



Nature of Pediatric Leukemia in Hiwa Hematology/ Oncology Hospital: A Single Cancer Center Experience

Khadeeja Mohammed Najeeb* Dana Ahmad Abdullah Nawshirwan Gafoor Rashid*****

Abstract

Background and objectives: Acute lymphoblastic leukemia is the most common type of blood cancer in children. This study aimed to address various sociodemographic and diagnostic findings of pediatric patients with acute lymphoblastic leukemia that have been recorded in the data system of Hiwa Hematology/Oncology Hospital.

Methods: This retrospective cross-sectional study was performed on 100 patients aged <18 years with acute lymphoblastic leukemia in Hiwa Hematology/Oncology Hospital, from January 2020 to July 2023. A standard spreadsheet was used to report patients' sociodemographic data and diagnostic findings, including complete blood count, bone marrow blast count, immunophenotyping, and genetic mutation.

Results: Most patients had B-cell acute lymphoblastic leukemia (92%), aged <6.0 years (52%), underweight (69%), A⁺ blood group (33%), and negative gene mutation (98% for protein 190 and 97% for protein 210). There was no significant correlation between both leukemia subtypes regarding age ($p \leq 0.745$), gender ($p = 0.461$), body mass index ($p = 0.849$) and season of diagnosis ($p \geq 0.355$). However, a significant difference ($p < 0.001$) was seen for blood group distribution. No significant alterations ($p \leq 0.05$) were seen in the mean hemoglobin, platelets and bone marrow blasts between both leukemia subtypes, while a significant difference ($p = 0.002$) in the mean leukocyte levels was seen.

Conclusions: B cell-subtype pediatric acute lymphoblastic leukemia is more common in our locality and is not related to age, gender, body mass index and season of diagnosis but is directly correlated to blood group.

Keywords: Cross-sectional study, Genetic mutation, Immunophenotyping, Pediatric blood cancer, Recorded data system

*MBChB, KHCMS Hematopathology, Hiwa Hematology/ Oncology Hospital, Sulaimani Directorate of Health, Kurdistan Region, Iraq. E-mail: xa.2010.alin@gmail.com (Corresponding author)

**MBChB, PhD, Hematopathology. Department of Basic Medical Sciences, College of Medicine, University of Sulaimani, Sulaimani, Kurdistan Region, Iraq. E-mail: dana.abdullah@univsul.edu.iq

***MBChB, HDCH, FKHCMS, Clinical Hematology and a Senior Specialist at Hiwa Hematology/ Oncology Hospital, KHCMS- Sulaimani Clinical Hematology Center, Shorsh General Teaching Hospital. E-mail: rashid.nawshirwan1973@gmail.com



Introduction

Acute lymphoblastic leukemia (ALL) is a hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow (BM), peripheral blood (PB), and extra-medullary sites.^{1,2} It is the most frequently diagnosed malignancy in children, representing around one-fourth of all cancers in the age group 0-14 years.³ Generally, ALL accounts for approximately 20 - 30% of pediatric cancers.⁴ The highest incidence of childhood leukemia per 100,000 individuals in 2018 was recorded in Malaysia (8.0) and the Republic of Moldova (7.2), while the lowest incidence appeared in Sub-Saharan Africa (3.4), Bhutan and Bangladesh (0.90 each).⁵ The breakpoint cluster region (BCR) gene with the Abelson tyrosine kinase (ABL) (BCR-ABL) is an active tyrosine kinase that is expressed by the Philadelphia (Ph) chromosome. It is formed upon the t (9;22) reciprocal translocation that fuses the BCR gene with the ABL. The most common BCR-ABL isoforms are P210 and P190; both have an identical sequence and domain organization, but P190 is shorter and more common in ALL than P210.⁶ Hence, chromosomal aberrations are the hallmark of ALL, including translocated BCR-ABL. A variant with a gene expression profile similar to that of Ph-positive ALL but without the BCR-ABL rearrangement has also been identified.^{7,8} Generally, risk stratification has been based on clinical factors, including age, ethnicity, leukocyte count and response to chemotherapy; however, the documentation of recurrent genetic changes has aided in improving specific prognoses and guiding management.⁹ Additionally, severe obesity is associated with a worse survival rate of ALL and according to the World Health Organization (WHO), body mass index (BMI) of $<18.50 \text{ kg/m}^2$ is defined as underweight, from 18.50 to $<24.90 \text{ kg/m}^2$ is average weight, $\geq 25-29.9 \text{ kg/m}^2$ is overweight or pre-obesity, and $\geq 30 \text{ kg/m}^2$ is

obesity.^{10,11} Common ALL symptoms include fever, weight loss, night sweats, easy bleeding/bruising, fatigue, dyspnea and infection.¹² Diagnosis of ALL is established by the presence of $\geq 20\%$ lymphoblast in the BM or PB. Evaluation for morphology, flow cytometry, immunophenotyping, cytogenetic test, and complete blood count with differential and smear to evaluate the other hematopoietic cell lines, coagulation profiles and serum chemistries.¹³ The backbone of ALL treatment remains multi-agent chemotherapy with vincristine, corticosteroids and an anthracycline with allogeneic stem cell transplantation for eligible candidates.^{14,15} Globally, the survival rate of ALL has increased tremendously over the last four decades, with 5-years overall survival reaching 90% in developed countries.^{12,16} Iraq has a considerable burden of newly diagnosed ALL due to its polluted environment and poor health facilities. Between January 1st, 2000, to December 31st 2019, 8570 cases of pediatric leukemia (0-14 years old) in Iraq were documented, for an average of 429 new cases per year.^{17,18} However, there needs to be more data on pediatric ALL in our locality. Thus, this study was designed to present the sociodemographic and diagnostic findings and incidence of pediatric ALL that have been recorded in the Hiwa Hematology/Oncology Hospital data system.

Patients and methods

This cross-sectional retrospective hospital record-based study involved 100 pediatric patients with ALL from January 2020 to July 2023 at Hiwa Hematology/Oncology Hospital, Sulaimaniyah, Iraq, using a convenient sampling method. Patients aged <18 years with confirmed ALL using flow cytometry of PB and BM aspiration were included, while those with other types of blood cancer were excluded. Flow cytometry criteria for cases to be assigned as B-cell ALL was that the vast majority of blast cells from





PB and/or BM are expressing human leukocyte antigen DR-isotype (HLA-DR), terminal deoxynucleotidyl transferase (TdT) and CD19 markers, while CD79a, CD22, and CD34 are frequently, but not always expressed with no expression of CD20, kappa, and lambda by B-cells. Regarding the T-cell ALL, the vast majority of blast cells from PB and/or BM are mainly expressing CD7, CD3, CD1 and CD2 with no expression of surface CD3, CD16, CD56, and CD34.^{19,20} A standard spreadsheet was used to report pediatric patients' sociodemographic data, including age, gender, ABO blood group, weight and height, to determine BMI. Also, patients' diagnostic findings were reported, including complete blood counts at presentation, BM blast counts, immunophenotyping to determine leukemia subtypes, and molecular investigation to determine BCR-ABL gene mutation (protein 190 and 210 expressions). Ethical clearance was obtained from the Ethical Committee of the Kurdistan Higher Council of Medical Specialties (KHCMS), Iraq. The data were analyzed using Statistical Package for the Social Sciences (Chicago, USA). The chi-square test was used for categorical variables, while the Kolmogorov-Smirnov test, independent sample t-test and Mann-Whitney U test were used for parametric and non-parametric quantitative variables. A p-value of ≤ 0.05 was considered a significant difference.

Results

The mean patients' age was 6.69 ± 7.78 years (ranging from 4.0 months to 16 years), and most of them (52%) were < 6.0 years, followed by 6.0-12 years (29%), then > 12 years (19%). The boys and girls were equally distributed (50%). Mean BMI was 17.89 ± 3.6 kg/m², and most patients were underweighted (69%), while 24% had healthy weight and 7.0% were overweight, as illustrated in Table (1).

Table (1): Sociodemographic distribution of patients with acute lymphoblastic leukemia.

Variable	Number	Percentage
Age (Years)		
< 6.0	52	52
6.0-12	29	29
> 12	19	19
Gender		
Female	50	50
Male	50	50
Body mass index (Kg/m ²)		
Underweight	69	69
Normal weight	24	24
Overweight	7.0	7.0

Regarding the BCR-ABL genetic mutation, 98% were negative and 2.0% were positive for P190. While, 97% were negative, and 3.0% were positive for P210, as shown in Table (2).

Table (2): P 190 and P 210 distribution among patients with acute lymphoblastic leukemia.

Variable	Negative No. (%)	Positive No. (%)
P190	98 (98)	2.0 (2.0)
P210	97 (97)	3.0 (3.0)

Regarding the immunophenotyping using flow cytometry, 92% of patients were diagnosed as B cell-ALL, while only 8.0% were T-cell ALL. The mean age of B-cell ALL patients was 6.67 ± 4.73 years, which was closely near the age of T-cell ALL patients (6.88 ± 5.67 years) ($p=0.745$). The majority of B-cell ALL were females (51.1%, $n=47$) rather than males (48.9%, $n=45$), whereas the majority of the T-ALL were males (62.5%, $n=5.0$) rather than females (37.5%, $n=3.0$) ($p=0.461$). The mean BMI of patients with B-cell ALL was 17.84 ± 3.55 kg/m², slightly lower than T-cell ALL patients (18.51 ± 4.36 kg/m²) ($p=0.849$). Interestingly, ABO blood phenotype has a





substantial association with the type of ALL ($p < 0.001$), in which most B-cell ALL patients had blood type A⁺ (32.6%), followed by B⁺ (29.3%) and O⁺ (27.2%), then A⁻ and AB⁺ (4.3% each), O⁻/ AB⁻ (1.1%), while no one had B⁻ (0.0%). On the other hand, most patients with T-cell ALL had A⁺ (37.5%), followed by B⁺/B⁻ (25.0%), AB⁺ (12.5%), while no one had AB⁻, O⁺, O⁻ or A⁻ (0.0%). In respect to the season of diagnosis, most B-cell ALL patients were detected in Spring (41.3%), followed by Autumn (23.9%) and Winter (20.7%), then Summer (14.1%). At the same time, most patients with T-cell ALL were diagnosed in Summer (37.5%), followed by Spring and Autumn (25% each), and then winter (12.5%) ($p = 0.355$), as shown in Table (3).

Table (3): Compares the characteristics of pediatric patients to the type of acute lymphoblastic leukemia (ALL).

Variable	Type of Leukemia			p-value
	B-cell ALL (n=92)	T-cell ALL (n=8)	Total (n=100)	
Gender				
Female	47 (51.1)	3.0 (37.5)	50 (50)	0.461
Male	45 (48.9)	5.0 (62.5)	50 (50)	
ABO Blood group				
A ⁺	30 (32.6)	3.0 (37.5)	33 (33)	<0.001**
A ⁻	4.0 (4.3)	0.0 (0.0)	4.0 (4.0)	
B ⁺	27 (29.3)	2.0 (25.0)	29 (29)	
B ⁻	0.0 (0.0)	2.0 (25.0)	2.0 (2.0)	
AB ⁺	4.0 (4.3)	1.0 (12.5)	5.0 (5.0)	
AB ⁻	1.0 (1.1)	0.0 (0.0)	1.0 (1.0)	
O ⁺	25 (27.2)	0.0 (0.0)	25 (25)	
O ⁻	1.0 (1.1)	0.0 (0.0)	1.0 (1.0)	
Season				
Spring	38 (41.3)	2.0 (25)	40 (40)	0.355
Summer	13 (14.1)	3.0 (37.5)	16 (16)	
Autumn	22 (23.9)	2.0 (25)	24 (24)	
Winter	19 (20.7)	1.0 (12.5)	20 (20)	

** : Highly significant difference

Moreover, the mean levels of hemoglobin (Hb), white blood cell (WBC) and platelets (PLT) in the B-cell ALL patients were 9.31 ± 2.37 g/dL, 31.16 ± 49.20 10⁹/L and 83.85 ± 102.42 10⁹/L, respectively, which were lower than the levels in T-cell ALL patients (10.43 ± 2.59 g/dL, 64.89 ± 35.58 10⁹/L and 92.13 ± 112.75 10⁹/L, respectively). Whereas BM blasts in B-cell ALL patients were $85.90 \pm 13.56\%$, slightly higher than those with T-cell ALL ($82.43 \pm 15.58\%$). The p-values for Hb, WBC, PLT and BM blasts% were 0.206, 0.002, 0.395 and 0.505, respectively, as shown in Table (4).

Table (4): Compares the hematological parameters of pediatric patients to the type of ALL.

Hematological parameter	Type of leukemia			p-value
	B-cell ALL (n=92)	T-cell ALL (n=8)	Total (n=100)	
Hb (g/dL)	9.31 ± 2.37	10.43 ± 2.59	9.40 ± 2.39	0.206
WBC (10 ⁹ /L)	31.16 ± 49.20	64.89 ± 35.58	33.86 ± 48.98	0.002*
PLT (10 ⁹ /L)	83.85 ± 102.42	92.13 ± 112.75	84.51 ± 102.70	0.395
BMB (%)	85.90 ± 13.56	82.43 ± 15.58	85.60 ± 13.68	0.505

ALL: Acute lymphoblastic leukemia, BMB: Bone marrow blasts, Hb: Hemoglobin, PLT: Platelet, WBC: White blood cell. The values were expressed as mean \pm SD. Hb was analyzed using the independent sample t-test, and others were analyzed using the Mann-Whitney U test. *: Significant difference

Discussion

The mean age of pediatric patients in this study was 6.69 ± 7.78 years, and most patients (52%) were aged < 6.0 years. This means smaller age groups are more vulnerable to getting the disease that might be correlated to rapid cell lineage propagation





and growth. Another almost similar study in Iraq by Al-Hadad et al. on 1425 pediatric patients with ALL stated that the median age of pediatric patients with ALL was 5.0 years, ranging from 1.0 to 14.8 years, while most of their patients were aged 1.0 to 5.0 years old (56%).¹⁸ In contrast to this study, Li et al. study on 705 pediatric patients, reported the average age at diagnosis was 17.52 ± 14.37 years, with an incidence peak between 2.0 – 4.0 years.² These disparities might be related to the sample size, ethnicity, hereditary, and geographical location. Both genders were equally affected in this study (50%), which means sex is not related to the incidence of the disease in pediatrics in our locality. On the contrary, male predominance was reported by Al-Hadad et al. (55%), (58.4%), Rafieemehr et al. and Li et al. (64.82%).^{2,18,21} The cause for gender disparity among studies is not clear; however, ALL is more common among males and might be related to sexual hormones.²¹ The mean BMI of patients with ALL was 17.89 ± 3.6 kg/m², and most patients were underweight (69%). Underweight refers to low weight for age when a child can be either thin or short for their age.²² In this regard, low BMI was seen in most pediatric ALL patients (53.6%) in a study conducted by Bahoush et al.²³ Based on the ABO blood system, most patients were A (37%), and the least were AB⁻/O⁻ (1.0% each). These findings imply that A blood group may lead to an increased risk of pediatric ALL, that are not agree with that of Li et al. who found that most pediatric ALL patients had O blood group (41.02%); however, they reported that most minor patients had AB blood group (6.72%).² Also, Alavi et al. reported that the most frequent blood type of pediatric ALL was the O (56.5%).²⁴ Disputes between the ABO blood group distributions, which may be in association with various regions and different ethnicities. One of the most often used genetic aberrations is the Ph chromosome,

which may designate a poor prognosis.²⁵ In this study, 98% and 97% of the patients with ALL were negatives for P190 and P210, respectively. These outcomes give a positive hope to the treatment strategy and a good prognosis. Similarly, Li et al. found that most ALL patients were negative for Ph chromosome mutation (82.32%).² Several studies on pediatric patients with ALL generally obtained a positive Ph chromosome ratio of <10%, with the ratio mostly being ~5%.² The T-cell ALL usually demonstrates a worse prognosis than B-cell ALL.²⁶ The current study revealed that 92% of patients were diagnosed with B-cell ALL, which is in agreement with Li et al. who found that 77.78% of ALL were B-cell type.² Consequently, ALL subtypes are not significantly correlated to ages, gender, and BMI, which means these values do not affect the incidence of ALL subtypes. However, the ALL subtype was significantly associated with ABO blood type as most B-cell ALL patients had blood type A⁺ (32.6%), and no one had B⁻ (0.0%). Most patients with T-cell ALL had A⁺ (37.5%), while no one had AB⁻, O⁺, O⁻ or A⁻ (0.0%). Despite these variations among blood groups and incidence of ALL subtype, children with A⁺ (33%) are more vulnerable to getting ALL and AB⁻/O⁻ had the least chance (1.0%). Most B-cell patients were detected in Spring (41.3%), while most T-cell patients were found in Summer (37.5%). However, the seasonal distribution had no significant effect on the incidence of pediatric ALL and its subtypes. In this regard, Li et al. found the peak incidence of pediatric ALL in Winter and Spring (25.39%).² Moreover, the Hb and PLT with BM blasts% are not significantly correlated with ALL subtypes. Whereas WBC levels were significantly correlated with the ALL subtypes, indicated by a 2-fold higher level of WBC count in T-cell ALL than in B-cell type. Generally, higher WBC is seen in children than adults, and an almost 10-fold





higher median WBC is seen in patients with T-cell than B-cell ALL. Patients with favorable cytogenetics typically have lower WBC, whereas the poorer prognosis patients present with higher WBC.²⁷

Conclusions

Pediatric ALL was predominantly detected in our locality among children aged <6.0 years, especially B-subtype that was not related to age, gender, BMI and season of diagnosis; however, directly correlated to the blood group. Additionally, pediatric ALL did not result from BCR-ABL gene mutation in most patients, which facilitates the treatment modes.

Conflict of interest

The authors declare no conflict of interest in this study.

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