUTOLOGOUS CAR-T CELL THERAPY

Level of evidence 2 Grade of recommendation B

DEFINITION

The treatment consists of genetically modifying the patient's T cells to express the chimeric antigen receptor (Chimeric Antigen Receptor - CAR) specific to a particular tumor antigen, identify and eliminate malignant cells.[1] Genetic manipulation of T lymphocytes to express CAR can be carried out using viral vectors or other non-viral techniques. The owner of the product registration is responsible for the security, quality, and efficiency measures.

LEUKAPHERESIS

The production of CAR-T cells begins with the collection of peripheral blood lymphocytes. As a registered product, the production must contain written documents with all the technical instructions for the collection (equipment, supplies, reagents, and other determinants of qualification of the starting material) according to the process development of the product in controlled clinical trials. It is important to check the efficiency, security, and quality. The type of collection and patient's care can vary according to the technologies undertaken and must be defined and studied during the product development phase. It is the user's responsibility and professional health to apply the agreement's requirements as the instructions for the product registration holder.

According to the current legislation, before the procedure, patients must do serological tested for HIV, hepatitis B, and hepatitis C. If the product is cryopreserved and strategies to avoid cross-contamination are not available, molecular tests must be done (NAT - nucleic acid test) for these pathogens.[2]

Literature data show that it is possible to plan or develop the product with a collection of lymphocytes from non-mobilized patients, through peripheral or central veins using equipment such as COBE Spectra and Spectra Optia (Terumo BCT, Tokyo, Japan) or Fenwal Amicus.[3]

Studies have shown the efficiency of the lymphocyte collection to program the number of volumes to be processed during the collection.

A collection efficiency can be calculated through the formula:

$$\text{Efficiency (\%)} = \left[\frac{\text{total product lymphocyte count X product volume}}{\text{peripheral blood lymphocyte count X processed volumes}}\right] X100$$

A mean efficiency of 40 to 80% was reported in previous studies, and it is associated with lower efficiency in diseased patients, with a diagnosis of acute lymphoid leukemia (ALL) and low platelet.[4-6]

The number of volumes to be processed must be determined by clinical testing to obtain the number of lymphocyte cells established in this study, generally about 1 to 2 x10e9 CD3 + cells in previous studies.

The recommended anticoagulation in the studies is glucose and Citrate Solution (ACD) or an association of ACD with heparin, with the collection between 0.8 to 1.5 ml/min in COBE Spectra and Spectra Optia equipment or start with the collection between 65-80 mL/min and adjustment for blood cells and mononuclear cells of 6.8 and 1.5 respectively.[6-8]

CRYOPRESERVATION

Cryopreservation can be used in the CAR cells production in two stages: 1) freezing of mononuclear cells for subsequent processing and manipulation, 2) after the production of CAR T cells. The cryopreservation technical instructions following guidelines from Anvisa and controlled clinical trials must be available. The parameters can vary according to the technologies used. Studies must be done during the development phase of the product and must be performed following the instructions for using the product. The health care provider should know the established rules to use the product.

Previous studies evaluated the effects of cryopreservation with programmed freezing and maintenance at temperatures below -150ºC, with no study assessing the impact of freezing in a mechanical freezer for initial product development planning.

The literature on cryopreservation of mononuclear cells follows protocols described for freezing lymphocytes and hematopoietic progenitor cells with DMSO at 10%, after thawing recovering about 70% of nucleated cells, especially with 90% of CD3 cells, showing a suitable strategy for the production of CAR cells.[9, 10] Assessment of the impact on the transduction and the expansion of cells and the percentage of T cells and the CD4: CD8 ratio for cells' production has not been damaged by cryopreservation.[11]

Similarly, the cryopreservation of CAR T cells also follows the protocol of freezing lymphocytes, and the average recovery of the thawed product is at least 90%. Wang L and collaborators demonstrated that lower concentrations (2x10e6 cells / mL compared with 1x10e7 cells / mL) showed good viability.[12] Cryopreservation in this study affected CAR T cells' cytotoxic effect; however, the product's resuspension in culture for 18 hours kept in an incubator was enough to achieve similar cytotoxicity of fresh product. These findings have not been found in other studies, which will observe slightly less viability, being corrected with more infused.[13, 14]

INDICATION

Patients with non-Hodgkin's lymphoma (NHL) and ALL expressing CD19, relapsed or refractory, show unfavorable results. Although the product is based on cells with different patient and disease characteristics, this technology showed a clear benefit for high-risk patients with B-cell malignancies. Recent clinical studies show a complete response of more than 90%, with CAR T cells' persistence in some patients per year 2 years after administration.[15-17] The treatment's success led to FDA approval of the first cell therapy product, Tisagenlecleucel, which consists of autologous anti-CD19 CAR-T cells for pediatric treatment patients and young adults up to 25 years old with relapsed or refractory B-cell leukemia. The approval was based on a phase 2 multicenter clinical study that showed a complete remission rate of 81% in 3 months and an overall survival rate in 12 months of 76%.[18]

Axicabtagene ciloleucel was the second FDA-approved anti-CD19 CAR-T cell treatment for adult patients with refractory or relapsed aggressive non-Hodgkin's lymphoma (Diffuse Large B-Cell Lymphoma, Primary Mediastinal Large B-Cell Lymphoma, High-risk B-cell Lymphoma and Diffuse non-Hodgkin's lymphoma (B-cell transformed from follicular lymphoma). The approval was based on phase 2 multicenter clinical study results, which showed an objective response rate of 82%, with a complete response of 54% [19]. In 2018, Tisagenlecleucel was also approved for adult patients diagnosed with refractory and relapse Diffuse Large B Cell Lymphoma, high-risk B cell lymphoma, and Diffuse non-Hodgkin Lymphoma transformed from d (???) Follicular Lymphoma. Approval was based on phase 2, an open, multicenter study with a 50% response rate (32% complete response) in 68 patients who received a single infusion of CAR T cells. [20] In 2020, Brexucabtagene autoleucel, a product consisting of autologous anti-CD19 CAR-T cells for refractory or relapsed Mantle Cell Lymphoma, was also approved the FDA. The recognition was based on phase 2, multicenter study, which demonstrated a response in 85% with a complete response of 59% (considering the intention to treat) and overall survival of 61% in 12 months. [21]

As well as CAR anti-CD19 for chronic lymphoid leukemia (LLC) [25], a anti-BCMA CAR for treating patients with multiple myeloma,[22-24] as well as CAR anti-CD19 for chronic lymphoid leukemia (CLL)[25], also showing encouraging results but are still awaiting FDA approval

In Brazil, the indications must be defined through controlled clinical trials to guarantee that the registered product is useful as a proposed therapeutic alternative. Besides, this type of product can only be used when registered by Anvisa, or investigational products will only be used in controlled clinical studies previously approved by the Agency and other regulatory agencies.

CHEMOTHERAPY BEFORE CAR-T CELL INFUSION

The application of chemotherapy (QT) before the infusion of adoptive immunotherapy with T cells was based on several studies showing the beneficial effect of lymphodepletion with chemotherapy or radiation in immunotherapies with lymphocytes in tumors murine models. Subsequent studies in animal models and patients have demonstrated that QT before the administration of CAR T cells increases persistence and treatment outcomes. This benefit results from several effects, such as eliminating homeostatic cytokines, such as IL-2, IL-7, decrease in immunosuppressive cells (Tregs lymphocytes and suppressive myeloid cells), facilitating and promoting the expansion and persistence of modified T cells. IL-15, for example, is an endogenous cytokine known to stimulate the proliferation and function of T cells and is secreted in increasing amounts after conditioning chemotherapy. The greater area under the concentration of this cytokine curve is associated with a higher proliferation of CAR-T. Therefore, the effect goes beyond lymphodepletion, and perhaps the most appropriate term is conditioning regimen and not lymphodepletion chemotherapy.[26]

Some protocols do not indicate any pre-infusion chemotherapy of CAR T cells if the WBC is less than 1000 cells / µL. Most protocols suggest the use of fludarabine and cyclophosphamide, although the agents may vary according to the type of disease. Studies have shown that the addition of fludarabine to cyclophosphamide (Cy / Flu) was associated with a higher concentration of interleukin-7 (IL-7) and IL-15, with a higher level of CAR-T cells in a blood sample taken 1 month and 3 months after infusion, resulting in a better clinical result of anti-CD19 CAR T cells. The effect of fludarabine is multifactorial and should include a reduction in the anti-CAR response. Data show that the peak of CAR T cells in the first month is associated with a longer-lasting and more significant response.[27]

The regimens can be of high dosage with cyclophosphamide 60mg / kg (total dose) and fludarabine 25mg / m2 for 3 or 5 days or of low intensity. Studies show that low-dose regimens: cyclophosphamide of 30mg / kg or 900 to 1500mg / m2 of total dose with fludarabine 30mg / m2 per day x 3 days, have response rates comparable to high doses with the benefit of less toxicity. Some centers opt for bendamustine 90 mg / m2 for 2 days, mainly in the outpatient CAR T cell usage protocols.

A recent study analyzing 132 factors that could impact the overall survival and progression-free survival (SLP) of patients undergoing CAR T therapy showed that the biological effect, that is, favorable cytokine profile: increased IL-7 and MCP- 1 at day zero, is associated with higher rates of complete response and SLP. Before the infusion, chemotherapy's intensity contributes to a favorable cytokine profile, but it does not happen in all cases. Notably, the use of conditioning with intensity and higher doses of CART cells (2 x 107 / kg) is associated with more severe toxicities.[28]

It is suggested that the pre-CAR-T cell chemotherapy protocol be performed according to the registry holder's instructions.

COMPLICATIONS AND CARE

Early recognition of toxicities and immediate intervention are crucial to prevent unfavorable consequences after T-cell therapy. To achieve this goal, the training of professionals involved in patient care is essential for recognizing and managing toxicities, including doctors, nurses, pharmacists, critical care staff, and emergency medicine. The education of patients and their caregivers is also crucial.[29] It is also recommended that treatment with CAR-T cells should be carried out in bone marrow transplant units. It should be noted that the holder of the product registration must manage risks that provide for handling adverse events and long-term monitoring. The healthcare professional should use the product in accordance with the registry holder's guidelines and report related adverse events.

The most commonly found toxicities are the cytokine release syndrome and neurotoxicity described below.

CYTOKINE RELEASE SYNDROME

Cytokine release syndrome (CRS) is the most common complication after treatment with CAR-T cells. It is the result of a systemic inflammatory response caused

when cytokines, such as interleukin 6 (IL-6), gamma interferon (IFNg), and tumor necrosis factor (TNF), are released by activated T cells or by other cells of the immune system, such as monocytes/macrophages[1]. In general, cytokine release syndrome development occurred between 1 to 10 days (median onset of 3 days) after the infusion of CAR-T cells.[30]

The CRS has a wide variety of clinical signs and symptoms such as fever, malaise and constitutional symptoms; hypotension; hypoxemia; changes in coagulation factors; target organ dysfunction, including respiratory failure, cardiovascular impairment, and renal failure; hepatic impairment.[31] After diagnosis, severity should be assessed. Several centers have used the ASTCT Consensus Grading for Cytokine Release Syndrome. Three vital signs (temperature, blood pressure, and oxygen saturation) are used to assess the classification.[32]

The treatment of SLC includes early identification through frequent monitoring, and the administration of tocilizumab can be performed from grade 2 (grade 1 if fever for more than three days without other causes)[29], in addition to symptomatic measures.[33] Tocilizumab should not be administered more than four times during the episode of CRS[29]. In cases refractory to the use of tocilizumab and SLC grade 3 or 4, treatment with corticosteroids is indicated.[29, 33, 34].

NEUROTOXICITY

Neurotoxicity or neurotoxicity syndrome associated with immune effector cells is the second most common complication related to treatment with CAR-T cells. It can occur with the SLC or as an independent event, in this case, usually later. The average time to onset of the first neurological symptoms is 6 days (range, 1-34 days) after CAR T cells' infusion. [35] Symptom duration is generally between 2 and 9 days, although late complications may occur.[32, 35] Clinical manifestations include delirium; speech disorders; alteration in writing, impaired fine motor coordination; convulsions; and even intracranial hypertension and coma. Deterioration in writing proved to be an earlier symptom of neurotoxicity. Therefore, daily tests after the infusion of CAR T cells can assist in the identification of neurotoxicity, such as the use of the encephalopathy scale associated with immuno-effector cells (known as the ICE scale).[29, 32] The most recently used neurotoxicity graduation scale is that of the ASTCT consensus, which considers score on the ICE scale, level of consciousness, motor alteration, presence of convulsion, and elevation of intracranial pressure / cerebral edema.[32]

In the case of neurotoxicity, supportive care and diagnostic investigation with electroencephalogram to rule out electrical seizures and images of the skull to rule out cerebral edema are necessary.[34] Like SLC, neurotoxicity treatment is performed based on the severity of the disease. Tocilizumab is indicated in cases of neurotoxicity associated with SLC, but the use of tocilizumab does not appear to bring clinical benefits in isolated neurological syndrome cases. In this case, when observing neurotoxicity grade greater than or equal to 2, corticosteroids are indicated.[29, 34]

NK CELLS IMMUNOTHERAPY

Level of evidence 4 Grade of recommendation C

3.1 NK CELLS AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

NK cells are innate large granular lymphocytes capable of lysing altered cells without previous exposition, its hallmark is the presence of KIRs able to either inhibit or activate NK cells activity. Self, normal cells are spared from NK cell lysis since KIR inhibitory receptors sense self-class I HLA antigens.[36]

NK cells play a central role in the alloSCT graft-versus-leukemia effect[37] and early recovery of NK cells following alloSCT is associated with fewer relapses and improved survival.[38] Since Perugia's group study on a T depleted haploSCT for advanced AML, with superior results for those that received donor to recipient mismatched NK cells,[39] several attempts have been made to enhance the GVL effect utilizing this strategy with variable results. Such variability probably reflects differences in conditioning regimen, disease burden at transplant, graft components, and posttransplant immune suppression. Based on these observations, the adoptive transfer of in vitro activates or expanded NK cells have been tested in the SCT scenario utilizing several strategies[40-42] with variable results.

The development of PTCy-based GvHD prophylaxis [43] for haploSCT could take advantages of NK cell alloreactivity; however, cyclophosphamide appears to cause a profound depletion of NK cells soon followed by the in vivo expansion of "immature" "dysfunctional" NK cells [44] in spite of it, long term results are comparable to Match Unrelated Donor MUD SCT.[45] In an attempt to augment the GVL effect in the PTCy-Haplo SCT, peripheral blood mononuclear cells expanded with membrane-bound IL-21 antigen-presenting cells (mbIl-21),[46] administered in day -2, +7, and +28 after transplant is presently been tested with encouraging results.[47]

NK CELLS ADOPTIVE IMMUNOTHERAPY OUTSIDE SCT SCENARIO

Based on the above-mentioned studies, NK-cell adoptive immunotherapy (NK-AI) could be an option for obtaining a "graft-versus-leukemia" effect in the absence of alloSCT, particularly for myeloid leukemias. Haploidentical NK-cell infusions in patients with relapsed or refractory AML have been shown to be well tolerated, with remission reported in five of 19 patients [48] and four of nine patients [49] when given after cyclophosphamide and fludarabine, and in four of six patients when administered after two cycles of intensive chemotherapy.[50] In a recent study, haploidentical NK-cell infusions followed by rhIL-15 administration, remission was achieved in 35% of patients with refractory acute myeloid leukemia; however, SC dosing of rhIL-15 after lymphodepletion prolongs drug exposure leading to cytokine release syndrome and neurotoxicity in 56% of patients [51]

In a recent Phase 1 trial, we were able to in vitro expand NK cells co-culturing with mbIl-21 from all donors, and the response was observed in 78.6% with 50% of CR. NK cells infusions were safe, and dose limit toxicity or cytokine released syndrome were not observed (submitted manuscript). Of interest, we documented CNS responses suggesting this same strategy i.e. systemic infusion of mbIL-21 expanded/activated NK cells could be used for CNS tumors. It also important to point out that the IV infusion of such an active NK cell, not only display an impressive anti-tumor activity, but also dismiss the need for the utilization of post infusion Interleukin administration. [52]

Although still in experimental, the effectivity and the lack of toxicity particularly when utilized without the systemic administration of Interleukin, might suggest that NK cell adoptive immunotherapy is a promising alternative, particularly for elderly patients unfit for SCT or for those without a donor.

We recommend the adoptive NK cells treatment only in clinical trials, and it is the sponsor and the researcher's responsibility to verify the safety, quality and efficiency, and the requirements and post-treatment monitoring. Furthermore, concerning manufacturing, production equipment, such as bioreactor or automated platforms, needs to be linked to a research product in an approved clinical trial in Brazil or a registered product.

MESENCHYMAL CELLS

Mesenchymal stem cells (MSC) are multipotent cells from the bone marrow or other hematopoietic tissues (umbilical cord, fetal liver), which can differentiate in vivo and in vitro in tissues of mesenchymal origin (cartilage, muscles, fat). Besides, these cells support the growth and differentiation of hematopoietic progenitor cells in the bone marrow microenvironment. In animal models, these cells are capable of leading to the engraftment of hematopoietic cells. In in vitro joint culture experiments, mesenchymal stem cells (MSC) suppress the proliferation of activated lymphocytes in a dose-dependent manner and without restriction on HLA antigens.[53-55]

ACUTE GRAFT-VERSUS-HOST-DISEASE (A-GVHD)

Level of evidence 1 Grade of recommendation A

Due to its immunomodulatory profile, several researchers have reported their experience with the use of mesenchymal stem cells for the treatment of refractory a-GVHD.[56-58]

Le Blanc *et al.* published in 2004 a case report of a nine-year-old boy with severe GVHD-a refractory to various treatments and who achieved remission with the infusion of mesenchymal cells from his mother.[56]

More recently, a phase II study by the same author reported the use of infusion of mesenchymal stem cells to treat severe refractory GVHD. In this study, 55 patients with severe GVHD, resistant to corticosteroids were studied. The authors infused a median dose of MSC of 1.4 x 106 per kg of weight. Twenty-seven patients received one dose, 22 patients received two doses and six patients received three to five doses of cells obtained from their donors with varying degrees of compatibility and kinship. Thirty patients obtained a complete response and nine showed improvement. Importantly, no patient experienced adverse events to or immediately after the infusion. Three patients had relapse and one patient had acute myeloid leukemia again, originating from the patient himself. Patients who had a complete response had lower transplant-related mortality one year after the infusion when compared to those with partial or no response (11 [37%] of 30 vs 18 [72%] of 25; p = 0.002) and best overall 2-year survival after HSCT (16 [53%] of 30 vs four [16%] of 25; p = 0.018). These responses were not related to the type of donor or HLA compatibility [57]

Von Bonin *et al* published in 2009 their experience with the use of mesenchymal cells in 13 patients, of which only two obtained a complete response with the initial infusion. Eleven patients received another

immunosuppressive treatment associated with new infusions of mesenchymal cells and of these, five (45%) responded. The reported survival was 31%.[58]

Martin et al recently reported their experience with Prochymal R (Osiris Therapeutics, Inc., Columbia, MD), a preparation of human mesenchymal cells expanded by culture and from unrelated donors, formulated for intravenous injection. One hundred and sixty-three patients received the product and 81 patients received placebo as treatment for refractory GVHD. The group treated with Prochymal R obtained an overall response of 82%, but the difference in relation to the control group was found only in patients with a-GVHD-involving the liver (76% x 47%, OR 3.6 [95% CI 1.1- 11.2], p <0.05) and intestine (82% x 68%, OR 2.2 [95% CI 1.1-4.4], p <0.05).[59]

Kebriaei et al reported in 2009 a phase II study with 31 patients divided into two groups according to the dose of mesenchymal cells (2 x 106 or 8 x 106 MSC / Kg). ProchymalR was used. The difference of this study is that the patients received this preparation as an initial treatment for patients with a-GVHD in conjunction with corticosteroids. Ninety-four percent of patients responded, 77% complete and 16% partial. No toxicities to the infusion or ectopic tissue formation were observed.[60]

In the phase III study with this same product, a total of 260 patients, from six months to 70 years of age, were evaluated from August 2006 to May 2009 and randomized 2: 1 to receive eight intravenous infusions of remestemcel-L or placebo for four weeks in addition to the Institution's standard second-line therapy. Four additional infusions were indicated for patients with incomplete response by day 28. Safety and efficacy were assessed at 180 days of follow-up and the primary objective was the complete durable response (DCR), defined as complete resolution of the signs of GVHD by up to 28 days after treatment. The primary objective was not achieved in the intention to treat analysis (35% x 30%; P = 0.42). In a post hoc analysis, patients with hepatic involvement who received at least one infusion of remestemcel-L had a higher DCR, and higher rates of complete or partial response when compared to those who received placebo (29% x 5%; P = .047). Among high-risk patients (aGVHD grades C and D), remestemcel-L also demonstrated a higher global response on day 28 (58% x 37%; P = 0.03). In addition, pediatric patients had a better overall response with SCD than those who received placebo (64% versus 23%; P = .05).[4]

Early intervention is important in the treatment of GVHD-a since there is a circular cascade of cell activation and production of inflammatory cytokines. [61]. It is reasonable to hypothesize that the sooner immunomodulation is offered, the greater its effectiveness since fewer clones will be activated and less cytokines will be produced. Accordingly, the Kebriaei [60] study found a high response rate, with no associated toxicity.

Dotolli GM *et al.* reported results from 46 patients treated with infusion of mesenchymal cells (MSC) for rescue of steroid-refractory Grade II to IV a-GVHD (78% grade IV). Patients received a median cumulative dose of MSC of 6.81 × 106 / kg (0.98-29.78 × 106 / kg) over a median of three infusions (1-7). The median time between the diagnosis of GVHD-a and the first infusion of MSC was 25.5 days (6-153). Half of the patients showed clinical improvement (23/46). Of these, three patients obtained a complete response (13%), 14 (61%) partial response and six (26%) transient partial response. The estimated probability of two-year survival was 17.4%. Only two patients (4.3%) had transient adverse events (nausea, vomiting and blurred vision) during the infusion. No patient had a serious adverse event. These results suggest that this therapeutic modality is safe and should be considered for the Treatment of steroid-refractory GVHD, especially in countries where second-line agents are less accessible.[62]

A recent meta-analysis did not find, however, a clear beneficial effect of the use of mesenchymal cells to treat a-GVHD and therefore, further randomized studies are needed to better establish the role of this therapeutic modality.[63] Furthermore, it is advisable that the treatment using a product based on mesenchymal cells for GVHD-a be carried out after authorization by Brazilian regulatory agencies such as Anvisa. The registry holder is fully responsible for proving safety, quality, effectiveness, and the requirements and post-treatment monitoring.

A. CHRONIC GRAFT-VERSUS-HOST-DISEASE (C-GVHD)

Level of evidence 4 Grade of recommendation C

Like a-GVHD, c-GVHD is an important and frequent complication of allogeneic hematopoietic stem cell transplantation, and one of the biggest causes of morbidity, mortality and impact on the quality of life of transplant patients.[64] As MSC are involved in tissue repair and modulation of immune responses in vivo and in vitro, its use for c- GVHD has also been evaluated by different researchers with surprising initial results.[65]

Weng JY and colleagues recently reported the results of the treatment of 19 patients with refractory

chronic graft disease treated with infusions of mesenchymal cells from April 2005 to October 2008. There was a response in 73.7% of patients and 10 of 19 patients could reduce by more than 50% or discontinue immunosuppressants altogether. The authors conclude that the treatment was effective in rescuing these patients.[66]

Zhang LS and collaborators [67] also reported their results of infusing mesenchymal cells from identical HLA donors, haploidentical donors or volunteers in 12 patients with refractory GVHD. There were no side effects related to the infusions, the global response was 75% (9/12) and complete resolutions were observed in patients with cutaneous (3/12), pulmonary (1/3), articular (1/5) involvement, hepatic (3/10), oral cavity (4/12) and ocular (2/7), regardless of the type of donor used. The median follow-up of this study was 1152 (795-1914) days, the leukemia-free survival was 91.7% (11/12) and the overall survival 75% (9/12). The CD4 / CD8 ratio and the proportion of regulatory T cells were significantly higher than before treatment. The verification of a complete response in patients with bronchiolitis obliterans (pulmonary GVHD) is consistent with studies that demonstrate the usefulness of these cells in various inflammatory diseases of the lungs, and even in idiopathic pulmonary fibrosis.[68]

Weng J et al. reported their results of infusing these cells in 22 patients with severe ocular sicca syndrome secondary to chronic graft disease, with improvement in symptoms in 55.54% of treated patients.[69] These results imply the need for further clinical studies to assess the potential of using this procedure in intractable and lethal situations, as is the case of refractory chronic graft disease. The use of products based on refractory DECH-c mesenchymal cells will only be carried out in controlled clinical studies previously approved by Anvisa and other regulatory agencies.

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GYNECOLOGIC GRAFT-VERSUS-HOST DISEASE

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GYNECOLOGICAL ADJUVANT THERAPY

The incidence of genital GVHD varies according to published studies, ranging of 24.9% to 69% of the HSCT recipients affected.[1-5] However, it is likely that this prevalence is underestimated because it only included patients who reported symptoms, and there might be underreporting.[3]

The median time to presentation of genital symptoms ranges from 7 to 10 months after transplantation; whereas, late-onset is not uncommon after one year. It is usual for oligosymptomatic patients who are sexually inactive to have a slow/delayed diagnosis if there is no systematic genitals examination, risk factors valuation, and preventive guidance.[2,7]

The pre-transplant clinical evaluation of women includes recommendations about genital GVHD, including early manifestations and complications and the importance of regular gynecological check-ups to help prevent severe gynecological complications, which often can become irreversible and have a significant negative impact on the quality of life.[8]

RISK FACTORS FOR FEMALE GENITAL GVHD

The main risk factor for the development of genital GVHD is the use of peripheral blood as the source of the progenitor cells for the transplant, representing a risk three times higher than that obtained from bone marrow cells[.9]

Type of conditioning, donor, parity, age, and presence of vaginal infection at the time of transplantation do not appear to have an impact on the incidence of genital GVHD.[8] However, oral mucosa and/or ocular conjunctiva involvement, as well as extensive areas of skin, are signs of genital injuries by the association[.9]

CLINICAL FEATURES

In 68% of cases, the symptoms affect only the vulva, whereas, in 26%, both the vulva and the vagina are involved, so in that case, vulvar lesions usually precede the vaginal lesions.[8] Isolated vaginal involvement is very rare and often asymptomatic, which makes limiting sequelae more common.[9]

The time lag between the start of vulvar and vaginal symptoms offers an opportunity to start prophylactic measures to prevent the occurrence of more severe complications, such as vaginal stenosis, with consequent impairment of sexual function.[3,8]

The genital GVHD symptoms may include dysuria, vaginal and vulvar dryness, vulvar buring, sensitivity of the vulva and vaginal introitus to touch or when washing, vulvar pain, vaginal bleeding after intercourse, and dyspareunia.[6,10,11]

Discharge is mentioned by 25% of patients with vaginal involvement, especially in the early stages, but in its mild form, it may be asymptomatic and detected only in the gynecological exam.[3]

Vulvar dryness is reported by up to 80% of women with genital GVHD and dyspareunia by up to 50% of them, impacting sexual activity.[3] Introital pain results from inflammation of the vestibular glands openings (Bartholin's and Skene's glands), erosions or vulvar fissures, and less frequently, from labial fusion. Deep dyspareunia occurs in patients with synechiae or vaginal shortening. Amenorrhea and pelvic pain, especially in women with cyclic hormone replacement, might be a vaginal synechiae sign or internal and/or external cervix os stenosis, resulting in hematocolpos and hematometra, and they are considered severe symptoms, respectively.[12,13]

TABLE 1 - Graft-versus-Host Disease main symptoms and signs in the Female Genital Tract

Symptoms	Signs
- Vulvar and vaginal dryness - Vulvar hyperemia - Discharge - Dyspareunia - Dysuria - Postcoital bleeding - Sensitivity and pain on touch the vulva.	- Vulvar erosions and fissures - Labial Fusion - Leukeratoses - Introital stenosis - Complete vaginal occlusion

The findings at physical examination resemble the symptoms of erosive lichen planus, and in the early stages, it can see erosions, erythema and tenderness around Bartholin`s and Skene's glands with increased pain sensitivity apart from interlabial fissures.[9]

Since other mucous membranes' involvement might increase genital involvement risk, women with oral and/or ocular involvement need to be submitted to gynecological examination even if asymptomatic. If a gynecologist is not available, the clinician should perform the physical examination, although vaginal involvement may be underdiagnosed.[9]

In the later stages, the studies include loss of vulvar architecture caused by labial adhesions narrowing of the vaginal introitus, clitoral agglutination, vaginal sinechiae, and circumferential fibrous banding. There may be decreased elasticity and shortening of the vaginal canal, mainly synechiae, making it difficult or impossible to visualize the cervix and get Pap test. These symptoms also make sexual intercourse difficult or impossible[1]. GVHD main signs and symptoms in the female tract genitals summarized in Table 1.

Histological confirmation is recommended only in the absence of diagnostic manifestations of GVHD in other organs. The early and later stages with functional sequelae must be adequately corrected the estrogenic deficiency caused by a chemo-induced ovarian failure. So that the GVHD findings on physical examination are not confused with hypoestrogenism sign[1,14].

GVHD FEMALE GENITAL CLINICAL CLASSIFICATION

According to the clinical score for organ evaluation described in Table 2, genital impairment can be classified as mild, moderate, or severe.

Jagasia and his collaborators developed a consensus for GVHD's diagnosis and a severity score, adapted and published by Kornik and his collaborators, suggesting active research on asymptomatic cases[15].

TABLE 2 - Diagnosis and grading of genital chronic graft – versus-host disease - National Health Guidelines.15

	E0	E1	E2	E3
Genital Female	No signs	Mild signs and symptomsa with or without discomfort on examinationb	Moderate signs and may have symptoms with or without discomfort on examinationb	Severe signs with or without symptoms
		Any of following: Erythema on vulvar mucosal surfaces Vulvar lichen planus-like features Vulvar lichen sclerosis-like featuresc	Any of following: Erosive inflammatory chances of the vulvar mucosad Ulcersd Fissures in vulval folds d	Any of the following: Labial fusionc Clitoral hood agglutinationc Vaginal scaring c Fibrous vaginal banding Vaginal shortening Synechia Dense sclerotic changes complete vaginal stenosis

a) Symptoms are not specific and can represent premature gonadal failure or infection
b) To be determined by specialist or trained medial provider; discomfort is defined as vulvar pain elicited by gentle touch with cotton swab in any of the following sites: vestibular glands, labia majora or minora.
c) Diagnostic sign.
d) Distinctive sign.

a Symptoms are not specific and can represent premature gonadal failure or infection

b To be determined by specialist or trained medial provider; discomfort is defined as vulvar pain elicited by gentle touch with cotton swab in any of the following sites: vestibular glands, labia majora or minora.

c Diagnostic sign.

d Distinctive sign.

PREVENTIVE MEASURES

Hormonal therapy instituted early on, whether systemic or topical, correcting the ovarian failure caused by the use of medicines in the conditioning phase, maintains the physiological characteristics of the genital tract, facilitating early detection of symptoms of GVHD[16].

Besides, women orientation in the pre-transplant evaluation, warning them for possible complications, its initial manifestations and probable sequelae, as well as periodic gynecological evaluation , mostly when GVHD manifests in other organs, such as oral mucosa and skin; it prevents many times irreversible sexual activity impairment, and also other gynecological complications.

It is recommended estriol as a 1 mg/g cream or 1 mg vaginal suppository, applied 2 to 3 times a week during the entire transplant phase until D + 100 or until the beginning of systemic hormonal therapy. As it attenuates the vulvovaginal epithelium atrophy caused by ovarian failure and accentuated by corticosteroid action, it maintains vaginal lubrication and elasticity, allowing sexual activity and facilitating the early diagnosis of GVHD lesions6.

It is vital to encourage a return to sexual activities when possible after platelet normalization. Sexual activity favors vaginal GVHD early diagnosis, and it prevents synechiae formation in the early stages of manifestation.[1,17] Using lubricated condoms relieves discomfort and protects against contamination during sexual intercourse.[17]

EARLY TREATMENT

Vulvar and vestibular lesions often appear as very sensitive erosions, even to (the underwear touching?) the touch of underwear. Ultra-potent topical corticosteroids as ointments or creams, which have better absorption and emollient action, are the most suitable at this stage. Clobetasol propionate 0.05% can be applied directly to the lesions once or twice a day until the erosions disappear, followed by tapering dose until complete suspension. A compress, or bathing in lukewarm water before administering corticosteroids facilitates their absorption. The administration of 1mg/g estriol in the vulvar vestibule avoids atrophic changes and consequently, vaginal dryness sensation, it must be maintained to improve sexual function after controlling the condition.[14]

Support measures, such as the use of emollients and topical moisturizers, sitting in a lukewarm bath, and the application of viscous xylocaine, can ease the discomfort, particularly during sexual intercourse.[9,14]

Damage to the vaginal mucosa may include ulcerations, erosions, loose synechiae and vaginal discharge. The use of 25mg hydrocortisone in the form of vaginal suppository, once or twice a day, is recommended until early reevaluation in 15 to 30 days, decreasing the dose once the symptoms have been controlled and then maintaining twice-weekly administrations and gradually reducing the dose until complete suspension. Also, the use of 1mg/gestriol in vaginal suppository or cream is recommended at least three times a week to counteract atrophy induced by hypoestrogenism and aggravated by corticosteroids. For vaginal synechiae, stenosis and narrowing prevention, patients are encouraged to regular intercourse, and if without a partner, vaginal dilator use is recommended twice a week.[14,18,19]

In a series of 11 patients, Spiryda et al.14 described the use of vaginal cream consisting of a 200 mg oral suspension of cyclosporine diluted in an oily base twice daily for four weeks followed by weaning for two months, until suspension. They observed healing of vaginal erosions after two weeks with its concomitant use with vaginal dilators, thereby avoiding the need of surgery to correct stenosis in 4 of the 11 women studied. The seven women who underwent surgery to correct synechiae and vaginal stenosis continued to use the medicine after surgery, and in 6-12 weeks, they were able to have sexual intercourse. Only one patient showed no improvement with clinical or surgical treatment due to thick synechiae.

Another alternative, with controversial results, is topical calcineurin inhibitors, such as 0.1% tacrolimus in ointment or cream, for vulvar and vaginal use, respectively. It would have the advantage of having less thinning epidermis. However, it is poorly tolerated because it can cause significant stinging and burning effect especially when applied to inflamed or non-intact mucosa.8 Finally, local treatment asso-

ciating corticosteroid and estrogen appeared to decrease the progression from mild to severe lesions, preventing surgical treatment. Thus, the earlier the treatment, the lower the sequelae rate.[17]

TREATMENT OF LATE COMPLICATIONS

Late complications, such as adhesions and occlusions in various segments of the genital tract, can be separated manually or incised under anesthesia with subsequent use of steroids and topical estrogen therapy.20,22 Dilation and drainage or hysterectomy may be necessary in extreme cases of collections in the cervical canal and uterine cavity (hematometra).[23]

SEXUALITY

Women undergoing HSCT develop several sexual problems that are not addressed to their doctors and experienced a decline in life quality. Deyer and his collaborators observed that 66% of women reported sexual difficulties, including decreased libido in 61.6% of them.[24]

These sexual dysfunctions have multifactorial causes such as medication, depression, estrogen, and androgen deficiency, decreased energy and self-esteem. Systemic GVHD and genital involvement worsen the condition with dyspareunia and sequelae that make sexual life impossible. It is essential to take care of triggering factors and a multidisciplinary approach valuing and seeking to resolve complaints about these women's general well-being.[11,25]

Several guidelines were published in the literature for gynecological care for women undergoing HSCT, with few differences. However, all expose the importance of blocking menstrual flow, clarifying the possibility of impaired hormonal and reproductive function after conditioning, as well as guidance on the first signs of genital GVHD, periodic gynecological examination, even in asymptomatic women, getting a Pap smear test, hormonal treatment for early ovarian failure and sexual dysfunction management.

They also address pediatric patients' evaluation for GVHD signs and pubertal status, as the lack of estrogen can prevent secondary sexual characteristics development.[1,5,6,8,9,14,16,25-30]

Besides, the presence of a gynecologist composing the multidisciplinary team of bone marrow transplant centers is of great importance for the approach in all phases, helping in the total recovery and providing an improvement in the quality of life of transplanted women[31] Table 3 summarizes the main precautions for GVHD management in the female genital tract.

TABLE 3 - Graft-versus-host disease management in the female genital tract

Type of intervention	Score
Vulvar discomfort	
Avoid chemical and mechanical irritants (soaps and intimate hygiene products)	B4
Wash the genital area with warm water, allow air circulation, and clean from front to back.	B4
Apply emollient to the vulva	B4
Water-based lubricants	
Vulvovaginal symptoms and low estrogen level	
Topical estrogen	B4
Encourage regular intercourse for sexually active women.	B4
Orient vaginal dilators 2 to 3 times a week for women with vaginal narrowing, stenosis, or obliteration.	B4
Topical Therapy for DECH-c Vulvovaginal	
- Hydrocortisone 25 mg in vaginal suppository	B4
- Clobetasol propionate gel 0.05% on the vulva	B4
- Betamethasone ointment on the vulva	B4
- Tacrolimus 0.1% ointment on the vulva and cream on the vagina	B2B
Surgical Therapy	
- Surgical lysis of adhesions with or without vaginal reconstruction followed by six months of dilator therapy.	B4
Pediatric Considerations	
Although data on GVHD genital incidence and treatment during childhood are less reported , the valuation of the same risk factors valid for adults, and care with early management through the mother or the caregiver's guidance may avoid late diagnosis with irreversible complications.	

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DIAGNOSIS AND TREATMENT OF GVHD

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INTRODUCTION

Around 50% of patients who undergo a hematopoietic stem cell transplant (HSCT) develop graft-versus-host disease (GVHD), with varying degrees of clinical severity and mortality rates of up to 20%[1,2]. The current guidelines will focus on the diagnosis, staging, grading, prophylaxis, and treatment of acute (aGVHD) and chronic GVHD (cGVHD).

DIAGNOSIS OF ACUTE GRAFT-VERSUS-HOST DISEASE (AGVHD)

The main risk factors for aGHVD are: HLA-mismatch between donor and recipient; gender disparity between donor and patient; conditioning regimen intensity; prophylaxis regimen used; progenitor stem cell source (peripheral blood > bone marrow > umbilical blood cord[3].

The skin, gastrointestinal (GI) tract, and liver are the most commonly affected organs in aGVHD. End-organ manifestations are characterized by a maculopapular rash (skin), nausea, vomiting, anorexia, and diarrhea (gut), and elevated bilirubin, canalicular enzyme, and, less often, transaminase levels (liver)[4,5].

ACUTE GVHD (AGVHD) STAGING AND CLASSIFICATION

The Mount Sinai Acute GVHD International Consortium (MAGIC) has recently allowed for a better standardization of the criteria for classification and data collection related to aGVHD[6]. It is currently regarded as the most appropriate method for the diagnosis, staging, and grading of aGVHD[6,7], as shown in tables 1 and 2, below:

TABLE 1 - MAGIC Target Organ aGVHD Staging

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 or anorexia	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/dayb
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexiaa	Adult: 500–999ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day
2	Maculopapular rash 25 – 50% BSA	3.1-6 mg/dL		Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day

3	Maculopapular rash > 50% BSA	6.1-15 mg/dL		Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/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).

a. A diagnosis of aGVHD is suspected when anorexia is associated with weight loss, nausea lasting for at least 3 days, or accompanied by vomiting ≥ 2 episodes/day for at least 2 days; b. one episode of diarrhea corresponds to approximately 200 ml of stool volume in adults and 3ml/kg in children (< 50 kg).
MAGIC: Mount Sinai Acute GVHD International Consortium. BSA: body surface area. Adapted from A.C. Harris *et al.* /Biol Blood Marrow Transplant 22 (2016) 4e10.

TABLE 2 – MAGIC Overall Clinical Grading of aGVHD

Overall grading	Skin (erythema)	Liver (Bilirubin)	Upper GI tract	Lower GI tract (stool output per day)
0	0	0	0	0
I	1-2	0	0	0
II	3	1	1	1
III	0-3	2-3	0-1	2-3
IV	4	4	0-1	4

Magic: Mount Sinai Acute GVHD International Consortium
Adapted from: A.C. Harris *et al.* / Biol Blood Marrow Transplant 22 (2016) 4e10.

GVHD PROPHYLAXIS8

Table 3 depicts the main GVHD prophylaxis regimens used in myeloablative, non-myeloablative, and reduced-intensity conditioning allogeneic HSCT, including peripheral blood stem cell (PBSC) and haploidentical transplants, along with their corresponding levels of evidence and grades of recommendation.

TABELA 3 - Main GVHD prophylaxis regimens used, with levels of evidence and grades of recommendation

Type of allo-HSCT	Prohylaxis Regimen	Level of Evidence
MA allo-HSCT from related and unrelated donors	Calcineurin inhibitor and Methotrexate (MTX)9–15	Level 1a, grade of recommendation A
	Calcineurin inhibitor and Mycophenolate Mofetil (MMF)14–19	Level 1a, grade of recommendation B
	High-Dose Post-Transplant Cyclophosphamide (50 mg/kg on D+3 and D+4) 20–24	Level 2b, grade of recommendation C
RIC and NMA allo-HSCT from related donors	Calcineurin inhibitor and MMF25	Level 4, grade of recommendation C
HLA-identical allo-HSCT from related and unrelated donors using PBSC as stem cell source	Rabbit Antithymocyte Globulin (rATG) < 6 mg/kg26–33	Level 1a, grade of recommendation A
Haploidentical allo-HSCT – Baltimore protocol	High-Dose Post-Transplant Cyclophosphamide (50 mg/kg on D+3 and D+4) plus a calcineurin inhibitor and MMF34–36	Level 2b, grade of recommendation B
Haploidentical allo-HSCT – Beijing protocol	High-Dose rATG (10 mg/kg), MMF, calcineurin inhibitor, and MTX37	Level 2b, grade of recommendation B

allo-HSCT: allogeneic hematopoietic stem cell transplant; MA: myeloablative; NMA: non-myeloablative; RIC: reduced-intensity conditioning; HLA: human leukocyte antigen; PBSC: peripheral blood stem cells.

TREATMENT OF AGVHD

Grade I aGVHD: optimize prophylaxis regimen, adjusting for calcineurin inhibitor trough levels, and add topical agents (corticosteroids or tacrolimus). No systemic immunosuppression is recommended[38] – Level of evidence 1b, Grade of recommendation A.

Grade II-IV aGVHD: start systemic treatment with methylprednisolone (MP) at a dose of 2mg/kg/day or its prednisone equivalent[39] – **Level of evidence 1a, Grade of recommenation A**. Concomitant calcineurin inhibitor (cyclosporine or tacrolimus) prophylaxis should not be withdrawn. For less severe forms (grade IIa aGVHD), start MP at a dose of 0.5-1mg/kg/day, escalating up to 2 mg/kg if worsening occurs after 72h[40] – Level of evidence 1b, Grade of recommendation A. Non-absorbable glucocorticoids (beclomethasone and budesonide) have also been used in the treatment of mild upper or lower GI aGVHD (500-1000 ml/stool output/day) as an adjuvant to systemic corticosteroids[41,42] – **Level of evidence 1b, Grade of recommendation A.**

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 lack of improvement after 5-7 days after initial therapy with MP 2mg/kg/day[8] – Level of evidence 5, Grade of recommendation D. Studies on the second-line treatment of aGVHD are highly heterogeneous, with hardly comparable results, great drug and interrater variability, as well as variability across centers. Since no superiority of one agent over another has been proven to date, the choice of the most appropriate approach should be individualized and dependent upon the following factors: previous therapy, drug interaction, availability, accessibility, and center expertise[8] – **Level of evidence 2b, Grade of recommendation C**. Table 4 shows the main treatment options for the second-line treatment of grade II-IV aGVHD.

TABLE 4 - Second-line therapy for grade II-IV aGVHD, with levels of evidence and grades of recommendation

MMF	Level of evidence 2b, Grade of recommendation C43–46	Complete Response (CR) and Partial Response (PR) rates of up to 77% in 6 months.
Extracorporeal Photopheresis (ECP)	Level of evidence 2a, Grade of recommendation B47–58	Overall response rates (ORR) of 84% in aGVHD of the skin and 65% in that of the gut
ATG	Level of evidence 2b, Grade of recommendation C59,60	ORR between 20% and 50%, particularly in aGHVD of the skin
Basiliximab	Level of evidence 2b, Grade of recommendation B61,62	Response rates of approximately 80%, with an overall survival of 30% at 5 years
Infliximab and Etarnecept	Level of evidence 2b, Grade of recommendation C63	ORR of approximately 70%, particularly in aGVHD of the gut
Ruxolitinib	Level of evidence 1b, Grade of recommendation A64–69	REACH2* phase III study showed an ORR of 62% at 28 days, compared to a 39% ORR in the control group

MMF: mycophenolate mofetil; ATG: antithymocyte globulin; GVHD: graft-versus-host disease.

CHRONIC GRAFT-VERSUS-HOST DISEASE (CGVHD)

With a prevalence of 30-70% among allogeneic HSCT recipients, cGVHD remains the main cause of long-term post-transplant morbidity and mortality in this population[70–72]. The cumulative incidence of cGVHD at 2 years in patients undergoing related or unrelated, bone marrow or peripheral blood stem cell allogeneic HSCT, as defined by the National Institute of Health (NIH) criteria, was 34%[73].

DIAGNOSIS OF CGVHD AND ITS DIFFERENTIATION FROM AGVHD

The 2014 NIH Consensus recognized two main categories of (acute and chronic) GVHD. The clinical manifestations, and not the actual time of onset of symptoms, are the basis for classifying a case as of acute or chronic GVHD[73]. Table 5 depicts the established categories for acute and chronic GVHD.

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

aGVHD: 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)

CLINICAL SCORING SYSTEM BY TARGET ORGAN

The target organs comprised by the cGVHD scoring system include the skin, mouth, eyes, GI tract, liver, lungs, joints, fasciae, and urogenital (UG) tract. Each organ or body part receives a score within a 4-point (0-3) scale, in which "0" represents absence of involvement and "3" reflects severe involvement74. Table 6 displays each of the cGVHD severity levels.

TABLE 6 - Chronic GVHD severity

Mild cGVHD Involvement of 1 or 2 organs AND organ score of 1 AND a lung score of 0
Moderate cGVHD ≥3 organs with a score of 1 OR at least 1 organ with a score of 2 OR a lung score of 1
Severe cGVHD At least one organ with a score of 3 OR a lung score of 2

cGVHD: chronic graft-versus-host disease.

The use of the 2014 NIH criteria for the diagnosis of cGVHD is both feasible and reliable in pediatric patients. However, specific adjustments in such criteria are needed to better assess the degree of lung and ocular involvement, since pulmonary function tests (PFTs) and Schirmer's test, respectively, are technically difficult to perform in children younger than 6 years of age[75,76].

TREATMENT OF CHRONIC GVHD (CGVHD)

The main criteria for initiating systemic treatment for cGVHD comprise: score >2 in at least one organ, involvement of three or more organs with score 1, lung score 1 or 2, and mild cGVHD with high-risk features (thrombocytopenia <100.000/mm3 and use of immunosuppressants at cGVHD diagnosis)77. The standard treatment consists of prednisone at a dose of 1mg/kg/day and cyclosporine[78,79]. **Level of evidence 1c, Grade of recommendation A.**

DEFINITION OF REFRACTORINESS TO SYSTEMIC TREATMENT

Progression of cGVHD after 2 weeks of systemic therapy (prednisone 1 mg/kg/day), stable disease while on prednisone (>0.5 mg/kg/day) for 4-8 weeks, or inability to reduce the dose of prednisone to < 0.5 mg/kg/day80. **Level of evidence 5, Grade of recommendation D.**

INDICATIONS FOR SECOND-LINE THERAPY OF CGVHD

Worsening of cGVHD manifestations in a primarily involved target organ, absence of any treatment response after one month, or inability to reduce the dose of prednisone to < 1 mg/kg/day within two months[79]. Table 7 depicts the main agents used in the second-line therapy of cGVHD.

TABLE 7 - Main agents used in the second-line therapy of cGVHD, with levels of evidence and grades of recommendation

Extracorporeal Photopheresis (ECP)	Level of evidence 1b, Grade of recommendation A57,81–85	Mucocutaneous manifestations, with complete response (CR) rates of > 80% and significant improvement of sclerotic cGVHD.
Mycophenolate Mofetil	Level of evidence 4, Grade of recommendation B86,87	Overall response rates (ORR) vary between 23% and 79% in several case series
Sirolimus	Level of evidence 4, Grade of recommendation B88–90	ORR varying between 63% and 81% in several case series
Rituximab	Level of evidence 2b, Grade of recommendation B80,91,92	Mucocutaneous and musculoskeletal manifestations, with an ORR of approximately 70%
Imatinib	Level of evidence 2b, Grade of recommendation B92,93	Cutaneous, ocular, and gut manifestations, with an ORR between 50% and 80%
Methotrexate	Level of evidence 4, Grade of recommendation B94,95	ORR varying between 58.8% and 71% in most case series
Ibrutinib	Level of evidence 2b, Grade of recommendation B96,97	ORR of 67%, with a 21% CR rate
Ruxolitinib	Level of evidence 4, Grade of recommendation C98	ORR of 57%, with a 1-year overall survival of 81%

cGVHD: chronic graft-versus-host disease.

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ADJUVANT DERMATOLOGICAL THERAPY

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Hematopoietic stem cell transplantation (HSCT) is associated with several skin manifestations including acute and chronic graft-versus-host disease (GVHD), disease relapse, opportunistic infections, and drug reactions, which can overlap with each other. The assertive diagnosis must be carried out before establishing a treatment plan[1].

Acute GVHD (aGVHD) is a common complication in the early period post HSCT and the skin is often the first and most commonly affected organ. Symptoms begin [1-3] weeks after HSCT and appear as maculopapular lesions, sometimes painful and/or pruritic, initially on the side of the neck, face, palms, plants, and ears, with the possibility of progression to erythroderma and bullous lesions similar to Steven Johnson's syndrome/NET [2,3]. The role of skin biopsy in diagnosis is still controversial [4,5].

Chronic GVHD (cGVHD) is the most important late complication of HSCT. The skin is the organ most commonly involved and occurs in approximately 75% of patients [6]. The NIH [7] consensus in 2014 suggested clinical manifestations for the diagnosis of cutaneous cGVHD: poikiloderma, lichen planus, and scleroderma alterations (morphea, lichen sclerosus, mobile, and non-mobile scleroderma). Other non-diagnostic findings include depigmentation, vitiligo, alopecia, and erythematopapular lesions with desquamation. Rarer clinical presentations include pityriasis rosea like, psoriasiform changes, and follicular keratosis [8]. Cutaneous manifestations of cGVHD are associated with itching and pain, reduced joint mobility, and increased risk of wound infections 9. The immunomodulation resulting from prolonged therapy base on corticosteroids and a large number of second-line steroid-sparing therapies remains the focus of treatment for cGVHD.

Patient support is the basis for the treatment of cutaneous GVHD regarding the prevention and proper handling of dermatological changes and their symptoms, such as control of itching and pain; prevention of changes in joint mobility; topical treatment of erosions, ulcerations, and consequent superinfection.

Dermatological support includes direct skin therapy (DST), with the use of topical agents with anti-inflammatory and immunosuppressive action, and direct measures, with educational, psychosocial, and preventive actions, to control the symptoms and/or complications resulting from GVHD and of the drugs used to treat it. Unfortunately, responses to immunomodulation are often partial and patients continue to experience relapses of the disease and symptoms that impair quality of life. (Figure 1)

FIGURE 1

PREVENTION MEASURES

Photoprotection: anti-UVA and anti-UVB blockers (≥ SPF30)

Avoid sun exposure (especially between 10:00 and 16:00)

Protection with clothes

Avoid photosensitizing agents

TREATMENT

- **Intact skin**

  Symptomatic treatment with emollient and antipruritic agents

  Topical corticosteroids

Phototherapy (PUVA, UVA1, UVB, UVB-NB)
Topical calcineurin inhibitors (pimecrolimus and tacrolimus)

- **Manifestations of sclerosis affecting the joint**

Deep muscle massage/fascia
Assessment of muscle strength at each visit
Guidance on physical and occupational therapy
Stretching exercises
Isokinetic, isometric, isotonic exercises
Surgical release

- **Erosions and ulcerations**

Oral and topical antimicrobials
Debridement and occlusive dressings on wounds
Edema control

PEDIATRIC CONSIDERATIONS

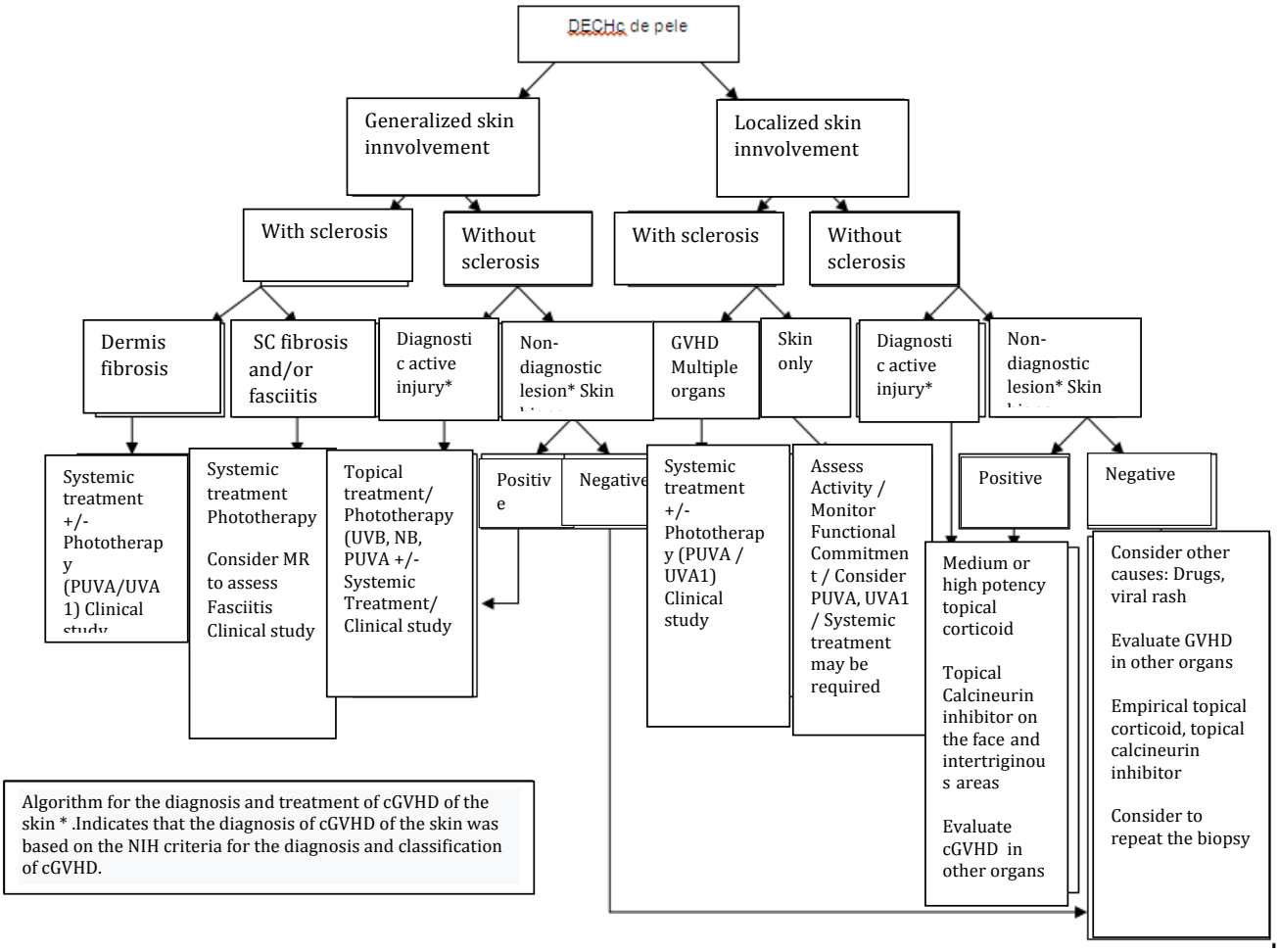
Systemic adverse effects of topical steroids can often occur in children due to the large surface area to be treated
Although low-potency topical steroids (1 to 2.5% hydrocortisone) are safe, medium and high potency steroids can be used in limited areas for a short time (<3-4 weeks)
Topical steroids under occlusion are not recommended
The use of potent steroids in children <1 year is not recommended

The treatment of aGVHD grade I (mild) should consist of the optimization of prophylactic regimens, for example, with adjustment of cyclosporine or tacrolimus doses to achieve therapeutic serum levels. The use of corticosteroids and topical immunomodulators and systemic antihistamines helps in the control of pruritus and skin lesions. There is no indication of systemic immunosuppression.

The manifestations of mild GVHD (skin and mouth) can be treated with topical immunosuppression, avoiding systemic immunosuppressive (SI)[10] therapy. Clinical control of the disease aims to reduce morbidity and mortality with supportive measures such as DST that can improve cutaneous symptoms and quality of life of patients. Also, the optimized use of DST can reduce the amount of systemic immunosuppression required1, a fundamental factor in patients at high risk of relapse, so as not to interfere with the graft-versus-tumor effect[11].

In moderate to severe GVHD, DST can be useful as an adjunct to increase the local response and facilitate the reduction of IS and toxicity. In the absence of poor prognostic factors, such as thrombocytopenia (<100 000/μL), topical agents can be used as the primary treatment of cutaneous GVHD without the need for ISI (Figure 2).[9]

FIGURE 2 - Algorithm for the diagnosis and therapeutic orientation of cutaneous GVHD [9]



REVENTIVE MEASURES FOR THE DEVELOPMENT AND EXACERBATION OF GVHD

Ultraviolet (UV) radiation can cause exacerbation of cutaneous GVHD [12]. Photoprotection includes avoiding sun exposure, using chemical and physical photoprotectors that protect against UVA and UVB radiation (titanium dioxide, Mexoryl SX, or avobenzone), and wearing clothes with fabric that allows photoprotection.

AVOIDING PHOTOSENSITIZING AGENTS

Several prescribed medications are associated with drug phototoxicity skin rashes, which appear as lesions similar to severe sunburn and/or itching. The list of these medications is extensive, but voriconazole deserves special attention because of its frequent use and its association with phototoxic reactions and increased risk of cutaneous squamous cell carcinoma [13,14].

LOCAL THERAPIES AND CARE TO KEEP THE SKIN BARRIER INTACT

On intact skin, lubrication with emollients reduces itching and maintains the integrity of the skin barrier, which is essential for innate immunity. Formulations based on 3-10% urea are also effective, but care must be taken as they can be irritating when applied to inflamed skin in children and elderly patients.

DIRECT SKIN THERAPY (DST)

DST should be maintained as long as symptoms are present

• TOPICAL STEROIDS (LEVEL OF EVIDENCE 1B, LEVEL OF RECOMMENDATION A)

This is the first-line treatment for GVHD and mild to moderate cutaneous GVHD. Steroids have effects in reducing inflammatory epidermal cells, in responses to dendritic cells, in the synthesis of pro-inflammatory factors and collagen production. The degree of potency of topical corticosteroids is prescribed according to the affected site, vehicle, anatomical region, and depth of the lesion (epidermis - dermis - subcutaneous). (Figure 3). Thus, high potency such as clobetasol propionate and fluocinolone acetonide is prescribed for small areas and for a short time in lesions located on the body, palms and soles, and low and medium potency for face and more extensive and long-term areas, such as triamcinolone, desonide and hydrocortisone [15]. The scalp is the exception to the rule, where high-power corticosteroids can be used in vehicles based on solutions or oils.

For epidermal changes in GVHD such as ichthyosiform, lichenoid, and papules with desquamation, vehicles in the form of ointments may be used.

For scleroderma forms, high potency corticosteroids class 1 (for example clobetasol propionate) or class 2 (fluocinonide) should be indicated as first-line therapy.

For localized skin changes, steroids can be occlusive applied to increase effectiveness (products containing steroids in adhesive plastics or simply covering the cream with plastic).

For large areas, we should give preference to vehicles in the form of an emulsion or creamy lotion for ease of use.

The adverse effects of topical corticosteroids include skin atrophy, vascular dilation, acneiform rash, and hypopigmentation.

FIGURE 3 - Use of topical corticosteroids in cGVHD

Corticoid potency	High power Ex. clobetasol propionate 0.05%/ Betamethasone Dipropionate 0.05%	Moderate Power Ex-mometasone furoate 0.1%/ Betamethasone valerate 0.05%/ fluticasone propionate 0.05%	Low power Ex: hydrocortisone
Face	It should be avoided	2 x day 6-12 months	2 x day Prolonged use
Body	2 x day 4-12 weeks		
Palms and soles	2 x day It can be used under occlusion to increase the response. Prolonged use may occur		

• TOPICAL CALCINEURIN INHIBITORS (LEVEL OF EVIDENCE 2B, LEVEL OF RECOMMENDATION C)

Topical tacrolimus is widely used as a corticosteroid-sparing agent for atopic dermatitis. It acts by reducing the expression of cytokine in the skin, and it is effective for GVHD with mild and moderate cutaneous and oral involvement [15-17]. It can be used as a first-line treatment alone or in combination with topical steroids. In contrast to corticosteroids, tacrolimus does not affect collagen synthesis and can be used in areas of skin with signs of steroid atrophy and the appearance of stretch marks [3].

Oral antihistamines

Pruritus in GVHD can have several origins such as dry skin, skin lesions, or the only symptom of disease activity. The 2nd generation oral antihistamines (less hepatic metabolism), such as fexofenadine, epinastine, and bilastine, and the 1st generation for more intense cases such as hydroxyzine are indicated to reduce itching. For refractory symptoms, the use of gabapentin or low dose thalidomide (100mg) may be associated.

• ULTRAVIOLET RADIATION THERAPY (LEVEL OF EVIDENCE 2B, LEVEL OF RECOMMENDATION C)

The experience with the use of ultraviolet radiation for the treatment of other inflammatory diseases stimulated the use of phototherapy with ultraviolet radiation A associated with psoralen-PUVA method and phototherapy with narrow-band ultraviolet B (UVBNB) to treat GVHD refractory to systemic corticotherapy [18 -22]. The mechanism of action is related to the reduction of inflammation and cutaneous sclerosis, mediated by depletion of antigen-presenting cells in the skin and reduction of interactions with donor T cells. Phototherapy also increases the production of vitamin D, which appears to increase regulatory T cells (T regs), involved in the pathology of GVHD 23.

PUVA is generally well tolerated with a high skin response rate and mild adverse effects. There is no evidence of the effectiveness of PUVA for the involvement of internal organs, but it should be considered in patients with cGVHD in whom additional systemic immunosuppression increases the risk of infection or interferes with the graft-versus-tumor response[19]. Feldreich et al.[24] evaluated the response to PUVA treatment in 33 patients with aGVHD affecting the skin and other organs in a retrospective study, with a global response (complete and partial) of 64% and survival in 6 months of 64% and questioned a possible systemic effect of PUVA in other affected organs besides the skin.

PUVA is reserved for the treatment of dermal lesions (cGVHD mobile and non-mobile sclerosis), while UVBNB is indicated for vitiligo, lichen planus like, follicular keratosis, children, low skin phototypes (fair skin), and localized morphea. Reports on the use of UVBNB in scleroderma have been increasing.[25]

In all phototherapy modalities, long-term carcinogenesis and photoaging should be considered. However, the literature review involving 11 studies with approximately 3400 participants suggests that UVBNB phototherapy remains the safest modality 26. The current trend is to opt for UVBNB phototherapy due to the lower risk of photocarcinogenesis and phototoxic reactions to drugs [27,28].

OPICAL THERAPY AND CARE FOR NON-INTACT SKIN

Skin erosions and ulcerations in cGVHD are complicated by poor nutrition, impaired skin barrier function, chronic disease, and concomitant immunosuppressive therapy. Primary and secondary infections in the lesions can be evaluated by microbiological cultures for bacteria, viruses, mycobacteria, and fungi. The differential diagnosis of non-infectious skin lesions includes vasculitis, recurrent malignancy, GVHD, hypersensitivity, drug reactions, eczema, and primary skin cancer. In the naked area, topical antimicrobials (mupirocin and fusidic acid), products containing 1% silver sulfadiazine, and alginate hydrogel, protective films based on petrolatum can be used to improve healing.

Recalcitrant wounds should be treated together with the plastic surgeon and/or dermatologist, and those with slow healing can be treated with products based on hyaluronic acid, collagen, fibroblasts, and keratinocytes. Hyperbaric oxygen therapy has been used in wounds with little oxygenation. Compressive therapy may be indicated to facilitate drainage in wounds with surrounding edema.

The appropriate use of dermatological support therapies helps to manage skin changes after HSCT and quality of life. Multidisciplinary follow-up plays an important role in the effectiveness of treating cutaneous changes in GVHD.

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ORAL GRAFT-VERSUS-HOST DISEASES

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ABSTRACT

The management of graft versus host disease (GVHD) requires a multidisciplinary team, including dentists among others professionals. In 2015 to standardize treatment approaches the Brazilian Society of Bone Marrow Transplantation published recommendation on the management of oral GVHD. Here we update these recommendations including the results of studies published after 2015.

INTRODUCTION

Graft-versus-host disease (GVHD) is a common complication in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) and is responsible for high morbidity and mortality [26]. GVHD can present in acute and chronic form and usually involves several organs such as: eyes, mouth, skin, liver, intestine and lungs.

The involvement of the mouth in acute GVHD is less frequent than in chronic GVHD, but no less important. Usually in both situations, the oral manifestation of GVHD implies in pain, difficulties on speech, and restriction of food intake, which imply in decrease in quality of life [18, 19]

There are few published papers addressing the manifestation and treatment of oral acute GVHD. In the other hand, for oral chronic GVHD, there are many papers addressing its clinical and histopathological characteristics and management.

This consensus aims to update the previous recommendations of the 2015 Consensus of the Brazilian Society of Blood Marrow Transplantation on the management of oral GVHD, throughout the literature review of papers published after 2015.

METHOD

A systematic literature review was carried including papers published after 2015 to 2020. A bibliographic search was carried out using the Pubmed database, including full papers written in English, Spanish or Portuguese. The research was directed to the location of descriptors in titles, abstracts and MeSH of publications with help descriptors (GVHD OR Graft vs Host Disease AND (therapy OR treatment OR treating) AND (Oral Manifestations OR Mouth OR buccal).

RESULTS

The search resulted in a total of 44 publications, 4 (9%) were excluded after reading the titles. The 40 selected papers were distributed by the six revisors, from which the data used in this study were extracted.

ACUTE ORAL GRAFT-VERSUS-HOST DISEASE (GVHD)

Although the mouth is not considered a target organ, oral manifestations of acute GVHD can be present in about 0.8% of patients undergoing allogeneic hematopoietic stem cell (HSCT) transplantation who have the acute systemic GVHD.[7, 18, 38]

The diagnosis of acute oral GVHD can be considered as a diagnosis of exclusion. Clinically, it is characterized by the presence of erythema, inflammation, nonspecific ulcerations, atrophy of the oral mucosa and redness of the lips, coinciding with neutrophilic grafting. It is important to point out that, although the oral manifestations of acute GVHD resemble those of oral mucositis, however, oral mucositis is re-

lated to the toxicity of the conditioning regime and it usually presents a resolution prior to or coinciding with neutrophilic grafting [15, 18, 21, 32].

Infections related to the Herpes viridae family are often found in the oral cavity and are related to the degree of immunosuppression induced by the conditioning regime [15, 36, 37]. Clinically herpetic viral lesions in the oral cavity are characterized by ulcerations and pain and may be present even when using antivirals prophylaxis. These injuries are related to increased morbidity [9, 36]. The diagnosis of oral viral infection is usually clinical, but it and can be complemented with a cytological exam (Papa Nicolao), or PCR for Herpes virus.

TREATMENT

The treatment for oral acute GVHD is mainly topical that can be associated with the systemic treatment protocol for acute GVHD. Mouthwashes with corticosteroids with dexamethasone (0.1mg/mL) and clobetasol (0.5mg/mL) associated or not with tacrolimus (tracolimus 0.1%)[18, 27] can be use with good response treatment. Patients should be instructed to hold the medication for 5 minutes in the mouth and then, spit out the medication. Food intake, oral hygiene should be avoided for 10-15 minutes after the mouthwash.

The prophylactic use of antifungals is recommended when using mouthwashes with corticosteroids, due to the increased risk of fungal infection. Usually, it is recommended the use of mouthwash with subsequent swallowing of suspension of nystatin [32, 35].

There are one study showing the use of low power laser therapy for treatment of acute GVHD [30] and so far, no recommendation can be done for this treatment modality.

CHRONIC ORAL GRAFT-VERSUS-HOST DISEASE (GVHD)

The incidence of chronic oral GVHD is approximately 70% to 83% of patients submitted to allogeneic Hematopoietic Stem Cell Transplantation (HSCT).[22, 24] These manifestations may involve the entire oral mucosa, the labial mucosa and even the major and minor salivary glands.

Chronic oral GVHD is clinically characterized by the presence of white lacy lesions similar to oral lichen planus (lichenoid lesions), erythema, inflammation and atrophy of the mucous membranes and also by the presence of oral ulcerations. These changes can be observed in all sites of the oral cavity. Clinically, it can be observed as a single or multiple lichenoid lesion, isolated or associated with redness and ulceration [14, 32]. In the perioral tissues, chronic GVHD can lead to sclerotic lesions and, consequently, to a decrease in mouth opening. [6, 14, 35]

Chronic GVHD in salivary glands can occur regardless of clinical manifestations in the oral mucosa. [2, 16, 34]. The dryness of the oral cavity can be assessed clinically during the inspection of the oral cavity.[2] Clinical criteria of hyposalivation such as adherence of the wooden spatula to the cheek mucosa, absence of salivary lake in the sublingual region, in addition to the presence of labial dryness can be useful for the diagnosis of dry mouth. Xerostomia can be assessed by the patient's complaint about the needs of fluids to facilitate the ingestion of dry foods.[2, 23]

In addition to the salivary glands, the salivary ducts are also affected by chronic GVHD, which can lead to the formation of pseudocysts of mucous retention (mucocele). Patients can report the formation of small cysts in any region of the mouth, but especially the hard palate, when stimulated by food intake. Ulceration can replace the pseudo cyst when it broken. [32]

In addition to changes in the structures of the salivary glands, and consequently, in the salivary flow, biochemical and proteomic changes in saliva have been reported. [3, 5, 17]

Usually, salivary changes do not respond to systemic treatment of chronic GVHD and it may persist as late effects.[2, 4, 5, 8, 34] Persistent and late changes in saliva are associated with an increased risk of oral infections, especially fungal infections. In addition, they are associated with an increased incidence of dental caries and periodontal disease.[5, 10, 14, 28, 31] Salivary changes associated with changes in the oral microbiota may be associated with the presence of dysgeusia in these patients.[33]

EVALUATION CRITERIA

The assessment of chronic GVHD activity as well as the criteria for assessing treatment response were published by the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: NIH Consensus in 2015.[19, 22]

Diagnostic signs and symptoms for chronic oral GVHD include the presence of lichen-like lesions (lichenoid lesions), characterized by the presence of lacy white lines on the oral mucosa. These changes are typically seen in the buccal mucosa and tongue but can be present in the entire oral mucosa and even in the labial vermilion. The lichen-like lesions may or may not be associated with erythema or ul-

cerations, which are not considered as diagnostic features for chronic oral GVHD.[19]

The presence of white plaque without lichenoid characteristics are no longer considered as a clinical diagnostic criteria for chronic oral GVHD. However, these lesions must be considered, evaluated and biopsied, due the high risk of malignant transformation.[19, 25]

Distinctive signs and symptoms for chronic oral GVHD include hyposalivation, presence of mucous retention cyst (mucoceles), oral mucosa atrophy, ulcerations and pseudomembranous ulcerations. In the presence of ulcerations and oral inflammation, fungal, viral or bacterial infections, as well as neoplastic lesions, should be excluded.

Signs and symptoms found in both chronic and acute GVHD are referred as common features and include the presence of inflammation and atrophy in the oral mucosa, erythema and pain.[22]

The objective assessment of the therapeutic response in the oral cavity considers the presence of erythema in the mucosa (color intensity and percentage of the area involved), lichen-like lesions (percentage of the area involved); ulcerations (percentage of the area involved) described on an evaluation scale ranging from 0-12 graduation points. [22]

The subjective evaluation of the therapeutic response includes the presence and intensity of sensitivity to spices, foods, liquids or flavors. This assessment should be made in consideration of the patient's perception during the last week prior to the assessment and is described on a scale of 0-10. For children, the same issues must be addressed, however a sensitivity scale between 0-3 must be used.[22]

Topical treatment of chronic oral GVHD aims to improve symptoms (mainly pain, tenderness and dry mouth), maintain oral functionality and restore mucosal integrity. This can be associated with systemic immunosuppressive treatment, mainly in refractory or difficult to control cases (figure 1). However, special care must be taken when using topical corticosteroids, mainly due to the increased risk of developing oral infections mentioned at the beginning of the chapter.

The performance of oral hygiene during all phases of treatment is extremely important and should be performed after meals and after topical use of corticosteroids. However, due to the variation in the presentation of chronic oral GVHD and the presence of chronic oral pain, oral hygiene must be adapted to the individual conditions of each patient. The use of 0.2% neutral sodium fluoride to prevent tooth decay in the form of mouthwash can be indicated as prophylaxis.[11, 26, 27, 32, 35]

Since the publication of the NIH consensus in 2015, new treatment options for chronic GVHD with oral involvement have been published. These protocols are directed to cases of chronic GVHD refractory to the use of systemic corticosteroids and to calcineurin inhibitors and include Tocilizumab,[21] Ruxolitinib. [1, 20] As topical treatments for chronic oral GVHD associated or not with systemic treatment, the use of platelet rich fibrin gel (PFR) [29] and, low-power laser therapy have been reported with satisfactory results, but with low scientific evidence. [12, 13, 30]

A list of topical management of oral GVHDC is shown in figure 1 (Adapted from Carpenter et al, 2015[6] and Wolff et al., 2011[39]

FIGURE 1- Supportive therapy for the treatment of oral chronic GVHD

Indication	Preparation	Agent	Concentration	Rating	Comments
Lichenoid lesions / erosions / ulcers	Rinse	Clobetasol Budesonide Dexamethasone Tacrolimus Triamcinolone Prednisolone Clobetasol: Tacrolimus 1: 1	0.5mg / mL (0.05%) 0.3 mg / mL (0.03%) 0.1 mg / mL (0.01%) 1 mg / mL (0.1%) 0.1 mg / mL (0.01%) 3 mg / mL (0.03%) Not specified	AIa BIIa AIII AIII BIIa BIII CIII	Requires nystatin prophylaxis due to the risk of fungal infections
	Gel, paste, ointment	Clobetasol gel Tacrolimus ointment Fluocinonide gel	0.05% 0.1% 0.05%	AIa BIIa BIII	
	Intralesional injection	Triamcinolone	40mg/mL; 0,5mL/cm2	CIIb	

	PUVA/UVB	Psoralen		CII	Refractory disease
Mucosal pain	Rinse Not applicable	Lidocaine Kaolin-pectin-diphenhydramine-lidocaine 1: 1: 1 Low power laser therapy (infrared) for pain relief	2% Not applicable Not applicable	BIII BIII CIII	Do not swollen lidocaine – risk for pneumonia
Xerostomia*	Toothpaste / Liquid Gel Bubble gum Rinse Gel or spray Pills	Sodium fluoride Salivary stimulants Water sipping Oral lubricants Pilocarpine Cevimeline	According to the manufacturer Per need Per need Per need 5-10 mg X 3-4/d 15-30 mg X 3/d	AIb AIII AIII BII BIIa BIII	

Adapted from Carpenter, *et al,* 2015[6] and Wolff, *et al*., 2010[39]

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OCULAR GRAFT-VERSUS-HOST DISEASE

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INTRODUCTION

Chronic Graft versus host disease (cGVHD) is still the main complication of allogeneic hematopoietic stem cell transplantation (HSCT). GVHD prevention strategies should be established, the diagnosis promptly recognized, and treatment started as early as possible to minimize complications and risks. (Higman and Vogelsang, 2004) Recommendations and guidelines for the diagnostic assessment and treatment of GVHD proposed for this consensus were organized according to a system based on scientific evidence, ranked by the strength of recommendation and the quality of the evidence. (Guyatt *et al*., 2008)

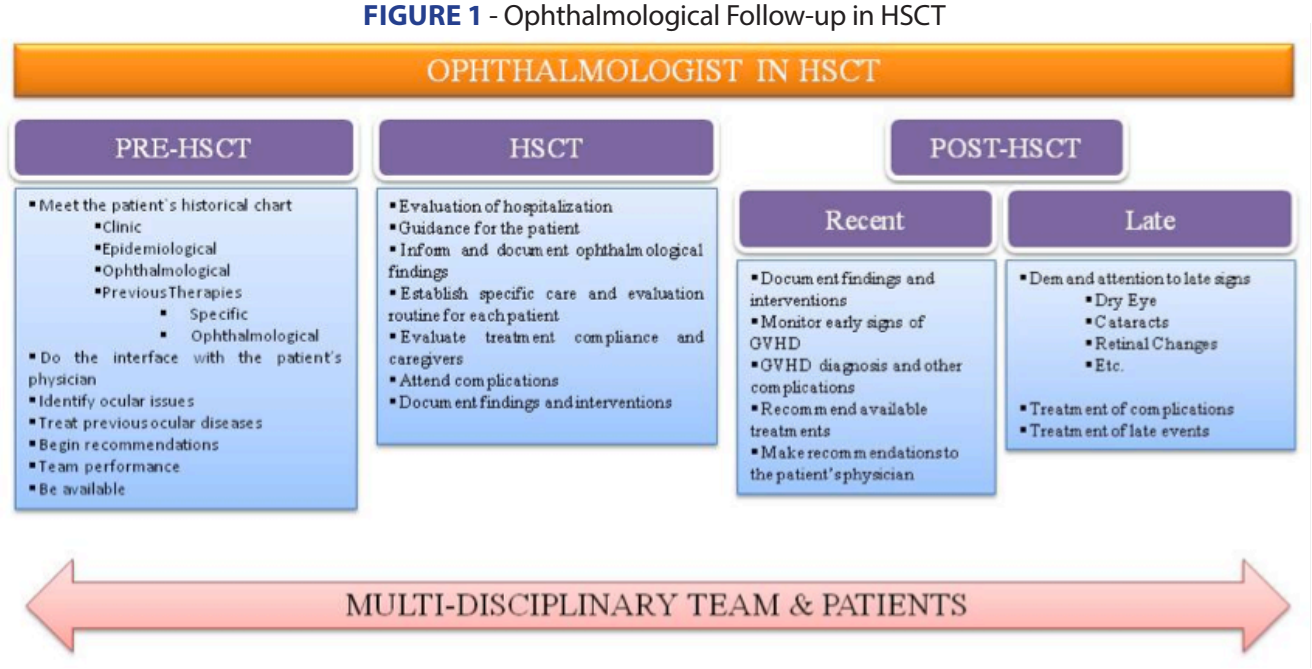
The most commonly clinical presentatiomn found in ocular GVHD is the dry eye disease, occurring, with varied intensity of clinical presentation, symptoms and involvement of the structures of the ocular surface and the tear film. However, it is a disease with complex pathophysiological mechanisms that involve loss of homeostasis of the ocular surface, changes in the composition of the tear film and glands, such as the main lacrimal gland and the meibomian glands. It constitutes a characteristic framework for the diagnosis of chronic GVHD, it occurs in most patients, typically 6 months after allogeneic HSCT. (Nassiri *et al.*, 2013)

The definition of Dry Eye Disease from the Dry Eye Workshop (DEWS) 2017 indicates that is a multifactorial disease of the tear and ocular surface that results in symptoms of discomfort, visual disturbances and instability of the tear film, with potential damage to the eye. It is accompanied by high osmolarity of the tear film and inflammation of the ocular surface, in which neurosensory changes also have an etiological role. (Craig *et al*., 2017) The pathophysiology of Dry Eye Disease related to GVHD is probably derived from the attack of T lymphocytes of the donor to receptor antigens, causing fibrosis and destruction of the conjunctiva, meibomian glands and the lacrimal gland, leading to a state of mixed dry eye, i.e, due to aqueous deficiency (lacrimal gland damage) and evaporative (lipid deficiency and meibomian gland dysfunction) which causes important damage to the ocular surface. (Shikari *et al*., 2013) There is a similarity between Sjögren's Syndrome (SS) and the dry eye secondary to GVHD since both have autoimmune inflammatory infiltration, although in GVHD the primary involvement is ductal and in Sjögren's Syndrome (SS) there is an immune-mediated inflammatory infiltrate affecting the glandular acinus. (Lee *et al.*, 2003) However, studies by Ogawa et al. demonstrated that there is more fibrosis in GVHD than in SS, and that the presence of the donor's fibroblasts in the ocular surface tissues of recipients with GVHD, such as in the lacrimal gland, may play a role in the pathophysiology of dry eye in chronic ocular GVHD. (Ogawa *et al.*, 2005)

Signs and symptoms of ocular GVHD occur according to the severity of tissue damage, compensatory mechanisms and stage of the disease from its inflammatory phase to the healing phase. Symptoms of fluctuating vision, foreign body sensation, irritation and red eye, photophobia and excessive tearing are described. Several complications, such as Meibomian glands dysfunction, pseudomembranous conjunctivitis, punctate and filamentary keratitis, cataracts secondary to the use of corticosteroids, narrowing and corneal perforation, secondary infection to ocular surface are in the published reports. (Rocha *et al*., 2000)

Ophthalmological evaluation must be performed before HSCT in order to assess the occurrence of previous ocular surface disease, proper identification of other risk factors and education of the patient regarding ocular symptoms after the procedure. Figure 1 shows the main aspects to be considered in the ophthalmological follow-up of patients undergoing HSCT.

FIGURE 1 - Ophthalmological Follow-up in HSCT



INCIDENCE AND RISK FACTORS FOR OCULAR GVHD

GVHD has an incidence of 25 to 70% of patients undergoing HSCT and the variability of rates reflects the adoption of new conditioning strategies, modalities of transplant and the lack of sensitive and specific markers for screening of this complication. The performance, on an increasing scale, of procedures with so-called unrelated donors, transplants in older patients, use of peripheral stem cells, adopted strategies of prophylaxis, among others, can explain different incidence rates. (Lee and Flowers, 2008, Lee *et al.,* 2003)

Ocular involvement in chronic GVHD can affect 40 to 60% of transplant recipients. There are some well-known risk factors related to the occurrence of ocular GVHD such as: non-Caucasian recipient patients, recipients of donors with positive serology for Epstein-Barr Virus (EBV) and Diabetes Mellitus. The severity of chronic GVHD and the number of organs involved, as well as previous dry eye, are also related to a higher incidence of ocular GVHD. (Nassiri *et al.*, 2013) In addition to the classic risk factors mentioned, it is also important to consider the occurrence of acute GVHD, use of peripheral stem cells, types of conditioning and prophylaxis. (Munir and Aylward, 2017)

The severity of chronic GVHD and the number of organs involved, as well as previous eye changes, such as signs and symptoms of dry eye prior to the procedure, are also related to a higher incidence of the ocular form of the disease. (Na et al., 2015) (Inamoto et al., 2019) (Giannaccare *et al.,* 2017). Table 1 summarizes the main risk factors associated to ocular GVHD

TABLE 1. Risk factors for ocular GHVD

Related to Recipient	Related to the Procedure
Age: older recipients	Use of Antithymocyte Globulin
Non-caucasian	Use of Total Body Irradiation
Diabetes Mellitus type 2	Donors with Incompatibilities
Previous ocurrence of acute GVHD	Donors with positive serology for Epstein-Barr Virus
Chronic GVHD GII to IV	Use of Peripheral Stem Cells
More than two organs involved in GVHD	Unrelated Donors
Previous Dry Eye Disease	Female donor for male donor

DIAGNOSTIC CRITERIA FOR OCULAR GVHD

The diagnosis of dry eye and ocular surface disease secondary to ocular GVHD is essentially clinical. It is important to quantify associated symptoms (standardized questionnaires as the OSDI - Ocular Surface Disease Index), to evaluate the tear volume (Schirmer's test and meniscometry), and tear stability (measure of the tear film break-up time and assessment of meibomian gland), osmolarity, conjunctival hyperemia and integrity of the ocular surface with the vital staining with 1% Green Lissamine, 1% Bengal Rose and 2% Sodium Fluorescein. In addition, a complete ophthalmological assessment including visual acuity, intraocular pressure, biomicroscopy and funduscopy should be performed on every patient prior and after allogeneic HSCT. Some diagnostic criteria have been developed and applied such as the NIH Consensus (Jagasia *et al*., 2015) and the International Chronic Ocular Graft-Versus-Host Disease Consensus Group (ICOGCG). (Ogawa *et al*., 2013)

The 2005 NIH Consensus established a standardized-criteria for the diagnosis of chronic GVHD and rating of disease severity through a scoring system, considering its impact on daily life activities. (Filipovich *et al*., 2005) In 2015, NIH launched a report to clarify the controversies related to the minimum criteria for the diagnosis of chronic GVHD (Table 2) and to refine the definition of the subcategories of chronic GVHD and the score of the specific gravity of the organ (Table 3). (Jagasia *et al*., 2015)

TABLE 2 – Signs and symptons of chronic GVHD according to NIH criteria (2015)

OrgAN Local	OR	DIAGNOSIS (Enough to establish the diagnosis for chronic GVHD)	DISTINCT (Seen in chronic GVHD, but insufficient individually for the diagnosis of chronic GVHD)	OTHER CHARACTERISTICS OR NON-CLASSIFIED ENTITIES*	COMMON (present in both acute and chronic GVHD)
Eyes			Dry, sand feeling, or pain Conjunctival scarring Keratoconjunctivitis sicca Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	

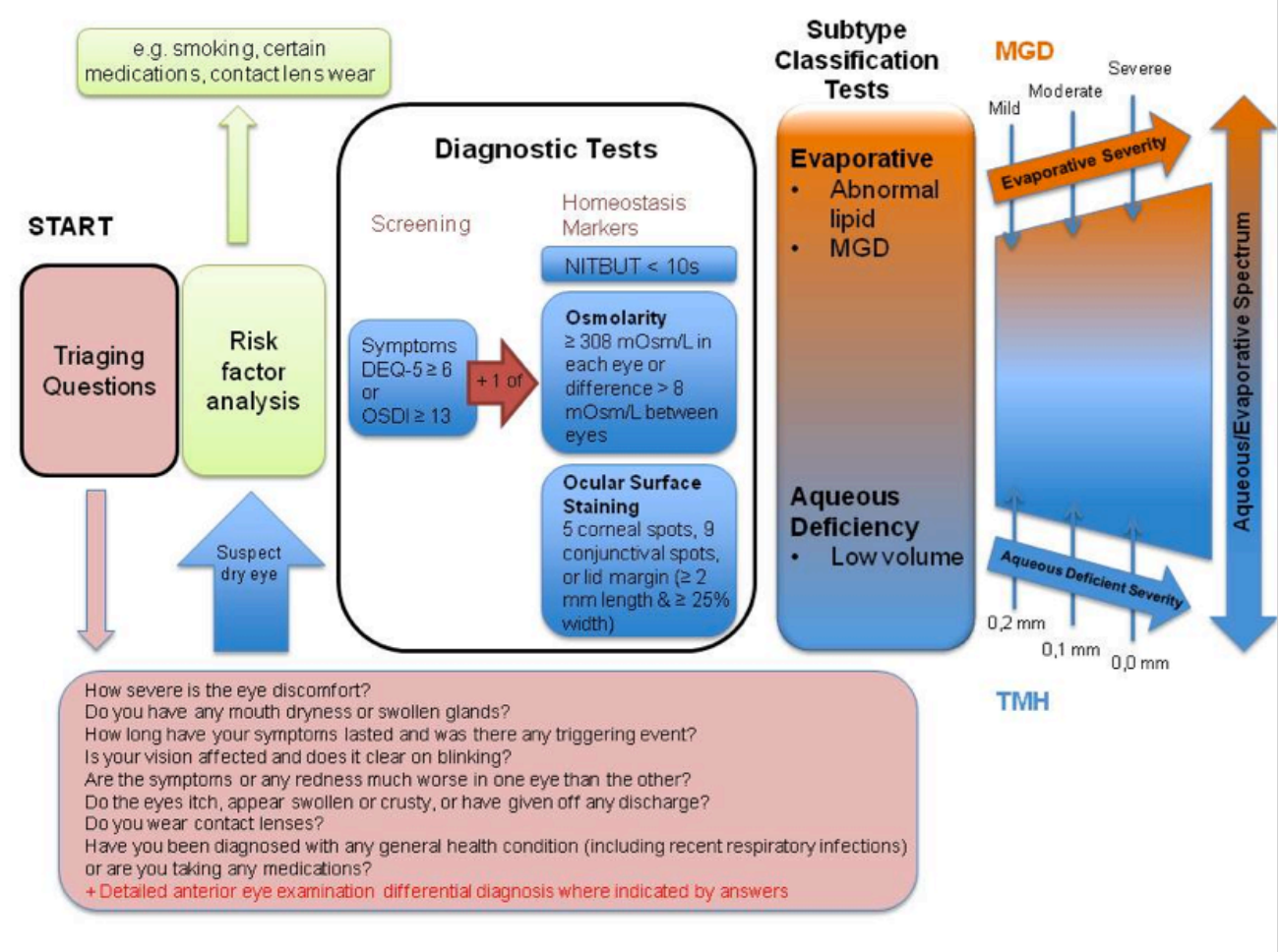
Source: Clinical Protocol and Therapeutic Guidelines, Immune suppression for Prophylaxis and Treatment of Acute and Chronic Graft-versus-host disease (GVHD) in Hematopoietic Stem Cell Transplants. (Jagasia et al., 2015)

TABLE 3 - Eyes Score for chronic GVHD according to NIH criteria (2015)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES Keratoconjunctivitis sicca, confirmed by the ophthalmologist: ☐ Yes ☐ No ☐ Not examined	☐ No symptoms	☐ Mild symptom of dry eye does not affect basic daily activities (it requires lubricant eye drops < 3 times a day)	☐ Moderate symptom of dry eye partially affects the daily activities (it requires lubricant eye drops > 3 times a day or tear duct ligature), without worsening visual acuity	☐ Severe symptoms of dry eye that significantly affect daily activities Or unable to work due to ocular symptoms Or vision loss due to keroconjunctivitis sicca.

Ocular symptoms of dry eye, foreign body sensation or recent onset of ocular pain; and the findings of conjunctival scarring; keratoconjunctivitis sicca; and confluent areas of punctate keratitis are defined as manifestations of chronic GVHD by the NIH report, while the manifestation of photophobia, periorbital hyperpigmentation and blepharitis (erythema of the eyelids with edema) are considered as unclassified manifestations. (Filipovich *et al.*, 2005) (Arai *et al.*, 2011) According to the NIH 2015 report, there are no specific diagnostic criteria for the eyes and dry eye is insufficient in itself to establish a diagnosis of chronic GVHD. Alterations of ocular surface and lacrimal gland are not considered diagnostic of chronic GVHD, as they may have other causes, e.g. secondary infections, medications or total body irradiation. Based on the NIH classification system, the diagnosis of ocular GVHD cannot be made in the absence of systemic GVHD. (Jagasia *et al.,* 2015)

According to the latest Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS II), Dry Eye diagnosis is considered if presence of symptoms and at least 1 positive test of homeostasis markers (such as tear film parameters, ocular surface staning or tear osmolarity). The investigation of dry eye starts with symptom evaluation through questionnaires, such as DEQ-5 or OSDI, followed by diagnostic tests of tear film stability (tear film break-up time) and tear volume, osmolarity and ocular surface staining with fluorescence and green lysamine (observing the cornea, conjunctiva and palpebral margin) (Figure 2). (Wolffsohn *et al.*, 2017) In the initial diagnosis, it is important to exclude conditions that can mimic dry eye such allergy and toxicity and, with the help of screening questions, evaluate risk factors, such as environmental exposure, medication in use and associated symptoms. Dry eye symptoms in the absence of clinical signs can suggest neuropathic pain. Meibomian gland evaluation is important and may be perfomed by quantification of expressibility and secretion pattern, tear lipid layer thickness and dynamics Tear volume is an important parametres measured by Schirmer test or tear meniscus height. Such parameters evaluate severity and classifiy subtypes as evaporative (associated to melbomian glands dysfunction, reduction of the lipidic layer and lacrimal instability) or aqueous deficiency (associated to lacrimal gland dysfunction and low tear volume) or mixed form. (Wolffsohn *et al.*, 2017)



In order to provide a stronger definition, rating, assessment and staging of ocular GVHD, the International Chronic Ocular Graft-Versus-Host Disease Consensus Group (ICOGCG) has launched a set of criteria that might help include ocular GVHD as a sufficient diagnostic signal itself for the diagnosis of chronic GVHD. (Ogawa *et al.,* 2013) The proposed diagnostic criteria for ocular GVHD include: (1) OSDI (Ocular Surface Disease Index) symptom questionnaire, (2) score for Schirmer I test (without anesthesia), (3) staining with corneal fluorescein and (4) conjunctival injection. Table 4 shows the scores for ocular criteria and the sum of the points obtained must be checked as to the presence or absence of systemic GVHD as shown in Table 5. A study compared the usefulness of the diagnosis between the 2005 NIH criteria and the ICOGCG criteria and showed that the stricter ICOGCG criteria better differentiated ocular GVHD (Pathak *et al.,* 2018).

TABLE 4 - Chronic ocular GVHD severity scale - ICOGCG.

Severity	Schirmer ITest	Corneal fluorescein staining	OSDI	Conjunctival Hyperemia
0	15 >	0	< 13	None
1	11-15	< 2	13-22	Mild/moderate
2	6 -10	2-3	23-32	Severe
3	£ 5	£ 4	> 33	

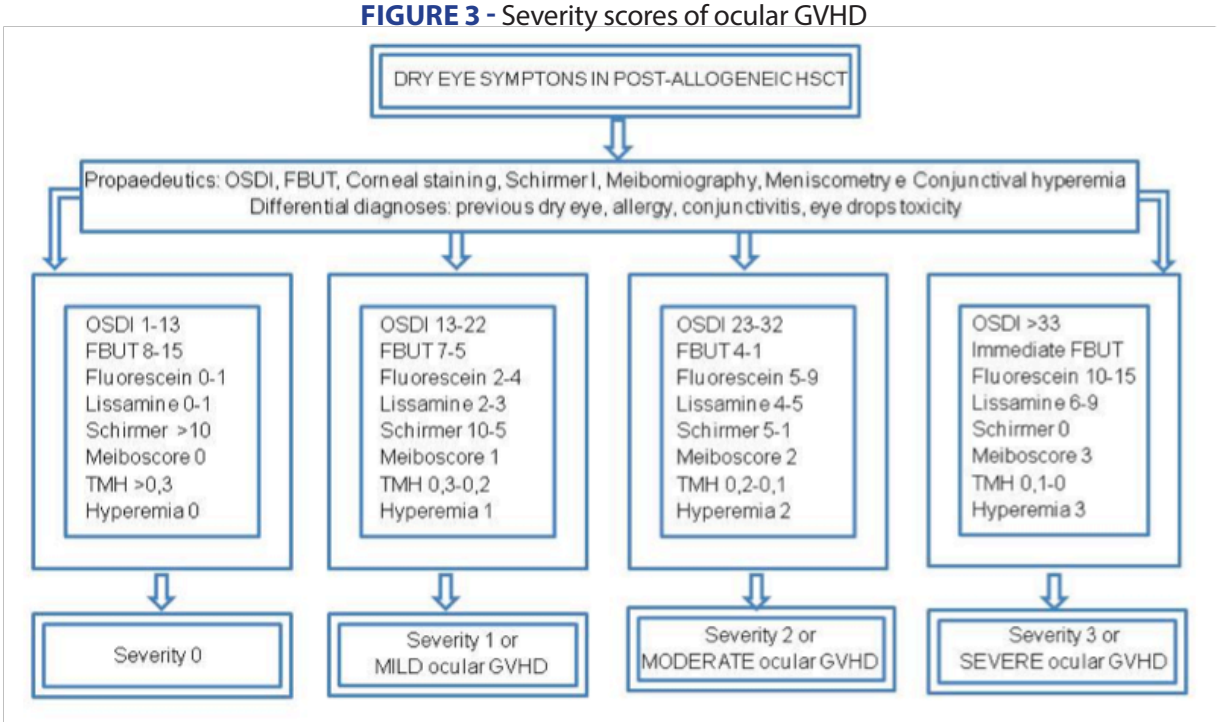
TABLE 5 - Diagnostic criteria of Chronic ocular GVHD – ICOGCG.

	Negative	Probable GVHD	Definitive GVHD
Systemic GVHD (-)	0-5	6-7	≥ 8
Systemic GVHD (+)	0-3	4-5	≥ 6

Diagnosis of chronic ocular GVHD: total score (Schirmer Test + corneal fluorescein staining+ OSDI + conjunctival hyperemia) = Negative: 0-4; Mild/moderate: 5-8; Severe: 9-11 and presence or not of systemic GVHD.

Figure 3 shows diagnostic criteria and severity scores for the investigation of ocular GVHD.

FIGURE 3 - Severity scores of ocular GVHD



TREATMENT

Treatment of ocular GVHD can be a challenge due the great diversity of clinical presentations, intensity of symptoms and potential complications. (Flowers and Martin, 2015) The main objectives of the treatment for chronic ocular GVHD refer to the reduction of symptoms, control of disease activity and prevention of permanent tissue damage and complications. Whenever possible, it should be monitored carefully and periodically by an ophthalmologist. (Inamoto *et al.,* 2019) Although topical therapy is usually enough to control the eye disease, systemic immune suppression should be considered in cases of moderate and severe disease.(Wolff *et al.*, 2010) (Dietrich-Ntoukas *et a*l., 2012)

The use of artificial lubricants is often the first step to treat dry eye secondary to GVHD, improving not only eye discomfort, but also visual quality. Distinct composition of eye drops regarding to viscosity, active compomnents and presence or quality of preservatives. Autologous serum eye drops, a biological tear substitute, presents characteristics in addition to its lubricating properties, due to its anti-inflammatory and epitheliotrophic characteristics, since it has epithelial growth factors, cytokines and supplement factors. The effectiveness of its use to improve symptoms has been extensively described in the literature. (Inamoto *et al.,* 2019) (Munir and Aylward, 2017)

Topical anti-inflammatory mediators such as corticosteroids, immunosuppressives and tetracycline derivatives contribute to better control of symptoms, in addition to slowing or preventing deterioration of ocular tissues. (Inamoto *et al.,* 2019) The use of topical corticosteroids, one of the main therapeutic choices, must be done with caution due to the important side effects that may result from its prolonged use. Numerous complications can be caused by its improper use, such as damage in the re-epithelialization, infections, corneal defect, cataract and secondary glaucoma. (Dietrich-Ntoukas *et al*., 2012) Some studies showed satisfactory results with the use of 0.05 to 0.1% cyclosporine and 0.05% tacrolimus as an alternative to prolonged use of corticosteroids. (Sall et al., 2000) (Abud et al., 2016) Acetylcysteine 5 to 10% may also be useful in treatment due to its mucolytic effects, although its effectiveness has not been investigated in clinical studies. (Dietrich-Ntoukas *et al.,* 2012)

Several other therapeutic modalities related to local and environmental eye care were evaluated as treatment options for ocular GVHD. Lacrimal punctum occlusion, either by temporary plug or permanent cauterization, is an option for patients with moderate symptoms. The use of soft or scleral contact lenses is also effective to improve symptoms of discomfort. Other options include application of warm compresses, hygiene and control of eyelid changes, as well as avoiding places with low humidity and hazardous environment exposure. Blepharitis must be addressed with warm compresses and eye drops or antibiotic and anti-inflammatory ointment, although some studies also suggest that oral therapy with tetracycline or doxycycline for 3 to 6 weeks reduces local inflammatory processes, improve lipid secretion of the Meibomian gland and lipid layer of the tear film. (Dietrich-Ntoukas *et al.,* 2012) (Frucht-Pery *et al.*, 1993) Oral omega-3 supplementation may improve tear film stability and has been used in recent years, although randomized studies do not show its effectiveness. (Deinema *et al.,* 2017)

Surgical procedures may be necessary in specific and refractory cases. Options as tarsorrhaphy, grafting and transplants of the limbus and amniotic membrane may be performed. In severe cases, corneal damage and perforation may occur, with a potential risk of vision impairment. (Peris-Martinez *et al.*, 2001) (Meller *et al.,* 2009)

Tables below show the recommendations for the assessment and treatment of ocular GVHD (Table 6), criteria used for strength of recommendation (Table 7) and the level of scientific evidence (Table 8). And in Figure 4 a flow chart with treatment recommendations for ocular GVHD.

TABLE 6 - Recommendations for GVHD as to ophthalmologic manifestation and recommendation score.

Recommendations for assessment and treatment of ocular GVHD	Levels of recommendation and evidence
Ophthalmologic Assessment Before transplantation From 3 to 6 months after transplantation In the diagnosis of chronic GVHD in any organ of the body	a-3 a-2 a-3
First-line systemic treatment for ocular GVHD Corticosteroids	a-1
Second-line systemic treatment ou subsequent treatment for ocular GVHD Extracorporeal Photophoresis Rituximab Sirolimus Mycophenolate mofetil	c-2 c-2 c-2 c-2
Topic treatment Preservative-free artificial tears Artificial tears/viscous ointment Cyclosporine 0,05% - 0,1% Tacrolimus Plugs for lacrimal punctum occlusion Corticosteroids Heated compresses and eyelid hygiene Scleral Lenses Mucin secretagogue eye drops Occluding glasses Antibiotics eye drops and ointment Autologous serum eye drops Platelet-derived eye drops Partial Tarsorrhaphy Superficial epithelial debridement Amniotic membrane transplantation Limbo-keratoplasty stem cell transplantation	 a-2 a-2 b-1 b-1 b-2 b-2 b-2 b-2 b-2 b-2 b-3 c-2 c-2 c-2 c-3 c-3 c-3
Other treatmentss Low-dose oral tetracyicline/doxycycline Oral omega-3 supplement	b-2 c-1

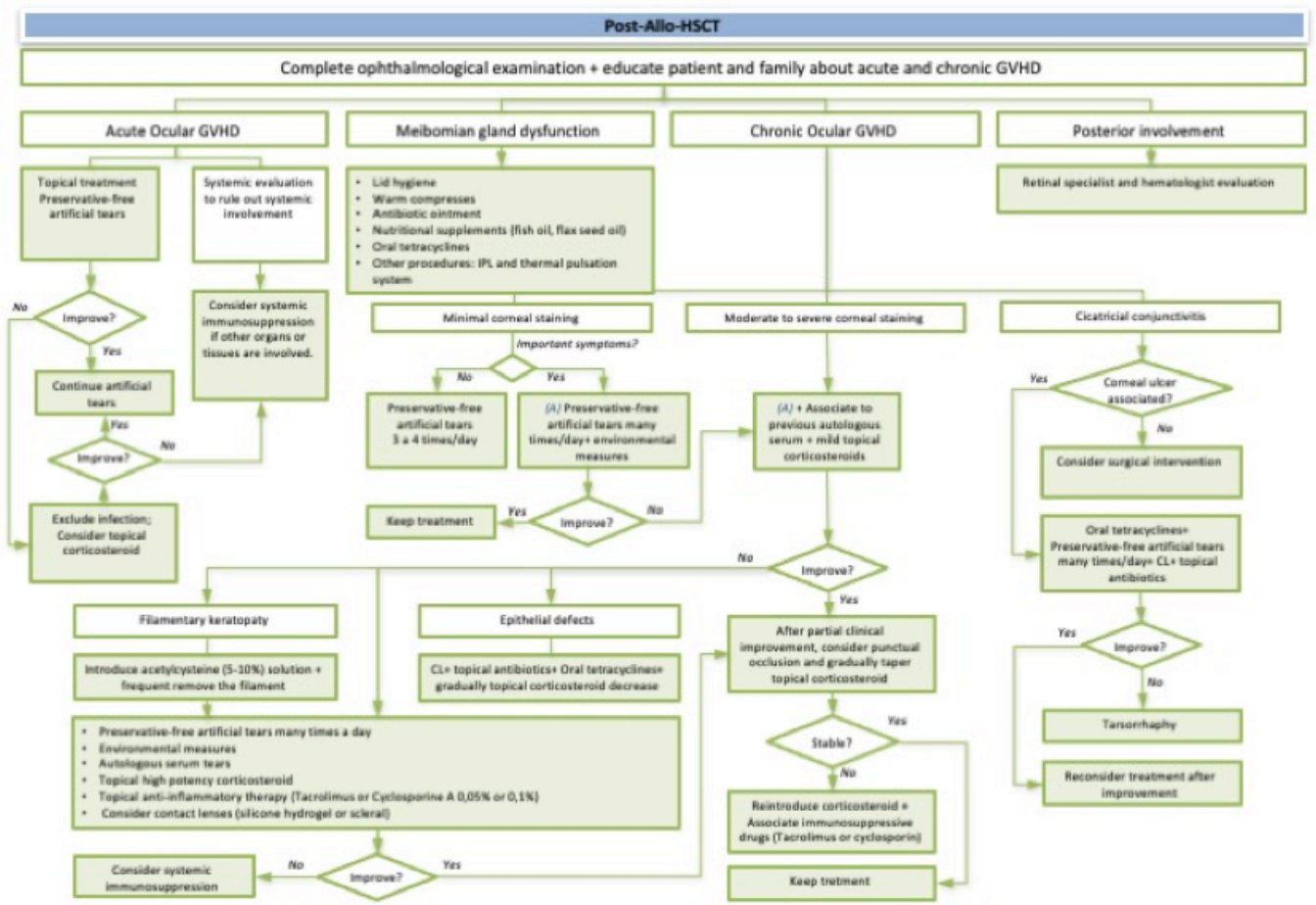
TABLE 7 - Assessment of the level of recommendation for treatment modalities

Strength of recommendation	
Strength of level of recommendation	Definition of the level of recommendation
A	It should always be offered
B	It should always be offered
C	The evidences of effectiveness are not enough to support or to be against; or the evidences may not compensate the adverse consequences or the cost of approach. Optional.
D	Moderate evidence that prove the lack of effectiveness or adverse results support a recommendation against the use. It shouldn't usually be offered.

TABLE 8 - Assessment of scientific evidence level

Quality of evidence for the recommendation	
Quality of evidence	Definition of level of evidence
I	Evidence of 1 controlled and appropriately randomized trial
II	Evidence of 1 well-designed clinical trial without randomization, from cohort or case-controlled analytical studies or from various time series or results from uncontrolled experiments
III	Evidences from opinions of respected authorities based on clinical experience, descriptive studies or expert committee report
III-1	Various reports of retrospective evaluations or small uncontrolled clinical trials
III-2	Only one small uncontrolled clinical trial, or retrospective evaluations
III-3	Only case reports available

FIGURE 4 - Ophthalmologic Treatment Flowchart



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PREVENTION AND TREATMENT OF INFECTIOUS COMPLICATIONS POST HSCT

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INTRODUCTION

The current version of the "Recommendations for the Prevention and Treatment of post-HSCT Infections" has been structured in tables and divided into the following sessions: 1) pre-transplant screening; 2) prophylactic measures; 3) laboratory monitoring; 4) management of febrile neutropenia; 5) empirical and preemptive antimicrobial therapies; 6) antimicrobial therapy for documented infectious events; and 7) post-transplant vaccination program.

In addition to the bibliographic update, new topics were added to the current version, such as the risk stratification for invasive fungal diseases, prophylaxis of CMV infection with letermovir, the debated topic of antibacterial prophylaxis during neutropenia, febrile neutropenia treatment duration, preemptive approach in adenovirus and HHV6 infections, and the reemergence of yellow fever and measles as a consequence of low vaccine coverage. Concerning the revaccination program, we cite the introduction of PCV13 for adult patients and the recombinant herpes zoster vaccine only for autologous transplant recipients. The latter is currently only available in private vaccination clinics.

Lastly, we would like to highlight the important changes in the management of respiratory viruses due to the COVID-19 pandemic, with the implementation of contact and aerosol precautions in HSCT units. Complete information concerning SARS COV-2 and COVID-19 have been posted in the website of SBTMO and has been updated as needed.

The strength of recommendations and quality of evidence were based on the grading system of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) summarized in

FIGURE 1- Grading system of the ESCMID.

STRENGTH OF RECOMMENDATION	QUALITY OF EVIDENCE
• **Grade A:** ESCMID strongly supports the recommendation for use • **Grade B:** ESCMID moderately supports the recommendation for use • **Grade C:** ESCMID marginally supports the recommendation for use • **Grade D:** ESCMID is against the use of the recommendation	• **Level I:** evidence from at least one properly designed randomised, controlled trial • **Level II:** evidence from at least one well designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments • **Level III:** evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

1. PRE-TRANSPLANT SCREENING FOR AUTOLOGOUS OR ALLOGENEIC HSCT		REFERENCES
1.1.	Assessment: Colonization by a multi-resistant germ (MDR). Method: Colonization surveillance swab for MDR (MRSA, VRE, CRE, ESBL). Comment (Evidence): Each center should propose a screening strategy appropriate to its epidemiology to reduce intra-hospital transmission, in conjunction with the local Infection Control Program. (BII)	[1–3]
1.2.	Assessment: Previous bacterial infections. Method: Anamnesis, physical examination, imaging tests, and review of previous events. Comment (Evidence): Attention to recurrent infectious events, MDR pathogens, and latent infections. Previous infections by MDR agents will be considered when choosing the empirical drug at the time of febrile neutropenia (BII)	[4,5]
1.3.	Assessment: Risk stratification for invasive fungal disease (IFD) Method: The level of risk for IFD in allogeneic HSCT recipients depends on several factors, including host characteristics, underlying hematological disease conditions and the type of transplantation that will be performed. Anamnesis, physical examination, imaging tests, and review of previous events. Risk factors: high doses of corticosteroids, prolonged neutropenia, IFD 6 months before transplantation. Allogeneic stem cell transplant patients are generally at high risk with factors such as GVHD, CMV disease, cord blood and haploidentical donors and active leukemia at time of transplant increasing the risk further. Patients who are not in complete remission pre-transplant are at higher risk of IFD post-transplant. Comments (Evidence): Risk stratification identifies those patients who will benefit most from mold active versus yeast active prophylaxis and those who can be safely managed with monitoring and clinically driven interventions for IFD (AII).	[6–13]
1.4.	Assessment: Previous viral infection Method: Medical history and specific serologies (HSV, CMV, EBV, HIV, HCV, HBV, HTLV). Comments (Evidence): Order HBsAg, anti-HBs, anti-HBc, and anti-HCV serology for recipient and donor and NAT for the donor. It is crucial to screen viral hepatitis for the right prophylaxis or treatment (AII).	[4,14]
1.5.	Assessment: Dengue, Chikungunya Zika. Method: Inquiry about the epidemiological risk. Serological screening for D / R is not recommended. Comment (Evidence): Check whether the candidate and/or donor come from an endemic or epidemic region; or had a recent travel to such regions. If symptomatic, collect NAT (and/or NS1 in the case of DENV). If positive, wait 30 days for stem cell (SC) harvesting or transplant (AII).	[15]
1.6.	Assessment: Screening of respiratory virus infections. Method: Immunofluorescence assay or multiplex PCR in respiratory samples (nasopharynx swab or nasal wash) before admission. Comment (Evidence): With the emergence of COVID-19, the screening of respiratory viruses in asymptomatic patients became mandatory before admission to HSCT (AII).	[16,17]

1.7.	Assessment: Yellow Fever Method: There is no recommendation for serological screening for D/R. Consider vaccinating D and/or R before HSCT. Comment (Evidence): The whole country has recommendation of yellow fever vaccination. About 30% of the individuals vaccinated before transplantation maintain antibodies after HSCT (BII). Check if the donor has been vaccinated recently. If yes, wait 30 days for SC harvesting or HSCT.	[18–22]
1.8.	Assessment: Latent tuberculosis infection (LTBI) Method: Investigate the occurrence of previous TB, TB in household contacts, or diagnose LTBI by tuberculin skin test (TST) or by interferon gamma release assays (IGRA), e.g., the QuantiFeron TB test (QTF-TB). Comment (Evidence): Previous history of TB, contact with TB, positive PPD or reactive QTF-TB indicate latent TB. Recipient with TST ≥ 5mm is considered reactive (positive). In a population vaccinated with BCG, the IGRA is recommended because it does not cross-react with Mycobacterium bovis, present in BCG (BII).	[23,24]
1.9.	Assessment: Chagas disease Method: Enzyme immune assay (EIA), immunofluorescent assay (FA) or hemagglutination inhibition assay (HIA). Perform two different tests. If discordant, repeat with Western blot or chemiluminescence. Comment (Evidence): Inquiry D/R about residence in an endemic area, houses that favors the presence of the vector, blood transfusion before 1992, having family members or a mother with Chagas positive serology. False negative serology may occur. In such cases, the information acquired in the survey must be valued and the recipient should be monitored after HSCT (AII).	[18,25]
1.10.	Assessment: Toxoplasmosis Method: Toxoplasmosis serology (IgG and IgM) from donor and recipient. Comment (Evidence): More than 70% of cases are due to reactivation. Higher risk if D-/R+. Positive IgM or high levels of IgG may indicate recent infection. In such cases, PCR test should be performed and if positive, the patient should be treated (AII).	[26]
	Evaluation: Strongyloidiasis Method: Investigation by stool examination, and/or serology, or empirical therapy. Comment (Evidence): In general, the tests have low sensitivity. Empirical pre-HSCT therapy with ivermectin 200 mg/kg/d for 2 days is recommended. Repeat treatment after 2 weeks. Alternative schedule is albendazole 400 mg 12/12h for 7 days (AII).	[27,28]

2. PROPHYLACTIC MEASURES		REFERENCES
2.1.	Situation: Antibacterial prophylaxis in the neutropenic phase. Conduct: Ciprofloxacin or levofloxacin. Comment (Evidence): The consensus does not recommend using antibacterial prophylaxis in the routine, given the high prevalence of quinolone-resistant enterobacteria and the risk of selecting multidrug-resistant strains (MDR). Consider only in centers where the frequency of resistance to quinolones is low (<30%), a controlled MDR infection/colonization rate and high bloodstream infection prevalence. In other centers, the benefit is questionable and is not indicated. Antibacterial prophylaxis is not recommended in children during the neutropenia (DI) phase. Caution about QT prolongation toxicity, especially in situations with concomitant use of QT prolongations drugs (as voriconazole)	[29–36]
2.2.	Situation: Antibacterial prophylaxis in late post-engraftment phase. Conduct: Oral penicillin. Alternatives: macrolides, quinolones, or 2nd generation cephalosporins. Comment (Evidence): Recommended only in patients with GVHD, for preventing S. pneumoniae, or in cases of recurrent respiratory infection and hypogammaglobulinemia. (BII)	[23]
2.3.	Situation: Documented hypogammaglobulinemia (serum IgG <400 mg / dl). Conduct: Immunoglobulin replacement (IVIG) dose 500mg / kg / month. Comment (Evidence): Decreases the number of infectious episodes in patients who need replacement. It is not recommended in patients without documentation of hypogammaglobulinemia. (BIII)	[37–39]
2.4.	Situation: Primary antifungal prophylaxis (PAP) at High risk Recommendation: Mold-active PAP is recommended. Posaconazole (AI); voriconazole (BI); caspofungin (CIII); micafungin (CIII). Children: voriconazole for patients >2 years of age (AII); or posaconazole in > 13 years (AII). Alternatives include liposomal amphotericin B (B-II); micafungin (B-II); and, with less strength of evidence, aerosolized liposomal amphotericin B (C-II) and caspofungin (C-II). If posaconazole and voriconazole are selected, TDM is recommended with target concentrations similar to those recommended for adults. Comment (Evidence): There are 3 phases after the transplant which reflect the risk of IFD: neutropenia (early), a-GVHD and the early immune recovery (late), and late a-GVHD or c-GVHD, together with late immunologic recovery (very late) High Risk patients (adaptated Girmenia 2014) Early phase from day 1 to 40: Active acute leukemia at the time of trans- plantation (AII), CB transplantation (AII), Grade III-IV a-GVHD after any type of transplantation (AII), Transplantation from MMRD or UD and 1 or more of the following additional risk factors: grade II a-GVHD, steroid dose >2 mg/kg/day for at least 1 week, CMV disease, recurrent CMV infection, prolonged neutropenia (PMN < 500/mL for more than 3 weeks), iron over- load (BIII) , Steroid refractory/dependent a-GVHD after any type of transplantation (AIII). Late Phase (from day 41 to 100): Acute grade III-IV GVHD after any type of transplantation (AII), Transplantation from MMRD or UD and 1 or more of the following additional risk factors: grade II a-GVHD, steroid dose > 2 mg/kg/day for at least 1 week, CMV disease, recurrent CMV infection, recurrent neutropenia (PMN < 500/mL for more than 1 week) (BIII), Steroid refractory/dependent a-GVHD after any type of transplantation (AIII) Very Late Phase after Transplantation (Day > 100) Persistent or late-onset grade III-IV a-GVHD (AII), Persistent or late-onset steroid refractory/ dependent a-GVHD after any type of transplantation (AII), Persistent or late-onset grade II a-GVHD after transplantation from MMRD or UD (BIII) Extensive c-GVHD when preceded by an a- GVHD (AII)	[7,12,40–47]
2.5.	Situation: Primary antifungal prophylaxis (PAP) at standard risk. Recommendation: Candida active PAP is recommended. Fluconazole (AI); voriconazole (BI); micafungin (BI). In children fluconazole (AI). Comment (Evidence): Standard Risk: Early Phase after Transplantation (Day 0-40): All remaining patients not included in the high-risk category (AI) Late Phase after Transplantation (Day 41-100): All remaining patients not included in the high-risk category (BII). Very Late Phase after Transplantation (Day > 100): Limited c-GVHD in patients who receive only a nonsteroid immunosuppression and "de novo" c-GVHD (BIII).	[7,12,45,48]

2.6.	Situation: Primary Antifungal Prophylaxis (PAP) at low risk Recommendation: No prophylaxis Comment (Evidence): Early Phase after Transplantation (Day 0-40). Autologous HSCT: Fluconazole can be used in the phase of intense neutropenia to prevent Candida infections, especially in the presence of mucositis. No patient undergoing allogeneic HSCT is considered to be at low risk at this stage Late Phase after Transplantation (Day 41-100) No patient undergoing allogeneic HSCT may be considered at low risk for IFD during this phase. Very Late Phase after Transplantation (Day > 100) Absence of any type of GVHD and no steroid therapy (AII).	[7,12,45]
2.7.	Situation: Prophylaxis for herpes simplex virus (HSV) and varicella-zoster (VZV). Recommendation: Acyclovir or Valacyclovir. Comment (Evidence): Beginning in conditioning up to 1 year after BMT or up to 6 months after the end of immunosuppression, whichever comes last (allogeneic HSCT) (AI).	[49,50]
2.8.	Situation: Prophylaxis for Cytomegalovirus (CMV). Recommendation: Letermovir. Comment (Evidence): Indicated for positive CMV IgG receptors. The benefit is more significant at high risk: cord, use of post-cyclophosphamide, HLA mismatch, and T cell depletion (e.g., ATG, alemtuzumab). Perform CMV qPCR before prophylaxis (less effective if DNAemia is present). Start as soon as possible and keep until D + 100 (AI). Pay attention to the dose adjusted for concomitant use of cyclosporine. There is no data in pediatrics for the use of letermovir. Prophylaxis with acyclovir or valacyclovir for HSV / VZV should be maintained (AI).	[51]
2.9.	Situation: Prophylaxis for HBV Recommendation: lamivudine; alternative entecavir or tenofovir Comment (Evidence): Indicated in the following situations: AntiHBc + donor with negative HBV DNA; AntiHBc / AntiHBs + receptor with negative HBV DNA. For AntiHBc+ receptor with AntiHBs- and HBV DNA - recommended prophylaxis is entecavir 0.5mg/day. Follow-up with monthly transaminases when using prophylaxis, if increased, request HBV DNA. Prophylaxis duration: from the first conditioning day (if not in use) to 1 year after autologous HSCT and two years after allogeneic HSCT or six months after the end of immunosuppression (whichever comes later) (AII).	[14,52]
2.10.	Situation: Prevention of respiratory viruses (RV). Recommendation: HSCT should be postponed in symptomatic patients (AII). Only patients who tested negative in pre-HSCT RV screening can be admitted for transplantation (AII). Daily surveillance of respiratory symptoms is crucial (AIII). Rapid diagnosis and precautions implementation according to specific diagnosis (AII). In units with HEPA rooms, the positive pressure should be reverted or turned off if respiratory viruses are diagnosed (AII). Comment (Evidence): Only recipients of allogeneic HSCT <2 years of age with a high risk of progression to RSV pneumonia can be considered for treatment with palivizumab (CIII). Due to the current circulation of SARS CoV-2 worldwide, masks and contact precautions besides hand hygiene is strongly recommended in HSCT units (AII).	[17,53]
2.11.	Situation: Prevention of hemorrhagic cystitis (HC) caused by BK virus (BKV). Recommendation: Hyperhydration (BII) and bladder irrigation (CII). Comment (Evidence): HC prophylaxis is based on hyperhydration and bladder irrigation to reduce urothelial damage, which occurs mainly in myeloablative conditioning with cyclophosphamide, busulfan and total body irradiation. Asymptomatic BKV viruria is frequent after HSCT (> 60%) and there is no correlation between viral load and hematuria severity. Monitoring of BKV in urine or blood is not recommended. Fluoroquinolones are not recommended because ineffectiveness in viral replication and severity of CH, and the risk of increasing resistance to quinolones (DII).	[54,55]

2.12.	Situation: Tuberculosis prophylaxis Management: Prophylaxis with INH for 6 to 9 months for recipients with latent TB. An alternative is to enter prophylaxis if the recipient develops chronic GVHD (BIII). Comment (Evidence): Prophylaxis with INH has been controversial due to the late occurrence of TB and adverse events (in general, rare). Main risk factor is chronic GVHD. Maintain prophylaxis for 6 months or until the condition stabilizes (BII).	[56,57]
2.13.	Situation: Prophylaxis for Toxoplasmosis and Pneumocystosis. Conduct: TMP/SMX. Comment (Evidence): TMP/SMX is active against T.gondii, P.jiroveci (AII adults; AI children), Listeria and Nocardia. Although less effective, the alternative drug is dapsone 100 mg/day (AII). Half of the cases of toxoplasmosis occur before d+30. Thus, prophylaxis should be started soon after engraftment and maintained until d+180 or more in patients who continue to receive IS and/or have chronic GVHD. There is no evidence that prophylaxis can be safely stopped if CD4+ count is normal (as in HIV +) because other risk factors may persist (BIII).	[26,58]5

3. Laboratory monitoring		References
3.1.	Situation: CMV monitoring. Method: Perform qPCR (AII) or pp65 antigenemia (BII) weekly. Comment (Evidence): In all CMV seropositive recipients (R+) at least 1x a week up to D + 100. R- / D- do not require monitoring. CMV monitoring should be done regardless of the use of prophylaxis with letermovir. CMV monitoring should be prolonged in HSCT with a mismatch, cord blood or haplo without Pt-Cy; in patients who reactivated up to d + 100; who had acute or chronic GVHD; with persistent immunodeficiency or who used prophylaxis with letermovir. When using qPCR, monitoring should be carried out keeping the same type of sample, the same method of DNA extraction and quantification (including WHO quantification standard) (AII), and the results must be available within 48 hours. Monitoring with AG should start after engraftment.	[59]
3.2.	Situation: Monitoring of EBV. Method: quantitative PCR (qPCR) weekly Comment (Evidence): Recommended for groups at risk for post-HSCT lymphoproliferative disease (DLPT): cord, HLA mismatch; in vivo or in vitro depletion of T cells; mismatch in EBV serology; splenectomy and previous HSCT (AII). Monitoring starts in D+7 until D+100; may be extended, at least monthly, in case of GVHD using ISS or previous reactivation of EBV during the first year (BII).	[60]
3.3.	Situation: Monitoring of HHV-6 reactivation. Method: quantitative PCR (qPCR) Comment (Evidence): Routine HHV-6 DNA screening is not recommended for pre-emptive or prophylactic therapy (DII)	[86]
3.4.	Situation: Adenovirus monitoring (ADV). Method: qPCR in feces or blood weekly. Comment (Evidence): In high-risk groups e.g., children with cord blood HSCT or unrelated, severe GVHD (grade III-IV); severe lymphopenia (<200/L) (IIA children). Adults with cord or haploidentical HSCT; Severe GVHD (grade III-IV); severe lymphopenia (<200/L); alemtuzumab treatment (BII adults). In feces, viral load above 106 copies/gram of feces predicts viremia and indicates the time to start blood monitoring. In the absence of stool screening, blood monitoring can begin immediately after transplantation and be maintained until D + 100 (BIII children, CIII adults).	[61]

3.5.	Situation: Aspergillosis Method: Serum Galactomannan (GM) by EIA, 2-3x/week during the early engraftment phase has a high sensitivity and negative predictive value (NPV) for IA (AII). Serial screening is not recommended in patients on mold-active prophylaxis (DII). Children: GM testing can be used both as a screening tool in pediatric patients considered at high risk for developing IA (B-II) as well as a diagnostic tool in pediatric patients suspected of having developed IA, e.g. those with clinical symptoms or imaging abnormalities (B-II). Comments (Evidence): Better performance of the test with 2 consecutives values above 0.5 (AI). Monitoring should be combined with imaging tests and clinical evaluation. After grafting, the risk of developing IFD by filamentous fungus is associated with GVHD and the use of corticosteroids. Serum monitoring is not recommended in patients who have filamentous fungus prophylaxis. (DII). Decrease of the ODI during the first two weeks of antifungal therapy is a reliable predictor of a satisfactory response in cancer patients	[46,62–69]
3.6.	Situation: Control of response to the treatment of invasive aspergillosis (AII) Method: Galactomannan (GM) by EIA, 2-3x/week Comments (Evidence): In monitoring response to the treatment of invasive aspergillosis; the persistence of positive GM is indicative of a poor prognosis. The 1. 3 beta D glucan test may be positive for several agents such as Candida, Aspergillus, P. jirovecci, without discriminating between them.	[62]
3.7.	Situation: Monitoring of Chagas disease Method: Qualitative PCR in decreasing frequency. Comment (Evidence): In D+ and/or R+ for Chagas. PCR monitoring should start on admission, then weekly for 2 months, every other week between 2 and 6 months of HSCT and annually after 6 months. If benznidazole is introduced pre-emptively, monitor marrow and hepatic toxicity. There is no benefit of prophylaxis compared to preemptive therapy (BIII).	[18,25]

4. Febrile neutropenia (FN) management		References
4.1.	Situation: Diagnosis of febrile neutropenia. Method: Fever surveillance, clinical investigation, and blood culture collection. Comment (Evidence): During neutropenia, monitor for fever or other signs or symptoms suggestive of infection—detailed clinical examination, identifying signs of sepsis, infectious foci. Blood culture collections are mandatory before the start of antimicrobials (AII).	[70]
4.2.	Situation: Introduction of empirical antimicrobials. Method: escalating or de-escalating antimicrobials. Escalation = monotherapy with piperacillin-tazobactam, or cefepime, or ceftazidime. De-escalation = β-lactam + aminoglycoside; β-lactam +/- aminoglycoside +/- tigecycline; association of polymyxin B / E; use of new drugs with spectrum for MDR. Comment (Evidence): An institutional management algorithm appropriate to the local antimicrobial profile is recommended. Empirical therapy should be started within 60 minutes after the onset of fever. This measure reduces mortality. If no hemodynamic instability, history of infection, or previous colonization by MDR pathogen, an escalation strategy is recommended. Carbapenems as an initial drug are discouraged due to their association with pseudomembranous colitis. The de-escalation strategy should be used in clinical instability situations, previous history of MDR, or epidemiological situation of MDR outbreak in the unit (AI).	[5,70–77]h

4.3.	Situation: Criteria for modifying antimicrobial therapy in FN. Method: Detection of microbiological and / or clinical failure. Comment (Evidence): Development of new clinical signs or hemodynamic instability during the initial empirical treatment. Persistent fever in the absence of clinical or microbiological documentation is not an indication of empirical modification in a stable patient. Persistent fever should be conducted with an intensification of the diagnostic approach. Therapy adjustment should be made according to the antibiogram of the isolated agent. The minimum spectrum of coverage for empirical therapy is enterobacteria and for Pseudomonas spp (AII).	[71,76,78,79]
4.4.	Situation: Treatment duration in the FN. Method: Consider the criteria for withdrawal. Comment (Evidence): The course of antimicrobial treatment should be guided by documentation of infection and neutrophil recovery (> 500 cells / mm^3). In patients with fever resolution, no infection documentation, and stability, the empirical therapy may be suspended after 3 or 5 days. In cases of documented infection, the treatment duration will depend on the type of infection (AII).	[74,80,81]

5. Empiric and Pre-emptive Therapies		References
5.1.	Situation: Empiric antifungal therapy Recommendation: Caspofungin (AI), Lipossomal Amphotericin B (BI), voriconazole (BII) Comment (Evidence): Empirical therapy is indicated for neutropenic patients who persist with fever for more than 4 days using broad spectrum antibiotic therapy at places without quick access to diagnosis of IFD (e.g., galactomannan) or in high-risk epidemiological situations. (construction-related outbreaks, etc.). Children: This approach should be initiates in high-risk neutropenic patients after 96h of fever of unclear cause that is unresponsive to broad spectrum antibacterial agents (BII) and be continued until resolution of neutropenia in the absence of suspected or documented invasive fungal disease BII. Four prospective randomized clinical trials have been performed in pediatric haemato-oncologic populations.	[82–85]
5.2.	Situation: Pre-emptive antifungal therapy Recommendation: Voriconazole; isavuconazole. Alternatives: Lipossomal Amphotericin B or Amphotericin B lipidic complex Comments (Evidence): The preemptive strategy uses antigenic or molecular fungal markers (beta 1.3 glucan, galactomannan, or fungal PCR), surveillance of radiological changes (chest and sinus CT scans) and clinical data. This treatment strategy has already been shown to decrease the use of antifungals without impacting mortality related to fungal infection. The use of biomarkers has limitations in the case of prophylaxis for filamentous fungi, as it reduces the sensitivity of the test in this situation. False positive results may also occur in patients with intestinal GVHD and mucositis (adult AII, CI children). Children: a diagnostic-driven treatment strategy can be recommended in children (A-II) if the diagnostic infrastructure allows timely access to CT imaging, GM testing and the ability to undertake bronchoscopies with bronchoalveolar lavage and appropriate microbiologic assessment.	[69,86–93]
5.3.	Situation: Preemptive therapy for CMV Recommendation: Induction therapy with ganciclovir (GCV) or valganciclovir (VGV). Foscarnet can be used during neutropenia (AI). Comment (Evidence): Preemptive therapy should be introduced after CMV qPCR positive or AG positivity (≥ 1 positive / 300,000 cells). The cut-off of the viral load for the introduction of GCV must be defined locally according to the standardized kit and may vary according to the patient's risk. High risk = cord, haplo, T cell depletion, and HLA mismatch (lower cut-off). Low risk = remaining HSCTs or using letermovir (highest cut-off). If viremia is on the rise after two weeks, consider increasing the dose of GCV (CIII). The duration of preemptive therapy is ≥14 days and maybe suspended after that period with a negative qPCR result. G-CSF can be used in case of hematopoietic toxicity by GCV. During preemptive therapy, suspend prophylactic ACV. Oral valganciclovir should not be used in patients with severe GI GVHD (AII)	[94]

5.4.	Situation: Pre-emptive therapy for EBV. Recommendation: Weaning/withdrawal of immunosuppression (AII). In selected cases, consider weekly rituximab, from 1-4 doses, until negative EBV qPCR (AII). Comment (Evidence): Post-transplant PTD risk groups are severe acute GVHD (refractory to corticosteroids), severe chronic GVHD, high or rising EBV viral load, and use of mesenchymal cells. To date, there are no studies that indicate a viral load cut-off to start preemptive therapy. Consider the dynamics of EBV viral load. If the viral load is high or increases, withdraw SI is desirable. If symptoms, or persistence of high CV, start therapy with rituximab (CIII).	[60,95]
5.5.	Situation: Pre-emptive therapy for HHV-6. Recommendation: Consider therapy with GCV or FCV just in few conditions. Comments (Evidence): Pre-emptive therapy with GCV for 21 days in risk groups with HHV-6 positive DNAemia AND compatible neurological condition, excluding other causes, OR DNAemia with delayed engrafting/myelosuppression with no other explanation (CIII).	[96]
5.6.	Situation: Pre-emptive therapy for ADV. Recommendation: Reduce immunosuppression (AII) and cidofovir therapy (BII). Comment (Evidence): Patients with disseminated disease could receive therapy with cidofovir 3–5 mg/kg/week for 2–3 weeks; after that, every two weeks. Alternative scheme is cidofovir 1 mg / kg 3 times / week (BII). Hyperhydration and the use of probenecid can reduce nephrotoxicity.	[61]

6. Antimicrobial therapy for documented infections		References
6.1.	Situation: Bacterial infections. Conduct: Clinical and laboratory diagnosis of the disease; specific treatment. Comment (Evidence): The choice of therapy should be guided by syndrome and isolated agent (including susceptibility test). There is no indication of expanding the antimicrobial spectrum beyond what is necessary to treat documented infectious syndrome in non-neutropenic situations.	[97]
6.2.	Situation: Candidemia or Acute Invasive Candidiasis Recommendation: Caspofungin; micafungin; anidulafungin. Alternatives: Lipossomal Amphotericin B; Amphotericin B lipidic complex or voriconazole. Comments (Evidence): Therapy should be continued for 14 days after the first negative blood culture in the absence of other metastatic foci. Ocular fundoscopy and echocardiography are recommended for all patients. Central venous catheter (CVC) should be removed as early as possible when it is the source of infection. Specie confirmation is necessary to adequate therapy.	[98,99]
6.3.	Situation: Invasive aspergillosis Recommendation: Voriconazole (AI); isavuconazole (AI); Lipossomal Amphotericin B (BII); Amphotericin B lipidid complex (CIII). Children other than neonates: Voriconazole is recommended as the first line agent to treat IA in all children except neonates (AII). L-Ampho B –(BII) Caspofungin (CII). Neonates: Lipossomal Amphotericin B is the first choice in neonates (AIII). Comments (Evidence): Attention to drug interactions, renal impairment. Treatments with voriconazole should be monitored by serum voriconazole level. Treatment duration depends on clinical response and immune reconstitution or recovery from GvHD. Regions where the resistance rate is > 10% give preference to amphotericin or the combination of voriconazole and caspofungin.	[46,62,100–104]

6.4.	Situation: Mucormycosis. Recommendation: Liposomal Amphotericin B (AII); Amphotericin B lipidic complex (no CNS involvement) (BIII); Isavuconazole (BII) Posaconazole oral suspension (CII) – not indicated as first therapy, only for post induction maintenance/secondary prophylaxis. Comments (Evidence): Local debridement of all necrotic tissue is strongly recommended. Posaconazole tablets or intravenous are not yet available in Brazil. Posaconazole is not allowed for children under than 13 years old.	[105,106]
6.5.	Situation: Fusariosis Recommendation: Voriconazole (AII); Liposomal Amphotericin B (BII); Amphotericin B Lipid Complex (CIII); isavuconazole (no data). Comments (Evidence): Combination therapy can be considered in persistently neutropenic patients with therapeutic failure. Surgical debridement of localized lesion should be considered. Monitoring serum levels of voriconazole. Few pediatric studies, most studies of invasive fusariosis in pediatric immunosuppressed patients used combination therapy based on azole.	[107–111]
6.6.	Situation: CMV disease Recommendation: Intravenous Ganciclovir (AII); foscarnet (if GCV resistance or toxicity) (AIII). Alternatives are cidofovir (2nd line) (BII) or foscarnet + GCV in full doses (3rd line) (CII). Comment (Evidence): The addition of intravenous immunoglobulin (IVIG) can be considered for the treatment of CMV pneumonia (CIII). For other manifestations of CMV disease, the addition of IgIV (IBD) is not recommended. Intravitreal injections of GCV or foscarnet can be used to treat CMV retinitis combined with systemic therapy (BII). Valganciclovir can be used in place of GCV IV or foscarnet, except in patients with severe gastrointestinal GVHD (BII). Doses need to be adjusted to the patient's renal function (AII).	[94]
6.7.	Situation: Disease due to EBV and PTLD. Recommendation: Reduce SI and rituximab weekly for up to 4 weeks (AII). An alternative is the transfer of adaptive immunity by infusion of donor lymphocytes (DLI) if specific EBV (CII). Comment (Evidence): In cases of disease (hepatitis, pneumonitis, or CNS disease) due to suspected or confirmed EBV or PTLD (with biopsy), therapy should be started as soon as possible (AII). Factors of good prognosis are age <30 years, benign disease, absence of acute GVHD, reduced ISS at diagnosis, and drop in viremia after initial therapy.	[60,95,112,113]
6.8.	Situation: Influenza A or B. Recommendation: Oseltamivir. Comment (Evidence): The introduction of oseltamivir is recommended in all individuals with suspected or documented influenza infection (AII). Oseltamivir may be withdrawn if diagnostic tests rule out influenza.	[114]
6.9.	Situation: Respiratory syncytial virus (RSV) Recommendation: Supportive therapy consider the use of ribavirin at high risk (BIII). Consider IVIG as an adjuvant (BIII). Comment (Evidence): Consider immunodeficiency score for low risk (score 0-2), medium risk (3-6) and high risk (7-12). The following factors are considered in the score: neutropenia <500; lymphopenia <200; age> 40; GVHD using steroids; myeloablative conditioning and HSCT for <1 year (BII). High risk of complications comprises a patient with RSV or RSV pneumonia detected before grafting, lymphopenia <0.3 x 109 / L (most important), GVHD using IS, or neutrophils <0.5 x 109 / L.	[115,116]

6.10.	Situation: Parainfluenza, adenovirus, metapneumovirus, rhinovirus, coronavirus. Recommendation: If documented before HSCT, postpone conditioning (BII). Supportive therapy considers the use of IVIG if hypogammaglobulinemia (<400 mg / dL). Comment (Evidence): If recurrent or severe respiratory infections with IgG hypogammaglobulinemia <400mg / dL, IVIG replacement may be performed. Perform IgG dosage monthly.	[46]
6.11.	Situation: BK virus hemorrhagic cystitis (BKV). Recommendation: Supportive treatment. Antiviral treatment is controversial. Comment (Evidence): There is no effective antiviral for BKV hemorrhagic cystitis. Treatment is based on supportive therapy (hyperhydration, bladder irrigation, platelet transfusions to reduce bleeding, and pain management). Treatment with cidofovir IV is controversial (absence of randomized controlled studies), but it may be an option although there is uncertainty regarding efficacy, doses, and risk-benefit in the face of renal side effects. Intravesical cidofovir can be used in severe cases with evaluation by an ID physician.	[54,55]
6.13.	Situation: Tuberculosis Conduct: RHZE for 2 months + RH 4 months. In HSCT recipients, therapy may be prolonged according to clinical response. Comment (Evidence): The most common form is pulmonary, with symptoms similar to the immunocompetent host (fever, weight loss and persistent cough). Clinical suspicion can be masked in patients with lung GVHD (investigate TB always). Acid fast bacilli (AFB) shows low sensitivity (60%), and culture is the gold standard for TB diagnosis (but may take 30 days). Currently, PCR is most recommended yielding fast results and allowing prompt introduction of treatment. There are molecular tests that already detect resistance to rifampicin (AII).	[117,118]
6.14.	Situation: Pneumocystosis. Conduct: Sulfamethoxazole-trimethoprim. Comment (Evidence): The consensus recommends diagnostic confirmation by specific tests. Full dose therapy should be administered for at least 14 days. Secondary prophylaxis should be maintained for the duration of IS (AII). Corticosteroid use may be necessary in cases of hypoxemia. Alternatives are pentamidine (BII), primaquine + clindamycin or atovaquone (CIII).	[119]
6.15.	Situation: Toxoplasmosis Conduct: Sulfadiazine + pyrimethamine for 4 to 6 weeks (AII). Add leucovorin due to hematological toxicity of pyrimethamine. Comment (Evidence): Non-specific presentation. Investigate neurological and ocular conditions. Other presentations are fever with no apparent cause and interstitial pneumonia. Diagnosis by PCR for T. gondii or immunohistochemistry in biopsy or BAL. C-reactive protein or procalcitonin have no role in the diagnosis.	[26,27]

7. POST-TRANSPLANT REVACCINATION PROGRAM						References (120–123)
Inactivated vaccines						
Vaccine	Start	Doses	Interval	Chronic GVHD	Children	Autologous
PCV13	3-4 mo	3	1 mo	4th dose	Idem	Idem
PPV23	12 mo	1	>8 w after PCV	Idem	-	-
Hib	3-4 mo	3	1 mo	Idem	Idem	Idem
DTP-Hib	6 mo	3	1 mo	Idem	Idem	Idem
MCV	6 mo	2	1 mo	Idem	Idem	Idem
DTaP	6 mo	3	1-2 mo	Idem	Idem	Idem
IPV	6 mo	3	1-2 mo	Idem	Idem	Idem
INF	6 mo	1	Annually	2 doses	2 doses (<9 yr)	Idem
HBV	6 mo	3	0-1-6 mo	Idem	Idem	Idem
HAV	6-12 mo	2	6 mo	Idem	Idem	Idem
HPV	6-12 mo	3	0-2-8 mo	Idem	Idem	Idem
HZV rec	d50-d70	2	1-2 meses	Recombinant vaccine. Only autologous HSCT		

ATTENUATED VACCINES						
Vaccine	Start	Doses	Interval	Chronic GVHD	Children	Autologous
LAVV	24 mo	1	1m	Contraindicated	2 doses	Idem
LAZV	Contraindicated in HSCT recipients					
MMR	24 mo	1	1m	Contraindicated	2	Idem
YFV	24 mo	1	-	Contraindicated	> 9 meses	Idem

OTHER SPECIFIC COMMENTS	
PCV13	At Reference Centers for Special Immunobiological Agents (CRIEs) and at Basic Health Units (UBS), children under 5 yr may receive PCV10. In private clinics, PCV13 is preferred. In patients with chronic GVHD, a 4th dose of PCV13 may be administered 6 months after the 3rd dose. In general, children respond better to PCV13, but have more fever and local reactions than adults (AI).
PPV23	Those who have already received PPV23, can take 1 dose of PCV13 after ≥ 6 months. If gammaglobulinemia <3g/L, severe GVHD, or rituximab for less than 6m, maintain with prophylactic antibiotics + IgIV and wait to perform PPV23 (BI).
Hib	Cord blood and non-myeloablative transplantation have the same response rate (BII). Chronic GVHD does not interfere in the response (AII).
DTaP	The adult formulation (dTaP) is poorly immunogenic. Use DTaP for adults and children (BII).
INF	Annually, for life, or at least up to 6 m after the end of IS. Children <9 years at the first vaccination or those with chronic GVHD should receive 2 doses (one month apart) (AII).
HAV	Serology (IgG) is recommended to evaluate specific antibodies and the need of vaccination. More than 90% of HSCT recipients maintain antibodies for up to 5 years. The response to HAV vaccine in HSCT recipients is poor (~ 30%) (CII).
HBV	R-/D-: vaccinate after 6-12 months of HSCT. R-/D antiHBc +: vaccinate before HSCT (0-10-21) and give HBIg (BII). R antiHBc +: vaccinate after 6 months of HSCT. If anti-HBs +, monitor monthly and vaccinate if anti-HBs <10mIU / mL (BIII). In children, attention to the pediatric dose of the vaccine. Age and chronic GVHD decrease the response to HBV vaccine.
HZV rec	So far, only approved for autologous HSCT (AI).
Attenuated vaccines	Only after 24m of HSCT and in patients without IS and without chronic GVHD.
LAVV	More than 90% of HSCT recipients have had zoster after the 2nd year of HSCT. Therefore, chickenpox vaccine would benefit only a few patients (DII). The attenuated varicella vaccine may be indicated in children (2 doses) and in VZV seronegative adults (1 dose).
MMR	In case of measles outbreak, MMR can be anticipated to the 12th month of HSCT and in patients with mild IS (BII).
YFV	To date, there are no reports of serious adverse events in HSCT recipients vaccinated against YF. Consider vaccination before transplantation, since 30% of vaccinees maintain antibodies after HSCT (BIII).

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ENDOCRINOPATHIES AFTER PEDIATRIC HSCT: SCREENING RECOMMENDATIONS AND MANAGEMENT

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ABSTRACT

Endocrine disorders after pediatric hematopoietic stem cell transplantation are the consequence of the interaction between the underlying disease, host characteristics, and treatment, including exposure to pre- and peri-transplantation agents (chemotherapy and radiotherapy). Moreover, post-transplantation factors comprising graft versus host disease and its treatment, especially glucocorticoids, also contribute to hormone deficiencies or endocrine diseases. Endocrinological changes may be divided into six major groups: 1) Growth disorders; 2) Thyroid diseases; 3) Gonadal dysfunction; 4) Adrenal failure; 5) Bone mineral density deficit; 6) Metabolic syndrome. The goal of this paper is to define screening recommendations for diverse endocrine diseases and management approaches, addressing the following important issues: define populations at risk for a particular endocrine disturbance, recommendations during follow-up, and management strategies for treatment focusing on controversial remarks.

KEYWORDS: bone marrow transplantation; graft vs host disease; glucocorticoids; growth disorders; adrenal insufficiency; thyroid gland/radiation effects; gonads/drug effects; adiposity; atherosclerosis; bone and bones/metabolism.

INTRODUCTION

Endocrinological changes post-hematopoietic stem cell transplantation (HSCT) may be interpreted as a result of the synergistic interaction between the underlying disease, host characteristics, exposure to pre- and peri-HSCT factors (chemotherapeutic agents, conditioning regimen and radiotherapy, RT), and post-HSCT factors, including graft versus host disease (GVHD). Endocrinopathies are among the most frequent late effects associated with pediatric HSCT, affecting nearly 60% of subjects receiving HSCT before 10 years of age, and with the onset between 0.8 to 9.5 years after HSCT.[1-3]

Endocrine abnormalities changes in patients after HSCT may be divided into six major groups: 1) Growth disorders; 2) Thyroid diseases; 3) Gonadal dysfunction; 4) Adrenal failure; 5) Bone mineral density deficit; 6) Metabolic syndrome. The goal of this paper is to define populations at risk for a particular endocrine disturbance, propose recommendations during follow-up, and management strategies for treatment focusing on controversial remarks.[3,4]

METHODS

These recommendations were carried out by a group of experts in the field of late effects and endocrinological complications after HSCT, and are not based on evidence derived from randomized controlled trials (scarce or nonexistent), but are supported by retrospective studies and international guidelines that have identified late endocrine complications, and their associated risk-factors. When those studies are

not available, strategies are based on knowledge derived from non-transplant patients. The recommendations should not be interpreted as mandatory for all recipients; good medical practice and judgment dictate that certain recommendations may not be applicable in individual patients.[2,3,5]

GROWTH DISORDERS

Growth is usually one of the most disturbed events among children treated for cancer, and it may be also adversely affected by HSCT, especially depending on the disease pre-HSCT and other factors, particularly cranial RT in doses ≥ 18 Gy at younger ages, and less frequently due to chemotherapy. Total body irradiation (TBI) at a single fraction dose of 10 Gy or a fractionated dose of 12 Gy may lead to growth hormone (GH) deficiency. Those patients exposed to a dose of cranial RT ≥ 30 Gy are at a higher risk for GH deficiency. Growth may be additionally affected by severe illness, malnutrition, GVHD, prolonged glucocorticoids, other hormonal deficiencies, including hypothyroidism, and hypogonadism.[2,6,7]

HSCT recipients treated with recombinant human GH (rhGH) may still grow poorly after TBI due to end organ resistance. Early pubertal onset (more common after cranial RT) may accelerate growth and initially mask GH insufficiency.[5,7] Concerns have been raised among original cancer recurrence and second neoplasms in pediatric patients treated with rhGH. Studies have not supported recurrence while data among second neoplasms showed an initial 3-fold increase, however with decline over time, with no risk associated with subsequent brain tumors.[5,7-10]

GROWTH DISORDERS RECOMMENDATIONS

- HSCT recipients who had not attained final height should be evaluated every 6 months regarding height, weight, body mass index (BMI), growth velocity and pubertal stage (Tanner).
- Patients subjected to cranial RT ≥ 30 Gy should have pituitary hormones routinely assessed, including GH axis.
- Survivors growing poorly should have thyroid function evaluated.
- Consider risks versus benefits of rhGH replacement therapy.

THYROID DISEASES

Thyroid dysfunctions are recognized as one of the major endocrine complications after HSCT and include subclinical hypothyroidism, overt hypothyroidism, hyperthyroidism (rare), autoimmune thyroiditis, and thyroid nodules (thyroid cancer).[3,5,11] Thyroid gland is particularly sensitive to the effects of RT especially at a very young age, in females, cumulative doses of RT ≥ 20 Gy, with prolonged interval since exposure, and GHVD. Notably, thyroid cancer risk decreases at RT doses > 30 Gy, in which there is both ablation and fibrosis of thyroid tissue. Single-dose ablative TBI is the major risk factor associated with a 50% of incidence of overt hypothyroidism, whereas fractionated TBI is associated with an incidence of 15% at a median 4 years after HSCT. Nonetheless, isolated chemotherapy (busulfan and cyclophosphamide) may lead to hypothyroidism, frequently transient, in 11% of patients. Treatments given prior to HSCT are also important factors, such as neck and/or cranial RT.2,12 The transfer of autoimmunity from graft donors may cause autoimmune thyroid disease, comprising hypothyroidism or hyperthyroidism.[3,4]

Subclinical hypothyroidism is the most frequent type of thyroid dysfunction, occurs in 7-15% of patients in the first year after HSCT, in which thyroid-stimulating hormone (TSH) is between [5-10] mIU/L and a normal free thyroxine (FT4). There are no recommendations in patients exposed to RT so treatment should be individualized.[13-16] Overt hypothyroidism is another scenario, with TSH >10 mIU/L, low-normal FT4 levels, and clinical symptoms. In this case, sodium levothyroxine is strongly indicated.[15]

Thyroid nodules are usually present approximately 10 years after exposure to RT and are very likely to be malignant, being considered a second neoplasm.[13,14,16]

As a consequence of the high prevalence of thyroid disease in the general population, patients should have their thyroid assessed before undergoing HSCT. It is not suggested to evaluate thyroid function immediately after HSCT, because dysfunctions among this period are usually due to sick euthyroid syndrome, an entity that does not need treatment.[17] Thyroid antibodies help differentiate RT-induced hypothyroidism from autoimmune causes. Cervical ultrasound should be performed in those with altered thyroid palpation. Thyroid nodules should be carefully evaluated and, depending on the ultrasound imaging, a fine-needle aspiration biopsy should be performed. The management of thyroid cancer secondary to neck RT follows the same guidelines as in the primary disease.[2,3,5,13,14,16]

THYROID DISEASES RECOMMENDATIONS

- Survivors with any neck RT should have TSH and FT4 performed one year after HSCT, and yearly thereafter, unless clinical symptoms (e.g., poor growth velocity).
- Palpation of thyroid gland should be performed in every clinical examination.
- The role of cervical ultrasound in screening thyroid nodules is still controversial.

GONADAL DYSFUNCTION

Gonadal dysfunction is highly prevalent in HSCT recipients, generally higher in women (99% in females, and 92% in males). The conditioning regimens for HSCT, comprising chemotherapy alone (alkylating and platinum-based agents) or associated with TBI may lead to a high prevalence of gonadal damage, which manifests as delayed puberty, post-pubertal gonadal insufficiency, or impaired fertility. Gonadotropins comprising luteinizing hormone (LH) and follicle stimulating hormone (FSH) may also be compromised by cranial RT ≥ 30 Gy administered prior to TCTH.[2-5]

MALES

In male patients, chemotherapy may damage spermatogenesis (Sertoli cells), particularly at cumulative doses of cyclophosphamide ≥ 7.5 gm/m^2 leading to oligospermia and/or azoospermia. Leydig cells (testosterone producing) appear to be more resistant to the toxic effects of drugs than Sertoli cells, and manifest dysfunction at doses ≥ 20 gm/m2 of cyclophosphamide. Concerning RT, germ cells are also more sensitive, with permanent azoospermia likely after [6-10] Gy, while testosterone insufficiency occurs only at doses ≥ 20 Gy. There is a synergistic effect between cytostatic drugs and RT leading to azoospermia, but testosterone secretion generally unimpaired so that most patients complete puberty at an expected time.[2-5,18-20] GVHD has also been responsible for transitory changes in the germinal epithelium leading to azoospermia in patients not exposed to RT.[20,21] Sperm cryopreservation should be indicated prior to treatment if possible. Sex hormone replacement therapy follows similar guidelines as in other non-cancer populations.[2-5,20]

FEMALES

In contrast to males, the ovary has no difference between gonadotoxic effect on hormonal production or fertility (oocyte production), being both sections equally damaged (premature ovarian failure). Older age (> 10 years), and pubertal status at the time of exposure increase the risk of ovarian dysfunction, being associated with lower doses of RT among pubertal (5-10 Gy) versus prepubertal girls (10-15 Gy). TBI leads to definitive gonadal failure in almost all patients who were already pubertal at the time of HSCT.[5,18,22] The association of cyclophosphamide and busulfan in HSCT conditioning regimens may

also lead to delayed pubertal development and/or permanent damage to ovarian function, even though dose thresholds are less well-established.[5,6,23] Patients who recovered ovarian function years after HSCT may later lead to early menopause.[24] Cryopreservation of ovarian cortical tissue before treatment may be a source of oocytes, and a possibility for reproductive purposes.[25] Sex hormone replacement therapy follows similar guidelines as in other non-cancer populations. Nonetheless, if there is an increased thrombotic risk, transdermal estrogen should be preferred. Replacement therapy does not increase the risk of breast cancer secondary to RT, and/or the recurrence of primary disease.[2,3,5]

GONADAL DYSFUNCTION RECOMMENDATIONS

- Periodic monitoring of pubertal development, sexual and reproductive function after high doses of alkylating, TBI, and/or cranial RT.
- In at-risk males (exposed to alkylating doses and/or TBI): periodically assess testicular volume that may be a sign of impairment of germinal epithelium. Monitor total testosterone, LH, and FSH after age 13-14. Consider semen analysis if desired.
- In at-risk females: periodic follow-up with estradiol, LH, and FSH at age 12-13.
- Discuss with patient and/or guardians the possibility of infertility.
- Encourage patients who want to preserve their fertility to seek for specialized services.

ADRENAL FAILURE

Therapy with glucocorticoids in high doses or during a prolonged period may suppress the pituitary-adrenal axis and cortisol secretion. Cranial RT ≥ 30 Gy may rarely compromise adrenocorticotropic hormone (ACTH) secretion. Chronic fatigue, weakness, anorexia, nausea, vomiting, weight loss, postural hypotension, hyponatremia, hypokalemia and hypoglycemia occasionally are signs and symptoms of primary or secondary adrenal failure. Function usually recovers gradually once exogenous glucocorticoid therapy is discontinued, although retrieval time is quite variable, from days to months, and ACTH suppression may persist one year after therapy withdrawal.[2,4]

The adrenal gland is radioresistant. Even though referred incidence of adrenal failure in HSCT recipients is usually low, certainly many cases remain undiagnosed and the recommended main approach is prevention. Patients with prolonged exposure to glucocorticoids (e.g., in GVHD) should have adrenal axis evaluated after exposure ends, particularly if suspicious symptoms of hypoadrenalism are present. Consider the possibility of adrenal insufficiency and "stress doses" in patients receiving long-term glucocorticoids who develop acute illness[2,4]

ADRENAL FAILURE RECOMMENDATIONS

- In patients with chronic GHVD after prolonged glucocorticoid, therapy withdrawal should be gradual.
- Patients withdrawing from prolonged glucocorticoids should have "stress doses" during acute illness.

BONE MINERAL DENSITY DEFICIT

Another potential endocrine complication of HSCT is bone loss, characterized by low bone mineral density (BMD), presented in 24-48 % of patients, usually [3-12] months after HSCT. Bone fragility is multifactorial and depends on a complex interaction between pre, peri-and post-transplant treatments. Preferential differentiation of mesenchymal stem cells towards adipogenesis, rather than osteogenesis is a suggested additional mechanism for BMD deficit.[3-5,26-29] All survivors of HSCT are at risk for bone loss, possibly due to the following risk factors: advanced and younger age at HSCT (due to reduced bone ac-

quisition during puberty), Caucasian ethnicity, female sex, low weight/ BMI, TBI, cranial RT, untreated endocrinopathies (hypogonadism, GH deficiency or hyperthyroidism), granulocyte colony-stimulating factor (G-CSF) treatment, renal dysfunction, calcium and vitamin D deficiency, GHVD, and its treatment with prolonged glucocorticoids (particularly dexamethasone), methotrexate, and calcineurin inhibitors (cyclosporine, and tacrolimus).[4,27,30] An initial evaluation of serum calcium, phosphorous, parathyroid hormone, renal function, and 25OH vitamin D is usually recommended. Bone turnover markers may be assessed, but their value in clinical practice is limited, especially in growing children and adolescents.27 Dual-energy X-ray absorptiometry (DXA) is used for evaluation of BMD. In adults, a T-score < -2.5 indicates osteoporosis and between -1.0 and -2.5 means osteopenia.[31] In children, the whole body (without head) and lumbar spine (L1-L4) are the sites for assessing bone mass. A Z-score < -2.0 indicates a low BMD for age, and preferably should be adjusted for height.[32] A T-score < -2.5 in adults or a Z-score < -2.0 in children should be considered for treatment with bisphosphonates.[5,27]

A healthy lifestyle with an adequate dietary calcium intake, physical activity, and sun exposure (if possible), while avoiding smoking and alcohol or carbonated beverages should be encouraged. If 25OH vitamin D levels are under 30 ng/mL, supplementation is indicated.[33]

BONE MINERAL DENSITY DEFICIT RECOMMENDATIONS

- All survivors are encouraged to have a healthy lifestyle with adequate calcium intake, regular physical activity, and sun exposure.
- All survivors should undergo a BMD evaluation through DXA one year post-transplant.

Longitudinal data indicate patients at risk, and repeated evaluations depend on previous results.

- A Z-score < -2.0 in children with multiple fractures should be considered for bisphosphonates therapy, even though the optimal schedule is not determined so far.

METABOLIC SYNDROME

The components of the metabolic syndrome (MetS), known as the risk factors for cardiovascular disease (CVD) are, as follows: abdominal obesity, insulin resistance (IR), diabetes mellitus (DM), dyslipidemia, and hypertension.[1,34]

All survivors of pediatric HSCT experience components of the MetS at a higher rate than in the general population, possibly due to host factors, such as obesity and family history, in addition to cranial RT, TBI and transplant complications (i.e., GVHD, liver disease, and hormonal deficits). It is well known that prolonged treatment with immunosuppressive drugs, such as glucocorticoids and calcineurin inhibitors (tacrolimus) affect beta cell function, but survivors who were off immunosuppressive treatment may also experience metabolic derangements. Conditioning with TBI damages pancreatic islet cell, leading to impaired glucose metabolism, associated with changes in body composition known as the sarcopenic obesity, characterized by increased fatness and decreased lean mass.[3,34-39] Other factors may contribute to persistent metabolic derangements after HSCT such as: immune system dysfunction, inflammatory mechanisms, leptin resistance and changes in microbiome composition.[3,40]

Accelerated atherosclerosis and premature CVD are one of the most important causes of morbidity and mortality among long-term survivors after HSCT, and are related either to the allo-reaction or to the early appearance of the components of the MetS. The most frequent cardiovascular events are coronary heart disease and cerebrovascular accidents, with an incidence of 7.5% in 15 years, and 22% over 25 years.[1,2,41,42]

It is recommended to initiate surveillance of asymptomatic individuals one year after HSCT, screening recipients treated with abdominal RT, including TBI, by measuring body weight, and metabolic profile. [1,2,3,5] Non-pharmacologic lifestyle modifications remain the first step in the management of metabolic derangements in HSCT survivors. Insulin-sensitizers (metformin) are not recommended to IR so far. There is also no specific guidance in the management of dyslipidemia in HSCT survivors treated during childhood. [3,39]

METABOLIC SYNDROME RECOMMENDATIONS

- Routine clinical assessment of BMI, waist-to-height ratio, and blood pressure for all HSCT recipients one year and yearly after, especially if RT exposure.
- Survivors treated with any abdominal RT should be screened with fasting glucose (and glycated hemoglobin, HbA1c), insulin, homeostatic model assessment (HOMA1-IR), and lipids every 2 years. In those with lab alterations, follow-up must be individualized.
- Counseling on a healthy lifestyle with diet and physical exercise.
- Appropriate drug therapy of CVD risk factors should be performed based on specific published guidelines.

CONCLUSIONS

Survivors of pediatric HSCT are a heterogeneous population as they are exposed to different underlying diseases, and various pre-transplant treatment options. The transplantation itself is quite diverse, and comprises multiple conditioning regimens, and important post-transplant adverse effects. Thus, they are vulnerable to late-onset endocrine effects, which may exacerbate adverse general health outcomes. The better understanding of the epidemiology and risk factors of the endocrine dysfunctions, the importance of longitudinal follow-up for early diagnosis and management, and the development of strategies in order to minimize worsened general health outcomes may possibly increase the quality of life in this particular group of patients.

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SINUSOIDAL OBSTRUCTION SYNDROME (SOS)

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1.INTRODUCTION:

Hepatic venocclusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially fatal complication that occurs mainly after myeloablative conditioning (MAC) hematopoietic stem cell transplantation (HSCT), but may occur rarely after reduced intensity conditioning (RIC), autologous HSCT, exposure to hepatotoxic chemotherapy outside the context of transplantation or after liver transplantation. It was initially described in patients who ingested marijuana tea containing pyrrolizidine alkaloids, and was first described in 1979. [1]

It is a disease related to hepatic vascular injury, characterized by damage to small vessels, mainly affecting the sinusoidal endothelium, which results in complications such as intrahepatic congestion, liver damage and portal hypertension. SOS was previously called hepatic venocclusive disease, until several studies suggested that the injury of the hepatic sinus endothelium was greater than the injury to the hepatic veins. [2]

It is characterized in clinical grounds by painful hepatomegaly, weight gain and jaundice, although anicteric forms may occur, most commonly in the pediatric population. It may evolve to multiple organ dysfunction (with mortality exceeding 80%), pulmonary disorders (pleural effusion, pulmonary infiltrates and hypoxia), renal failure and/or neurological deterioration (confusion and encephalopathy). The incidence is approximately 5 to 13%, even more common in the pediatric group [3] in which can reach 20-30% up to 60%. It occurs in approximately 10-15% of allogeneic HSCT with MAC conditioning and less than 5% of the autologous or RIC conditioning. [4]

2.PATHOPHYSIOLOGY:

The basic structural component of the liver is the hepatocytes, which correspond to 80% of the organ volume and are distributed in liver slides with various functions. Through the hepatocytes flow the biliferous canaliculi, which join distally forming increasingly larger ducts, resulting in the hepatic ducts. Among the hepatocytes plaques pass the hepatic sinusoids, which are fenestrated blood capillaries that receive oxygenated blood from the hepatic artery and nutrient-rich blood from the hepatic portal vein. The normal flow in the portal vein is hepatopetal, that is, directed to the liver.

Between the sinusoids and hepatocytes, we have the Space of Disse, where the microvilli of the hepatocytes extend. Hepatic sinusoids are coated by endotelial cells, whose function is filtration and removal of metabolites.

The initial event in VOD/SOS is endothelial injury of the hepatic sinusoid, with loss of cohesion between the endothelial cells, with extravasation of red blood cells into the Space of Disse, with embolization through centrolobular vein and subsequent postsinusoidal obstruction. [1]

The etiologies of endothelial injury are conditioning regimens (mainly busulfan and cyclophosphamide metabolites), cytokines produced by injured tissues, microbial products resulting from the breaking of the mucosal barrier, drugs used during transplantation (as granulocyte colony-stimulating factors or calcineurin inhibitors), the grafting process and alloreactivity.

Chemotherapeutic drugs are metabolized by cytochrome P450, producing toxic metabolites that are converted by the glutathione enzymatic system into non-toxic metabolites to later be eliminated. The centrolobular regions of the liver are poor in glutathione and for this reason are more sensitive to the action of toxic agents. The immaturity of this enzymatic system in the pediatric group may explain the higher incidence of SOS in children. The higher incidence after allogeneic HSCT and in unrelated transplants, suggests the participation of alloreactivity in the pathophysiology of VOD/SOS. Activated sinus endotelias (CES) cells increase the production of cytokines, heparanase and expression of adhesion molecules with loss of cytoskeletal structure, space formation that facilitates the extravasation of red blood cells, leukocytes and cellular debris into the Space of Disse, with narrowing of the sinusoids . [5]

The increase in tissue factor and plasminogen activating factor (PAI-1) lead to a procoagulant and hypophybrinolytic state, with consequent fibrin clot formation , narrowing and obstruction of the hepatic sinusoid (Figure 2.C.). [5]

Detachment of endothelial cells seems to be correlated with nitric oxide deficiency caused by post-conditioning toxicity. Nitric oxide deficiency promotes increased production of metalloproteinase matrix 9, responsible for the detachment of endothelial cells. Obstruction of blood flow is promoted by the proliferation of perisinusoidal star cells and subendothelial fibroblasts in the terminal hepatic vein, followed by the deposition of the extracellular matrix. Then fibrosis extends to the liver parenchyma leading to blockage in the blood output of the liver, leading to hepatic congestion and development of post-sinusoidal portal hypertension. [3]

3. RISK FACTORS:

The analysis of risk factors with the identification of subgroup of patients at higher risk for developing severe forms of the disease are necessary for early intervention and prevent the development of multiple organ dysfunction (MOD). [6][7]

There are three types of risk factors: directly related to transplantation; related to the patient or underlying disease; liver-related factors.

3.1. HSCT RELATED FACTORS:

-Allogeneic HSCT is at higher risk when compared to autologous HSCT

-Unrelated donor

-Donor with mismatch

-T-cell depletion-without-depletion transplant

-Myeloablative conditioning

-Conditioning regimen with high doses of bussulfan or oral formulation; melphalan; Cyclophosphamide.

-High doses of total body irradiation (TBI)

-Second myeloablative transplant

-Interval between diagnosis and HSCT > 13 months

-Pharmacological Prophylaxis of graft-versus-host disease (GVHD): association of sirolimus, metotrexate and tacrolimus; cyclosporine and metotrexate.

3.2. FACTORS RELATED TO THE PATIENT OR THE DISEASE:

- Low age in children and advanced age in adults

-Hepatitis B/C positive serology

-Positive serology for cytomegalovirus

-Low Karnofsky Index (<90%)

-Metabolic syndrome

-Active disease at HSCT

-High levels of ferritin

-Female women on hormonal contraceptives

-Use of parenteral nutrition up to 30 days before HSCT

-Thalassemia, advanced malignancy, acute leukemia, acute CHS, late platelet grafting

-Genetic factors (GSTM1 polymorphism, C282Y hemochromatosisallallery, MTHFR 677CC/1298CC haplotype)

3.3. LIVER-RELATED FACTORS:

-Transaminases above 2.5 times normal upper limit

-Bilirubin level above 1.5 times normal upper limit

-Low albumin level

-Active viral hepatitis

-Cirrhosis

-Liver or abdominal irradiation

-Iron overload (high serum ferritin levels)

-Previous use of gentuzumab ozogamicin [8]

-Hepatotoxic drugs

3.4. PAEDIATRIC RISK FACTORS:

-Hemaphagocytic Lymphohistiocytosis

-Adrenoleukodystrophy

-Osteopetrosis

-Neuroblastoma with high doses of chemotherapy

-Age (< 1-2 years)

-Low weight

-Chronic myelomonocytic leukemia (CMML)

-Juvenil Mielomomonocytic leukemia (JMML)

-Hemoglobinopathies

3.5. RISK SCORE FOR VOD DEVELOPMENT AFTER ALLOGENEIC HSCT:

A risk score for the development of SOS/VOD may be useful in identifying high-risk patients to seek preventive strategies for this complication that can be fatal. Recently the Center for International Blood and Marrow Transplant Research (CIBMTR) developed a pre-transplant risk score through the evaluation of 13,097 patients submitted to the first allogeneic HSCT between 2008 and 2013 and prognostic factors for the development of SOS/VOD up to D+100 after transplantation were identified through analysis with multivariate logistic regression model. Variables with significance in the risk score:

-Age (children > adults)

-Performance score (Karnofsky) < 90%

-Use sirolimus

-Hepatitis B/C (positive hepatitis B and C or only Positive B)

-Conditioning regimen (MAC regimen with melphalan, fludarabine, busulfan with serum level monitoring; TBI)

Status pre-HSCT / Underlying disease (bone marrow aplasia, Hodgkin and non-Hodgkin lymphoma, myelodysplastic syndrome, advanced chronic myeloid leukemia, and myeloproliferative syndromes).

The model can be brought into clinical practice with an online risk calculator, accessible to the public via the link below:

https://www.cibmtr.org/ ReferenceCenter/Statistical/Tools/Pages/VOD.aspx

With the use of the tool, patients at high risk for developing SOS/VOD may have a closer follow-up and modifications in the conditioning regimen may be discussed. The identification of high-risk patients may also facilitate early initiation of drug therapy with defibrotide from the first symptoms of SOS/VOD, which demonstrated improvement in survival of patients who developed the complication. [9]

4. CLINICAL MANIFESTATIONS:

They are due to portal hypertension, usually occur during first 21 days of HSCT, but may occur later in 15 to 20% of cases (21-508 days). It can range from mild clinical manifestations with spontaneous resolution in a few weeks to multiple organ dysfunction (MOD), with high mortality. Given the severity of the condition, daily monitoring of weight, abdominal circumference, diuresis and water balance is necessary for early diagnosis of the complication. [3] [6]

The characteristic clinical manifestations are:

- Weight gain, generally not responsive to diuretics

- Hyperbilirubinemia

- Painful hepatomegaly

-Ascites

The diagnosis of VOD/SOS is classically based on the clinical criteria of modified Baltimore or Seattle, and exclusion of differential diagnoses.

More than 30% of children and 12% adults may evolve with SOS/VOD and be anicteric. Therefore, the importance of applying the various diagnostic criteria, since in Baltimore criteria jaundice is mandatory. Therefore, the proposal of the EBMT criteria. [4]

Modified Seattle Criteria	Baltimore Criteria	EMBT Criteria (6)
Presence in the first 21 days of HSCT of 2 or more criteria: Bilirubin >2 mg/dL Painful hepatomegaly Weight gain > 2% of baseline	Presence within the first 21 days of HSCT Bilirubin ≥ 2 mg/dL and at least 2 of the following: Painful hepatomegaly Weight gain >5% Ascites	Classic VOD/SOS Presence within the first 21 days of HSCT Bilirubin ≥ 2 mg/dL and at least 2 of the following Weight gain >5% Ascites Painful hepatomegaly Late VOD/SOS Classic SOS after 21 days or histological diagnosis or 2 or more criteria below (and evidence with ultrasound) Bilirubin >2 mg/dL Painful hepatomegaly Weight gain > 5% Ascites

Children:(10)

Presence of 2 or more parameters:

- Unexplanied refractoriness to platelet transfusion
- Weight gain for 3 consecutive days even with diuretic use or weight gain >5% basal weight
- Hepatomegaly (best if confirmed by imaging as US, CT or MRI)
- Ascites (best if confirmed by imaging such as US, CT, or MRI)
- Bilirubin rising above baseline for 3 consecutive days or increase > 2mg/dL in 72h

5. DIFFERENTIAL DIAGNOSIS:

-Volume overload
-Constrictive pericarditis
-Drugs causing liver injury and cholestasis
-Sepsis
-Infectious hepatitis
-Parenteral nutrition and biliary complications
-Cholestasis
Graft-versus-host disease

6. SEVERITY DEGREES:

According to EBMT criteria:

Adults(4)(5)

	Mild	Moderate	Severe	Very Severe
Onset of symptoms	7 days	5-7 days	≤4 days	Any time
Bilirubin (mg/dL)	≥2 and <3	≥3 <5	≥5 and <8	≥ 8
Increase in BT			Double in 48 hs	
AST/ALT	≤ 2x	>2 and ≤ 5x	>5 and ≤ 8x	>8x
Weight gain (%)	<5	≥5 a < 10	≥5 a < 10	≥ 10
Creatinine (relative to baseline pre-HSCT)	<1.2x	≥1.2 and <1.5x	≥1.5 and <2x	≥ 2x or multiple organ dysfunction

B.Children(10)

	Mild	Moderate	Severe	Very severe
AST/ALT	≤ 2x	>2 and ≤ 5		>5 x
Refractoriness to platelet transfusion	<3 days	3-7days		>7 days
Bilirubin (mg/dL)	<2	<2	<2	>2
Increase in BT				Double in 48 hs
Ascites	Minimal	Moderate	Moderate	Paracentesis
Clotting studies	Normal	Normal	Changed	Need to reset coagulation factors
Renal function (ml/min)	89-60	59-30	29-15	<15
Lung function (o2 need)	<2L/min	>2L/min	Vm	Vm
Central Nervous System Impairment	Out	Out	Out	Cognitive impairment

7. DIAGNOSIS:(3)(3)

The diagnosis is essentially clinical and based on the clinical criteria of modified Baltimore or Seattle, as previously described. Level of evidence: High and Degree of recommendation: Strong (1A)

Given the high mortality of severe SOS/VOD (> 80%), daily monitoring of the patient should be performed from conditioning to at least 14 days after transplantation, especially when the patient presents risk factors; monitor for jaundice, weight gain, positive water balance, ascitis, edemas, hepatomegaly, emphasizing that in the pediatric population it is not uncommon to absence of jaundice.(12)

-Percutaneous liver biopsy should be avoided due to risk of bleeding; transjugular liver biopsy can minimize the risk of bleeding and enables measurement of hepatic vein pressure.

-Potential Proposed Biomarkers: plasminogen activation inhibitor 1, von Willebrand factor, thrombomodulin, soluble intercellular 1 binding molecule, tumorigenicity suppressor 2, angiopoietin 2, hyaluronic acid, interleukin-6, interleukin-10, CD97. (13) Level of evidence: Low and Degree of recommendation: Weak (2C)

-**Ultrasonography:** many studies report the importance of the test to exclude other diagnoses. Some findings that may be present are hepatomegaly, splenomegaly, vesicle wall thickening (> 6mm), enlargement of portal vein diameter > 8 mm in children and 12mm in adults, hepatic vein diameter < 3 mm, ascites and visualization of paraumbilical vein. (11) Level of evidence: Moderate and Degree of recommendation: Weak (2B)

-**Doppler ultrasound:** approximately 83% sensitivity and specificity of 87% in the presence of 6 following criteria:

1.Flow modulation in the portal vein
2.Decrease in density and spectral
3.Hepatofugal flow or maximum speed less than 10 cm/second
4.Portal vein congestion (index≥ 0.1)
5.Resistive hepatic artery (index ≥ 0.75)
6.Single-phase flow in the hepatic vein
7.Demonstration of flow in the periumbilical vein
-MRI

8.PROPHYLAXIS

-Iron quelation prior to HSCT
-Avoid use of alcohol and hepatotoxic drugs
- If possible reduced intensity conditioning regimen
-2-day interval between busulfan and cyclophosphamide
-1 day interval between busulfan and melphalan
-Pharmacokinetics study of busulfan

-**Avoid G-CSF:** used to accelerate the recovery of neutropenia, but increases the adhering molecules (VCAM-1 and E-selectin) and can activate endothelial cells. [14]

-**Ursodeoxycholic acid:** a randomized, double-blind, placebo-controlled study showed a lower incidence of SOS in the group that received ursodeoxycholic acid prophylaxis at a dose of 300 mg twice daily, or 900 mg in patients weighing over 90 kg. [15] It should be initiated before conditioning and maintained up to d+90 post HSCT in allogeneic or high-risk autologous HSCT. Level of evidence: Low and Degree of recommendation: weak (2C)

-**Defibrotide:** there is no strong evidence in adults; only 1 randomized study in the pediatric age group demonstrated a reduction in the incidence of SOS but without benefit in survival. [11]

Children with risk factors: 6.25 mg/Kg EV 4 times a day. (9) Degree of recommendation 1A

Adults: 6.25 mg/Kg EV 4 times a day. (9) Degree of recommendation 2B

-**Heparin:** There is no strong evidence for use in adults. Systematic reviews cannot demonstrate benefits in SOS prevention or overall survival for both autologous and allogeneic, possibly due to the great heterogeneity of randomized controlled studies, with variations in the starting of prophylaxis and/or duration. [16] [17] [18]

Degree of recommendation 2B

MEDICINES USED FOR VOD PROPHYLAXIS[11]

Prophylaxis	Level of evidence	Recommendation
Defibrotide (pediatric population)	High	Strong
Ursodeoxycholic acid (pediatric population)	High	Strong
Non Fractionated Heparin	Low	Weak
Low molecular weight heparin	Low	Weak
Ffp	Low	Weak
Antithrombin III	Low	Weak
PGE 1 (prostaglandin E1)	Low	Weak

MAIN STUDIES IN PROPHYLAXIS (EXCEPT GUIDELINES AND EDITORIALS)[19]

Author/year	SOS Internship	Type of study	Patients(defibrotide/ control)/controle)	Dose
Corbacioglu,2006	Not applicable	Retrospective:cohort/ historical control	20 (9;11) children	40 mg/Kg/day EV
Quereshi, 2008	Not applicable	Prospective: cohort/ historical control	103 (47;56) children	20 mg/Kg/day EV
Corbacioglu,2012	Not applicable	Prospective, multicenter randomized	356 (180;176) children	6.25 mg/Kg/dose every 6 hs EV
Zhang, 2012	Not applicable	Review	-	-
Park, 2013	Not applicable	Retrospective single center	49 (40 adults, 9 children)	200-400mg/day
Hopps, 2015	Not applicable	Review	-	-
Cheuk,2015	Not applicable	Review	-	-

9.TREATMENT:

The treatment of VOD / SOS may include supportive and intensive care in addition to specific therapy with defibrotide. Supportive care and clinical monitoring are critical in the management of VOD/SOS throughout the HSCT.

Daily reports of various parameters such as abdominal circumference and weight are recommended in order to promptly capture the clinical diagnosis criteria and to record in a timely manner all dynamic changes and evaluate the responseto treatment and disease progression. [3]

1.Supportive treatment:

The basis of supportive treatment in patients with VOD is clinical care, particularly in water balance. The total amount of fluids should be restricted and diuretic therapy instituted. Renal replacement therapy may be required in severe cases. Patients with multiple organ failure will need management in an intensive care environment. Initial discussion with a specialized hepatology unit is advised about other therapeutic options. [15].

In addition to the use of diuretics, ultrafiltration, hemodialysis and water restriction, oxygen support, paracentesis and thoracentesis may also be necessary. It is also recommended to maintain hemoglobin level around 8g/dL and avoid transfusion of incompatible ABO platelets.

2.Defibrotide: 25 mg/kg/day divided into 4 daily doses for 21 days or until multiple organ dysfunction resolution. Level of evidence: High and Degree of recommendation: Strong (1A)

Defibrotide is the only drug licensed for treatment of moderate/severe VOD/SOS. It consists of a combination of oligodeoxirribonucleotides derived from the intestinal mucosa of the pig and has antithrombotic, profibrinolytic and anti-inflammatory properties, in addition to the protective effect for the endotelium. [11] [20]

Common adverse reactions are (>1% to <10%): intracranial, gastrointestinal, pulmonary, epistaxis, hematuria, bleeding at the catheter site.

MAIN STUDIES WITH DEFIBROTIDE FOR SOS TREATMENT. [19] (EXCEPT GUIDELINES AND EDITORIALS)

Author/year	SOS Internship	Type of study	Patients(defibrotide/ control)/controle)	Dose
Haussmann, 2006	Severe (10) Moderate (17)	Prospective/case series	2 phases: Prophylaxis SOS: 71 children, 13 developed SOS Preemptive antithrombin III (91 children,14 developed OsOs)	60 mg / day (i.v.)
Sucak, 2007	Severe (6) Moderate (4) Grave (4)	Retrospective/ single center	14 adults	Starting dose: 10 mg/kg/ day, gradual increase up to 25 mg/kg/day (n = 4) (i.v.).
Bulley, 2007		Retrospective/ single center	14 children	33 mg/kg/day at 38.5 mg/ kg/day (i.v).
Ho, 2007	Review	-	-	-
Ho, 2008	Review	-	-	-
Richardson, 2010	Severe (all patients)	Phase 2 (prospective, randomized, multicenter)	149 (arm A=75; arm B=74) 101 adults and 49 children	
Richardson, 2013	-	Review (security)	-	-

3.CORTICOSTEROIDS:

Therapy with steroids in high doses may be an option in some cases where defibrotide is not available. The recommended schedule consists of intravenous methylprednisolone 500 mg /m2 per dose every 12 hours for six doses, followed by a gradual reduction to 2 mg/kg/day for 3 days, and subsequently decrease according to the preference of the attending physician (21)

Level of evidence: Low and Degree of recommendation: Weak (2C)

4.ASCITIC FLUID DRAINAGE WITH PERITONEAL DIALYSIS CATHETER:

Use of a peritoneal dialysis catheter for intraabdominal fluid removal, in children with severe VOD followed by intravascular fluid administration to preserve perfusion and renal function, preventing MOD. [22]

Level of evidence: Very low and Degree of recommendation: Weak (2D)

5.TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS):

Has been reported in a few case series.
Level of evidence: Very low and Degree of recommendation: Weak (2D)

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TRANSFUSIONAL SUPPORT IN HSCT

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CELL THERAPY AND HEMOTHERAPY CONSENSUS

1.MOBILIZATION AND COLLECTION OF PERIPHERAL HEMATOPOIETIC PROGENITOR CELL (HPC)

The mobilization of CD34+ cells for peripheral blood and the collection of peripheral hematopoietic progenitor cells mobilized by apheresis (HPC-A) is a crucial procedure and has as objective: the collection of an adequate number of HPC, the reduction of complications related to the collection, the prevention of failure and the optimization of available resources. [1,2]

ALLOGENEIC TRANSPLANT

Mobilization with growth factor

Use of Filgrastim (G-CSF) in the dose 10ug to 20/kg/day in one or two administrations by subcutaneous route, for 4 to 5 days, with the first collection on day 4 or 5. The last dose should preferably be administered 2 to 3 hours before the collection of the sample for the quantification of CD34+ cells in peripheral blood and 3 to 4 hours before the beginning of the apheresis procedure. [1]

The minimum dose of CD34+ cells to be collected and infused should be 2 x 106/kg per transplant. Higher doses lead to faster grafting, on the other hand, very high doses are related to an increased incidence of chronic graft versus host disease (GVHDc). Therefore, the most appropriate target dose with current data varies between 4 and 5 x 106/kg per transplant. [1] The collection of allogenic HPC-A should be whenever possible by peripheral venous access.

AUTOLOGOUS TRANSPLANT

Mobilization with growth factor

Filgrastim (G-CSF) at dose 10 to 20ug/kg/day in one or two administrations by subcutaneous route, with the first collection on day 5. [1,2] The last dose should be administered about 2 to 3 hours before sample collection for quantification of CD34+ cells in peripheral blood.

Mobilization with chemotherapy

Patients who have no indication for treatment with chemotherapy but who have risk factors or have failed to mobilize with the use of GCS-F can benefit from the association chemotherapy and G-CSF in the mobilization process. In this mobilization, cyclophosphamide (Cy) is usually used at a dose of 2 to 4 grams/m2. Other options: vinorelbine 35 mg/m^2 in single dose or etoposide 375 mg.

Use of plerixafor

Plerixafor can be used in association with G-CSF or chemotherapy + G-CSF regimens, in patients with high risk of failure or with previous history of mobilization failure, at a dose of 0.240 mg/kg of body weight, subcutaneous route the night before the collection, 9 to 12 hours before the quantification of CD34+ cells and apheresis collection. [2]

Target dose of CD34+ cells to be collected

The minimum dose of CD34+ cells to be infused should be 2 x 106/kg per transplant. The optimal dose to be collected and infused is 5 x 106/kg per transplant.[2]

Mobilization with G-CSF alone leads to a CD34+ cell peak between the 4th and 6th day of use.[1] For patients mobilized with chemotherapy+ G-CSF this quantification normally starts between the 8th and 10th day after the end of chemotherapy administration, during the hematological recovery phase, when the leukocyte count is over 1000 cells/uL. [2]

HPC-A Collection (Autologous and Allogeneic)

High volume apheresis (volume of blood processed more than 4 times the patient's volemia) consistently **increases CD34+ collection yield in patients and** improves final stem cell collection. However, electrolyte monitoring and replacement is important to avoid adverse reactions from hypocalcemia or hypopotassemia. In the case of allogeneic unrelated donation, it is recommended that a maximum of 24L be processed in one or two consecutive days of collection in adult patients. [1] **In pediatric patients**, who weigh less than 15 kg are usually transfused to achieve a target hemoglobin (Hb) of 12g/dL and a platelet count of more than 40,000/uL. The prime of the apheresis kit should be performed with red blood cells if their weigh is less than 20Kg. Prophylactic transfusion of platelets is recommended if the platelet count is less than 30,000/uL and a processing proposal of at least three volemia is proposed.[2]

2. BONE MARROW (BM) HARVEST

Collection by apheresis has been the most used strategy to obtain progenitor cells for autologous and allogenic non-apparent transplants, the collection of bone marrow is an alternative collection for donors who do not accept mobilization with G-CSF or do not have adequate venous access. Allogeneic bone marrow collection has a lower incidence of graft versus host disease (GVHD) and should be the first option in patients with aplastic anemia. Bone marrow should not be the preferred source of HPC when cryopreservation is needed. In order to avoid dilution with peripheral blood, it is recommended to perform multiple punctures and aspirate the maximum volume of 5 mls at each puncture. The syringes should be washed with a heparin solution at each aspiration. The volume to be collected should respect the target of 10-15 ml/kg of recipient, not exceeding the volume of 20 ml/kg of donor. [3] It is recommended to evaluate the need for pre-deposited autologous blood collection in allogeneic BM collections, to avoid donor exposure to allogeneic transfusion. [4 The recommended cell dose for bone marrow collection is total nucleated cell (TNC) ≥ $3x10^{[8]}$/kg of nucleated cell and it is associated with a lower rate of graft failure. Minimum cell dose eecommended is TNC $2x10^{[8]}$/kg[4] When red cell removal of bone marrow product is necessary such as due to major ABO incompatibility or if it is cryopreserved, an attempt should be made to collect a larger volume, as there will be a loss of about 20% of the nucleated cells collected with processing.

3.PROCESSING AND CRYOPRESERVATION OF HPC-A

There are two main cryoprotective solutions used in HPC freezing. A) Dimethylsulfoxide (DMSO) associated with a protein source (autologous plasma or human albumin) combined with an equal volume of cells in order to obtain a final DMSO concentration of 10%. B) DMSO associated with hydroxetilamide (HES) and a protein source, usually human albumin, in final concentrations of 5%, 6% and 4%, respectively. [6,7] Studies indicate that the solution that associates HES with DMSO is superior to the one that uses DMSO alone. EBMT recommends the association of ACD-A cryoprotectant solution at a dose of 0.05 to 0.25 mL per mL of product to reduce the risk of lump formation. [5]

Regarding the concentration of nucleated cells for cryopreservation of HPC, some centers prefer to perform cryopreservation in low doses, i.e., with the final concentration between 100 and 200 x106 cells/mL.8 Other centers have already demonstrated that the final concentration up to 300 x106 cells/mL is safe. 9 The ideal rate of freezing of HCT is 1 to 2º C per minute. Ideally, equipment should be used that allows freezing of the bags at programmed temperature, but many centers have opted for the use of mechanical freezers at minus 80º C. [6,10]

Storage

The products can be stored in a mechanical freezer with a temperature between -80º C and -150º C or in tanks containing liquid nitrogen or vapor phase. Storage in freezers at -80º C has been increasingly used, when the transplant will be performed in a few weeks or months after cryopreservation, however there are reports of clinical use of cryopreserved bags with DMSO + HES in freezers at -80º C for up to 4148 days.[10] Tanks containing liquid nitrogen appear to be safer in maintaining temperature however, additional care is required in this type of storage due to the risk of cross contamination between products.[11]

4-TRANSPORT, THAWING AND INFUSION OF HPC

The transport must take place in rigid, resistant outer packaging of adequate size to the volume of bags to be transported.

For fresh products: The temperature should be kept between 2 and 24ºC positive (preferably close to 4ºC). And the total time between the end of the collection and the beginning of the infusion should not exceed 48 hours. For cryopreserved products in a mechanical freezer (-80°C), the temperature must be kept at or below - 65°C until the moment of thawing, and for cryopreserved products in nitrogen (- 150°C), the bags must be kept at a temperature of less than -130°C.[12]

Thawing: To reduce the risk of serious adverse events, ideally the maximum DMSO volume is 1ml DMSO/Kg receiver weight/day. If the DMSO volume is higher than this limit, consider dividing the infusion into two or more consecutive days. For pediatric patients, especially those of lower weight, removal of DMSO may reduce the risk of adverse effects.[13]

Pre medication: The hydration as well as the use of mannitol before the HPC infusion, leads to an increase in diuresis and prevents renal damage caused by the deposit of free hemoglobin present in the product to be infused. Diphenhydramine, dipyrone and hydrocortisone are often administered to prevent allergic, non-hemolytic fevers and/or DMSO-related reactions.[13]

Thawing: Cryopreserved products should be thawed in a water bath with distilled water or saline at 37ºC (+-1ºC). The use of sterile plastic bags during thawing process can help reduce contamination in cases of bag breakage and product leakage.

Infusion: Transfusion equipment without leukocytes filter should be used for infusion and the recommended rate is 10mL/minute for thawed products and 6mL/Kg of receiver weight/hour for fresh products.

Reactions related to DMSO: DMSO is the main cause of adverse events during the infusion of cryopreserved products. The administration of >1ml/kg DMSO in 24 hours is the recommendation for the prevention of adverse events. Patients often report coughing, and taste of preservative during administration, which can be reversed by reducing the infusion rate. Changes in vital signs can be observed such as hypertension, tachycardia or bradycardia.

Cytokine Release Syndrome

Cytokine release syndrome is a systemic inflammatory response syndrome related to immune hyperstimulation or aberrant immune activation, leading to elevated levels of cytokines and inflammation. This complication can present mild symptoms of fever and chills, but it can sometimes lead to severe conditions with hemodynamic instability, which can culminate in multiple organ failure.[14] Non-infectious fevers occur in 80% to 90% of haploidentical transplant recipients between days 0 and +6. They usually refer soon after administration of cyclophosphamide and are associated with class II incompatibility and higher CD3 + graft cell dose.[15]

5-TRANSFUSION SUPPORT IN BONE MARROW TRANSPLANTATION (BMT)

As general recommendation, blood transfusion (RBC concentrates and platelet concentrates) intended for BMT candidate patients should be leukoreduced, i.e., contain less than 5.0 x 106 leukocytes per unit aiming at preventing non- hemolytic febrile reaction and anti-HLA alloimmunization. For prevention of CMV, the recommendation is leukoreduction or the use of blood products from seronegative donors for CMV.[16]

In addition, these blood components and granulocyte concentrates should be irradiated to prevent transfusional GVHD. [17] The duration of use of irradiated products should be based on the time of immune reconstitution of the patient and in general for autologous BMT should be initiated at least 2 weeks before collection of HPC and extend to 3 months after transplantation and for allogeneic BMT at least before the onset of conditioning to 6 months after transplantation.

SPECIAL SITUATIONS

1.Platelet Refractory (RP)

Patients submitted to BMT may develop platelet refractoriness after repeated transfusions of allogeneic platelet concentrates. Their causes may be non-immune (> 80% of cases) and immune (< 20% of cases).18

The diagnosis can be confirmed by calculation of platelet increment (CCI) after transfusion of recent platelets (< 48 hours of collection), identical ABO verified in two different and preferably subsequent moments. ICC values below 5000/µl collected between 15 minutes and 1 hour after transfusion (1hour ICC) or ICC values below 2500/µl collected between[18] and 24 hours after transfusion (24hour ICC) define the case as platelet refractory.

The management of PR involves the suspension of non-immune factors, when possible, the research of anti-HLA class I antibodies which is responsible for 80% of the cases of immune PR, in addition to the

cross-examination with patient serum. In immune PR it is recommended the use of platelet concentrate compatible with the antibody identified in the receptor[19], ideally compatible with the four antigens (HLA-A and HLA-B). When the response is unsatisfactory other causes such as anti-HPA or non-immune factors should be investigated.

2.Granulocyte transfusion

Granulocyte transfusion is used to prevent infections in patients with neutropenia or neutrophil function disorders [20] and to treat severe neutropenia (granulocytes < 500/µL) associated with bacterial and fungal infections that are not responsive to appropriate antibiotic therapy and of broad spectrum. However, there are still no randomized studies that prove its clinical efficacy in treating infections and that demonstrate improved survival.[20,21]

The process for granulocyte transfusion requires some care with the donor, product, and recipient. In general, candidates for donation must follow the same clinical criteria of suitability as a conventional blood donation, have carried out laboratory screening for infectious diseases transmissible by blood within 72 hours of collection and receive mobilizing agents (corticosteroids and G-CSF) at least 12 hours before collection. The granulocyte concentrate collected by apheresis, must contain above 1x1010 leukocytes/unit/dose for an adult recipient and have ABO compatibility respected. It should be infused irradiated and as soon as possible after the collection is completed.[22]

6-ALLOGENEIC BMT WITH ABO INCOMPATIBILITY

Approximately 30% of allogenic related transplants and 50% of unrelated transplants will have some degree of ABO incompatibility.

The main immuno-hematological consequences of ABO-incompatible transplants are summarized in **table 2**.

TABLE 2 - Immuno-hematological consequences of ABO TCTH incompatible

ABOIncompatibility	Consequences	Causes
Major	Acute hemolytic response	Infusion of incompatible red blood cell
	Delay in the grafting of granulocytes and platelets	Loss of progenitor cells hematopoietic in the process of RBC removal of the product.
	Delay in erythroid grafting	Presence osf isohemaglutinin anti d-nor
	Pure aplasia of red series	Persistence of anti-donor isohemoaglutinin.
Minor	Acute hemolysis	High isohemaglutinin titles in donor plasma
	Late hemolytic reaction	Donor B lymphocytes producing anti-receptor isohemaglutinin (passage lymphocyte syndrome)

CONDUCT TO MINIMIZE THE RISKS OF INFUSION:

The risks of infusion of the product with ABO incompatibility can be minimized by manipulation of the graft associated or not with measures to reduce the anti-donor isohemoagglutinins circulating in the recipient and by adequate hemotherapic support.

TABLE 3 - Procedures for handling TCPH with ABO incompatibility. Modified from Worel, 2016

ABO incompatibility	Grafting manipulation	Receiver care
Major		
Receiver with title of isohemoaglutinin anti-donor ≥ 1:32	HPC-BM RBC removal of product	- Infusion of plasma with donor ABO type - Therapeutic Plasmapheresis - Proper hemotherapic support
	HPC-A < 20 mL red cells: infusion without manipulation ≥ 20 mL red cells: deseritrocitation	
Receiver with title of isohemoaglutinin anti-door ≤ 1:16	HPC-BM RBC removal* HPC-A Infusion without manipulation	Proper hemotherapic support
Minor		
Donor with isohemaglutinin title anti receiver ≥ 1:256	HPC-BM or HPC-A Plasma removal	Proper hemotherapic support
Donor with isohemaglutinin title anti receiver ≤ 1:128	HPC-BM Plasma removal	Proper hemotherapic support
	HPC-A Infusion without manipulation	

* Some centers have opted for infusion without manipulating the graft. **HPC-A =** hematopoietic progenitor cells of mobilized peripheral blood collected by apheresis; **HPC-BM =** hematopoietic progenitor cells from bone marrow.

Red blood cell removal

It consists of the process of removing erythrocytes from the product to be infused. It can be manual or automated, however, to minimize the costs of the process, most services use the manual technique, with the help of a sediment agent, usually the hydroxyethyl starch (HES) at 6% of high molecular weight, added to the product in the proportion 1:4 to 1:8. There is no consensus on the maximum volume of red blood cells to be safely infused. Most services limit this volume to 10 to 40 mL for adults. In pediatrics, some authors recommend transfusion of up to 0.4 mL/Kg and others consider infusion of up to 3mL/Kg safe. [24]

Plasma Removal

Removal of excess plasma from the product by centrifugation (400 to 4000xg for 10 to 20 minutes). The cellular loss in this process is usually less than 5%.

Reduction of the isohemoagglutinins anti donor of the receiver

It is possible to reduce the titration of the anti-donor isohemoagglutinides circulating in the receptor by means of therapeutic plasmapheresis or by infusion of secretory plasma, AB or isogroup with the donor.[25.26]The American Society of Apheresis (ASFA) considers the indication of plasmapheresis in BMT with ABO major or bidirectional incompatibility as category II with GRADE 1B for HPC-BM and GRADE 2B for HPC-A and guides the performance of the procedure before the infusion of the graft, with human plasma or albumin or a combination of these.

7 – DONOR LYMPHOCYTE INFUSION (ILD)

Infusion of donor lymphocytes (ILD) may be requested in cases of relapse of disease, reduction of chemotherapy, viral infections difficult to control, among others.[27] The efficacy of lymphocyte infusion varies according to the type and volume of the underlying disease, leading to 70-80% complete response in cases of cytogenetic or hematologic relapse of acute myeloid leukemia (CML) while less than 40% of patients with recurrent acute leukemia respond to the ILD.[28]

Donor evaluation:

The medical evaluation of the donor prior to the collection of lymphocytes is mandatory under current legislation and the eligibility criteria are the same used for blood donors, and serology for cytomegalovirus (CMV).

Lymphocyte collection:

Lymphocytes can be obtained from the buffy coat of whole blood, however, the collection through apheresis equipment can offer a greater amount of CD3+ cells and is the most used. For the apheresis cell collection process, an adequate venous access should be obtained and the need for central venous catheter implantation should be avoided. Each apheresis session should process 2 to 2.5 volemia and if the number of cells needed is not obtained, a second procedure can be performed[29]

Donor Mobilization:

There is no need for any medication to collect lymphocytes from the donor, however, when the ILD is programmed (prophylactic) or highly probable, a small aliquot of the product obtained for CTH collection for transplantation can be separated.

Some studies show that previous use of G-CSF promotes T cell hyperresponsiveness, with polarization to the Th2 strain, induction of regulatory T cells and tolerogenic dendritic cells, which reduces the risk of graft disease against the host and maintains the benefits of graft cells against the disease[30]. Some centers choose to use CD3+ cells obtained on the day of CTH collection for transplantation, as long as the collection was by apheresis,

Storage of collected cells:

The collected cells should be kept refrigerated and preferably transfused as soon as possible after collection in case of fresh infusion.

Doses and treatment schemes:

The dose of lymphocytes to be infused depends on the type of BMT, patient or disease, and should be defined by the transplant team taking into consideration the potential risk of GVHD, as well as the aggressiveness of the disease to be treated. Patients at higher risk of developing GVHD, such as those undergoing hapalodectid transplantation, can start infusions with a low dose : 1 x 105 CD3+/Kg cells from the recipient for preemptive use.[31]

.For therapeutic use, a staggered dose regimen starting with the 1 x 106 Cd3+/Kg dose of the recipient, and subsequent doses of 5 x 106, 1 x 107 , 5 x 107 Cd3+/Kg cells of the recipient is the most commonly used. The interval between doses can vary from 3 weeks to 3 months and, as well as the dose increase, will depend on the response of the patient and the degree of graft disease against the host.[30,31]

8-ANTI-HLA DONOR DESENSITIZATION PROTOCOLS WITH HLA INCOMPATIBILITY.

The presence of donor-specific anti-HLA antibody (HLA De) is associated with grafting failure.[32] Research for these antibodies is indicated for partial HLA compatible transplants and haploidemic transplants. The risk of grafting failure depends on the level of antibodies detected and the properties this antibody presents. Polytransfused and multiparous patients are more likely to present antibodies. Whenever possible, another donor should be tried for which the patient does not present anti-HLA De antibody. [33]

The presence of anti-HLA De antibodies with MFI (Mean Fluorescence Intensity) above 2000 is an indication of desensitization protocols to reduce or eliminate these antibodies, which should be discussed among BMT team, hemotherapy team and histocompatibility laboratory. The strategies involve:

Depletion of antibody producing cells: a) use of rituximab (action on B lymphocytes): (375mg/m2) 1 day after intravenous immunoglobulin; b) Bortezomib (action on plasma cells): optional medication, being done 3-4 applications before starting plasmapheresis, therefore about 3 weeks before the start of conditioning.

Reduction of antibodies already formed - plasmapheresis: generally 3 sessions with exchange of 1.5 plasma volemia and replacement of 100% volume with 5% albumin before starting the conditioning. It cannot be performed during conditioning or on D+3 and D+4 when the cyclophosphamide is infused in haploid transplants. Another plasmapheresis session can be performed on D-1 if anti-HLA antibodies persist until this preterm and strategy phase.

Neutralization of antibodies with: a) Intravenous immunoglobulin (IgEV): 1 g/kg performed one day after the last session of plasmapheresis; b) infusion of leukocytes irradiated from the donor ("buffy coat"): obtained from a unit of whole blood from the donor collected in D-2, about 40-50 ml of buffy coat is administered the day before the infusion. The inclusion of this technique has obtained good results, even when the use of plasmapheresis and EV immunoglobulin has not decreased or eliminated the Anti- HLA De antibodies. An option to obtain the buffy coat of whole blood is the use of 40 ml of the bag of hematopoietic peripheral blood progenitor cells collected 1 day before the infusion.[34]

The combination and number of strategies used will depend on the risk and level of anti- HLAde antibodies. Some factors are considered additional risks: presence of multiple antibodies, presence of the same anti-HLA mismatch from a previous transplant and son-to-mother donation.[34] The reduction of anti-HLA antibodies and should be monitored during the protocol: after the plasmapheresis, before starting the conditioning and before the infusion of hematopoietic progenitor cells and after the infusion. Patients may have increased levels of anti-HLA antibodies on D-1 (rebound), in which case 1 or 2 additional sessions of plasmapheresis and/or intravenous immunoglubulin may be performed on D+1 and D+2 days. The choice protocol should take into account the risk of graft failure, higher than those with anti-HLA antibody >5000 MFI and antibody persistence during conditioning. Use of buffy coat should be considered in patients with very high levels of MFI or persistence of antibodies after other techniques used.

9-INDICATION OF PHLEBOTOMY IN IRON OVERLOAD POS BMT

After the transplant, patients may have iron overload due to transfusion support, which will not be eliminated without therapeutic intervention. Results from studies on the impact of iron overload on thalassemia and the normal population indicate the need for normal iron levels in the post TMO period. In the chaos with ferritin above 2500ug/L, transferrin saturation close to 100%, there is a high risk of liver damage and irreversible tissue damage.[35]

With erythropoesis re-established after a successful transplant, phebotomy is a therapeutic option to drug treatment, being a safe, effective, low cost alternative, but only applicable to patients with sustained hematopoiesis, and cannot be used in the immediate phases of transplant. Iron chelators can be used, but it is a more expensive alternative and requires care due to renal toxicity, when used in conjunction with cyclosporine.[36]

10 – ACCREDITATION OF HEMOTHERAPY AND CELL THERAPY SERVICES

Any health care, especially the more complex ones such as haematopoietic stem cell transplantation and other forms of cell therapy, needs some elements to achieve good health care, such as: registration of activities that make it possible to identify improvements in care and research practice; implementation and monitoring of practices based on quality standards and reporting and dissemination of treatment results applied to patients.37 Although hematopoietic stem cell transplantation has

evolved a lot in the last 50 years, this procedure is still associated with high morbidity and mortality.38 Another aspect that requires much attention is the use of healthy donors, family or not, in the therapeutic process.

Internationally, there are 2 organizations that have defined standards and accreditations in these 3 areas: FACT (Foundation for the Accreditation of Cellular Therapy) in the United States of America founded in 1996 and JACIE (Joint Accreditation Committee of ISCT) , founded in 1999 by ISCT and EBMT.

Generally the patterns of operation are defined in three major areas: 1- collection of cells for transplantation or cell therapy; 2- laboratory processing, storage, distribution and infusion of hematopoietic cells and 3- clinical part of patient care during the transplantation period. The requests can be partial for all

3 areas or separately: be global for adults and pediatrics or separately. In all 3 sessions are addressed aspects such as requirements for the facilities; training of personnel and training; quality control of inputs used; control of updating and implementation of technical procedures; evaluation, selection and care of the donor; databases and registration, and items appropriate to each session. The continuous evaluation of the program performance is based on the analysis of specific indicators such as morbidity, mortality, incidence of adverse events in the area and the reporting of data to National Centers, for example, RBT and International (CIBMTR).38

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HSCT FOR ACQUIRED BONE MARROW FAILURE SYNDROMES

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ABSTRACT

Severe aplastic anemia (SAA) is a potentially fatal disease in the absence of adequate treatment. Allogeneic hematopoietic stem cell transplantation (HSCT) is considered as first-line treatment for patients up to 40 years with an HLA-identical related donor and those up to 18 years with an HLA-identical unrelated donor. HSCT with an HLA identical donor, related or unrelated, should also be considered for patients who were refractory to first-line immunosuppression. Salvage haploidentical HSCT may be considered for younger patients without an HLA-identical donor. Recently a consensus document was established on behalf of the Brazilian Society of Bone Marrow Transplantation (SBTMO) to discuss HSCT in the setting of SAA. Recommendations from this expert panel are presented in this report.

Keywords: Severe Aplastic Anemia, Paroxysmal nocturnal hemoglobinuria, and Hematopoietic Stem Cell Transplantation

INTRODUCTION

Aplastic anemia (AA) is characterized by bone marrow failure associated with bone marrow hypoplasia/aplasia. AA can be hereditary or acquired, an important distinction, given that hereditary presentations do not respond to immunosuppression [1]. Most cases are acquired and without an etiologic trigger, in which an autoimmune pathophysiology is inferred [2]. Acquired AA is a rare disease with an incidence of 2 to 3 cases per million and with two incidence peaks, the highest around 20-30 years and the second after 60 years [3]. AA is defined as severe (SAA) when bone marrow biopsy has a cellularity <30% associated with at least two hematological criteria of severity: neutrophil count <500/µL, platelets <20,000/µL, and reticulocyte count <60,000/µL [4]. SAA is a potentially fatal disease in the absence of adequate treatment, with death related to infections or severe bleeding in most cases.

FIRST-LINE TREATMENT OF ACQUIRED SAA

First-line treatment of acquired SAA depends on the patient's age, the availability of an HLA-identical donor, and the absence of contraindications for hematopoietic stem cell transplantation (HSCT) [5]. Patients up to 40 years with an HLA-identical related donor and those up to 18 years with an HLA-identical unrelated donor should undergo HSCT as their first-line treatment (*level of evidence 2C*) [5]. If a matched unrelated donor HSCT cannot be performed in less than 2 months, immunosuppression should be applied. Those not eligible for upfront transplant due to age or lack of a histocompatible donor should receive treatment with horse antithymocyte globulin (ATG), cyclosporine (CSA), and eltrombopag (*level of evidence 1B*) [5]. The combination of these three drugs results in an overall hematological response rate of 94%, surpassing the historical results of 61% obtained after the combination of horse ATG and CSA [5,6]. 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 in comparison with horse ATG [7,8]. The results of the combination of rabbit ATG, CSA, and eltrombopag for the first-line treatment of acquired SAA are 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. Eligibility for HSCT should be reevaluated and considered as salvage for those eligible. An HLA identical donor, related or unrelated, should be preferred. In younger patients without a histocompatible related or unrelated donor, a haploidentical HSCT may be considered (*level of evidence 2C*) [5]. Patients without a donor or with a contraindication to HSCT should undergo a second-line drug treatment.

HLA-IDENTICAL RELATED ALLOGENEIC TRANSPLANT FOR ACQUIRED SAA

Related HSCT is the first-line treatment in acquired SAA for patients up to 40 years who have an HLA-identical related donor *(level of evidence 2C)* [5]. An EBMT registry study did not demonstrate an improvement in 5-year overall survival (OS) in patients over 40 years transplanted in different periods: 61% from 2001 to 2009 *versus* 58% from 2010 to 2018 (*P*=0.7), despite the improvement in supportive care recently [9]. In recent years, another study from EBMT and CIBMTR with 499 patients with SAA older than 50 years undergoing HSCT did not identify age as an independent variable associated with death, but found worse OS in patients with performance status <90% [10].

When HSCT is indicated as a first-line treatment for acquired SAA, it should be performed as soon as possible. The delay in performing HSCT is independently associated with the risk of death after the procedure [11,12]. Thus, any patient with newly diagnosed SAA who is a candidate for HSCT should be subjected to HLA typing together with all of his/her siblings. Immunosuppressive treatment should be discouraged in the weeks when results of HLA typing is pending.

The source of HSC for HSCT in SAA should always be bone marrow *(level of evidence 2C)*. An EBMT registry study with 1886 patients with SAA who underwent HLA-identical related HSCT observed an 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), over 20 years (74% *versus* 64%, P=0.001), and over 50 years (69% *versus* 39%, *P*=0.01). The incidence of graft-versus-host disease (GVHD) was higher in the group that received peripheral blood as a source of HSC: 17% versus 11% (P=0.001) and 22% versus 11% (*P*=0.0004) for acute and chronic GVHD, respectively [11]. Another EBMT registry study demonstrated that the use of peripheral blood HSC is the independent variable that most increases the risk of death after HSCT: *hazard ratio* (HR) of 1.66, *P*<0.001 [12].

Rabbit ATG should always be used in the conditioning regime for related HSCT *(level of evidence 2C)* [13,14]. 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), respectively [14]. 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) [14]. EBMT registry studies also showed that the use of rabbit ATG is an independent variable associated with better OS after HSCT [11,12].

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 *(level of evidence 2C)*. One of the conditioning regimens used for this purpose is the combination of high-dose cyclophosphamide (CY) (200 mg/kg) with rabbit ATG. A series of 61 consecutive transplants conditioned with CY 200 mg/kg associated with rabbit ATG 2.5 mg/kg for 5 days (Thymoglobulin©) demonstrated an incidence of acute GVHD grades II-IV of 23%, chronic GVHD of 32%, primary rejection in only two patients, and an 6-year OS of 87% [15]. One of the main limitations of this conditioning regimen is a higher mortality rate in patients over 20 years, HR of 2.0 and *P*<0.00001 in multivariate analysis [11]. Trying to circumvent this problem, the EBMT conducted a study in which patients with SAA older than 30 years were conditioned with fludarabine (Flu) 30 mg/m^2/day for four days, CY 300 mg/m^2/day for four days, and rabbit ATG 3.75 mg/kg/day for four days (Thymoglobulin©) and compared with a historical control of patients conditioned with CY 200 mg/kg and rabbit ATG [16]. A lower graft rejection rate (0% *versus* 11%, *P*=0.09) and a better OS were observed in the group that received Flu (HR 0.44, *P*= 0.04) [16]. A recent CIBMTR study analyzed 955 patients with SAA who underwent related HSCT between 2000 and 2014 [17]. The 5-year OS after conditioning with Flu/CY/ATG, CT/ATG, CY ± Flu, and busulfan (Bu)/CY were 91%, 91%, 80%, and 84%; *P*=0.001 [17]. Conditioning with Bu/CY was associated with a higher risk of death, HR of 2.44, *P*=0.03 [17]. Thus, the recommended condition regimens for HLA related HSCT are *(evidence level 2C)*:

CY 200 mg/kg + rabbit ATG 5 - 7.5 mg/kg;

Flu 120mg/m^2 + CY 120 mg/kg + Rabbit ATG 5 - 7.5 mg/kg. Recommended for patients over 30 years, polytransfused, or with comorbidities;

regimens containing Bu should only be used in special situations.

The ideal immunosuppression regimen after HLA-identical related HSCT in SAA consists in combination of a calcineurin inhibitor (tacrolimus or cyclosporine A) with methotrexate *(level of evidence 1B)* [18,19]. The calcineurin inhibitor must be started on day -1 and must be maintained for at least one year after HSCT with a slow withdrawal afterwards. 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).

UNRELATED ALLOGENEIC TRANSPLANTATION FOR ACQUIRED AAS

All patients up to 60 years without an HLA-identical related donor must be registered for unrelated donor search. Second-line unrelated HSCT should be considered in younger patients, less than 40 years, and refractory to first-line immunosuppressive treatment *(level of evidence 2C)* [20]. Salvage unrelated HSCT may be considered in those aged between 40 and 60 years, with a good *performance status*, in the absence of significant comorbidities, and with the availability of a 10:10 compatible donor in high-resolution HLA typing.

A study conducted in Europe compared the outcomes of unrelated HSCT in the upfront setting with a historical control of related HSCT, and immunosuppression in children with SAA [21]. There was no difference in OS between the three groups, but the event-free survival was higher in patients undergoing related (87%) and unrelated (92%) HSCT compared to those treated with immunosuppression (40%). Thus, patients up to 18 years without an identical HLA-related donor can be submitted to upfront unrelated HSCT as long as the donor search and the procedures for carrying it out does not take more than 2 months given the risks of persistent severe pancytopenia *(level evidence 3B)* [21,22].

The ideal unrelated donor must be identical in HLA high-resolution typing for *locus*: HLA-A, -B, -C, -DRB1, and -DQB1 (compatibility 10:10) *(evidence level 2C)*. Unrelated HSCT with donors with one or more allelic incompatibility have an increased risk of primary graft failure, post-HSCT complications, and mortality [23].

As recommended for related HSCT, bone marrow is the preferred source of HSC for unrelated HSCT *(level of evidence 2C)* [12]. Peripheral blood HSC may be used only when bone marrow collection is not feasible [24,25].

The recommended conditioning regimens for unrelated HSCT are *(evidence level 2C)*:

Flu 120mg/m^2 + CY 120 mg/kg + rabbit ATG 5 - 7.5 mg/kg $\pm$ TBI 200 cGy. The addition of TBI at a dose of 200 cGy reduces the incidence of primary failure, especially in adult and/or polytransfused patients [26].

Similarly to HLA-identical related HSCT, the ideal post-HSCT immunosuppression regimen consists in the association of a calcineurin inhibitor with short-course methotrexate *(level of evidence 1B)*. The calcineurin inhibitor should be started on day -1, being maintained for at least during the first year after HSCT and with slow tapper afterwards. Methotrexate should be used on the short-course schedule (15 mg/m^2 on day +1 and 10 mg/m^2 on day +3, day +6, and day +11).

The haploidentical HSCT platform with post-CY can be a conditioning option for unrelated HSCT, especially in the presence of HLA incompatibility *(level of evidence 4)* [27].

HAPLOIDENTICAL TRANSPLANTATION FOR ACQUIRED AAS

Haploidentical HSCT should be considered as a rescue treatment for patients who are younger (< 40 years) and fail immunosuppressive treatment and who do not have an identical HLA donor (related or unrelated) (level of evidence 4) [28].

The choice between an unrelated donor with an HLA incompatibility or a haploidentical related donor must be made individually. The main issues that must be evaluated in making this decision are: 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).

The donor and recipient should be identical on at least one allele in high resolution typing for *locus*: HLA-A, -B, -C, and -DRB1, and the best donor is the one with fewer incompatibilities. In the case of more than one donor with the same degree of compatibility, the selection of the most suitable donor should prioritize: the absence of incompatibility in the *host-versus-graft direction*, ABO isogroup, serostatus for CMV, younger donors, donor weight, and gender

[29,30]. The search of DSA is mandatory and the presence of a high titer of DSA practically excludes this donor, due to the risk of rejection. In cases where there is no possibility of selecting another donor, desensitization protocols can be performed [31].

Based on national experience, the recommended conditioning regimen for haploidentical HSCT consists in the association of *(evidence level 4)*:

Flu 150 mg/m^2 + CY 29 mg/kg + TBI 400 cGy single dose [32]. 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 and can be considered mainly for patients with less exposure to prior immunosuppression [30,32].

The source of HSC must be the bone marrow (level of evidence 4) [30,33,34]. The use of peripheral blood as a HSC source after stimulation with G-CSF is only recommended when bone marrow collection is not possible. GVHD prophylaxis consists on the association of CY 50 mg/kg/day on days +3 and +4, mycophenolate mofetil from day +5 to +35, and calcineurin inhibitor from day +5 to +365 with slow withdrawal after this period (level of evidence 4) [30,33,34].

Although promising, haploidentical transplantation is still not recommended in the upfront treatment of AAS until the results of prospective studies (NCT02833805).

ALLOGENEIC TRANSPLANT FOR PNH

Paroxysmal nocturnal hemoglobinuria (PNH) is a disorder caused by a somatic mutation in the phosphatidylinositol glycan A (PIGA) gene, an enzyme responsible for anchoring different proteins in the cell membrane. This enzyme deficiency results in reduced or absent expression of CD55 and CD59 proteins on the surface of red blood cells, making them susceptible to attack by the complement system [35]. Clinically, PNH can manifest itself through the occurrence of intravascular hemolysis, thromboembolic manifestations, and bone marrow failure syndrome [36]. The use of complement inhibitors, such as eculizumab, has allowed PNH patients with significant hemolysis (LDH above 1.5 times the upper limit of normality associated with target organ damage) to experience symptomatic improvement and reduced risk of death [36,37]. The largest series of HSCT in PNH reports the outcomes of 211 patients with PNH transplanted between 1978 and 2007, observing worse overall survival in those with previous episodes of venous thromboembolism [38]. Thus, the indication of allogeneic transplantation in PNH is now restricted to patients with significant bone marrow failure syndrome or clonal evolution to myelodysplastic syndrome/acute myelogenous leukemia *(level of evidence 2C)*. The ideal conditioning regime for HSCT in PNH with bone marrow failure is of reduced intensity, and the conditioning platforms mentioned above for SAA can be adopted *(level of evidence 2C)*. Patients who were using eculizumab apparently can continue to use it until the beginning of conditioning without the occurrence of unexpected adverse events *(level of evidence 4)* [39].

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