Induction outcomes of acute non-burkitt lymphoblastic leukaemia: a data from the Child's Central Teaching Hospital in Baghdad 2011-2015

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ABSTRACT

INTRODUCTION: Advances in the study and treatment of paediatric acute lymphoblastic laeukemia are often cited as the paradigm of success in modern clinical trial and translational-research based medicine.

OBJECTIVE: To study the outcomes of induction phase in the treatment of acute lymphoblastic leukaemia in the Haematology-oncology ward of Central Child Teaching Hospital.

METHODS: A retrospective study was conducted on the records of children diagnosed as ALL and recieved induction phase at the Chik's Central Traeching Hospital in Baghdad from 2011-2015.

359 patients below the age of 15 years were included.

RESULTS: Age varied from two months to 14.4 years with a mean age of 5.1±3.2 years. Induction remission in 276 (87.9%), deaths in 35 (11.1%), loss to follow up in 3 (1.0%) patients. Presumptive infection was 1st cause of death in 23 (8.2%) followed by bleeding in 4 (1.3%) of patients.

CONCLUSION: ALL is still a common malignancy in children. Mostly they are of L2 type with standard risk. After induction the majority will pass into remission which is improving in Iraq comparing to the previous published studies. However, mortality is relatively high compared to that in developed countries and infection is the major cause of death.

Key words: Acute lymphoblastic leukemia, Induction mortality, Infection.

INTRODUCTION

Acute leukaemia, the most common form of cancer in children, comprises approximately 30% of all childhood malignancies.[1] Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children. It accounts for one-fourth of all childhood cancers and 72% of all cases of childhood leukaemia.[2] The peak incidence of ALL occurs between 2 to 5 years of age. The incidence of ALL is higher among boys than girls, and this difference is greatest among pubertal children.[3] Due to improvement of treatment of ALL, survival rates have improved dramatically since the 1980s, with a current five-year survival rate of approximately 78%.[1]

The are many classifications of ALL based on morphologic, immunologic, cytogenetic, and molecular genetic characterizations of leukaemic lymphoblast confirming the biologic heterogeneity of this disease.[4] The widely used morphological classification is the French-American-British (FAB) Cooperative Working Group classification which classy ALL into L1, L2, and L3.[5,6] Others are based on Monoclonal antibodies directed against human leukaemia-associated antigens, DNA content by flow cytometry, and genetic translocation. These different classifications aid setting of the diagnosis, treatment and prognosis of ALL.[7-11]

The typical symptoms and clinical findings are manifestations of the underlying anaemia, thrombocytopenia, and neutropenia, which in turn reflect the failure of normal haematopoie-

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sis.[12] Pallor, fatigue, bone pain, petechiae, purpura, bleeding, and fever are commonly present. Lymphadenopathy, hepatomegaly, and splenomegaly are frequent manifestations of extra-medullary leukaemic spread.[13] In ALL, anaemia exists in approximately 80% of patients on diagnosis. One half of patients has leukocytosis and in 20 % it exceeds 50,000/ mm^3.[14] Neutropenia of < 500 granulocytes/ mm^3 is a common phenomenon and is associated with an increased risk of serious infection.[15] Thrombocytopenia occurs in most patients; approximately 75% have < 100,000 platelets/ mm^3.[16] Definitive diagnosis depends on finding of the specific leukaemic cells in a slide of bone marrow aspirate stained with Romanovsky dye and by the use of special histochemical stains.[17]

CNS leukaemia is found at diagnosis of fewer than 5% of children with ALL.[18] With the institution of CNS preventive therapy, routine lumbar puncture (LP) with intra-thecal therapy has become an integral part of ALL treatment protocols.[19] Clinically demonstrable testicular disease is rarely present at initial diagnosis; however, occult testicular disease can be diagnosed by biopsy in 25% of newly diagnosed boys.[20]

TREATMENT: It includes induction, consolidation and maintenance phases. In addition to therapy directed to the CNS. Most of the treatment protocols take two to three years to complete, although the specific regimen varies depending upon immune-phenotype and risk category. [21]

Induction Therapy: The aim of induction is to induce remission which means that the patients have no evidence of leukaemia in the bone marrow and peripheral blood, and absence of detectable CNS or extra-medullary disease.[22,23] Remission after induction in children with ALL has improved remarkably over recent years with a success rate of 95 %.[12]

Infection is the major cause of treatment-related mortality during the induction phase, so prophylactic antibiotics should be considered in high-risk patient groups and during periods of increased risk.[24] After complete remission has been achieved, subsequent therapy is required. Post induction therapy usually consists of consolidation and continuation phases.[25]

Optimal management of the child with ALL requires good supportive care including the rational use of blood component therapy, detection and treatment of infections, attention to the metabolic and nutritional needs, and psychosocial support for patient and family.[26]

In Iraq, years earlier a study was conducted to measure the induction outcome at the Child's Central Teaching Hospital where most of the patients were using pre-phase steroid; a step that has been excluded from treatment protocol thereafter. So, this study is designed to measure the outcomes of induction phase in the treatment of acute lymphoblastic leukaemia in the Heamatology-oncology ward of Central Child Teaching Hospital from 2011-2015.

METHODS

Settings and study design: A retrospective descriptive study was conducted at Haematology-Oncology Department at the Child's Central Teaching Hospital during 2016 based on the record of patients with ALL who were admitted during the period between 1st of January 2011 to 31st of December 2015.

Ethical consideration: The protocol of this study was approved by the research committees at the Iraqi Board for medical specialization and at Al-Karkh Health Directorate. Agreement of the hospital administration was also taken to get the data form the records of the patients. Data were kept confidential and only used for the purpose of this study in accordance to the regulations of ministry of Health in Iraq.

Definition of the participants and exclusion criteria: During the studied period, 359 patients below the age of 15 years were included; all were newly diagnosed patients as acute lymphoblastic leukaemia at the Hematology-Oncology unit of the Child's Central Teaching Hospital.

For those patients, data were taken from the medical recording systems (files) that kept in the oncology ward and the medical notebook of each patient that contains all detailed information about inpatients admissions and outpatient's visits. These data included patients' age and gender, residence, duration of onset before referral, date of diagnosis, place

of treatment, and results of biochemical profile, chest X-ray, complete blood count, bone marrow aspiration and cerebrospinal fluid (CSF) examination, and Immune phenotype for some of the patients. Details of induction phase of treatment, progress of the disease during induction, outcome at day 35 from starting chemotherapy, time of death and its presumptive cause were also retrieved.

The final analysis was done on 314 patients after exclusion of 45 patients due to the following reasons: 9 patients with ALL L3 due to their need for different treatment protocol, 5 patients who died before the start of induction therapy, 26 patients because their parents did not accept to start therapy, and 5 patients who have started their treatment outside Iraq and visiting our centre just for follow-up.

In all patients the diagnosis of ALL was established by experienced laboratory haematologists who examined a bone marrow aspirate taken under general anaesthesia. Acute leukeamia was confirmed when the bone marrow slides contained at least 25% lymphoblasts.[12] Morphological classification of the blast cells was done in most patients according to FAB system. Diagnosis of T-cell leukaemia was based on certain clinical and / or laboratory criteria; age >10 years, male gender, mediastinal mass, high initial WBC count, and nuclear clefting of blast cells by microscopical examination. Immunophenotyping examination were done for some of those patients, while cytogenetic study was not done because it was not available in our centre during the studied period.

According to the treatment protocol received, patients were divided into 2 main groups. ***Group I***: those treated with modified MRC UKALL 2003 protocol. ***Group II***: treated with Non-Hodgkin's Lymphoma/ Berlin-Frankfort-Munster (NHL/BFM-95) Protocol for T- Cell leukemia. At relevant time, parents or legal guardians are ask to give their written informed consent before starting the treatment.

According to the cell type of acute leukaemia (precursor B or T), we classify patients into risk groups for treatment protocol. ***Standard risk (group A)*** for patients with precursor B-cell ALL whose age are between 1-9 years and initial WBC count < $50x10^9$/l. ***Intermediate risk (group B)*** includes patients with precursor B-cell but their age and initial WBC counts fall outside the range identified in group A. Both A and B groups are treated by MRC UKALL 2003 protocol.[27] while ***high risk (group C)*** includes patients with clinical and morphological suspicion or proved immunophenotypically as T- cell ALL and treated by NHL/BFM-95 protocol.[28]

After starting induction with MRC-UKALL 2003 protocol, we assess BM response at day 28 or 35 by routine light microscope and categorize the response as:[23] M1 marrow < 5% blasts, M2 marrow 5-25% blasts, and M3 marrow >25% blasts. CNS involvement was diagnosed by the consensus criteria as follows:[58] CNS-1: where no evidence of leukaemic lymphoblasts in the CSF. CNS-2: < 5 WBCs/μl with definable blasts on cytocentrifuge examination, or traumatic LP.[29] CNS-3: ≥ 5 WBCs/μl with blast cells or cranial nerve palsy.

Outcome of Induction: The outcome of induction is assessed at day 28 or 35 from the start of treatment.[30] The outcome could be:

Complete remission (CR): Patient's peripheral blood values must be within the normal range, and the bone marrow must be of normal cellularity, with fewer than 5% lymphoblasts.[23] Those who failed to attain CR after 35 days of induction therapy were regarded as no remission. If BM is diluted at day 28 but fulfilling the criteria of remission at day 35 or 42, it is considered as remission.

Induction death: Induction death was defined as death within 35 days from starting chemotherapy.[23]

Loss of follow up: It is considered when the family decided to stop treatment and get their child out of the hospital on their responsibility. All patients were received supportive therapy like blood and/or their products, antibiotics, and antifungal treatment according to clinical condition.

Statistical analysis: Statistical package for social sciences version 20 (SPSS 20) was used for data analysis. Kaplan Meier cohort analysis was used to test the significance of studied factor upon survival.

RESULTS

This study enrolled 314 patients as Acute

Table 1 | Demographic distribution of study sample

Variable	N = 314	%
Sex		
Male	175	55.7
Female	139	44.3
Age Group		
< 1 year	10	3.2
1-9 years	265	84.4
10-14 years	39	12.4
Year of Diagnosis		
2011	38	12.1
2012	50	15.9
2013	96	30.6
2014	67	21.3
2015	63	20.1
Province		
Baghdad	114	36.3
Other provinces	200	63.7

Table 2 | Clinical characteristics of studied sample

Variable	N=314	%
Duration of Symptoms		
< 6 weeks	257	81.8
6 weeks - 6 months	55	17.5
> 6 months	2	0.6
Subtype		
L1	138	43.9
L2	147	46.8
T-cell leukaemia	21	6.7
Undifferentiated	8	2.5
Treatment Protocol		
Standard Risk *	201	64.0
Intermediate Risk **	92	29.3
T-cell ALL protocol	21	6.7
Clinical Features		
Pallor	302	96.2
Fever	287	91.4
Splenomegaly	225	71.9
Hepatomegaly	206	65.8
Bleeding	115	36.6
Lymphadenopathy	108	34.5
Mediastinal Mass	25	8.0

* One patient out of 201 (0.5%) did not respond to standard Risk Protocol and then changed to High Risk Protocol at day 15.

** Two patients out of 92 (2.2%) did not respond to Intermediate Risk Protocol and then changed to High Risk Protocol at day 8.

non-burkitt Lymphoblastic Leukaemia patients who received treatment during 2011-2015. The annual rate of new cases diagnosed and treated in our centre is 62.8 case/ a year. Age varied from two months to 14.4 years with a mean age of 5.1± 3.2 years. Males are commonly affected than females 175 (55.7), for other demographic features see **table 1**.

Table 2 shows the presenting features of the sample. Of them, 201 patients (64.0%) were of standard risk and 92 (29.3 %) were of intermediate risk. Pallor was the commonest presenting symptoms 302 (96.2 %) and splenomegaly is the commonest signs reported in 225 patients (71.9 %).

Table 3 shows the haematologic, serum uric acid and CNS status of the sample.

After induction of therapy 276 (87.9 %) achieved remission, and 35 patients (11.1 %) died. In 23 patients (65.7 %), infections were the cause of death, **see table 4**. **Figure 1** shows the Kaplan Meier curve of survival.

DISCUSSION

Acute lymphoblastic leukaemia is the most common childhood cancer. It constitutes approximately 25% of cancers in children. We found that the children between 1-9 years were mostly affected; 265 patients (84.4 %), while those below age of one year was the least affected; 10 patients (3.2 %). This was nearly compatible to the results of Abdullah[31] in his study conducted in our centre on children diagnosed with ALL from 2009-2011 and Ghali[32] in a study conducted at Children Welfare Teaching Hospital Al-Rasafa in Baghdad from 2000 to 2009. Also, it is nearly similar to the results of many other studies from China,[33] India,[34] and Jordan.[35]

Male to female ratio in our study was 1.25: 1. A result which is similar to that from other national and nearby countries; Abdullah find it 1.34:1,[31] Ghali HH 1.2:1,[32] and Halalsheh in Jordan1.3:1.[35] Studies from China[33] and India[34] though have shown a male predominance but their ratios were relatively higher; 1.63:1 and 2.1:1 respectively. This may be attributed to some genetic or enviromental causes.

We reported that the number of ALL diagnosed and started treatament have increased progressively. the highest number was diagnosed in 2013, 96 patients (30.6%), which is nearly double compared to the result in the

Table 3 | Laboratory findings of studied sample

Variable	N=314	%
Initial Hb level		
< 6 g/dl	68	21.7
6-10 g/dl	209	66.5
> 10 g/dl	37	11.8
Not Recorded	1	0.3
Initial WBC Level (10^9/L)		
< 10	126	40.3
10-49	122	39.0
≥ 50	65	20.8
Platelets (10^9/L)		
< 20	86	27.4
20-100	178	56.7
> 100	50	15.9
Serum uric acid level		
Normal (< 420 µmol/l)	276	87.9
Elevated (≥ 420 µmol/l)	34	10.8
Not Recorded	4	1.3
Initial CSF cells		
CNS1	294	93.6
CNS2	13	4.1
CNS3	4	1.3
Not Recorded	3	1.0

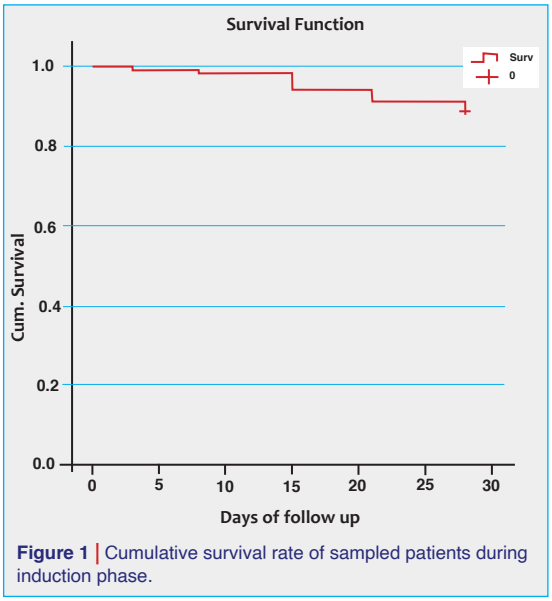

Figure 1 | Cumulative survival rate of sampled patients during induction phase.

2012, 50 (15.9 %). This was because in 2013 the Children Welfare Teaching Hospital, the hospital which has the catchment area from Al-Rasafa in Baghdad, has been closed for reconstruction leaving our centre as the only centre in Baghdad to receive children with haematologic malignancies. Baghdad was the most frequent province of residence of patients in our study 114 (36.3%), other patients were mostly from the nearby provinces like Babil, Anbar, Najaf, Diwania, Karbala, and Muthana which they did not have pediatric haematology centers at the time of the study.

Table 4 | Induction outcome and causes of morality during induction phase

Variable	N=314	%
Induction Outcome		
Remission	276	87.9
Loss to follow up	3	1.0
Died	35	11.1
Cause of Death		
Infection	23	65.7
Infection & bleeding	4	11.4
Bleeding	4	11.4
Tumour lysis syndrome	2	5.7
Thrombo-embolic Stroke	2	5.7
Alive	279	88.9

Most of the patients, 257 (81.8%), in our series had their symptoms for less than 6 weeks before diagnosis and it was very rare to see a delay for more than 6 months, only in 2 patients (0.6 %). This is similar to the data reported by Abdullah[31] and Ghali.[32] The acuteness of alarming symptoms of ALL, in addition to the rapid response of the family and the primary care physicians and the availability of basic investigations could explain this result.

The commonest symptoms at presentation were pallor 302 (96.2), followed by fever 287 (91.4%) compareable to those reported by Abdullah[31] (pallor 96.2%, fever 86.6%). We reported that splenomegaly was the commonest sign elicited in those patients 225 (71.9%) followed by hepatomegaly seen in 206 patients (65.8 %). Abdullah[31] nearly reported similar figures. However, Ghali[32] has reported less fever and more common hepatomegaly than splenomegaly in his study. Advani from India agrees with Ghali's result regarding hepatomegaly.[33]

Regarding the laboratory investigations, on presentation most of the patients, 277 (88.2%), were having a hemoglobin level of less than 10 g/dl. And in 209 patients (66.5%) the hemoglobin level was between 6-10 g/dl. Nearly same percentage was reported by Abdullah.[31] Ghali has reported anemia in only 51.5%.[32]

WBC count over 50 x10^9/l is a marker of a high-risk group of patients. In 248 patients

(79 %), the initial WBC count was less than 50 x10^9/L, and only 65 patients (20.3 %) have their count over 50 x10^9/l. Most other national and international studies were reported a higher rate of WBC count of more than 50 x10^9/l; in Iraq, it ranged between 24.6 %[31] and 26.4 %,[32] while it was less than a third of patients in the report of the Berlin-Frankfurt-Munster group[36] and 28.8 % in a study from Pakistan.[37]

In our study, primary CNS involvement (CNS-3) was seen only in 4 patients (1.3%) which is slightly less comparing with previous Iraqi studies where it was 2.5 % [31] and 3.6%,[32] and with a study from western countries where it was 2.4 %.[36] We found that CNS-2 grade in 13 patients (4.1%) which is also lower than that reported by Abdullah 7.1%,[31] and Fadoo 5.8%.[37]

The commonest subtype of ALL in our series was L2 reported in 147 patients (46.8 %). Abdulla and Ghali have also reported that L2 is the commonest ALL subtype though of more percentages 68.6 and 73.8 % respectively.[31, 32]

The outcome of induction phase reveals that we achieved remission in 276 patients (87.9%), while unfortunately death was reported in 35 patients (11.1%), and we lost follow up of 3 patients (1.0%) which is far away from the Western studies like Schrappe et al,[36] in a study conducted in three European countries Germany, Austria, and Switzerland, has reported a much better outcome than ours where remission achieved in more than 97 % with only 1 % death and another 1% abandonment.

This study showed a better outcome of induction phase but higher mortality rate than that of Abdullah conducted in our centre years ago:[31] 85% achieved complete remission, 5.7% death and 6.4% loss to follow up. the higher rate of loss of followup in Abdullah's study might be the cause for lower mortality despite higher remission rate. Ghali's has reported 15.6 % mortality rate in his study,[32] which is higher than ours.

The commonest presumptive cause of death was infection 23 (65.7 %) followed by bleeding in 4 patients (11.4 %) and other 4 patients (11.4 %) died because of infection and bleeding.

Compared to Schrappe et al,[36] who claims achiving remission in 97 %, we are still behide. Attention for applying infection control policies, raising the infrastructures of the hospital to improve hygiene, proper use of antiobiotics, and good education of families about the seriousness of infections and how to pretect the child during induction phase from them are very important factors that we should work on in order to improve our rate of remission and to safe our children this draedful fate.

CONCLUSION

ALL is still a common malignancy in children. Mostly they are of L2 type with standard risk. The commonest presentation were anaemia and fever. More than two thirds of the patients have hepatosplenomegaly. CNS involvement is not common. After induction the majority will pass into remission which is improving in Iraq comparing to the previous published studies. However, mortality is relatively high compared to that in developed countries and infection is the major cause of death.

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Abbreviations list: Acute lymphoblastic leukaemia (**ALL**), Bone marrow (**BM**), Central Nervous system (**CNS**), Cerebrospinal fluid (**CSF**), Complete remission (**CR**), Cubic millimetre (**mm³**), Deoxyribonucleic acid (**DNA**), French-American-British (**FAB**), Lumbar puncture (**LP**), Medical Research Council United Kingdom Acute lymphoblastic leukaemia (**MRC UKALL**), Microliter (**µl**), Non-Hodgkin's Lymphoma/ Berlin-Frankfort-Munster group (**NHL/BFM**), Number (**N**), Statistical package for social sciences (**SPSS**), White blood cell (**WBC**).

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