

HEMATOLOGICAL PREDICTORS OF OUTCOME IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA IN DUHOK

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ABSTRACT

Background: While numerous studies have addressed the outcome of childhood acute lymphoblastic leukemia (ALL) in western developed countries, there is a scarcity of data in developing countries. This study explores the hematological predictors of outcomes in childhood acute lymphoblastic leukemia in Duhok city- Kurdistan Iraq.

Method: the current study represents a cross-sectional study, conducted in Hivi Pediatric hospital and Zheen oncology center in Duhok, Iraq, and 116 patients were enrolled. The main features of childhood ALL, hematological predictors, type of therapy, and risk factors were analyzed to assess their effect on treatment outcome and survival rate.

Results: Median age of the study cohort was 5 years and the male-to-female ratio of 1.4:1. 87.9% of the cases were B-ALL while 12.1 were T-cell. Blood counts revealed a mean WBC count of $54.34 \times 10^9/L$, mean hemoglobin of 7.913 g/dl, and mean platelet count of $68.96 \times 10^9/L$. Complete remission (CR) rate was 92.2%, the overall 5-year survival (OS) was 76.7%, and relapse-free 5-year survival (RFS) was 73.3%. Patients with B-cell ALL had significantly higher OS compared to patients with T-cell (p value=0.01). Patients stratified into high-risk groups had significantly lower RFS and OS compared to the intermediate and standard risk groups (p value=0.04, 0.008 respectively). Patients aged >10 years had significantly lower RFS (p value=0.001). Other factors such as age<1 year, PLT count, Hb count, and gender did not predict poor outcome.

Conclusion: Immunophenotype, age>10 years and risk stratification are important predictors of outcome in childhood ALL in our study, most notably, the patients' survival rates were inferior to similar reports from western developed countries, The key areas for future work should include wider implementation of MRD and cytogenetic analysis in risk stratification to improve the outcome of childhood ALL.

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Keywords: Acute lymphoblastic leukemia; childhood; Iraq, Predictors; Outcome.

Acute lymphoblastic leukemia (ALL) is the most frequent childhood malignancy worldwide with a prevalence of 25-30% of cancers in children, 75% of cases occurring in patients less than 10 years¹. Although it affects children of all ages, the incidence peaks between two and five, with a small male predominance 1.2:1¹. ALL is a heterogeneous disease; distinct subtypes have different biological,

cellular, and molecular properties, therapeutic responses, recurrence risks, and prognosis, phenotypic and genotypic variation in childhood ALL is significant and is important for both diagnosis and prognosis¹. Modern procedures incorporate sophisticated risk stratification models to decide the type and amount of therapy a patient will receive in order to account for this heterogeneity¹. The level of therapy

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intensity for ALL is determined by the likelihood of relapse, which is estimated using a combination of clinical, cytogenetic, and morphological response criteria². However, because a large proportion of relapses occur in the standard-risk group, the risk groupings defined by these characteristics are somewhat nonspecific³. Cytogenetic and minimal residual disease (MRD) studies help risk stratification even further. MRD is not usually accessible in developing countries, despite being the most sensitive and specific predictor of relapse risk³. The emergence of measurable residual disease and with the advent of tyrosine kinase inhibitors targeting BCR-ABL1, monoclonal antibodies targeting CD20 (rituximab), antibody-drug conjugates targeting CD22 (inotuzumab ozogamicin), and bispecific antibodies (blinatumomab) have led to improvement over the past 40 years, and over 90% of patients can now anticipate long-term disease-free survival in developed countries with scarce information on outcomes in developing countries, some low- and middle-income countries have reported an average survival rate as low as 35%, the causes were attributed to poverty, nutritional status, therapy abandonment and infectious causes^{1,4-6}. This study aims to provide information on the outcome by outlining the main features of childhood ALL, including hematological predictors, the outcome of therapy as well as risk factors associated with survival in Duhok city-Kurdistan, Iraq.

MATERIALS AND METHODS

patients

This cross-sectional study was conducted at Hivi Pediatric hospital and Zheen oncology center in Duhok, Iraq. From March 2014 through December 2020, data

from 116 patients' records, aged 16 years old or less were collected. Exclusion criteria were: age > 16 years; incomplete patient information, and patient refusal. As a result, seven patients were excluded from the study. Patients were allocated to risk groups based on age at diagnosis, WBC count, and failure to achieve remission at induction, patients were stratified as standard risk group if age at diagnosis < 10 years old with WBC count < 50 x 10⁹/L, intermediate-risk group if age ≥ 10 years and if WBC counts ≥ 50 x 10⁹/L and high-risk group if WBC count ≥ 100 x 10⁹/L or if⁷. fail to remit at induction⁷. The study was approved by the Kurdistan Board of Medical Specialties Ethics Committee and consent were obtained from all parents/guardians after explaining to them what the research entails.

Diagnostic procedures

The diagnosis was made through peripheral blood sample and bone marrow examination. Diagnosis was made by finding ≥ 20% lymphoblasts in the peripheral blood and/or bone marrow aspirate¹. confirmation of the diagnosis and subtyping was done by either immunohistochemistry or flow cytometry immunophenotyping on peripheral blood or bone marrow aspiration. Two lasers, four colors, and six parameters flow cytometry were used to examine the samples. EuroFlow™ Panel was used with the following monoclonal antibodies (MAb): CD19, CD20, CD10, CD22, cytoplasmic (c) CD79a, c and surface (s) IgM for B-lineage, CD1a, CD2, cCD3 and sCD3, CD4, CD5, CD7, and CD8 for T-lineage, CD13, CD33, CD64, CD15, CD16, CD11b, CD14, CD117, and cytoplasmic MPO for myeloid lineage, and CD34, CD45, CD36, CD38, HLA-DR, CD56, and nTdT as non-lineage markers..

All MAb were purchased from BD Biosciences (BD Biosciences, San Jose, CA, USA)⁸. Central nervous system (CNS) involvement was established by the detection of blasts in cerebrospinal fluid by a spinal puncture. blood samples from 20 out of 116 patients were sent for analysis of BCR_ABL1 rearrangement using RT-PCR at the time of enrollment.

Therapy protocols

Two main protocols were implicated for treatment namely: UKALL 2011 and BFM-ALL (Berlin-Frankfurt-Munster)¹. Standard-risk group patients were given regimen A of the UKALL protocol while the intermediate patients were given regimen B of the UKALL protocol and the BFM-ALL protocol was designated for high-risk group patients. Only 20 patients out of the 116 patients were sent for the BCR-ABL translocation and tyrosine kinase inhibitors (TKIs) was implemented in the treatment of one patient with positive BCR-AB^{1,10}. the standard-risk group patients received three-drug induction therapy namely vincristine, steroids, and asparaginase for 4 weeks while the intermediate-risk group additionally received daunorubicin, the high-risk group receiving the BFM protocol received an additional four doses of vincristine as well as L-asparaginase^{10,11}. All patients received three doses of intrathecal methotrexate in induction with patients who had blasts in the CSF receiving 2 additional doses¹. Following induction patients are assessed for complete hematological remission by bone marrow aspiration, Patients who accomplished hematological complete remission (HCR) proceeded to the intensification and post-remission consolidation.

While patients who did not achieve CR and had a matched sibling were recommended to undergo BMT⁹. Complete hematological remission was defined as no detectable blasts in Peripheral blood and CSF, blasts less than 5% in bone marrow, while relapse was defined as the presence of blasts in peripheral blood or CSF more than 5% marrow blasts following induction. From the time of diagnosis of acute lymphoblastic leukemia until the date of last follow-up or death, the overall survival (OS) was determined. Relapse-free survival (RFS) time was measured from the time of complete hematological response to the time of relapse excluding patients who never entered remission.

Statistical Analysis

Demographic parameters were summarized; for continuous data, means and ranges were used, whereas, for categorical variables, frequency and percentages were used. Comparisons between categorical variables were carried out using the Chi-square test and Fisher's exact test as appropriate. Survival and event-free survival curves were presented using the Kaplan–Meier method. Statistical significance was defined as a P-value of less than 0.05. SPSS version 26 was used for all the analyses (SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 116 patients with ALL were included in the study, with a median age of 5 years (range 0.1 to 15 years). The study included 68 males and 48 females with a ratio of 1.4:1 Clinically, splenomegaly was noticed in 64.7%, hepatomegaly in 51.7%, and lymphadenopathy in 79.3% of the 116 patients. Additionally, clinical examination revealed pallor in 87.9%, fever in 82.8%,

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bone pain in 56.9%, and bleeding tendency in 42.2%,

Blood counts revealed, median hemoglobin of 7.600 g/dl (range 3.9–11.9), a median leucocyte count of 16.5 x 10⁹/L (0.7–596), and a median platelet count of 42.00 x 10⁹/L (range 1–434)

Moreover, lineage analysis revealed that B cells were the most predominant type with 102 cases (87.9%) Furthermore, it was found that common B-ALL subtype was the most frequent among B-ALL at 88.2%, while mature B subtype was the least

frequent at 2%. T cells only accounted for 14 cases (12.1%), Among T-ALL cases, cortical T-ALL was the most frequently encountered subtype accounting for 10 cases (71.4 %). Notably, out of the categories of the patients (high risk, intermediate-risk, and standard risk), the standard risk group was the most frequent with 64 cases (55.1%), followed by the intermediate-risk group with 36 cases (31.1%) and lastly the high-risk group which had 16 cases (13.8%) (Table 1).

Table 1 Demography and baseline features in 116 pediatric ALL patients

Characteristics	No	%
Age (years)	Median 5(0.1-15)	
Gender	Male	68
	female	48
	Mean =52.48±87.3	
WBCx10 ⁹ /l	<50	82
	>50	11
	>100	23
	Mean=7.85±1.84	
Hb g/dl	<10	98
	>10	18
	Mean=68.57±76.4	
PLT10 ⁹ /l	<100	93
	>100	23
immunophenotype	B cell	102
	-Common B*	90
	-Pre-B*	4
	-Pro-B*	6
	-mature -B*	2
	-t cell	14
	-Cortical T**	10
	-Pre-T**	3
	-Pro-T**	1
Risk stratification	Standard	64
	Intermediate	36
	high	16
treatment	UKALL A	65
	UKALL B	36
	BFM	13
	LMP	2

*% out of Subgroup B ALL; **% of the subgroup T-ALL

All patients were treated and evaluated for response to the treatment. Out of 116 patients treated: 101 patients were treated with UKALL protocol (65 patients treated

on regimen A and 36 patients treated on regimen B), 13 patients were treated with BFM protocol, and 2 were treated with LMB (lymphoma malignant B type)

regimen. Only 20 patients out of the 116 patients were sent for the BCR-ABL translocation and tyrosine kinase inhibitors (imatinib) were implemented in the treatment of the one patient with positive BCR-ABL. Notably, complete hematological remission was achieved in 107 (92.2%) patients while 4 (3.5%) patients died during the induction of chemotherapy. After a median follow-up of 52 months (range 12-93 months), 75 patients (70.1%) continued in complete remission, out of these patients 70 patients remained alive while 5 patients died of infection. Relapse occurred in 32 (29.9%) patients. Out of the patients who relapsed, 14 (43.8%) are alive and achieved remission while 18 (56.2%) of the relapsed patients died (Fig 1.). Sites of relapse were bone marrow, CNS, and testicles. Relapse in bone marrow alone occurred in 22 (68.8%) patients, CNS alone in 8 (25%) patients, combined bone marrow and CNS in 1 (3.1%) patient, and testicular in 1 (3.1%).

Survival

The 5-year overall survival of childhood ALL patients in the current study was 76.7%, with a median survival of 51

months (fig.1A). The 5-year relapse-free survival (RFS) was 73.3% (fig.1B). Although patients treated with UKALL A and UKALL B had significantly better RFS in comparison to patients with BFM protocol (81.2%,66.6% and 56.2% respectively) $p=0.008$, there was no significant difference in CR or OS (overall survival) (table 2). Patients with B-cell ALL had significantly higher OS compared to T-cell (p value=0.01) with no significant differences in HCR and RFS. Patients stratified into the high-risk group had significantly lower RFS and OS compared to the intermediate and standard-risk group (p -value= 0.04,0.008 respectively) (table 2) Patients aged >10 years had significantly lower RFS compared to patients less than 10 years p -value=0.001. Other factors such as high WBC count, low PLT count, low Hb concentration, and gender did not predict poor outcomes.

Allogenic hemopoietic stem cell transplantation (Allo-HSCT)

Eight patients were sent for stem cell transplantation (SCT); one died after transplantation, one relapsed, and the remaining 6 achieved remission after SCT.

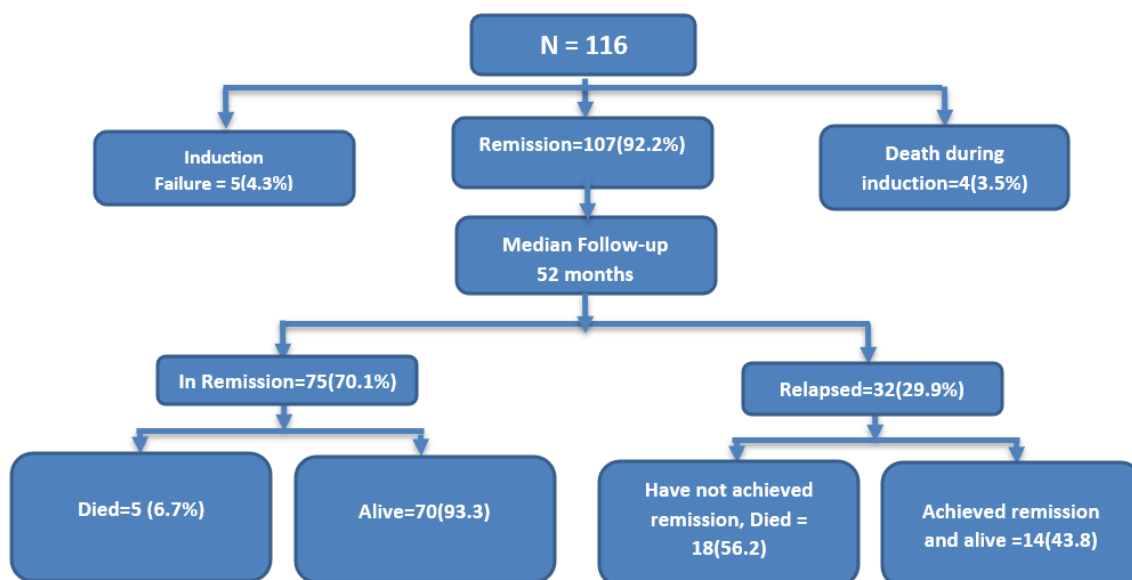


Fig. 1 Outcome of childhood acute lymphoblastic leukemia

Table 2 Differences in outcomes according to some prognostic variables among patients' cohorts

Baseline characteristics	HCR (%)	P-value	RFS (%)	P-value	OS (%)	P-value
Age at diagnosis						
<10year	90.5	0.8	75.7	0.001	78.9	0.1
>10 years	100		61.9		66.6	
Gender						
Male	94.1	0.6	67.6	0.2	73.5	0.3
Female	95.8		81.2		81.25	
WBC count						
<50,000 ⁹ /L	89.2	0.7	75	0.2	79.7	0.6
>50,000 ⁹ /L	100		68.7		68.75	
Immunophenotype						
B-cell	92.1	0.7	75.4	0.2	80.3	0.01
T-cell	92.8		57.1		50	
Risk group						
Standard	89	0.9	81.25	0.04	84.3	0.008
Intermediate	94.4		66.6		75	
high	100		56.2		50	
Treatment						
UKALL A	89.9	0.09	81.5	0.04	83.07	0.1
UKALL B	94.4		66.6		75	
BFM	100		53.8		53.8	

DISCUSSION

This study included 116 ALL patients aged between 1 month and 15 years. The reported HCR rate (92.2%) of this study was comparable to many western countries as well as some nearby countries such as Jordan^{12,13,14,15}. Similarly, the induction mortality rate of 3.5% in our study lies within the range limits reported in childhood ALL worldwide although studies from some developing countries have reported induction death rates ranging from 12.8% to 22.6%, these high numbers are mainly attributed to infectious causes as well as chemotherapy-related toxicity^{4,5,6,12,13,15}. With a 5-year OS of 76.7% and RFS of 73.3%, the overall outcome from this cohort study is lower than several published from developed Western countries with countries like the Netherlands and Germany which reported a 5-year OS of 91% and 91.8%

respectively^{13,15}, and some developing countries such as Jordan were also reported to have a 5-year OS and RFS of 89% and 80% respectively¹².

Interestingly a recent paper published from Children Welfare Teaching Hospital in Baghdad, Iraq revealed a lower 5-year RFS and 5-year OS rate (of 62.2%,46.3% respectively)¹⁶. The lower 5-year OS and RFS might be related to poor adherence to therapeutic guidelines and the lack of BMT in certain high-risk patients due to financial constraints and/or a lack of local BMT. Other, as-yet-unspecified variables might, however, have influenced the OS and RFS numbers. BCR-ABL1 positivity in ALL is associated with aggressive disease and is a poor prognostic factor, especially in children, however after implementation of TKIs these patients have been said to have higher RFS and OS^{1,18,19,20}, since only 20 of our patients

were sent for the BCR-ABL1 its effect on The OS and RFS could not be assessed, appropriate detection techniques should be selected to improve the detection rate of fusion genes, to significantly improve the prognosis.

One of the most important factors that have been reported as a predictor of ALL outcome is the immunophenotype of the patient. OS of patients with the B-cell phenotype in this study were significantly higher than those with the T-cell phenotype ($p=0.01$) although T-ALL had previously been considered to have a worse outcome than those with B-ALL. Several studies now argue that survival is similar between the two patient groups with appropriate treatment intensification of T-ALL^{10,21,22,23}, the survival disadvantage for T-cell ALL in this study may be attributed to the fact that patients with T-cell ALL are generally older than those with B-cell ALL and, therefore, have poorer tolerance to chemotherapy, especially dexamethasone and L-asparaginase, and a greater proportion of patients with B-cell ALL has favorable genetic subgroups (egg, ETV6–RUNX1, and high hyper diploidy)^{21,23,24}. Characterization at the antigenic level, which may be relevant for later diagnosis of minimum residual disease(MRD) is another important feature of immunophenotyping²⁵. Patients stratified as a standard risk had significantly higher OS and RFS compared to the intermediate and high-risk groups ($p= 0.008$ and 0.04 respectively), this may be attributed to the fact that patient in our study was stratified without cytogenetic analysis or MRD in most cases since cytogenic analysis and MRD have just recently been available in our region, cytogenetic analysis and MRD have provided insight into the variation in

the response to chemotherapy drugs among patients, explaining both the differences in toxicities and response to therapy^{20,21,23,24,25}. Shortly, it can be envisioned that ALL will be molecularly characterized and defined, thus enabling us to deliver better-tailored therapy and thus improving the outcomes of high-risk and intermediate-risk patients. Similarly, we found that patients treated with UKALL regimens had significantly higher RFS compared to those treated with the BFM regimen with p values of 0.04 .

The former may potentially be explained by that BFM-type chemotherapy in centers with limited medical resources could lead to drug related complications as well as those treated with the BFM protocol were all-in high-risk groups, therefore, may have unfavorable cytogenetics in comparison to the other subgroups. In this study, patients aged >10 years had significantly lower RFS (P value= 0.001) this finding is in agreement with the several other studies.5]. In previous studies, a significant impact of age <1 year and of high WBC $50 \times 10^9/L$ of pediatric ALL patients outcome had been observed^{10,17,19} However, we didn't detect any significant impact of the above-mentioned prognostic factors on the survival of patients in this cohort study. This could be attributed to the small subgroup sizes. Amid the limitations of the current study, is the lack of usage of minimal residual disease, monitoring, and cytogenetics at enrollment or follow-up. However, such a limitation is shared by other studies from developing countries^{4,5}, where resources or expertise are restricted. Minimal residual testing has recently been introduced in our centers and it has been integrated into the routine follow-up of

patients, which hopefully will have a beneficial effect on future patients.

CONCLUSION

The results of this study confirm the importance of Immunophenotype, age and risk stratification as predictors of outcome in childhood ALL in our study, most notably, compared to similar findings from developed nations, the patients' survival rates were lower. Future research should focus on expanding the use of cytogenetic and MRD data in risk classification to improve the outcome of childhood ALL.

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پوخته

پاشگوتن: دگهل کۆ گلهک فهکولین لسه ئهجامین نهخوشیا لیوکیمیا لیمفوبلیستیکا زاروکینی (ALL) ل وهلاتین پیشکەفتی بین رۆژنأفایی هاتینه دهست نیشانکرن، ل وهلاتین پاشکەفتی کیمی یا داتیان یا هه. ئهف فهکولینه ئهجامین پیشبینین نهخوشیا لیوکیمیا لیمفوبلیستیکا زاروکینی ل باژیر دهوکی- کوردستانا عیراقی فهکولیت. ریباز(ریک): فهکولینا نها فهکولینهکا ههفسهری به، کۆ ل نهخوشخانهیا هیفی یا زاروکان و ناغهندا ژین یا زانستی گرییا ل دهوکی ل عیراقی هاتیه کرن، و ۱۱۶ نهخۆش هاتینه تومارکرن. تاییهتمهندیین سهرمکی بین (ALL) یا زاروکینی، پیشبینین زانستی خوینی و نهخوشیان، جورئ تیمارکرن (چارهسهریا دهرونی)، و فاکتهرین مهترسی بین هاتینه شروقهکرن و کاریگهریا وان لسه ئهجامین چارهسهرکرن و ریزهیا زیندی بوونی ب ههلسهنگین.

ئهجام: تهمنین نافین بین کوما فهکولینی (۵) سال و ریزهیا نیر و مئ ۱:۴.۱ بوو. ۸۷.۹٪ ژ کهيسان (ALL) بوون ددهمهکدا (۱۲.۱) ژ T.Cell بوون. ژمارا خوینی یا نافین 54.34* 109 L هیموگلوبینا ژ 7.913 g/dl , ژمارا پهلهکین خوینی 109/L.68.96 x ریزهیا تهمام 92.2% (CR) بوو، تیکرای گشتی یی زیندی بوو یا (۵) پینج سالی 76.7 بوو، و زیندی بوونا (۵) پینج سالی یا بی فهگس 73.3% (RFS) بوو. نهخوشین ب هوکاری B-Cell ALL ب شیوازمکی زانستی نهگهري زیندی بوونی بلنتره ب بهراوردی دگهل T.Cell (ب نهگهري = 0.01). نهخوشین کۆ دنآف کوما مهترسی دا ل گوری نافین خهتهرین نافین و ستاندارد RFS and OS گرنگ کیمتر بوون (ب ریزا = 0.04, 0.008 ب نیزیکی). نهخوشین (۱۰) ده سالی زیدتر خودانی RFS کیمتر بوون (ب ریزا = 0.001). فاکتهرین دی بین وهکی تهمنی (۱) سالی، هژمارا PLT، هژمارا Hb، و رهگس پیشبینیا ئهجامین خراب نهکر.

ئهجام: ئیمونوفونو تایپ، تهمنی (۱۰) سالی و زیدتر مهترسیا د فهکولینا مهدا پیشبینین گرنگ ئهجامی نهخوشیا خوینی یا زاروکینی (ALL)، نهخاسمه، ریزا زیندیبوونا نهخوشان کیمتر بوو وهکی ههمان راپورتین وهلاتین پیشکەفتی بین رۆژنأفایی. جهین سهرمکی بو خهباتا پاشهروژئ دقیت ب شیوهکی بهرفههتر بن. پیکئینانا MRD و شروقهکرن پیکهاتن و پهرمههنا شانا د ستراتیجیا مهترسیا داکو ئهجامین نهخوشیا خوینی (ALL) یا زاروکینی

الخلاصة

التنبؤ الدموي بنتائج سرطان الدم الليمفاوي الحاد من الطفولة في دهوك

الخلفية: بينما عالجت العديد من الدراسات نتائج سرطان الدم الليمفاوي الحاد في مرحلة الطفولة (ALL) في البلدان المتقدمة الغربية، هناك ندرة في البيانات في البلدان النامية. تستكشف هذه الدراسة المؤشرات الدموية للنتائج في سرطان الدم الليمفاوي الحاد في مرحلة الطفولة في مدينة دهوك - كردستان، العراق.

الطريقة: تمثل الدراسة الحالية دراسة مقطعية أجريت في مستشفى هيشي للأطفال ومركز زين لدراسة الأورام في دهوك بالعراق، وتم تسجيل 116 مريضاً. تم تحليل السمات الرئيسية لسرطان الدم الليمفاوي الحاد في مرحلة الطفولة، والتنبؤات الدموية، ونوع العلاج، وعوامل الخطر لتقييم تأثيرها على نتيجة العلاج ومعدل البقاء على قيد الحياة.

النتائج: كان متوسط عمر مجموعة الدراسة 5 سنوات، وكانت نسبة الذكور إلى الإناث 1.4:1.87.9٪ من الحالات كانت سرطان الدم الليمفاوي الحاد في مرحلة الطفولة B، بينما 12.1 كانت الخلايا التائية. كشفت أعداد الدم عن متوسط عدد WBC قدره $54.34 \times 10^9/L$ ، ومتوسط هيموجلوبين قدره 7.913 جم/ديسيلتر، ومتوسط عدد الصفائح الدموية $68.96 \times 10^9/L$. كان معدل الهدوء الكامل 92.2٪ (CR)، وكان إجمالي البقاء على قيد الحياة لمدة 5 سنوات 76.7٪ (OS)، والبقاء الخالي من الانتكاس لمدة 5 سنوات (RFS) كان 73.3٪. المرضى الذين يعانون من سرطان الدم الليمفاوي الحاد للخلايا البائية في مرحلة الطفولة عاشوا لفترة أطول بكثير من أولئك الذين يعانون من الخلايا التائية ($p = 0.01$). كان البقاء على قيد الحياة لمدة 5 سنوات خالية من الانتكاس والبقاء العام لمدة 5 سنوات للمرضى المعرضين لخطر كبير أقل بكثير من تلك الخاصة بالمرضى ذوي المخاطر المتوسطة والمرضى المعرضين للمخاطر القياسية (p قيم 0.04 و 0.008، على التوالي). كان لدى المرضى الذين تزيد أعمارهم عن 10 سنوات بقاء أقل بكثير بدون انتكاس لمدة 5 سنوات (p value = 0.001). عوامل أخرى مثل العمر 1 عام، عدد PLT، عدد Hb، والجنس لم تتنبأ بنتائج سيئة.

الاستنتاج: يعد النمط المناعي، والعمر < 10 سنوات، والتقسيم الطبقي للمخاطر من المؤشرات المهمة للنتيجة في سرطان الدم الليمفاوي الحاد في مرحلة الطفولة في دراستنا؛ وعلى وجه الخصوص، كانت معدلات بقاء المرضى أقل من التقارير المماثلة الواردة من البلدان الغربية المتقدمة. وينبغي أن تشمل المجالات الرئيسية للعمل في المستقبل التنفيذ على نطاق أوسع.