HSCT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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INTRODUCTION

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

- intra chromosomal amplification of chromosome 21 (iAMP21)

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

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

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

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

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

II. ALO SCT RECOMMENDATIONS

A) Indication of ALO TCH in First Remission:

A1) PATIENTS WITH RISK FACTORS RELATED TO THE DIAGNOSIS

Risk factors at diagnosis

Age> 40 years
Leukocyte count:> 30x109 / L in B cell ALL and > 100 x 109 T cell ALL (except CD1a +)
Cytogenetic changes:
- Complex karyotype (5 or more chromosomal abnormalities).
- t (9; 22) (q34; q11.2)
- t (4; 11) (q21; q23)
- t (8; 14) (q24.1q32)
- Low hypoploidy (30-39 chromosomes)
- Molecular rearrangements involving KMT2A, BCR / ABL,
- Ph-like ALL;

A.2- PATIENTS WITH RESPONSE RELATED RISK FACTORS:

Risk factors after induction

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

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

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

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

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

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

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

A) Allo SCT indication in second remission:

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

C) Indication of Allo SCT in special situations:

c.1) Patient unable to achieve remission Active disease: Transplant not Usually Indicated outside clinical trial with MRD > 1x10-1 (1%)

c.2) When the MRD reached is > 10-3 (0,1%) immediately after first line treatment, one Patient, after first line of treatment, with DRM > 10-3 immediately pre-SCT should consider the risk/benefit of further treatment to deepen pre-SCT response. Ideally MRD < 0,1% pre SCT should be pursued, using 1 or 2 cycles of therapeutics of high efficacy and low toxicity strategies like bi-specific Monoclonal Antibodies (Bas linatumumab). In the context of impossibility case of no access of usingto these drugs, and and exclusive on conventional chemotherapy available access to high toxicity regimens (such as IDA-FLAG), consider (ponder risk vs benefit) following direct to ALLO SCT, with myeloablative conditionings, with positive MRD .

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

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

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

IV ) Conditioning
IV.1) Suggested myeloablative conditionings

a) TBI-based: Recommended primarily for patients between 03 and 40 years
b) Other options: BuFlu, BuMel, BuCy
IV.2) Reduced intensity conditioning: recommended in patients at higher risk of SCT-related mortality, especially after age >40 or years.

V) Stem Cell Source 63,64:
PBSC, BMSC, and UCBSC are all good sources of graft options. The decision process has several variables to be considered: disease status and relapse risk, center experience, local policies, and donor availability. The SBTMO 2020 ALL Consensus Committee has created a table with factors that can discreetly suggest one source or another (regarding BM and PSC) (Table 2). See also special considerations of stem cell source in the Haplo Transplant setting session.

TABLE 2 - choice of stem cell source

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

VI. SPECIAL PARTICULARITIES:

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

VI.2 Ph-like ALL: A new subtype of ALL identified by the expression of genes that cluster with BCR-ABL1. This new entity is called “Ph-like” and represents 15 to 20% of adolescents and young adults. These patients show unfavorable results and 25.8% disease-free survival in 5 years. This group of patients with “Ph-like” has kinase activation favoring an increase in lymphoblast proliferation. Breaks in the “Ph-like” ALL affect only ABL with genes other than BCR. Some of these fusions are sensitive to tyrosine kinase inhibitors in vitro 18.

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

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

Although few data are available, in the era of TKIs, autologous transplantation may be a reasonable option for consolidation in those who achieve negative MRD and are not candidates for allogeneic transplantation. [19]
VI.4) Haploidentical transplantation (*): In ALL:

Only about 45% of ALL patients with an indication for transplantation are able to perform the procedure, either due to difficulty in finding a donor or due to early relapse.

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

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

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

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

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

The choice of the best source of progenitor cells in haploidentical transplants is still a controversial topic, several publications show a higher incidence of GVHD[8-10] with the use of peripheral blood progenitor cells, in addition, some works have associated this source with lower incidence of relapse8, while other studies have not seen this association910. The preferential use of the peripheral blood source to allow the freezing of cells and ensure the infusion of transplants in the year 2020 during the pandemic, may allow one to bring more information on this subject.

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

- GVHD prophylaxis: Recommended use of post-transplant cyclophosphamide- PTCy- over ATG
- Graft: Bone marrow seems to result in better survival after haplo-HCT, although the best source of progenitor cells is still controversial
- Conditioning: TBI in myeloablative regimens seems to result in better relapse-free survival
VII. Post-Transplant follow-up
Recommendation:
- Measurable/Minimal Residual Disease (MRD) at D+30, +60, +90, +180 and +360
- Chimerism at D+30, +90, +180 and +360

The follow-up of post-BMT chimerism is an important tool in risk assessment for relapse, and is usually performed at D+30, +90, +180 and +360. However, MRD has been shown to be more sensitive and specific for this purpose, and should be performed in D+30, +60, +90, +180 and +360[25]. This measure should be maintained every 03 months for another year by clinical decision. It is still questionable whether, in cases where MRD is available, the association of chimerism remains useful.

Patients with CSF involvement pre-BMT are at an increased risk of CNS relapse[26]. For them, monitoring with post-transplant serial punctures can be an interesting strategy, especially when performed by flow cytometry, which is capable of increasing the sensitivity of the exam[27]. However, there is no consensus on the frequency of this analysis or the management if a relapse is detected.

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

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

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

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

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

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

MRD status associated with other relevant prognostic factors for SCT
- a. Flow Cytometry
- b. PCR

The early achievement of MRD negativity in both pediatric and adult patients with ALL has prognostic impact regardless the presence of conventional risk factors, therapies, methods, time of MRD assessment, cutoff levels and leukemia subtypes[34]. Children and adult Ph1 negative ALL patients with persistent MRD after consolidation therapy are indicated for alloSCT in CR[35,36,37,38–45]. In patients undergoing non-pediatric inspired regimens (eg, hyperCVAD), MDR ≥10–4 after 1-3 cycles of chemotherapy is an indication of alloSCT[42]. In patients with ALL MRD ≥10–3 (0.1%) before alloSCT, treatments to reduce tumor burden should be considered[46,47] when possible, but this does not exclude alloSCT. The risk of increased toxicity must also be considered. Levels of 10-3 and 10-4 MRD post-alloSCT were always highly predictive of relapse[37,46,48].

Adult patients with Ph1+ ALL, KMT2A -MLL gene rearrangement, and early T-cell precursor ALL (ETP-ALL) are immediately eligible for alloHSCT[48,49]. Ph like / iKZF1 and iKZF1 plus deletion, iAMP21, will be recommended for transplantation if they do not achieve a complete remission by the end of induction therapy[48,49–51]. Adult Ph1+ ALL patients, who achieved MRD <0.1% within 3 months of treatment, with access to blinatumomab and ponatinib may decline from alloSCT in CR[150]. AlloSCT has no impact on the outcome in hypodiploid B-ALL in CR[1], mainly for patients with MRD ≥ 0.01% at the end of induction[52]. Time points for MRD assessment are < 30 days pre-alloSCT and D+30, +60, +90, +180 and +360 post-SCT by flow cytometry (MFC) and/or RTqPCR and eventually by NGSS4–57. RTqPCR for BCR-ABL1 should be the eligible method for monitoring MRD in Ph1+ ALL[48,58]. MFC is widely available, so laboratories must have complete standardization of pre, post and analytical processes, including the evaluation of not less than 1 million cells per tube, to obtain a reliable MRD detection result[55,57,59–61]. In addition, it should be emphasized that MRD assays should be performed by analysts experienced in this type of evaluation, due to the impact of the results on clinical practice[62].
TABLE 1 - Summary: Allo SCT Recommendations in Adult ALL:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendation</th>
<th>Degree of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL Ph negative Adult (&gt;40 y)</td>
<td>Standard</td>
<td>A</td>
</tr>
<tr>
<td>Standard risk 1st CR</td>
<td>Standard</td>
<td>A</td>
</tr>
<tr>
<td>High risk 1st CR</td>
<td>Standard</td>
<td>D</td>
</tr>
<tr>
<td>2 RCC</td>
<td>Standard</td>
<td>D</td>
</tr>
<tr>
<td>Refractory</td>
<td>Generally Not Recommended</td>
<td>D</td>
</tr>
<tr>
<td>ALL Ph Positive Adult (&gt; 40 y)</td>
<td>Standard</td>
<td>B</td>
</tr>
<tr>
<td>1 CR with previous TKS</td>
<td>Standard</td>
<td>B</td>
</tr>
<tr>
<td>2 CR com TKS previous</td>
<td>Standard</td>
<td>B</td>
</tr>
<tr>
<td>Refractory</td>
<td>Clinical Option</td>
<td>D</td>
</tr>
<tr>
<td>ALL Ph Negative Young Adult (20-40y)</td>
<td>Clinical Option</td>
<td>A</td>
</tr>
<tr>
<td>Basic risk 1st CR (*table 1)</td>
<td>Clinical Option</td>
<td>A</td>
</tr>
<tr>
<td>High risk 1st CR (*table 1)</td>
<td>Clinical Option</td>
<td>A</td>
</tr>
<tr>
<td>2 RC</td>
<td>Standard</td>
<td>D</td>
</tr>
<tr>
<td>Refractory</td>
<td>Generally Not Recommended</td>
<td>D</td>
</tr>
<tr>
<td>LLA Ph Positive Young Adult (18-40)</td>
<td>Clinical Option</td>
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</tr>
<tr>
<td>1st CR with previous TKS (see table 1)</td>
<td>Clinical Option</td>
<td>B</td>
</tr>
<tr>
<td>2nd CR with previous TKS</td>
<td>Standard</td>
<td>B</td>
</tr>
<tr>
<td>Refractory</td>
<td>Clinical Option</td>
<td>D</td>
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Recommendation of Autologous SCT in Adult ALL:

<table>
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<th>Recommendation</th>
<th>Degree of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLA Ph negative in 1st RCC</td>
<td>No</td>
<td>A</td>
</tr>
<tr>
<td>LLA Ph positive in 1st RCC</td>
<td>Clinical Option</td>
<td>C</td>
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REFERENCES


56. van Dongen JJM, van der Velden VHJ, Brüggemann M, Orfao A. Minimal residual disease diag-


