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HSCT FOR ACUTE MYELOID LEUKEMIA

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

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

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

SCT FOR AML IN FIRST COMPLETE REMISSION

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

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

TABLE 1 - ELN AML risk stratification

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

RISK OF TRANSPLANT RELATED MORTALITY (TRM)

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

HSCT SHOULD BE OFFERED TO AML PATIENTS IN SECOND CR.

Conditioning Regimens

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

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

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

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

UNRELATED TRANSPLANTS

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

HAPLOIDENTICAL SCT

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

HSCT FOR THE ELDERLY

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

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

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

AUTOLOGOUS HSCT

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

MINIMAL RESIDUAL OR MEASURABLE DISEASE (MRD)

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

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

POST HSCT CR MAINTENANCE

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

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

NOTES ABOUT DONOR SELECTION

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

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

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

RECOMMENDATIONS

HSCT Allogeneic (related or unrelated)

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

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

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

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

Conditioning Regimens

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

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

Haploidentical SCT

Level of evidence A2
Category recommendation: B

Autologous HSCT

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

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

3)Accept to APL second molecular remission (B2)

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