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CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA

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

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

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

TABLE 1: ELN and WHO' defined AML mutations

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

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

MINIMAL RESIDUAL DISEASE (MRD)

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

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

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

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

ALLOGENEIC HSCT IN FIRST COMPLETE REMISSION

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

TABLE 2. 2022 LNT risk stratification

RISK CATEGORY	GENETIC ABNORMALITY
Favorable	t(8;21)(q22;q22.1); RUNX1::RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB::MYH11
	NPM1 mutation without FLT3-ITD
	MCEBPA b-ZIP mutation in frame
Intermediary	NPM1 mutation with FLT3-ITD
	NPM1wt with FLT3-ITD (without additional adverse abnormalities)
	t(9;11)(p21.3;q23.3)/MLLT3-KMT2A
	Genetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1)/DEK::NUP214
	t(v;11q23.3)/rearranged KMT2A
	t(9;22)(q34.1;q11.2)/ BCR::ABL1
	t(8;16)(p11;p13)/KAT6A::CREBBP
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2,MECOM(EVI1)
	–5 or del(5q); –7; –17/abn(17p)
	Complex karyotypes, monosomies
	ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2 mutations
	TP53 mutation

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

CONDITIONING REGIMENS

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

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

POST HSCT MAINTENANCE THERAPY

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

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