SBTMO

MANUAL OF THE YOUNG TRANSPLANTER

HEMATOPOIETIC CELL TRANSPLANTATION AND CELLULAR THERAPY

FERNANDO BARROSO DUARTE • NELSON HAMERSCHLAK • CARMEM BONFIM

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Summary

EDITORIAL

Dear colleagues and readers

The idea of creating this manual for young transplant specialists is to fill a gap that serves all those who wish to begin the fascinating and challenging world of Hematopoietic Cell Transplantation and Cell Therapy . SBTMO has been running this program for five years and we believe that the excellent training of new professionals, both doctors and multidisciplinary professionals, is one of the pillars of a modern, inclusive society that keeps an eye on the current Brazilian reality, but also plants seeds for the future.

We would like to thank all our colleagues who contributed to this work and who, in doing so, help us confirm the famous phrase from the song by the brilliant composer from Ceará, Belchior: "It is you who love the past and who do not see that the new always comes."

Let's keep going!

Fernando Barroso Duarte, Carmem Bonfim and Nelson Hamerschlak

01
SBTMO – YOUNG PHYSICIAN HANDBOOK - WHAT DOES A YOUNG PHYSICIAN NEED TO KNOW TO PURSUE A CAREER IN HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

MARY E. FLOWERS, MD

INTRODUCTION

Hematopoietic cell transplantation (HCT) presents enormous challenges and requires advance medical training of a multidisciplinary team, financial support (federal, local, private and others) and hospital commitment for this high complex treatment of hematological diseases. When I was invited to write a chapter for this Handbook for Young Transplanters, I asked what would be of interest for young physicians to know about pursuing a career in Hematopoietic cell transplantation (HCT) and cellular therapy. I thought that writing about the steps I took in my own HCT academic career trajectory would be of value as an example that worked for one individual but would fall outside the scope of this Handbook. Therefore, I will list here the elements necessary to pursue a career in HCT and Cellular Therapy, Finally, I end by providing an advised that served me well in achieving a successful life and career as follow:[1]

Below is a list of necessary steps and some of important characteristics to build a career in HCT and Cellular Therapy.

1. A solid medical education including immunology
2. Residence in onco-hematology
3. HCT and immunology training.
4. Be curious
5. Eager to learn more likes
6. Likes to work hard
7. Interested in clinical research in HCT and cellular therapy field
8. Prefers working collaboratively than seeking success solo.
9. Passion for excellence and compassionate patient care

Be always aware of your weakness and strength, work extremely hard and, finally, surround yourself with bright people, but also GOOD people!

For additional Tips for Success As an Academic Clinical Investigator see article by Lee, SJ in JAMA which include surround yourself with people of high ethical standards, skills, work habits and compatibility[1].

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02

MODALITIES OF HEMATOPOIETIC CELL TRANSPLANTATION

CELSO ARRAIS-RODRIGUES

INTRODUCTION

Advances in transplantation techniques and supportive care have improved the safety and efficacy of hematopoietic cell transplantation (HCT). However, selection of the appropriate transplantation modality remains critical to optimizing patient outcomes.

The three primary modalities – allogeneic, syngeneic, and autologous HCT-each offer distinct advantages and challenges.

This chapter examines these modalities, with particular emphasis on allogeneic and autologous HCT, focusing on their advantages, disadvantages, indications, and characteristics.

ALLOGENEIC HCT

Allogeneic HCT involves the infusion of hematopoietic cells from a genetically non-identical donor. Donors may be related (typically a sibling or other family member) or unrelated (selected from donor registries, including both matched and mismatched donors).

This modality is widely used for malignant and severe non-malignant diseases because it exploits the graft-versus-tumor (GVT) effect-a critical immune advantage that can significantly reduce relapse rates[1].

Donor selection is primarily based on human leukocyte antigen (HLA) compatibility. Even minor mismatches can increase the risk of graft-versus-host disease (GVHD), an immune complication that contributes to morbidity while sometimes enhancing the anti-tumor effect. Because only a minority of patients have an optimally related HLA-identical donor, alternative sources – such as haploidentical donors or cord blood units – are increasingly being used to ensure access to transplantation[2]. Conditioning regimens for allogeneic HCT, aimed at eradicating malignant cells while minimizing toxicity, vary widely and will be discussed in subsequent chapters[3,4].

Graft-versus-tumor (GVT) effect

The GVT effect is an immune phenomenon in which donor-derived immune cells, primarily T lymphocytes and natural killer (NK) cells, recognize and eliminate residual malignant cells after transplantation.

While the GVT effect is fundamental to the curative potential of allogeneic HCT, its benefits are often associated with an increased risk of GVHD, as immunosuppressive therapies used to control GVHD can also dampen the GVT response[2].

Graft-versus-Host Disease (GVHD)

GVHD is a potentially life-threatening complication that occurs when donor immune cells, particularly T lymphocytes, recognize the recipient's tissues as foreign and mount an immune attack. Prevention and management strategies for GVHD include careful donor selection, prophylactic immunosuppressive regimens, and novel approaches such as selective depletion of alloreactive T cells[5,6].

A major clinical challenge in allogeneic HCT is to balance the beneficial GVT effect with the deleterious consequences of GVHD. Overlapping donor immune cells mediate both responses, prompting the investigation of strategies that selectively enhance GVT while minimizing GVHD. These include in vitro T-cell depletion to remove or inactivate alloreactive T cells while preserving those responsible for anti-tumor activity, the use of post-transplant cyclophosphamide to reduce alloreactive T cells without significantly compromising the GVT effect, and the use of

novel immunomodulatory therapies targeting inflammatory pathways to preserve or enhance the GVT response while controlling GVHD.

In addition to GVHD, patients undergoing allogeneic HCT are at significantly increased risk of opportunistic infections compared to patients receiving autologous or syngeneic transplants. This increased susceptibility is due to the profound immune reset and extensive immunosuppressive therapy required to prevent and control GVHD. Long-term follow-up and comprehensive supportive care - including prophylactic antimicrobial regimens - are essential to manage these risks and improve outcomes. Despite these challenges, the potential curative effect of allogeneic HCT makes it a cornerstone in the treatment of high-risk hematologic malignancies[1-3].

KEY POINTS FOR ALLOGENEIC HCT:

• Advantage of the GVT effect, in which donor T cells and NK cells eliminate residual cancer cells through antigen recognition and cytotoxic activity.

• Risk that donor-recipient differences may induce acute or chronic GVHD, increasing morbidity and mortality.

• High risk for opportunistic infections due to immune reset and intensive immunosuppression.

2. Syngeneic HCT

Syngeneic HCT is the modality in which transplantation is performed with cells from an identical twin, virtually eliminating the risk of GVHD due to complete HLA matching. However, the same genetic identity also precludes the occurrence of a graft-versus-tumor (GVT) effect. While syngeneic HCT is very rarely performed due to the scarcity of monozygotic twins, its outcomes have been evaluated in specific clinical contexts.

Syngeneic HCT could serve as an alternative to autologous HCT for selected patients in whom autologous stem cell collection has failed. However, due to the lack of GVT effect, syngeneic HCT is not considered a reasonable substitute for allogeneic HCT in malignancies where the anti-tumor benefit of GVT effect is critical to reduce relapse rates[5,6,7].

3. Autologous HCT

Autologous HCT uses the patient's own hematopoietic cells, eliminating donor incompatibility and the risk of GVHD. It is primarily used to treat certain **lymphomas**, multiple myeloma and other malignancies for which high-dose chemotherapy is a mainstay of treatment. Cells are collected from the patient prior to the administration of high-dose chemotherapy and are later reinfused[4].

Although this approach carries virtually no risk of immune complications, it may be associated with a higher risk of disease relapse due to the lack of GVT effect. High-dose chemotherapy is used to achieve maximum disease eradication prior to reinfusion. This approach is necessary to overcome chemoresistance, although it is associated with significant toxicity[1], with the main risks being chemotherapy- and/or radiotherapy-related, such as infections, organ toxicity, and relapse of the primary disease.

The lack of GVT effect is a critical limitation of autologous HCT, often requiring close post-transplant monitoring and maintenance strategies.

KEY POINTS FOR AUTOLOGOUS HCT

• Eliminates donor-related immune complications.

• High-dose regimens allow for disease control but increase treatment-related toxicity.

• Relapse remains a significant concern due to the absence of a graft-versus-tumor effect.

4. Comparative Overview and Considerations

There are several key factors to consider when selecting the appropriate modality for HCT:

Disease Characteristics: The biology of the disease often dictates whether GVHD is necessary

(favoring allogeneic HCT) or whether the risks of GVHD can be avoided with autologous HCT.

Patient Factors: Age, comorbidities, and overall performance status play a critical role in selecting a conditioning regimen and assessing the risk of complications.

Donor Availability: While syngeneic HCT is limited to identical twins, the feasibility of allogeneic HCT depends on the availability of a suitable matched of mismatched donor.

Long-Term Outcomes: Allogeneic HCT offers potential curative benefits but must be balanced against the risks of GVHD and mortality. Autologous HCT minimizes immune risks but may result in a higher relapse rate.

CONCLUSION

Selection of the appropriate modality for hematopoietic cell transplantation is a nuanced process that must be individualized according to the patient's disease characteristics, donor availability, and overall health status. Allogeneic HCT is particularly beneficial for patients who require GVT effects, whereas autologous HCT is indicated for patients who require intensive chemotherapy. As advances in supportive care and conditioning protocols continue to evolve, careful tailoring of HCT modalities will remain a critical component in improving patient outcomes.

TABLE 1: Comparison of Hematopoietic Cell Transplantation Modalities

MODALITY	DONOR	GVHD RISK	RELAPSE RISK
Allogeneic HCT	HLA-matched or mismatched donor (non-twin)	High	Lower *(GVT effect)*
Syngeneic HCT	Identical twin	Negligible	Higher
Autologous HCT	Self	None	Higher

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03
HEMATOPOIETIC STEM CELL SOURCES

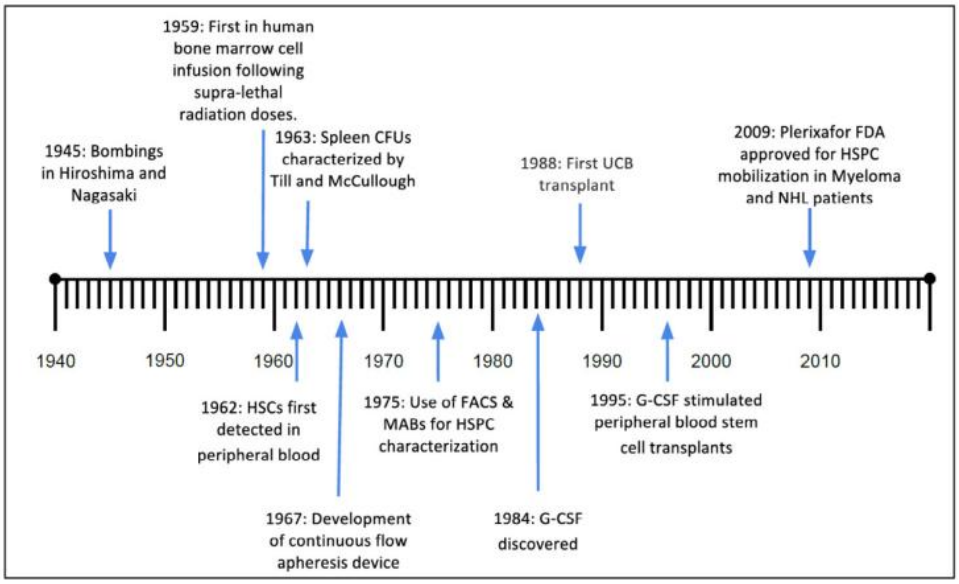
EDUARDO JOSÉ DE ALENCAR PATON
MARCOS DE LIMA

The choice of a hematopoietic stem cell source is crucial to an allogeneic hematopoietic cell transplant (HCT). The interest for hematopoietic stem cells (HSCs) began at the end of world war II, following the bombings in Hiroshima and Nagasaki in 1945 when studies of the biologic effects of radiation began. Since then bone marrow (BM) was identified as the source of cells capable of engraftment and hematopoietic recovery after radiation exposure. Those hematopoietic stem cells (HSC) are in charge of blood cell production (hematopoiesis) during the life spam of an organism. HSCs are, by definition, pluripotentials, one single HSC is able to generate each of different functional haematopoietic and immune cell types. Specific genes are involved in the maintenance, or self-renewal of HSCs and in the formation of each specific haematopoietic lineage.: from red cells that are responsible for oxygen transport; megakaryocytes and its cytoplasm fragments, the platelets, that interact with blood vessels and coagulation factors to promote clotting; and the cells of the immune system that are active against microbial infections. In the embryo, hematopoiesis begins in the aorto-gonadomesonephros region and then shifts to the fetal liver, and subsequently to the bone marrow, where HSCs will reside for the life of the mammalian organism.

As Prof. Dr. Robert Peter Gale elegantly hypothesized: "unlike aquatic organisms whose haematopoietic cells are largely shielded from environmental radiations by the water those of adult terrestrials are predominately in the bone marrow cavity. This translocation coincides with time when fully terrestrial organisms first appeared. Hematopoietic cells are among the most sensitive to damage from exposure to ionizing radiations and when vertebrates moved from sea to land radiogenic DNA damage rates were >20 percent higher than now. Placing haematopoietic stem cells in the bone marrow cavity reduces radiation exposure by 10–40 percent. Consequently, it seems reasonable to hypothesize this translocation might be driven by the radiation shielding provided by bone and overlying tissues".

Bone marrow (BM) was the stem cell source since the first successful allogeneic HCT in 1968 and remained the only source of stem cells for the two decades that followed until experimental work demonstrating that peripheral blood (PB) stem cells can be enriched by pretreatment with certain chemotherapy agents and haematopoietic growth factors that resulted in the first peripheral blood stem cell transplant in 1986. In parallel, the recognition of cord blood (CB) as a rich source of stem cells led to the successful use of cord blood as a third stem cell source in allogeneic HCT in the late 80s (Figure 1).

FIGURE 1: clinical cellular therapy. FACS indicates fluorescence-activated cell sorting; MABs, monoclonalantibodies; FDA, US Food and Drug Administration; NHL, non-Hodgkin lymphoma. S.R. Panch et al. / Biol Blood Marrow Transplant 23 (2017) 1241–1249



The advantages and disadvantages for both the patient and donor as well as specifc disease-related considerations must be taken when selecting the most appropriate stem cell source for HCT.

The use of bone marrow (BM) as HSC source is advantegeous in the non malignant diseases HCT indications due to its less T lymphocytes content that results in less GVHD and more powerful graft-versus-tumour (GVT) effect is not required. BM is also the preferred source from pediatric donors, although successful harvest by bone aspiration requires hospitalization and general anesthesia.

Peripheral blood (PB) has become, in the last twenty years, the preferred HSC source and has clear advantages over BM, notably, an increased number of CD 34 + (HSC marker) and CD 3 + (T lymphocytes marker) cells, allowing fast engraftment and more powerful GVT effect and, although associated with higher rates of GVHD than BM, is the main HSC source when treating malignant diseases especially in reduced intensity conditioning (RIC) transplant . PB HSC can be subject of manipulations such as enrichment ou depletion of cells subsets that allow more stable graft function, increased GVT without concomitant increased GVHD rates and even faster immunological recovery preventing post transplant opportunistic infections.

Umbilical cord blood were a common and frequent HSC source until the development of haploidentical transplants, with a less degree of HLA compatibility demand, lower GVHD rattes due to lower immuogenicity of of newborn's alloreactive imune cells, preserved GVT power, counterbalanced by its slower imune recovery and consequently emergence of opportunistic infections and a higher transplant related mortality rate. Table 1 shows the different characteristics of each HSC source and table 2 shows the diferences in the composition of the diferente sources.

TABLE 1: Sources of HSPC an their characteristics

	PB	BM	Cord Blood
Donor characteristics			
Transplant donor type	Haploidentical donor,* MSD, MUD	Haploidentical donor, MSD, MUD	MUD
Collection risk†	Apheresis related severe adverse events ~1/1000	Surgical risk (severe adverse events) ~1/100	Postdelivery Absent/none reported
Graft characteristics			
Relative CD34 content	50×	10×	1×
Relative T cell content	100×	10×	1× (naive T cells)
Minimum cell dose for engraftment‡	Autologous: 2×10^6 $CD34^+$ cells/kg Allogeneic: 4×10^6 $CD34^+$ cells/kg	Same as for PB grafts	Single cord: 2.5×10^7 TNC/kg Dual cord: 1.7×10^7 TNC/kg/cord unit
Collection volume, mL	~300	~1000	~100
Relative graft procurement cost§	~2×	~2.3×	~1-2×
HLA matching criteria‖	6/6 (MSD) 7/8 (haploidentical donor) 8/8-12/12 (MUD)	Similar to PB	4-6/6
Recipient characteristics			
Disease type	Preferred source for malignant disease¶	Preferred source for non-malignant disease	Used for either
Speed of engraftment	Faster	Moderate	Slower
Anti-tumor effect	Higher	Lower	Higher
Acute/chronic GVHD risk	Higher	Moderate	Lower

TABLE 2: differences in the composition of the different sources.

	Peripheral blood (×10⁶/kg)	Bone marrow (×10⁶/kg)	Ratio of PB to BM
CD34	7.3	2.4	3
CD3	701	49	14
TCR α/β	663	42	14
TCR γ/δ	26	2	13
$CD3^+CD4^+$	393	26	15
$CD4^+CD45RA^+$	188	11	17
$CD4^+CD45RO^+$	169	10	17
$CD3^+CD8^+$	236	18	13
$CD3^+CD4^-CD8^-$	45	5	9
$CD19^+$	93	15	6
$CD16^+CD56^+CD3^-$	77	6	13
$CD45^+CD14^+$	599	25	24

Adapted from Körbling and Ottinger (Körbling and Anderlini 2001)

Several studies (Table 3) support the slightly benefits of PB over BM in malignant diseases HCT indications.

Currently, PB HSC yields allow graft manipulations such as depletion or enrichment of cells subsets to improve engraftment rates and GVT effect, decrease GVHD rates and even accelarate immunological recovery to prevent opportunistic infections as show in table 4.

TABLE 3: Studies comparing HSC sources outcomes

	Peripheral blood	Bone marrow	*P*-value
SCTCG meta-an, 1:1. HLA id sib (S.C.T.C Group 2005)	*N* = 538	*N* = 554	
Neutrophil engraftment (days)	14	21	<0.001
Platelet engraftment (days)	14	22	<0.001
Acute GVHD (%)	41	38	0.5
Grade III/IV acute GVHD (%)	26	21	0.03
Chronic GVHD (%)	73	56	0.01
Extensive GVHD (%)	51	35	0.01
3-Year NRM (%)	16	25	0.04
3-Year relapse (%)	21	27	0.01
3-Year DFS (%)	59	53	0.02
3-Year OS (%)	62	59	0.17
Holtick meta-an, Rel and URD (Holtick et al. 2015)	*N* = 653	*N* = 677	
Neutrophil engraftment (days)	16	20	<0.001
Platelet engraftment (days)	13	19	<0.001
Acute GVHD (HR)	Reference	1.03	0.67
Grade III/IV acute GVHD (HR)	Reference	0.75	0.07
Chronic GVHD (HR)	Reference	0.72	<0.001
Extensive GVHD (HR)	Reference	0.69	0.006
NRM (HR)	Reference	0.98	0.91
Relapse (HR)	Reference	1.3	0.07
DFS (HR)	Reference	1.04	0.6
OS (HR)	Reference	1.07	0.43
Anasetti. RCT. MA. UD (Anasetti et al. 2012)	*N* = 273	*N* = 278	
Neutrophil engraftment (days)	Reference	5 days later	0.001
Platelet engraftment (days)	Reference	7 days later	0.001
Engraftment failure (%)	3	9	0.002
Acute GVHD (%)	≈50	≈50	NS
Chronic GVHD (%)	53	41	0.01
Extensive GVHD (%)	48	32	0.001
2-Year NRM (%)	≈25	≈25	0.66
2-Year relapse (%)	≈30	≈30	0.74
2-Year DFS (%)	≈45	≈45	0.38
2-Year OS (%)	≈50	≈50	0.33
Savani. Registry. RIC (Savani et al. 2016)	*N* = 9011	*N* = 837	
Neutrophil engraftment (days)	16	20	<0.001
Acute GVHD (%)	24	17	0.005
Chronic GVHD (%)	36	29	<0.001
2-Year NRM (%)	20	18	0.19
2-Year relapse (%)	35	43	<0.001
2-Year DFS (%)	44	39	0.009
2-Year OS (%)	50	47	0.05
Ruggeri. Registry. Haplo donor (Ruggeri et al. 2018)	*N* = 191	*N* = 260	
Neutrophil engraftment (days)	17	18	0.001
Acute GVHD (%)	38	21	0.01
Grade III/IV acute GVHD (HR)	14	4	0.01
Chronic GVHD (%)	32	36	0.28
2-Year NRM (%)	23	23	0.61
2-Year relapse (%)	22	26	0.38
2-Year DFS (%)	54	49	0.39
2-Year OS (%)	56	55	0.57
2-Year GRFS	43	44	0.82
Simonin. Registry. Paediatrics. (Simonin et al. 2017)	*N* = 719	*N* = 1743	
Neutrophil engraftment (days)	16	19	0.001
Acute GVHD (odd ratio)	Reference	1.07	0.55
Chronic GVHD (%)	44	21	<0.001
3-Year NRM (%)	20	12	0.002
3-Year relapse (%)	26	29	0.29
3-Year DFS (%)	54	59	<0.001
3-Year OS (%)	62	67	<0.001

Meta-an Meta-analysis, *Sib* Sibling, *Rel* Related, *UR* Unrelated, *NS* Not significant, *MA* Myeloablative, *RIC* Reduced intensity conditioning

TABLE 4: PB HSC manipulation

CD34 enrichment yields stem cell prep- arations with low contaminating T- and B-cells.
CD3/CD19 depletion preserves large numbers of NK cells in the grafts. TCR a αß/CD19 depletion provides large numbers of NK cells and y8 T cells with very low amounts of TcRaß T-cells. DLI with CD45RA-depleted T-cells might reduce the risk of GvHD. Donor regulatory and conventional T-cell adoptive immunotherapy with no post-transplant immune suppression provide low incidence of leukemia relapse and chronic GVHD when employed together with a CD34+ selected graft.
Virus antigen-specific donor- or third- party-derived T-cells can be utilized post-transplant in patients with therapy- refractory viral infections.

The choice of HCT sources depends on several factors such as type of disease, donor and receptor ages, donor venous access, donor cirurgical risk and mainly donor willing.

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04
WHAT SHOULD WE KNOW ABOUT HLA TO SELECT THE BEST DONOR?

ALBERTO CARDOSO MARTINS LIMA
MARGARETH AFONSO TORRES

KEY POINTS

• The HLA Laboratory provides histocompatibility testing and donor selection consultation to HCT programs.

• DSA evaluation is essential in all HLA-mismatched HCT and must consider complete donor's typing at 11 HLA loci.

• HLA mismatching and HLA-DPB1 permissiveness impact HCT differently depending on whether CNI-based or PTCy-based GVHD prophylaxis is used.

INTRODUCTION: HLA SYSTEM IN ALLOGENEIC HCT

The Human Leukocyte Antigen (HLA) system is crucial in allogeneic hematopoietic cell transplantation (HCT)[1]. This complex is the most polymorphic genetic system in humans and is divided into classes I, II, and III. The class I region includes the *HLA-A*, *-B*, *and -C* genes, while class II region contains the *HLA-DRB1*, *-DRB3/4/5*, *-DQA1*, *-DQB1*, *-DPA1*, and *-DPB1* genes. In the HCT setting, the *HLA-A*, *-B*, *-C*, *-DRB1*, *-DQB1*, and *-DPB1* loci are defined as the classical histocompatibility genes, as they can trigger intense bidirectional alloreactive responses in host-versus-graft and graft-versus-host directions, thus presenting as graft rejection and acute and chronic graft-versus-host disease (GVHD), respectively[1].

For this reason, a 12/12 HLA-matched sibling donor (MSD) is traditionally considered the optimal donor for HCT, as it generally yields the best survival outcomes[2]. According to classical Mendelian genetics, there is only a 25% likelihood that a patient will have an MSD. Hence, for patients without an MSD, alternative donor options are available, including matched unrelated donors (MUD), mismatched unrelated donors (MMUD), umbilical cord blood (UCB) units, and haploidentical donors[2].

In this context, the HLA laboratory offers expert consultation and histocompatibility methods, including HLA typing, HLA antibody testing, and chimerism analysis, to support clinical teams in choosing the optimal donor and enhance post-HCT monitoring[3,4].

HISTOCOMPATIBILITY METHODS

HLA Typing

HLA typing can be performed using DNA-based methods, including sequence-specific oligonucleotides, sequence-based typing (SBT), and next-generation sequencing (NGS)[1]. These methods differ in resolution, with NGS providing up to 11-loci results simultaneously at the highest resolution. This cutting-edge method sequences the full length of HLA genes, including exons,

introns, and untranslated regions, thus providing optimal resolution. Consequently, NGS replaced SBT as the new gold standard for HLA typing in HCT.

The name of an HLA allele consists of up to eight digits (for example, *A*02:01:01:01*), which are separated into up to four sets by the presence of a colon (:), which serves as field delimiters and are detailed below[1]:

The first two digits (first field) describe the allelic group and are called "low-resolution" typing.

The third and fourth digits (second field) include specific alleles with one or more amino acid substitutions in the antigen recognition domain (ARD). An HLA typing considering the third and fourth digits is called "high-resolution" typing.

The fifth and sixth digits (third field) include alleles that differ by synonymous substitutions.

The seventh and eighth digits (fourth field) include alleles that differ only by differences in introns and the 5' and 3' untranslated regions. An HLA typing considering the eight digits is called "allelic resolution" typing.

In allogeneic HCT, the HLA matching between donor-recipient pairs must be established at least in high resolution (second field)[3]. In addition, some suffixes added after the eighth digit indicate the expression status of an HLA allele. For example, the suffix 'N' indicates null alleles. HLA mismatches with differences outside the ARD can be grouped in the same P or G groups (for example, *DRB1*14:01* and *DRB1*14:54* mismatches are assigned as *DRB1*14:01P*) and are treated as "functionally matched" alleles[2].

It is paramount that all patients referred for HCT and their respective donors must have their initial HLA typing confirmed with a new sample before the graft infusion[3]. This confirmatory (or verification) typing aims to rule out potential errors in the pre-analytical, analytical, or post-analytical steps of the initial HLA typing and should be performed prior to the start of the conditioning regimen. More details on sample collection requirements for first and confirmatory HLA typing are available in another reference document[4].

HLA Antibody Testing

HLA antibody methods comprise solid-phase assays based on Luminex technology and the crossmatch test[5]. Regarding Luminex assays, there are currently three available panels for assessing HLA antibodies: Pooled Antigen Beads, Phenotype Beads, and Single Antigen Beads (SAB). The Pooled and Phenotype panels are applied for antibody screening, while SAB panels are used for antibody identification and donor-specific HLA antibodies (DSA) assignment[5].

The SAB testing is conducted with serum samples, and the DSA strength is measured by mean fluorescence intensity (MFI), which is only a semi-quantitative metric and does not reliably represent the titer of a DSA. Indeed, the DSA's titer is determined only by titration, with several serial dilutions[5]. The widespread use of SAB assays enabled the routine implementation of virtual crossmatch (VXM) as a surrogate for crossmatch testing in the HCT setting[3]. The VXM is an *in silico* assessment, comparing the patient's HLA antibodies profile to the donor's HLA-mismatched antigens. For optimal accuracy, VXM must use an updated patient's serum sample and consider the complete donor's high-resolution HLA typing at 11 loci (*HLA-A, -B, -C, -DRB1, -DRB3, -DRB4, -DRB5, -DQA1, -DQB1, -DPA1,* and *-DPB1*)[4]. However, despite the SAB assay being the current gold standard for HLA antibody evaluation, it presents well-known limitations that can yield false-positive and false-negative results[5]. Accordingly, VXM accuracy can be severely compromised, and a standard crossmatch may help mitigate these issues[4].

The crossmatch test is performed by incubating the patient's serum with the donor's T and B lymphocytes, which can be carried out by complement-dependent cytotoxicity or flow cytometry[5]. The flow cytometry crossmatch has advantages such as enhanced sensitivity to detect low-level antibodies, less labor-intensive, and more user-friendly interpretation. However, the crossmatch testing also presents drawbacks, including the detection of non-HLA antibodies, interference of therapeutics (i.e., Rituximab), and the requirement of donor cells, which may be unfeasible in some HCT settings (i.e., UCB units or international MUD/MMUDs).

Importantly, DSA testing should be ordered at the beginning of the donor search and repeated before the final donor request and the initiation of the preparatory regimen[3,4].

Chimerism Testing

Chimerism analysis is critical for post-HCT monitoring. This method evaluates engraftment and informs the occurrence of graft rejection or relapse after HCT[6]. It also guides treatment decisions, such as immunosuppressive adjustments or donor lymphocyte infusion.

The primary method used is Short Tandem Repeat (STR), which has a sensitivity of 2% to 5%, limiting its ability to detect low levels of donor or recipient cells[6]. Lymphocyte subpopulations, such as T, B, natural killer, myeloid, and CD34+ cells, can be isolated to enhance STR's sensitivity and provide more detailed cell-specific chimerism analysis[4]. The NGS, Digital PCR, and Quantitative PCR are highly sensitive methods that accurately quantify donor/recipient chimerism[6].

Chimerism monitoring is recommended at days +30, +60, +90, +180, and +360 after HCT[6]. It is also essential to store the genetic material of both the patient and donor for chimerism analysis to provide a baseline for pre-transplant evaluation[4]. In sum, regular monitoring of chimerism kinetics allows HCT teams to optimize long-term patient outcomes.

CLINICAL IMPACT OF HISTOCOMPATIBILITY FACTORS IN ALLOGENEIC HCT

High-resolution HLA mismatching

Donor-recipient high-resolution mismatching at *HLA-A*, *-B*, *-C*, and *-DRB1* has been consistently associated with increased risks of grade III-IV acute GVHD and worse overall survival following unrelated donor HCT using calcineurin inhibitors (CNI) based GVHD prophylaxis[7-9]. This negative impact has been observed in HCT for malignant and nonmalignant diseases, with myeloablative and reduced-intensity conditioning, using either bone marrow or peripheral blood as the stem cell source[7].

In MMUD transplants with *in vivo* T-cell depletion, either with anti-thymocyte globulin or alemtuzumab, the adverse effects of single HLA mismatching are reduced, while two or more HLA mismatches are linked with impaired survival. Moreover, in 7/8 MMUD transplants with CNI, three additional mismatches at low-expression loci, such as *HLA-DQB1*, *-DRB3/4/5*, and *-DPB1*, are associated with poorer survival following HCT[7]. More recently, *HLA-DRB3/4/5* mismatching in the ARD was reported to have inferior survival following 10/10 MUD transplants for malignancies.

Conversely, in the 7/8 MMUD setting with CNI-based prophylaxis, the *HLA-C*03:03/C*03:04* mismatch is classified as permissive, showing similar survival to 8/8 MUD HCT[7]. Likewise, donor-recipient HLA mismatches in the same P/G group are also clinically permissive[2]. In 8/8 MUD transplants with conventional prophylaxis, a single *HLA-DQB1* mismatch is not correlated with increased mortality after unrelated donor HCT[2].

Novel HLA permissiveness models have been proposed to analyze the impact of *HLA-B* leader and class I peptide-binding motifs (PBM) matching in unrelated donor transplants[8,9]. Recent studies showed that 7/8 *HLA-B* MMUD with a leader mismatch or 7/8 MMUD with a class I PBM GvH mismatch were related to a higher incidence of acute GVHD and inferior survival after allogeneic HCT under CNI-based prophylaxis[8,9]. Moreover, the impact of HLA mismatching in MMUD transplants with PTCy is controversial. Most but not all studies[9-11] show that PTCy significantly reduces the incidence of acute and chronic GVHD and improves survival after MMUD transplants[10,11].

High-resolution mismatches at *HLA-A, -B, -C,* and *-DRB1* loci are also associated with impaired survival after single or double UCB transplants[7]. In contrast, in haploidentical allo-HCT with PTCy, the degree of HLA mismatching has not been correlated with worse survival or higher GVHD. Therefore, HLA matching is not prioritized in haploidentical donor selection[12].

Donor-specific HLA antibodies

In patients referred for HCT, HLA antibodies may develop following previous blood transfusions, pregnancies, or HLA-mismatched transplants. When a patient is sensitized, DSA are defined as the HLA antibodies targeting donor HLA mismatches[5].

Numerous observational studies have consistently demonstrated that DSAs are associated with substantial risks of graft failure, delayed engraftment, and reduced survival following HLA-mismatched HCT, either in upfront or salvage transplants. This detrimental effect has been observed after HCT with MUD, MMUD, UCB, and haploidentical donors with PTCy, T-cell depletion, or Beijing platform[13].

A recent meta-analysis, including 15 studies with 2,436 patients, demonstrated that DSA-positive patients had an odds ratio of 7.47 for experiencing primary graft failure compared to the patients without DSA. Moreover, increased levels of DSA's MFI correlate with a higher risk of primary graft failure after HCT. Accordingly, it is recommended to avoid DSAs whenever possible. If a suitable DSA-negative donor is unavailable, a desensitization protocol and post-transplant DSA monitoring should be implemented[13].

HLA-DPB1 Permissiveness

Approximately 80% to 85% of patient/unrelated donor pairs present *HLA-DPB1* mismatches due to a recombination hotspot between the *HLA-DQB1* and *-DPB1* loci. Since finding a *DPB1*-matched MUD is often unfeasible, it is essential to distinguish mismatches that are clinically tolerable (i.e., permissive *HLA-DPB1* mismatches) from those linked to poorer transplant outcomes (i.e., nonpermissive *HLA-DPB1* mismatches)[14].

In this sense, the "T-cell epitope" (TCE) model was developed to classify *HLA-DPB1* mismatches as permissive and nonpermissive. In this model, the *HLA-DPB1* alleles are classified into three different immunogenicity groups: TCE1 (high), TCE2 (intermediate), and TCE3 (low). *HLA-DPB1* mismatches within the same TCE group are classified as permissive, whereas those mismatches across distinct TCE groups are defined as nonpermissive[14].

Notably, several multicenter international studies have validated the clinical relevance of the TCE model in unrelated donor HCT for malignancies using standard GVHD prophylaxis[14]. These studies showed that nonpermissive *DPB1* mismatches were associated with a higher incidence of grade III-IV GVHD, increased non-relapse mortality, and worse overall survival, although with lower relapse. Hence, current MUD/MMUD selection criteria recommend avoiding nonpermissive TCE DPB1 mismatches to enhance transplant outcomes. Nevertheless, under PTCy-based GVHD prophylaxis, recent evidence suggests that the adverse effects of nonpermissive *DPB1* mismatching are abrogated, resulting in survival outcomes similar to those of *DPB1*-matched and permissive mismatched groups[9].

DONOR SELECTION CRITERIA IN ALLOGENEIC HCT

Criteria for prioritizing MUD, MMUD, UCB, and haploidentical donors have been published and are described elsewhere[7,12]. Importantly, current MUD and MMUD selection parameters apply only to HCT with CNI-based GVHD prophylaxis[7].

While specific guidelines for selecting MMUDs using PTCy have not yet been published, existing evidence indicates that the negative effects of HLA mismatching are significantly lessened under PTCy-based prophylaxis[10,11,15]. In this context, donor age and the presence of DSA appear to be the primary factors to prioritize when selecting MMUDs with PTCy[15]. Therefore, further research is warranted to establish PTCy-specific recommendations for MMUD selection.

Other non-HLA factors, such as donor age, cytomegalovirus status, sex match, ABO compatibility, donor availability, and the urgency of HCT, are crucial to optimize donor selection[2,7,12]. A detailed discussion of these criteria is beyond the scope of this review.

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05

TYPE OF STEM CELL DONOR: RELATED, UNRELATED, HAPLOIDENTICAL AND UMBILICAL CORD BLOOD

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Allogeneic hematopoietic cell transplantation (HCT) is the treatment of choice for a variety of malignant and non-malignant disorders. For many patients, this treatment is the only option with the potential for cure or prolonged remission. The aim of HCT is to replace the patient's hematopoiesis with HC taken from a donor, so a prerequisite is the identification of a suitable donor[1].

We can divide donors into 2 types: related and unrelated donors. A related donor can be a matched sibling or a haploidentical (partially matched) family relative. An unrelated donor can be a volunteer, HLA-matched or mismatched, or the cell graft from cryopreserved cord blood unit. In patients with malignant and non-malignant diseases who require allogeneic HCT, choosing a compatible, HLA genotypically identical, related donor is the best therapeutic option. The possibility of having a matched sibling donor varies depending on ethnicity and family size, approximately only 25-30% patients have such a donor[2].

RELATED DONORS

The related donor workup for the patient's full biological siblings starts with high- resolution HLA molecular typing. Besides HLA compatibility, others factors should be analyzed: donor age; weight disparity (very important for marrow donors), gender, CMV serological status, ABO compatibility, etc. The analysis of these factors is especially important when more than one HLA-matched donor was found. Among non-HLA factors, donor age was the most significant predictor of overall survival. Sometimes, unrelated donors may be preferred when a related donor is likely to carry the same genetic mutation as the patient.

For patients who do not have an HLA-matched family donor, alternative donors can be used, such as HLA-matched and mismatch unrelated donors from bone marrow donor registries, umbilical cord blood cells (UCB) or haploidentical donor[3].

The trends in the use of donor types differs between the adult and pediatric population: in pediatric transplants (recipients younger than 18), matched related donor (MRD) transplants represent the largest donor group, while in adults, unrelated donor (MUD) transplants represent the largest one (www.cibmtr.org). This finding can be partially explained by the fact that more than 25% of HCT are being performed in recipients >55 years of age, so the chance of a higher age in matched sibling donors is also greater. Furthermore, smaller families in the Western world decrease the likelihood of identifying a MRD. Since 2007, the number of transplants with

stem cells from an unrelated donor has been higher than the number from matched sibling donors.

UNRELATED DONORS

As only 25-30% of patients have MRD, a search for HLA-matched unrelated donors led to the first unrelated donor transplant in 1979. The probability of identifying a matched donor changes accordingly to the definition of 'HLA matching', which depends on the level of resolution and on which loci are tested. Donor-recipient HLA compatibility is an important factor to determining overall success and transplant-related mortality and HLA incompatibilities at >1 locus is associated with additive detrimental effects, although this depends on the GVHD prophylaxis[2]. Most of the classic data used calcineurin-methotrexate combinations for GVHD prevention. The introduction of post-transplant cyclophosphamide (PTCy) has changed the field by allowing a variety of mismatched transplants.

National and International Registries require laboratories to perform high-resolution typing for unrelated donor-recipient pairs using sequence-based methods for HLA-A, B, C, DRB1 and DPB1. As HLA typing technologies offer a rapid, cost-effective multiplexed NGS-based typing for all 11 loci (HLA-A, -B, -C, - DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, -DPA1), it has become more feasible to provide a complete high-resolution typing[3].

Over 40 million donors are now registered in the international database (*www.bmdw.org*). Nevertheless, many patients will not have a MUD due to the extremely great diversity of HLA alleles. Donor age is another important characteristic associated with survival: in the unrelated donor setting, younger donors (<35 years old) elicit improved survival. One study suggested a young MUD may be better than older related donors: disease-free survival was higher, and relapse lower for allo-HCT using younger MUDs compared to older MRDs, while the risk of NRM and GVHD was lower with older MRDs, without a survival advantage[4]. This has to be carefully considered given the costs associated with MUD procurement.

The probability of finding a fully MUD varies according to the patient's ethnicity, and ranges from 16 to 80%. Another important aspect is donor availability: the National Marrow Donor Program found that nearly 50% of registered donors were unavailable when identified as a potential donor due to changes in personal circumstances or inability to contact[5].

Much of the improvement in results with HSCT in recent years is due to technical advances, such as better HLA typing, new infection prevention and treatment protocols, as well as advances in the prophylaxis of graft-versus-host disease GVHD (14). Recently, an randomized trial, BMT CTN 1703, has showed that Posttransplant cyclophosphamide with tacrolimus and MMF (Ptcy/Tac/MMF) as GVHD prophylaxis in patients HLA-matched (all patients received a reduced intensity conditioning regimen with PBSC grafts) had higher 1-year GRFS compared to Tac/MTX (53% versus 35% at 1 year) without increased risk of relapse or death. These results demonstrated that a PTCy/Tac/MMF, which has become standard of care for mismatched transplants, should also become the standard of care for GVHD prophylaxis from matched donors receiving reduced intensity conditioning[6]. Whenever an 10/10 MUD is unavailable, a single mismatch at HLA-A, -B, -C, or -DRB1 may be acceptable despite the increased risk of TRM when utilizing calcineurin-based GVHD prophylaxis. PTCy in HLA-mismatched unrelated donor showed less incidence of acute and chronic GVHD and non-relapse mortality[7], and the utilization of this donor source is increasing rapidly.

UMBILICAL CORD BLOOD (UCB)

The first UCB transplant was performed in 1988 and since then it has become an alternative for patients without an HLA-compatible donor. UCB cells can be used for both children and adults, however the limited cellularity of UCB units may contribute to greater graft failure and longer time for immunological reconstitution, making the UCB transplantation infrequent in adults. The minimum of TNC dose of 3.0×10^7/kg and prefreeze CD34+ cells of 1.5×10^5/kg for

single unit are recommended. When a UCB unit with the appropriate cell dose is not found, it is recommended to look for another unit and infuse 2 two units: double CB transplant[5]. Unit quality is critical and influenced by processing and cryopreservation techniques. The transplantation of units with a CD34 + cell viability of ≥ 80 % by flow cytometry is preferred.

UCB has the major advantage of rapid availability and a markedly reduced stringency of HLA-matching compared with adult unrelated donor. However, the incidence of graft failure and mortality rates were higher when the recipient and the CB unit were mismatched at ≥ 2 HLA high- resolution[5]. Later reports showed that even in pediatric population, the number of UCB transplants steady decreases while haploidentical transplants are increasing.

HAPLOIDENTICAL DONOR

The first haploidentical (Haplo) HCT performed in 1970 resulted in intense toxicity and GVHD. Over the last 10 years, however, haplo transplantation has become mainstream. The use of PTCy, a non-T-cell-depleted platform, has improved engraftment rates and immune reconstitution posttransplant and has showed results comparable to HLA-matched unrelated donor transplantation[8]. Now GVHD prophylaxis for adults receiving haplo donor (HD) HCT is almost exclusively with PTCy *(www.cibmtr.org)*. When compared with UCB, haplo transplants have some advantages: shorter time for donor identification, the possibility for a repeat stem cell donation, donor lymphocyte infusion (DLI) and lower cost[9].

Some publications suggested that HD are a better choice than MUDs because haplo HCT offers the same or better clinical outcomes while having the advantage of cost-effective and fast donor workup[10]. However, anti-HLA antibodies against the donor's mismatched HLA antigens (DSA) may cause graft failure and should be avoided whenever possible . DSA remains one of the main barriers to transplantation with HD[11]. This is more common in multiply transfused, multiparous patients.

Younger donors are preferred over those of older generations since younger donor age may be associated with lower relapse rates. Whether HLA factors such as impact of mismatching in the GVH direction for HLA-DRB1, non-permissive DPB1 mismatch, HLA-B leader mismatch or mismatch number take precedence over non-HLA factors such as donor relationship and non-inherited maternal and paternal antigens (NIMA/NIPA), sex, ABO mismatch, NK cell alloreactivity (KIR matching), donor-recipient CMV serostatus, disease type and regiment intensity is unclear. CMV serostatus is less impactful when Letermovir is available. Mismatched transplants are associated with more viral reactivations, delayed immune recovery and often poor graft function, and require care at specialized centers

DPB1 mismatch, B leader mismatch and KIR mismatch calculator can be found at the EMBL-EBI website: *https://www.ebi.ac.uk/ipd/kir/matching/ligand/*. Fuchs (2017)10 generated a haploidentical donor selection algorithm based on a large multi-institutional database: *https://haplodonorselector.b12x.org/v1.0/*.

CONCLUSIONS

HLA identical sibling donor remains the gold standard donor type. In the absence of such donor, most patients in need will have a MUD, mMUD, CB or haploidentical donor. Choice of donor is now often based on institutional experience, financial considerations (related transplants are cheaper than unrelated CB or mMUD and MUD), diagnosis and speed of procurement. We now live in an era where most patients in need of allogeneic transplantation will have a donor.

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06
CONDITIONING REGIMENS

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Pre-hematopoietic cell transplantation (HCT) conditioning regimens, also known as preparative regimens, consist of chemotherapeutic agents and/or irradiation designed to facilitate hematopoietic cell engraftment. Traditionally, HCT relied on high-dose alkylating agents or total body irradiation (TBI), known as myeloablative regimens. However, in recent decades, reduced-intensity and non-myeloablative regimens have been developed and are now widely used for older or unfit patients. The intensity of conditioning is directly associated with early toxicity, non-relapse mortality (NRM), and relapse incidence (RI).

Didactically, the effects of conditioning regimens can be categorized into two main mechanisms[1]:

Myeloablation – Primarily mediated by alkylating agents (e.g., busulfan, melphalan) and high-dose TBI. The conditioning regimen depletes the host bone marrow, eliminating both healthy and malignant cells, thereby creating space for the graft to restore hematopoiesis. This effect also reduces the risk of relapse by eradicating residual malignant cells at the time of HCT.

Immunoablation – Typically achieved with purine analogs (e.g., fludarabine), lymphodepleting alkylators (e.g., cyclophosphamide), and TBI (at either high or low doses). By depleting the recipient's T-cell compartment, immunoablation prevents immune-mediated graft rejection. In allogeneic HCT, the graft-versus-tumor (GVT) effect plays a crucial role in minimizing relapse of the underlying malignancy.

It is important to note that most conditioning agents exert both myeloablative and immunoablative effects to varying degrees.

CIBMTR/EBMT OPERATIONAL DEFINITIONS

Historically, definitions of conditioning intensity were vague, with no uniform consensus. To address this, the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Society for Blood and Marrow Transplantation (EBMT) proposed standardized operational definitions based on existing evidence[1,2]:

Myeloablative Conditioning (MAC): These regimens induce profound pancytopenia, which is typically irreversible, making stem cell support essential for survival. MAC is associated with high early toxicity and increased NRM, but it effectively reduces relapse. The adopted operational criteria for MAC regimens include: 1) TBI ≥ 800 cGy (fractionated dose); 2) intravenous busulfan ≥ 6.4 mg/kg; 3) melphalan ≥ 140 mg/m^2; 4) thiotepa ≥ 10 mg/kg; and 5) the BEAM regimen (carmustine, etoposide, cytarabine, and melphalan);

Examples: Cyclophosphamide + TBI 12 cGy (CyTBI), busulfan 12.8 mg/kg + cyclophosphamide (BuCy);

Reduced-Intensity Conditioning (RIC): These regimens lead to prolonged pancytopenia, often causing significant morbidity and mortality; however, autologous hematopoietic recovery is expected. By definition, RIC regimens do not meet the criteria for either MAC or nonmyeloablative conditioning;

Examples: Fludarabine + reduced-dose melphalan 100 mg/m^2 (FluMel), fludarabine + busulfan 6.4 mg/kg (Bu2Flu), cyclophosphamide 200 mg/kg;

Nonmyeloablative Conditioning (NMA): These regimens cause minimal or no pancytopenia, and autologous recovery occurs if stem cell infusion is not provided. NMA allows older or unfit patients to undergo allogeneic transplantation with minimal early toxicity. Immunoablation, combined with high donor CD3+ and CD34+ cell numbers, promotes full donor engraftment. In essence, stem cell rescue is optional;

Examples: Fludarabine + TBI 2 cGy (FluTBI), fludarabine + cyclophosphamide + TBI 2 cGy (FluCyTBI).

It is important to note that while conditioning regimens for allogeneic transplantation vary across these three intensity levels, autologous HCT primarily relies on MAC regimens, as its main objective is to eradicate residual malignant cells or deepen disease response through high-dose cytotoxic chemotherapy.

TRANSPLANT CONDITIONING INDEX

While the above-mentioned operational definitions of conditioning intensity are widely adopted in the scientific literature and have been crucial for standardization, they have notable limitations. These definitions do not account for novel myeloablative agents with limited non-hematological toxicity (e.g., treosulfan, thiotepa), which differ from the traditional toxicity profiles outlined in the MAC/RIC paradigm. Additionally, they do not consider the impact of certain drugs added to MAC regimens over time (e.g., etoposide, cytarabine) that help reduce RI or the increased immunoablative intensity of purine analogs (eg. fludarabine, clofarabine).

To address these gaps, the Transplant Conditioning Index (TCI) was introduced,[3] assigning weighted scores to individual conditioning agents based on their type and dose (Table 1).

TABLE 1: The Transplant Conditioning Index - intensity weighted scores

COMPONENT	DOSE LEVEL (LOW)	DOSE LEVEL (INTERMEDIATE)	DOSE LEVEL (HIGH)	ADDED POINTS FOR EACH DOSE LEVEL
TBI fractionated (Gy)	≤5	6–8	≥9	1
Busulphan (mg/kg)	≤6.4 iv	9.6 iv	12.8 iv	1
Treosulfan (g/m2)	30	36	42	1
Melphalan (mg/m2)	<140	≥140	≥200	1
Thiotepa (mg/kg)	<10	≥10	≥20	0.5
Fludarabine (mg/m2)	≤160	>160		0.5
Clofarabine (mg/m2)	≤150	>150		0.5
Cyclophosphamide (mg/kg)	<90	≥90		0.5
Carmustine (mg/m2)	≤250	280–310	≥350	0.5
Cytarabine (g/m2)	<6	≥6		0.5
Etoposide (mg/kg)	<50	≥50		0.5

Notes: *iv* intravenously; *TBI* total body irradiation.

TCI is calculated by summing the weighted scores of each agent used in a conditioning regimen. The final score is then categorized into three stratification levels: low (1-2), intermediate (2.5-3.5), or high (4-6). Studies have shown that TCI is independently associated with both early and late NRM and RI. Moreover, it has demonstrated superior predictive performance for these outcomes compared to the traditional RIC-MAC classification[3,4].

UNDERLYING DISEASES AND CONDITIONING INTENSITY

Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS): A prospective, randomized BMT-CTN trial demonstrated that MAC resulted in superior relapse-free survival (RFS) but was associated with higher NRM and lower RI in young patients compared to RIC[5]. Conversely, the EBMT RICMAC randomized trial, which primarily included patients with MDS, found no significant differences in RFS or overall survival (OS) between RIC and MAC regimens[6].

Acute Lymphoblastic Leukemia (ALL): In children and young adults (≤21 years), a large randomized trial demonstrated that high-dose TBI plus etoposide resulted in superior 2-year OS and RI compared to busulfan- or treosulfan-based regimens[7]. However, in adults, both randomized and retrospective studies have shown no clear significant differences in transplant outcomes between MAC and RIC HCT[8,9].

Other Hematologic Malignancies: Prospective, randomized trial data on conditioning regimen intensity remain limited. However, registry-based and retrospective studies consistently show that MAC regimens are associated with higher NRM but lower RI, whereas RIC/NMA regimens have lower NRM but higher RI, ultimately leading to comparable long-term disease-free survival and OS[10].

Non-Malignant Diseases: In aplastic anemia and immunodeficiencies, RIC and NMA regimens with intensified immunoablative effects are commonly used. In hemoglobinopathies, MAC regimens are generally preferred for children and young adults due to the increased risk of graft failure with less intensive approaches.

TABLE 2 – Main risks of transplant failure according to specific risk factors

RISK FACTORS	IMPACT
Disease-specific factors	
Advanced disease status at HCT	relapse > NRM
Unfavorable cytogenetics/molecular genetics	relapse > NRM
High/very high disease risk index	relapse > NRM
MRD positivity	relapse > NRM
Patient-specific factors	
Older age	NRM > relapse
Poor performance status	NRM > relapse
High HCT-comorbidity index	NRM > relapse
Transplant-specific factors	
HLA disparity	NRM > relapse
CMV incompatibility	NRM > relapse

Notes: *HCT* Hematopoeitic cell transplantation; *CMV* Cytomegalovirus

OTHER FACTORS AFFECTING THE CHOICE OF CONDIONING REGIMENS

As highlighted earlier, conditioning regimens possess distinct toxicity and efficacy profiles. Beyond the specific type of underlying disease, several factors related to the patient, disease, and transplantation must be considered when selecting a regimen according to the main risk of treatment failure post-HCT (NRM or RI) (Table 2)[10]. A crucial prognostic factor is the presence of measurable residual disease (MRD) prior to HCT in ALL and AML. In AML patients with MRD positivity, RIC regimens have been linked to significantly higher RI and lower OS compared to MAC regimens[11]. In the context of ALL, the use of blinatumomab has become an important tool for achieving MRD negativity prior to HCT[12].

The Disease risk index (DRI) is a prognostic tool for transplant outcomes, and HCT recipients with AML/MDS in the high/very high-risk DRI categories have poorer survival rates due to relapse. Retrospective analyses have shown that MAC regimens improve OS and reduce RI compared to RIC in patients with low/intermediate DRI AML. However, no significant difference has been found in the high/very high-risk group[13]. Furthermore, a randomized trial demonstrated no advantage of MAC in patients with cytogenetically intermediate and high-risk AML in first remisson[14].

Performance status, age, and the HCT-comorbidity index (HCT-CI) are also independent risk factors for long-term survival post-HCT and should be considered when selecting the intensity of the conditioning regimen. An HCT-CI ≥ 1 or lower performance status at HCT are strongly associated with higher NRM in patients undergoing MAC compared to RIC[15,16]. Furthermore, for patients over 50 years old, RIC and MAC regimens seem to yield similar outcomes[17].

Other important factors to consider when choosing a conditioning regimen include the Geriatric Assessment in older patients, frailty, type of donor, HLA mismatching, local resources, center experience, and planned post-HCT maintenance therapy.

NOVEL CONDITIONING AGENTS

In recent years, novel conditioning strategies have been developed to achieve enhanced myeloablation without increasing toxicity. For instance, treosulfan, an innovative alkylating agent, is utilized in combination with other drugs or TBI in what are known as reduced-toxicity myeloablative regimens[18]. Total marrow irradiation (TMI) and total lymphoid irradiation (TLI) deliver high doses of radiation specifically to the bone marrow and lymphoid organs, while sparing other tissues[19]. Additionally, an anti-CD45 radioconjugate[13] I-apamistamab seems to provide targeted myeloablative conditioning in the bone marrow, thereby reducing non-hematological toxicity[20].

KEY POINTS:

- Conditioning intensity is directly related to NRM and RI.
- TCI can stratify novel drugs and conditioning regimens more effectively than the MAC-RIC classification.
- The choice of a conditioning regimen should consider factors such as the underlying disease, patient age, DRI, MRD status, performance status, and HCT-CI.
- Novel conditioning strategies may enhance disease control while minimizing non-hematological toxicity.

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07
INDICATIONS FOR AUTOLOGOUS TRANSPLANTS AND RESULTS

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INTRODUCTION

For this chapter, although there are several indications for autologous stem cell transplantation (auto-HCT), we will talk about the most important indications, whether due to the epidemiology of the disease, or the frequency of auto-HCT. Thus, we will address multiple myeloma and **lymphomas**, drawing attention to the main evidence for the indication of auto-HCT.

MULTIPLE MYELOMA

Autologous hematopoetic cell transplant (auto-HCT) has long been part of standard treatment for Multiple Myeloma (MM). Conditioning consists of high dose intravenous melphalan (MEL), usually in the dose of 200mg/m^2 (or 140mg/m^2 for patients with kidney impairment). Other regimens (such as MEL in higher doses or combined with TBI, alkylating agents or anthracyclines) have been tested and resulted in increased toxicity with no clear benefit over MEL 200mg/m^2[1].

Since auto-HCT is an aggressive therapy and MM predominantly affects the elderly, a comprehensive eligibility assessment by an expert is warranted at diagnosis, which is often based on age, comorbidities and frailty, rather than on age alone. It is also important to reassess eligibility after a few cycles of treatment if a previously fit patient is acutely ill due to disease activity at diagnosis[2]. In addition, there are several approaches to mitigate HCT toxicity, which must not be overlooked, such as the use of cryotherapy, growth factors, amifostine and nausea prophylaxis[3].

As the treatment of MM continues to evolve, the role of auto-HCT is often reassessed in the literature, as seen in Table 1. Some of the older studies which used obsolete conventional chemotherapy induction regimens observed both event-free (EFS) and overall survival (OS) benefit of frontline auto-HCT[4,5]. The latter, however, has consistently not been demonstrated in more recent trials that employed the combination of bortezomib, lenalidomide and dexamethasone (VRd) as induction regimen, but frontline auto-HCT still showed a significant progression-free survival (PFS) benefit and remained standard practice[6,7]. Such lack of OS benefit is explained by the high percentage of transplant-naive patients who were rescued with auto-HCT at relapse. Given that patients may become transplant-ineligible during the disease course; the predominant practice worldwide is to incorporate auto-HCT in first-line treatment whenever possible in order to allow patients to take advantage from this therapy. Newer studies also included frontline auto-HCT in the trial design, but their aim was to evaluate quadruplet regimens with the incorporation of anti-CD38 monoclonal antibodies and did not seek to isolate the impact of auto-HCT itself. However, ongoing clinical trials promise to challenge frontline auto-HCT again by replacing it with additional cycles of quadruplet regimens or even anti-BCMA CAR-T cell therapy (NCT04934475, NCT05257083).

TABLE 1: Results of autologous HCT in Multiple Myeloma

STUDY	GROUPS	MEDIAN EFS/PFS (MONTHS)	OS
IFM 904	VMCP/BVAP vs VMCP/BVAP + HCT	EFS 18 vs 27 (P=0.01)	12% vs 52% (P=0.03) at 5 years
MRC75	ABCM vs VAMPC + HCT	PFS 19.6 vs 31.6 (P<0.001)	median OS 42.3 vs 54.1 (P=0.04)
IFM 20096	VRd + HCT vs VRd	PFS 50 vs 36 (HR 0.65; P<0.001)	81% vs 82% at 4 years
DETERMINATION7	VRd vs VRd + HCT	PFS 46.2 vs 67.5 (HR 1.53; P<0.001)	79.2% vs 80.7% at 5 years

HCT, hematopoetic cell transplant. EFS, event-free survival. PFS, progression-free survival. OS, overall survival. VMPC; vincristine, melphalan, cyclophosphamide and prednisone. BVAP; carmustine, vincristine, doxorubicin and prednisone. ABCM; doxorubicin, carmustine, cyclophosphamide and melphalan. VAMPC; vincristine, doxorubicin, methylprednisolon. e and cyclophosphamide. VRd; bortezomib, lenalidomide and dexamethasone. HR, hazard ratio.

Tandem (i.e, two consecutive) auto-HCT may be used in high-risk MM and plasma cell leukemia, but it is important to note that not all patients eligible for a single HCT are physically or mentally fit for tandem. In addition, recent studies provided indirect evidence that the incorporation of new therapies in more aggressive five-drug induction regimens and consolidation with a single HCT may dismiss the need for tandem[8].

Relapsed patients are candidates for a second transplant if there was a long remission after the first auto-HCT, which may be defined as 18-24 months or even 36 months if maintenance therapy was used. Since this issue was not evaluated by any recent randomized trial incorporating new drugs, expert opinion and resource availability often influence the decision on proceeding to a second auto-HCT[2].

Other monoclonal gammopathies also benefit from auto-HCT. Approximately 50-65% of patients with light-chain (AL) Amyloidosis achieve organ response after transplant. However, the advent of frontline Dara-VCd, which is more tolerable for most patients, led some experts to recommend auto-HCT only if a complete (CR) or even measurable residual disease (MRD) response is not achieved[9]. Patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) syndrome virtually always show at least a partial neurological improvement with auto-HCT, which is indicated when there is disseminated bone marrow involvement and radiotherapy is not a useful option. In both diseases, it is preferable to administer a few cycles of a bortezomib-containing regimen prior to transplant and attention must be paid to the high frequency of engraftment syndrome. Splenomegaly in POEMS patients is associated with higher transfusion requirement and delayed engraftment[10]. There is a growing interest in monoclonal gammopathy of renal significance (MGRS) and auto-HCT seems to result in better overall response rates than other treatments, but high-quality data is lacking to make strong recommendations[11].

DIFFUSE LARGE B-CELL LYMPHOMA (DLCL):

Studies incorporating autologous transplantation as consolidation, after achieving remission in intermediate-risk and high-risk IPI patients, have not yet demonstrated evidence of benefit[12-14]. In

addition to IPI, adverse biological characteristics such as tumor cell of origin (COO) (CGB x ABC), presence of MYC rearrangement, BCL-2 and BCL-6 (double/triple-hit) have been studied in this context, without benefit[15].

Relapses of aggressive NHL, after initial therapy, have a poor prognosis. Salvage regimens with conventional chemotherapy provide two-year survival rates of less than 25%. The randomized study PARMA TRIAL[16] demonstrated that auto-HCT is the treatment of choice in chemosensitive relapse. EFS rates at 8 years were 36% for the transplant arm and 11% for DHAP rescue.

In the CORAL trial[17], less than 25% of patients who relapsed within 1 year of diagnosis achieved long-term DFS with auto-HCT. Although this group of patients is currently indicated for CAR-T therapy, the CIBMTR study[18], with DLBCL who received either an auto-HCT (2013-2019) or CAR-T treatment with axicabtagene ciloleucel (2018-2019) in a PR, with half relapsing less than 12 months after diagnosis, compared the clinical outcomes between the 2 cohorts. In the univariable analysis, the 2-year progression-free survival (52% vs 42%; P =0.1), but consolidation with auto-HCT was associated with a superior overall survival (OS) (69% vs 47%; P = 0 .004) at 2 years. In the multivariable regression analysis, treatment with auto-HCT was associated with a significantly lower risk of relapse/progression rate (hazard ratio = 1.49; P =0.01) and a superior OS (hazard ratio = 1.63; P =0.008).

FOLLICULAR LYMPHOMA (FL)

Currently, for the majority of patients with FL without early disease-related events, survival approaches that of the general population, the prognostic impact of early progression within 24 months of chemotherapy treatment (POD24), with 50% OS in 5 years, compared to 90% in patients without early progression[19-22]. The management of relapse should be based on the time of relapse, whether early (POD24) or late. For young patients with POD24, consolidation with high-dose chemotherapy and auto-HCT should be considered[23]. Data from the CIBMTR and the National LymphoCare Study (NLCS) demonstrated that patients with a relapse of less than 1 year when transplanted had a higher five-year OS than those who did not undergo auto- HCT (73% versus 60%, P = 0.05). In multivariate analysis, early use of auto- HCT was associated with significantly reduced mortality (RR: 0.63; 95% CI: 0.42 to.94; P = 0.02)[24].

MANTLE LYMPHOMA:

After induction treatment, consolidation in first remission with high dose chemotherapy and auto- HCT is recommended. This recommendation is based on restrospective case series and a prospective study from the pre-rituximab era[25-31]. Progression-free survival ranged from 48 to 68% in 4 years in these studies and overall survival from 61 to 80%. The subpopulations of patients that can most benefit are those with blastoid / pleomorphic morphology and with a high MIPI risk score. TP53 mutation carriers do not appear to benefit.

Currently, this recommendation has been questioned by studies that use BTK inhibitors in induction or guide the indication of auto HCT due to the presence of minimal residual disease (MRD). The Triangle study evaluated the use of ibrutinib (I) in combination with chemotherapy in induction and maintenance, evaluating the need to perform auto-HTC in the first line. After 31 months median follow-up, group Auto-HCT+I was superior to group Auto-HCT with 3-year failure-free survival of 88% (95% CI 84–92) versus 72% (67–79; hazard ratio 0·52 [one-sided 98·3% CI 0–0·86]. Superiority of group Auto-HCT over group I was not shown with 3-year failure-free survival 72% (67–79) versus 86% (82–91; hazard ratio 1·77 [98·3% CI 0–3· 76]; p=0·9979). A greater benefit for group Auto-HCT+I was observed

in patients with high p53 expression versus group A (HR 0·14 [98·3% CI 0·00–0·57]) and high-risk biology (high combined MIPI or p53 immunohistochemistry expression >50%; HR 0·31 [98·3% CI 0·00–0·78][32]. Another recent study showed that there was no benefit to auto HTC in patients with negative MRD. Of MRD+ patients showed who converted to MRD- post auto-HCT had 3 yr OS of 100% and PFS of 100%, whereas those who remained MRD+ post auto-HCT had 3 yr OS of 63.6% and PFS of 48.8%[33].

PERIPHERAL T CELL LYMPHOMA

Prospective studies have demonstrated the feasibility and benefit of auto-HCT as part of the frontline strategy in nodal PTCLs[34-36]. In the final analysis of the largest conducted prospective phase II trial including auto-HCT in first remission, the Nordic study (NLG-T-01)[36], evaluated the outcomes of 166 patients, of which 62 were classified as having PTCL-NOS. This study demonstrated that 71% of patients completed the therapeutic sequence and 90 patients were in CR 3 months after transplantation. The overall response rate was 78%; and at a median of 60 months although 82% of patients had advanced disease at diagnosis.

Brentuximab therapy improved the response to first-line treatment mainly in anaplastic **lymphomas**, although the ECHELON-2 study was not designed to evaluate the use of auto-HCT, 67% of patients with ALK– sALCL on the BV+ CHP arm were in CR at EOT; 36% of these patients received consolidated auto-HCT 59% of patients with non-sALCL had a CR at EOT; 29% of these patients received consolidated auto-HCT. Across all patients (ALK– sALCL and non-sALCL) who achieved CR following A+CHP, patients who underwent auto-HCT had a lower risk of experiencing a PFS event. The PFS hazard ratio (HR) was 0.36 (95% CI,0.17-0.77), equating to a 64% reduction in the risk of a PFS event in patients who underwent auto-HCT. The estimated 3-year PFS in patients who underwent auto-HCT was 80.4% vs 54.9% in patients who did not undergo auto-HCT; at 5 years, the estimated PFS was 65.3% vs 46.4%, respectively[37].

HODGKIN LYMPHOMA

The indication of auto HTC for HL originates from 2 randomized studies that show an increase in PFS in relation to conventional chemotherapy[38,39]. The results of Pembrolizumab, gemcitabine, vinorelbine, and liposomal doxorubicin (P-GVD) followed by auto-HCT are very good with 95% of patients achieved CR and 96% are progression-free at 30 months. At part II of the P-GVD study patients received 4 cycles of P-GVD and those who achieved CR proceeded to 13 cycles of pembrolizumab maintenance (200mg IV every 21 days). After a median follow-up of 23.4 mos, 2-year PFS was 51% (95% CI 33-80). Stage IV disease at enrollment was significant for higher risk of progression (PFS 18% vs 69%, p=0.03)[40]. Although many authors try to demonstrate the lack of benefits of auto HTC in the face of new therapies, the standard approach for relapsed or refractory (RR) classical Hodgkin lymphoma (HL) following front-line treatment failure is second line therapy aimed to achieve complete response (CR), followed by consolidation with high dose therapy and auto-HCT.

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08

PART I: HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT) IN MYELOPROLIFERATIVE SYNDROMES: ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME

FERNANDO BARROSO DUARTE

INTRODUCTION

Acute or chronic myeloproliferative syndromes may, in general, have indications for hematopoietic stem cell transplantation (HCT), but this indication can vary depending on certain aspects, such as risk stratification and the absence of effective treatment. For example, in acute promyelocytic leukemia (APL) t(15,17) /PML-RAR), the use of all-trans retinoic acid, and in chronic myelogenous leukemia (CML) t(9,22)/ BCR-ABL, the use of tyrosine kinase inhibitors shows excellent response with clinical treatment alone.

Other relevant points in the indication for HCT include the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI)[1] and the comprehensive geriatric evaluation, which is addressed in a specific chapter. This chapter will focus on the main conditions: Acute Myeloid Leukemia (AML), Myelodysplastic Syndromes (MDS), Chronic Myelogenous Leukemia (CML), and Myelofibrosis.

ACUTE MYELOID LEUKEMIA (AML)

AML is the condition for which we perform the most allogeneic transplants, as it is the only curative option. However, not all patients with indications for HCT can undergo the procedure[2,3]. Factors such as age, comorbidities, frailty, family structure, and even access to the procedure interfere in this decision[4].

In AML, we typically use the European LeukemiaNet (ELN) risk stratification, based on molecular and cytogenetic alterations, grouping patients into favorable, intermediate, and adverse risk categories to guide therapeutic decisions (Table 1)[5]. In patients with favorable risk, HCT is not indicated in first complete remission (CR1); however, in cases of intermediate and adverse risk, HCT should be considered. In this context, measurable residual disease (MRD) plays a crucial role as a determinant for conditioning type, whether myeloablative or reduced intensity (Table 1)[6].

In relapsed cases, regardless of stratification, HCT should be considered. With the option of alternative donors (unrelated mismatched and haploidentical), it is rarely impossible do not find a donor. What truly impacts the decision is the combination of patient and disease-related factors[7].

Regarding post-HCT maintenance, there are still controversies. It is suggested that in cases with FLT3 mutation, FLT3 inhibitors may be used, such as

TABLE 1: 2022 ELN risk classification by genetics at initial diagnosis[6]

RISK CATEGORY	GENETIC ABNORMALITY
Favorable	•t(8;21)(q22;q22.1)/RUNX1::RUNX1T1a,b •inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 a,b •Mutated NPM1a,c without FLT3-ITD •bZIP in-frame mutated CEBPAd
Intermediate	•Mutated NPM1 a,c, with FLT3-ITD •Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) •t(9;11)(p21.3;q23.3)/MLLT3::KMT2Aa,e •Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34)/DEK::NUP214 •t(v;11q23.3)/KMT2A-rearrangedf •t(9;22)(q34.1;q11.2)/BCR::ABL1 •inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2::MECOM(EVI1) • t(3q26.2v)/MECOM(EVI1)-rearranged •−5 or del(5q); −7; −17/abn(17p) • Complex karyotypeg , Monosomal karyotypeh • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2i • Mutated TP53j

Notes: *The Frequencies, response rates and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.*

[a] *Mainly based on results observed in intensive treatment trials. Risk assignment may change during the treatment course based on results from analyses of measurable residual disease.*

[b] *Concurrent KIT and/or FLT3 gene mutations do not alter risk categorization.*

[c] *AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.*

[d] *Only in-frame mutations affecting the basic leucine zipper (bZIP) region of CEBPA, irrespective of whether they occur alone or in combination with other CEBPA mutations.*

[e] *The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.*

[f] *Excluding KMT2A partial tandem duplication (PTD).*

g Complex karyotype: 3 or more unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities described in this table.

[h] *Monosomal karyotype: presence of two or more distinct autosomal monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosomal abnormality (excluding core-binding fator AML).*

[i] *Presence of these mutations in AML with myelodysplasia-related changes or AML secondary to therapy defines adverse-risk AML.*

[j] *TP53 mutation = a variant allele fraction of at least 10%; irrespective of the TP53 mutation and allelic status information; TP53 mutant state is significantly associated with AML with complex and monosomal karyotype.*

sorafenib, which is not available for this indication in our country, and Midostaurin, or even in more specific situations, Gilteritinib and Quizartinib[8].

MYELODYSPLASTIC NEOPLASMS/SYNDROMES (MDS)

In MDS, treatment is based on patient risk stratification into low risk (LR) or high risk (HR) groups[9]. Risk can be calculated using scoring systems, with the Revised International Prognostic Scoring System (IPSS-R) being the most commonly used. This system directs therapy based on hematological and cytogenetic characteristics but does not include genetic mutations. Recently, with the incorporation of molecular data, a new clinical-molecular prognostic model, the IPSS-M, was developed. This model adds somatic mutations in 31 genes, stratifying patients into six risk groups: very low, low, moderate-low, moderate-high, high, and very high risk[10]. Mutations such as TP53, RUNX1, EZH2, FLT3, and mutations in the RAS pathway have adverse outcomes, while mutations in the splicing factor SF3B1 are associated with favorable outcomes and prolonged survival[10,11].

Allogeneic hematopoietic cell transplantation (allo-HCT) should be performed in eligible high-risk MDS patients who are physically fit, have good performance status, and a suitable donor available as soon as possible. For patients with low-risk MDS, transplantation is generally not recommended, except in situations involving deep cytopenias, progressive increase in blasts in the bone marrow (≥15%), high transfusion requirements (≥2 units/month for 6 months), or the presence of high-risk mutations[12].

Patients who are candidates for allo-HCT and have been exposed to multiple therapies, such as growth factors, lenalidomide, hypomethylating agents, should be considered for transplant. Young patients with hypoplastic MDS should be considered for allo-HCT as soon as possible[11].

In patients with an indication for allo-HCT and the absence of an HLA-matched sibling donor, a search for unrelated donors should be initiated. Although compatible unrelated donors (MUD) and HLA-identical sibling donors are suitable options for MDS patients, as in other diseases, the use of haploidentical donors has progressively increased, showing satisfactory long-term outcomes[13].

Regarding the conditioning regimen, it is currently still based on the patient's clinical condition, with myeloablative conditioning (MAC) being used only in eligible patients who are physically fit and generally younger[13]. In elderly patients over 60 years of age, allogeneic HCT with reduced-intensity conditioning (RIC) becomes an alternative, as age alone should not be a criterion for exclusion[14]. A comprehensive geriatric assessment combining various aspects of health, including comorbidity index (HCT-CI), performance status, physical function, cognition, psychological assessment, nutritional status, social support, medication review, and biomarkers, can detect elderly patients eligible for HCT who may not be identified through performance status evaluation alone[13].

Induction therapy using hypomethylating agents (HMAs) or chemotherapy may be considered while awaiting pre-transplant assessment; however, allo-HCT should be performed as soon as possible to prevent disease progression[12]. In a Latin American study with 258 MDS patients, prior treatment with hypomethylating agents and chemotherapy before HCT showed better survival in MDS patients[15].

Relapse after allo-HCT remains one of the leading causes of treatment failure. Risk factors for relapse include somatic genomic alterations, and post-transplant monitoring with donor chimerism and measurable residual disease assessment is essential for early detection and possibly preventive treatment[7] (Dimitriou et al., 2023). When feasible, donor lymphocyte infusion (DLI) and a second allo-HCT are the recommended therapeutic options in this context[12].

08

PART II: HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT) IN LYMPHOID DISEASES

NELSON HAMERSCHLAK

INTRODUCTION

In this chapter, we will mainly address transplantation in lymphoid diseases: Hodgkin's lymphoma, acute lymphocytic leukemia, diffuse large B cell lymphoma, and mantle cell lymphoma. We know that transplantation can also be used in high-risk T lymphomas, follicular lymphoma, chronic lymphocytic leukemia and T prolymphocytic leukemia. However, these are rarer diseases where the procedure has limited use.

HODGKIN LYMPHOMA

Auto hematopoietic cell transplantation (HCT) in relapsed /refractory Hodgkin lymphoma results in 5-year progression- free survival (PFS) of around 60% and overall survival (OS) of 80%. This approach is the standard of care for these patients. Complete remission before transplant and the use of maintenance therapy for patients at high risk of relapse could improve these results[16,17]. Today, allogeneic HCT is the only strategy for curing patients who relapse from an autologous HCT. Brentuximab and check- point inhibitors could be used as a bridge therapy. Interestingly, haplotransplantation appears to be better than unrelated donor transplantation in these patients and with comparable results to those with transplantation from related donors[16,17].

ACUTE LYMPHOCYTIC LEUKEMIA

HCT is considered standard therapy for patients with high-risk acute lymphocytic leukemia (ALL) in first complete remission and for patients with subsequent remission after induction failure or relapsed ALL). For patients with standard-risk ALL in first remission, HCT is a good choice, while it should be used with clinical discretion in patients with unexpected treatment-related toxicities (e.g., prolonged severe cytopenias), liver alterations, thromboembolic complications, etc.), which prevent adequate continuation of conventional therapy. Patients with active disease are considered an exception in the choice of this therapeutic modality because the results are not at all encouraging[18]. The main clinical risk factors include age (the more advanced, the worse) and white blood cell count at diagnosis. Generally, high risk is considered to be >30,000/mm^3 for B-cell precursors and 100,000/mm^3 for T-cell precursors. Patients with certain phenotypic markers may have a poor prognosis, such as early T leukemias with low expression of CD1a, CD8 and CD5, and also some patients with concomitant myeloid markers. However, the two main points to consider today are: genetics and minimal residual disease[18].

Patients with Ph+ ALL have been defined as a very high-risk subtype. Currently, treatment results for patients with Ph+ and Ph-ALL are comparable. Using protocols with Ponatinibe, for example, allows the clinician to even dispense with bone marrow transplantation in cases of complete response with negative minimal residual disease. In adolescent and young adult patients, a significant proportion of Ph-ALL patients have a gene expression profile similar to that of BCR::ABL1+ ALL (Ph- like). This subtype is extremely aggressive, and transplantation should be considered[19]. Every transplant physician who has a patient with ALL must have three main objectives: to transplant in complete remission, to consider that transplant with negative minimal residual disease has a better prognosis, and preferably to use total body irradiation in conditioning[20].

HCT IN DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

In diffuse large B cell lymphoma (DLBCL), autologous HCT is used in patients who relapsed after the first- line therapy and following salvage chemotherapy, mainly in patients who achieve complete remission. The procedure in these cases has an OS; and PFS of around 40-50%. Three studies from different anti-CD 19 chimeric antigen receptor (CAR) T cells compared CAR T and autologous HCT. Two of them showed better results with car T versus autologous HCT[21]. So, the choice of one over another therapy has to be based oin cost and risk- benefit analysis. Autologous -HCT is still considered the standard of care for patients with late relapse (>12 months) in partial or complete remission after salvage therapy., It could be considered in very high- risk patients. Nowadays, allo-geneic HCT should still be considered a curative option for patients relapsing after CAR T[21,22].

MANTLE CELL LYMPHOMA (MCL)

Auto-logous HCT has contributed significant ly to improving the outcome for patients with mantle cell lymphoma (MCL), mainly after the addition of rituximab and high-dose cytarabine (HD-ARAC) to the induction treatment, improv ing PFS and OS. Rituximab is used as a mainte nance therapy. The TRIANGLE study published recently showed that the addition of iIbrutinib to RCHOP-HD-ARAC induction, followed by maintenance, improved first-line treatment of MCL, and we do not know if au-tologous HCT is still necessary. It has recently been demonstrated that patients in complete remission and with minimal residual disease negative by liquid biopsy can dispense with transplantation. TP53- mutated MCL is still an issue, and clinical trials are necessary to devel-op guidelines for this kind of patient. Allogene-ic-HCT as salvage therapy could benefit around 40% of the patients, depending on disease sta-tus before the procedure. The advent of CAR T cells for MCL, such as DLBCL, will likely further limit the use of allogeneic HCT.

08

PART III: HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT) IN CHRONIC MYELOPROLIFERATIVE NEOPLASMS

VANEUZA ARAÚJO MOREIRA FUNKE

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)[23]. This document will review the main relevant points in Hematopoietic Cell Transplants (HCT) for this group of diseases.

PHILADELPHIA-POSITIVE MYELOPROLIFERATIVE DISEASE

CHRONIC MYELOID LEUKEMIA

HCT INDICATIONS

Imatinib mesylate, nilotinib, bosutinib or dasatinib are the treatments of choice for newly diagnosed chronic phase (CP) chronic myeloid leukemia (CML)[24-27].

Recently, asciminib, an allosteric inhibitor that binds a myristoyl site of the BCR-ABL1 protein has been studied both in resistant and first line scenarios[28,29]. Ponatinib has been used for CML resistant to other TKI and patients harboring T315I mutants[30]. Considering all these effective and safe therapies, the indications for hematopoietic cell transplantation (HCT) have been restricted to resistant cases and advanced disease. However, in Brazil, due to low access to third line TKIs, it may be used earlier.

The main indications for hematopoietic stem cell transplantation (HCT) for adult CML patients in the tyrosine kinase inhibitor (TKI) era can be summarized below:

a) Advanced phase disease: in accelerated phase (AP), HCT 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. It can also be indicated in case of unmanageable intolerance to all TKIs[31-34]. In blast crisis (BC), it should always be considered, preferably after a preliminary course of TKI therapy with or without chemotherapy[34,35].

b) Chronic Phase: in case of failure of imatinib, in accordance with the European LeukemiaNet 2020 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 HCT, if the former is unavailable[34].

c) T315I mutation, if ponatinib or asciminib is unavailable[34].

HLA COMPATIBILITY, CONDITIONING AND CELL SOURCE

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[36,37].

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[38-40].

Matched or mismatched unrelated donors or haploidentical transplants are acceptable in the absence of an HLA-identical sibling donor[41,42].

Use of imatinib mesylate and of second generation TKIs (dasatinib, nilotinib or bosutinib) previously to HCT 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[43,44].

GVHD Phrophylaxis

Graft-versus-host disease (GVHD) prophylaxis should be based on a calcineurin inhibitor (cyclosporin, tacrolimus) plus methotrexate for matched related donors[45]. 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[46]. There is evidence for using Anti thymocyte globulin (ATG) for related transplants using peripheral blood as stem cell source or unrelated matched or mismatched transplants[47]. Recently, post-transplantation cyclophosphamide has been demonstrated to be superior to ATG in unrelated transplant in a BMT-CTN study[48], but there is no study in Brazil, where there is high CMV prevalence and low access to CMV prophylaxis with letermovir[49]. Post-transplantation cyclophosphamide is the standard prophylaxis when using haploidentical donors[50].

MONITORIZATION AND RELAPSE THERAPY

Post-transplant monitoring of BCR-ABL shall be performed using real time quantitative polymerase chain reaction (RT-qPCR) for the entire life of the patient, since there are reports of very late relapse (>20years after HCT)[51]. A recommendation for monitorization schedule is showed in table 2.

Molecular relapse was defined formerly as progressively increasing BCR-ABL/ABL1 gene transcripts in at least two consecutive results and loss of major molecular response (>0,1%). However, there is very little evidence of the relapse definition using the current RT-qPCR method in patients previously treated with TKIs[52,53].

In case of molecular relapse, consider donor lymphocyte infusions (DLI) escalated doses at three-month intervals (table 2). 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. In case of hematologic relapse in CP or cytogenetic relapse, consider DLI, starting at higher doses (1×10^7, 5×10^7, 1×10^8 CD3+ cells/kg), or a TKI, or a combination of these. In case of hematologic relapse in AP or BC, consider the use of a TKI plus DLI[54-58].

First or second generation TKI 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. TKIs may also be combined with DLI. Prompt and long-lasting responses are usually seen under TKI therapy for CML relapsing in CP. Response tends to be worse and less durable in AP or BC relapse[55-58].

In patients previously resistant or intolerant to imatinib mesylate, consider using a second generation TKI alone or in combination with DLI. 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[55-58].

Consider using post-transplant TKI prophylaxis for two years in patients at a high risk for relapse (>1st CP and AP/BC). There is no evidence for maintenance therapy with TKI for patients transplanted in chronic phase[58-60].

In case a post-transplant BCR-ABL fusion gene mutation is detected, the mutational profile should be considered when choosing the most appropriate TKI. If the mutation is detected pre-transplant, mutational analysis should be repeated after relapse, since there are reports of new mutations, different to those identified pre transplant[61].

A second allogeneic HSCT may be considered in case of TKI- and/or DLI- resistant relapse, if a suitable donor is available, in the absence of contraindications[62].

TABLE 1: European LeukemiaNet 2020 chronic myeloid leukemia treatment recommendations[34,37]

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-HCT)
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 HCT, donor search.
Ponatinib failure	High risk of progression, early allo-HCT 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-HCT soon after CP2 is achieved.

ACA: additional chromosomal aberrations; ALL: acute lymphoblastic leukemia; allo-HCT: 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[54-58]

Time after HSCT	MONITORING	RESULT	INTERVENTION
2 years	Quantitative RT-PCR every 3 months	Molecular relapse: increasing BCR-ABL/ABL ratio in two measures: relapse cutoff defined by local lab	Consider escalated dose DLI. For related transplants: CD3+/Kg: 10^6 ⟶ 5 x 10^6 ⟶ 10^7 ⟶ 5 X 10^7 ⟶ 10^8 every 3 months. For unrelated transplants: 1 log less: 10^5 ⟶ 5 X 10^5 ⟶ 10^6 ⟶ 5 X 10^6 ⟶ 10^7 Hold dose if chronic GVHD signs or symptoms
3-5 years	Quantitative RT-PCR every 6 months		
After 5 years	Quantitative RT-PCR every year		
Any time	Cytogenetics if positive PCR	Cytogenetic relapse	Consider DLI as above and TKI *
Any time	Complete blood count	Hematologic relapse	Consider DLI as above and TKI *

DLI = donor lymphocyte infusions; GVHD = graft-versus-host disease; RT-PCR = real time polymerase chain reaction; * choice of TKI depending of pre transplant response and mutational analysis.

PRIMARY MYELOFIBROSIS, POLYCYTHEMIA VERA, ESSENTIAL THROMBOCYTHEMIAA

INTRODUCTION

HCT is the only curative therapy for primary myelofibrosis (PMF), or MF derived from polycythemia vera (PV), and essential thrombocythemia (ET)[23]. We will review current indications and management of HCT for this indication.

STRATIFICATION

Patients with PMF often have a dismal prognosis, with a mean overall survival of only six years after diagnosis[63]. Even so, the clinical course is highly heterogeneous, and survival may vary from a few months to more than 10 years[63,64]. Therefore, prognosis may be better estimated by scoring systems, among which the Dynamic International Prognostic Scoring System plus (DIPSS plus)[65] is one of the most applied. Polycythemia vera and essential thrombocythemia, in turn, have a more favorable prognosis, and patients should only be referred for allogeneic HCT in case myelofibrosis or leukemic transformation develop. At fibrotic phase PV or ET, the MYSEC prognostic index can be used (http://www.mysec-pm.eu)[66].

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)[67] and the Clinical-Molecular Myelofibrosis Transplant Scoring System (MTSS)[68] to be applied. This may help in the clinical decision-making process when assessing eligibility for transplantation, particularly in DIPSS plkus intermediate 1 patients. In most centers in Brazil there is no access to mutation profile, and DIPSS or DIPSS plus must then be used[69].

INDICATION

Transplant indication should be based on the MIPSS 70+ score and MTSS score when available. If molecular evaluation is unavailable, allogeneic HCT should be performed in intermediate-2 and high-risk DIPPS or DIPPS plus score patients[70]. HSCT may sometimes be considered for patients classified as intemediate-1 risk, particularly in younger patients and those with high transfusion dependency, more than 2% blasts in peripheral blood, or with an unfavorable karyotype[71].

CONDITIONING REGIMEN AND STEM CELL SOURCE

It has not yet been defined what the ideal conditioning regimen is in transplantation for PMF patients. For patients under the age of 50, MAC is recommended while RIC is the preferred regimen for those over 50 years old[72]. Fludarabine associated with busulfan or melphalan are the most used regimens[73,74]. There is a recent report of association to thiotepa[74]. There is no evidence of superiority between these 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[74].

The use of conditioning regimens containing fludarabine and busulfan with serum level control seems to reduce relapse without increasing transplant-related mortality. Non-myeloablative conditioning has also a higher rate of graft failure[71].

PBSCs are the preferred stem cell source, and bone marrow is also acceptable[71].

DONOR

HLA-matched unrelated donors are an acceptable alternative for patients without an HLA-identical sibling donor[71]. HLA-mismatched related or unrelated donors may also be acceptable, although with generally worse results[75,76].

There are recent data published on results of haploidentical transplantation in PMF. In 2019, the EBMT group published a retrospective report of 56

patients. 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%. At two years, overall survival was 56%, the incidence of relapse was 19%, and non-relapse mortality was 38%[75].

A CIBMTR study on 1597 patients found that MSD-HCTs were superior, and there was no significant difference in HCT outcomes from haploidentical and MUDs[76]. These studies have demonstrated that haploidentical transplantation is feasible, with a comparable overall survival to unrelated transplants[75,76].

PRE-TRANSPLANT STRATEGIES

SPLENECTOMY

Routine splenectomy prior to transplant is not recommended in patients with splenomegaly, except in cases with a spleen size greater than 20cm[71]. Splenic radiation, in turn, can be considered and may result in lower relapse rate[77].

RUXOLITINIB

Ruxolitinib is a Janus kinase (JAK) 1/2 inhibitor involved in the pathophysiology of PMF. Despite its effectiveness in controlling PMF symptoms, it should not be regarded as an alternative to HSCT, since it does not affect the natural history of the disease. Hence, it should not delay referral for transplantation[70].

Some studies have evaluated pre-transplant use of ruxolitinib. In a prospective, phase II study of 21 patients, ruxolitinib was started 60 days before conditioning, gradually decreased in four days, until complete withdrawal one day before conditioning[78]. Another prospective phase II study investigated ruxolitinib use for at least eight weeks pre-transplant, with a gradual reduction of 5 mg every four days and withdrawal four days before stem cell infusion[79]. In both studies the drug was safe.

In conclusion, ruxolitinib therapy prior to HSCT seems to be safe and to improve overall survival in patients who are referred for transplantation[78,79].

DONOR LYMPHOCYTE INFUSION

JAK2-V617F allele burden has been shown to be related to relapse after HSCT[80]. For patients with PMF and evidence of minimal residual disease (MRD) or clinical relapse, discontinuation of immunosuppressive drugs, use of DLI or a second HSCT are treatment strategies of choice. In the MRD setting, preemptive therapy with DLI has shown favorable results compared to salvage therapy and should thus be regarded as a potentially useful approach[81].

TABLE 3: HSCT indications for Myeloproliferative Neoplasms

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

AP: Accelerated phase CML; BP: Blast phase CML; CML: Chronic myeloid leukemia; S: standard; 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; TKI: tyrosine kinase inhibitor.

*CO: circulating blasts, high risk mutations

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09

ACQUIRED APLASTIC ANEMIA AND PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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INTRODUCTION

Severe aplastic anemia (SAA) is a rare, life-threatening disorder characterized by pancytopenia and bone marrow hypoplasia or aplasia, in the absence of neoplastic infiltration or fibrosis. SAA is classified as either inherited or acquired (immune-mediated). Inherited SAA results from genetic defects and is more common in pediatric patients, whereas immune-mediated SAA, which can occur at any age, arises from autoimmune destruction of hematopoietic stem cells.

Unlike immune SAA, inherited forms do not respond to immunosuppressive therapy (IST) and are usually associated with characteristic phenotypes. Immune SAA, however, often responds to IST, although hematopoietic stem cell transplantation (HSCT) remains the preferred treatment for younger eligible patients. Without treatment, the disease is frequently fatal due to severe infections or hemorrhagic complications, particularly in patients with profound cytopenias who require frequent red cell and platelet transfusions.

Long-term complications include clonal evolution (e.g., myelodysplastic syndrome, acute leukemia), paroxysmal nocturnal hemoglobinuria (PNH), and **iron overload**, all of which contribute to morbidity. Treatment decisions are guided by disease severity (per Camitta criteria), patient age, and the availability of a matched related donor. Supportive care remains essential and plays a crucial role in improving survival outcomes.

FIRST-LINE TREATMENT FOR IMMUNE ACQUIRED SAA

Hematopoietic stem cell transplantation from an HLA-matched sibling is the preferred treatment for patients under 40 years of age. In pediatric patients, matched unrelated donor (MUD) transplantation is also considered first-line therapy if the procedure can be performed within 2–3 months. If a timely transplant is not feasible, IST should be initiated, preferably with horse-derived antithymocyte globulin (h-ATG), cyclosporine, and eltrombopag.

HLA typing for the patient and family should be performed immediately upon diagnosis in all candidates for HSCT. Bone marrow is the preferred stem cell source in SAA to minimize the risk of chronic graft-versus-host disease (GVHD).

The conditioning regimen for matched related donor (MRD) HSHT consists of cyclophosphamide (CY) 200 mg/kg and rabbit ATG 5–7.5 mg/kg. For MUD HCT, the recommended regimen includes fludarabine 120 mg/m^2, CY 120 mg/kg, rabbit ATG 5–7.5 mg/kg, and total body irradiation (TBI) 200 cGy.

GVHD prophylaxis involves a calcineurin inhibitor (CNI) (tacrolimus or cyclosporine A) combined with a short course of methotrexate. The calcineurin

inhibitor is typically maintained for up to one year, followed by a gradual taper to prevent disease relapse and GVHD.

SECOND-LINE TREATMENT FOR IMMUNE ACQUIRED SAA

Patients who do not respond to first-line IST should undergo bone marrow reassessment to exclude clonal evolution. For those younger patients who are refractory or relapsed after initial IST, alternative donor transplantation should be prioritized especially in the absence of significant comorbidities. A MUD HSCT is the first choice if available and if transplantation can be performed within a reasonable timeframe. If a suitable MUD is not identified, haploidentical transplantation serves as a viable alternative, with recent Brazilian data demonstrating encouraging event-free survival rates. The decision between a mismatched unrelated donor (MMUD) and a haploidentical related donor should be individualized, taking into account factors such as the urgency of transplantation, neutrophil count, recipient's age, donor characteristics (age, gender, ABO/CMV compatibility), and the presence of donor-specific anti-HLA antibodies (DSA).

Based on national experience, the recommended conditioning regimen for haploidentical HSCT consists of Fludarabine 150 mg/m^2, Cyclophosphamide (CY) 29 mg/kg, and Total Body Irradiation (TBI) 400 cGy in a single dose. The use of an increased total body irradiation (TBI) dose has been linked to lower primary graft rejection rates. However, its long-term effects, particularly in younger patients, remain uncertain, including potential impacts on fertility and other late complications. The role of rabbit antithymocyte globulin (ATG) in conditioning for haploidentical HCT is still debated, though it may be considered in patients who have not previously received ATG during IST. Bone marrow is the preferred stem cell source to reduce the risk of chronic GVHD. GVHD prophylaxis is based on post-transplant cyclophosphamide (PTCY), which includes cyclophosphamide (CY) at 50 mg/kg/day on days +3 and +4, mycophenolate mofetil (MMF) at 45 mg/kg/day from day +5 to +35, and a CNI (tacrolimus or cyclosporine) from day +5 to +365. This regimen is also recommended for mismatched unrelated donor transplants, with the CNI gradually tapered after one year to reduce the risk of relapse.

Haploidentical transplantation is currently being investigated as first line therapy in clinical trials at specialized centers, particularly for young patients with very severe SAA (absolute neutrophil count < 200/µL) and for those with severe, life-threatening infections where urgent intervention is required, and there is insufficient time to wait for an IST response.

PAROXYSMAL NOCTURAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematologic disorder characterized by hemolysis (destruction of red blood cells), bone marrow failure, and thrombosis. It is caused by a mutation in the PIGA gene, which leads to a deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on the surface of blood cells. This defect makes red blood cells highly susceptible to complement-mediated lysis. Diagnosis is made by flow cytometry, identifying GPI-anchor protein deficiency on blood cells (e.g., CD55/CD59 absence). LDH is a reliable marker of intravascular hemolysis and is often elevated in PNH.

Treatment options for PNH primarily focus on complement inhibition, with HSCT reserved for cases associated with SAA or refractory disease. Eculizumab, a C5 inhibitor, effectively reduces intravascular hemolysis and thrombosis risk, significantly improving survival. Ravulizumab, a long-acting C5 inhibitor, provides similar benefits with less frequent dosing, improving convenience and adherence. Proximal complement inhibitor targeting C3 and Factor B inhibitors, have been more recently approved and may offer additional treatment options, particularly for patients with suboptimal responses to C5 inhibition.

HSCT remains the only curative approach for PNH but is typically considered for patients with severe bone marrow failure. A history of thrombosis has been identified as an adverse prognostic factor for HSCT outcomes, whereas patients without this complication tend to have better results, similar to those observed in HSCT for SAA. Given its frequent association with aplastic anemia and other bone marrow failure syndromes, PNH management requires a multidisciplinary approach to optimize long-term outcomes.

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10
COMORBIDITY INDEX AND GERIATRIC ASSESSMENT

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In the evaluation of transplant candidates, in addition to age, traditional tools used to determine transplant prognosis include disease status at the time of transplant, donor type, graft source, and performance status (Karnofsky/ECOG-PS scale). However, additional tools to more accurately assess comorbidities and physiological age may provide better discrimination for transplant outcomes. Below, the most common tools used in pre-transplant evaluation for hematopoietic cell transplantation (HCT) will be briefly discussed.

HEMATOPOIETIC CELL TRANSPLANTATION COMORBIDITY RISK (HCT-CI)

The HCT-Comorbidity Index (HCT-CI) is one of the most commonly used tools to evaluate comorbidities in the hematopoietic cell transplantation (HCT) setting. Initially developed to enhance the risk stratification of non-relapse mortality (NRM), as the presence of comorbidities has long been recog- nized as a significant prognostic factor in oncology.[1]

The HCT-CI model incorporates 17 comorbidities, categorized into scores ranging from 1 to 3 (Table 1). It has shown significantly greater discriminative power compared to the Charlson Comorbidity Index (CCI), which was primarily based on age and comorbidity burden, both for predicting non-relapse mortality (NRM) and overall survival (OS). The HCT-CI has been validated in multiple retrospective and prospective multicenter studies and effectively summarizes the impact of relevant co- morbidities on hematopoietic cell transplantation (HCT) outcomes.[2-4]

Additionally, the HCT-Comorbidity Index (HCT-CI) can predict the risk of developing post-transplant complications, the occurrence of acute graft-versus-host disease (GVHD) grades III and IV, as well as subsequent mortality following the diagnosis of acute GVHD grades II or II-IV.[5]

Recent modifications have been introduced to the HCT-CI to improve its discriminative power such augumented HCT-CI[6]. One additional point was assigned to patients aged 40 years or older, creating a new combined score: the comorbidity/age score[7]. This HCT-CI demonstrates greater statistical power in predict- ing non-relapse mortality (NRM) compared to the HCT-CI alone. Furthermore, the HCT-CI score can also be used in combination with other scales that incorporate additional specific risk variables. It is one of most common tool used to evaluate comorbidity in HCT setting and also predicts OS in the post-transplant cyclophosphamide era[8]. (calculator: *http://www. hctci.org/home/calculator*).

EUROPEAN BONE MARROW TRANSPLANTATION SCORE (EBMT SCORE)

The score was developed by the European Bone Marrow Transplantation (EBMT) group and is based on five key characteristics:

1. Patient age: categorized as ≤20 years, 20-40 years, and >40 years;
2. Disease stage: classified as early, intermediate, and advanced;
3. Interval be- tween diagnosis and transplant: divided into <12 months and ≥12 months;
4. Donor type: classified as related or unrelated;
5. Combination of donor and recipient sex: specifically, female donor/male recipient versus all other combinations. These factor are used to calculate the score, which helps assess transplant outcomes and risks.

The score provides a straightforward tool to quick evaluate the chances and risks of hematopoietic stem cell transplantation (HCT) for a patient prior to the procedure. With a variable score ranging from 0 (best) to 7 (worst), it is applicable to all hematological disorders, for both allogeneic and autologous HCT (score 0-5), and is valid for both standard and reduced-intensity conditioning regimens. Survival outcomes are poorer for older patients, those transplanted in advanced disease stages, those with a longer time interval between diagnosis and transplant, and those with an incompatible donor, compared to younger patients transplanted early in the disease stage with a well- matched donor[9]. The EBMT risk score was validated in Various hematologic disorders (ie, AML, myelodysplastic syndromes, ALL, CML, multiple myeloma, non-Hodgkin lymphoma and aplastic anemia), which predicted survival, TRM, and death from relapse[10-12]. The EBMT score was also combined with comorbidity specific information[13].

PRETRANSPLANTATION ASSESSMENT OF MORTALITY (PAM) SCORE

The PAM (Pre-transplantation Assessment of Mortality) score was developed to predict all-cause mortality after hematopoietic cell transplantation (HCT) and includes eight factors: age, donor type, disease risk, conditioning regimen, serum creatinine, serum alanine aminotransferase (ALT), forced expiratory volume in one second (FEV1), and pulmonary diffusing capacity for carbon monoxide (DLCO). One advantage of this scoring system is that it incorporates actual laboratory values to assess organ function, rather than relying on dichotomized patient scores.

Due to the evolution of allogeneic HCT (allo-HCT) strategies, including the increased use of non-myeloablative conditioning regimens, the PAM score was re-evaluated and simplified nine years later[14]. The revised model omitted FEV1, DLCO, ALT, and creatinine values; added donor/recipient cytomegalovirus (CMV) status; incorporated the Disease Risk Index (DRI) for disease risk stratification; and used HLA compatibility to re-categorize unrelated donors. The modified PAM score demon- strated improved predictive value for patients undergoing myeloablative conditioning[15].

EASIX - ENDOTHELIAL ACTIVATION AND STRESS INDEX

The Disease Risk Index (DRI) was developed to assess the impact of disease type and status (e.g., acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], and myelodysplastic syndromes [MDS]) on survival outcomes (Table 2)[16]. Researchers from two leading transplant centers in the United States—the Dana-Farber Cancer Institute and the Fred Hutchinson Cancer Research Center (FHCRC)—collaboratively developed the DRI scoring model. The DRI provides critical prognostic information related to the risks of relapse and relapse-related mortality following hema- topoietic cell transplantation (HCT). It is considered an essential complement to patient-risk assessment tools, such as the HCT-Comorbidity Index (HCT-CI) and Karnofsky Performance Status (KPS), when making clinical decisions.

However, the DRI does not account for advanced molecular prognostic features of certain diseases or the assessment of measurable residual disease (MRD). As a result, it needs to be used in conjunction with other tools and clinical evaluations to provide a more comprehensive risk assessment for HCT

patients. DRI also predicts OS in the post-transplant cyclophosphamide era[8]. Calculator: *https://cibmtr.org/CIBMTR/Resources/Research-Tools-Calculators/Disease-Risk-Index-DRI-Assignment-Tool*

DISEASE RISK INDEX (DRI)

The Endothelial Activation and Stress Index (EASIX) is a biomarker-based prognostic model that relies on three laboratory values: serum creatinine, lactate dehydrogenase (LDH), and platelet count[17-18]. It is calculated using the formula: LDH (U/L) × creatinine (mg/dL) / platelets ($\times 10^9$/L). EASIX predicted mortality and transplant-associated microangiopathy (TAM) after HCT in a multicenter cohort.Its prognostic value remained independent of the HCT-CI and EBMT risk scores[18].

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN OLDER ADULTS AND GERIATRIC ASSESSMENT

We are living in an era where aging is a global phenomenon, and this trend is also occurring in Brazil[19]. Reaching old age exposes populations to a greater risk of adverse health events, with one of the most significant risks being the development of cancer and chronic diseases. Incidence rates of most cancers, including hema- tological malignancies, increase significantly after the age of 70–80 years.

Many older adults are diagnosed with high-risk hematologic malignancies that are difficult to cure without the use of allogeneic hematopoietic cell transplantation (HCT). However, older adults are also more likely to have comorbid conditions, which has led to higher rates of morbidity and mortality, complicating treatment decisions for individuals of advanced chronological age[20]. Age related changes and comorbidities often require individualized modifications to standard therapies to improve tolerability and safety. Numerous studies have increasingly highlighted the importance of tailoring cancer treatment for older adults patients[21-22].

Several frailty assessment tools used in geriatric medicine have been applied to older adults and less fit patients undergoing chemotherapy, including those with hematological malignancies. Many medical societies recommend that all older adults with cancer undergo a geriatric assessment using these tools before starting oncologic treatment. Due to the complexity of managing older patients with cancer, these assessments are essential for optimizing treatment plans and improving outcomes[23-25].

In recent years, significant advances have led to an increased use of allogeneic hematopoietic cell transplantation (HCT), extending its application to older and more comorbid adults, a trend also observed in Brazil[26-27]. Allogeneic HCT in elderly patients is feasible, and age alone should not be a barrier to transplantation. However, transplant-related toxicities and non-relapse mortality (NRM) remain significant challenges in this population.

GERIATRIC ASSESSMENT (GA)

GA represents the gold standard for health as- sessment in older adults. It is a multidisciplinary tool used in geriatrics and geriatric oncology, encompassing multiple health domains such as comorbidity, functional status, nutrition, poly- pharmacy, psychological health, and social cir- cumstances. Recently, GA and biomarkers have emerged as promising tools to refine risk estimates for older adults undergoing HCT. Numer- ous studies have demonstrated the benefits of using GA to detect vulnerabilities, frailty, cogni- tive impairment, and to guide prognostication and interventions prior to HCT[28-30].

Optimal prognostication in older populations likely requires evaluating vulnerabilities across multiple health domains and incorporating biomarkers. Composite scores for HCT outcomes have been developed, integrating the HCT-Comorbidity In- dex (HCT-CI), age, instrumental activities of daily living (IADL), and biomarkers[6,31].

The BMT CTN 1704 study recently developed and validated the CHARM risk score, which stratifies risk for non-relapse mortality and overall mortality in older adults. CHARM out- performs the HCT-CI alone and assigns a total score based on seven health variables:

1. In creasing age,
2. Higher HCT-CI scores,
3. Low- er albumin levels,

4. Higher C-reactive protein levels,
5. Greater weight loss over the preceding year,
6. Lower patient-reported performance status scores, and
7. Lower cognitive scores on the Montreal Cognitive Assessment (MoCA).

A CHARM calculator is available online at: [CHARM Risk Calculator] *(https://cibmtr.org/CIBMTR/Off- Nav/DevSandbox/CHARM-Risk-NRMCalculator)*.

The CHARM score also predicts worse frailty, disability, cognitive decline, and serious organ toxicities[32-33].

DECISION-MAKING BEFORE HCT

The best approach to decision-making before HCT requires balancing the risks of disease relapse and non-transplant-related mortality. The comorbidities scores such as HCT-CI, EBMT score and so on provides valuable information on a patient's potential tolerance to the transplant process, accurate- ly stratifying NRM risks. Meanwhile, the Disease Risk Index (DRI) evaluates relapse probabilities. In clinical practice, combining these tools may offer a more accurate and precise prediction of post-transplant survival rates.

The use of Comprehensive Geriatric Assessment (CGA) is promising for predicting outcomes in elderly HCT candidates. All older adults being considered for HCT should undergo CGA, including assessments of functionality, cognition, polypharmacy, comorbidity, and nutrition, to guide decision-making and interventions prior to transplantation (tools examples in Table 3). While the CHARM risk calculator provides a new tool for estimating NRM, overall mortality, frailty, disability, and cognitive decline, further validation in diverse populations, includ- ing Brazil, is needed.

In conclusion, integrating CGA, comorbidities scores, DRI, and emerging tools like CHARM can enhance risk stratification and improve outcomes for older adults undergoing HCT.

TABLE 1: HCT-CI Score and Augmented HCT-CI[22]

HCT-CI	
Comorbidity	**Definition**
Arrhythmia	Any type of arrhythmia requiring antiarrhythmic treatment at any point in the patient's medical history.
Cardiac Disease	Coronary artery disease*, CHF, MI, or EF ≤ 50%
Inflammatory Bowel Disease	Crohn's disease or ulcerative colitis requiring treatment at any point in the medical history of the patient
Diabetes	Requiring insulin or oral hypoglycemic treatment continuously for 4 weeks before conditioning
Inflammatory Bowel Disease	Transient ischemic attack or stroke
Psychiatric Disorder	Any disorder requiring continuous treatment for 4 weeks before conditioning
Mild Hepatic Disease	Chronic hepatitis, bilirubin > ULN to 1.5xULN, or ALT/AST > ULN to 2.5xULN, with at least two measurements of each 2-4 weeks before conditioning
Obesity	Patient with BMI > 35kg/m^2 for patients > 18 years or BMI ≥ 95th percentile for age ≤ 18 years
Infection	Requires antibiotic treatment starting before conditioning and continuing beyond D0
Rheumatologic Disease	Requiring specific treatment at any point in the medical history of the patient.
Peptic Ulcer	Diagnosed by previous endoscopy or radiological diagnosis
Moderate/Severe Renal Disease	Serum creatinine > 2mg/dl (at least two measurements 2 or 4 weeks before conditioning), on dialysis, or history of previous kidney transplant
Moderate Pulmonary Disease	Corrected DLCO and/or FEV1 of 66-80% or dyspnea with minimal exertion
Previous Malignant Disease	Has received treatment at any point in the medical history, excluding non-melanoma skin cancer
Valvular Heart Disease	At least moderate severity, prosthetic valve, or symptomatic mitral valve prolapse
Severe Pulmonary Disease	Corrected DLCO and/or FEV1 ≤ 65% or dyspnea at rest requiring oxygen
Moderate/Severe Hepatic Disease	Cirrhosis, bilirubin > ULN to 1.5xULN or ALT/AST > ULN to 2.5xULN, with at least two measurements of each 2-4 weeks before conditioning.
Elevated Ferritin	≥ 2500 with a recent measurement before conditioning
Mild Hypoalbuminemia	< 3.5-3.0 with a recent measurement before conditioning
Thrombocytopenia	< 100,000 with a recent measurement before conditioning
Moderate Hypoalbuminemia	< 3 with a recent measurement before conditioning

Abbreviations: HCT-CI and HCT-CI augmented: Hematopoietic Stem Cell Transplantation Comorbidity Index; CHF: congestive heart failure; MI: acute myocardial infarction; EF: ejection fraction; ULN: upper limit of normal; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: forced expiratory volume in the first second

TABLE 2: Disease Risk Index

Disease Risk Index (DRI)		
Disease	Disease Risk	
AML with favorable cytogenetics	Low	
CLL		
CML		
Indolent B-cell NHL		
ALL	Intermediate	
Intermediate-risk cytogenetics AML		
Intermediate-risk cytogenetics MDS		
Myeloproliferative disease		
Multiple myeloma		
HL		
Diffuse Large B-Cell Lymphoma Transformed Indolent B-Cell Lymphoma		
NHL		
Mantle Cell Lymphoma		
Nodal T-cell lymphoma	High	
AML with adverse cytogenetics		
MDS with adverse cytogenetics		
Extranodal T-cell lymphoma		
Stage	Stage Risk	
Any RC (Remission Complete)	Low	
1ª RP (Relapse Partial)		
No treatment		
Chronic phase CML		
2a RP or subsequent (if RIC)		
2a RP or subsequent (if MAC)	High	
Induction failure		
Active relapse		
Accelerated or blastic phase CML		
Global Assessment		
Disease Risk	Risk Stage	DRI
Low	Low	Low
Low	High	Intermediate
Intermediate	Low	
Intermediate	High	High
High	Low	
High	High	Very High

Abbreviations: AML (Acute Myeloid Leukemia), MDS (Myelodysplastic Syndromes), CML (Chronic Myeloid Leukemia), NHL (Non-Hodgkin Lymphoma), ALL (Acute Lymphoblastic Leukemia), HL (Hodgkin Lymphoma), DLBCL (Diffuse Large B-Cell Lymphoma), CR (Complete Remission), PR (Partial Remission), RIC (Reduced Intensity Conditioning), and MAC (Myeloablative Conditioning).

TABLE 3 – Geriatric assessment tools used in HCT[34]

Domains	TOOLS
Physical function	Instrumental Activities of Daily Living Timed Up and Go Grip strength 4-meter walk Number of falls
Comorbidity	HCT-CI
Nutritional status	Weight loss Body mass index Albumin Mini-MAN
Cognition	Mini-Mental Status Exam Montreal Cognitive Assessment Orientation-Memory-Concentration Test Clock test
Psychological	Geriatric Depression Scale Mental Health Inventory
Polypharmacy	>5 medications

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11
NON-INFECTIOUS COMPLICATIONS

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Hematopoietic cell transplants (HCT) use a preparatory or conditioning regimen, high-dose chemotherapy to eradicate resistant tumor cells in patients with malignant diseases, and the autologous hematopoiesis in patients undergoing allogeneic transplants. Acutely, most chemotherapy is associated with nausea, vomiting, and a variable degree of mucosal damage, that presents as oral mucositis and diarrhea. Temporary alopecia only starts at least a week after the chemotherapy. The total body irradiation (TBI), also used in some allogeneic transplants, causes some parotid glad swollen, and mild skin erythema on the days it is administered. The conditioning therapy causes pancytopenia, that usually lasts for a couple weeks before the hematological reconstitution happens (engraftment), predisposing the patient to infections, risk of bleeding and need of platelets and red blood cell transfusions.

The highest benefit of the HCT is the chance of curing the underlying disease, but some patients may have treatment-related toxicities that are so severe that may cause death; this is called **transplant-related mortality** (TRM) or non-relapse mortality (NRM), defined as death without malignant disease activity occurring within 100 days after the HCT. The chance of TRM depends on several patient factors (underlying disease, disease stage, age, presence of organ dysfunctions), type of transplant (lowest in autologous, followed by HLA-identical related and unrelated and highest in HLA-mismatched HCT), conditioning regimen (myeloablative *vs.* reduced toxicity and reduced intensity) and the occurrence of HCT-related complications. Overall, the chance of dying due to the transplant itself ranges from 2-5% after autologous HCT, 5-10% after allogeneic HCT from matched sibling donors[1], 27-32% after unrelated and haploidentical family donors[2] and up to 50% in unrelated cord blood HCT[3].

The most frequent life-threatening complications are infections and graft-versus-host disease (GVHD) after allogeneic HCT[1], discussed in other chapters. Other important short term severe complications, unique to HCT, are secondary to endothelial damage (veno-occlusive disease, transplant-related microangiopathy, engraftment syndrome), hemorrhagic cystitis, and graft rejection[4].

Veno-occlusive disease (or sinusoidal obstruction syndrome - SOS) usually occurs in the first two weeks post-HCT and presents as right upper quadrant pain, worsening thrombocytopenia or refractoriness to platelet transfusions, increased direct bilirubin, ascites, weight gain due to edema and may progress to renal, respiratory and multi-organ failure, with a 30% to 50% mortality. Predisposing factors are hepatic abnormalities, **iron overload**, and the use of myeloablative conditioning. The probability of each patient to develop VOD by day 100 can be estimated with the CIBMTR calculator. Iron chelation prior to

the HCT and the use of ursodiol (Ursacol®) can decrease the chance of developing VOD. The only specific therapy is defibrotide, initiated as soon as possible, ideally within two days of the VOD onset, associated or not to pulse steroids[5-7].

Transplant-associated microangiopathy (TMA) occurs within the first three months post-HCT, more often after allogeneic myeloablative HCT, tandem autologous HCT for neuroblastoma, with the use of TBI in HLA-mismatched HCT, in patients using calcineurin inhibitors, developing GVHD and having cytomegalovirus reactivations. Diagnosis is based on the presence of at least four of the seven criteria: 1) Severe hypertension, usually with the need of multiple anti-hypertensives; 2) anemia (despite neutrophil engraftment); 3) thrombocytopenia/ refractoriness to transfusions; 4) LDH above normal; 5) presence schistocytes in the peripheral smear; 6) soluble C5b-9 (sC5b-9) above normal (currently unavailable in Brazil); 7) proteinuria (≥1 mg/mg) random urine protein-to-creatinine ratio[8]. Pathology may reveal arteriolar occlusions when biopsies are performed and massive intestinal bleeding (usually without diarrhea) and pericardial effusions are also frequent presentations. TMA may be very severe, with 50%-60% mortality. The use of prophylactic eicosapentaenoic acid (EPA from Omega-3 supplements) and N-acetylcysteine[9] have been shown to dramatically decrease the incidence of TMA in children. Treatment includes complement inhibitors[10], that are unfortunately extremely expensive; if they are not available, the discontinuation of calcineurin inhibitors, replacing them with steroids, and prompt initiation of plasmapheresis may be lifesaving[11].

Engraftment syndrome occurs in up to a third of the patients due to cytokine release around the time of engraftment, the hematological recovery after the HCT. It may cause fever, skin rash, peripheral and noncardiogenic pulmonary edema, increased bilirubin, transaminases, creatinine, or even unexplained encephalopathy in severe cases. Treatment usually includes steroids 1-2 mg/kg/day for a few days, followed by rapid tapering[4].

Hemorrhagic cystitis may be a painful transplant-related complication that lasts for several weeks post-HCT[12]. Within the first days after the HCT, hemorrhagic cystitis is usually due to the direct toxicity of the cyclophosphamide metabolites in contact with the urothelium. It may be prevented with hyperhydration, the use of Mesna and frequent diuresis within the first day after receiving cyclophosphamide to decrease the chemical damage of the bladder. Later after HCT, hemorrhagic cystitis is usually due to viral infections: BK virus (a type of polyomavirus) and adenovirus. Severe cases can be devastating and predispose the patient to other infectious complications. Urologists frequently advise continuous bladder irrigation but is frequently fails to improve the bleeding. The urethral catheter gets often obstructed, causing severe pain. Cidofovir, intravenous and intravesical, can be used to treat BKV[13] and adenovirus[14] -associated cystitis

Graft failure occurs rarely after HCT. Primary graft failure is the absence of neutrophil recovery to ≥500/mcL after the HCT and secondary graft failure or rejection **is usually** an immune-mediated process, when the engraftment of the donor cells is followed by a sudden or progressive decrease in the proportion of donor cells (chimerism), with either normal autologous blood counts or with a hypoplastic marrow. Poor graft function is the dependence on blood and/or platelet transfusions and/or growth factor support without relapse of the underlying disease or active infections[15] while maintaining donor chimerism. These are very worrisome situations and patients must be thoroughly evaluated by experienced teams. A second HCT may be necessary to offer an optimal hematopoietic engraftment.

Long-term complications are frequent and related to several factors as the underlying disease, the chemotherapy and irradiation used to treat the cancer, the conditioning regimen, and the development of chronic GVHD, as

discussed elsewhere. The most frequent long-term complications are **hypothyroidism**, earlier onset **cataracts**, **osteonecrosis** due to prolonged steroid use in patients with GVHD, **ovarian/ testicular insufficiency**, **premature menopause**, **infertility**, and **decreased growth** in children. These are all, unfortunately, rather common. **Iron overload** from prior transfusions may cause several endocrinological, cardiac and hepatic long-term side effects, but can be easily treated with monthly phlebotomies and/or chelation. **Secondary neoplasms** (myelodysplastic syndrome, acute myelogenous leukemia, thyroid, oral mucosa, skin and breast cancer) can also occur many years after the transplant, so patients and clinicians must be aware and vigilant of this possibility.

In conclusion, the risks and benefits of the HCT must be carefully addressed for each patient. Despite the inherent risks, HCTs may benefit most patients. The prompt recognition and adequate treatment of transplant-related complications may help to overcome HCT-related toxicities and increase the chance of curing our patients.

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12
ACUTE AND CHRONIC GRAFT-VERSUS-HOST DISEASE

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INTRODUCTION

Graft-versus-host disease (GVHD) can occur after allogeneic hematopoietic cell transplantation (allo-HCT) 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% after allo-HCT recipients develop aGVHD[2]. The main risk factors for aGVHD are HLA-mismatching between donor and recipient or unrelated donor, gender disparity (female to male), myeloablative conditioning, TBI-based conditioning, progenitor stem cell source (peripheral blood > bone marrow), and older donor age[3,4].

With a prevalence of 30-70% among allo-HCT recipients, cGVHD remains the main cause of long-term post-transplant morbidity and mortality in this population[5]. Risk factors associated with cGVHD are HCT with HLA-mismatched or unrelated donor, use of a female donor for a male recipient, grafting with mobilized blood, prior aGVHD, and older donor and recipient age[3].

TABLE 1: Examples of GVHD prophylaxis regimens

TYPE OF ALLO-HCT	PROPHYLAXIS REGIMEN
MRD/MUD MAC allo-HCT	Calcineurin inhibitor/methotrexate ± ATG
	Calcineurin inhibitor/MMF ± ATG
	PTCY ± calcineurin inhibitor/MMF
	PTCY/sirolimus/MMF
	Abatacept/calcineurin inhibitor/methotrexate
MRD/MUD RIC and NMA allo-HCT	PTCY/calcineurin inhibitor/MMF
	Calcineurin inhibitor/MMF ± ATG
	PTCY/sirolimus/MMF
	Cyclosporine/sirolimus/MMF
Haploidentical allo-HCT	PTCy/calcineurin inhibitor/MMF
	PTCy/sirolimus/MMF
Haploidentical allo-HCT – Beijing protocol	High-dose rATG/MMF/calcineurin inhibitor/MTX

allo-HCT allogeneic hematopoietic cell transplant; *MAC* myeloablative; *RIC* reduced-intensity conditioning; *PTCY* post-transplant cyclophosphamide; *NMA* non-myeloablative.

GVHD PREVENTION

The combination of a calcineurin inhibitor (eg. cyclosporine or tacrolimus) plus methotrexate or mycophenolate mofetil (MMF) has been the standard GVHD prophylaxis regimen for allo-HCT. However, the excellent results of post-transplant cyclophosphamide in haploidentical related donor HCT have led to its use in HLA-(mis) matched related and unrelated donor grafts as well[6-8]. Sirolimus, low dose Antithymocyte Globulin (ATG) (4-6 mg/kg) and more recently abatacept are other drugs used[9].[9] A summary of the main regimens is shown in Table 1.

ACUTE GRAFT VERSUS HOST DISEASE (AGVHD)

Clinical manifestations

The primary organs affected by aGVHD are the skin, gastrointestinal (GI) tract, and liver. Initially, the skin exhibits a maculopapular erythema, commonly appearing on the nape, ears, shoulders, palms, and soles. This rash can expand, becoming confluent, itchy, and, in severe cases, painful, resembling Stevens-Johnson syndrome. Both upper and lower GI tract may be involved, with symptoms such as nausea, vomiting, diarrhea, and abdominal pain, with severe cases presenting high-volume, potentially bloody diarrhea. Liver involvement generally appears in conjunction with skin and/or GI symptoms, marked by elevated bilirubin and alkaline phosphatase levels[10].

Staging and classification of acute GVHD (aGVHD)

More recently, in 2016, the Mount Sinai Acute GVHD International Consortium (MAGIC) established standardized criteria for the classification and data collection related to aGVHD, as shown in Tables 2 and 3[11]. The initial grading of aGVHD is important for evaluating the response to treatment, as well as correlating with overall survival after HCT. Patients who develop moderate or severe forms of the disease (global grades II-IV) face a significantly higher mortality rate compared to those with milder forms. Notably, grade II can be further divided into IIa or IIb. The first subtype involves upper and/or mild lower GI involvement and has a better prognosis, showing greater sensitivity to lower doses of systemic therapy along with non-absorbable enteral steroids[12,13]. An app for grading of acute GVHD can be accessed at *https://www.uzleuven.be/egvhd*.

TABLE 2: MAGIC Classification - GVHD Target Organ Staging[11]

Stage	Skin (erythema)	Liver (Bilirubin)	Upper GIT	Lower GIT (diarrhea vol./day)
0	No erythema	<2 mg/dL	Absent or intermittent nausea, anorexiaa or vomiting	<500 ml or <3 episodes/day (adults)b,c
1	Maculopapular Rash <25% BS	2-3 mg/dL	Persistent nausea, anorexiaa or vomiting	500-999 ml or 3-4 episodes/day (adults)b,d
2	Maculopapular Rash 25-50% BS	3.1-6 mg/dL		1000-1500 ml or 5-7 episodes/day (adults)b,e
3	Maculopapular Rash >50% BS	6.1-15 mg/dL		>1500 ml or >7 episodes/day (adults)b,f
4	Generalized erythroderma (>50% BS) e bullous and scaly lesions >5% BS	>15 mg/dL		Severe abdominal pain, ileus, or bleeding

BS body surface [a] To be suggestive of GVHD: anorexia must be associated with weight loss, nausea for at least 3 days, or accompanied by ≥ 2 episodes/day of vomiting for at least 2 days. [b] Diarrhea is equivalent to about 200 ml for adults and 3ml/kg for children (< 50 kg). [c] Diarrhea < 10ml/kg/day or < 4 episodes/day for children. [d] Diarrhea 10-19.9 ml/kg/day or 4-6 episodes/day for children. [e] Diarrhea 20-30 ml/kg/day or 7-10 episodes/day for children. [f] Diarrhea > 30 ml/kg/day or > 10 episodes/day for children.

TABLE 3: MAGIC Classification – Overall clinical grade[11]

Grade	Skin	Liver	Upper GIT	Lower GI
0	0	0	0	0
I	1-2	0	0	0
II	3	1	1	1
III	0-3	2-3	0-1	2-3
IV	4	4	0-1	4

ACUTE GVHD TREATMENT

The selection of initial therapy for aGVHD takes into account the organs involved, the severity of the symptoms, the prophylactic regimen employed, and, to some extent, the importance of the graft-versus-leukemia (GVL) effect in the specific clinical context. First line therapy consists of topical and/or systemic steroid therapy (Table 4). In case of steroid-refractoriness or steroid dependence, second line therapy should be started (Table 5 and Table 6).

TABLE 4: First-line therapy for grade I-IV aGVHD

Grade	Treatment
I	Topical agents for skin (steroids or tacrolimus) Calcineurin inhibitor trough levels at therapeutic range No systemic immunosuppression is recommended
IIa	Start MP 0.5-1mg/kg/day, escalating up to 2 mg/kg if worsening occurs after 72h12,13 Topical agents for skin (steroids or tacrolimus). Non-absorbable enteral steroids (beclomethasone and budesonide) for mild upper or lower GI aGVHD Calcineurin inhibitor trough levels at therapeutic range
IIb-IV	Start methylprednisolone 2mg/kg/day or prednisone equivalent12 Topical skin and GI therapy Calcineurin inhibitor trough levels at therapeutic range

[a] Grade IIa: anorexia, nausea, emesis or diarrhea < 1 L day (children < 20 mL/kg/day) with or without rash covering < 50% of the body surface area (BSA) and not progressing rapidly within the first 6-24 hours with 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)
aGVHD acute graft versus host disease; GI: gastrointestinal.

TABLE 5: Definitions of steroid refractoriness or resistance, steroid dependence, and steroid intolerance for aGVHD and cGVHD[14]

	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	

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

TABLE 6: Second-line therapy for grade II-IV aGVHD[15]

Therapy	Comment*
Ruxolitinib	The only approved small molecule for second line therapy or beyond for aGVHD. The phase III REACH2 study16 showed a 28-day Overall Response Rate (ORR) of 62% compared to 39% in the control group.
Remestemcel-L	Mesenchymal stromal cells; ORR 70%. Only approved for children and adolescents.[17]
Extracorporeal photopheresis	ORR of 84% in aGVHD of the skin and 65% of the GI tract (off label).
MMF	Complete Response (CR) and Partial Response (PR) rates of up to 77% in 6 months (off label).
ATG	ORR between 20% and 50%, particularly in aGVHD of the skin (off label).
Basiliximab	ORR of approximately 80% (off label).
Infliximab and Etarnecept	ORR of approximately 70%, particularly in aGVHD of the GI tract (off label).

MMF mycophenolate mofetil; ATG antithymocyte globulin; aGVHD acute graft-versus-host disease. * Note that 'off label' indicates these treatments are not approved by the FDA for aGVHD.

Chronic Graft-Versus-Host-Disease (cGVHD)

The pathophysiology of chronic graft-versus-host disease (cGVHD) involves inflammation, cellular immunity, humoral immunity, and fibrosis[18]. This immunological complication resembles autoimmune diseases. Clinical manifestations almost always appear within the first two years after transplantation[19].

CGVHD DIAGNOSIS AND STAGING

As in the 2005 NIH consensus criteria[2], the 2014 version[20] recognizes two main categories of GVHD (acute and chronic). Acute GVHD (aGVHD) includes: (1) classic aGVHD, which occurs before 100 days post-HCT, without diagnostic or distinctive signs of chronic GVHD (cGVHD); (2) late-onset (de novo GVHD), persistent (previous unsolved aGVHD), or recurrent aGVHD (previous resolved aGVHD), which presents changes of classic aGVHD but without diagnostic or distinctive signs of cGVHD, and occurs after 100 days post-HCT.

Both in the 2005[2] and 2014 NIH consensus[20], cGVHD included (1) classic cGVHD, without characteristics of aGVHD; (2) overlap syndrome, in which characteristics of both aGVHD and cGVHD appear simultaneously. Clinical manifestations, not the time of symptom or sign onset after HCT, that determine whether GVHD is acute or chronic[20]. Diagnostic signs and symptoms are manifestations that establish the presence of cGVHD without the need for further tests or evidence of other affected organs, usually represented by lichenoid lesions or sclerosis[20]. Distinctive signs and symptoms are not commonly found in aGVHD but are not considered sufficient to establish a precise diagnosis of cGVHD (eg. vitiligo, ocular sicca). Common signs and symptoms are observed in both aGVHD and cGVHD. For the diagnosis of cGVHD, at least one diagnostic manifestation of cGVHD or at least one distinctive manifestation confirmed by biopsy, laboratory tests, specialist evaluation (eg. ophthalmologist, gynecologist), or radiological imaging, in the same or another organ, unless otherwise indicated, is required (Table 7).

Once cGVHD is diagnosed according to the 2014 NIH consensus criteria, the severity of organ involvement should be evaluated using the NIH organ scoring forms (Figure 1). Organs are rated on a scale from 0 to 3, based on the extent of symptoms or signs they exhibit. The total severity of cGVHD must be determined by evaluating eight organs or sites: skin, mouth, eyes, GI tract, liver, lungs, joints/fascia, and genital tract. The overall severity of cGVHD is categorized as mild, moderate, or severe (Table 8)[20]. An app for grading of chronic GVHD can be accessed at *https://www.uzleuven.be/egvhd*.

TABLE 7: Signs and Symptoms of chronic GVHD[20]

Organ or Site	**Diagnostic** *(Sufficient to Establish the Diagnosis of chronic GVHD)*	**Distinctive*** *(Seen in chronic GVHD, but Insufficient Alone to Establish a Diagnosis)*	**Other Features or Unclassified Entities**	**Common** *(Seen with Both Acute and chronic GVHD)*
Skin	Poikiloderma Lichen planus–like features Sclerotic features morphea-like features Lichen sclerosus–like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric, affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) Premature gray hair	

Mouth	Lichen planus–like changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis KCS Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus–like features Lichen sclerosus–like features	Erosions Fissures Ulcers		
Females	Vaginal scarring or clitoral/labial agglutination			
Males	Phimosis or urethral/ meatus scarring or nstenosis			
GI Tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase > 2 × upper limit of normal ALT > 2 × upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy BOS§	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung diseasell	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis¶	Edema Muscle cramps Arthralgia or arthritis	

Hematopoietic and Immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies (AIHA, ITP) Raynaud's phenomenon	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

ALT alanine aminotransferase; *AIHA* autoimmune hemolytic anemia; *ITP* idiopathic thrombocytopenic purpura. ∗ In all cases, infection, drug effect, malignancy, or other causes must be excluded. § BOS can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ (see text). Pulmonary entities under investigation or unclassified. ¶ Diagnosis of chronic GVHD requires biopsy.

FIGURE 1: NIH organ scoring[20]

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score: **%** FEV1 ☐ *Pulmonary function tests* ☐ Not performed	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*[‡]) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs[‡] and females with or without discomfort on exam	☐ Moderate signs[‡] and may have symptoms with discomfort on exam	☐ Severe signs[‡] with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Photographic Range of Motion (P-ROM)

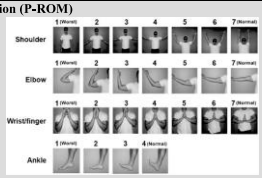

TABLE 8: NIH Global Severity of chronic GVHD[20]

MILD CGVHD 1 or 2 involved organs Maximum grade 1 on involved organs Lung 0 Severe cGVHD At least 1 organ grade 3 OR Lung grade 2 or 3	**MODERATE CGVHD** 3 or more involved organs Grade 1 in each organ OR At least 1 organ grade 2 (except lung) OR Lung grade 1

Key Points

1. Skin: The highest score will be used for the calculation of overall severity.
2. Lung: FEV1 is used instead of the clinical score for the calculation of overall severity.
3. If an organ abnormality is unequivocally explained by a cause not associated with GVHD, the score for that organ will be zero for the calculation of overall severity.
4. If an organ abnormality is attributed to multifactorial causes (GVHD plus other causes), the organ score will be used for the calculation of overall severity regardless of the contributing causes (the organ score will not be disregarded).

CHRONIC GVHD THERAPY

First-line therapy for mild cGVHD consists of ancillary treatments such as topical steroids, topical tacrolimus, enteral beclomethasone/budesonide, and others. For moderate and severe cases, systemic prednisone at 0.5-1.0 mg/kg/day, with or without ancillary therapy, is typically prescribed.[19] Other systemic immunosuppressive agents, eg. calcineurin inhibitors, may also be added or kept along in first-line therapy as steroid-sparing drugs[21]. Unlike aGVHD, the median duration of systemic treatment for cGVHD is around 23 months, with 15% of patients still needing systemic immunosuppressive therapy seven years after beginning their initial treatment[22].

A recent Brazilian multicenter study involving 354 patients reported a failure-free survival (FFS) rate of 89% at 6 months, 71% at one year, and 52% at two years after initial therapy for cGVHD requiring systemic immunosuppressive therapy[23].[23] These findings indicate that nearly half of these patients will need second-line therapy or beyond (Table 9). Over the past decade, four new drugs (ibrutinib, ruxolitinib, belumosudil, and axatilimab) have received FDA approval for steroid-refractory and steroid-dependent cGVHD[24-27]. Of these, two have been approved by ANVISA in Brazil to this date. The pivotal trials leading to these approvals suggest improved FFS. These drugs target specific pathological mechanisms of cGVHD and work to preserve or even stimulate regulatory T cells, promoting immune tolerance. However, access to these drugs remains limited to private centers in Brazil[28].[28]

TABLE 9: Second-line therapy of cGVHD[15]

Therapy	Comment*
Ruxolitinib	Second line and beyond. 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).[24]
Belumosudil	Third line and beyond. 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.[26]
Axatilimab	Third line and beyond. ORR 74% in the 0.3-mg dose group.[27]
Ibrutinib	Second line and beyond. ORR of 67%, with a 21% CR rate.[25]
Extracorporeal Photopheresis	Mucocutaneous manifestations, with complete response (CR) rates of > 80% and significant improvement of sclerotic cGVHD (off label)
MMF	Overall response rates (ORR) vary between 23% and 79% in several case series (off label).
Sirolimus	ORR varying between 63% and 81% in several case series (off label).
Rituximab	Mucocutaneous and musculoskeletal manifestations, with an ORR of approximately 70% (off label).
Imatinib	Cutaneous, ocular, and gut manifestations, with an ORR between 50% and 80% (off label).
Methotrexate	ORR varying between 58.8% and 71% in most case series (off label).

cGVHD: chronic graft-versus-host disease; MMF: mycophenolate mofetil* Note that 'off label' indicates these treatments are not approved by the FDA for cGVHD.

KEY POINTS:

• Both acute and chronic GVHD are common complications following allo-HCT and are associated with significant morbidity and mortality.

• Post-transplant cyclophosphamide has been increasingly used as GVHD prophylaxis for HLA-(mis) matched and related/unrelated HCT.

• Acute and chronic GVHD are distinguished by symptoms and signs rather than the time of onset.

• Novel promising therapies have recently been approved for GVHD.

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13

MANAGEMENT OF INFECTION IN HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

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Infection is a frequent event in patients undergoing hematopoietic cell transplantation (HCT), and it can be life-threatening if not properly managed or if it occurs during high-risk periods after HCT. To mitigate the increased risk of infection, standardized routines and recommendations for screening, prophylaxis, empirical and preemptive therapies, vaccination, and access to a broad diagnostic panel are essential for the management of transplant recipients. Special attention should be paid to neutropenia, mucositis, and graft-versus-host disease (GVHD). This chapter is organized in tables and divided into the following sections: 1. pre-transplant screening and prophylactic measures; 2. management of febrile neutropenia and antibacterial resistance; 3. laboratory monitoring and preemptive antimicrobial therapies and 4. post-transplant vaccination program. Further details can be found in the current version of the Recommendations for the Prevention and Treatment of Post-HSCT Infections (1).

SESSION 1: Pre-Transplant Screening and Prophylactic Measures for Auto- or Allo-HCT

1.1. Mandatory Pre-Transplant Serologies

Medical history and a panel of serologies—including HSV, CMV, EBV, HIV, HCV, HBV (HBsAg, anti-HBs, anti-HBc), HTLV, and Trypanosoma cruzi (Chagas disease)—are mandatory according to Brazilian regulatory requirements. These tests must be performed for both autologous and allogeneic transplant recipients, as well as allogeneic donors.

Serologic screening is a core component of the eligibility assessment for both donors and recipients, and results should be recent (within three months prior to HCT).

Malaria screening—by thick/thin blood smear or nucleic acid testing (NAT), if available—should be performed for all recipients and donors originating from or exposed to endemic areas. Additional serologies may be considered based on the patient's epidemiological risk and medical history.

1.2. Evaluation of Previous Infections (Recipients and Donors)

Thorough anamnesis, physical examination, review of medical records, imaging, and laboratory workup should be conducted to assess any history of previous or ongoing infections. Special attention should be given to:

- Recurrent or chronic infections
- Multidrug-resistant (MDR) pathogens
- Latent infections (e.g., TB, HBV)
- Invasive fungal infections

Efforts must be made to clarify the etiology of any unresolved infections to define appropriate prophylactic or therapeutic strategies. As a rule, HCT should be postponed in recipients presenting active or uncontrolled infections.

1.3. Assessment of Latent Tuberculosis Infection (LTBI)

Evaluation should include a history of prior TB, TB exposure among household contacts, and screening with a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA), such as the QuantiFERON-TB Gold (QTF-TB) test.

If LTBI is diagnosed, treatment is recommended and should ideally be initiated prior to transplantation.

1.4 Risk Stratification for Invasive Fungal Disease (IFD)

The risk of invasive fungal disease (IFD) depends on multiple factors, including host characteristics, the underlying hematologic disease, transplant type, and transplantation phase. Accurate stratification requires detailed medical history, physical examination, and imaging studies.

- Recipients should be classified according to their risk for:
- Invasive candidiasis – primarily associated with severe mucositis.

Mold infections – based on prior invasive fungal infection (IFI), donor type and conditioning regimen, duration of neutropenia, and the occurrence of GVHD.

Risk stratification helps determine which patients will benefit from mold-active versus yeast-active antifungal prophylaxis and which patients can be safely managed through monitoring and clinically driven interventions.

1.5 Screening for Respiratory Viral Infections, Including COVID-19, Before Admission

All patients should undergo screening for respiratory viruses prior to hospital admission using immunofluorescence or multiplex PCR on respiratory specimens (e.g., nasopharyngeal swab or nasal wash).

With the emergence of COVID-19, screening of asymptomatic individuals for respiratory viruses has become mandatory before HCT.

1.6 Screening for Multidrug-Resistant (MDR) Organism Colonization

Screening should follow institutional protocols and local epidemiology and may include:

- Rectal swab or stool cultures for CRE, VRE, MDR Pseudomonas aeruginosa
- Nasal swab for MRSA

This helps inform the need for isolation precautions or specific antimicrobial strategies.

Prophylactic Measures

1.7 HSV and Varicella-Zoster Virus (VZV) Prophylaxis

Prophylaxis with acyclovir or valacyclovir should begin at the start of the conditioning regimen and continue until one-year post-HCT or six months after discontinuation of immunosuppressive therapy—whichever is longer—in allogeneic HCT recipients.

For autologous recipients, the duration should be adapted according to pre- and post-HCT therapy protocols.

1.8 Cytomegalovirus (CMV) Prophylaxis

Letermovir prophylaxis is recommended for CMV-seropositive adult recipients (R+), beginning within the first week after HCT and continuing through day +100. The dose should be adjusted based on concurrent cyclosporine use.

Concomitant HSV/VZV prophylaxis with acyclovir or valacyclovir should be maintained.

1.9 Antibacterial Prophylaxis During the Neutropenic Phase

Use of quinolones (e.g., levofloxacin, ciprofloxacin) remains controversial. It may be considered in centers with:

- High rates of bloodstream infections
- Controlled MDR colonization or infection rates
- Quinolone resistance below 30%

1.10 Primary Antifungal Prophylaxis (PAP)

Choice of antifungal agent depends on IFD risk stratification and clinical context (e.g., pre-engraftment phase, presence of GVHD):

- Low risk for mold: Fluconazole or micafungin (for azole-intolerant patients) is recommended for candidemia prevention, particularly in autologous HCT.
- Intermediate risk for mold: Fluconazole or micafungin with galactomannan surveillance.
- High risk for mold infections: Posaconazole, voriconazole, or isavuconazole are preferred. Alternatives include liposomal amphotericin B and micafungin.
- If voriconazole is used, therapeutic drug monitoring (TDM) is advised.

1.11 Prophylaxis for Toxoplasmosis and Pneumocystis pneumonia

Trimethoprim-sulfamethoxazole (TMP/SMX) is effective against T. gondii, P. jirovecii, Listeria, and Nocardia. If TMP/SMX is contraindicated, dapsone 100 mg/day is an alternative.

Prophylaxis should begin shortly after engraftment and continue until day +180, or longer in patients ongoing immunosuppression or with chronic GVHD.

1.12 Prophylaxis for HBV, LTBI, and Others

Refer to the current version of the Recommendations for the Prevention and Treatment of Post-HCT Infections for further details.

SESSION 2: Febrile Neutropenia and Multidrug-Resistant (MDR) Pathogen Management

2.1. Empirical Antimicrobial Therapy
Each institution should establish a management algorithm tailored to its local antimicrobial resistance profile to guide the initiation of empirical therapy.

Empirical antibiotics must be initiated within 60 minutes of fever onset, as this prompt intervention has been shown to reduce mortality.

In the absence of hemodynamic instability, prior infection history, or MDR colonization, monotherapy with piperacillin-tazobactam or cefepime is recommended.

The use of carbapenems as first-line agents is discouraged due to their potential association with Clostridioides difficile infection (pseudomembranous colitis).

Broad-spectrum agents such as meropenem, ceftazidime-avibactam, or combination regimens should be considered in the following scenarios:

- Clinical instability
- Known colonization or previous infection with MDR organisms
- Ongoing MDR outbreak in the treatment unit

2.2. Modification of Antimicrobial Therapy in Febrile Neutropenia
Persistent fever in a clinically stable patient without documented infection—either microbiological or radiological—is not an indication for empirical escalation or modification of therapy.

Instead, persistence of fever should prompt a diagnostic reassessment, including imaging and repeated cultures.

In contrast, if new clinical findings or hemodynamic instability develop during empirical treatment, therapy should be adjusted based on:

- Antibiogram of any isolated organism
- Local microbiological epidemiology if cultures remain negative

2.3. Duration of Antimicrobial Therapy in Febrile Neutropenia
Antibiotic discontinuation should be guided by documented infection and clinical response.

In patients who become afebrile, remain hemodynamically stable, and have no identified infectious focus, empirical therapy may be safely discontinued after 3 to 5 days. In cases of documented infection, the duration of treatment will depend on: the site and type of infection, pathogen susceptibility and clinical evolution

SESSION 3: Laboratory Monitoring and Preemptive Antimicrobial Therapies

3.1 Antifungal Preemptive Therapy
Routine monitoring of fungal biomarkers—such as serum galactomannan—should be performed to detect infection before clinical or radiological signs appear. Testing is recommended once or twice weekly. If results are positive (defined as two consecutive positive tests), a more thorough evaluation should be initiated, including bronchoscopy with bronchoalveolar lavage and microbiological assessment, followed by the initiation of antifungal therapy.

Recommended regimens include:

- **Voriconazole:** 6 mg/kg every 12 hours on day 1, followed by 4 mg/kg every 12 hours; or
- **Isavuconazole:** 200 mg three times daily on days 1 and 2, followed by 200 mg once daily.
- Alternative options include **liposomal amphotericin B** or **amphotericin B lipid complex.**

This preemptive strategy has been shown to reduce antifungal use without increasing mortality. However, note that mold-active prophylaxis may reduce the sensitivity of galactomannan testing. False positives may also occur, particularly in patients with gastrointestinal GVHD or mucositis.

3.2 Anti-CMV Preemptive Therapy

Cytomegalovirus (CMV) monitoring should be performed using quantitative PCR (qPCR) or antigenemia assays once or twice weekly—even in patients receiving letermovir prophylaxis. The threshold for initiating antiviral therapy must be defined locally, based on the assay used and the patient's risk profile, including whether letermovir is in use. Preemptive antiviral treatment options include:

- **Ganciclovir (GCV):** 5 mg/kg every 12 hours; or
- **Valganciclovir (VGV)**: 900 mg every 12 hours.

Important considerations:

- Oral valganciclovir should be avoided in patients with severe gastrointestinal GVHD.
- **Foscarnet** (90 mg/kg every 12 hours) may be used during neutropenia.
- Antiviral treatment should be maintained for at least 14 days and may be discontinued one week after a negative qPCR result.
- Dose adjustments are necessary in case of renal impairment.
- If viremia persists or increases after two weeks, consider drug resistance or a refractory infection.

3.3 Other Relevant Laboratory Monitoring

For high-risk patients (see reference 1), monitoring for **Epstein-Barr virus (EBV)** and **HHV-6** should be considered. Patients receiving prophylaxis for chronic infections such as hepatitis B should continue laboratory surveillance according to established protocols.

Whenever possible, therapeutic drug monitoring (TDM) should be performed for antifungal and antimicrobial agents to ensure efficacy and prevent toxicity.

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14

WHAT DO WE HAVE TO KNOW ABOUT PEDIATRIC HCT

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OVERVIEW

Hematopoietic cell transplantation (HCT) differs significantly between adult and pediatric patients, with major distinctions in underlying diseases, transplant types, preparatory regimen intensity, and complications. In pediatric patients, allogeneic HCT and bone marrow as the stem cell source are more com- monly used due to the higher prevalence of non-malignant diseases (NMD) such as immu- nodeficiencies, inborn errors of metabolism, acquired and inherited bone marrow failures syndromes (**IBMFS**), and hemoglobinopathies. The use of peripheral blood as the stem cell source should be avoided due to the increased risk of graft-versus-host disease, which is particularly concerning in children. Most of the NMD are very rare, and do not pose an imminent risk of death, making it challenging to select the best treatment for this group[1]. Children and adolescents also tolerate more myeloablative preparatory regimens compared to older adults, though they are at increased risk for endothelial-related complications like veno-occlusive disease and thrombotic microangiopathy. Additionally, drug metabolism in pediatric patients, particularly in younger children, requires careful monitoring due to significant variations in pharmacokinetics influenced by factors such as age, body surface area, and obesity. These factors emphasize the importance of performing these transplants in centers with expertise in this popu- lation, especially when dealing with infants. With improvements in survival rates, pediatric patients now face many decades of life after transplant, making long-term surveillance crucial. Monitoring for late effects, especially endocrinological complications and cancer, is essential to optimize outcomes and quality of life after transplant.

HCT INDICATIONS IN PEDIATRICS

For pediatric patients with **severe aplastic anemia (SAA)**, HLA-identical sibling donor HCT is the optimal treatment, offering survival over 90% at two years. If only an unrelated donor is available, but HCT is not performed within three months of diagnosis, immunosuppression (IST) should be initiated. Conditioning uses Cy, ATG and, in MUD, also fludarabine and TBI 200 cGy, with excellent results[6,7]. Haploidentical HCT is another promising treat- ment option for patients who have failed IST or even as a first-

line treatment for selected patients[8]. IBMFS are a heterogeneous group of genetic disorders with different biological mechanisms, such as the repair mechanism in Fanconia anemia (FA), the maintenance of telomeres in dyskeratosis congenita (DKC), and the biogenesis of ribosomes in Shwachman-Diamond syndrome (SDS) and Dia- mond-Blackfan syndrome[9-11]. HCT should be indicated as soon as patients begin to develop pancytopenia and before severe infections and clonal evolution. In Fanconi anemia and DKC, the use of nonmyeloablative conditioning is essential and the long-term risk of secondary malignancies such as neck squamous cell carcinoma and leukemias are of great concern, so we strongly recommend patients to continue follow-up after HCT, emphasizing prevention and early detection of disease-related complications[12]. Sickle cell disease (**SCD**) is considered the main inherited hemoglobin disorder. Patients 1 to 9 years face a 32-fold higher risk of death due to SCD compared to the general population[2]. Excellent survival rates after HCT with a matched sibling donor and a low incidence of GVHD suggest that HCT should ideally be performed in children younger than 5 years before complications arise[3]. Currently, there is limited data from HCT involving non-HLA identical sibling donors, with higher rejection and GVHD rates, as well as regimen-related toxicities. Nonmyeloablative haploidentical HCT using thiotepa, TBI and PT-Cy have excellent overall survival in adults but high graft failure rates in children[4,5]. Please also refer to the specific chapter about hemoglobinopathies (SCD and thalassemia) in this series. Indications for HCT in inborn errors of immunity are mainly divided into Severe Combined Immunodeficiency (SCID) and non-SCID patients. In most cases, transplanting before severe infections occur, with well-matched related or unrelated donors, is associated with better outcomes. When possible, and considering comorbidities, myeloablative regimens are associated with a more robust donor engraftment and immune recovery. **In inborn errors of metabolism (IEM)**, early HCT can halt neurological decline and improve quality of life. Worldwide, mucopolysaccharidoses (MPS I and II) and X-linked adrenoleukodystrophy are the major indications, though selected cases of Krabbe disease, metachromatic leukodystrophy, and other IEM can also benefit[13]. The success of transplantation largely depends on disease stage and pre-existing neurological damage, as donor engraftment in the brain takes 3-6 months, allowing for continued disease progression initially. Long-term follow-up is crucial, particularly for patients with mucopolysaccharidoses, due to ongoing complications, especially orthopedic issues[14].

Most children with **acute leukemias** can be successfully treated with well-established chemotherapy regimens and HCT is used only to those with very specific risk of not being cured with chemotherapy or failing first line treatment. The only pediatric leukemia treated with autologous HCT is acute promyelocytic leukemia in second molecular remission; all other should be transplanted with the best available allogeneic donor[3,15]. The use of 1200 cGy-TBI and etoposide in the conditioning regimen, instead of busulfan-based strategies, increased the chance of curing pediatric **acute lymphoblastic leukemia** from 75% to 91% in an excellent prospective study[16]. However, when the patient has a refractory B-cell disease or relapses after HCT, the best treatment option is cellular therapy with autologous anti-CD19 CAR-T cells (chimeric antigen receptor), available in our country under research protocols (ClinicalTrials.gov ID NCT06101381 University of Sao Paulo and NCT05705570 Hospital Israelita Albert Einstein) and com- mercially (Kymriah®), although very expensive. The treatment of pediatric **acute myelogenous leukemia** often includes HCT due to presenting high-risk genetic features, poor disease response or relapsed disease. The chemotherapy-related toxicities and infections, especially due to resistant bacteria and aspergillus, may be life-threatening, so these children must be treated in very specialized centers. Although no cellular therapy is not currently available for myeloid diseases, early HCT strategies may cure

patients who are not in complete remission[17], very different from lymphoid diseases, but early strategies of decreasing immunosuppression, infusion of donor leukocytes, and maintenance therapies are also necessary. The treatment of relapsed pediatric Hodgkin, Burkitt and large cell **lymphomas** usually include autologous HCT, but lymphoblastic and anaplastic large cell **lymphomas** are treated with allogeneic HCT to consolidate chemotherapy-induced remission after relapsed disease. Pediatric **germ-cell tumors** in second remission are also treated with autologous HCT using strategies that are similar to the treatment in adults. However, **brain tumors** and **high-risk neuroblastoma** are unique. Autologous HCT is used in frontline therapy to avoid brain irradiation in young children, including thiotepa, the chemotherapy agent that best crosses the blood-brain barrier, in one or repeated (tandem) HCT cycles[18]. Autologous HCT is used to improve the grim prognosis of disseminated or mycN amplified neuroblastomas, but consolidation with irradiation to the primary site, retinoic acid, anti-GD2 immunotherapy, and eflornithine (DFMO) are needed to avoid relapse[19].

LONG-TERM FOLLOW-UP

Long-term monitoring is crucial for assessing organ damage and improving the quality of life for pediatric patients after HCT. A multidisciplinary team should conduct this monitoring, emphasizing the need for regular communication between transplant centers and primary care centers. Late effects after HCT are multifactorial: prior therapy for primary malignancy, intensity of conditioning, stem cell product (e.g., bone marrow, peripheral stem cells or cord blood), donor (e.g., autologous, allogeneic, unrelated), quality of donor to recipient match, complications of the transplant process (e.g., GVHD), complications in the post-transplant period, underlying disease, host genetic factors, and lifestyle behav- iors. Prevention and recognition of late effects, followed by prompt intervention, are essential for enhancing long-term outcomes in survivors[20,21]. The main recommendations related to screening and prevention post-HCT late effects are in table 1.

TABLE 1: Long-term follow-up after HCT in children[20,21]

RECOMMENDATION	
Hematologic complications	
Hematologic recovery	CBC at routine clinical visits for at least 10 years post-HCT
Iron overload	Monitor serum ferritin until normalized Iron quantification by MRI (liver and cardiac) Treatment of choice: phlebotomy (Iron chelation may be considered in patients ineligible for phlebotomy)
Hemoglobinopathy	Chimerism at least every 3 months in year 1 post-HCT and every 6 months in year 2
Immunity and Infections	
Vaccination	Inactivated vaccines may begin 3 to 6 months after HCT Full vaccination program considering age and country recommendations
Hypogammaglobulinemia	Supplemental IVIG for selected HCT recipients with IgG levels < 400mg/dL
Ocular complications	
	Ask about eye symptoms at each visit Attention to risk of premature cataracts (TBI, Busulfan, Glucocorticoids) Monitor intraocular pressure Special attention to patients with Hurler syndrome
Respiratory complications	
	Ask about pulmonary symptoms at each visit Pulmonary function testing every 3 months in the first year, every 6 months in the second year, and then annually for 5 years after HCT CT chest imaging in symptomatic patients and consider pulmonology consultation
Oral and Dental complications	
	Oral exam at each visit (screen for cGVHD) Evaluation by a dentist at 6 months, 1 year, and annually (more frequent screening for special cases (e.g., Fanconi anemia) Attention to tooth development Avoid smoking, sugar beverages, oral piercing
Cardiac and Vascular complications	
	Assessment of blood pressure, weight and body mass index at each visit Dyslipidemia and Metabolic syndrome management Attention to cardiomyopathy (previous radiation and anthracycline chemotherapy)

Gastrointestinal complications	
	Ask about GI symptoms at each visit Check liver function at least every 1-2 months during the year 1, then yearly in allo-HCT Monitoring viral infections
Renal and urinary complications	
	Evaluate renal function at 6 months, 1 year, then yearly Monitor blood pressure
Endocrine complications	
	Monitor height, weight and body mass index Children have a higher risk of growth velocity abnormality (consider endocrinology consultation) Monitor children for onset and progression of puberty (including history of menarche//menstrual symptoms) Assess thyroid function
Sexual health, fertility and pregnancy	
	Discuss sexual function (screening/managing dysfunction) Ginecology/urology consultation Patients desiring pregnancy: fertility specialist Counselling regarding safer sex practices and contraception
Muscle, connective tissue, skeletal and dermatologic complications	
	Evaluate glucocorticoid-induced myopathies, cGVHD-associated polymyositis Perform range of motion evaluation Optimize Ca and Vitamin D Encourage regular dermatological self-examination (dermatology consultation if necessary) Avoid direct sun exposure
Neurologic, cognitive complications, psychosocial health and quality of life	
	Neurologic clinical evaluation Cognitive development; Neurocognitive testing Audiologic evaluation Review current symptoms, distress, medication adherence Encourage healthy diet, activity, adequate sleep Patient mental health (questionnaire)
Subsequent malignant neoplasms	
	Counseling and auto examination Reduce UV skin exposure, avoid high-risk behaviors Consider personal and family history and encourage recommended screening

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15

MINIMAL/MEASURABLE RESIDUAL DISEASE FOR DECISION MAKING IN HEMATOPOIETIC CELL TRANSPLANTATION IN ACUTE LEUKEMIA

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Minimal/measurable residual disease (MRD), by definition, is the persistence of therapy-resistant neoplastic cells detected in patients in remission from hematologic malignancies. Therefore, in patients with acute leukemia, MRD assessments should be performed only for whose that achieved morphologycal remission[1]. MRD is an important predictor of disease relapse[2-4] used to assess response after induction and consolidation therapy to decide on treatment intensification, including allogeneic Hematopoietic Cell Transplantation (alloHCT). All previous MRD results obtained during initial treatment should be evaluated for alloHCT decision. MRD response differs between different genetic subtypes: patients with adverse cytogenetic risk tend to have persistent MRD later in the course of treatment and consequently to decide on alloHCT[1,5]. It should be emphasized that MRD tests must achieve adequate sensitivity for clinical decision-making, regardless of the method of detection. Information about the sensitivity must be included in the patient's report as the limit of detection (LOD) and lower limit of quantification (LLOQ)[1,6]. However, the sensitivity of the method depends directly on the quality of the sample. An adequate sample must be obtained, avoiding hemodilution. For that, the first pool of BM collection, with a volume of 2 mL, should be addressed to MRD testing to avoid sample coagulation, it is important to homogenize it with the anticoagulant by sequentially inverting the tube. Clotted and hypocellular samples from aplastic BM after chemotherapy are not suitable for MRD testing, which requires adequate cell numbers and DNA/RNA quantities.[8] BM should be the sample of choice for MRD assessment, as the sensitivity of the tests reaches >1 log difference compared to peripheral blood (PB)[9] although some molecular tests can be performed using peripheral blood[1]. No less important is ensuring that the laboratory uses standardized and validated protocols, and also participates in external quality controls for the MRD method used[1,6].

The clinical relevance of MRD varies according to the type/classification of leukemia, the time points of assessment and the level of MRD. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) have major differences in their biology characteristics and clinical behavior, and should be adressed separately.

MRD IN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

MRD has been incorporated into pediatric ALL clinical trials for more than 20 years[10] in both pediatric trials and pediatric-inspired therapeutic protocols for adults in which, the relevant time points for MRD assessment are predetermined. Persistence of MRD >0.01% (10-4) after consolidation is predictive of relapse and indicative for therapy intensification[11]. The median time to hematologic relapse has been shown to be 7.6 months vs 4.9 months for patients with MRD >0.01% vs 0.1%, respectively. Patients with MRD < 0.01% may have na intermediate prognosis and should be considered for MRD-based treatment intervention in the future[11]. In most protocols, the relevant time point will be 2 to 3 months from diagnosis[11]. Pediatric patients with high genetic risk such as *KMT2A::AFF, IKZF* plus, hypodiploidy (<

44 chromossomes or DNA index < 0.8) and patients with early T-precursor ALL immunophenotype are eligible for alloHCT based on MRD positivity (>10-4) at the end of induction or consolidation therapy. On the other hand, patients with *TCF3::HLF* fusion transcript represent a rare subset with low sensitivity to conventional chemotherapy and a dismal prognosis, and should be considered early for alloHCT from a matched donor as soon as clinical remission is achieved, regardless of MRD response[12].

Pre-HCT ALL MRD: should be evaluated as close to transplantation as possible, especially in relapsed/refractory patients, due to the risk of increased tumor burden since the last MRD assessment. MRD > 0.01% (10-4) is associated with a higher risk of relapse after alloHCT[11,13]. In this situation, treatment with less toxicity to reduce tumor burden is recommended as a bridge to alloHCT. In B-cell precursor ALL, for example, CD3/CD19 bispecific T-cell engaged (BiTe) therapy with bispecific monoclonal antibody (BiTE) or with anti-CD22 are options for patients with access to these therapies[11,14]. It is essential to inform flow cytometry laboratories about the use of monoclonal antibody therapy, as MRD strategies must be tailored to targeted therapy situations. Post-HCT ALL MRD: MRD is essential for early detection of relapse in the post-alloHCT setting and for establishing pre-emptive therapies to avoid overt leukemia relapse. The assessment moments are not widely consensual, but vary around D+30 to 40, D+60, D+100 to 120, D+180, D+360[15]. Table 1 shows the most available methods for ALL MRD detection[10,16].

MRD IN ACUTE MYELOID LEUKEMIA (AML)

The classification of AML shows that it is a set of very different diseases, characterized by great variability of genotypes and immunophenotypes, which are often unstable after treatment, making the evaluation of MRD technically more complicated and less sensitive than ALL MRD. Therefore, to date, the MRD level considered most clinically relevant in AML is 0.1%, although detection methods potentially achieve higher sensitivity[1]. However, patients with quantifiable MRD below the detection limit <0.1% had lower relapse-free survival than patients with undetectable MRD[17] Thus, there is a trend toward a reduction in the threshold considered clinically relevant for AML MRD. The persistence of MRD after the second cycle of intensive chemotherapy is associated to poorer outcome[18]. The definition of MRD persistence by quantitative polymerase chain reaction (qPCR) is ≥ 2% above the method LOD or copy number reduction of less than 3 to 4 logs compared to the diagnostic sample[1]. Next Generation Sequencing (NGS) -MRD positivity is provisionally defined as ≥ 0.1% variant allele frequency (VAF). Although NGS-MRD test negativity is defined as <0.1% VAF, results <0.1% are considered low-level molecular MRD (MRD-LL) and may still be associated with adverse outcomes[1]. Multiparametric Flow Cytometry (MFC) -MRD test positivity is defined as > 0.1% of CD45-expressing cells with the target immunophenotype, both leukemia associated immunophenotypes (LAIPs) and different from normal (DfN) immunophenotypes (Figure 1)[19].

MRD positivity (MRD+) at the end of consolidation is an indication for intensification of treatment with HCT if the patient meets eligibility criteria (Figure1)[19]. However, MRD-LL detection in *NPM1*-mutated AML that is provisionally defined as <2% above the LOD, is associated with a very low relapse risk when measured at the end of consolidation chemotherapy[1] and does not require therapeutic intervention, but rather monitoring. MRD is useful for deciding on alloHCT in patients with favorable and intermediate genetic risk of relapse, according to European LeukemiaNet (ELN) risk stratification (Table 2)[1,20]. Patients with ELN adverse genetic risk benefit from alloHCT regardless of the MRD result[1,20]. Favorable-risk ELN patients with persistent MRD after induction have alloHCT as an option but may be considered for additional therapy if they achieve MRD negativity, and does not require therapeutic intervention, but rather monitoring MRD should be monitored[18]. Patients with intermediate-risk ELN should undergo alloHCT in first clinical remission (CR1) if eligible. For MRD-negative, borderline-fit patients, watchful waiting with serial MRD assessment may be an alternative[18]. MRD+ prior HCT is associated with a higher risk of relapse and poor outcome[21], but it is important to emphasize that this situation does not contraindicate transplantation[1]. Patients

with MRD+ AML may benefit from myeloablative conditioning (MAC) to decrease post-transplant relapse[18]. MRD-directed therapies could be considered for unfit patients for intensive conditioning, Persistence of molecular disease, such as *NPM1* and *FLT3-ITD* mutations, may necessitate further therapy to eradicate MRD before HCT[18]. However, there are limited data on the efficacy of reducing AML tumor burden in the pre-transplant setting to reduce the post-HCT relapse rate, and the benefit is still unclear. The main risks of offering MRD-directed therapy prior to HCT are relapse and complications of treatment that may limit access to HCT[18].

Monitoring MRD after HCT can identify patients at risk of relapse and can guide decisions about therapeutic intervention, such as withdrawal of immunosuppression, donor lymphocyte infusion, or chemotherapy to prevent overt relapse[22]. Time points for MRD assessment after HCT are not consensual, but have been done around D+30, D+60, D+100, D+180, D+360[22]. The definition of MRD relapse for now is defined as conversion from MRD negativity to MRD positivity, regardless of the MRD technique, or MRD increase >1 $\log_{10}$ between 2 positive samples measured in the same tissue (PB or BM) in patients with MRD-LL[1]. Figure 1 summarizes

TABLE 1: Methods for MRD assessment in ALL, their sensitivity and applicability[10,16]

	Multipatametric Flow Cytometry	**IgH/TCR RQ PCR**	**Fusion genes RQ PCR (ex: *BCR::ABL1, KMT2A*)**	**Next Generation Sequencing**
Requires patient specific design	No	Yes	No	No
Sensitivity	4 colors - 10-4 8 colors - 10-5 8 colors NGF - 10-6	10-4 – 10-5	10-4 – 10-5	10-5 – 10-7
Quantification	absolute	semi	semi	absolute
Diagnostic information needs (baseline sample)	No	Yes	No	No
Applicability	>90%	90-95%	30-40%	>95%
Turnaround time	hours	weeks	days	1week
Time points / applications	All patients Front-line therapy Post-relapse Pre- and post-HCT After immunotherapies	All patients Front-line therapy Post-relapse Pre- and post-HCT After immunotherapies	Method of choice for patients with gene fusions	All patients Front-line therapy Post-relapse Pre- and post-HCT After immunotherapies
Additional information	Identification of heterogeneity of whole population	Well standardized Does not identify clonal evolution	Well standardized	In standardization Identification of clonal evolution

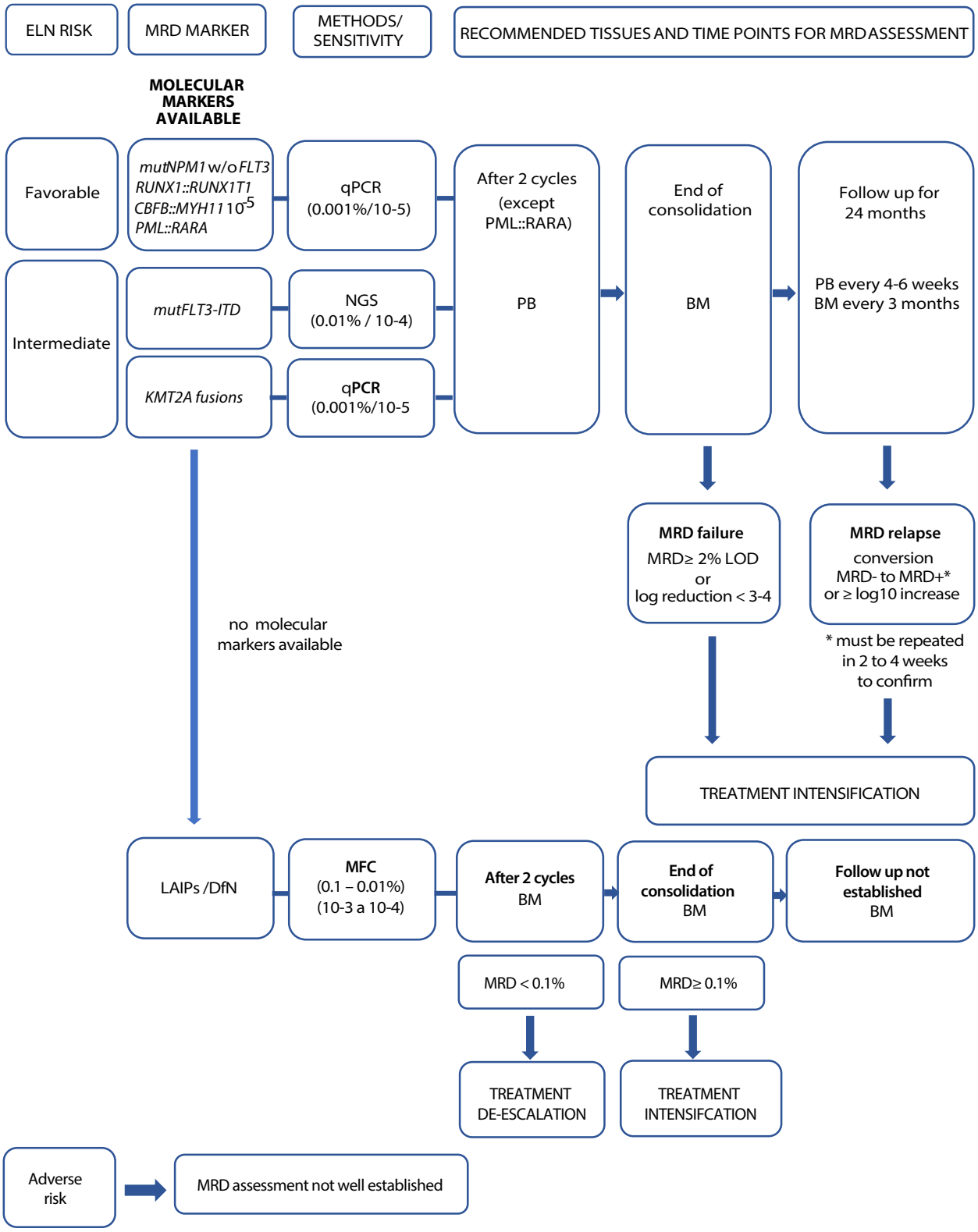
Abbreviations: RQ-PCR, real-time quantitative Polymerase chain reaction, NGF: Next Generation Flow, HCT: hematopoietic cell transplantation.

the time points and most appropriate methods for assessing MRD according to the AML subtype. Regardless of the MRD detection method, patients with undetectable MRD have a real risk of relapse for some reasons, such as: amount of MRD below the detection limit of the test, differences in MRD kinetics according to genetic risk, along with technical limitations for MRD detection[23]. All these aspects must be taken into account when interpreting MRD results to make clinical decisions.

TABLE 2: 2022 ELN risk classification by genetics at initial diagnosis[19]

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 Mutated *NPM1* without *FLT3-ITD* bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3-ITD* Wild-type *NPM1* with *FLT3-ITD* (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3)/MLLT3::KMT2A Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23.3;q34.1)/*DEK::NUP214* t(v;11q23.3)/*KMT2A* rearranged t(9;22)(q34.1;q11.2)/*BCR::ABL1* t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* t(3q26.2;v)/*MECOM(EVI1)* rearranged 25 or del(5q); 27; 217/abnormal(17p) Complex karyotype, monosomal karyotype Mutated *ASXL1, BCOR, EZH2, RUNX1,SF3B1, SRSF2, STAG2, U2AF1*, and/or *ZRSR2* Mutated *TP53a*

FIGURE 1: Methods, time points, samples for clinical decision-making based on AML DRM according to European LeukemiaNet (ELN) 2021 recommendations19



Abbreviations: MRD: measurable disease, qPCR: quantitative polymerase chain reaction, NGS: next generations sequencing, MFC: multiparametric flow cytometry, PB: peripheral blood, BM: bone marrow, LAIPs: leukemia associated immunophenotype, DfN: different from normal imunophenotype. LOD: limit of detection.

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16
HCT FOR HEMOGLOBINOPATHIES

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INTRODUCTION

Inherited hemoglobin disorders are estimated to be the most prevalent monogenic diseases worldwide, with a global carrier frequency exceeding 5%. Deletions or point mutations in the α- or β-globin genes cause abnormalities in hemoglobin synthesis or structure, leading to α and β thalassemia syndromes or structural hemoglobin variants, respectively[1,2]. Sickle cell disease (SCD) is the most common hemoglobin disorders, followed by severe forms of thalassemia syndromes[2]. In Brazil, an estimated 70,000 to 100,000 people are living with hemoglobinopathies, with sickle cell disease being the most prevalent[3]. While new promising therapeutic options are emerging, hematopoietic cell transplantation (HCT) remains the only widely available curative option[1].

HCT FOR SICKLE CELL DISEASE

Definition and Epidemiology

SCD is a frequent hematological disease, affecting predominantly afro descendants. The physiopathology consists of a point mutation of beta globin that replaces a glutamate with a valine, giving rise to hemoglobin S, which undergoes a polymerization when deoxygenated, resulting in sickling of red blood cells (RBCs). This process causes, among other disorders, hemolytic anemia and episodes of crises, such as vaso-occlusive crisis, splenic sequestration crisis and stroke[4]. In the treatment of sickle cell anemia, current therapies for SCD remain limited to hydroxyurea, L-Glutamine, red blood cell transfusion and HCT.

In Brazil, hemoglobinopathies were detected in 3.7% of the adult population. The Ministry of Health reports an incidence of sickle cell trait of 1 in 35 live births and estimates that three thousand children with SCD are born yearly. Although the survival rate has improved for adults with sickle cell disease, their life expectancy remains two decades lower than that of the general population, as chronic complications interact with unrelated conditions[5].

ALLO-HCT WITH AN HLA IDENTICAL SIBLING

Currently, young patients with SCD who have an HLA-identical sibling donor should be referred for evaluation at a transplant center, preferably at preschool age. In a large series of 1000 transplants (Table 1), 5-year EFS and OS were 91.4% and 92.9%, respectively. Age at transplantation was directly related to transplant outcome. EFS and OS were 93% and 100% in patients transplanted < 5 years[6]. Symptomatic adult patients with an HLA-identical sibling donor should also be evaluated at a transplant center, as the long-term risks and complications associated with HCT have gradually decreased in this group. However, allo-HCT is constrained by the availability of compatible donors,

insufficient information, and some risks of early and late-onset regimen-related toxicities[7]. Allo-HCT, with an HLA-identical sibling in Brazil, has been available through the Brazilian public health system since 2015 (Brazil, 2015; Brazil, 2017).

CONDITIONING REGIMEN

Myeloablative intensity conditioning, which involves busulfan (Bu) and cyclophosphamide (Cy) with ATG or busulfan (Bu) and fludarabine (Flu) with ATG, has been considered as the standard regimen for HLA identical sibling HCTs[8]. It's important to emphasize the significance of adding ATG to conditioning regimens, as its inclusion reduces the incidence of GVHD and lowers the rejection rate from 22.6% to 2.9 %[9] . In adults, a non-myeloablative conditioning for patients > 14 years have been successfully described (table 1)

ALTERNATIVE DONORS

While some small patient series using unrelated donors have been published, high rates of relapse, regimen-related toxicities, and GVHD have confined this option to patients with severe complications such as stroke and those who do not respond to hydroxyurea[10].

Considering recent data, a nonmyeloablative haploidentical HCT with thiotepa and cyclophosphamide after transplantation (PT-Cy) provides a viable curative option with excellent outcomes. In contrast, for children, it is currently recommended that haploidentical HCT only be conducted in clinical trials due to the high graft failure rates observed in these studies[11].

TABLE 1: Recent results of SCT in patients sickle cell disease

Author/Year	N	Age med (range)	Conditioning Regimen	SCD Free Survival
HLA IDENTICAL SIBLINGS				
Gluckman E, 2017	1000	9,4 (0,26-54)	BuCy/+Flu/+TT(ATG)	91,4%
Damlaj M, 2024	200	26 (14-43)	Alemtuzumab/TBI;	88,2%
MATCHED UNRELATED DONORS				
Gluckman E, 2020	71	9,3 (2-43)	Flu/TT/Treo or BuCy	88% (OS)
HAPLOIDENTICAL DONORS				
Kassim A, 2024	70	19,1(14-25)	Flu/Cy/TT/TBI	94,7 (>18 y) 68,4% (<18y)

Abrev: Bu: bulsufan, TT: thiotepa, Treo: treosulfan, Cy: cyclophosphamide, Flu: fludarabine, TBI: total body irradiation, ATG: anti-thymocyte globulin.

HCT FOR THALASSEMIA

Definition and Epidemiology

Thalassemia is a hereditary disease characterized by the absence or significant reduction of one or more globin chains that form hemoglobin. The pathogenesis of thalassemia arises from unbalanced globin chain production, resulting in ineffective erythropoiesis, increased hemolysis, and disrupted iron homeostasis. Clinical treatments for severe thalassemia involve lifelong transfusions, supportive iron chelation, and HCT[12]. According to data from the Brazilian Thalassemia Association (*Abrasta*) of the more than 1,600 registered thalassemic patients in Brazil, 283 have thalassemia major, and 222 have thalassemia intermedia[13].

Allo-HCT with an HLA Identical Sibling

More than 2000 patients have been transplanted worldwide with HLA identical siblings. Risk

TABLE 2: Pesaro Classification for risk assessment prior to SCT in pediatric patients

Risk factor	Class 1	Class 2*	Class 3
Iron Chelation therapy	Regular	Regular/Irregular	Irregular
Hepatomegaly > 2 cm	No	No/Yes	Yes
Portal fibrosis	No	No/Yes	Yes

*Minimum 1 and maximum 2

stratification has been well established by the Pesaro group for children (Table 2). Better HLA typing and better supportive care, have improved transplant results even for class 3 Pesaro patients.

In patients without risk factors, HCT from an HLA-identical family donor presents a thalassemia-free survival rate of over 90%[14]. The best transplant outcomes are achieved with a fully compatible sibling donor in pediatric patients under 6 years of age who have no comorbidities. This is accomplished using myeloablative conditioning with cyclophosphamide and busulfan or busulfan and fludarabine, both regimens associated with anti-thymocyte globulin (ATG) and utilizing bone marrow as the source of hematopoietic cells[14] (Table 3). In Brazil, since 2008, 16 out of 18 patients transplanted with HLA-identical donors for transfusion-dependent thalassemia are alive, demonstrating the effectiveness of this treatment[8].

ALTERNATIVE DONORS

Although data from unrelated donors have a limited number of patients, recent data from the literature show overall survival results similar to those found in patients undergoing HCT with HLA Identical Sibling[14].

Initial data from haploidentical HCT with PT-Cy indicated high engraftment failure rates. However, recent findings resulting from modifications in conditioning, such as increasing total body irradiation from 2 Gy to 4 Gy or incorporating immunosuppression in the preconditioning (two cycles of dexamethasone and fludarabine), have demonstrated a significant improvement in outcomes[15].

TABLE 3: Recent results of HCT in patients with transfusion dependent thalassemia

Author/Year	N	Age med (range)	Conditioning Regimen	Thalassemia Free Survival
HLA IDENTICAL SIBLINGS				
Chunfu Li, 2019	677	6(1-25)	BuCy/+Flu/+TT(ATG)	89%
Yesilipek, MA, 2022	1020	7 (1-29)	Bu/Treo and Cy/Flu;	82%
Agarwal RK, 2025	350	8,8(5,5-11.5)	FluBuCy-ATG	84,6%
MATCHED UNRELATED DONORS				
Yuelin He, 2020	212	6(2-23)	BuCy/+Flu/+TT(ATG)	88,9%
Yesilipek, MA, 2022	255	7(1-29)	Bu/Treo and Cy/Flu	82%

[1]Only Pesaro class 1 and 2

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17
HEMATOPOIETIC STEM CELL TRANSPLANTATION IN AUTOIMMUNE DISEASES

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INTRODUCTION

Hematopoietic stem cell transplantation (HCT) is a treatment option for severe and refractory autoimmune diseases (ADs) when conventional treatments fail to control and slow the progression of the disease. The main objective of HCT is to 'reset' the immune system by eliminating autoreactive T and B cells, enabling their regeneration and the resurgence of a more tolerant and less inflammatory immune repertoire[1-3]. In ADs, HCT, in addition to causing functional restitution of the immune system, induces the diversification of the regulatory T cell (Treg) population, reestablishing immunological tolerance to self and non-self-antigens, thereby enabling homeostasis of the immune system[4-6].

When HCT is indicated, the autologous modality is the most widely used treatment for diseases such as multiple sclerosis (MS), systemic sclerosis (SS) and Crohn's disease (CD). There are reports of clinical case series, including some randomized studies, which demonstrate that HCT has the ability to induce long-term remission without the need for continuous immunosuppression, surpassing the efficacy of conventional treatments in some cases[1,2,7].

Allogeneic HCT is used in ADs, although less frequently than autologous transplantation, due to its associated risks, such as graft-versus-host disease (GvHD) and non-relapse mortality. However, allogeneic HCT may be considered in cases of severe and refractory ADs where other therapeutic options have failed[8].

The European Society for Blood and Marrow Transplantation (EBMT) reports that allogeneic HCT can induce long-term disease control in a significant proportion of patients with refractory autoimmune diseases, especially in younger patients[8,9]. However, the efficacy of allogeneic HCT is not yet fully understood. In specific ADs, the intensity of conditioning and the presence of GvHD influence long-term results[9]. Thus, despite the possibility that allogeneic HCT induces remission, it should be limited to selected cases and clinical trials due to the risks associated with the procedure[8,9].

Chimeric antigen receptor T-cell (CAR-T) therapy is considered promising for the treatment of autoimmune diseases, especially those mediated by B cells, such as systemic lupus erythematosus (SLE). This technique aims to modify or suppress aberrant immune responses, offering a more selective and effective option compared to HCT[10-12]. The therapy targets B cells through receptors such as CD19, which has shown promising results in early clinical trials for autoimmune diseases[11,13]. The resulting profound B-cell depletion may help to 'reset' the immune system, similar to the effect observed with HCT, but potentially with less toxicity[13].

Another more specific area is the engineering of Treg cells to express antigen-specific chimeric antigen receptors (CARs). This approach has the potential to modulate the immune system more precisely, promoting immune tolerance without

the side effects of systemic immunosuppression[14]. CAR-Tregs are then engineered to migrate to specific sites of inflammation and exert immunosuppressive functions more effectively than polyclonal Tregs[14]. However, challenges remain in identifying target antigens, long-term safety and the control of adverse effects such as cytokine release syndrome[14].

INDICATION CRITERIA

It is estimated that approximately 5% of the world's population is affected by ADs[15].

HCT has been used in ADs with significant results, but there are doubts regarding the precise indications for its use. In its guidelines, the SBTMO recommends non-myeloablative autologous HCT as the therapeutic standard for MS and SS and as a clinical option for CD[16].

Table 1 shows the categorization of type of indication for HCT procedures in ADs and strength of evidence according to the EBMT. Table 2 shows an adaptation of the indications according to the disease status of Ads[17].

In conclusion, HCT should always be considered as an option for severely-ill ADs patients who are refractory to conventional treatments. Autologous HCT is considered a Grade I Standard of Care for people with highly active relapsing-remitting MS and SS who have not responded well to other disease-modifying therapies and should be considered a Grade I clinical option in selected cases of CD.

TABLE 1: Categorization of type of indication for hematopoietic cell transplantation procedures in autoimmune diseases[17]

Categories	Settings where HCT ought to be performed
Standard of care (S)	Indications are well defined, and results compare favorably (or are superior) to those of non-transplant treatment approaches.
Clinical option (CO)	Indications for which the results of small patient cohorts show efficacy and acceptable toxicity of the HCT procedure, but confirmatory randomized studies are missing, often because of low patient numbers. The broad range of available transplant techniques combined with the variation of patient factors such as age and co-morbidity makes interpretation of these data difficult. Our current interpretation of existing data for indications placed in this category supports that HCT is a valuable option for individual patients after careful discussions of risks and benefits with the patient, but that for groups of patients the value of HCT needs further evaluation. Transplants for indications under this heading should be performed in a specialist centre with major experience in HCT with an appropriate infrastructure as defined by JACIE standards
Developmental (D)	Indications when the experience is limited, and additional research is needed to define the role of HCT. These transplants should be done within the framework of a clinical protocol, normally undertaken by transplant units with acknowledged expertise in the management of that disease or that type of HCT. Protocols for D transplants will have been approved by local research ethics committees and must comply with current international standards. Rare indications where formal clinical trials are not possible should be performed within the framework of a structured registry analysis, ideally an EBMT noninterventional/ observational study. Centres performing transplants under this category should meet JACIE standards

Generally not recommended (GNR)	Comprises a variety of clinical scenarios in which the use of HCT cannot be recommended to provide a clinical benefit to the patient, including early disease stages when results of conventional treatment do not normally justify the additional risk of an HCT, very advanced forms of a disease in which the chance of Success is so small that it does not justify the risks for patient and donor, and indications in which the Transplant modality may not be adequate for the characteristics of the disease. A categorization like GNR does not exclude that centres with expertise on a certain disease can investigate HCT in these situations. Therefore, there is some overlap between GNR and D categories, and further research might be warranted within prospective clinical studies for some of these indications
Grade	**Strength of the evidence supporting the assignment of a particular category**
Grade I	Evidence from at least one well-executed random trial.
Grade II	Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments
Grade III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees.

HCT: Hematopoietic cell transplantation

TABLE 2: Proposed classification of hematopoietic cell transplantation indications for autoimmune diseases in adults[17]

Disease	Disease status	MSD Allo	Auto	CAR-T
Multiple Sclerosis	Highly active RR-MS failing DMT. Progressive MS with AIC, and Aggressive MS Progressive MS without AIC	D/III D/III GNR/III	S/1 CO/II GNR/III	D/III D/III
Systemic sclerosis		D/III	S/I	D/iii
Crohn's disease		D/III	CO/II	
SLE		D/III	CO/II	D/III
Rheumatoid arthritis		D/III	CO/II	
JIA		CO/II	CO/II I	
Monogenic AD		CO/II	GNR/II	
Vasculitis	ANCA+, BD, Takayasu, and others	GNR/III	CO/II	
PM-DM		GNR/III	CO/II	
Autoimmune cytopenias		CO/II	CO/II	
NMOSD		D/III	CO/II	
CIDP, MG and SPS		GNR/III	CO/II	
Type 1 diabetes		GNR/III	CO/II	
RCD Type II		GNR/III	CO/II	
Primary ID		CO/II	NA	

KEY POINTS

• Autoimmune diseases affect approximately 5% of the global population.

• Hematopoietic stem cell transplantation (HCT) should be considered as a therapeutic option for severe and refractory autoimmune diseases in select cases.

• HCT should be performed in experienced transplant centers by multidisciplinary teams familiar with managing autoimmune diseases.

• For individuals with relapsing-remitting disease, autologous HCT is a standard of care for multiple sclerosis (MS) and systemic sclerosis (SS), and a clinical option for selected cases of Crohn's disease (CD), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), vasculitis, juvenile idiopathic arthritis, and autoimmune cytopenias.

• Allogeneic HCT and chimeric antigen receptor T cell therapy should only be used in clinical research protocols for autoimmune diseases.

Allo: Allogeneic; AD: autoimmune disease; ANCA: antineutrophil cytoplasmatic antibodies; Auto: autologous; BD: Bechet disease; CAR-T: chimeric antigenreceptorT-cell;NMOSD:Neuromyelitisoptica spectrum disorder; CIDP: chronic inflammatory demyelinating polyneuropathy; CO: clinical option; D: developmental; DMT: disease modifying treatments; GNR: generally not recommended; ID: immunodeficiency; JIA: juvenile idiopathic arthritis; MG: myasthenia gravis; MS: multiple sclerosis; AIC: Autoimmune cholangiopathy; NA: not applicable; PM-DM: polymyositis and dermatomyositis; RCD: refractory celiac disease; RR-MS: relapsing-remitting multiple sclerosis; S: standard care; SLE: systemic lupus erythematosus; SPS: stiff person syndrome

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18
CELLULAR THERAPY

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NATURAL KILLER CELLS

Natural Killer cells were described 40 years ago and still there are several unsettled aspects of its function and mechanisms. Although a lymphocyte, NK cells are innate lymphocytes that challenged the paradigm that lymphocytes were adaptive immune system cells while dendritic cells, monocytes/macrophages and granulocytes were the cellular element of innate immunity.

The name Natural Killer was coined based on their main characteristic: the ability to react and kill malignant cells within a few hours without prior exposure, a characteristic of the innate immune system.

Later, it was observed that individuals that lack NK cells were more susceptible to severe or lethal viral infections, while in severe systemic inflammation, as in Hemophagocytic Syndromes, NK cells are diminished and/or dysfunctional – an anti-viral role as well as its role in destroying stressed and over activated cells was then discovered. NK cells serve as the first barrier against malignant and virus-infected cells while also playing a role in removing hyperreactive normal cells.

HOW NK CELLS RECOGNIZE A TARGET WITHOUT PREVIOUS EXPOSITION TO IT?

The discovery of KIR receptors (Killer Immunoglobulin-like receptor) that interact with HLA- class I molecules and inhibit NK cells activation, partially clarified the above question and gave rise to the "missing self" theory, "whatever does not belong to us, must be destroyed"[1]. Eventually, activating KIR receptors were described as well. The set of (haplotype) of KIRs of an individual can have predominantly inhibitory KIRs (A haplotype) or activating KIRs (B haplotype). In addition, NK cells express natural receptors (also inhibitory or stimulatory); some of which are very well-preserved molecules that enable NK cells to perceive membrane abnormalities mostly related to biophysical alterations such membrane electric potential alterations, or a cell surrounded by an acid milieux such as malignant cells with their anaerobic metabolism.

To predict the net effect of a specific KIR haplotype and the natural receptors is challenging. Furthermore, other factors also may play a role in

the modulation of these interactions, including the nature of the microenvironment milieux, target cells, nearby cells as regulatory T cells (Tregs), and myeloid derived suppressor cells[2,3]. In simplified systems, as in vitro studies or immunodeficient animal models, the main inhibitory or stimulatory set of receptors have been studied according, respectively, to the absence or presence of its ligands on the target cell – the so-called KIR mismatch (KIR MM); upon information derived from those studies, models of ideal NK cell/target combination are being tested to predict NK cells activity. Table I show a simple way of predicting NK cells alloreactivity based in KIR receptors and their ligands. However, it must be kept in mind the role of natural receptors in this equation. In short, target cells ligands for activating receptors can surpass the ones for inhibitory receptors and vice e versa, resulting either in activation or inhibition, respectively.

It is important to point out that NK cells, particularly the CD56dim cells (see below) express receptors for the Fc region of immunoglobulins (CD16) (just like monocytes/macrophages do) and is the most important cell to kill a target opsonized by antibodies.

TABLE 1: NK cell alloreactivity or Graft versus Leukemia (GVL) effect prediction

		Donor HLA Type (Predicted KIR Receptor)		
		Homozygous group C1 (KIR2DL2, KIR2DL3)	Homozygous group C2 (KIR2DL1)	Heterozygous group C1+C2 (KIR2DL2, KIR2DL3, KIR2DL1)
Recipient HLA Type (Known KIR Ligand)	Homozygous group C1 (C1,3,5,6)	No GVL	GVL	GVL
	Homozygous group C2 (C2,4,7,8)	GVL	No GVL	GVL
	Heterozygous group C1+C2	No GVL	No GVL	No GVL

		Donor HLA Type (Predicted KIR Receptor)	
		Bw4+ (KIR3DL1)	Bw4- (none)
Recipient HLA Type (Known KIR Ligand)	Bw4+	No GVL	No GVL
	Bw4-	GVL	No GVL

NK CELLS SUBTYPE

According to its phenotype there are two main NK cells subtypes: CD56bright and CD56dim, immature and mature cell, respectively. However, although "immature", CD56bright NK cells can recognize targets without previous exposition and, upon activation, secrete a variety of chemokines, cytokines and growth factors involved in both innate and adaptive immune activation, thereby exerting a regulatory function. Regulatory regulatory or CD56bright NK cells NK cells are predominantly tissue resident cells while cytotoxic NK or CD56dim NK cells predominate in the peripheral blood and are one of the major IFN-γ producing cells[4].

Once considered as immature and dysfunctional NK cells, the regulatory function of CD56bright NK cells has been increasingly accepted. Their importance was highlighted during the COVID-19 pandemic in a study that demonstrated the direct correlation between severity and lethality of COVID-19 infection and a diminished number of regulatory NK cells[5]. CD56bright or regulatory NK cells predominantly express natural receptors (inhibitory or stimulatory) with minimal or no expression of KIR receptors that are abundantly expressed in CD56dim, or cytotoxic NK cells. Between these two main subtypes there are functional interactions and/or phenotypic variations that ensure high variability and effective immunosurveillance[4,6]. Finally, as mentioned above, cytotoxic NK cells express immunoglobulins receptors (CD16) and are the main cell type involved in antibody-dependent cell-mediated cytotoxicity (ADCC). Notably, the predominant mechanism of action of rituximab is the activation of NK cells to mediate ADCC.

NK CELLS AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

NK cells are the first population of donor-derived peripheral blood lymphocytes to numerically reconstitute after allogeneic hematopoietic stem cell transplantation. Normal NK cell numbers are generally observed within the first month after transplantation, regardless of the graft source[7,8]. Early reconstituting NK cells exhibit a regulatory CD56bright phenotype, representing 40–50% of NK cells in the first few months, whereas they constitute only 5–10% in healthy adults, and only acquire the predominantly CD56dim NK phenotype after several months[9].

According to a machine learning model in allogeneic transplant, the intensity of NK cell recovery correlates with event free survival (EFS) and overall survival (OS) after the transplant, implying that NK cells are a very important component of the GVL effect and that the bone marrow microenvironment after high dose chemotherapy stimulate NK cell activation and expansion. It is even possible that multiple myeloma favorable response to autologous HSCT derive from NK cells expansion pos transplant and its GVL effect.

NON-GENETICALLY MODIFIED NK CELL ADOPTIVE IMMUNOTHERAPY

NK cells are very active against malignant myeloid cells and, apparently, for malignant plasmacytes as well. NK cell immunotherapy has been studied predominantly in those two diseases.

Lymphocyte Adoptive Immunotherapy has become a very hot topic since the excellent results of CAR-T cells for ALL or NHL (see related session). A challenging aspect of CAR-T cell therapy is its toxicity, and, in this scenario, NK cells emerge as a good immunotherapy candidate since independently of the number of cells infused or the HLA identity, their infusion causes no or very few immediate or long-term toxic effects. In addition, NK cells are known to stimulate innate and adaptive cells, resulting in specific T and B cells activation[10]. Achieving an adaptive, antigen-specific immune response with long-term memory, while avoiding the adverse effects associated with CAR-T cell therapy, would be ideal. In addition, to be able to obtain GVL effect without the toxicity of the HSCT would be highly desirable, as the curative potential of HSCT relies on this mechanism. The main obstacle for NK cell therapy

is the difficulty to obtain an ex-vivo expanded, clinical grade number of cells with the necessary purity and activity. Most of the published studies (Table II) utilize only one infusion of NK cells, some without any in vitro activation, followed by either Interleukin 2 (IL-2) or IL-15 with the intent of in vivo activation of the infuse cells. Of all listed Phase I/II studies, the ones with best results are those that utilized in vitro activated NK cells, and those that combined high dose lymphodepletion with the infusion of hyper-activate non-genetically modified NK cells expanded in the presence of feeder cells[11,12]. As seen above we believe that lymphodepletion before non-genetically modified NK cells immunotherapy needs to be of higher intensity than the lymphodepletion for genetically modified T cells.

The efficacy of infused NK cells observed in phase I clinical trials to treat AML is astonishing[13]. As a parallel, Venetoclax, a new drug that associated with hypometilating agents is increasingly becoming a standard component of AML remission induction and maintenance had less than 20% of efficacy for AML when utilized alone in a Phase I clinical trial[14]. As can be seen in Table II, some studies, particularly the ones already cited above[11,12], obtained 72% to 78,6% of overall response suggesting NK cell immunotherapy could have an important role for the treatment of AML. There are also few studies with CAR-NK cells and non-genetically modified NK cells with promising initial results[15].

TABLE 2: Main clinical trials on non-genetically modified NK cells[13]

Author	# Patients	Lymphodepletion	Product activation	NK cells/infusion	# infusion/in vivo activation	ORR %	CR %	NK PB peak day	NK expansion % Patients	Chimerism %	HSCT %/(#patients)	Disease	obs
Miller (16)	19	Cy/Flu 2X/5X	Overnight IL2	2 x 10^7	1/IL-2	26	26	7	NA	1 to 8	no	R/R AML	
Curti (17)	13	Cy/Flu 1X/5X	none	2.7 x 10^6	1/IL-2	46	23	10	NA	2 to 18	no		R/R AML (5) CR MRD+ (2) CR (6)
Bachanova (18)	42	Cy/Flu 2X/5X	Overnight IL2	3.4 – 3.6 x 10^6	1/IL-2	21	12	7 - 14	10	10	9.5% (4 pts)	R/R AML	
	15	Cy/Flu 2X/5X	Overnight IL2	2.6 x 10^7	1/IL-2	53	20	7 - 14	27	27	40% (6pts)	R/R AML	IL-2 DT
Dolstra (19)	11	Cy/Flu 4X/4X	cultured CB NK (IL2, IL15)	3.0 x 10^7	1/no	••	••	8	NA	21 PB 3.5 BM	no	CR HR AML	
Björklund (20)	16	Cy/Flu 2X/4X TBI	Overnight IL2	6.7 x 10^6	1/no	37.5	25	7 - 14	NA	41	31% (5pts)	R/R AML	
Cooley (21)	26	Cy/Flu 2X/5X	Overnight IL15	3.4 -9.6 x 10^6	1/IL-15 IV	32	24	7 - 14	36 d14	100 d7 42 d14	26.5% (11)	R/R AML	
	16	Cy/Flu 2X/5X	Overnight IL 15	2.6 x 10^7	1/IL-15 SC	40	6	7 - 14	27% d14	100 d7 33% d14		R/R AML	56% CRS
Romee (22)	9	Cy/Flu 2X/5X	Memory NK cell*	0.5 -10 x 10^6	1/IL-2	55	45	7 - 14	NA	90-day 7	no	R/R AML	*Culture IL15, IL12.IL18
Vela (11)	20	HD CT	mboIL-15 K562	6.76 x 10^6	1 & 2/II-2	72	72	7	NA	46.7	50% (10)	R/R AML+	T-ALL B-ALL BP - AL
Silla (12)	13	HD CT	mboIL-21 K562	9 x 10^6	6/no	78.6	50	7	NA	NA	38% (5)	R/R AML	

CAR CELLS

Chimeric Antigen Receptor (CAR) therapy has revolutionized cellular immunotherapy, significantly impacting the landscape of hematopoietic cell transplantation (HCT). The concept emerged in the late 1980s when researchers first engineered T cells to recognize tumor antigens independently of major histocompatibility complex (MHC) presentation[16-18]. Early-generation CARs, composed of an antigen-binding domain fused to a single signaling motif, demonstrated limited efficacy due to poor expansion and persistence. The addition of co-stimulatory domains such as CD28 and 4-1BB in second-generation CARs greatly enhanced their function, leading to the first FDA-approved CAR-T therapy, tisagenlecleucel (Tisa-cel), in 2017 for B-cell malignancies. Subsequent advancements introduced third-generation CARs with dual co-stimulatory signals and fourth-generation "armored" CARs capable of cytokine secretion and immune checkpoint modulation[19,20].

CAR-NK therapy has emerged as an alternative with unique advantages in HCT, including a lower risk of GVHD, innate immune activity beyond CAR-mediated targeting, and the potential for off-the-shelf use[21,22]. CAR-NK cells have demonstrated efficacy in B-cell malignancies and are being investigated for post-HCT relapse prevention, particularly in acute myeloid leukemia (AML), where CAR-T therapy has faced challenges due

to antigen heterogeneity. Additionally, CAR-NK cells are being explored for infection control post-transplant, targeting viral reactivations such as CMV and EBV[23,24].

CAR-T CELLS

The development of chimeric antigen receptor (CAR) T cell therapy has revolutionized the treatment of relapsed or refractory hematologic malignancies[25]. Since 2017, the U.S. Food and Drug Administration (FDA) has approved multiple autologous CAR-T cell therapies to treat certain relapsed or refractory hematologic malignancies. These include Tisagenlecleucel (Kymriah), Axicabtagene Ciloleucel (Yescarta), Brexucabtagene Autoleucel (Tecartus), Lisocabtagene Maraleucel (Breyanzi), Ciltacabtagene Autoleucel (Carvykti) and Idecabtagene Vicleucel (Abecma) (Table III).

After receiving regulatory approvals, several real-world studies have been carried out to assess the efficacy and safety of CAR-T in more diverse and representative patient populations. Although the real-world meta-analysis included a broader patient population, its findings remained consistent with clinical trial outcomes in aggressive non-Hodgkin lymphoma, regarding ORR, CR, and median OS and PFS for both therapies. In real-world settings, the estimated ORRs were 73.4% for Axicabtagene Ciloleucel (Axi-cel) and 57.7% for Tisa-cel, compared to 83% in the ZUMA-1 trial and 53% in the JULIET trial[26]. Similarly, estimated real-world CR rates, based on the best response, were 51.0% for Axi-cel and 39.0% for Tisa-cel, aligning with the 58% CR in ZUMA-1 and 39% in JULIET. The occurrence rates of any-grade and grade ≥3 CRS and ICANS events were lower in real-world studies, potentially due to variations in grading criteria and the earlier or preventive use of interventions like corticosteroids or tocilizumab to manage these adverse events in clinical practice[26]. These findings further support the safety and effectiveness of CAR T cell therapy in patients with DLBCL.

The overall results of CAR-T therapy for ALL have been remarkable. At three months, the cumulative incidence of MRD-negative CR reached 76.9%. Additionally, the 2-year overall survival rate was 64.6%, with leukemia-free survival at 48 and a relapse incidence of 45.5%. Non-relapse mortality at two years stood at 6.5% (4–9.6), while the 2-year cumulative incidence of subsequent HSCT was 33.3%, and second CAR-T infusions were administered in 12.4% of cases[27]. Patients with relapsed or refractory acute lymphoblastic leukemia (ALL often receive CAR-T therapy to achieve deep remission before proceeding to transplant[16,27]. CAR-T therapy has been investigated as a method to clear minimal residual disease (MRD) before HSCT. The presence of MRD at the time of transplant is a strong predictor of relapse, and pre-transplant CAR-T therapy has shown promise in eradicating MRD, thereby improving long-term transplant success28[35]. Relapse remains a major challenge after HCT, particularly in high-risk leukemia patients. Post-transplant CAR-T infusion is being explored as a strategy to prevent disease recurrence. Studies have demonstrated that administering CAR-T cells post-HCT can help maintain remission, particularly in patients with persistent MRD[29].

CAR-NK CELLS

CAR-NK cells offer several advantages over CAR-T cells. One key benefit is the lower risk of graft-versus-host disease (GVHD), as NK cells lack T-cell receptors, reducing the risk of alloreactivity. Additionally, their "off-the-shelf" availability enhances clinical application, as CAR-NK cells can be derived from universal donors, cord blood, or induced pluripotent stem cells (iPSCs), allowing for immediate access and scalability. Another important advantage is their dual mechanisms of action: in addition to CAR-mediated antigen targeting, NK cells retain their innate cytotoxic function, enabling them to eliminate tumor cells through multiple pathways, including antibody-dependent cellular cytotoxicity (ADCC) [22,30].

PRE- AND POST-TRANSPLANT APPLICATIONS

Like CAR-T cells, CAR-NK cells are being investigated as a bridge to HCT in patients with refractory hematologic malignancies. Studies

have shown that CAR-NK therapy can induce high response rates in relapsed/refractory B-cell malignancies, including patients who have failed prior CAR-T therapy[22].

Clinical trials are exploring the use of CAR-NK cells to prevent relapse in acute myeloid leukemia (AML), where traditional CAR-T approaches have been less effective due to the heterogeneity of AML-associated antigens. Studies phase I explored different targets as CD33 and NKG2D. Early results from a Phase 1 trial using a CAR NK cell therapy targeting NKG2D in relapsed or refractory AML, indicate that the treatment is well-tolerated, with no observed instances of GVHD, CRS, or neurotoxicity to date. While the data is still in its early stages, the therapy shows promise, with three out of six patients achieving a CR[31]. The primary data from the Phase I trial have demonstrated the initial efficacy and safety of CD33 CAR NK cells in patients with relapsed or refractory AML (R/R AML). While these results are promising, further studies with larger sample sizes and extended follow-up are needed to more fully assess the long-term efficacy and durability of the treatment[32].

Cellular immunotherapy using CAR-T and CAR-NK cells has shown promising results, but several challenges still need to be addressed to optimize their long-term effectiveness and accessibility. One significant limitation is the persistence of CAR-T cells, particularly in post-transplant settings, where their durability tends to be reduced. Strategies such as enriching T cell products with memory-like phenotypes, providing cytokine support (e.g., IL-15), and combining different therapeutic approaches are being investigated to enhance longevity[33].

Another obstacle is the risk of relapse due to antigen escape, where tumor cells evade treatment by downregulating targeted surface markers, as seen with CD19 loss in B-cell malignancies. To counter this, researchers are developing dual-targeting CAR constructs, such as CD19/CD22 or CD123/CLEC12A, to improve recognition and prevent resistance.

Managing therapy-related toxicities remains a priority, particularly for CAR-T cells, which are associated with conditions like cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In contrast, CAR-NK therapy has demonstrated a more favorable safety profile. Ongoing efforts aim to refine dosing regimens and incorporate safety features like suicide genes and control switches to mitigate adverse effects.

Finally, the production and cost of CAR-based therapies pose significant barriers to widespread clinical implementation. The complexity of manufacturing personalized treatments limits accessibility. However, advances in gene-editing technologies and the development of "off-the-shelf" CAR-NK therapies derived from universal donors may help to reduce costs and increase accessibility.

Integrating cellular therapy into HCT is revolutionizing the treatment of hematologic malignancies. CAR-T and CAR-NK therapies provide potent anti-tumor effects, both as a bridge to transplant and as a relapse-prevention strategy post-HCT. While challenges remain in optimizing persistence, safety, and manufacturing, ongoing advances in gene engineering and cellular therapy design will likely to further enhance HCT outcomes. As research progresses, cellular therapies will continue to play a crucial role in improving the efficacy, safety, and accessibility of HCT for patients worldwide.

TABLE 3: Commercially Available CARs Therapies and Their Relationship to HCT

Tisagenlecleucel	
Target:	CD19
Diseases	DLBCL, young ALL, FL
Dosing:	$0.2–5.0 \times 10^6$ CAR+ T cells/kg (≤50 kg) $0.1–2.5 \times 10^8$ CAR+ T cells (>50 kg)
Axicabtagene Ciloleucel	
Target:	CD19
Diseases	DLBCL, FL
Dosing:	2×10^6 CAR+ T cells/kg (Max: 2×10^8 CAR+ T cells)
Brexucabtagene Autoleucel	
Target:	CD19
Diseases	MCL, adult ALL
Dosing:	2×10^6 CAR+ T cells/kg (Max: 2×10^8 CAR+ T cells)
Lisocabtagene Maraleucel	
Target:	CD19
Diseases	DLBCL, CLL
Dosing:	$50–110 \times 10^6$ CAR+ T cells (single infusion)
Ciltacabtagene Autoleucel	
Target:	BCMA
Disease	MM
Dosing:	$0.5–1 \times 10^6$ CAR+ T cells/kg
Idecabtagene Vicleucel	
Target:	BCMA
Diseases	MM
Dosing:	$300–460 \times 10^6$ CAR+ T cells
CAR-NK (Investigational)	
Target:	CD19, CD33, NKD2D, etc.
Dosing:	Varies depending on the study

Legend: Difuse Large B-Cell lymphoma (DLBCL); follicular lymphoma (FL); multiple myeloma (MM); Mantle cell lymphoma (MCL); Chronic lymphocytic leukemia (CLL).

DONOR LYMPHOCYTES INFUSIONS

Graft versus Leukemia effect (GVL) is recognized as the cellular mechanism through which HSCT can cure leukemia34. Over the past 30 years, the infusion of lymphocytes derived from the stem cell donor or unmanipulated Donor Lymphocyte Infusions (DLI) has been recognized as a form of immunotherapy capable of inducing durable remissions by enhancing the GVL effect35. However, DLI carries risks including graft-versus-host disease (GVHD) and aplasia. Nonetheless, because post-HCT relapse has a dim prognosis, DLI is now an established therapeutic option for managing disease relapse after allogeneic hematopoietic cell transplantation (allo-HCT). The efficacy of DLI depends on factors such as the type of disease, as well as the dose, timing, and interval of the infused lymphocytes. Response rates vary depending on the underlying disease36-38.

There are three primary indications for DLI: prophylactic, preemptive, and therapeutic37,38.

Prophylactic DLI as maintenance therapy to prevent relapse after allo-HCT, even in the absence of clinical evidence of disease recurrence.

Preemptive DLI in patients who are in hematological remission but show incomplete or declining donor chimerism, minimal measurable disease (MMD), or molecular or cytogenetic signs of subclinical relapse.

Therapeutic DLI to manage hematological relapse or graft failure, preferably following disease control achieved through chemotherapy or targeted therapy.

Recommended DLI doses per kg body weight can vary according to different scenarios and donor type (Table 1)

In general, DLI can be administered alone or in combination with other therapies to enhance its anti-tumor effect. However, the integration of DLI into treatment algorithms varies depending on disease-specific factors—most notably, the

TABLE 4. Recommended DLI doses and timing - adapted from the 2024 EBMT guidelines on DLI[39]

SCENARIOS	Matched Donor	Matched Unrelated	Mismatched/Haploidentical	Number of DLIs
Prophylactic (3 months)	1×10^5	1×10^5	1×10^5 *	1-3
Prophylactic (6 months)	1×10^6	1×10^6	5×10^5	1-3
Pre-emptive (3 months)	$1–5 \times 10^5$	1×10^5	1×10^5	1-3
Pre-emptive (6 months)	$1–3 \times 10^6$	1×10^6	5×10^5	1-4
Therapeutic (post-therapy)	1×10^7	1×10^7	1×10^6	1-4

sensitivity of the malignancy to the graft-versus-leukemia (GvL) effect.

The 2024 EBMT guidelines on DLI incorporate classifications originally proposed at a 2010 National Cancer Institute workshop on post-allo-HCT relapse. Based on this framework, disease sensitivity to DLI is categorized as follows39:

High sensitivity: chronic myeloid leukemia (CML), myelofibrosis, low-grade non-Hodgkin lymphoma (NHL), and multiple myeloma.

Intermediate sensitivity: chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and Hodgkin lymphoma.

Low sensitivity: acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL).

Balancing the efficacy of DLI with the risk of adverse effects, particularly graft-versus-host disease (GVHD), is essential. The risk of post-DLI GVHD is influenced by several factors, including donor type and HLA matching, cell dose, timing and frequency of administration, prior history of GVHD, and whether immunosuppressive therapy is ongoing at the time of infusion. Therefore, it is crucial to adhere to established prerequisites, appropriate dosing, and timing for DLI administration39.

To mitigate GVHD risk while preserving or enhancing the GVL effect, various forms of DLI manipulation have been proposed. These include the selective depletion or enrichment of specific donor T-cell subsets, as well as engineered products that incorporate "suicide switches"—molecular mechanisms designed to inactivate via drugs or inert molecules, infused T cells if GVHD occurs, thereby improving safety40.

TABLE 5. Recommended prerequisites for DLI use - adapted from the 2024 EBMT guidelines on DLI[39]

CATEGORY	Criteria	Exceptions/Special Considerations
Timing Post-Transplant	At least day 90 after transplantation.	May be adjusted based on donor type, graft source, GVHD prophylaxis, and conditioning regimens.
Infection Status	Absence of infection.	-
Immunosuppressive Medications	No systemic immunosuppression (e.g., calcineurin inhibitors, mycophenolate) for 3–6 weeks prior.	Longer delay in mismatched donor transplants. - In high-risk cases (unfavorable disease, mismatched settings, or center experience), DLI may be given earlier (with increased GVHD risk). - Mobilized PBMCs + short-term immunosuppression have been used in some cases. - Not recommended under ongoing immunosuppression (to avoid counteracting DLI effects).
GVHD Considerations	Prophylactic DLI: - Absolute contraindication: Active acute/chronic GVHD. - Relative contraindication: History of corticosteroid-sensitive acute GVHD (grade 2–4) or moderate/severe chronic GVHD (case-by-case evaluation). Pre-emptive/Therapeutic DLI: - History of acute GVHD (grade 2–4) or moderate/severe chronic GVHD not an absolute contraindication.	Requires careful benefit-risk assessment with the patient. - Timing of GVHD episodes relative to relapse/DLI must be considered. - Proceed with extreme caution.

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19
REDOME

DANIELLI OLIVEIRA

Created in 1993, the Brazilian Bone Marrow Donors Registry (REDOME) has been, part of the National Transplant Policy of the General Coordination of the National Transplant System (CGSNT) of the Ministry of Health since 2000. It is under the technical coordination and management of the National Cancer Institute (INCA). It is maintained by resources from the Unified Health System (SUS), meeting the demands of patients from all over Brazil, assisted by the public and private sectors.

The main attributions of REDOME include the management of the registry of voluntary bone marrow donors, the management of the registry of Brazilian patients who need hematopoietic stem cell transplantation, the selection and identification of compatible donors for Brazilian patients, and the organization of donor logistics for the performance of clinical-laboratory evaluation and all steps until effective donation.

REDOME is the only Bone Marrow Donor Registry authorized to operate in this segment, which means that all Brazilian patients who need a hematopoietic stem cell transplant must be registered in the Registry so that this type of transplant can be performed.

The Brazilian Registry is part of the World Marrow Donor Association (WMDA) which brings together registries from more than 50 countries, allowing foreign donors to donate to Brazilian patients and, in return, Brazilian donors to donate cell products to international patients.

In 2024, REDOME had a total of more than 5.9 million registered donors, being the third largest donor registry in the world, and, since September 2023, it has been internationally certified by WMDA, demonstrating the quality of its processes in compliance with international standards and promoting the safety of patients and donors. In Brazil, 65% of patients who undergo transplantation with unrelated donors use national donors (REDOME) while the remaining 35% use international donors – a result considered satisfactory compared to other international registries.

Following current legislation and international recommendations, the entire donation process is voluntary, altruistic, and anonymous. Thus, REDOME acts to ensure the autonomy of the donor and respect the privacy of donors and patients.

The physicians who work in transplant centers have a fundamental role in the execution of activities related to REDOME:

1. Patient registration to search for compatible unrelated donors in the REDOMENET system.

   1.1 To register patients, the doctor must be previously registered in the REDOMENET system (https://redomenet.inca.gov.br/redome/login)

   1.2 The patient's registration must be approved by a transplant center, by the criteria established by the Technical Regulation of the Ministry of Health

   1.3 To maintain the patient search process, the physician responsible for the registration must update the clinical information within a maximum interval of 3 months

   1.4 Information regarding the search process, such as the selection of possible compatible donors and the performance of confirmatory compatibility tests, will only be sent to the physician responsible for the registration and REDOME does not share information on the status of the search with patients and/or family members

   1.5 Only after approval by the patient's medical team, confirmatory compatibility tests will be performed

2. Collection of hematopoietic stem cells from matched donors, for transplantation (complete information available in the REDOME Transplant Center Manual)

   2.1 The doctor of the transplant center team must send the request on the REDOME prescription form, indicating the source and quantity of cells desired

   2.2 The acceptance of the prescription and the dates for collection depend on factors such as the availability of the donor and collection centers to perform the procedure

   2.3 Throughout the evaluation and collection process, the information regarding the donor will be forwarded by REDOME, to preserve the confidentiality and anonymity of the donation

3. Evaluation and Collection of REDOME Donors for Hematopoietic Stem Cell Transplantation (complete information available in the REDOME Collection Center Manual)

   3.1 The medical teams of the transplant centers are also responsible for carrying out the clinical and laboratory evaluation of donors selected by REDOME (workup process)

   3.2 The evaluation criteria must comply with current legislation, as well as the standards described in the Collection Centers Manual and the REDOME Donor Protection Policy

   3.3 All communication regarding the donor must be carried out with the REDOME team, with an emphasis on preserving the confidentiality and anonymity of the donation.

"It is you who love the past and who do not see that the new always comes."

Belchior - Composer

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