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Outcome of adult acute lymphoblastic leukemia, a single-center experience

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Abstract:

BACKGROUND: Adult acute lymphoblastic leukemia (ALL) has a dismal outcome within the optimal situations as the 5-year overall survival (OS) is not reaching 40%.

OBJECTIVE: The objective of this study was to evaluate the outcome of adult ALL in Erbil, Iraq, and to see the factors predicting better survival among them.

PATIENTS AND METHODS: We analyzed data from 71 adult ALL patients aged 14–81 years (mean age: 28.6 years). Diagnosis is based on the peripheral blood film, bone marrow examination, and flow cytometry.

RESULTS: The median OS was 21 months and the median relapse-free survival (RFS) was 13 months. The 3-year OS and the 3-year RFS were 49.3% and 40.8%, respectively, while the 5-year OS and the 5-year RFS were 37.5% and 32.5%, respectively.

CONCLUSION: Factors predicting better survival included in the study; age at diagnosis, remission achievement at first induction, risk assessment, and allogeneic stem cell transplantation optimal response.

Keywords:

Adult acute lymphoblastic leukemia, overall survival, Philadelphia chromosome

Introduction

Acute lymphoblastic leukemia (ALL) is an aggressive malignancy of precursor T and B lymphoid cells.^[1] Age has a major influence on the incidence and outcome of ALL. While it is one of the common malignancies in the pediatric age group,^[2-4] ALL is rare in adults. It has a bimodal distribution, having the first peak in 4–5 years and the second peak after 50 years of age. Overall, the age-adjusted incidence is 1 per 100,000 population.^[5]

ALL has a very disappointing outcome in adults with a 5-year overall survival (OS) not reaching 40%, unlike its outcome in pediatrics which has a 5-year (OS) exceeding

80%. These are due to the increasing incidence of adverse prognostic factors, having more comorbidities, and dose reductions that are needed for increasing age.^[6-10]

While most of these data come from the developed countries where ALL has been extensively studied, there is little information and study in the developing and undeveloped countries regarding the characteristics and outcome of this serious disease.

This study is an attempt to understand the outcome of adult ALL in a single-center hospital in Iraq, to know whether its outcome is comparable with the rest of the world or not, as sometimes the diagnostic and therapeutic approaches are strict within

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the standard guidelines due to many regional-related factors.

Patients and Methods

Patients

In this retrospective cohort study, 71 diagnosed ALL cases are included aged 14–81 years (mean age: 28.6 years), from January 2012 to November 2018 in Nanakali hospital for hematologic disorders and cancer in Erbil-Iraq with the past follow-up dated December 31, 2021. Any of the following features if present, the patient would be excluded from the study; ALL younger than 14 years, ALL transformed from chronic myeloid leukemia or other myeloproliferative neoplasms, ALL cases who received chemotherapy previously for any cancer, lymphoblastic lymphoma (LL), Burkitt's leukemia/lymphoma (ALL-L3).

Diagnosis

Diagnosis is made by detection of 20% lymphoblast in the peripheral blood and/or bone marrow, confirmed by flow cytometry on the peripheral blood or bone marrow aspirate sample. The assessment of the central nervous system (CNS) involvement was done by examining cerebrospinal fluid (CSF).

Patients were grouped as standard risk if they have none of the following and high risk for having any of the following: Age 35 years and older, white blood cell (WBC) $>30 \times 10^9/l$ for B lineage or $>100 \times 10^9/l$ for T lineage, presence of BCR-ABL rearrangement, CNS involvement at presentation, and failure of complete remission after 4 weeks of induction therapy.^[11]

Treatment

Three chemotherapy protocols and best supportive care are used for treatment, including the medical research council United Kingdom ALL (UKALL XII) protocol, Hyper-CVAD, and Dana-Farber protocol. Patients who were positive for BCR-ABL, a tyrosine kinase inhibitor (TKI) were added for their treatment. Allogeneic stem cell transplant (ASCT) is suggested for candidate high-risk patients.

For induction response evaluation, bone marrow aspirate was examined at the end of induction. Hematologic complete remission was defined as undetected blast in the peripheral blood, cerebrospinal fluid, and $<5\%$ blasts in the bone marrow with no leukemic infiltration of other organs.^[12,13]

The appearance of blast in peripheral blood, CSF, or anywhere or increased marrow blast after achieving remission was defined as relapse.^[12,13] The time from the

diagnosis of ALL to the date of death or last follow-up was determined as OS.^[14] Relapse-free survival (RFS) was defined as the time from remission to relapse or nonrelapse death.^[14]

Data analysis

Data analysis was done using Statistical Package for the Social Statistical Package for the Social Sciences (SPSS, version 26, IBM, NY, United States of America). Qualitative data are expressed as frequency and percentage and quantitative data as mean and median. For the identification of an association between different parameters, Chi-square and *t*-test were used. Survival rates were analyzed using Kaplan-Meier method. $P \leq 0.05$ were considered statistically significant.

The ethics committee of the Kurdistan Higher Council for Medical Specialties approved this article. Informed consent was taken from patients and Nanakali Hospital for blood disorders and cancer.

Results

Initial presentation

In this study, 71 patients were included. The median age was 21 years (range: 14–81 years). Among them, 18 (25.4%) patients were ≥ 35 years, 37 (52.1%) patients were males and 34 (47.9%) patients were females. The male-to-female ratio is 1.08:1.

Blood indices include a median hemoglobin of 9 g/dl (range: 5.0–13.0 g/dl), median platelet count $43 \times 10^9/l$ (range: $2-258 \times 10^9/l$), median leukocyte $26.0 \times 10^9/l$ (range: undetected– $546 \times 10^9/l$), and median peripheral blast of 66% (range: 0%–98%).

By using flow cytometry, 20 (28.2%) patients were T-lineage ALL and 51 (71.8%) patients were B-lineage ALL. Out of the 53 patients who were <35 years, 16 (30.2%) patients are T-lineage and 37 patients (69.7%) are B-lineage, while among 18 patients who were ≥ 35 years, four of them (22.2%) were T-lineage and 14 (77.8%) were B-lineage ($P = 0.516$).

Among the B-ALL patients, 21 (41.2%) patients had WBC $>30 \times 10^9/l$ ($P = 0.383$) and only 10 of them (19.6%) had WBC $>100 \times 10^9/l$, whereas among T-ALL patients, 6 (30%) patients had WBC $>100 \times 10^9/l$ ($P = 0.346$).

According to age, 10 (18.9%) patients out of the 53 who were <35 years had WBC $>100 \times 10^9/l$ opposite to the 6 (33.3%) patients out of the 18 who were ≥ 35 years ($P = 0.204$).

Significant lymphadenopathy was found in 18 (25.4%) patients and the most common site was cervical lymphadenopathy either alone or with other sites.

Splenomegaly was found in 32 (45.1%) patients, among them, 7 (9.9%) patients had huge spleen (range: 19–20 cm). Regarding hepatomegaly, it is found only in 14 (19.7%) patients.

Philadelphia (PH) chromosome was found only in 10 (14.1%) patients. Its incidence was (27.8%) among those aged ≥ 35 years opposite to (9.4%) among the younger patients ($P = 0.009$).

Among the 16 patients who have $WBC > 100 \times 10^9/L$, PH chromosome was found in 9 (56.3%) patients opposite to the 1 (1.8%) patient in the group with lower WBC ($P = 0.0001$).

CSF study at presentation showed that only 1 (1.4%) patient had CNS disease for having blasts in the CSF.

There were two patients with a history of hypertension and two patients with Down syndrome making comorbidities to be (5.6%) in this study.

Overall, 34 (47.9) patients were grouped as having standard risk disease and the remaining 37 (52.1%) patients had high-risk diseases. Table 1 shows patients' characteristics.

Remission induction

Induction chemotherapy was given with curative intent to 67 (94.4%) patients, the remaining 4 (5.6%) patients were treated with supportive therapy for having poor performance status and old age.

Among the treatment protocols, UKALL XII was the most commonly used treatment plan by the physicians' decision, used for 37 (52.1%) patients, while 28 (39.4%) patients were treated with Hyper-CVAD and Dana-Farber protocol used just for 2 (2.8%) patients.

Assessment of remission induction showed that 63 (88.7%) patients got remission after induction, 4 (5.6%) patients were found to have persistent disease after first induction with the remaining 4 (5.6%) patients who were treated just with supportive care. Remission rates were (92.5%) and (77.8%) for < 35 years and ≥ 35 years of the age groups, respectively ($P = 0.089$).

Among the patients who received UKALL XII, remission was found in 35 (94.6%) patients comparing to the Hyper-CVAD which was found to have induced remission in 26 (92.9%) out of the 28 patients. Moreover, both of the patients who received the Dana-Farber protocol were achieved remission.

Regarding the PH chromosome, it was found that all patients got remission with the first induction.

Table 1: Characteristics of patients

Variables	n (%)
Sex	
Male	37 (52.1)
Female	34 (47.9)
Age (years)	
<35	53 (74.6)
≥ 35	18 (25.4)
High WBC according to type	
High WBC	27 (38)
Normal or low WBC	44 (62)
WBC > 100	
WBC > 100	16 (22.5)
WBC < 100	55 (77.5)
Type by flow cytometry	
B-cell	51 (71.8)
T-cell	20 (28.2)
PH chromosome	
Positive	10 (14.1)
Negative	45 (63.4)
Not done or unknown	16 (22.5)
Comorbidity	
No comorbidity	67 (94.4)
Hypertension	2 (2.8)
Down syndrome	2 (2.8)
Risk assessment	
High risk	37 (52.1)
Standard risk	34 (47.9)
Treatment	
Supportive	4 (5.6)
UKALL XII	37 (52.1)
Hyper-CVAD	28 (39.4)
Dana-Farber	2 (2.8)
Transplant	
Transplanted	10 (14.1)
Not transplanted	61 (85.9)

ALL: Acute lymphoblastic leukemia, UKALL: United Kingdom ALL, WBC: White blood cell, PH: Philadelphia, CVAD: Cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone

Three patients were died due to neutropenic sepsis after the induction, among them, two received Hyper-CVAD and one received UKALL.

Survival

The OS in this study is 39.4% with median OS of 21 months and the median RFS of 13 months [Figure 1].

There is no statistical significance in OS for both sexes, OS was (37.8%) and (41.2%) for males and females, respectively ($P = 0.998$) [Figure 2a], whereas age has its own effect on OS, the OS was (49.1%) for < 35 years and (11.1%) for ≥ 35 years of age ($P = 0.00011$) [Figure 2b]. OS was (25.9%) for patients with initial high WBC and (47.7%) for those who had no high WBC initially ($P = 0.160$) [Figure 2c].

PH chromosome-positive patients had an OS of (30%) opposite to the (44.4%) for PH-negative

patients ($P = 0.195$) [Figure 2d]. Meanwhile, the OS was 61.8% and 18.9% for standard risk and high-risk patients, respectively ($P = 0.00010$) [Figure 2e].

Regarding the effect of remission to induction on OS, the OS was zero for those who did not get remission to initial induction and 44.4% for those who had remission to initial induction ($P = 0.00010$) [Figure 2f].

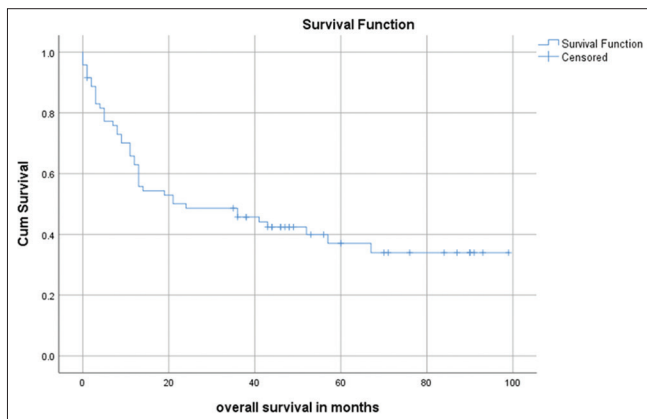


Figure 1: Kaplan-Meier survival curve of overall survival

The 3-year OS was 49.3% and the 3-year RFS was 40.8% while the 5-year OS and the 5-year DFS were 37.5% and 32.5%, respectively.

Regarding the impact of age, the current study showed that the 3-year OS was (60.4%) and (16.7%) for <35 years and ≥ 35 years of age, respectively (32 patients out of 53 patients who were younger than 35 years are alive after 3 years of diagnosis, while three patients out of the 18 patients who were ≥ 35 years old are alive) ($P = 0.001$), and the 3-year RFS was (50.9%) and (11.1%) ($P = 0.003$) for each group, respectively (27 patients out of the 53 patients who were <35 years had 3-year RFS while two out of the 18 patients who were ≥ 35 years had 3-year RFS).

Meanwhile, the 5-years OS was (42.4%) and (14.3%) for <35 years and ≥ 35 years of age, respectively (out of 33 patients who were <35 years, 14 of them were alive after 5 years from their initial diagnosis while only one out of the seven patients who were ≥ 35 years old was alive after 5 years from the initial diagnosis) ($P = 0.162$), whereas the 5-year RFS was (36.4%) and (14.3%) for the aforementioned, respectively ($P = 0.257$). Table 2

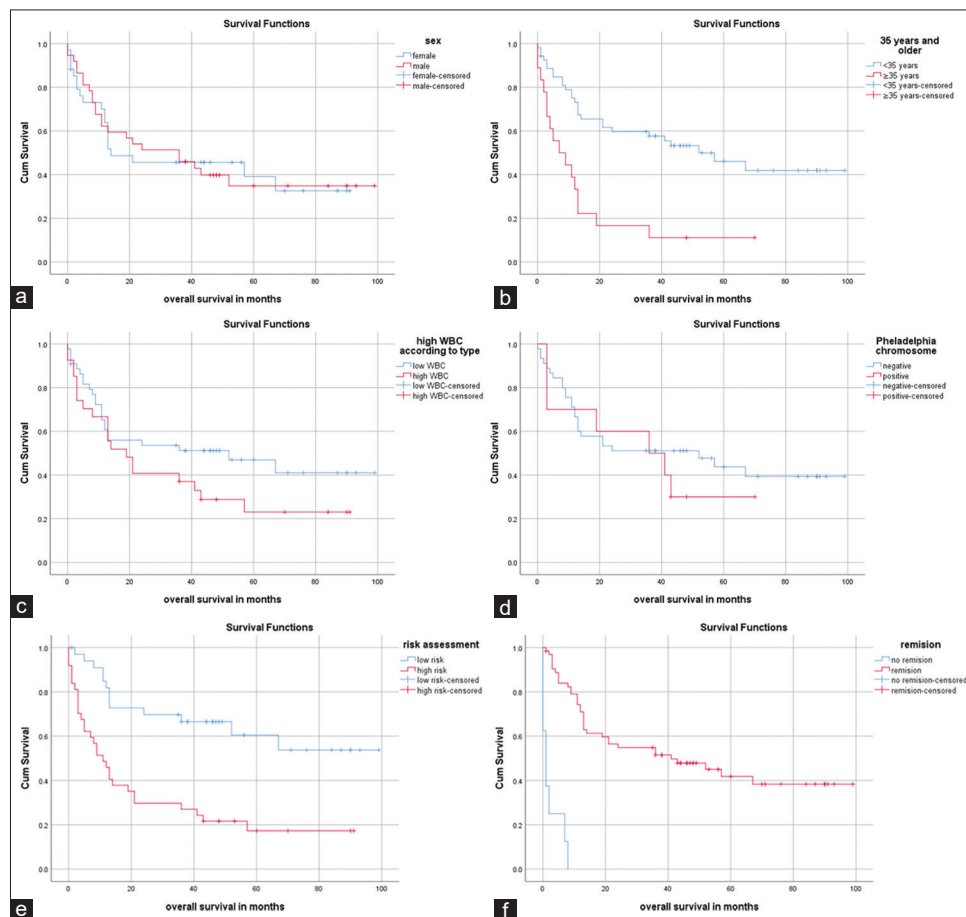


Figure 2: Kaplan-Meier survival curve of overall survival. Comparison between (a) Male and female. (b) <35 years and ≥ 35 years. (c) High WBC and low WBC. (d) Philadelphia positive and negative. (e) High risk and low risk. (f) Remission and resistance to induction. WBC: White blood cell

Table 2: Five years overall survival and 3 years overall survival according to different parameters with their *P* value

Baseline characteristics	3 years OS	<i>P</i>	5-year OS	<i>P</i>
Sex				
Male	54.0	0.402	36.8	0.934
Female	44.1		38.0	
Age (years)				
<35	60.3	0.001	42.4	0.162
≥35	16.6		14.2	
WBC				
<100	49.0	0.948	44.8	0.120
>100	50.0		18.1	
Type				0.721
B-Cell	49.0	0.940	39.2	
T-Cell	50.0		33.3	
PH chromosome				
Negative	53.3	0.242	44.8	0.280
Positive	60.0		14.2	
Risk assessment				
Standard	70.5	0.000	52.6	0.060
High	29.7		23.8	
Induction chemotherapy				
UKALL XII	56.7	0.064	45.8	0.303
Hyper-CVAD	42.8		28.5	
Remission				
Remission	55.5	0.003	41.6	0.102
No remission	0.0		0.0	
Transplant				
Transplanted	90.0	0.005	37.5	1.0
Not transplanted	42.6		37.5	

PH: Philadelphia, ALL: Acute lymphoblastic leukemia, UKALL: United Kingdom ALL, OS: Overall survival, WBC: White blood cell, CVAD: Cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone

shows 5-year OS and 3-year OS according to different parameters with their *P* value.

Relapse and death

In this study population, 26 (36%) patients were relapsed, most of the relapses occurred within the first 3 years from the diagnosis (22 patients, 84.6%).

In correlation with other risk factors, relapse rates were 39.6% and 27.8% for <35 years and ≥35 years of age, respectively (*P* = 0.367), whereas its 31.4% and 50.0% for B-cell and T-cell, respectively (*P* = 0.143), and its 40% for both PH-positive and -negative patients (*P* = 0.548).

Regarding the relapse risk with the use of different chemotherapy protocols, its 37.8% and 39.3% for UKALL XII and Hyper-CVAD, respectively (*P* = 0.462).

On the other hand, relapse rates were 32.8% for transplanted patients who got relapsed after allogeneic

stem cell transplantation (allo-SCT) and 60% for nontransplanted patients (*P* = 0.098).

Among the 43 death events, 19 (44.2%) patients died due to relapsed resistant disease and 17 (39.5%) patients are dead due to neutropenia-related events during the induction or later during the course of treatment. Other death causes include sudden death, CNS disease, and unknown which no available data were present.

Among the 21 patients who received UKALL XII protocol and are dead, 12 of them died due to relapsed resistant disease and only five due to febrile neutropenia, whereas for the 18 dead patients treated with Hyper-CVAD protocol, seven patients died of relapsed resistant disease and eight patients due to febrile neutropenia.

Discussion

In this study, the outcome of 71 newly diagnosed ALL patients in a single tertiary center was analyzed, in an attempt to understand more about the outcome of adult ALL in developing countries.

The 5-year OS of 37.8% in this study is quite comparable to most of the studies in the USA, Italy, Germany, Spain, and France.^[6,7,9,11,15] It is expected also to see a high remission rate after the first induction, as well as a very poor outcome for the primary resistant diseases.^[16-18]

Age at diagnosis remains one of the dominant prognostic markers.^[15,19-22] There were significant differences in remission induction, OS, and RFS between younger and older participants. The survival declines rapidly with increasing age, especially after 35 years. These are supported by the higher incidence of poor prognostic markers with increasing age.^[21] These differences in outcome were not seen between both genders in our study, as is seen in some literature such as in Sweden, putting the male sex in the list of poor prognostic markers.^[21]

Regarding the role of initial WBC count, the current study shows inferior outcomes for those presenting initially with high WBC count but this was statistically not significant. This is partly contributing to inferior outcomes with increasing age as the incidence of initial high WBC count is more with older patients.^[18,19,22,23]

The frequency of PH chromosome among the study patients is lower than most published literatures such as in Italy and the USA,^[24,25] could be due to the lack of data for a significant number of our patients. However, higher rates were observed among older patients as reported by most working groups on adult ALL.^[21,25,26] In comparison between positive and negative participants

for PH chromosome, the remission rate is higher in the positive group that could be explained by the role of TKI^[18,25] that was included in the treatment plan for them, but OS and RFS were lower with the positive group.^[15,19,24,27,28] though statistically it is not significant.

Nearly, one-third of the patients are T-lineage ALL. Historically, T-ALL has inferior outcomes compared to B-ALL due to many reasons including patients with T-ALL are generally older, have higher WBC count, are more resistant to chemotherapy, and more extramedullary relapses are seen among them. On the other hand, higher favorable genetic subtypes are observed among B-ALL.^[23,26] These differences in outcome are not seen in this study as there are no statistically significant differences in OS and RFS at 3 and 5 years between the two groups.

Overall, the general risk assessment is well known to have a major influence on survival.^[15] This study confirms high-risk patients have inferior 5-year OS, 5-year RFS, 3-year OS, and 3-year RFS.

Different chemotherapy protocols had been used, mainly UKALL XII and Hyper-CVAD, which showed no difference in remission induction; however, OS was superior with UKALL XII, although not reached a statistically significant level. As known in other studies, Hyper-CVAD protocol may lead to more death incidence and this is mainly a consequence of neutropenic sepsis caused by severe marrow suppression in patients treated with Hyper-CVAD.^[24,29]

Transplantation has its own survival impact as seen in our study showing survival advantage for the group that underwent transplantation.^[29-31] Although more than half of the patients in this study were high-risk patients, only 10 of them received allo-SCT as consolidation, mostly due to the lack of transplant center in this hospital and difficulties in access to it with economic and other factors related to this part of the world. Survival is expected to be higher if this were done for all the indicated patients.

Conventionally, late relapses are uncommon among adults suffering from ALL.^[11,15,31] Relapses are seen in more than one-third of our patients, most of them occurring within the first 3 years of diagnosis. This confirms early relapses are more common than late relapses among adult ALL patients as reported in other literatures.

Conclusion

Significant factors contributing to survival outcomes include age, risk assessment, remission induction, and transplantation. Survival can be improved by

better supportive care for preventing and controlling neutropenic sepsis and consolidating candidate patients with allo-SCT.

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Conflicts of interest

There are no conflicts of interest.

References

1. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. *Lancet* 2008;371:1030-43.
2. McNeer JL, Raetz EA. Acute lymphoblastic leukemia in young adults: Which treatment? *Curr Opin Oncol* 2012;24:487-94.
3. Locatelli F, Maschan A, Boissel N, Strocchio L, Alam N, Pezzani I, et al. Pediatric patients with acute lymphoblastic leukemia treated with blinatumomab in a real-world setting: Results from the NEUF study. *Pediatr Blood Cancer* 2022;69:e29562.
4. Hijiya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm FG, et al. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. *JAMA* 2007;297:1207-15.
5. Faderl S, O'Brien S, Pui CH, Stock W, Wetzler M, Hoelzer D, et al. Adult acute lymphoblastic leukemia: Concepts and strategies. *Cancer* 2010;116:1165-76.
6. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. *J Clin Oncol* 2011;29:532-43.
7. Larson S, Stock W. Progress in the treatment of adults with acute lymphoblastic leukemia. *Curr Opin Hematol* 2008;15:400-7.
8. Abboud MR, Ghanem K, Muwakkit S. Acute lymphoblastic leukemia in low and middle-income countries: Disease characteristics and treatment results. *Curr Opin Oncol* 2014;26:650-5.
9. Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet* 2020;395:1146-62.
10. Ma H, Sun H, Sun X. Survival improvement by decade of patients aged 0-14 years with acute lymphoblastic leukemia: A SEER analysis. *Sci Rep* 2014;4:4227.
11. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood* 2007;109:944-50.
12. Buchmann S, Schrappe M, Baruchel A, Biondi A, Borowitz M, Campbell M, et al. Remission, treatment failure, and relapse in pediatric ALL: An international consensus of the Ponte-di-Legno Consortium. *blood* 2022;139:1785-93.
13. Teachey DT. Remission: More than meets the eye. *Hematol, the journal of nuclear medicine* 2017;58.
14. Driscoll JJ, Rixe O. Overall survival: Still the gold standard: Why overall survival remains the definitive end point in cancer clinical trials. *Cancer J* 2009;15:401-5.
15. Thomas X, Danaïla C, Le QH, Sebban C, Troncy J, Charrin C, et al. Long-term follow-up of patients with newly diagnosed adult acute lymphoblastic leukemia: A single institution experience of 378 consecutive patients over a 21-year period. *Leukemia* 2001;15:1811-22.
16. Topp MS, Gökbuget N, Zugmaier G, Klappers P, Stelljes M, Neumann S, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol* 2014;32:4134-40.
17. Gökbuget N, Dombret H, Ribera JM, Fielding AK, Advani A,

- Bassan R, *et al.* International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia. *Haematologica* 2016;101:1524-33.
18. Bassan R. Novel approaches for therapy of resistant acute lymphoblastic leukemia. *J Clin Oncol* 2018;36:1811-22.
19. Vidriales MB, Pérez JJ, López-Berges MC, Gutiérrez N, Ciudad J, Lucio P, *et al.* Minimal residual disease in adolescent (older than 14 years) and adult acute lymphoblastic leukemias: Early immunophenotypic evaluation has high clinical value. *Blood* 2003;101:4695-700.
20. Allahyari A, Hashemi SM, Nazemian F, Karimi M, Kazemi MR, Sadeghi M. The relationship between risk factors and survival in adult acute lymphoblastic leukemia. *Iran J Cancer Prev* 2016;9:e5045.
21. Kozłowski P, Lennmyr E, Ahlberg L, Bernell P, Hulegårdh E, Karbach H, *et al.* Age but not Philadelphia positivity impairs outcome in older/elderly patients with acute lymphoblastic leukemia in Sweden. *Eur J Haematol* 2017;99:141-9.
22. Rego MF, Pinheiro GS, Metze K, Lorand-Metze I. Acute leukemias in Piauí: Comparison with features observed in other regions of Brazil. *Braz J Med Biol Res* 2003;36:331-7.
23. Morita K, Jain N, Kantarjian H, Takahashi K, Fang H, Konopleva M, *et al.* Outcome of T-cell acute lymphoblastic leukemia/lymphoma: Focus on near-ETP phenotype and differential impact of nelarabine. *Am J Hematol* 2021;96:589-98.
24. Faderl S, Kantarjian HM, Thomas DA, Cortes J, Giles F, Pierce S, *et al.* Outcome of Philadelphia chromosome-positive adult acute lymphoblastic leukemia. *Leuk Lymphoma* 2000;36:263-73.
25. Candoni A, Rambaldi A, Fanin R, Velardi A, Arcese W, Ciceri F, *et al.* Outcome of allogeneic hematopoietic stem cell transplantation in adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia in the Era of tyrosine kinase inhibitors: A registry-based study of the Italian blood and marrow transplantation society (GITMO). *Biol Blood Marrow Transplant* 2019;25:2388-97.
26. Shin DY, Kim I, Kim KH, Choi Y, Beom SH, Yang Y, *et al.* Acute lymphoblastic leukemia in elderly patients: A single Institution's experience. *Korean J Intern Med* 2011;26:328-39.
27. Wrzesień-Kuś A, Robak T, Pluta A, Zwolińska M, Wawrzyniak E, Wierzbowska A, *et al.* Outcome of treatment in adults with Philadelphia chromosome-positive and/or BCR-ABL – Positive acute lymphoblastic leukemia-retrospective analysis of Polish Adult Leukemia Group (PALG). *Ann Hematol* 2006;85:366-73.
28. de França Azevedo I, da Silva Júnior RM, de Vasconcelos AV, das Neves WB, de Barros Correia Melo FC, Melo RA. Frequency of p190 and p210 BCR-ABL rearrangements and survival in Brazilian adult patients with acute lymphoblastic leukemia. *Rev Bras Hematol Hemoter* 2014;36:351-5.
29. Dhédin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, *et al.* Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. *Blood* 2015;125:2486-96.
30. Hunault M, Harousseau JL, Delain M, Truchan-Graczyk M, Cahn JY, Witz F, *et al.* Better outcome of adult acute lymphoblastic leukemia after early genotypical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: A GOELAMS trial. *Blood* 2004;104:3028-37.
31. Ganzel C, Wang XV, Rowe JM, Richards SM, Buck G, Marks DI, *et al.* At three years, patients with acute lymphoblastic leukaemia are still at risk for relapse. Results of the international MRC UKALLXII/ECOG E2993 trial. *Br J Haematol* 2020;191:37-43.