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Original Article

Paediatrics Section

Epidemiological, Clinical and Paraclinical Characteristics of Childhood Acute Lymphoblastic Leukaemia in Sana'a, Yemen

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ABSTRACT

Introduction: Acute leukaemia is one of the most common types of cancers among children. There is only restricted number of studies about childhood leukaemia in Yemen, hence the importance of performing this study.

Aim: To assess the epidemiological, clinical and para-clinical characteristics of childhood acute lymphoblastic leukaemia in Sana'a, Yemen.

Materials and Methods: This was a descriptive retrospective study. It included 177 children younger than 15 years with Acute Lymphoblastic Leukaemia (ALL), who were diagnosed in the period from May to September 2011 to 2017 in the Childhood Leukemia Management Center (CLMC) in Sana'a, Yemen. The diagnosis was based on clinical characteristics, bone marrow morphology and immunophenotyping. The data was analysed using SPSS program. Chi-square test with Yate correction and Fisher tests were used to identify the significance of associations.

Results: Majority of patients 129 (72.8%) were between 1-9 years and male to female ratio was 1.53 to 1. The most common presenting features were fever (89.3%), pallor (89.3%) and bone pain (71.3%). Immunophenotyping was done for 126 patients; 99 (78.6%) had precursor B-cell and 27 (21.4%) had T-cell ALL. Ninety two (52.6%) of patients were classified as standard risk and 83 (47.4%) were high risk; most of them were T-cell ALL. Response to chemotherapy in induction phase was excellent with complete remission rate of 94.2%. Relapse was 16.5%; 62.9% of them were medullary relapses. Mortality during induction was 15.6%. Infection was the most common cause of death (37.8%), followed by haemorrhage (11.1%).

Conclusion: ALL is considered a significant health problem in Yemen. It needs high awareness and more attention from the governorate regarding improving the capacities of health facilities on health information, diagnosis and treatment.

Keywords: Immunophenotyping, Mortality, Prognosis

INTRODUCTION

According to the International Agency for Research on Cancer (IARC) in 2018, there were 18.1 million new cases and 9.6 million deaths from cancer; about one-half of the cases and over one-half of the cancer deaths in the world were in Asia [1]. Leukaemias were among the most common malignancies in children throughout the world; Acute Lymphoblastic Leukaemia, (ALL), accounts for about 30% of all cases of cancers in children [2].

Results from Brazil, Egypt, Middle East, Pakistan and Jordan found that the age group between 1-9 years was the most affected [3-7]. Male patients were more predominant than female [3,4,6,8]. Fever, pallor and anaemia were the most common presenting complains in many studies [5,6,9]. By immunophenotyping, precursor-B ALL constituted the majority of ALL (above 84%) while T-cell ALL represented only less than 16%, this was obvious in Middle East, Jordan, United States and Pakistan [5,7-9]. In the contrary, T-cell ALL was more predominant (26.6%) in one study in Egypt [4].

Based on National Cancer Institute (NCI), classification of risk groups, high risk patients were ranged from 30.4% in Middle East [5] to 46.0% in Brazil [3] and 58.4% in Egypt [4]. Remission rate was more than 90% in many studies [3-5,9]. The relapse was above 20% in Pakistan [9] while in other studies in Brazil [3] and Egypt [4], it was 16% and 17.5%, respectively. The most common site of relapse was medullary in some studies [4,7,9]. The most common causes of patients mortality from ALL were infections followed by haemorrhage and time of death was mainly during induction phase of treatment [9].

Unfortunately, published studies in Yemen about clinical, pathological features and outcome of acute lymphoblastic leukaemia in children are scanty.

In a study in Hadhramout, incidence of cancer among children was estimated to be 1.9 per 100,000; leukaemia accounted for 23% of cases [10]. Another study conducted in Aden reported 483 cases of cancer among children <15 years age comprising 12.7% of all registered patients. The most frequent cancer among children was leukaemia (33.1%) [11].

This study was undertaken to assess the epidemiological, clinical and para-clinical characteristics of childhood acute lymphoblastic leukaemia in Sana'a, Yemen.

MATERIALS AND METHODS

This study was retrospective, carried out in Childhood Leukemia Management Center (CLMC) in Sana'a Yemen which is considered a referral center from many areas in Northern part of Yemen. The study was performed during the period from May 2011 to September 2017. The data was collected from the medical records of 177 children, under 15 years with newly-diagnosed Acute lymphoblastic leukaemia. Cases of non-ALL leukaemia were excluded. Moreover, age ≥15 years was excluded. The study proposal was approved by the ethical committee of CLMC.

A pre-designed questionnaire composed of 32 questions was used to collect the epidemiological characteristics as age, sex, residence and clinical characteristics including presenting symptoms and signs, para-clinical characteristics like haemoglobin count, White

Blood Cell count (WBC), bone marrow and immunophenotyping and prognostic risk assessment and outcome.

The children were diagnosed by bone marrow morphology and flow cytometry. Leukaemia was suspected when the bone marrow contained more than 5% blasts (usually replaced by 80-100% blasts) and CNS leukaemia required presence of blast cells by cytocentrifuge examination [12]. National Cancer Institute (NCI) defined patients between 1-10 years old and their initial WBC <50,000/μL as a standard risk and those younger than 1 or older than 10 years of age or having an initial leukocyte count of >50,000/μL are considered as a high risk [13]. Complete remission was defined as no clinical or para-clinical evidence of the disease, normal blood count, with minimal level of 500/mm^3 granulocytes, 75000/mm^3 platelets and 12 g/dL haemoglobin with no blasts cells seen on the blood smear and less than 5% blast cells in bone marrow examination [12].

STATISTICAL ANALYSIS

Data were collected, entered, reviewed and analysed using SPSS package version 23 and the results were presented using suitable tables. Frequency (%) was used to describe the qualitative variables. Mean and standard deviation were used to describe the quantitative variables as the data is normally distributed. Chi-square, Chi-square with Yate correction and Fisher tests were used to show the significance of association between the outcome and its risk factors at level of significance 0.05.

RESULTS

During the study period, total of 218 children were diagnosed as acute leukaemia. Among them 177 (81.2%) were ALL.

The majority of patients were between 1-9 years, 129 (72.8%) and the mean age was 6.6 (SD±3.6) years. There were 107 (60.5%) male and 70 (39.5%) female with male to female ratio of 1.53 to 1. Immunophenotyping was done for 126 patients and illustrated that 99 (78.6%) had precursor-B ALL and 27 (21.4%) had T-cell ALL [Table/Fig-1].

Variable	Overall (n=177)		Precursor-B (n=99)		T-cell (n=27)		p-value
	freq.	%	freq.	%	freq.	%	
Age at diagnosis							
<1 yrs.	3	1.7	2	100.0	0	0.0	0.128
1-9 yrs.	129	72.8	73	83.0	15	17.0	
10-15 yrs.	45	25.4	24	66.7	12	33.3	
Sex							
Male	107	60.5	56	75.7	18	24.3	0.345
Female	70	39.5	43	82.7	9	17.3	
Residence							
Sana'a city	34	19.2	21	87.5	3	12.5	0.235
Sana'a	23	13	13	86.7	2	13.3	
Amran	14	7.9	6	60.0	4	40.0	
Dhamar	20	11.3	13	76.5	4	23.5	
Ibb	24	13.6	14	66.7	7	33.3	
Taiz	16	9	8	66.7	4	33.3	
Hodeidah	17	9.6	9	100.0	0	0.0	
Others	29	16.5	15	83.3	3	16.7	
Total	177	100	99	78.6	27	21.4	

[Table/Fig-1]: General characteristic of the patients.

The most common presenting features were fever (89.3%), pallor (89.3%) and bone pain (71.3%). Seizure was present in 7.3% and testicular swelling in 1.7% patients only. Moreover, majority of the patients had WBC less than 50000 cell/μL, 116 (70.3%), while those with WBC more or equal to 50000 cell/μL comprised about (29.7%) 49 patients. The majority of T-cell ALL (72%) had WBC ≥50000 cell/μL while only (23.4%) of precursor-B ALL had WBC ≥50000 cell/μL and this association was statistically significant. Central Nervous System (CNS) involvement by CSF cytology was present in 2.8% [Table/Fig-2].

Variable	Overall (n=177)		Precursor-B (n=99)		T-cell (n=27)		p-value
	freq.	%	freq.	%	freq.	%	
Clinical feature							
Fever	158	89.3	88	88.9	21	77.8	0.238
Bone pain*	107	71.3	61	70.1	14	63.6	0.743
Bleeding	79	44.6	45	45.5	12	44.4	0.926
Hepatomegaly	82	46.3	44	44.4	15	55.6	0.305
Splenomegaly	94	53.1	53	53.5	18	66.7	0.223
Lymphadenopathy	88	49.7	46	46.5	18	66.7	0.063
Gingival hypertrophy	5	2.8	2	2.0	0	0.0	1.000
Orbital swelling	2	1.1	1	1.0	0	0.0	1.000
Seizure	13	7.3	8	8.1	2	7.4	1.000
Testicular swelling	3	1.7	3	3.0	0	0.0	0.839
SC nodule	1	0.6	0	0.0	1	3.7	0.484
Pallor or anaemia	158	89.3	87	87.9	22	81.5	0.586
WBC (cell/μL)°							
<50000	116	70.3	72	76.6	7	28.0	<0.001
≥50000	49	29.7	22	23.4	18	72.0	
CNS involvement							
Yes	5	2.8	3	3.0	1	3.7	1.000
No	172	97.2	96	97.0	26	96.3	
Total	177	100	99	78.6	27	21.4	

[Table/Fig-2]: Clinical and para-clinical features of the patients.
*This is calculated only for children >3 years
°some data were missing

[Table/Fig-3] shows that ninety six (54.2%) of patients were stratified as standard risk and eighty one (45.8%) were high risk, according to NCI/Rome criteria. High risk patients constituted 88.9% of T-cell ALL and only 40.4% of precursor-B ALL and this difference was statistically significant (p-value <0.001). By day 28 of treatment, 162/172 (94.2%) were in complete remission. Among those patients, induction remission was achieved in 94 of the 98 patients (95.9%) of precursor B-ALL compared with 24 of the 27 (88.9%) of with T-cell ALL. Relapse was seen in 16.5% of all patients. Of these relapses, 62.9% were medullary, 25.9% extramedullary and 11.1% combined relapse. Extramedullary relapse mostly affect the CNS (80%) then testicular relapse (20%).

[Table/Fig-4] shows the mortality among enrolled patients were 25.4%. No significant difference between T-cell and precursor-B in mortality among ALL patients was detected. The most common cause of death was infection (37.8%). Majority of patients died during consolidation or maintenance phases (66.7%) followed by induction phase (15.6%).

DISCUSSION

This cross-sectional study was performed on 177 children diagnosed as ALL in a referral center in Sana'a, Yemen. More males were diagnosed than females, this is consistent with other studies performed in Brazil, Egypt, Middle East, Jordan, United States, Pakistan and Turkey [3-5,7-9,14], as well as in Yemen [10,11,15]. In this study, the majority of patients were in the age group less than nine years, this is consistent with many other studies in Brazil, Egypt, Middle East and Pakistan [3-5,9], as well as in Yemen [10,11]. In this study, children older than nine years accounted only for 25.4% and this was consistent with other studies which was performed in Brazil, Egypt, Pakistan and two different areas in Yemen that

Variable	Overall (n=177)		Precursor-B (n=99)		T-cell (n=27)		p-value
	freq.	%	freq.	%	freq.	%	
Patient risk							
Standard risk	96	54.2	59	59.6	3	11.1	<0.001
High risk	81	45.8	40	40.4	24	88.9	
Remission after induction*°							
Yes	162	94.2	94	95.9	24	88.9	0.350
No	10	5.8	4	4.1	3	11.1	
Relapse*°							
Yes	27	16.5	11	11.8	4	16.0	0.578
No	137	83.5	82	88.2	21	84.0	
Relapse							
Medullary	17	10.4	7	7.5	1	4.0	0.169
Extramedullary	7	4.3	2	2.2	3	12.0	
Combined	3	1.8	2	2.2	0	0.0	
No relapse	137	83.5	82	88.2	21	84.0	
Extramedullary relapses site							
CNS	8	80	2	50.0	3	100.0	0.549
Testicular	2	20	2	50.0	0	0.0	
Total	177	100	99	78.6	27	21.4	

[Table/Fig-3]: Prognosis of patients with ALL.
*There were 4 patients who died before starting treatment (before induction)
°The other date were missing

Variable	Overall (n=177)		Precursor-B (n=99)		T-cell (n=27)		p-value
	freq.	%	freq.	%	freq.	%	
Mortality							
Yes	45	25.4	21	21.2	8	29.6	0.857
No	132	74.6	78	78.8	19	70.4	
Cause of death							
Infection	17	37.8	12	57.1	1	12.5	0.119
Haemorrhage	5	11.1	3	14.3	2	25.0	
Haemorrhage and infection	4	8.9	0	0.0	1	12.5	
Unknown	11	24.4	3	14.3	2	25.0	
Others*	8	17.8	3	14.3	2	25.0	
Time of death							
Before starting treatment	4	8.9	1	4.8	0	0.0	0.401
During induction	7	15.6	4	19.0	2	25.0	
During consolidation or maintenance	30	66.7	16	76.2	5	62.5	
After finishing treatment	4	8.9	0	0.0	1	12.5	
Total	177	100	99	78.6	27	21.4	

[Table/Fig-4]: Mortality of patients with ALL.
*include CNS infiltration, acute fulminant hepatitis, chemotherapy related complications and acute renal failure

show a frequency of around 22-29% in this age group [3,4,9-11]. In contrast, one study in the Middle East showed the frequency to be slightly lower, (18.4%), among this age group [5].

Fever, pallor/anaemia, hepatomegaly, splenomegaly and lymphadenopathy were the most frequent presenting clinical features in this study. This coincides with other studies in the Middle East [5] and Brazil [3]. In a study from South-Central Asia, fatigue, fever, bleeding, chest pain, and splenomegaly were often seen in children with leukaemia [16].

CNS involvement was seen only in 2.8% of patients in this study which coincides with one study from Turkey [14] but lower than other studies in Brazil and Egypt [3,4]. This may be because the studies used less sensitive methods for detection of CNS involvement. High WBC at diagnosis (more than or equal to 50000) was present in 29.7% of patients which is consistent with a study from Pakistan (30%) [6], but lower than another study from Egypt, (39.6%) [4] and higher than other studies from Brazil, Middle East and Turkey in a frequency of (21-24.6%) [3,5,14]. The majority of T-cell ALL patients (72%), had high WBC (more than or equal to 50000) while only 23.4% of precursor-B ALL patients had high WBC. This was consistent with other studies which estimated that patients with T-cell ALL have higher initial WBC than patients with precursor-B ALL [3,4,8].

In this study, T-cell ALL represented a slightly higher percentage, this coincides with a study from Egypt [4]. This may be due to environmental factors or socioeconomic status. In contrast to other studies which showed less frequency of T-cell subtype (≤16%) [5,7-9,14]. T-cell ALL was associated with poor prognostic factors as male, over nine-year-old and increased WBC (more than or equal to 50000) at diagnosis. This coincides with one study in Brazil [3].

A 45.8% of patients in this study were in the high risk group according to NCI/Rome risk classification. Of those patients, 88.9% of T-cell subtype and 40.4% of precursor-B ALL were classified as a significant high risk group. This is consistent with 2 other studies from Brazil [3] and Egypt [4] where high risk group classification was seen in more than 87% of T-cell ALL, while in between 40-47% of precursor B-cell ALL patients were classified as high risk group. This is may be due to more prevalence of T-cell ALL among older age groups and patients with hyperleukocytosis.

At the end of induction phase of treatment, 94.2% of patients achieved complete remission in this study. This is in agreement with studies from Brazil, Middle East and Pakistan and Turkey that showed a complete remission rate of 92-97% [3-5,9,14]. This reflects using effective treatment protocols.

Relapse was documented in 16.5% of patients which is consistent studies from Egypt, Unites States and Turkey in which the relapse was in the range of 15 to 20% of ALL patients [4,8,14] while in contrast to one study in Jordan in which the relapse rate was only 9% [7]. The most common relapse site was medullary (62.9%), followed by CNS relapse (29.6%) and combined relapse (11.1%). This is similar to studies from Egypt [4] and Turkey [14] in which medullary relapse was detected in (59.3%, 71.4%), CNS relapse in (29.6%, 17.8%) and combined relapse in (11.1%, 3.6%), respectively. The most common cause of death was infection (37.8%). This is consistent with other studies in Pakistan and Turkey [9,14].

Limitation(s)

Small sample size and incomplete data in some files represent major study limitations.

CONCLUSION(S)

ALL is considered a significant health problem in Yemen. It needs high awareness about the disease and more attention from the governorate regarding improving the capacities of health facilities on health information, diagnosis and treatment. Using more sensitive methods for relapse detection should be used. Close observation and follow-up of patients during initiation of treatment could reduce mortality in this critical period. More sensitive methods should be used for relapse detection. Larger multicenter studies are needed for more conclusive results.

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