DOI: 10.46765/2675-374X.2021v4n1p61-71

HSCT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

[1]Marco Aurelio Salvino, [2]Maura Valerio Ikoma, [3]Rodolfo D. A. Soares , [4]Andreza A. F. Ribeiro, [5]Liane Esteves Daudt, [6]Claudio Castro Galvão, [7]Belinda Pinto Simões, [8]Maria Aparecida Zanichelli

[1]Universidade Federal da Bahia-Hospital São Rafael- BA, [2] Maura R V Ikoma- Colturato -Hospital Amaral Carvalho,Jau-SP, Sabin Medicina Diagnóstica, [3]Rodolfo D.A. Soares-Universidade Federal do Rio Grande do Norte, [4]Andreza A.F. Ribeiro-Hospital Israelita Albert Einstein, [5] Liane Esteves Daudt-Universidade Federal do Rio Grande do Sul, [6] Claudio Castro Galvão-Santa Casa de Porto Alegre-RS, [7] Belinda Pinto Simões-Ludwig-Maximilians-Universität München, LMU, Alemanha- [8]Maria Aparecida Zanichelli-Hospital Sirio Libanes.

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

II. ALO SCT RECOMMENDATIONS

A) Indication of ALO TCTH 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;
- 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.

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

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

*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.[7] Factors such as comorbidities[8], 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[7.]
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[6], 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 remissionActive disease: Transplant not Usually Indicatedusually 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, onePatient, 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 persuit, 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 exclusiveonly 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, speciallyespecially after age >40 -45yearsras-old.

V) Stem Cell Source 63,64:

PBSC, BMSC and UCBSC are all good source of graft options. The decision process has several variables to be considered: disease status and relapse risk, center experience, local policies, pandemia, donor availbility: The SBTMO 2020 ALL Consensum Comitte has create 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

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

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 vitro18

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 an 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 20.

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 9/1021.

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 association[910]. 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 purpose24, and should be performed in D+30, +60, +90, +180 and +36025. 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 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 exam27. 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 CR1[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 alloSCT42. In patients with ALL MRD ≥10–3 (0.1%) before alloSCT, treatments to reduce tumor burden should be considered46,47 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-allo SCT 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[48,42]. 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 CR150. AlloSCT has no impact on the outcome in hypodiploid B-ALL in CR1, mainly for patients with MRD ≥ 0.01% at the end of induction[53]. 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 NGS54–57. RTqPCR for BCR-ABL1 should be the eligible method for monitoring MRD in Ph1+ALL48,58. 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:

Indication	Recommendation	Degree of recommendation
ALL Ph negative Adult (>40 y)		
Standard risk 1st CR	Standard	A
High risk 1st CR	Standard	A
2 RCC	Standard	D
Refractory	Generally Not Recommended	D
ALL Ph Positive Adult (> 40 y)		
1 CR with previous TKS	Standard	B
2 CR com TKS previous	Standard	B
Refractory	Clinical Option	D
ALL Ph Negative Young Adult (20-40y)		
Basic risk 1st CR (*table 1)	Clinical Option	A
High risk 1st CR (*table 1)	Clinical Option	A
2 RC	Standard	D
Refractory	Generally Not Recommended	D
LLA Ph Positive Young Adult (18-40)		
1st CR with previous TKS (see table 1)	Clinical Option	B
2nd CR with previous TKS	Standard	B
Refractory	Clinical Option	D

Recommendation of Autologous SCT in Adult ALL:

Indication	Recommendation	Degree of Recommendation
LLA Ph negative in 1st RCC	No	A
LLA Ph positive in 1st RCC	Clinical Option	C

REFERENCES

1. Rowe JM. Optimal management of adults with ALL. *Br J Haematol* [Internet]; v. 144, n. 4, p. 468-83, 2009. Available from: http://doi.wiley.com/10.1111/j.1365-2141.2008.07513.x

2. Pui C-H, Carroll WL, Meshinchi S, Arceci RJ. Biology, Risk Stratification, and Therapy of Pediatric Acute Leukemias: An Update. *J Clin Oncol* [Internet]. v, 29, n.5, p. 551-65, 2011. Available from:http://ascopubs.org/doi/10.1200/JCO.2010.30.7405

3. Stelljes M, Marks DI. Acute Lymphoblastic Leukemia in Adults. In: The EBMT Handbook [Internet]. 2019. p. 531–8. Available from: http://link.springer.com/10.1007/978-3-030-02278-5_71

4. O'Connor D, Enshaei A, Bartram J, Hancock J, Harrison CJ, Hough R, et al. Genotype-Specific Minimal Residual Disease Interpretation Improves Stratification in Pediatric Acute Lymphoblastic Leukemia. *J Clin Oncol [Internet]*. v. 36, n.1, p. 34-432018. Available from: https://ascopubs.org/doi/10.1200/JCO.2017.74.0449

5. Short NJ, Jabbour E, Albitar M, de Lima M, Gore L, Jorgensen J, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts [Internet]. Vol. 94, *American Journal of Hematology*. Wiley-Liss Inc.; 2019 [cited p. 257–65, 2020 Sep 23]. Available from: https://pubmed.ncbi.nlm.nih.gov/30394566/

6. Rank CU, Schmiegelow K. Optimal approach to the treatment of young adults with acute lymphoblastic leukemia in 2020. *Semin Hematol* [Internet]. 2020; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0037196320300275

7. Wieduwilt MJ, Stock W, Advani AS, Luger SM, Larson RA, Tallman MS, et al. Superior Survival with Post-Remission Pediatric-Inspired Chemotherapy Compared to Myeloablative Allogeneic Hematopoietic Cell Transplantation in Adolescents and Young Adults with Ph-Negative Acute Lymphoblastic Leukemia in First Complete Remission: Compar. *Blood* [Internet]. 2019;134(Supplement_1):261. Available from: https://ashpublications.org/blood/article/134/Supplement_1/261/426110/Superior-Survival-with-PostRemission

8. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* [Internet]; v. 106, n. 8, p. p. 2912-2919, 2005 Available from: https://ashpublications.org/blood/article/106/8/2912/21830/Hematopoietic-cell-transplantation-HCTspecific

9. Rubin J, Vettenranta K, Vettenranta J, Bierings M, Abrahamsson J, Békássy AN, Håkansson Y, Frost BM, Arvidson J, Spendilow C, Winiarski J, Gustafsson B. Use of intrathecal chemoprophylaxis in children after SCT and the risk of central nervous system relapse.Bone Marrow Transplant; v. 46, n. 3, p.372-8, 2011. doi:

10. Hoelzer D, Thiel E, Arnold R, Beck J, Beelen DW, Bornhäuser M, et al. Successful Subtype Oriented Treatment Strategies in Adult T-All; Results of 744 Patients Treated in Three Consecutive GMALL Studies. *Blood* [Internet]. v. 114, n. 22, p. 324, 20 nov. 2009. Available from:https://ashpublications.org/blood/article/114/22/324/133064/Successful-Subtype-Oriented-Treatment-Strategies

11. Fielding AK, Rowe JM, Buck G, Foroni L, Gerrard G, Litzow MR, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. *Blood* [Internet]; v. 123, n. 6, p. 843-50, 2014. Available from:https://ashpublications.org/blood/article/123/6/843/32592/UKALLXIIECOG2993

12. Carpenter PA, Snyder DS, Flowers MED, Sanders JE, Gooley TA, Martin PJ, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome–positive leukemia. *Blood* [Internet]; v. 109, n. 7, p. 2791-3, 2007. Available from: https://ashpublications.org/blood/article/109/7/2791/125649/Prophylactic-administration-of-imatinib-after

13. Brissot E, Labopin M, Beckers MM, Socie G, Rambaldi A, Volin L, et al. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. *Haematologica* [Internet]; v. 100, n. 3. p. 392-9, 2015. Available from: http://www.haematologica.org/cgi/doi/10.3324/haematol.2014.116954

14. Ravandi F, Othus M, O'Brien SM, Forman SJ, Ha CS, Wong JYC, et al. US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. *Blood Adv* [Internet]. v.1, n.3, p. 250-9, 2016. Available from: https://ashpublications.org/bloodadvances/article/1/3/250/16011/US-intergroup-study-of-chemotherapy-plus-dasatinib.

15. Carpenter PA, Johnston L, Fernandez HF, Radich JP, Mauro MJ, Flowers MED, et al. Posttransplant feasibility study of nilotinib prophylaxis for high-risk Philadelphia chromosome positive leukemia. *Blood* [Internet]; v. 130, n.9, p. 1170-2, 2017. Available from: https://ashpublications.org/blood/article/130/9/1170/36982/Posttransplant-feasibility-study-of-nilotinib

16. Ravandi F. How I treat Philadelphia chromosome–positive acute lymphoblastic leukemia. *Blood* [Internet]. 2019;133(2):130–6. Available from:https://ashpublications.org/blood/article/133/2/130/39555/How-I-treat-Philadelphia-chromosomepositive-acute

17. Peters C, Locatelli F, Bader P. *Acute Lymphoblastic Leukemia in Children and Adolescents* [Internet]. *The EBMT Handbook*. 2019. p. 539–45. Available from: http://link.springer.com/10.1007/978-3-030-02278-5_72

18. Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang Y-L, Pei D, et al. Targetable Kinase-Activating Lesions in Ph-like Acute Lymphoblastic Leukemia. *N Engl J Med* [Internet]; v. 371, n. 11, p. 1005-15, 2014. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1403088

19. Giebel S, Labopin M, Potter M, Poiré X, Sengeloev H, Socié G, et al. Comparable results of autologous and allogeneic haematopoietic stem cell transplantation for adults with Philadelphia-positive acute lymphoblastic leukaemia in first complete molecular remission: An analysis by the ALWP of the EBMT. *Eur J Cancer* [Internet]; p.2018 . Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959804918307482

20. Bassan R at al. Minimal Residual Disease Assessment and Risk-based Therapy in Acute Lymphoblastic Leukemia. *Clinical Lymphoma, Myeloma & Leukemia*. v. 17, 2017. (S1), S2-9.

21. Shem-Tov N, Christophe Peczynski C, Labopin M, et al. Haploidentical vs. unrelated allogeneic stem cell transplantation for acute lymphoblastic leukemia in first complete remission: on behalf of the ALWP of the EBMT. *Leukemia*; v. 34, p. 2020. Available from: http://dx.doi.org/10.1038/s41375-019-0544-3

22. Al Malki MM, Yang D, Labopin M et al. Comparing transplant outcomes in ALL patients after haploidentical with PTCy or matched unrelated donor transplantation. *Blood Advances*; v. 4, n.9, p. 2020. Available from: https://ashpublications.org/bloodadvances/article/4/9/2073/455053/Comparing-transplant-outcomes-in-ALL-patients

23. Nagler A, Kanate AS, Labopin M, Ciceri F, Angelucci E, Koc Y, et al. Post-transplant cyclophosphamide versus anti-thymocyte globulin for graft-versus-host disease prevention in haploidentical transplantation for adult acute lymphoblastic leukemia. *Haematologica* [Internet]. 2020;haematol.2020.247296. Available from: http://www.haematologica.org/lookup/doi/10.3324/haematol.2020.247296

24. Terwey TH, Hemmati PG, Nagy M, Pfeifer H, Gökbuget N, Brüggemann M, et al. Comparison of chimerism and minimal residual disease monitoring for relapse prediction after allogeneic stem cell transplantation for adult acute lymphoblastic leukemia. *Biol Blood Marrow Transplant* [Internet]; v. 20, n.10, p.2014. Available from: http://dx.doi.org/10.1016/j.bbmt.2014.05.026

25. Short NJ, Jabbour E, Albitar M, de Lima M, Gore L, Jorgensen J, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts [Internet]. Vol. 94, *American Journal of Hematology*. Wiley-Liss Inc; p. 2019. p. 257–65. Available from: https://pubmed.ncbi.nlm.nih.gov/30394566/

26. Aldoss I, Al Malki MM, Stiller T, Cao T, Sanchez JF, Palmer J, et al. Implications and Management of Central Nervous System Involvement before Allogeneic Hematopoietic Cell Transplantation in Acute Lymphoblastic Leukemia. *Biol Blood Marrow Transplant* [Internet]. 2016;22(3):575–8. Available from: http://dx.doi.org/10.1016/j.bbmt.2015.10.016

27. Gong X, Lin D, Wang H, Wang Y, Liu B, Wei H, et al. Flow cytometric analysis of cerebrospinal fluid in adult patients with acute lymphoblastic leukemia during follow-up. *Eur J Haematol* [Internet]; v. 100, n.3, p.2018. Available from: http://doi.wiley.com/10.1111/ejh.13011

28. Ortí G, Sanz J, García-Cadenas I, Sánchez-Ortega I, Alonso L, Jiménez MJ, et al. Analysis of relapse after transplantation in acute leukemia: A comparative on second allogeneic hematopoietic cell transplantation and donor lymphocyte infusions. *Exp Hematol* [Internet].v. 62, p. 24-32, 2018. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0301472X18301206

29. Loren AW, Porter DL. Donor leukocyte infusions for the treatment of relapsed acute leukemia after allogeneic stem cell transplantation. *Bone Marrow Transplant* [Internet]; v. 41, n. 5, p. 483-93, 2008. Available from: http://www.nature.com/articles/1705898

30. Stein AS, Kantarjian H, Gökbuget N, Bargou R, Litzow MR, Rambaldi A, et al. Blinatumomab for Acute Lymphoblastic Leukemia Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant* [Internet]]; v. 25, n.8, p.1498-504, 2019. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1083879119302332

31. Choi HJ, Choi JY, Kim BK, An HY, Hong KT, Shin HY, et al. Combination Therapy With Chemotherapy, Donor Lymphocyte Infusion With Concurrent Blinatumomab in Relapsed/Refractory Acute Precursor B-Lymphoblastic Leukemia. *J*

Pediatr Hematol Oncol [Internet]. 2020; Available from: https://journals.lww.com/10.1097/MPH.0000000000001789

32. Pirosa MC, Leotta S, Cupri A, Stella S, Martino EA, Scalise L, et al. Long-Term Molecular Remission Achieved by Antibody Anti-CD22 and Ponatinib in a Patient Affected by Ph'+ Acute Lymphoblastic Leukemia Relapsed after Second Allogeneic Hematopoietic Stem Cell Transplantation: A Case Report. *Chemotherapy* [Internet]. v.63, n.4, p. 220-224, p. 2018. Available from: https://www.karger.com/Article/FullText/492941

33. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med* [Internet]. v.378, n.5, p. 439-48, 2018. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1709866

34. Bassan R, Brüggemann M, Radcliffe H-S, Hartfield E, Kreuzbauer G, Wetten S. A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. *Haematologica* [Internet]. v. 104, n.10, p. 2028-2039, 2019. Available from: http://www.haematologica.org/lookup/doi/10.3324/haematol.2018.201053

35. Borowitz MJ, Wood BL, Devidas M, Loh ML, Raetz EA, Salzer WL, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood* [Internet]; v. 126, n. 8, p. 964-71, 2015. Available from: https://ashpublications.org/blood/article/126/8/964/34749/Prognostic-significance-of-minimal-residual

36. Pui C-H, Pei D, Coustan-Smith E, Jeha S, Cheng C, Bowman WP, et al. Clinical utility of sequential minimal residual disease measurements in the context of risk-based therapy in childhood acute lymphoblastic leukaemia: a prospective study. *Lancet Oncol* [Internet]. v. 16, n.4, p. 465-474, 2015. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204515700823

37. Bar M, Wood BL, Radich JP, Doney KC, Woolfrey AE, Delaney C, et al. Impact of Minimal Residual Disease, Detected by Flow Cytometry, on Outcome of Myeloablative Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia. *Leuk Res Treatment* [Internet]; p. 1-9, 2014. Available from: https://www.hindawi.com/archive/2014/421723/

38. Gaipa G, Cazzaniga G, Valsecchi MG, Panzer-Grumayer R, Buldini B, Silvestri D, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. *Haematologica* [Internet]; v. 97, n. 10, p. 1582-93, 2012. Available from: http://www.haematologica.org/cgi/doi/10.3324/haematol.2011.060426

39. Zhao X-S, Liu Y-R, Zhu H-H, Xu L-P, Liu D-H, Liu K-Y, et al. Monitoring MRD with flow cytometry: an effective method to predict relapse for ALL patients after allogeneic hematopoietic stem cell transplantation. *Ann Hematol* [Internet]; v.91, n. 2, p. 183-92, 2012. Available from: http://link.springer.com/10.1007/s00277-011-1285-1

40. Sureda A, Bader P, Cesaro S, Dreger P, Duarte RF, Dufour C, et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: Current practice in Europe, 2015. *Bone Marrow Transplant;* v.50, n.8, p.2015.

41. Wood B, Wu D, Crossley B, Dai Y, Williamson D, Gawad C, et al. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. *Blood* [Internet]; v. 131, n. 12, p.2018. Available from:https://ashpublications.org/blood/article/131/12/1350/36632/Measurable-residual-disease-detection-by

42. Giebel S, Marks DI, Boissel N, Baron F, Chiaretti S, Ciceri F, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leuke. *Bone Marrow Transplant* [Internet]; 54, n. 6, p. 798-809, 2019. Available from: http://www.nature.com/articles/s41409-018-0373-4

43. Ribera J-M, Morgades M, Ciudad J, Montesinos P, Barba P, García-Cadenas I, et al. Post-Remission Treatment with Chemotherapy or Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT) in Adult Patients with High-Risk (HR) Philadelphia Chromosome-Negative (Ph-neg) Acute Lymphoblastic Leukemia (ALL) According to Their Minimal Resid. *Blood* [Internet]; p. 826, 2019(Supplement_1):826. Available from: https://ashpublications.org/blood/article/134/Supplement_1/826/426988/PostRemission-Treatment-with-Chemotherapy-or

44. Bader P, Kreyenberg H, Henze GHR, Eckert C, Reising M, Willasch A, et al. Prognostic Value of Minimal Residual Disease Quantification Before Allogeneic Stem-Cell Transplantation in Relapsed Childhood Acute Lymphoblastic Leukemia: The ALL-REZ BFM Study Group. *J Clin Oncol* [Internet]. v.27, n.3, p. 377- 384, 2009. Available from: http://ascopubs.org/doi/10.1200/JCO.2008.17.6065

45. Shen Z, Gu X, Mao W, Yin L, Yang L, Zhang Z, et al. Influence of pre-transplant minimal residual disease on prognosis after Allo-SCT for patients with acute lymphoblastic leukemia: systematic review and meta-analysis. *BMC Cancer* [Internet]; v. 18, n. 1, p. 755, 2018. Available from: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-018-4670-5

46. Bader P, Salzmann-Manrique E, Balduzzi A, Dalle J-H, Woolfrey AE, Bar M, et al. More precisely defining risk peri-HCT in pediatric ALL: pre- vs post-MRD measures, serial positivity, and risk modeling. *Blood Adv* [Internet]; v. 3, n. 21, p. 3393-405, 2019 Available from: https://ashpublications.org/bloodadvances/article/3/21/3393/422754/More-precisely-defining-risk-periHCT-in-pediatric

47. Eckert C, Hagedorn N, Sramkova L, Mann G, Panzer-Grümayer R, Peters C, et al. Monitoring minimal residual disease in children with high-risk relapses of acute lymphoblastic leukemia: prognostic relevance of early and late assessment. *Leukemia* [Internet]. iv.29, n.8, p. 1648-1655, 2015.Available from: http://www.nature.com/articles/leu201559

48. Lovisa F, Zecca M, Rossi B, Campeggio M, Magrin E, Giarin E, et al. Pre- and post-transplant minimal residual disease predicts relapse occurrence in children with acute lymphoblastic leukaemia. *Br J Haematol* [Internet]. v.180, n.5, p. 680-693, 2018. Available from: http://doi.wiley.com/10.1111/bjh.15086

49. Stanulla M, Dagdan E, Zaliova M, Möricke A, Palmi C, Cazzaniga G, et al. IKZF1 plus Defines a New Minimal Residual Disease–Dependent Very-Poor Prognostic Profile in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia. J *Clin Oncol* [Internet]. v. 36, n. 12, p. 1240-9, 2018. Available from: https://ascopubs.org/doi/10.1200/JCO.2017.74.3617

50. O'Connor D, Enshaei A, Bartram J, Hancock J, Harrison CJ, Hough R, et al. Genotype-Specific Minimal Residual Disease Interpretation Improves Stratification in Pediatric Acute Lymphoblastic Leukemia. *J Clin Oncol* [Internet]. v. 36, n.1, p. 34-43, 2018. Available from: https://ascopubs.org/doi/10.1200/JCO.2017.74.0449

51. Moorman A V, Robinson H, Schwab C, Richards SM, Hancock J, Mitchell CD, et al. Risk-Directed Treatment Intensification Significantly Reduces the Risk of Relapse Among Children and Adolescents With Acute Lymphoblastic Leukemia and Intrachromosomal Amplification of Chromosome 21: A Comparison of the MRC ALL97/99 and UKALL2003 Trials. *J Clin Oncol* [Internet]. v.31, n.27, p. 3389, 3396, 2013. Available from: http://ascopubs.org/doi/10.1200/JCO.2013.48.9377

52. Short NJ, Jabbour E, Albitar M, de Lima M, Gore L, Jorgensen J, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts [Internet]. Vol. 94, *American Journal of Hematology*. Wiley-Liss Inc.; 2019 [cited 2020 Sep 23]. p. 257–65. Available from: https://pubmed.ncbi.nlm.nih.gov/30394566/

53. McNeer JL, Devidas M, Dai Y, Carroll AJ, Heerema NA, Gastier-Foster JM, et al. Hematopoietic Stem-Cell Transplantation Does Not Improve the Poor Outcome of Children With Hypodiploid Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group. *J Clin Oncol* [Internet]; v.37, n.10, p. 780-9, 2019. 2019. Available from: https://ascopubs.org/doi/10.1200/JCO.18.00884

54. Pulsipher MA, Carlson C, Langholz B, Wall DA, Schultz KR, Bunin N, et al. IgH-V(D)J NGS-MRD measurement pre- and early post-allotransplant defines very low- and very high-risk ALL patients. *Blood* [Internet]; v. 125, n.22, p. 3501-8, 2015. Available from: https://ashpublications.org/blood/article/125/22/3501/34378/IgH-VDJ-NGSMRD-measurement-pre-and-early

55. Brüggemann M, Kotrova M. Minimal residual disease in adult ALL: technical aspects and implications for correct clinical interpretation. *Blood Adv* [Internet]; v. 1, n.25, p. 2456-66, 2017. Available from: https://ashpublications.org/bloodadvances/article/1/25/2456/15757/Minimal-residual-disease-in-adult-ALL-technical

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

nostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. *Blood* [Internet]; v.125, n. 26, p. 3996-4009, 2015. Available from: https://ashpublications.org/blood/article/125/26/3996/34323/Minimal-residual-disease-diagnostics-in-acute

57. Roshal M. Minimal Residual Disease Detection by Flow Cytometry in Multiple Myeloma: Why and How? *Semin Hematol* [Internet]. v. 55, n.1, p. 4-12, 2018. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0037196317301919

58. Nishiwaki S, Imai K, Mizuta S, Kanamori H, Ohashi K, Fukuda T, et al. Impact of MRD and TKI on allogeneic hematopoietic cell transplantation for Ph+ALL: a study from the adult ALL WG of the JSHCT. *Bone Marrow Transplant* [Internet]; v.51, n. 1, p. 43-50, 2016 Available from: http://www.nature.com/articles/bmt2015217

59. Delgado JA, Guillén-Grima F, Moreno C, Panizo C, Pérez-Robles C, Mata JJ, et al. A simple flow-cytometry method to evaluate peripheral blood contamination of bone marrow aspirates. *J Immunol Methods* [Internet]; v. 442, p. 54-8, 2017. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022175916303969

60. Arroz M, Came N, Lin P, Chen W, Yuan C, Lagoo A, et al. Consensus guidelines on plasma cell myeloma minimal residual disease analysis and reporting. *Cytom Part B Clin Cytom* [Internet]. v. 90, n. 1, p. 31-39, 2016. Available from: http://doi.wiley.com/10.1002/cyto.b.21228

61. Pierson-Perry, F J. *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures*; Approved Guideline - 2nd Edition (EP17-A2). 2012; Available from: https://clsi.org/media/1430/ep17a2_sample.pdf

62. Short NJ, Jabbour E, Albitar M, de Lima M, Gore L, Jorgensen J, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts. *Am J Hematol*; v. 442, p. 1487-1496, 2019.

63. Byrne M, Savani BN, Mohtt M, Nagler A,et al. Peripheral blodd stem cell versus *BM transplantation..Exp Hematol;* v. 44, n.; 7, p. 567, 2016.

64. Anasetti, Claudio,.et al. Peripheral Blood Stem Cells versus BM from Unrelated Donors. *N Engl J Med*; v. 367, p. 1487-1496, 2012.