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Characteristics and Event Free Survival in Pediatric Patients with Acute Lymphoblastic Leukemia in Sulaymaniyah, Kurdistan Region of Iraq

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ABSTRACT

Background: Cancer is the leading cause of mortality in pediatric, despite that it is still highly curable and in the last years there was significant increase in event free survival among pediatric cancer not just because of the improvement of chemotherapeutic protocol but rather because of improvement in supportive care. Acute Lymphoblastic Leukemia is the most common pediatric malignancy and it is different from adult ALL by better overall prognosis and it is seem to be a highly curable disease when compared with other solid tumors in pediatric.

Objective: To obtain local data of some demographic features, immunophenotypic pattern and risk category of children and adolescent with ALL and the correlation of each of this characteristic with the 3-year event free survival and to compare our result with local or international data.

Patients and Methods: A cross-sectional study conducted on 257 pediatric patients with ALL over a period of six year in Sulaymaniyah Governorate-Kurdistan region of Iraq from January 2007 to January 2013 were carried out to analyze the some demographic features, immunophenotype and the 3-year EFS. Data analyzed using SPSS software; version 13 and P-value obtained by Chi-square test.

Results: The mean age at diagnosis was 6.9±2.9 years and peak age group in our study was between 1–4 years with male predominance. Precursor B-cell was more common than T-cell. 3-year EFS was (71.98%) with significant correlation between gender and 3-year EFS; but no statistical correlation between the 3-year EFS in one hand and the age group, risk group and immunophenotype of ALL in other hand.

Conclusion: The ALL patterns and characteristic together with the 3-year EFS of our studied pediatric patients were similar to that observed in the regional and international study.

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Abbreviation

ALL: Acute Lymphoblastic Leukemia
SPSS: Statistical package for the social sciences
EFS: Event Free Survival
AML: Acute Myeloid Leukemia
BCR-ABL: Abelson (Abl) tyrosine kinase gene-break point cluster
MRD: Minimal Residual Disease
WBC: White Blood Cell
mm3: cubic millimeter
UKALL: United Kingdom Acute lymphoblastic Leukemia

Introduction

Among the different forms of cancer affecting children, the most commonly occurring is acute lymphoblastic leukemia (ALL). Fortunately, this illness is also one of the better understood and effective treatments are now available, tailored to different risk groups and enhanced by upgrades in supportive care [1-5].

In the more developed, high-income countries, survival rates have gone up to almost 90%, while in less prosperous countries, 30% of children are lost to the disease [6]. The main treatment for children with acute lymphocytic (lymphoblastic) leukemia (ALL) is

chemotherapy, which is usually given in 3 main phases: Induction; Consolidation (also called intensification); and Maintenance. The entire length of treatment is typically about 2 to 3 years, with the most intense treatment in the first few months.

With the current rate of approximately 80% of children being cured [7]. The improvements made have been mainly due to the development of intensive multiagent chemotherapy, identification of clinical and biologic variables predictive for outcome and their use in stratifying treatment, significant advances in supportive care, and development of large-scale, highly disciplined multi-institutional national and international clinical trials [8].

However, the international literature lists few studies from countries such as Iraq, where pediatric patient families and oncologists must navigate less favorable social and economic conditions. Our study aims to obtain local data of some demographic features, immunophenotypic pattern and risk category of children and adolescent with ALL and the correlation of each of this characteristic with the 3-year event free survival and to compare our result with local or international data. In order to realize our success in treatment of our patients with ALL and to discovering any possible limitations, finally trying to solve these limitations to improve our outcome.

Patients and Methods

A cross-sectional study of 257 pediatric patients with acute lymphoblastic Leukemia (ALL) who were diagnosed and treated in the pediatric department of Hiwa hematology center, Sulaymaniyah province of Iraq, over a period of six years from January 2007 to January 2013 was carried out to analyze the demographic features, risk category and the 3 years event free survival.

Diagnosis of ALL was based on morphological detection and immunohistochemistry staining confirmation of more than 20% Lymphoblast in the bone marrow aspirate sample. Inclusion criteria included all pediatric patients between the ages of 1-18 who were diagnosed morphologically as precursor B or T ALL by bone marrow aspirate sample, both gender with full recorded data. Exclusion criteria included all patients with other acute leukemia as mature B cell leukemia and acute myeloid Leukemia (AML), above the ages of 18 years, Infantile ALL, patients who were treated initially in other hematological center and those who were lost to follow up.

Limitations included molecular studies and cytogenetic studies, namely BCR-ABL and the unavailability of minimal residual disease (MRD) in our country at that time. The patients then categorized according to the UKALL 2003 version 7 into three risk groups; Group A (standard risk) were those patients with age between 1-10 years and initial WBC (White Blood Cell) count of less than 50.000 per mm3, group B (intermediate risk)were those patients with age more than 10 years and/or initial WBC (White Blood Cell) count of more than 50.000 per mm3, and group C (high risk) patients included all patients with slow early responders which defined as day 8 (regimen B) or 15 (regimen A) with bone marrow blasts percent more than 25% . Then all patients were treated according to the UKALL protocol 2003 version 7 and those who finished the chemotherapy followed carefully for the event free survival [9]. The study was approved by the study was approved by the Review Ethical Committee of Hiwa Hospital. Data were entered into Excel sheet and then transferred to SPSS-Descriptive analysis; Data analyzed using Statistical package for social sciences (SPSS) software; version 13. Means (standard deviations) or range and medians were used as appropriate. Pearson correlations were used evaluate correlation between continuous variables, while Mann–Whitney U test and Kruskal Wallis test were used as non-parametric tests to determine associations, as appropriate. P-value obtained by Chi-square test, P value less than 0.05 considered as significant statistically.

Results

Among 257 pediatric patients with ALL enrolled in this study, 163 (63.24%) patients were male and 94 (36.57%0) were female with male: female ratio of 1.73:1. Gender distribution showed in figure 1.

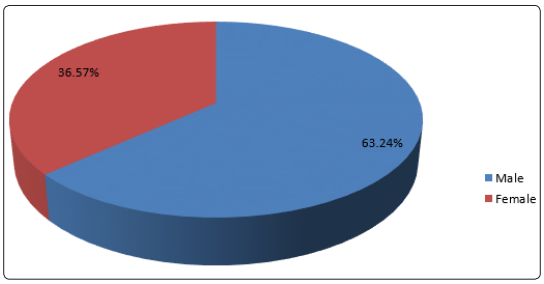

Figure 1: Gender distribution

A mean age at diagnosis was 6.9±2.9 years (range interval between 1.5–18 years). The peak age group in our study was between 1-4 years. Table 1 shows the number and percentage of the cases in relation to the age.

Table 1: Age distribution

Age	Frequency	%
1-4	101	29.3
5-8	59	23
9-12	48	19.1
13-18	49	18.7

Regarding the Immunophenotyping characteristic of our patients (according to the immunohistochemistry staining), 201 (78.21%) of the patients were precursor B-cell and 56 (21.79%) were of T-cell immunophenotype. The immunophenotype of ALL in our patients was showed in figure 2.

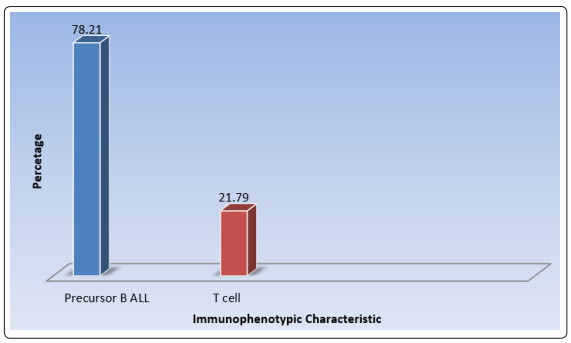

Figure 2: The immunophenotype of ALL

Our study showed that the majority of our patient fall in the low risk group (group A) which was occurred in 178 (69.26%) patients, followed by intermediate risk group (group B) in 55 (21.4%), and high risk (group C) in 24 (9.34%) of the patients as showed in figure 3.

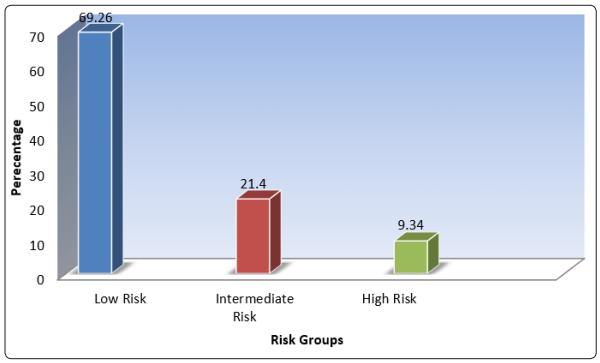

Figure 3: Risk Group Distribution

The study was showed that 185 (71.98%) of the patients had 3-year EFS as showed in figure 4.

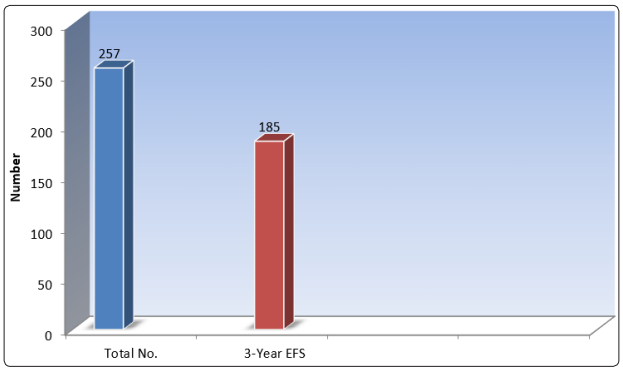

Figure 4: Three-years EFS

There was significant statistical relation between 3-year EFS and gender with a female patients showed better 3-year EFS (75.53%) than male (69.94), (Chi-square test P- value = 0.00313016). Table 2 shows the 3-year EFS in relation to gender.

Table 2: The 3-year EFS in relation to gender (P-value= 0.00313016)

3-year Event Free Survival (EFS)		
Gender	**3-year EFS Number/Total**	**Percentage (%)**
Male	114/163	69.94
Female	71/94	75.53
Total	185/257	71.98

The current study showed the 3-year EFS was decrease with age from 76.24% in (1-4 years) age group to 60% in (13-18 year) as shown in table 3, but this correlation was not statistically significant with P-value of 0.94576181.

Table 3: Age group to 3-year EFS correlation, P-value 0.94576181

Age groups/year	3-year Event Free Survival (EFS)	
	3-year EFS Number/Total	**Percentage (%)**
1-4	77/101	76.24
5-8	43/59	72.88
9-12	33/48	68.75
13-18	32/49	60
Total	185/257	71.98

The 3-year EFS were higher in precursor B-cell ALL with (74.13%) than the T-cell ALL with (64.29%) 3-year EFS, but this correlation was statically not significant with p-value of 0.55185751. The correlation between immunophenotype of ALL and 3-year EFS was shown in table 4.

Table 4: Immunophenotype of ALL to 3-year EFS, P-value=0.55185751

Immunophenotyping	3-year Event Free Survival (EFS)	
	3-year EFS Number/Total	**Percentage (%)**
Precursor B-cell	149/201	74.13
T-Cell	36/56	64.29
Total	185/257	71.98

The low risk group (group A) had better 3-year EFS (76.4%) than the intermediate risk group (65.45%) which in turn showed better 3-year EFS then the high risk group which was with (54.17%)3-year EFS. This statistical insignificant (P-value=0.56073884) showed in table 5.

Table 5: Risk group to 3-year EFS, P Value 0.56073884

Risk Group	3-year Event Free Survival (EFS)	
	3-year EFS Number/Total	**Percentage (%)**
Low (group A)	136/178	76.4
Intermediate (B)	36/55	65.45
High (group C)	13/24	54.17
Total	185/257	71.98

Discussion

Pediatric and adolescent cancer continues to be the leading cause of death in children up to the age of 18 years old, acute Leukemia's are the most common pediatric malignancy which compromised approximately one third of pediatric cancer. Acute Lymphoblastic Leukemia (ALL) is the most common type of acute leukemia in children which representing 75% of acute leukemia in pediatric. Acute Lymphoblastic Leukemia still important cause of mortality and morbidity among pediatric patients with cancer.

In this retrospective study conducted over a period of 6 years on 257 pediatric patients with acute lymphoblastic leukemia (ALL) in Sulaimaniya province of Kurdistan/ Iraq, we tried to study some demographic features of pediatric and adolescent ALL in addition to find any significant correlation between these demographic features of the patients, Immunophenotyping of ALL, and risk groups on one hand with the 3 years event free survival on the other hand.

This study showed male predominance with male: female ratio of 1.73:1. Male predominance was mentioned in an epidemiological study done on pediatric patients with acute lymphoblastic Leukemia less than 15 years of age registered from April 1999 to December 2004 at oncology unit of National Institute of Child Health and Children Cancer Hospital, Karachi Pakistan, which showed male: female ratio of 1.7:1 [10].

We found that the mean age at the time of diagnosis of ALL patients is 6.9±2.9 years (with range interval between 1.5–18 years) which is similar to the result of a cross-sectional study at the Pediatric Hematology Department of Dr. Sami Ulus Obstetrics

and Gynecology, Children's Health and Disease Training and Research Hospital between the years 2000 and 2009 on a total of 85 patients with ALL, this study showed that the mean age at diagnosis of the patients was 6.6±3.7 years (1.5–14 years) [11].

The most prevalent age group was between 1–4 years which occurred in 101 (29%) of the patients, the peak age group was similar to the most prevalent age group in a retrospective observational study using data from patients aged 1–17 who were newly diagnosed with ALL and admitted at the Oncology Department of the Sf. Maria Clinical Emergency Hospital for Children Iasi between January 2010 and December 2016, which also showed a peak age group 1–4 years in (44.8%) [12].

The most common immunophenotype of ALL in the studied patients (according to the immunohistochemistry staining) was precursor B-cell which happened in 201 (78.21%) of the patients followed by the T-cell immunophenotype in 56 (21.79%) patients. This result was similar to the immunophenotypic distribution of ALL according to central immunophenotyping study in Japan, which showed 85–90% cases of pediatric ALL belong to B-cell lineage and 10–15% belongs to T-cell lineage [13].

The vast majority of our patient fall in the low risk group (group A) which was occurred in 178 (69.26%) patients, followed by intermediate risk group (group B) in 55 (21.4%), and high risk (group C) in 24 (9.34%) of the patients which was similar to the result in UKALL2003 version 7 [9].

3 years EFS in this study occurred in 185 (71.98%) patients which is little bit less than the long-term survival result of more than 80% of pediatric patients with acute lymphoblastic leukemia (ALL) report from the children's oncology group, this less EFS in our study may related in a part to the lack of the molecular and cytogenetic risk stratification in our study because of the unavailability which in turn might result in treating some patients with missed high risk cytogenetic feature as a low risk group [14].

There was significant statistical relation between 3-year EFS and gender with a female patients showed better 3-year EFS (75.53%) than male (69.94), (P- value = 0.00313016). this less 3-year EFS in male gender may related in apart to testicular relapsed in male which considers as sanctuary site for chemotherapy due to the blood testicular barrier.

The 3-year EFS in our study was decrease with age from 76.24% in (1-4 years) age group to 60% in (13-18 year), but this correlation was not statistically significant with P-value of less than 0.05 (=0.94576181). Also this result was similar to the Outcomes in Pediatric Acute Lymphoblastic Leukemia-A Single-Center Romanian Experience (12) that showed higher EFS rates at 90-month follow-up were observed in patients aged between 1 and 4 years (83.24%).

Precursor B-cell ALL with showed a higher 3-year EFS (74.13%) than the T-cell ALL (64.29%), our result was similar the result of A Single-Center Romanian Experience with 3-year EFS rates for precursor B-cell better than T-cell ALL (78.9% and 64.9%, respectively) [12].

The 3-year EFS were more in low risk group (group A) (76.4%) when compared with the intermediate risk group (65.45%) and the high risk group which was with (54.17%) 3-year EFS. But it was statistical insignificant (P-value=0.56073884) possible do to the fact that more aggressive chemotherapies were given to higher risk group in our protocol treatment.

Conclusion

In conclusion, the patterns and characteristics together with the 3-year EFS of our studied pediatric patients with ALL were similar to that observed in the regional and international study. Male predominancy was observed in this study with male had less 3-year EFS than female. There was some clinical but no statistical correlation between the 3-year EFS in one hand and the age group, risk group and immunophenotype of ALL in other hand.

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