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JBMTCT

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Dear transplant colleagues

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

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

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

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

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

Fernando Barroso Duarte *Nelson Hamerschlak*

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Summary

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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HEMOGLOBINOPATHIES

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INTRODUCTION

In 2021 the Brazilian society of stem cell transplantation and cell therapy published the consensus guidelines regarding hematopoietic stem cell transplantation (HSCT) for hemoglobinopathies[1] (Costa et al., 2021). The current recommendations are detailed in table 1.

THALASSEMIA MAJOR

No changes have been added for thalassemia. HSCT with a matched sibling donor (MSD) or a related cord blood is the treatment of choice for young patients with transfusion dependent thalassemia[2-4]. Matched unrelated and haploidentical HSCT, using bone marrow graft, are a clinical option. Pre-transplant immunosuppression should be considered for Pesaro class 3[5-7].

SICKLE CELL DISEASE

Indications for HSCT in sickle cell disease (SCD) are summarized in table 2. Conditioning regimen should be myeloablative for patients ≤ 16 years old. For adults, fludarabine, busulfan and ATG is a safe and effective regimen[1,8,9]. The chemo-free regimen with alemtuzumab and TBI, pioneered by the NIH group, was successfully reproduced by other centers and is a good option for adults and patients with established organ damage[10]. Haploidentical HSCT with post-transplant cyclophosphamide has been used worldwide for almost all diseases and, in SCD, showed high rejection rates in the beginning. Improvements in the conditioning regimen were performed, including the use of pre-transplant immunosuppression, the increase in TBI dose from 2 cGy to 4 cGy and the addition of thiotepa, which significantly reduced rejection rates[5,11-13]. We consider haploidentical transplant as a clinical option in children with significant neurological alteration and in adults with the established indications.

SHOULD HSCT BE OFFERED TO ALL YOUNG CHILDREN WITH AN HLA IDENTICAL SIBLING DONOR?

The optimal timing for HSCT in SCD with MSD is not well established. Previous international reports showed excellent outcomes in young children. Patients younger than 5 years old had a 12% increase in overall survival (OS) and event free-survival (EFS) compared to those undergoing HSCT with 15 years or older. The risk of grade 2-4 acute graft-versus-host disease (GVHD) and chronic GVHD is significantly higher in patients older than 15 years old[14,15]. Despite potential complications of HSCT (GVHD, gonadal dysfunction), transplantation at an earlier age may prevent organ dysfunction, strokes, iron overload and improve patients' quality of life[16-19]. Therefore, an early referral to HSCT is strongly recommended.

HOW TO BALANCE THE RISK OF THE HSCT AND DISEASE IN ADULTS WITH SICKLE CELL DISEASE?

The medical dilemma in older SCD patients will be the assessment of established organ damage and the risk of transplantation. Timing of transplant will also be important for choosing the best available donor. The clinical course of SCD is extremely variable and no validated genetic risk score has been established so far. Most of the risk scores use phenotypic characteristics together with laboratory biomarkers and imaging parameters to define outcomes in SCD[20].

Several adult-specific risk models have been more recently described. One model was based on ***SCD-related multiple chronic conditions***. This model includes several established clinical complications of the disease and considers any of them to define high-risk disease. Patients with one complication (stroke any significant neurological event, pulmonary hypertension, recurrent priapism, retinopathy, chronic arthritis, leg ulcers or psychiatric diseases) had a lower OS and should be carefully evaluated before indication of HSCT[21]. Another model is the ***Phenotypic risk score for prediction of mortality in sickle cell disease (PReMSCD).*** An online risk score calculator is available at https://dir.nhlbi.nih.gov/lab/echo/PReMSCD/. The authors included 600 patients with ≥ 18 years old (median age of 33.5 years). With this model it has been possible were able to divide the patients in 4 well defined risk scores. These risk scores can help when considering HSCT for adults with SCD[22]. Considering the transplant related mortality, only one specific risk score was published. Wich score considers only age and type of donor. Children < 12 years old and MSD are considered in the low-risk category (EFS of 92%). Patients over 16 years with an MSD donor are considered as intermediate risk. All other types of donors and age older than 16 years are considered high risk[20]. This again favors an early referral to a transplant center for children with SCD. The hematopoietic cell transplantation-specific comorbidity index (HCT-CI), validated for hematological malignancies, were never validated for SCD, but should also be applied and can help guide transplant decisions[23].

TABLE 1. Hematopoietic stem cell transplantation for hemoglobinopathies.

	HLA identical sibling donor (bone marrow or cord blood graft)	Unrelated donor (bone marrow graft)	Haploidentical donor (bone marrow graft)
Transfusion dependent thalassemia	Standard of care	HLA identical (10/10) AND HLA DPB1 identical or with permissive mismatch	Clinical option
Sickle cell disease	Standard of care	Not recommended	Clinical option

TABLE 2. Indications for allogeneic HSCT in sickle cell disease.

CHILDREN	ADULTS
Patients who are using hydroxyurea and/or chronic transfusion and present at least one of the following complications: 1) Neurological alteration due to stroke, any neurological alteration persisting for more than 24 hours, altered imaging or cerebrovascular disease associated with sickle cell disease 2) Two or more severe vaso-occlusive crises (including acute chest syndrome) in the last year 3) More than one episode of priapism 4) Presence of more than one antibody in patients on a hypertransfusion regimen 5) Osteonecrosis in more than one joint	Same general indications for children. Consider also: 1) Administration of regular RBC transfusion therapy, defined as receiving 8 or more transfusions per year for 1 year to prevent vaso-occlusive clinical complications (ie, pain, stroke, and acute chest syndrome) 2) An echocardiographic finding of tricuspid valve regurgitant jet > 2.7 m/s
Absence of severe comorbidities that can increase transplant related mortality.	

HSCT, hematopoietic stem cell transplantation; RBC, red blood cell.

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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR MONOCLONAL GAMMOPATHIES: MULTIPLE MYELOMA AND AMYLOIDOSIS

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INTRODUCTION

The treatment of multiple myeloma (MM) has improved gratly in recent years. Given these advances, many question the need to use autologous HSCT in the first line. Still, despite the remarkable evolution of drug treatment, autologous HSCT remains essential in the approach of first-line therapy for patients with symptomatic MM eligible for this therapeutic modality, regardless of risk stratification or assessment of minimal residual disease after induction therapy.

UPDATE

Although the recommendations made in the last HSCT consensus document for MM remain unchanged[1], new studies have been published and below, we highlight the findings of the two most important ones, concerning patients eligible for transplantation.

The first under consideration is the DETERMINATION[2], which was initially created as a parallel study to the IFM 2009, but has been changed to include the use of maintenance therapy with lenalidomide until disease progression in both the RVD alone group and the RVD followed by autologous HSCT. In this study, patients were randomized to receive, after three cycles of RVD, autologous HSCT followed by two more cycles of RVD or three more cycles of RVD. Although there was no difference in overall survival, patients undergoing autologous HSCT had more remarkable progression-free survival, confirming a finding from the 2009 IFM and responding to a criticism of this study that maintained lenalidomide for only one year.

Another relevant study was the FORTE[3], which randomly evaluated the use of carfilzomib in association with cyclophosphamide and dexamethasone (KCd), followed by autologous HSCT or in association with lenalidomide and dexamethasone (KRd), followed or not by autologous HSCT. This study was critical because, one of the reasons that would justify not using autologous HSCT in the first line would be the more significant number of severe side effects related to this therapy, which was not verified, when comparing the KRd group with or without autologous HSCT. Patients who received KRd with autologous HSCT showed clinically significant benefit, compared with KRd without HSCT or KCd plus HSCT.

A piece of data that may lead to a need for a future change in the document generated in 2020[1], but which still needs more studies for its incorporation, was the benefit of the association of carfilzomib with the maintenance of lenalidomide[3], evaluated in the second randomization after the end of the three lines of treatments, because, in addition to demonstrating more adverse events than the isolated use of lenalidomide, it can impact the quality of life because it is used parenterally and may not present many benefits to patients undergoing transplantation.

Thus, we maintain the recommendations and evidence levels of the document generated in 2020, including those for allogeneic HSCT, whether for MM, as well as for amyloidosis, highlighting the need to incorporate more therapies for these patients, mainly in the public health system and the importance of improving access to autologous HSCT for patients with MM, who are the most submitted to transplantation in Brazil[4], but which is still not offered to most patients treated outside the supplementary health system.

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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA

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This summary is intended to update the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) 2020/1 consensus on HSCT for Acute Myeloid leukemia (AML)[1].

With advances in molecular medicine and target therapies, there has been significant improvement in the treatment of acute myeloid leukemia (AML) in recent years. Molecular pathways in leukemia cells such as the ones that leads to uncontrolled proliferation (FLIT3), differentiation blockage (IDH), or prevent apoptosis (BCL2), to mention only some involved in leukemia development, can now be targeted. This improvement came along with better quality of live and longer survival in some AML groups since target therapy, potentially toxic to the hematopoietic system, have very low systemic side effects when compared to chemotherapy (CT) alone and as such can be utilized in this predominantly elder population of patients. There are additional target drugs been developed to different pathways that will include other subtypes of AML such as secondary AML and TP53 mutated AML that, for now, remain challenging subtypes. CAR-T cell technology is also in development and its impact in AML treatment is eagerly awaited.

Both, WHO[2] and European LeukemiaNet (ELN)[3] (Table 1) recently published new guidelines including additional genetic abnormalities for risk categorization as well as number of blasts' thresholds for AML diagnosis. Although in those patients without specific mutations > 20% blasts are necessary for AML diagnosis, those with defined mutations should be diagnosed with > 10% of blasts either at the peripheral blood or bone marrow. In addition, a new category called SMD/AML syndrome was introduced where >10% of blasts with defined mutations are present and these patients are eligible to be treated either as SMD or AML[3].

TABLE 1: ELN and WHO' defined AML mutations

ELN (Blasts ≥ 10% in PB or BM)	OMS
Promyelocytic Leukemia t(15;17)(q24.1;q21.1)/PML::RARA	Promyelocytic Leukemia with PML::RARA
AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1	AML with RUNX1::RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ CBFB::MYH11	AML with CBFB::MYH11
AML with t(v;11q23.3)/ rearranged KMT2A	AML with rearranged KMT2A
AML with t(6;9)(p23;q34.1)/ DEK::NUP214	AML with fusion DEK::NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ GATA2, MECOM(EVI1)	AML with rearranged MECOM
AML with rare translocations	AML with fusion RBM15::MRTFA AML with rearranged NUP98
AML with mutated NPM1	AML with mutated NPM1
AML with mutated CEBPA bZIP in-frame	AML with mutated CEBPA
AML with t(9;22)(q34.1;q11.2)/BCR::ABL1*	AML with mutated BCR::ABL1
AML (≥ 20% of PB or BM blasts) or AML/MDS (10 to 19% of PB or BM blasts)	**AML with defined somatic mutations related to MDS**
With TP53 mutation	Complex karyotype with 3 or more abnormalities del(5q)/t(5q)/ ad(5q), -7/del(7q)/ad(7q), del 11q, del(12p)/ t(12p)/(ad(12p), -13/ del13q, i(17q), -17/ad(17p)/del(17p), del(20q), or idic(X)(q13) ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, o ZRSR2
With defined mutation related to MDS (ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, o ZRSR2)	
With defined mutation related to MDS: complex karyotype and/ or del(5q)/t(5q)/ad(5q), -7/del(7q), +8, del(12p)/ t(12p)/(ad(12p), i(17q), -17/ad(17p)/del(17p), del(20q), or idic(X)(q13)	
Non specified AML	AML defined by blast maturation
Myeloid Sarcoma	**Myeloid Sarcoma**
Down Syndrome related myeloid proliferation	
Down Syndrome related TAM	-
Down Syndrome related AML	-
Plasmacytoid dendritic cells neoplasm	Plasmacytoid dendritic cells neoplasm
Ambiguous lineage leukemia	Ambiguous lineage leukemia
Undifferentiated acute leukemia	Undifferentiated acute leukemia
Mixed Phonotype AL with t(9;22)(q34.1;q11.2)/ BCR::ABL1	Mixed Phonotype AL with t(9;22)(q34.1;q11.2)/ BCR::ABL1
Mixed Phonotype AL with t(v;11q23.3)/ rearranged KMT2A	Mixed Phonotype AL with t(v;11q23.3)/ rearranged KMT2A
Mixed Phonotype AL with B/myeloid, no specified	Mixed Phonotype AL with B/myeloid, no specified
Mixed Phonotype AL with T/myeloid, no specified	Mixed Phonotype AL with T/myeloid, no specified
	Ambiguous lineage AL with rearranged ZNF384 Ambiguous lineage AL with rearranged BCL1B
Diagnostic qualifiers	**Secondary AML**
Therapy related AML	Therapy related AML
MDS' secondary AML	AML-MR secondary to Myelodysplasia
MDS/Myeloproliferative' secondary AML	AML-MR secondary to Myelodysplasia
Germline predisposition related AML)	Germline predisposition related AML

*< 20% of blasts can be CML in blastic phase, TAM: Transient Abnormal Myelopoiesis; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia, AL: acute leukemia

MINIMAL RESIDUAL DISEASE (MRD)

The prognostic value of measurable MRD at determined treatment timepoints is now very well defined and once measured by the appropriate methods can be superior to the genetic risk categorization[4,5]. Multiparametric Flow cytometry (MFC) to measure it is validated but not yet completely standardized[6]; that is why the SBTMO MRD Working Group **strongly** recommends that MFC must be done in a well-equipped laboratory with expertise in such measurements. In Brazil, there are a few laboratories that can offer expertise assistance.

RT-PCR is indicated for MRD measurement only in *PML:RARA*, *CBF* LMA, and *NPM1* mutated AML[7] however, MFC should also be done to be sure there is no additional AML clones. Except for FLT3-ITD which detection by NGS appears to identify patients with high risk of relapse and death[8], NGS methodology to measure MRD is not yet well validated and should also be accompanied by MFC.

The recommendations for MRD assessment are after the second CT cycle, after consolidation, </= 4 weeks before HSCT; after transplantation there is no consensus on which time points it

should be measured. MFC should be measured in bone marrow samples while RT-PCR can be done in peripheral blood[6]. The SBTMO MDR Working Group recommendation is that MFC MRD measurement should be the preferred method utilized in the mentioned time points intercalated with RT-PCR when indicate.

ALLOGENEIC HSCT IN FIRST COMPLETE REMISSION

The new ELN risk categorization includes new genetic alterations and genetic predisposition mutations that influence treatment outcome (Table 2). Those prognostic risk factor should be utilized along with minimal residual disease (MRD) measurement during treatment to guide therapeutic strategies. Intermediate and high-risk AML are potential candidates for HSCT provided age related and comorbidities scores are applied and favorable. With the MRD measurement quality improved and validated it adds a treatment response criterion that should be taken into consideration for HSCT indication irrespective of the risk category. Patients with ELN favorable risk with positive MRD (>0.1%) should be considered for HSCT, if eligible[9].

TABLE 2. 2022 LNT risk stratification

RISK CATEGORY	GENETIC ABNORMALITY
Favorable	t(8;21)(q22;q22.1); RUNX1::RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB::MYH11
	NPM1 mutation without FLT3-ITD
	MCEBPA b-ZIP mutation in frame
Intermediary	NPM1 mutation with FLT3-ITD
	NPM1wt with FLT3-ITD (without additional adverse abnormalities)
	t(9;11)(p21.3;q23.3)/MLLT3-KMT2A
	Genetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1)/DEK::NUP214
	t(v;11q23.3)/rearranged KMT2A
	t(9;22)(q34.1;q11.2)/ BCR::ABL1
	t(8;16)(p11;p13)/KAT6A::CREBBP
	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 karyotypes, monosomies
	ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2 mutations
	TP53 mutation

In a retrospective CIBMTR analysis[10], including 3113 patients submitted to MAC or RIC conditioning regimen alloHSCT, the number of CT cycles to obtain CR, CR consolidation, and measurable MRD pre transplant impact on outcomes were recently evaluated. OS and RFS were superior in patients that obtained CR in the first cycle and in those who received CR consolidation. Detection of measurable MRD before myeloablative conditioning regimens (MAC) allotransplant had no influence in outcomes, while it did have when present before reduced intensive regimens (RIC) alloHSCT. For patients obtaining CR after 2 or 3 CT cycles, while having an inferior RFS or OS then those in CR after a single cycle, outcomes were superior to patients transplanted with primary induction failure. In spite that retrospective studies always have caveats, the SBTMO AML Study Group recommends that this data should be taken in consideration.

CONDITIONING REGIMENS

Although myeloablative conditioning regimens are the preferred strategy for HSCT in AML, patients with more than 60 years or with comorbidities have an increased risk of transplant related mortality (TRM). Likewise, patients with negative MRD before HSCT do not benefit from intense conditioning regimens.

Although waiting for more robust evidence, the addition of Venetoclax to Bu2/Flu (RIC) is apparently secure, not interfering with engraftment time or GVHD incidence[11,12].

POST HSCT MAINTENANCE THERAPY

The relevance of post-transplant maintenance therapy is increasingly appreciated. It is becoming clear that it could be a choice for patients that have pre transplant positive MRD, FLT3-ITD, and BCR-ABL mutations who have an increased relapsed rate. Dose and timing remain to be defined because of HSCT complexities such as GVHD or CMV activation along with multiple drugs usage. Among other combinations, hypomethylating agents and sorafenib with or without donor lymphocyte infusion are being studied[13-15].

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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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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 2022 update and summary of the recommendations of the Brazilian Society of Bone Marrow Transplantation Consensus Panel convened in 2020 for this field.

PHILADELPHIA-POSITIVE MYELOPROLIFERATIVE DISEASE

Chronic Myeloid Leukemia: Summary of Recommendations

1. Imatinib mesylate, nilotinib, bosutinib or dasatinib are the treatments of choice for newly diagnosed chronic phase (CP) chronic myeloid leukemia (CML)[2-10] (1B).

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

a. Advanced phase disease: In accelerated phase (AP), HSCT should be indicated if the response to second generation TKI therapy (dasatinib, nilotinib or bosutinib) is suboptimal, or in case of a T315I mutation when ponatinib or asciminib is unavailable[11-17]. In blast crisis (BC), it should always be considered, preferably after a preliminary course of TKI therapy with or without chemotherapy[18,19] (2B).

b. Chronic Phase: 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, asciminib) or HSCT, if the former is unavailable[19] (19) (1B).

d. T315I mutation, if ponatinib or asciminib is unavailable[15,18,19] (1B).

3. For young patients with an HLA-identical related or unrelated donor, myeloablative conditioning (MAC) should be used. Reduced intensity (RIC) or non-myeloablative conditioning should be reserved for patients over 60 years of age and/or with significant comorbidities[20-23](1B).

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 (1B)[24,25]. Post-transplantation cyclophosphamide should be used for mismatched unrelated and haploidentical donors (26) (1B).

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), can be used in the absence of other available sources[27–30]we conducted an individual-patient data meta-analysis using data from nine randomized trials enrolling 1,111 adult patients. Results: Compared with BMT, PBSCT led to faster neutrophil (odds ratio [OR] = 0.31; 95% CI, 0.25 to 0.38; P < .00001 (1B).

6. Matched or mismatched unrelated donors or haploidentical transplants are acceptable in the absence of an HLA-identical sibling donor[26,31] (1A).

7. 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[32–34] (2B).

8. Molecular relapse is defined as progressively increasing BCR-ABL/ABL1 gene transcripts in at least two consecutive results and loss of major molecular response (>0,1%)[34] (2B).

9. Use of imatinib mesylate and of second generation TKIs (dasatinib, nilotinib or bosutinib) 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[35–38](2B).

10. 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 TKI. 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 1-2 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 TKI, or a combination of these. In case of hematologic relapse in AP or BC, consider the use of a TKI plus DLI[39–44](1B).

11. Imatinib mesylate, nilotinib, bosutinib 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 (2B). TKIs may also be combined with DLI in the management of such cases, with better overall responses (2B). Prompt and long-lasting responses are usually seen under TKI therapy for CML relapsing in CP (2B). Response tends to be worse and less durable in AP or BC relapse[45,46] (2B).

12. In patients previously resistant or intolerant to imatinib mesylate, consider using a second generation TKI (nilotinib, bosutinib or dasatinib), when deciding upon use of a TKI alone or in combination with DLI (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[45,46] (2B).

13. Consider using post-transplant TKI prophylaxis for two years in patients at a high risk for relapse (>1st CP and AP/BC)[47–51] (2B).

14. 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[52](2B).

15. 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[53] (2B).

TABLE 1. European LeukemiaNet 2020 chronic myeloid leukemia treatment recommendations

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-HSCT)
Blast crisis at diagnosis	Start with imatinib, change to a 2nd generation TKI according to mutational 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 B CP (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 (19).

ACA: additional chromosomal aberrations; ALL: acute lymphoblastic leukemia; allo- HSCT: allogeneic hematopoietic stem cell transplant; AML: acute myeloid leukemia; BC: blast crisis; CVAD: cyclophosphamide + vincristin + doxorubicin + dexamethasone; 2CP: second chronic phase; FLAG-IDA: fludarabin + cytarabin + granulocyte-colony stimulating factor + idarubicin; HiperCVAD: hyperfractionated CVAD; TKI: tyrosine kinase inhibitor.

TABLE 2. Recommendations for post-HSCT monitoring and relapse therapy in CML patients (32-46)

TIME AFTER HSCT	MONITORING	RESULT	INTERVENTION
2 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: 106®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; GVHD = graft-versus-host disease; 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. The 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 six years after diagnosis[54]. Even so, the clinical course is highly heterogeneous, and survival may vary from a few months to more than 10 years[55]. Therefore, prognosis may be better estimated by several scoring systems, among which the Dynamic International Prognostic Scoring System plus (DIPSS plus)[56] is one of the most 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[56]. 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 (2B). At fibrotic phase PV or ET, the MYSEC prognostic index can be used (http://www.mysec-pm.eu). It has been shown to be able to stratify these patients into four categories: low risk (median survival not reached; intermediate-1: median survival 9.3 years), intermediate-2 (median survival 4.4 years) and high risk (median survival two years) [57].

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) [58] and the Clinical-Molecular Myelofibrosis Transplant Scoring System (MTSS)[59] 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 (2B).

INDICATION

Allogeneic HSCT remains the only curative option for myelofibrosis patients to date. Not all patients, however, benefit from this procedure. Hence, we recommend that transplant indication be based on the DIPPS or DIPPS plus score, whereby allogeneic HSCT should be performed in intermediate-2 and high-risk patients[60–63]. HSCT may sometimes be considered for patients classified as intemediate-1 risk[63], 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[63] (2B).

CONDITIONING REGIMEN INTENSITY

It has not yet been defined what the ideal conditioning regimen is in transplantation for PMF patients. Given the patients' average age at diagnosis, most regimens will be of reduced intensity, the ideal dose of which is not established. For patients under the age of 50, we recommend MAC; for those over 50 years old, RIC[64-66], which usually consists of fludarabine associated with busulfan or melphalan sometimes associated to thiotepa[67]. Despite no evidence of superiority between conditioning regimens, the melphalan regimen seems to obtain greater control of the disease, albeit with higher non relapse mortality than the regimen with busulfan, resulting in similar overall survival[64].

The MD Anderson group recently published a non-randomized, phase II study comparing two different levels of intravenous busulfan associated with fludarabine: 15 patients using low-dose busulfan (130 mg/m^2 for two days) and 31 patients with high-dose busulfan (100mg/m^2 for four days), including 27 patients with a serum level adjusted to an AUC of 4000. In an average follow-up of three years, patients using busulfan at a higher dose had an event-free survival of 58% against 27% of those who used low doses. In conclusion, the use of conditioning regimens containing fludarabine and busulfan with serum level control seems to reduce relapse without increasing transplant-related mortality[65]. Non-myeloablative conditioning has also a higher rate of graft failure[66] (2B).

DONOR

HLA-matched unrelated donors are an acceptable alternative for patients without an HLA-identical sibling donor[66]. HLA-mismatched related donors may also be acceptable, but further studies are needed to better address this issue[67] (2B).

The results of haploidentical transplantation in PMF still lack published data. One of the first reports was published in 2016, comparing the use of alternative donors (unrelated and haploidentical) with HLA-matched related donors in 95 patients with PMF between 2000 and 2014[68]. Although it was an analysis of a relatively few numbers of patients, including 23 haploidentical transplants, 20 of which in the last five years, the study showed a significant improvement in the survival of transplanted patients with PMF who used alternative donors during the period of 2011 to 2014 as compared to that of 2000 to 2010[68].

In 2019, the EBMT group published a retrospective report of 56 patients, with a median age of 57 years[67]. Myeloablative conditioning was chosen in 70% of the cases, 59% of which used thiotepa + fludarabine + busulfan with post-transplant cyclophosphamide; two thirds used bone marrow as stem cell source. The engraftment rate was 82%. The cumulative incidence of acute GVHD up to D + 100 was 28% (grade II-IV) and 9% (grade III / IV) and of chronic GVHD at 1 year was 45%. At two years, overall survival was 56%, the incidence of relapse was 19%, and non-relapse mortality was 38%. This study showed that haploidentical transplantation is feasible, with a comparable overall survival with that of unrelated transplants; however, efforts should be made toward decreasing the considerable transplant-related mortality rate found in this study.

STEM CELL SOURCE

PBSCs are the preferred stem cell source, but BM is also acceptable in this scenario[69](2B).

SPLENECTOMY

Routine splenectomy prior to transplant is not recommended in patients with splenomegaly, except in cases with a spleen size greater than 20cm[70,71]. Splenic radiation, in turn, may be considered within the context of clinical trials (2B).

RUXOLITINIB

Ruxolitinib 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[72].

In a prospective study evaluating the use of ruxolitinib prior to transplant, it was started 60 days before conditioning, gradually decreased in four days, until complete withdrawal one day before conditioning. Despite being shown to be safe in this group of 21 patients, no significant reduction was seen in the rate of graft failure or in the incidence of GVHD[72]. Another prospective phase II study investigated ruxolitinib use for at least eight weeks, with a gradual reduction of 5 mg every four days and withdrawal four days before stem cell infusion. This study also showed that the use of pre-HSCT ruxolitinib is safe: none of the patients had cytokine release syndrome, and the 2-year overall survival was 86%, suggesting a benefit in overall survival[73] (2B). In addition, other studies have shown that ruxolitinib is well tolerated during conditioning, and others have investigated its use at low doses until engraftment. In a study with a small number of patients who were kept under low dose ruxolitinib until D + 28, in two out of 12 patients this medication had to be discontinued. The average engraftment time was 12 days, there was no graft failure, and there was a low incidence of acute GVHD. However, the incidence of cytomegalovirus reactivation was 40%[74].

Robin et al.[75] published a phase II study evaluating the use of ruxolitinib six months before HSCT. Among the 76 patients included, 64 had a donor, 18 of whom were matched-sibling donors, 32 matched-unrelated donors and 14 mismatched-unrelated donors. Among the 64 patients who received ruxolitinib, 92% were transplanted at three months, 26% had a complete response, 20% had a partial response, and 54% had no response. All patients received RIC (fludarabine/melphalan) and GVHD immunoprophylaxis with cyclosporine and mycophenolate mofetil +/- antithymocyte globulin. Overall survival at 12 months was 68%, and disease-free survival was 55%. The cumulative incidence of grade II-IV acute GVHD was 66%, and non-relapse mortality was 42%[75].

It has been demonstrated that after HSCT, allele burden of JAK2-V617F is related to relapse. In such scenario, ruxolitinib has been investigated as preemptive therapy[76].

Therefore, we recommend ruxolitinib to be used at the highest tolerated dose, with gradual tapering every four days and complete withdrawal by one to two days prior to transplant[72]. According to a recent phase II study, its use prior to HSCT seems to be safe and to improve overall survival in patients who are referred for transplantation[72].

However, in the absence of randomized controlled trials, we recommend that all patients with interme-

diate-2 or high risk PMF and high-risk myelofibrosis secondary to PV or ET be referred for HSCT as soon as possible[73] (2B).

SUMMARY OF RECOMMENDATIONS:

• Allogeneic HSCT is indicated for high or intermediate-2 risk PMF patients and for high-risk myelofibrosis secondary to PV or ET. Intermediate-1 patients and those with severe thrombocytopenia, peripheral blasts or having high risk mutations can also be candidates for allogeneic HSCT (2B).

• The DIPSS plus classification is recommended. When possible, MIPSS70+ v2.0 or MTSS should also be used (2B).

• It seems reasonable to offer MAC for patients under 50 years old and RIC for those above this age or with comorbidities. When possible, levels of busulfan should be monitored (2B).

• In the absence of a matched sibling donor, alternative donors can be used (unrelated and haploidentical, in this sequence) (2B).

• Peripheral blood is the preferred source, but bone marrow can also be acceptable (2B).

• Pre-transplant splenectomy is not routinely recommended. It can be considered if splenomegaly is above 20 cm (2B).

• Relapse after HSCT should be managed with donor lymphocyte infusions[74] (2B).

• Monitoring of the JAK-V617F mutation should be performed after HSCT, since it is correlated with relapse[76] (2B).

• Pre-transplant ruxolitinib can improve both clinical condition and survival, but referral for HSCT should not be deferred, since this is the only curative procedure. When ruxolitinib is used, we recommend it at the highest tolerated dose (20mg BID), with gradual tapering every four days and complete withdrawal by one to two days prior to transplant (2B).

• Driver mutations and an NGS panel should be performed whenever possible, which might strengthen the indication for HSCT, particularly in intermediate-1 PMF patients (2B).

TABLE 3. HSCT indications for Myeloproliferative Neoplasms

DISEASE	MSD	MUD	MMUD	MMSD
PMF/DIPSS-PLUS				
Low Risk	GNR	GNR	GNR	GNR
Intermediate-1	CO*/2C	CO*/2C	CO */2C	CO*/2C
Intermediate-2 and high risk	S/2B	S/2B	S/2C	CO/2C
CML				
CP				
TKI failure (second or third line)	S/2B	S/2B	CO/2C	CO/2C
AP	S/2B	S/2B	CO/2C	CO/2C
BP	S/2B	S/2B	CO/2C	CO/2C
>1st CP	S/2B	S/2B	CO/2C	CO/2C

AP: Accelerated phase CML; BP: Blast phase CML; CML: Chronic myeloid leukemia; CO: clinical option; CP: chronic phase CML; DIPSS-PLUS: Dynamic International Prognostic Scoring System Plus; GNR: generally not recommended; HSCT: hematopoietic stem cell transplantation; MSD: matched-sibling donor; MMSD: mismatched-sibling donor; MUD: matched-unrelated donor; MMUD: mismatched-unrelated donor; PMF: primary myelofibrosis; S: standard; TKI: tyrosine kinase inhibitor.

*CO: circulating blasts, high risk mutations

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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMA

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INTRODUCTION:

The treatment of lymphoproliferative neoplasms has advanced in recent years with the introduction of many monoclonal and other targeted therapies. Despite these advances, haematopoietic stem cell transplantation (HSCT) remains important in the management of non-Hodgkin's lymphomas (NHL), especially in the scenario of recurrences (Table 1)[1].

In certain situations where HSCT does not show a great benefit, there are opportunities for studies with new therapies. In these scenarios, CAR-T cells have been performed in Diffuse Large B Cells Lymphomas patients when rescue chemotherapy and autologous HSCT led to partial remission (PR), which is unsatisfactory and has unclear benefit in terms of survival [2].

In Table 1 are described the main indications and therapies' level of evidence according to the subtypes of NHL.

LYMPHOMA SUBTIPE	AUTOLOGOUS	EVIDENCE	ALLOGENEIC	EVIDENCE
DLBCL (Diffuse Large B-Cell Lymphoma)	Relapse/Induction failure High risk CR1/PR!	1a 2c	Post autologous relapse	2c
Follicular	Early relapse In transformation 2nd line	2b 2b	Second or multiple relapses	2c
Mantle cell	1st CR/1st PR Relapse/failure	2b 2b	Post autologous relapse Refractory disease Blastoid variant/TP53 mutated	2c 2c 2c
PTCL (Peripheral T-Cell Lymphoma)	1st CR(ALK-)/PR 2nd CR/PR	2b 2c	ATLL/HETCL Induction failure or post autologous relapse	2c 2b

UPDATE

Although the indications for allogeneic HSCT remain unchanged from the previous document, currently CAR-T cell therapy has indications that compete with those for allogeneic HSCT. In an attempt to facilitate the choice between therapies in relapses after autologous HSCT or in patients who are refractory to rescue regimens and who do not benefit from the indication for autologous HSCT, we list below the main benefits of these 2 forms of treatment[3]:

CAR-T	Allo HSCT
Immediate antitumor effect	Can be performed in cytopenic patients
Effective against active disease	Low impact of previous therapies
Avoid risk of graft versus host disease (GVHD), with different toxicities	Longer follow up with known toxicities
Low procedure related mortality	Better availability and cost

In addition to the different benefits between the two therapies listed above, there seems to be a slight advantage for CAR-T when compared to allogeneic HSCT used in patients with DLBCL with more than 2 lines of treatment, an advantage that disappears when patients are evaluated regardless of the number of lines. of treatment[4].

Unlike follicular lymphoma and NHL T for which there is still no indication for CART in Brazil, either due to lack of benefits or unavailability, in marginal zone lymphoma allogeneic HSCT is beginning to lose ground in its indication in relapses after autologous HSCT for CART[5].

Although allogeneic HSCT begins to have questions about its indication in DLBCL and marginal zone lymphoma, the current unavailability of access to therapies with CART, keep its indication almost unchanged.

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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR MYELODYSPLASTIC SYNDROMES

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ABSTRACT

The document discuss key points in the management of patients with Myelodysplastic Disease, including therapeutic strategies, the role of new drugs available as well the Hematopoietic Stem Cell Transplantation (HSCT). Other issues evaluated were importance of molecular alterations since diagnosis to prognosis, use of comprehensive geriatric assessment for patient's selection, individualization of treatment, donor selection for HSCT and the role of blasts % and molecular mutations for the appropriate diagnosis.

Despite the new treatment options for Myelodysplastic Disease (MD), which include the association of drugs with Hypomethylants, mainly Venetoclax[1,2], monoclonal antibodies such as Magrolimab[3,4] and Sabatolimab[5,6], Hematopoietic Stem Cell Transplantation (HSCT) is still the only curative option.

The main discussion is the individualization of treatment, considering the condition of each patient, to define the best donor and type of conditioning and the possibilities of post-HSCT approaches, ranging from prophylactic or therapeutic Donor Lymphocyte Infusion (DLI), associated or not with medication[7].

Correct risk stratification has always been a preponderant aspect for the indication of HSCT, we know the importance of molecular alterations not only for the diagnosis, but also for the prognosis, and in this context we emphasize the IPSS-M[8], which refines the classification.

Another relevant point has been the use of comprehensive geriatric assessment, especially with patients over 60 years of age, as an aid tool.

In the current discussions, two points are important to be registered in this update, one of them is the 20% blast cutoff point, where it is argued that genetic-molecular characteristics prevail, and that this limit alone may not be fully adequate[9] and also the role of the bi-allelic TP53 mutation, which, when present, confers a poor prognosis independent of the blast count[10].

We can therefore conclude that a better understanding of the disease and individualization of treatment are the pillars of better management of these patients.

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CONSENSUS UPDATE

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES

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ABSTRACT

Autoimmune diseases are an important field for the development of hematopoietic stem cell transplantation (HSCT). The Brazilian Society for Cellular Therapy and Bone Marrow Transplantation (Sociedade Brasileira de Terapia Celular e Transplante de Medula Óssea, SBTMO) organized consensus meetings for the Autoimmune Diseases Group, to review the available literature on HSCT for autoimmune diseases, aiming to gather data that support the procedure for these patients. Three autoimmune diseases for which there are evidence-based indications for HSCT are multiple sclerosis, systemic sclerosis and Crohn's disease. The professional stem cell transplant societies in North America (ASTCT), Europe (EBMT) and Brazil (SBTMO) currently consider HSCT as a therapeutic modality for these three autoimmune diseases. The data are here updated.

Keywords: Autoimmune diseases. Hematopoietic stem cell transplantation. Multiple sclerosis. Systemic sclerosis. Crohn's disease.

Autologous hematopoietic stem cell transplantation (AHSCT) has been used worldwide as treatment for autoimmune disease patients[1]. The procedure aims 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. The three most important and current indications for AHSCT are multiple sclerosis, systemic sclerosis and Crohn's disease (Table 1)[1].

TABLE 1 - Randomized clinical studies on AHSCT for autoimmune diseases

STUDY	MAIN CONTRIBUTION TO THE FIELD
Multiple Sclerosis	
ASTIMS trial[2] *Italy and Spain (EBMT), intermediate-intensity regimen, 21 patients*	Transplanted patients improved in disability and had fewer relapses than conventionally-treated patients over a 5-year follow-up. All patients had highly inflammatory and active MS.
MIST trial[3] *Multicenter, non-myeloablative regimen, 110 patients*	Transplanted patients did not present new T2 lesions on MRI compared to those treated with mitoxantrone. No effect on disability, but most patients were in secondary-progressive phase.
Systemic Sclerosis	
ASSIST trial[4] *Single USA center, non- myeloablative regimen, 19 patients*	Autologous transplant was more effective than monthly intravenous cyclophosphamide in controlling skin thickening, lung function and quality of life, over a 24-month follow-up.
ASTIS trial[5] *European multicenter, non- myeloablative regimen, 156 patients*	Transplanted patients had higher overall survival, progression-free survival and quality of life than conventionally-treated patients over a 5-year follow-up.
SCOT trial[6] *USA multicenter, myeloablative regimen, 75 patients*	Transplanted patients had higher overall survival and progression-free survival than conventionally-treated patients over a 5-year follow-up.
Crohn's Disease	
ASTIC trial[7,8] *European multicenter, non- myeloablative regimen, 45 patients*	No differences in sustained remission composite scores (clinical, radiological and endoscopic) between transplanted and only mobilized patients. Secondary outcomes of disease activity, endoscopic activity and use of medical therapy favored transplanted patients.

AHSCT: autologous stem cell transplantation; MRI: magnetic resonance imaging.

The American Society for Cellular Transplantation and Therapy (ASTCT)[9,10], the European Society for Blood and Marrow Transplantation (EBMT)[11,12], the European League Against Rheumatism (EULAR)[13] and the Brazilian Society of Bone Marrow Transplantation (SBTMO)[14,15] currently consider AHSCT as part of the already established therapeutic strategies for these autoimmune disorders, apart from the research setting.

Since the last consensus meeting published in 2021[15], a few new studies have been added to the field, however not changing the recommendations. Novel studies include a regimen of lower intensity, with decreased dosage of cyclophosphamide for systemic sclerosis patients[16]. Although this trial shows less cardiac toxicity and shortened duration of neutropenia, it still has to be investigated by other centers and long-term outcomes should be compared to conventional treatment in a randomized controlled setting. A prospective multicenter study from the EBMT and partners also confirmed successful clinical outcomes of systemic sclerosis patients over a 24-month follow-up after AHSCT[17]. In multiple sclerosis, AHSCT was used as first line therapy in patients with aggressive disease, with successful clinical and radiological outcomes over median follow-up of 30 months[18]. Also, a Mexican group has reported their experience with one thousand transplanted patients using a split-cyclophosphamide dose strategy[19]. The authors claim that by splitting the total dose, the transplant regimen becomes safer to the heart. This approach, however, should be tested in other autoimmune disease settings, since cardiotoxicity is not a key problem in multiple sclerosis transplants as it is in other diseases such as systemic sclerosis[20,21]. In addition, reports on the long-term outcomes of these patients are pending. Very recently, the group from Chicago (USA) reported their "real-world" experience with more than 500 patients transplanted for multiple sclerosis[22]. The authors show positive outcomes for patients with the relapsing-remitting form of the

disease, who improve disability and sustain remission over time. On September 2nd, 2021, the Brazilian Federal Council of Medicine issued a favorable opinion on AHSCT as treatment for multiple sclerosis.

Allogeneic transplants for autoimmune diseases remain limited to the research setting, in view of the excessive toxicity and need to improve clinical protocols[11].

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 2). Allogeneic transplantation, however, should still be further evaluated in the experimental setting.

TABLE 2 – 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. Recommendations are categorized according to described in reference 11.

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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION 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 otherwise be lethal. 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[1–3], particularly in germ cell tumors (GCT).

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 conventional[5]. Follow-up includes serial image exams and of the serum markers HCG e AFP.

This is an update of the 2020 recommendations of the Sociedade Brasileira de Transplante de Medula Óssea (Brazilian Society of Bone Marrow Transplantation, SBTMO) for hematopoietic cell transplantation for solid tumors[6]. Main recommendations are summarized here, and new recommendations are marked and discussed. For the texts for the 2020 recommendations, please refer to the original paper[6].

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).

New recommendation: Poor-mobilizers should receive plerixafor (Level of Evidence: 4, Grade of Recommendation: C).

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).

STEM-CELL MOBILIZATION

G-CSF-mobilized peripheral blood stem-cell graft has largely replaced bone marrow[7]after appropriate pharmacologic mobilization, have largely replaced bone marrow as the principal source of HSCs in transplants. As it is currently common practice to perform tandem or multiple sequential cycles of HDCT, it is anticipated that collection of large numbers of HSCs from the peripheral blood is a prerequisite for the success of the procedure. Moreover, the CD34+ cell dose/kg of body weight infused after HDCT has proven to be a major determinant of hematopoietic engraftment, with patients who receive $> 2 \times 106$ CD34+ cells/kg having consistent, rapid, and sustained hematopoietic recovery. However, many patients with relapsed/refractory GCTs have been exposed to multiple cycles of myelosuppres-

sive chemotherapy, which compromises the efficacy of HSC mobilization with granulocyte colony-stimulating factor with or without chemotherapy. Therefore, alternative strategies that use novel agents in combination with traditional mobilizing regimens are required. Herein, after an overview of the mechanisms of HSCs mobilization, we review the existing literature regarding studies reporting various HSC mobilization approaches in patients with relapsed/refractory GCTs, and finally report newer experimental mobilization strategies employing novel agents that have been applied in other hematologic or solid malignancies.""container-title":"World Journal of Clinical Oncology"",""DOI":"10.5306/wjco.v12.i9.746"",""ISSN":"2218-4333"",""issue":"9"",""-journalAbbreviation":"World J Clin Oncol"",""language":"eng"",""note":"PMID: 34631440\nPMCID: PMC8479351"",""page":"746-766"",""source":"-PubMed"",""title":"Hematopoietic stem cell mobilization strategies to support high-dose chemotherapy: A focus on relapsed/refractory germ cell tumors"",""title-short":"Hematopoietic stem cell mobilization strategies to support high-dose chemotherapy"",""volume":"12"",""author":[{"family":"Porfyriou"",""given":"Eleni"},{"family":"Letsa"",""given":"Sylvia"},{"family":"Kosmas"",""given":"Christos"}],""issued":{"date-parts":[["2021",9,24]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Peripheral blood graft collection is more convenient and associated with faster hematopoietic recovery. However, these patients usually have been exposed to platinum and other alkylating agents and therefore mobilization failure is not uncommon. Corbingi et al have demonstrated the feasibility of a "on-demand" approach using plerixafor for patients with low peripheral CD34 cells following mobilization with G-CSF (poor mobilizers) in patients with relapsed/refractory germ cell tumors[8].

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)

Allogeneic stem cell transplantation in solid tumors

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

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TABLE 1. Selected conditioning regimens

INSTITUTION	CARBOPLATIN	ETOPOSIDE	CYCLOPHOSPHAMIDE	# TRANSPLANTS
MSKCC11dose-intense chemotherapy with paclitaxel and ifosfamide followed by carboplatin and etoposide (TICE	AUC=24	1,200mg/m2	x	3
Indiana12 *	2,100mg/m2	2,250mg/m2	x	2
MSKCC13	1,500mg/m2	1,200mg/m2	150mg/kg	2
Germany14	1,500mg/m2	1,500mg/m2	x	3
	Cisplatin	Etoposide	Ifosfamide	# Transplants
EORTC14etoposide, 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

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CONSENSUS UPDATE

VI CONSENSUS OF THE BRAZILIAN SOCIETY OF BONE MARROW TRANSPLANTATION (SBTMO) CONSENSUS ON GRAFT-VERSUS-HOST DISEASE (GVHD)

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Version 2022 updates of Version 2020 of the VI Consensus of the Brazilian Society of Bone Marrow Transplantation for Graft-versus-Host-Disease (GVHD) include:

Table 1: GVHD prophylaxis regimens used, with levels of evidence and grades of recommendation:

New evidence of GVHD prophylaxis with post-transplantation cyclophosphamide (PTCy) in myeloablative (MA) allogeneic hematopoietic stem cell transplantation (allo-HSCT) from matched related and matched and mismatched unrelated donors;

New evidence of GVHD prophylaxis with PTCy in reduced intensive conditioning (RIC) and non-myeloablative (NMA) allo-HSCT.

Table 2: First-line therapy for grade I-IV acute GVHD (aGVHD), with levels of evidence and grades of recommendation:

Included treatment for Grade I and IIa aGVHD;

Included definition of Grade IIa aGVHD and options of topical therapies.

Included Table 3: chronic GVHD (cGVHD) indication for systemic treatment.

Included Table 4 with first-line therapy of cGVHD, with criteria for initiating systemic treatment, and with levels of evidence and grades of recommendation.

Included Table 5: Definition of steroid refractoriness or resistance, steroid dependence, and steroid intolerance for aGVHD and cGVHD.

Table 7: Second-line therapy of cGVHD, with levels of evidence and grades of recommendation:

New level of evidence for ruxolitinib, Level 1b, Grade of recommendation A;

Included belumosudil.

INTRODUCTION

Graft-versus-host disease (GVHD) can develop after allogeneic hematopoietic cell transplantation (allo-HSCT) when immune cells from a non-identical donor (the graft) initiate an immune reaction against a transplant recipient (the host). Acute GVHD (aGVHD) and chronic GVHD (cGVHD) are multisystem disorders that are distinguished by their clinical findings, according to National Institutes of Health (NIH) consensus criteria[1].

Despite prophylactic treatment with immunosuppressive agents, 20-80% of recipients develop aGVHD after allo-HSCT[2]. The main risk factors for aGVHD 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 *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[4]. It is currently regarded as the most appropriate method for the diagnosis, staging, and grading of aGVHD[4,5]. The app for grading can be accessed at https://www.uzleuven.be/egvhd.

With a prevalence of 30-70% among allo-HSCT recipients, cGVHD remains the main cause of long-term post-transplant morbidity and mortality in this population[6–8]. The cumulative incidence of cGVHD at 2 years in patients undergoing related or unrelated, bone marrow or peripheral blood stem cell allo-HSCT, as defined by the NIH criteria, was 34%[3]. Risk factors associated with cGVHD were HSCT with HLA-matched unrelated donors, HLA mismatched related donors, or HLA-mismatched unrelated donors, use of a female donor for a male recipient, grafting with mobilized blood, and older donor and recipient age[3]. cGVHD is classified and severity is graded according to the widely-accepted NNIH consensus criteria[1].The app for the assessment of cGVHD can be accessed at https://www.uzlHYPERLINK "https://www.uzleuven.be/egvhd"euven.be/egvhd.

TABLE 1: GVHD prophylaxis regimens, with levels of evidence and grades of recommendation

TYPE OF ALLO-HSCT	PROPHYLAXIS REGIMEN	LEVEL OF EVIDENCE
MA allo-HSCT from matched related and matched and mismatched 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 PTCy (50 mg/kg on D+3 and D+4) 20–29 (for adults)	Level 2b, grade of recommendation C Level 3b, grade of recommendation B Level 2b, grade of recommendation B
RIC and NMA allo-HSCT	Calcineurin inhibitor and MMF30 PTCy (50 mg/kg on D+3 and D+431,32 (for adults)	Level 4, grade of recommendation C Level 2b, grade of recommendation B Level 1b, grade of recommendation A
HLA-identical allo-HSCT from related and unrelated donors using PBSC as stem cell source	Rabbit Antithymocyte Globulin (rATG) < 6 mg/kg33–40	Level 1a, grade of recommendation A
Haploidentical allo-HSCT – Baltimore protocol	High-Dose PTCy (50 mg/kg on D+3 and D+4) plus a calcineurin inhibitor and MMF41–43	Level 2b, grade of recommendation B
Haploidentical allo-HSCT – Beijing protocol	High-Dose rATG (10 mg/kg), MMF, calcineurin inhibitor, and MTX44	Level 2b, grade of recommendation B

Legend: GVHD: graft-versus-host disease; allo-HSCT: allogeneic hematopoietic stem cell transplant; MA: myeloablative; PTCy: post-transplant cyclophosphamide; NMA: non-myeloablative; RIC: reduced-intensity conditioning; HLA: human leukocyte antigen; PBSC: peripheral blood stem cells.

TABLE 2: First-line therapy for grade I-IV aGVHD, with levels of evidence and grades of recommendation

GRADE	TREATMENT	LEVEL OF EVIDENCE
I	Optimize prophylaxis regimen, adjust calcineurin inhibitor trough levels, add topical agents (corticosteroids or tacrolimus). No systemic immunosuppression is recommended45	Level of evidence 1b, grade of recommendation A
IIa (less severe forms)	Start MP 0.5-1mg/kg/day, escalating up to 2 mg/kg if worsening occurs after 72h46. Concomitant calcineurin inhibitor (cyclosporine or tacrolimus) prophylaxis should not be withdrawn Non-absorbable glucocorticoids (beclomethasone and budesonide) for mild upper or lower GI aGVHD (500-1000 ml/stool output/day) as an adjuvant to systemic corticosteroids47,48	Level of evidence 1b, Grade of recommendation A Level of evidence 1b, Grade of recommendation A
II-IV	Start MP 2mg/kg/day or its prednisone equivalent49. Concomitant calcineurin inhibitor (cyclosporine or tacrolimus) prophylaxis should not be withdrawn	Level of evidence 1a, Grade of recommendation A

Grade IIa: any combination that includes rash covering < 50% of the body surface area (BSA) and not progressing rapidly within the first 6-24 hours, anorexia, nausea, emesis or diarrhea < 1 L day (children < 20 mL/kg/day), and absence of liver involvement (bilirubin < 2 mg/dL in the absence of either hepatic complications or < 3 mg/dL if hepatic complications other than GVHD are present); mild GVHD confined to the skin which involves < 50% of the total BSA not rapidly progressing does not usually require treatment with prednisone50.

Legend: aGVHD: acute graft versus host disease; MP: methylprednisolone; GI: gastrointestinal.

TABLE 3: cGVHD indication for Systemic Treatment1 - Level of evidence 2b, Grade of recommendation B

GLOBAL SEVERITY	HIGH RISK FOR MORTALITY*	SYSTEMIC TREATMENT
Mild	No	No
Mild	Yes	Yes#
Moderate	No/Yes	Yes
Severe	No/Yes	Yes

* Platelets <100,000/mm3 or receiving steroids at time of diagnosis of cGVHD

The benefits of graft-vs.-tumor effect and the risk of cGVHD need to be weighed

TABLE 4: First-line therapy of cGVHD, with levels of evidence and grades of recommendation

Treatment	Level of evidence
Standard treatment consists of prednisone at a dose of 1mg/kg/day and cyclosporine2,51	Level of evidence 1c, Grade of recommendation A

Legend: cGVHD: chronic graft-versus-host disease.

Criteria for initiating systemic treatment for cGVHD: 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)52

TABLE 5: Definition of steroid refractoriness or resistance, steroid dependence, and steroid intolerance for aGVHD and cGVHD5 - Level of evidence 5, Grade of recommendation D

	AGVHD	CGVHD
Refractoriness or resistance	Progression of aGVHD within 3–5 days of therapy onset with ≥2 mg/kg/day of prednisone OR failure to improve within 5–7 days of treatment initiation OR incomplete response after >28 days of immunosuppressive treatment including steroids	cGVHD progression while on prednisone at ≥1 mg/kg/day for 1–2 weeks OR stable GVHD while on ≥0.5 mg/kg/day of prednisone for 1–2 months
Dependence	Inability to taper prednisone below 2 mg/kg/day OR recurrence of aGVHD activity during steroid tapering	Inability to taper prednisone below 0.25 mg/kg/day in at least two unsuccessful attempts separated by at least 8 weeks
Intolerance	Emergence of unacceptable toxicity due to the use of corticosteroids	

Legend: aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host disease.

TABLE 6: Second-line therapy for grade II-IV aGVHD, with levels of evidence and grades of recommendation

MMF	Level of evidence 2b, Grade of recommendation C53–56	Complete Response (CR) and Partial Response (PR) rates of up to 77% in 6 months.
Extracorporeal Photopheresis	Level of evidence 2a, Grade of recommendation B57–68	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 C69,70	ORR between 20% and 50%, particularly in aGVHD of the skin
Basiliximab	Level of evidence 2b, Grade of recommendation B71,72 Response rates of approximately 80%, with an overall survival of 30% at 5 years	
Infliximab and Etarnecept	Level of evidence 2b, Grade of recommendation C73	ORR of approximately 70%, particularly in aGVHD of the gut
Ruxolitinib	Level of evidence 1b, Grade of recommendation A74–79	REACH2* phase III study showed an ORR of 62% at 28 days, compared to a 39% ORR in the control group
Mesenchymal Stromal Cell infusion	Level of evidence 2c, Grade of recommendation B80	ORR 50%; the estimated probability of survival at 2 years was 17.4%.

Legend: MMF: mycophenolate mofetil; ATG: antithymocyte globulin; aGVHD: acute graft-versus-host disease.

TABLE 7: Second-line therapy of cGVHD, with levels of evidence and grades of recommendation

Extracorporeal Photopheresis	Level of evidence 1b, Grade of recommendation A67,81–85	Mucocutaneous manifestations, with complete response (CR) rates of > 80% and significant improvement of sclerotic cGVHD.
MMF	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 B91– 93	Mucocutaneous and musculoskeletal manifestations, with an ORR of approximately 70%
Imatinib	Level of evidence 2b, Grade of recommendation B93, 94	Cutaneous, ocular, and gut manifestations, with an ORR between 50% and 80%
Methotrexate	Level of evidence 4, Grade of recommendation B95, 96	ORR varying between 58.8% and 71% in most case series
Ibrutinib	Level of evidence 2b, Grade of recommendation B97, 98	ORR of 67%, with a 21% CR rate
Ruxolitinib	Level of evidence 1b, Grade of recommendation A99	ORR of 49.7% vs 25.6% for ruxolitinib and controls, respectively (odds ratio, 2.99; P<0.001); longer median failure-free survival for ruxolitinib than control, >18.6 months vs. 5.7 months (hazard ratio, 0.37; P<0.001), and higher symptom response, 24.2% vs. 11.0% (odds ratio, 2.62; P = 0.001).
Belumosudil	Level of evidence 2b, Grade of recommendation B100	ORR for belumosudil 200 mg daily x 200 mg twice daily was 74% (95% CI, 62-84%) and 77% (95% CI, 65-87%); symptom reduction with belumosudil 200 mg daily and 200 mg twice daily was 59% and 62%, respectively.

Legend: cGVHD: chronic graft-versus-host disease; MMF: mycophenolate mofetil.

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CONSENSUS UPDATE

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. Dermatological Support Therapy for Cutaneous GVHD 9

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 required[1], 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]

- Preventive 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.

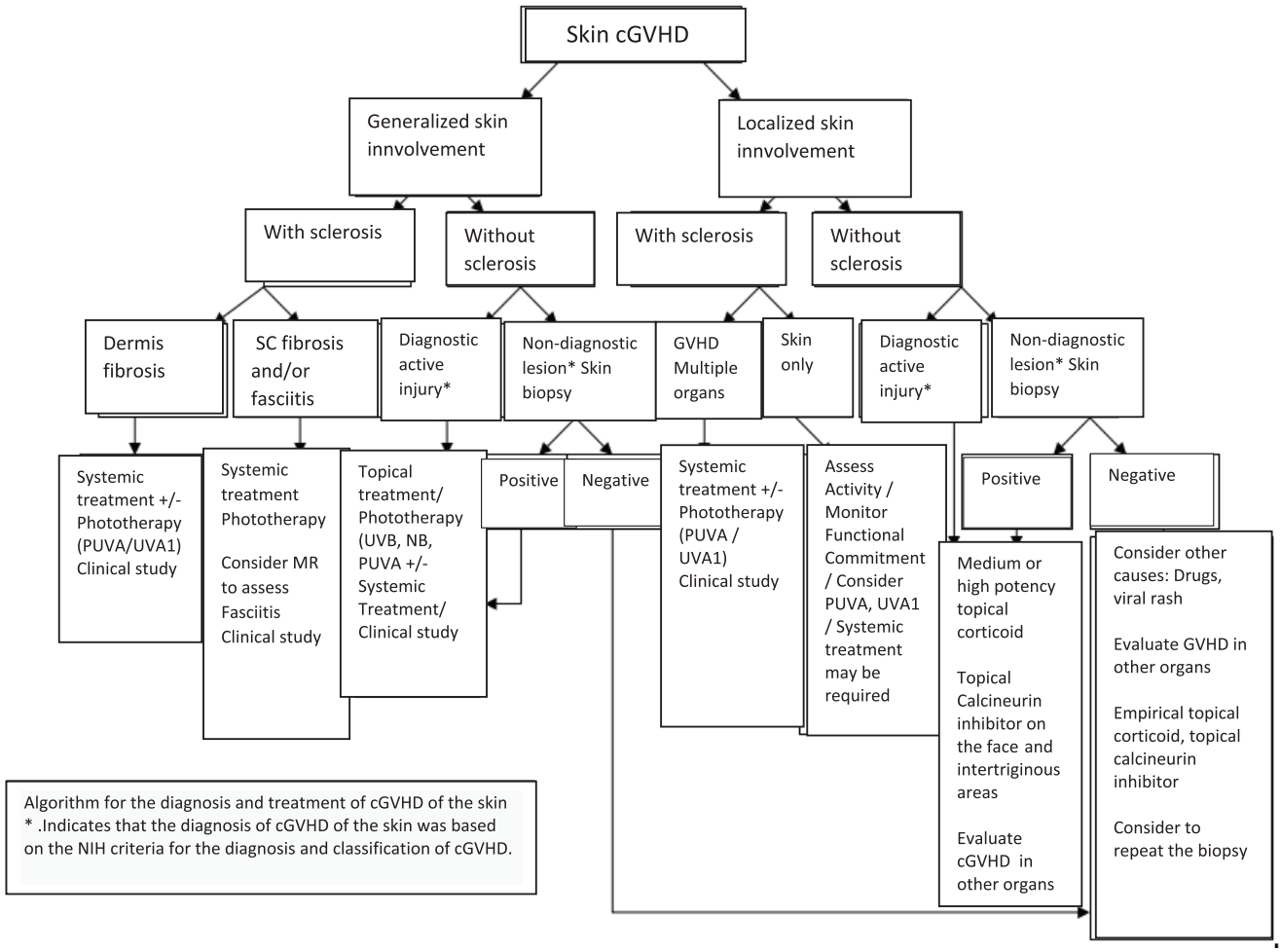
- Direct skin therapy (DST)

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

FIGURE 2. Algorithm for the diagnosis and therapeutic orientation of cutaneous GVHD 9



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].

TOPICAL 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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CONSENSUS UPDATE

RECOMMENDATIONS FOR SCREENING AND MANAGEMENT OF ENDOCRINOPATHIES AFTER PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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ABSTRACT

Endocrine disorders after pediatric hematopoietic stem cell transplantation result from the interaction between the underlying disease, host characteristics and treatment, including exposure to pre- and peri-transplant agents (chemotherapy and radiotherapy). In addition, post-transplantation factors, including graft-versus-host disease, and its treatment, especially glucocorticoids, also contribute to hormone deficiencies or endocrine disorders. Endocrinological alterations can be divided into six main groups: 1) Growth disorders; 2) Thyroid diseases; 3) Gonadal dysfunction; 4) Adrenal failure; 5) Osteometabolic disorders; 6) Obesity and metabolic syndrome. The purpose of this article is to update screening recommendations and management approaches for the various endocrine diseases, defining populations at risk, recommendations during follow-up, and treatment strategies, with attention to controversial issues.

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 disorders after pediatric hematopoietic stem cell transplantation (HSCT) result from the synergistic interaction between the underlying disease, host characteristics, exposure to pre- and peri-HSCT factors (chemotherapeutic agents, conditioning and radiotherapy regimen, RT) and post-HSCT factors, including graft-versus-host disease (GVHD) and its treatment.[1-4]

Endocrinopathies are the most frequent late effects associated with HSCT, with almost 60% of those affected having had HSCT before 10 years of age, and onset between 0.8 to 9.5 years after HSCT. They are divided into six main groups: 1) Growth disorders; 2) Thyroid diseases; 3) Gonadal dysfunction; 4) Adrenal failure; 5) Osteometabolic disorders; 6) Obesity and metabolic syndrome.[1-4]

The goal of this paper is to present, in Tables 1 and 2 (attached), a summary of the recommendations of the 2020/2021 Consensus[1], with revised aspects, supported by retrospective studies and international guidelines, and/or experience with non-transplanted patients, in order to define populations at risk and management strategies for the follow-up and treatment of endocrinopathies after HSCT, with attention to controversial issues.[4-10]

TABLE 1 - Screening recommendations for endocrinopathies after pediatric hematopoietic stem cell transplantation (HSCT)

Endocrinopathy	Related treatments	Population at risk	How to do the screening?	Frequency
Growth disturbances	Cranial RT TBI Glucocorticoid	Growing phase and exposed to the related treatments	Clinic: height, BMI, growth velocity, target height, Tanner stage Imaging: bone age Laboratory: FT4 and TSH, GH/IGF-1axis	Every 6 months
Thyroid diseases	Cervical RT Cranial and/or craniospinal RT TBI	Exposed to the related treatments	Clinic: thyroid palpation Laboratory: FT4 and TSH Imaging: thyroid US (controversial)	Yearly, start 1 year after HSCT
Gonadal dysfunction	Cranial and/or pelvic/ testicular RT TBI Alkylating drugs Heavy metals	Exposed to the related treatments	Clinic: Tanner stage Laboratory: Female > 12-13 years: E2, LH, FSH Male > 13-14 years: T, LH, FSH Semen analysis (fertility)	Yearly
Adrenal failure	Glucocorticoid Cranial RT	Exposed to high and prolonged glucocorticoid doses (GVHD) Cranial RT (rare)	Clinic: fatigue, anorexia, nausea, vomiting, weight loss, hypotension Laboratory: hyponatremia, hyperkalemia and hypoglycemia	After glucocorticoid therapy discontinuation and cranial RT (yearly)
Osteometabolic disturbances	Cranial RT and/or TBI Glucocorticoid Metotrexate Calcineurin inhibitors	All survivors	Bone mineral density (DXA)	Start 1 year after HSCT Repeat according to detected alteration
Obesity and metabolic syndrome	Cranial RT TBI	All survivors	Clinic: BMI, circumferences and blood pressure Laboratory: glucose, insulin, HOMA1-IR, glycated hemoglobin (HbA1c), lipids	Clinic: yearly Laboratory: every 2 years. If alteration, individualize each case

Abbreviations: RT: radiotherapy; TBI: total body irradiation; BMI: body mass index; FT4: free thyroxin; TSH: thyroid-stimulating hormone; GH: growth hormone; IGF-1: insulin-like growth factor 1; US: ultrasound; E2: estradiol; LH: luteinizing hormone; FSH: follicle-stimulating hormone; T: total testosterone; GVHD: graft-versus-host disease; DXA: dual energy x-ray absorciometry; HOMA1-IR: homeostase model assessment-insulin resistance. Adapted from van Iersel et al., 2021; Paetow et al., 2020 and Chow et al., 2016.

TABLE 2 - Management of endocrinopathies after hematopoietic stem cell transplantation (HSCT)

Endocrinopathy	General considerations	Complementary exams	How to treat?	Observations/controversies
GH deficiency	Investigate nutritional and pubertal disorders, or hypothyroidism Spinal RT: measure sitting height Pubertal spurt poor (limited trunk growth)	Bone age FT4 and TSH GH stimulation tests IGF-1	rhGH replacement after discussion of risks and benefits with oncologist and family	Recurrence and second malignancy No strategy improves pubertal growth No recommendation for short stature and non-GH deficient children
Hypothyroidism	Investigate graft donor-related autoimmune disease	FT4 and TSH Antithyroid antibodies	Sodium levothyroxin in overt hypothyroidism (TSH > 10 mIU/L)	There is no recommendation for treatment of borderline TSH (5-10 mIU/L) with normal FT4 Thyroid cancer risk
Thyroid cancer	Thyroid nodules or cervical lymph nodes in a thyroid exposed to RT Therapeutic 131-I-MIBG	US-guided fine needle aspiration (FNA) of suspicious nodule	Equal to thyroid cancer in the general population: thyroidectomy and therapeutic iodine if necessary	US in screening for nodules is controversial
Ovarian failure	Age of onset and progression of puberty, menstrual history, and libido Ovary poorly resistant to drugs and RT (hormonal and germ portions are equally impaired) Precocious menopause	E2, FSH, LH	E2 to induce puberty (adolescents) and improve bone, heart and psychological health in young adults Discuss fertility preservation: specialist services	Hormone replacement: transdermal route if thrombosis No increased risk of relapse or breast cancer Fertility preservation in prepubescent still limited
Male hypogonadism	Age of onset and progression of puberty, signs of hypoandrogenism Testicle is compartmentalized: Leydig is more resistant than Sertoli Alkylating drugs impair testis growth (germ epithelium)	T, LH (Leydig function indicates hormone production) FSH (Sertoli function indicates fertility) Sperm analysis (fertility, if desired)	Many male presents with spontaneous puberty and satisfactory hormone production despite infertility (Leydig function more resistant than Sertoli) Discussion of fertility preservation	T concentration that indicates replacement still controversial, consider if T < 300 ng/dL Fertility preservation in prepubescent still limited
Adrenal failure	Chronic fatigue, weakness, anorexia, nausea, vomiting, weight loss, postural hypotension, hyponatremia, hypokalemia, and hypoglycemia	Cortisol, ACTH and/or ACTH stimulation test	Discontinuation of prolonged high-dose glucocorticoid therapy should be gradual Consider "stress dose" during acute illness	Adrenal function usually recovers once exogenous glucocorticoid therapy is discontinued, but recovery time is variable
Low bone mineral density	Nutritional status and lifestyle Rule out hormone deficiency (hypogonadism and GH deficiency) Effect of medications (glucocorticoid)	25OH vitamin D Calcium, phosphorus, alkaline phosphatase, PTH and renal function DXA	Improve calcium intake and physical activity, encourage sun exposure if possible Vitamin D deficiency and other hormone deficits should be treated	Consider bisphosphonate if: Z-score < -2.0 (child) or T-score < -2.5 (adult), and/or multiple fractures Ideal regimen not yet defined
Obesity and metabolic syndrome	Sarcopenic obesity: assessing body composition and fat distribution Consider atherosclerosis and premature cardiovascular risk (epidemiological) Family history and lifestyle	Blood pressure Glucose, insulin and HOMA1-IR Glycated hemoglobin (HbA1C) Lipids	Healthy lifestyle: food and physical activity	Pharmacotherapy in obesity and insulin resistance Treatment of hypertension and dyslipidemia follows specific consensus

Abbreviations: GH: growth hormone; RT: radiotherapy; FT4: free thyroxin; TSH: thyroid-stimulating hormone; IGF-1: insulin-like growth factor 1; rhGH: recombinant human GH; MIBG: metaiodobenzilguanidine; US: ultrasound; E2: estradiol; LH: luteinizing hormone; FSH: follicle-stimulating hormone; T: total testosterone; ACTH: adrenocorticotropic hormone; PTH: parathyroid hormone; DXA: dual energy x-ray absorciometry; HOMA1-IR: homeostase model assessment-insulin resistance. Adapted from van Iersel et al. 2021; Paetow et al., 2020 and Chow et al., 2016.

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CONSENSUS UPDATE

HEMOTHERAPY SUPPORT IN HSCT

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ABSTRACT

Hemotherapy support is essential for Hematopoietic Stem Cell Transplantation (HSCT). In this article, we highlight the main points published in the 2020 SBTMO consensus and provide a brief update on the topic.

KEY POINTS

MOBILIZATION AND COLLECTION OF PERIPHERAL HEMATOPOIETIC PROGENITOR CELL (HPC)

Standard mobilization: filgrastim (G-CSF) 10 to 20µg/kg/day in one or two administrations for 5 days, with the first collection on day 5.[1]

Alternative mobilization (chemotherapy and G-CSF association): vinorelbine 35 mg/m^2; cyclophosphamide (Cy) 2 to 4 grams/m^2 or etoposide 375 mg.[1]

Rescue mobilization: plerixafor (0.24 mg/kg, 9 to 12 hours before collection) with G-CSF or chemotherapy + G-CSF.[1]

CD34$^+$ cells minimum dose: 2 x 10^6/kg per transplant (target dose of 4 to 5 x 10^6/kg).[1]

High volume apheresis (total blood volume processed more than 4 times patient's blood volume) increases the CD34+ collection.[1]

Pediatric patients with less than 20 kg: prime the apheresis kit with red blood cells and process at least three blood volume.[1]

BONE MARROW HARVEST

Collection target: 10-15 ml/kg of recipient, not exceeding 20 ml/kg of donor.

Recommended cell dose: ≥ 3x10^8/kg of total nucleated cell (TNC) with minimum of 2 x 10^8 TCN/kg.[1]

PROCESSING AND CRYOPRESERVATION OF HPC-A

Cryoprotective solutions: Dimethyl sulfoxide (DMSO) 10% or DMSO 5% + hydroxylamine (HES) 6%, both associated with a protein source.[1]

Final nucleated cell (NC) concentration: 100 to 500 x 10^6 NC/mL.[1, 2]

Freezing ideal rate: temperature reduction from 1 to 2° C per minute in a programmed freezing equipment or mechanical freezer.[1]

Storage: vapor phase or liquid nitrogen tank or mechanical freezer (-80 or -150° C).[1]

TRANSPORT, THAWING AND INFUSION OF HPC

Transport of fresh products kept the temperature between 2 and 24ºC (preferably close to 4ºC).[1]

Transport of cryopreserved products: if the cells were stored in -80º C mechanical freezer kept the temperature at or below - 65°C (dry ice); if the cells were stored in temperature below - 150°C, kept the temperature below -130°C.[1]

Premedication: hydration, diphenhydramine, dipyrone and/or hydrocortisone to prevent allergic, febrile types and/or DMSO-related reactions.[1]

Maximum DMSO volume: 1ml DMSO/Kg patient weight/day to reduce risk of adverse event. In lower weight pediatric patients consider removal of DMSO.[1]

Infusion: Do not use transfusion set device with leukocytes filter. Rate: 10 mL/minute for thawed products and 6mL/Kg of patient weight/hour for fresh products (maximum 4h).[1]

TRANSFUSION SUPPORT

Red blood cells (RBC), platelet and granulocyte concentrates intended for HSCT patients should be **leukoreduced and irradiated**.[1]

Platelet refractoriness: relative common in HSCT. Causes: non-immune (> 80%) or immune (< 20%). Calculation of platelet increment is important to confirm the platelet refractoriness diagnosis.[1]

Granulocyte transfusion is used to prevent (patients with neutropenia or neutrophil function disorders) or treat infections in severe neutropenia (granulocytes < 500/µL) patients. There are no randomized studies that prove its clinical efficacy.[1]

ALLOGENIC BMT WITH ABO INCOMPATIBILITY

Major or bidirectional ABO incompatibility: RBC removal if bone marrow. Measures to reduce the anti-donor circulation isohemagglutinins (donor ABO plasma infusion or therapeutic plasmapheresis) if isohemaglutinin anti-donor ≥ 1:32.[1]

Minor ABO incompatibility: Plasma removal if bone marrow or if HPC-A, isohemaglutinin anti-receptor ≥ 1:256.[1]

ABO blood component support: summarized in table 1.

DONOR LYMPHOCYTE INFUSION (DLI)

Medical evaluation of the donor is mandatory, and the eligibility criteria are the same used for blood donors.[1]

There is no need for any medication to prepare the donor for the collection.[1]

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.[1]

Each apheresis session should process 2 to 2.5 total blood volumes and if the number of cells needed is not obtained, a second procedure can be performed. There is a linear correlation between the number of CD3+ cells collected and the processed blood volume up to 12L.[1, 3]

Dose scheme depends on the type of BMT and disease, but a stagged regimen is recommended.[1]

ANTI-HLA DONOR DESENSITIZATION

The presence of donor-specific anti-HLA antibody with mean fluorescence intensity (MFI) above 2000 is indication of desensitization protocols.[1]

INDICATION OF PHLEBOTOMY IN IRON OVERLOAD POS BMT

Phlebotomy is a therapeutic option to drug treatment in patients with sustained hematopoiesis to reduce liver damage and irreversible tissue damage. It is indicated in cases with ferritin above 2500µg/L and transferrin saturation close to 100%.[1]

During the revision of the chapter published in the SBTMO consensus in 2020[1], we noticed the lack of a guidance on choosing the blood component to be transfused in the recipient undergoing transplantation with ABO incompatibility, which is now summarized in Table 1.[4]

There were few updates on the literature. We emphasize the safe nucleated cells concentration for cryopreservation, which can be up to 500,000 cells/mL after the cryoprotective solution addition.[2]

On the other hand, there have been many advances in Cell Therapy. SBTMO has published a technical manual on the topic that contains specific chapters of lymphocytes collection of by apheresis,[5] cryopreservation and transportation of mononuclear cells,[6] thawing and infusion of CAR-T cells,[7] among others.

At the national level, the current health legislation was updated.[8].

TABLE 1. Recommendation for post-transplantation transfusion support in ABO-incompatible HPC recipients.(4)

			Fase I	Fase II				Fase III
Receptor	Donor	Incompatibility type	All blood components	RBC concentrate	Platelet concentrate		Plasma	All blood components
					1st choice	Other choice		
A	O	Minor	A	O	A	AB; B; O	A; AB	O
B	O	Minor	B	O	B	AB; A; O	B; AB	O
AB	O	Minor	AB	O	AB	A; B; O	AB	O
AB	A	Minor	AB	A	AB	A; B; O	AB	A
AB	B	Minor	AB	B	AB	B; A; O	AB	B
O	A	Major	O	O	A	AB; B; O	A; AB	A
O	B	Major	O	O	B	AB; A; O	B; AB	B
O	AB	Major	O	O	AB	A; B;O	AB	AB
A	AB	Major	A	A	AB	A; B; O	AB	AB
B	AB	Major	B	B	AB	B; A; O	AB	AB
A	B	Bidirecional	A	O	AB	A; B; O	AB	B
B	A	Bidirecional	B	O	AB	B; A; O	AB	A

Phase I: from the beginning of patient preparation to the beginning of conditioning; **Phase II:** from the beginning of conditioning until the direct antiglobulin test becomes negative and the direct typing of the patient becomes the same as the donor; **Phase III:** from the moment when the direct and reverse typing of the patient is the same as the donor.

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