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Pattern, clinical and laboratory features from of adult acute lymphoblastic leukemia patients from Kurdistan-Iraq

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Abstract

Background and objectives: Acute lymphoblastic leukemia is a heterogeneous group of neoplasm resulting from clonal proliferation and tissue infiltration by leukemic lymphoblasts. Adult acute lymphoblastic leukemia is characterized by distinctive clinical and genetic features in comparison to childhood leukemia. This study aimed to outline the clinco-hematological features of adult Iraqi patients newly diagnosed with acute lymphoblastic leukemia in Kurdistan-Iraq. **Methods:** This study was conducted at Hiwa Cancer Hospital in Sulaimani City and Nanakali Hospital in Erbil City, Kurdistan, Iraq. A total of 109 patients of newly diagnosed acute lymphoblastic leukemia aged >15 years were included. Clinical history, physical examination, complete blood counts, with peripheral smear, bone marrow aspiration and immunophenotypic data (using flow cytometry) and genetic study were collected for all the enrolled cases. **Results:** The median age at diagnosis was 24 years with male to female ratio of 1.7:1. B- lineage was predominant at (76.1%), while T -lineage was less frequent, at 23.9%. Mean hemoglobin level was 9.1 g/dl (±2.3) with a range of (4-15.2) g/dl, white blood cells count had a range of (0.4-300) $\times 10^9$/L, with a mean of 47.5 $\times$109/L (±62.5). The mean platelet count was 79×10^9/L (±83), and a range of (3-490) $\times 10^9$/L. Fifty eight patients (53.2%) presented with lymphadenopathy, and seventy eight patients (71.6%) had organomegaly. Philadelphia chromosome was detected in 9.5% of cases. Fifty seven (52.3%) patients stra tified into high risk group **Conclusions:** Patients from our locality have some distinct disease characters from that were reported elsewhere.

Key words: Acute lymphoblastic leukemia, Adults; Clinical, Hematological.

Introduction

Acute lymphoblastic leukemia (ALL) is a malignancy of B or T lymphocytes in the bone marrow, blood and extramedullary sites. While ALL is primarily a disease of childhood, 75% occurring in children, it's the second most common acute leukemia of adulthood and represents a devastating disease when it occurs in adults[1]. Epidemiologically, it was estimated that approximately 6000 new cases of ALL are diagnosed annually in the United State, with about 80-85% being of B-lineage[2]. Acute lymphoblastic leukemia is characterized by variable clinical, hematological, immunophenotypic and genetic features that have a great impact on diagnosis and response to treatment[3]. Clinical manifestations of the disease reflect marrow involvement by lymphoblasts, in addition to extramedullary infiltration including; anemia, thrombocytopenia, neutropenia, fever, and organomegaly[4]. Over the last decades, leukemia used to be diagnosed on the basis of cytomorphology, while helpful, its accuracy was about 80% and large numbers of patients were misdiagnosed and subjected to inadequate treatment due to the overlap of morphological characteristics between myeloid and lymphoid cells[5]. Recently, flow cytometry (FC) have played a vital role, not only in the diagnosis of acute leukemia, but in identifying blast lineage for assessing disease prognosis and the detection of response to treatment through sensitive analysis of minimal residual disease (MRD). The prognostic factors for newly diagnosed patients with ALL can be broadly divided into those found at diagnosis and those which only become apparent on time of complete remission. Furthermore, it should be borne in mind that any prognostic factor may be affected or superseded by the intensity of therapy given

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to the patients[7]. In this cohort study, we aimed to evaluate the clinical and hematological features at diagnosis among adult ALL patients and to compare with other study at presentation as the scenario differs profoundly from pediatrics age group.

Materials and Methods

This is a prospective cohort study of 109 unselected adult Iraqi patients (aged 15- 72 years) diagnosed as ALL in the period between March 2012 to August 2017. Patients were enrolled from two different settings: Hiwa Cancer Hospital in Sulaimani city and Nanakali Hospital in Erbil city, Kurdistan, Iraq. The cases excluded were; Burkitt leukemia or chronic myeloid leukemia (CML) with lymphoid blast crisis.

Patients were stratified into the high clinical risk group, according to the definition of the MRC UKALL XII/ECOG E2993 trial, if they met one or more of the following criteria: 1) age ≥35 years, 2) white blood cell (WBC) count at diagnosis ≥30×10^6/L (for B lineage) and ≥100×10^6/L (for T lineage), 3) Philadelphia positive ALL.

In all cases, the diagnostic work–up comprised a combination of cytomorphology and immunophenotyping using flow cytometry [BD FACS Calibur flow cytometer (BD Biosciences, San Jose, CA, USA)] performed on peripheral blood and/or bone marrow aspiration, in addition to imaging techniques. Detailed clinical history, physical examination, and complete blood counts along with peripheral smear, and bone marrow aspiration data, were collected for all the enrolled cases. In addition, 96 patients (75 B-ALL and 21 T-ALL cases) were screened for Philadelphia chromosome positive (Ph+) ALL using RT-PCR. The work was approved by the ethics committee of Kurdistan Board of Medical Specialization (KBMs). Data documented and analyzed using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 25. Descriptive statistics presented as median, mean (± standard deviation) and frequencies as percentages. Chi-square test used for categorical variables. In all statistical analysis, level of significance (p value) set at < 0.05.

Results

The distribution of 109 adults ALL patients among different age categories is shown in, Figure 1. The majority of ALL cases were aggregated in <30 year age groups [72 patients (66.1%) of the whole cohort]. The incidence, then, progressively declined with less than 5% of ALL cases were in the 59+ year age. The median age was 24 years (range of 16-72 years), and male to female ratio is 1.7:1, Table 1.

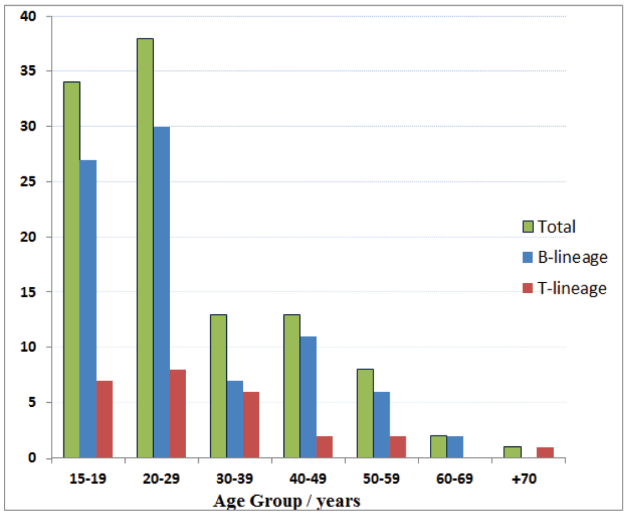

Figure (1): Age distribution of adult ALL cases as total and according to lineage.

Table (1): tients.

Characteristics		No.	%
Age / yrs.	Median=24 (15-72)		
Gender	Male	69	63.3
	Female	40	36.7
Hb Level	Mean=9.1±2.6(4-15.2)		
g/dl	< 10	81	74.3
	≥ 10	28	25.7
WBC $\times10^9$ /l	Mean=47.5±69.2(0.4-300)		
	< 50	78	71.6
	≥ 50	31	28.4
PLT $\times10^9$ /l	Mean=79±83(3-490)		
	< 50	55	50.5
	≥ 50	54	49.5
Immunophenotype	B Type	83	76.1
	T Type	26	23.9
Risk Stratification	High	57	52.3
	Standard	52	47.7
Lymphadenopathy	Yes	58	53.2
	No	51	46.8
Organomegaly	Yes	78	71.6
	No	31	28.4
Mediastinal widening	Yes	6	5.5
	No	103	94.5

Immunophenotyping using flow cytometry analysis revealed a predominance of B-ALL in the whole cohort (76.1%), while T-ALL was less frequent, at 23.9%, Table 1. Common B-ALL was the most frequent immunophenotypic subtype among B-ALL, at 77.1%, while pro-B subtype was the least frequent, at 4.8%. Among T-ALL cases, cortical T-ALL was the most frequently encountered subtype, at 34.6%, while the least was the medullary, at 15.4 %, Table 2. The distribution of B- and T-ALL among age groups is shown in, Figure 1. The cases of T-ALL have shown clustering in 15-19, 20-29 and 30-39 age groups, with a clear decline in the older age groups. Regarding B-ALL, majority of cases were in the 15-19, and 20-29 age groups, and it was least frequent in the 4th decade of life, with tendency to increase thereafter.

Mean hemoglobin (Hb) level in adult ALL patients was 9.1 g/dl (±2.6) with a range of (4-15.2) g/dl, Table 1, white blood cells count had a range of (0.4-300) $\times 10^9$/L, with a mean of 47.5 $\times 10^9$/L (±69.2). The mean platelet count was 79×10^9/L (±83), and a range of (3-490) $\times 10^9$/L. Cases of B-ALL had significantly lower mean Hb, mean WBC count and mean platelet count compared to T-ALL cases (Hb level 8.5 g/dl (±2.4)versus 10.9 g/dl (±2.3), WBC count 38.6×10^9/L(±57.3) versus $76.1(\pm 93.7)\times 10^9$/L and platelet count 74×10^9/L(±75) versus 95×10^9/L(±102); $p< 0.001$, $p< 0.001$ and $p= 0.014$, respectively).

Finally, a significant higher proportion of cases with Hb value <10 were observed in B-ALL compared to T-ALL (83.1% versus 46.2%; $p< 0.001$), Table 3. No significant difference in percentage of cases with WBC > 100×10^9/L or platelets count < 50×10^9/L found between B-ALL and T-ALL; $p= 0.144$ and $p= 0.341$, respectively, Table 3.

Table (2): ge subtypes among 109 ALL cases.

Subtype	No.	%
B-ALL	83	76.1
Common B-ALL	64	77.1
Pre B-ALL	15	18.1
Pro B-ALL	4	4.8
T-ALL	26	23.9
Cortical T-ALL	9	34.6
Pre T-ALL	7	26.9
Pro- T-ALL	6	23.1
Medullary T-ALL	4	15.4

Table (3): linical parameters, molecular features and risk status between B-ALL and T-ALL cases.

Characteristics		B-lineage (n=83) No.	%	T-lineage (n=26) No.	%	*P Value*
Hb Level	Mean ±SD (range)	8.5±2.4(4-15.2)		10.9±2.3 (6.5-15)		<0.001
g/dl	< 10	69	83.1	12	46.2	<0.001
	≥ 10	14	16.9	14	53.8	
WBC $\times 10^9$ /l	Mean ±SD (range)	38.6±57.3(0.4-300)		76.1±93.7 (3.1-300)		<0.001
	< 50	62	66	16	61.5	0.144
	≥ 100	10	10.6	6	38.5	
PLT $\times 10^9$ /l	Mean ±SD (range)	74±75 (3-357)		95±102 (8-409)		0.014
	< 50	44	53.0	11	42.3	0.341
	≥ 50	39	47.0	15	57.7	
Philadelphia chromosome	Positive	9	12.2	0	0.0	0.08
	Negative	66	87.3	21	100	
Risk Stratification	High	44	35.0	13	50.0	0.788
	Standard	39	47.0	13	50.0	
Lymphadenopathy	Yes	40	48.2	18	69.2	0.061
	No	43	51.8	8	30.8	
Organomegaly	Yes	59	71.1	19	73.1	0.844
	No	24	28.9	7	26.9	
Mediastinal widening	Yes	0	0.0	6	23.1	<0.001
	No	83	100.0	20	76.9	

In this study, fifty eight patients (53.2%) presented with lymphadenopathy (LAP) at time of diagnosis, and seventy eight patients (71.6%) had organomegaly, with no significant difference in frequency among B-ALL and T-ALL; p= 0.061 and 0.844 respectively, Table 1 and Table 3. Interestingly, six patients had mediastinal widening (5.5%), all were T-ALL (p- 0.0001), Table 3. Of the ALL patients, 96 patients were screened for BCR/ABL rearrangement using RT-PCR (75 patients with B-ALL and 21 patients with T-ALL). The molecular analysis revealed that 9 patients (9.4%) were positive for this rearrangement; all cases were of B-ALL type. Fifty seven patients (52.3%) were stratified into high risk (HR) group, Table 1; including 44(77.2%) B-ALL cases [9 patients had Philadelphia chromosome positive, 22 were > 35 year age, and 4 patients had WBC count > 50x109/l and 9 had WBC count > 100 x10^9/l]. On the other hand, 13 cases (50%) of T-ALL were assigned to HR group [7 patients aged > 35, and 6 patients had WBC count > 100 x10^9/l]. No significant difference in the percentage of cases in each risk group in B-ALL and T-ALL found; p= 0.79, Table 3.

Discussion

Acute lymphoblastic leukemia is a heterogeneous disease affecting children and adults at variable incidences. The National Cancer Institute, surveillance, Epidemiology and End Results (US-SEER) data revealed that 60.3% of ALL cases are diagnosed in patients below the age of twenty years; 10.3% between the ages of 20 and 34, 5.9% between 35-44 year old, and 6.7% between 44-54 years of age8. The median age of adult ALL patients in this study (24 years) approximates the median age figures reported worldwide (range from 25-34)9-13. It's worth mentioning that younger ages at diagnosis (<35 year) is probably the most important prognostic factor according to previous reaches as the overall survival decreases considerably with increasing age .While long term outcomes of ALL have improved significantly in younger age groups, elderly patients still have an inferior outcome[11, 14]. In this study, male predominance (M: F ratio= 1.7/1) reported was consistent with previous figures too [6,13,15,16].

Our figures for the proportion of B-ALL at 77.1% and T-ALL at 23.9% are consistent with most studies worldwide of these two immunophenotypic subtypes reported elsewhere at 67.2%-90% and 31.5%-80.4%, respectively[6,17-19].

Generally, the clinical and hematological features in our patients are similar to those reported from previous studies[3, 11, 12, 20-22]. However, mediastinal masses were less frequently encountered than previous studies ranging from (8.3%-41%)[20, 21, 22], but comparable to a report by Hamid TA, et al11, at 5.2%. The variation is most likely attributed to the higher frequency of T-ALL in the above studies.

The incidence of BCR/ABL rearrangement reported (9.4%) was lower than data from previous studies (15-48%)[10,11,13,22]. It has been reported that there is a geographical heterogeneity in the frequency of t (9; 22) in ALL, and it is lower in developing countries for unknown reason22. In addition, it has been shown by previous reports that the incidence of BCR/ABL1 in ALL increases with age, such that the less than 5% BCR/ABL1 ALL in children less than 10 years to 10- 20% in young adults and reaches as high as 50% in adults older than 60 years with B-ALL[23].

This study has stratified 52.3% of the adult ALL patients enrolled into HR category, a figure which is much lower than reported figures from some previous reports, at 76%10, 62.8%11, 70%[24]. This is probably attributed to the higher proportion of young adults in this study and the lesser frequency of Philadelphia positive ALL in comparison to previous works.

Conclusions

Acute lymphoblastic leukemia in adult Iraqi patients is characterized by some distinct clinical and molecular characters from ALL patients in other parts of the world. However, larger prospective studies including a wider age range study samples are recommended to allow a better distinction of the clinical and biological features of ALL among various age groups.

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