Epidemiological and clinical characteristics of adult acute lymphoblastic leukemia patients in Chile: A single-center analysis

Joaquín Jerez [a,b,*], Valentina Goldschmidt [a], María Carolina Guerra [a], José Luis Briones [a], Carlos Torres [a], Sebastián Hidalgo [a], Raimundo Gazitúa [a]

[a] Department of Hematology Fundación Arturo López Pérez, Chile
[b] Resident of Hematology, Universidad de los Andes, Chile

ARTICLE INFO

ABSTRACT

Background: Acute lymphoblastic leukemia represents 20% of acute leukemias in adults. Currently, there is limited data in Chile regarding the clinical, cytogenetic, and prognostic characteristics of this condition.
Methods: This is a retrospective, observational, and descriptive study of 67 patients treated for acute lymphoblastic leukemia at the Arturo Lopez Perez Foundation between 2018 and 2021. The main objective is to evaluate epidemiological and clinical characteristics, as well as identifying factors associated with improved overall survival and/or progression-free survival.
Results: 88% of the cases were B-lineage, mainly the common B phenotype. Cytogenetic analysis was performed in less than 50% of the patients, with lower yield than expected according to the literature. Molecular testing was performed in 86.5% of the patients, with the most frequent alteration being BCR-ABL. No study was performed to search for Ph-like abnormalities. The rate of complete response after induction was 83.3%, the majority of patients having negative minimal residual disease. Only 12% of the patients received consolidation with allogenic bone marrow transplant. At 2 years, the overall survival was 69% and the progression-free survival was 59%.
Conclusion: The results in terms of overall survival and progression-free survival are similar to those reported in the literature. Important diagnostic gaps prevent adequate prognostic characterization. Allogeneic consolidation transplantation was performed in a lower percentage than expected, highlighting the national deficit in access to this treatment.

1. Introduction

Acute lymphoblastic leukemia (ALL) is a neoplasm of lymphoid precursor hematopoietic cells, characterized by accumulating blasts in the bone marrow, peripheral blood, or other tissues (e.g. mediastinum). Although this disease is more commonly found in children, it represents approximately 20% of acute leukemias in adults [1]. Despite a higher incidence reported in the Hispanic population [2], data regarding this entity are scarce in Chile. In 2014, results from the national protocol known as "15–30" were reported. This was an adaptation of the Children's Oncology Group AALL0232 protocol [3], which included 68 patients between the ages of 15 and 32, and reported a 3-year overall survival of 61% [4]. T-lineage patients were not included. Subsequently, in 2021, results were reported for patients with BCR-ABL positive ALL. Thirty-five patients were analyzed under the "high-dose ALL" protocol, an adaptation of a pediatric ALL protocol for relapse associated with

Imatinib. The 3-year overall survival was 52%, with 55% of patients achieving negative measurable residual disease (MRD) at 3 months (which was the main predictor of survival) [5]. Both reports are from patients in the Chilean public health system, which serves approximately 80% of the population.

The Arturo López Pérez Foundation (FALP) is a non-profit organization that serves patients from both public and private health systems. The aim of this study was to report the results of patients with ALL treated at our center in the first line, with an emphasis on survival and clinical and cytogenetic characteristics.

2. Patients and methods

2.1. Study design and patient selection

This is an observational, retrospective, and descriptive study. It

included all patients over the age of 15 diagnosed with Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma treated at FALP between 2018 and 2021, both referred from the public health service or covered by the FALP oncology insurance. Diagnoses were confirmed by a bone marrow study and/or mediastinal mass biopsy, and the 2016 WHO classification was used for characterization. A routine cerebrospinal fluid study was performed at diagnosis. Clinical, laboratory, flow cytometry, cytogenetic, and molecular biology variables were assessed. Information was obtained through a review of the Electronic Clinical Record. Dates of death were obtained from the Civil Registry website (www.srcei.cl). The scientific ethics committee at our institution approved this study.

2.2. Procedures

The main chemotherapy regimens consisted of HyperCVAD and the Chilean young-adult protocol known as "15–30" [4]. In the case of BCR-ABL fusion gene detection, a tyrosine kinase inhibitor was added, and Rituximab was added for CD20-positive marker. Central nervous system involvement prophylaxis was performed using triple intrathecal chemotherapy, consisting of Methotrexate 15 mg, Betamethasone 4 mg, and Cytarabine 50 mg. Granulocyte colony-stimulating factors were not routinely used. Antimicrobial prophylaxis was administered according to local guidelines. The morphological response was evaluated at the end of induction, as well as MRD, which was assessed by flow cytometry with a sensitivity of 10^{-4}. In the case of BCR-ABL positive, it was also evaluated by RT-PCR technique.

2.3. Objectives and variables

The main objective of this study is to evaluate the epidemiological and clinical characteristics, as well as laboratory findings, of patients diagnosed with Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma. The secondary objectives include examining immunophenotypic and cytogenetic variables and identifying factors associated with improved overall survival and/or progression-free survival.

2.4. Statistical analysis

The survival analysis was performed using the Kaplan–Meier method, and differences were estimated using the log-rank or Gehan–Breslow–Wilcoxon method as appropriate. Differences in parametric variables were analyzed using the *t*-test, while non-parametric variables were analyzed using the chi-square test. The analysis was conducted using GraphPadPrism software, and a p-value < 0.05 was considered significant.

3. Results

Sixty-seven patients with ALL treated at FALP between 2018 and 2021 were registered. The median follow-up was 19 months. The median age at diagnosis was 29 years (Table 1), with a bimodal age distribution: an initial peak around 20 years and a second peak around 60 years (Fig. 1). In terms of clinical presentation, 14% presented with febrile neutropenia, 3% with superior vena cava syndrome (corresponding only to T-lymphoblastic lymphomas), and 1.5% with spontaneous tumor lysis syndrome. The remaining patients were mainly due to anemic syndrome and mucocutaneous bleeding. Regarding the diagnostic exams, most patients presented with pancytopenia and leucocytosis less than 20,000/uL.

According to the flow cytometry immunophenotyping study, and in accordance with what is described in the literature, B lineage ALL was the most common (88%), with a predominant representation of a common B-phenotype (86%) (Fig. 2). 42% of the cases showed CD20 expression. Regarding the T lineage, early T -cell precursor was not detected, as the diagnosis was made by histology of mediastinal masses,

Table 1
Clinical and laboratory characteristics at debut of patients with acute lymphoblastic leukemia.

| Age (median, range)	29	(15–86)
Sex (male, percentage)	33	(49.3%)
Health insurance (percentage)		
a) Public	80,60%	
b) Private	17,90%	
c) International	1,50%	
Oncology emergencies (percentage)		
Febrile neutropenia	14,29%	
Superior vena cava syndrome	3,12%	
Tumor lysis syndrome	1,59%	
Laboratory		
Hemoglobin (median, range)	8,50	(3,1–16)
White blood count (median, range)	11,200	(500–284,000)
Platelet (median, range)	42,500	(3000–308,000)
Blasts (median, range)	35,50%	(0–100%)
Creatinine (median, range)	0,86	(0,2–3,3)
Calcium (median, range)	8,80	(7,5–10,3)
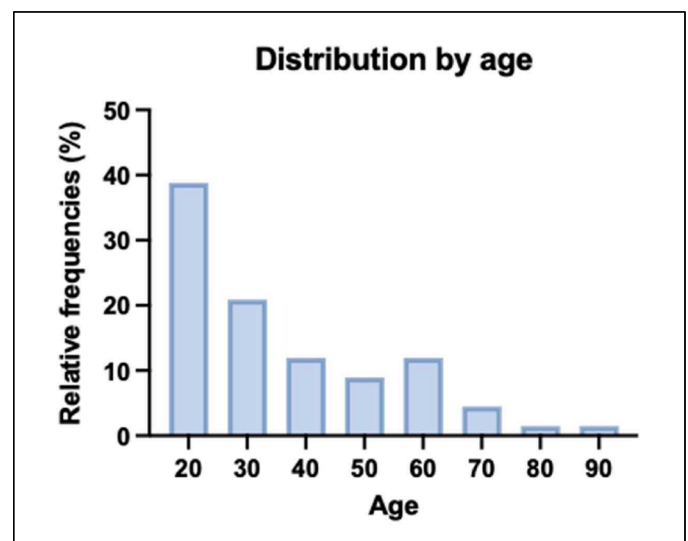
Fig. 1. Distribution by age range of patients with acute lymphoblastic leukemia.

without complementary flow cytometry. Cytogenetic analysis was performed only in 40% of the cases of B lineage ALL, and none of the cases of T lineage ALL. Of those analyzed, only 81% had sufficient mitoses for analysis. Of the karyotypes analyzed, 77% were normal (Fig. 3). In the total sample, altered karyotype information was available in 7.4% of patients, of which 40% corresponded to t(9;22) (which were also screened by molecular biology), one patient with a complex karyotype, and the rest with low hyperdiploidies. High hyperdiploidies and hypodiploidies were not observed.

In contrast to cytogenetic analysis, molecular biology was performed in 86.5% of the patients (practically all of the B lineage cases), being positive for BCR-ABL in 28%, ETV6-RUNX1 in 1.75%, and TCF3-PBX1 in 1.75%. There were no patients with KMT2A rearrangements, as it was not routinely performed. No BCR ABL-like study was performed.

Regarding the type of treatment, 58% received HyperCVAD regimen, 30% received pediatric 15–30 regimen, and in the remaining 12%, either different pediatric protocols (BFM or CALGB) or Dexamethasone/Vincristine were used as palliative management. Among BCR-ABL positive patients, 100% received a tyrosine kinase inhibitor, with Dasatinib being the most commonly used (81%), and Imatinib being used in the rest of the cases. All cases with CD20 expression received Rituximab during induction.

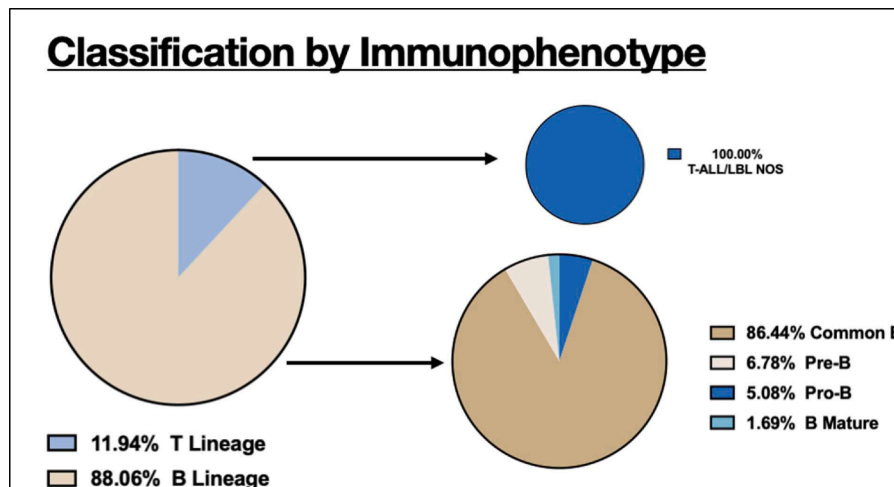The rate of complete morphological response after induction was

Fig. 2. Immunophenotype of patients with acute lymphoblastic leukemia. ALL = Acute Lymphoblastic Leukemia. LBL = Lymphoblastic Lymphoma.
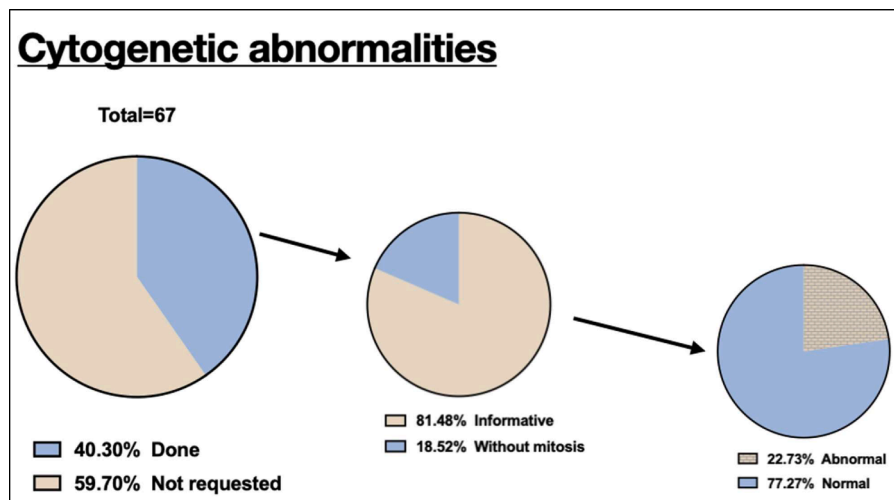

Fig. 3. Cytogenetic abnormalities in patients with acute lymphoblastic leukemia.

83.3%, with 76% of these also being MRD negative. Only 12% received an allogeneic transplant as consolidation. The median overall survival was not reached, and the progression-free survival was estimated to be 37 months (Fig. 4). At 2 years, the overall survival was 69% and the progression-free survival was 59%, and it was estimated to be 56% and 31%, respectively, at 5 years. The group of adolescent and young adult patients, defined as those in the 15–39 age range, were analyzed separately, and no significant differences were found in overall survival or progression-free survival. When survival analysis was restricted to patients between 15 and 20 years old, the estimated overall survival at 5 years was 60%. The estimated median overall survival of patients over 60 years old was 30 months.
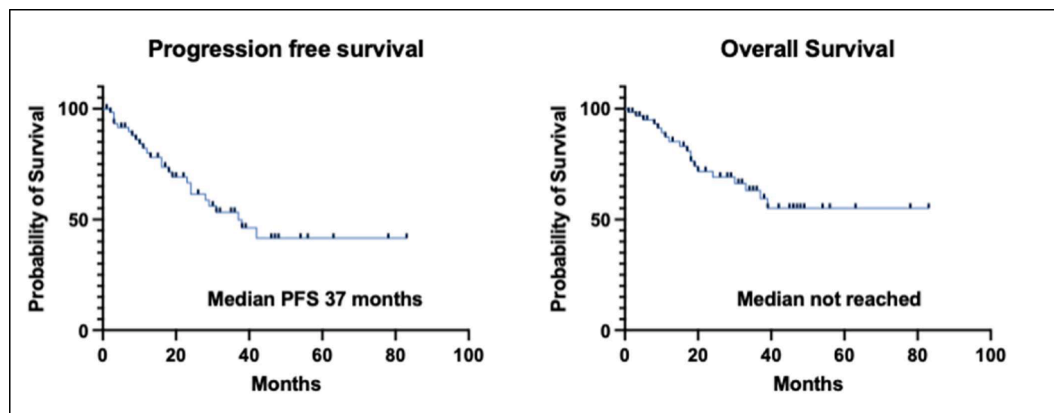

Fig. 4. Progression-free survival and overall survival in patients with acute lymphoblastic leukemia.

With regard to other parameters such as lineage, the presence of BCR-ABL, or chemotherapy regimen received, there were no significant differences (Fig. 5). However, there was a trend toward improved overall survival in the few patients who received allogeneic transplantation in their first remission.

4. Discussion

In general terms, this series represents a population that is representative of the national reality, with 80% of patients benefiting from the public health system (FONASA) and the remaining 20% from the private system. With the limited follow-up, the estimated overall survival results are very similar to the international series [1,6], despite the limited access to allogeneic transplantation in the first remission, which may be determine a low progression-free survival. On the other hand, our results with the HyperCVAD regimen are favorable, demonstrating its effectiveness and safety when administered in a national reference center with appropriate local measures, such as protected isolation, and antimicrobial prophylaxis. However, despite these encouraging results, there are relevant diagnostic gaps. In T-lineage acute lymphoblastic leukemia, overall survival and progression-free survival did not show significant differences compared with B-lineage ALL, although it has historically been established to have a better prognosis. In this aspect, we do not have an adequate antigen panel for the targeted search of early T precursor (ETP), an entity associated with poor prognosis in both children and adults [7]. We know that in T-ALL, cytogenetic abnormalities do not determine prognosis, but certain genetic mutations do, such as NOTCH1 and FBXW7, both associated with rapid responses to treatment [8], as well as mutations in RAS or PTEN, or mutations in TP53, which are associated with poor prognosis [9]. The role of these mutations at diagnosis versus the importance of MRD for clinical decision-making is still an unresolved issue.

Regarding B-lineage ALL, the study by immunophenotype allows for adequate differentiation of the different subtypes. Karyotyping allows for detecting certain numerical and/or structural alterations associated with prognosis. Among the most frequent alterations in adults with a well-established prognostic definition are hyperdiploidy (2–15%), hypodiploidy (5–10%), t(9;22) (15–25%), and t(4;11) (5–10%) [10]. In the case of the last two, the alterations can be detected by molecular biology, limiting the absolute yield of karyotyping. In our series, only 7.4% of the patients had an abnormal karyotype, which was lower than expected. This supports the notion that in countries with limited diagnostic resources, access to diagnostic technologies that have greater sensitivity for discriminating the risk of each patient should be prioritized, particularly in countries with limited access to allogeneic transplantation. More recently, Ph-like gene expression has been described in 25–30% of patients with ALLB. In 2016, the WHO recognized Ph-like ALL as a provisional entity, which was formalized in the 5th WHO update in 2022 [11]. This entity has a higher risk of induction failure, higher relapse rates, and lower survival [12]. It is more frequent in Hispanic people [13], which makes it especially important to can study this entity. Since the chromosomal rearrangements associated with this entity are not assessable by conventional karyotyping, there are FISH panels that can detect known genetic translocations such as ABL1, ABL2, RLF2, JAK2, EPOR, PDGRB, and CSF1R [14]. Currently exists a molecular classification for B-ALL, with relevant prognostic entities for recognition (e.g., PAX5 or DUX4) [15].

The study of MRD is currently a standard of care. Its prognostic relevance is not only related to achieving negative MRD status but also to the timing of its achievement [16]. It is necessary to properly standardize both the measurement technique and the timing of its acquisition. In our series, MRD measurements were performed in 88% of patients, often only after induction therapy, using flow cytometry. Consensus guidelines have established that MRD assessment should be performed not only at the end of induction and treatment, but also at 3 months after the start of chemotherapy (following first consolidation) [17], to ensure proper prognostic stratification. This underscores the need for clear local protocols regarding MRD testing. In this regard, the HyperCVAD protocol provides an ideal scenario, as the MRD kinetics in ALL have been studied in patients treated with this regimen [16], in addition to being an effective regimen adaptable to new drugs such as blinatumomab and Inotuzumab [18,19]. Finally, our BCR-ABL patient results are encouraging and the first to report on second-generation TKIs. Currently, there is evidence for Ponatinib in the frontline [21] and even chemotherapy-free regimens with combinations of TKIs and Blinatumomab with extraordinary results [20], which will likely become the standard of care.

The weaknesses of this study include short follow-up period, its
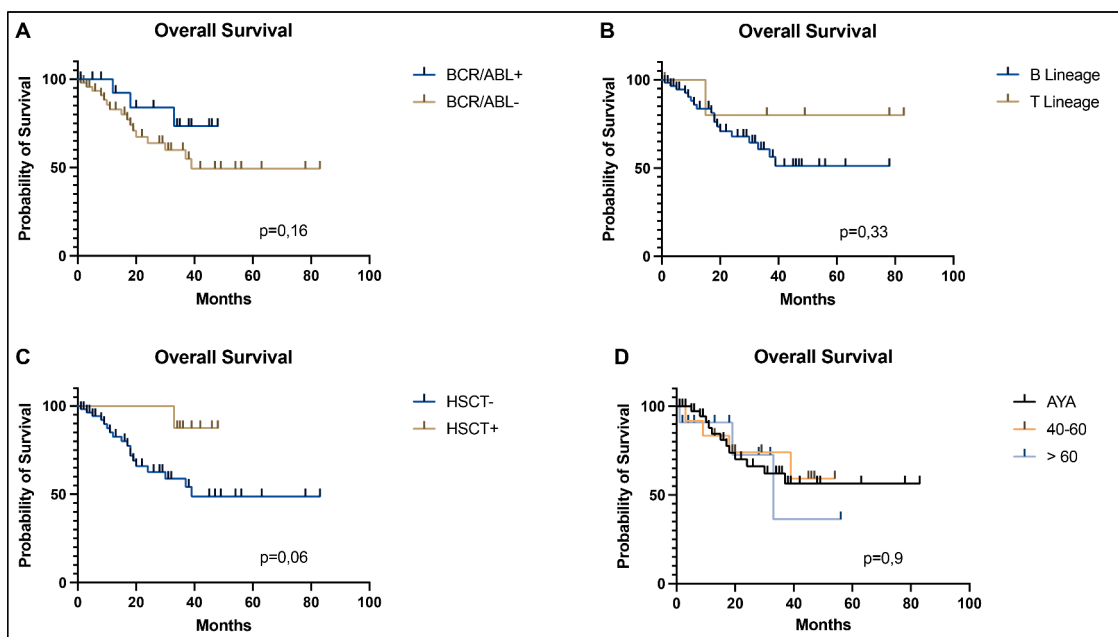

Fig. 5. Overall survival analysis in patients with acute lymphoblastic leukemia according to: presence of BCR-ABL (A), lineage (B), consolidation with HSCT in first remission (C) and according to age (D). HSCT = hematopoietic stem cell transplantation. AYA = adolescents and young adults.

retrospective nature, and the limitations mentioned in the discussion section regarding the absence of diagnostic elements for a more in-depth survival analysis. Additionally, despite being a representative series within the national context, it is essential to note that this is still a single-center analysis conducted in a specialized cancer center. Therefore, the findings may not be fully generalizable to the broader national context.

5. Conclusions

In this series of patients with ALL/LBL treated at a private center in Chile, but representative of the national reality, overall survival and disease-free survival are comparable to global statistics. However, the need to improve diagnostic tools is evident. In this regard, detecting the Early T subtype in T-ALL and the Ph-like gene expression in B-ALL are of great importance given their prognostic relevance. In addition, it is essential to protocolize the measurement of minimal residual disease. Regarding therapy, access to allogeneic transplant is limited, reflecting the country's need to increase the number of centers capable of providing this service.

Funding statement

Declaration of Competing Interest

The authors report that there are no competing interests to declare.

References

[1] G.M. Dores, S.S. Devesa, R.E. Curtis, M.S. Linet, Morton LM, Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007, Blood 119 (1) (2012) 34–43.

[2] J.M. Shoag, J.C. Barredo, I.S. Lossos, P.S. Pinheiro, Acute lymphoblastic leukemia mortality in Hispanic Americans, Leuk. Lymphoma 61 (11) (2020) 2674–2681.

[3] E.C. Larsen, M. Devidas, S. Chen, W.L. Salzer, E.A. Raetz, M.L. Loh, L.A. Mattano Jr, C. Cole, A. Eicher, M. Haugan, M. Sorenson, N.A. Heerema, A.A. Carroll, J. M. Gastier-Foster, M.J. Borowitz, B.L. Wood, C.L. Willman, N.J. Winick, S. P. Hunger, W.L. Carroll, Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from Children's Oncology Group Study AALL0232, J. Clin. Oncol. 34 (20) (2016) 2380–2388.

[4] B. Puga, C. Guerra, J. Molina, M.E. Cabrera, L. Pilleux, S. Calderón, C. Rojas, C. G. Vergara, H. Rojas, L. Muñoz, V. Lois, A. Aspillaga, A. Pizarro, Leucemia linfoblástica aguda estirpe B Philadelphia negativa en adolescentes y adultos jóvenes: resultados del Protocolo Terapéutico LLA 15-30, Programa Nacional de Cáncer del Adulto (PANDA), Ministerio de Salud, Chile [Adolescent and young adult Philadelphia negative B cell acute lymphoblastic leukemia: results of the Chilean protocol LLA 15-30], Rev. Med. Chil. 142 (6) (2014) 707–715.

[5] R. Benavente, F. Cid, B. Puga, J. Molina, F. Bass, A. Andrade, V. Monardes, A. Encina, M.E. Cabrera, Quimioterapia intensiva asociada a imatinib en leucemia linfoblástica aguda del adulto, Philadelphia positivo. Experiencia en un hospital público [Intensive chemotherapy with tyrosine kinase inhibitors in Philadelphia-positive acute lymphoblastic leukemia], Rev. Med. Chil. 149 (9) (2021) 1249–1257.

[6] S.E. Siegel, A. Advani, N. Seibel, L. Muffly, W. Stock, S. Luger, B. Shah, D. J. DeAngelo, D.R. Freyer, D. Douer, R.H. Johnson, B. Hayes-Lattin, M. Lewis, J. J. Jaboin, P.F. Coccia, A. Bleyer, Treatment of young adults with Philadelphia-negative acute lymphoblastic leukemia and lymphoma: hyper-CVAD vs. pediatric-inspired regimens, Am. J. Hematol. 93 (10) (2018) 1254–1266.

[7] N. Jain, A.V. Lamb, S. O'Brien, F. Ravandi, M. Konopleva, E. Jabbour, Z. Zuo, J. Jorgensen, P. Lin, S. Pierce, D. Thomas, M. Rytting, G. Borthakur, T. Kadia, J. Cortes, H.M. Kantarjian, J.D. Khoury, Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype, Blood 127 (15) (2016) 1863–1869.

[8] V. Asnafi, A. Buzyn, S. Le Noir, F. Baleydier, A. Simon, K. Beldjord, O. Reman, F. Witz, Tavernier E T, P. Turlure, T. Leguay, F. Huguet, J.P. Vernant, F. Daniel, M. C. Béné, N. Ifrah, X. Thomas, H. Dombret, E Macintyre, NOTCH1/FBXW7 mutation identifies a large subgroup with favorable outcome in adult T-cell acute lymphoblastic leukemia (T-ALL): a group for research on adult acute lymphoblastic leukemia (GRAALL) study, Blood 113 (17) (2009) 3918–3924.

[9] A. Trinquand, A. Tanguy-Schmidt, R. Ben Abdelali, J. Lambert, K. Beldjord, E. Lengliné, N. De Gunzburg, D. Payet-Bornet, L. Lhermitte, H. Mostafa, V. Lhéritier, J. Bond, F. Huguet, A. Buzan, T. Leguay, J.Y. Cahn, X. Thomas, Y. Chalandon, A. Delannoy, C. Bonmati, S. Maury, B. Nadel, E. Macintyre, N. Ifrah, H. Dombret, V Asnafi, Toward a NOTCH1/FBXW7/RAS/PTEN-based oncogenetic risk classification of adult T-cell acute lymphoblastic leukemia: a group for research in adult acute lymphoblastic leukemia study, J. Clin. Oncol. 31 (34) (2013) 4333–4342.

[10] K. Mrózek, N.A. Heerema, C.D. Bloomfield, Cytogenetics in acute leukemia, Blood Rev. 18 (2) (2004) 115–136.

[11] R. Alaggio, C. Amador, I. Anagnostopoulos, A.D. Attygalle, I.B.O. Araujo, E. Berti, G. Bhagat, A.M. Borges, D. Boyer, M. Calaminici, A. Chadburn, J.K.C. Chan, W. Cheuk, W.J. Chng, J.K. Choi, S.S. Chuang, S.E. Coupland, M. Czader, S.S. Dave, D. de Jong, M.Q. Du, K.S. Elenitoba-Johnson, J Ferry, J. Geyer, D. Gratzinger, J. Guitart, S. Gujral, M. Harris, C.J. Harrison, S. Hartmann, A. Hochhaus, P. M. Jansen, K. Karube, W. Kempf, J. Khoury, H. Kimura, W. Klapper, A.E. Kovach, S. Kumar, A.J. Lazar, S. Lazzi, L. Leoncini, N. Leung, V. Leventaki, X.Q. Li, M. S. Lim, W.P. Liu, A. Louissaint Jr, A. Marcogliese, L.J. Medeiros, M. Michal, R. N. Miranda, C. Mitteldorf, S. Montes-Moreno, W. Morice, V. Nardi, K.N. Naresh, Y. Natkunam, S.B. Ng, I. Oschlies, G. Ott, M. Parrens, M. Pulitzer, S.V. Rajkumar, A. C. Rawstron, K. Rech, A. Rosenwald, J. Said, C. Sarkozy, S. Sayed, C. Saygin, A. Schuh, W. Sewell, R. Siebert, A.R. Sohani, R. Tooze, A. Traverse-Glehen, F. Vega, B. Vergier, A.D. Wechalekar, B. Wood, L. Xerri, W Xiao, The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms, Leukemia 36 (7) (2022) 1720–1748.

[12] K.G. Roberts, S.C. Reshmi, R.C. Harvey, I.M. Chen, K. Patel, E. Stonerock, H. Jenkins, Y. Dai, M. Valentine, Z. Gu, Y. Zhao, J. Zhang, D. Payne-Turner, M. Devidas, N.A. Heerema, A.J. Carroll, E.A. Raetz, M.J. Borowitz, B.L. Wood, L. A. Mattano Jr, K.W. Maloney, W.L. Carroll, M.L. Loh, C.L. Willman, J.M. Gastier-Foster, C.G. Mullighan, S.P. Hunger, Genomic and outcome analyses of Ph-like ALL in NCI standard-risk patients: a report from the Children's Oncology Group, Blood 132 (8) (2018) 815–824.

[13] N. Jain, K.G. Roberts, E. Jabbour, K. Patel, A.K. Eterovic, K. Chen, P. Zweidler-McKay, X. Lu, G. Fawcett, S.A. Wang, S. Konoplev, R.C. Harvey, I.M. Chen, D. Payne-Turner, M. Valentine, D. Thomas, G. Garcia-Manero, F. Ravandi, J. Cortes, S. Kornblau, S. O'Brien, S. Pierce, J. Jorgensen, K.R. Shaw, C.L. Willman, C.G. Mullighan, H. Kantarjian, M. Konopleva, Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults, Blood 129 (5) (2017) 572–581.

[14] P. Shiraz, K.J. Payne, L. Muffly, The current genomic and molecular landscape of Philadelphia-like acute lymphoblastic leukemia, Int. J. Mol. Sci. 21 (6) (2020) 2193.

[15] E. Paietta, K.G. Roberts, V. Wang, Z. Gu, G.A.N. Buck, D. Pei, C. Cheng, R.L. Levine, O. Abdel-Wahab, Z. Cheng, G. Wu, C. Qu, L. Shi, S. Pounds, C.L. Willman, R. Harvey, J. Racevskis, J. Barinka, Y. Zhang, G.W. Dewald, R.P. Ketterling, D. Alejos, H.M. Lazarus, S.M. Luger, L. Foroni, B. Patel, A.K. Fielding, A. Melnick, D.I. Marks, A.V. Moorman, P.H. Wiernik, J.M. Rowe, M.S. Tallman, A. H. Goldstone, C.G. Mullighan, M.R Litzow, Molecular classification improves risk assessment in adult BCR-ABL1-negative B-ALL, Blood 138 (11) (2021) 948–958.

[16] R.D. Cassaday, P.A. Stevenson, B.L. Wood, P.S. Becker, P.C. Hendrie, B. M. Sandmaier, J.L. Radich, A.R. Shustov, Description and prognostic significance of the kinetics of minimal residual disease status in adults with acute lymphoblastic leukemia treated with hyperCVAD, Am. J. Hematol. 93 (4) (2018) 546–552.

[17] N.J. Short, E. Jabbour, M. Albitar, M. de Lima, L. Gore, J. Jorgensen, A.C. Logan, J. Park, F. Ravandi, B. Shah, J. Radich, H. Kantarjian, 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. 94 (2) (2019) 257–265.

[18] E. Jabbour, N.J. Short, N. Jain, P.A. Thompson, T.M. Kadia, A. Ferrajoli, X. Huang, M. Yilmaz, Y. Alvarado, K.P. Patel, G. Garcia-Manero, W. Macaroni, R. Garris, M. Konopleva, F. Ravandi, H. Kantarjian, Hyper-CVAD and sequential blinatumomab for newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: a single-arm, single-centre, phase 2 trial, Lancet Haematol. 9 (12) (2022) e878–e885.

[19] N.J. Short, E. Jabbour, F. Ravandi, M. Yilmaz, T.M. Kadia, et al., The addition of inotuzumab ozogamicin to hyper-CVAD plus blinatumomab further improves outcomes in patients with newly diagnosed B-cell acute lymphoblastic leukemia: updated results from a phase II study, Blood 140 (Supplement 1) (2022) 8966–8968.

[20] E. Jabbour, N.J. Short, N. Jain, X. Huang, G. Montalban-Bravo, P. Banerjee, K. Rezvani, X. Jiang, K.H. Kim, R. Kanagal-Shamanna, J.D. Khoury, K. Patel, T. M. Kadia, N. Daver, K. Chien, Y. Alvarado, G. Garcia-Manero, G.C. Issa, F. G. Haddad, M. Kwari, J. Thankachan, R. Delumpa, W. Macaron, R. Garris, M. Konopleva, F. Ravandi, H. Kantarjian, Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial, Lancet Haematol. 10 (1) (2023) e24–e34.

[21] J.M. Ribera, O. García-Calduch, J. Ribera, P. Montesinos, I. Cano-Ferri, P. Martínez, J. Esteve, D. Esteban, M. García-Fortes, N. Alonso, J. González-Campos, A. Bermúdez, A. Torrent, E. Genescà, S. Mercadal, J. Martínez-López, R García-Sanz, Ponatinib, chemotherapy, and transplant in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia, Blood Adv. 6 (18) (2022) 5395–5402.