Research Article

Induction outcome of Acute Lymphoblastic Leukemia at a single pediatric oncology centre of CCTH

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Abstract

Background: Acute lymphoblastic leukaemia (ALL), it's clonal proliferation and accumulation of lymphoblast in blood, bone marrow and other organs.
Objective: Evaluate of newly diagnosed ALL patients over three years, for their characters, risk groups and induction outcome
Patients and Method: A prospective study included, (240) children below the age of 15 years with newly diagnosed ALL-LI and ALL-L2 (Precursor B or T cell) type, were eligible for study, Demographic, clinical, and laboratory data of ALL patients at presentation and at the end of induction were reviewed.
Results: Of a total 240 ALL patients, only 221 of them participated in the study and underwent to the analysis. M:F ratio =1.3:1, (1-9.9) years, were more predominant age group. About two third of the patients were standard risk group. 91.4% of the patients with Precursor B cell ALL (PBC ALL). 4.8% of patients with initial CNS involvement, 85.5% (n 189/221) of patients completed induction therapy and reached 1st complete remission (CR1), while 11.3%(n 25/221), were died . The most common cause of induction death was infection (72%)
Conclusion: The early outcome for children with ALL at end of induction therapy was suboptimal, while slightly high percent of induction death with some patients abandoned treatment; only 85.5% survived the induction phase.

Key words: Acute Lymphoblastic Leukemia, Induction therapy, Outcome, Induction death.

INTRODUCTION

In general, leukemia is the most common childhood cancer, acute lymphoblastic leukemia (ALL), is most common type of leukemia in children. It constitutes approximately 25% of cancers in children below 15. [1,2,3] firstly the total WBC count at the time of diagnosis then age are the most significant prognostic variables of remission induction, remission duration, and long-term survival.[4] Impressive advances in the management of childhood acute ALL in recent decades have resulted in constantly increasing survival rates of children and adolescents with ALL.[5,6,7] With contemporary risk-adapted multiagent chemotherapy children with ALL have a chance of about 80% of long-term survival.[4, 5, 7, 8] All "ALL" regimens include certain treatment elements: remission induction, consolidation (intensification of remission), prevention of central nervous system leukemia and maintenance therapy. Remission induction rates with three or four drugs produce a 95% induction remission.[6, 9, 10]

Aim of study: Evaluate of newly diagnosed ALL patients over three years duration, for their characters, risk groups and induction outcome

PATIENTS AND METHODS

Patients: A prospective study was undertaken in oncology units of Child's Central Teaching Hospital (CCTH) at Baghdad over a period of three years from first of January 2013 to 30 first of December 2015. Of a total 665 children bellow the age of 15 years with newly diagnosed malignancy, (240) of them with ALL –LI and ALL-L2(Precursor B or T cell) type, were enrolled in study. The patients who were not enrolled

in study included (patients with ALL-L3, Acute Undifferentiated Leukemia "AUL", relapsed ALL patients, and all children ≥ 15 years old). The demographic, clinical, and laboratory data of the patients were collected at presentation and reviewed at the end of induction to document induction outcome and toxicity. All the patients stayed at the hospital during induction phase of therapy with daily follow up and we usually open a record's file for each newly diagnosed cancer patient to report these data. **Diagnosis:**. ALL was diagnosed when 25% lymphoblast or more were present in the bone marrow based mainly on standard morphological features of the leukemic cells, or based on flow cytometry of immunophenotyping on peripheral blood/bone marrow aspirate in some of cases, because it is not always available, Diagnosis of T- cell leukemia was depended on clinical suggestion when some of the following criteria exit (age >10 years, high initial WBC count, meditational widening, initial CNS involvement plus BM lymphoblast's morphology in all cases and confirmed by immunophenotyping studies of either peripheral blood or bone marrow in few cases because it is not always available. Detection of initial CNS involvement was based on the presence or absence of blasts on CSF cytospin analysis; patients with cranial nerve palsies or clinically or radiologically evident leukemic intracranial infiltration were also categorized as CNS involvement. **Treatment:** Age and WBC count, have been used to stratify patients at presentation into risk stratification, Standard risk "SR"(defined as WBC count less than 50×10^9/L and age (1 - 9.99 years) and High risk "HR"defined as WBC count 50×10^9/L or greater at any age or age 10 years or older with any WBC count at presentation, Children under 12 months of age were categorized as high risk and T cell-ALL always categorized as high risk , SR and HR ALL patients were treated with chemotherapy regimens modified from Medical Research Council protocol (United Kingdom Acute Lymphoblastic Leukemia- UKALL-protocol 2003), T-cell Leukemic Patients treated by (Berlin-Frankfürt-Münster 95/ T cell Non Hodgkin Lymphoma/T cell Leukemia protocol) "BFM 95/T-NHL/ T cell leukemia protocol". **Outcome Measures**: Remission status in patients who completed induction was determined by bone marrow (BM) evaluations at day 28 of induction and patients were considered to be in first complete remission (CR1) if(BM lymphoblasts were <5% on day 28 , Normal trilineage hematopoietic recovery and resolution of extra-medullary disease), Minimal residual disease testing was not performed because it's unavailable.

Induction failure: defined as patients had failure to achieve remission after 30 days of therapy when did not fulfill criteria of complete remission (CR).Of (240) ALL patients, 19 patients were excluded from the analysis of induction outcome because of following reasons that mention in table1, so

induction outcome was limited to(221) patients only.

Table 1: ALL patients before started treatment

Newly diagnosed ALL (L1 and L2)	Total NO.(%)
Before initial treatment	240
died before start treatment	4 (1.7)
abandoned before treatment	9(3.7%)
referred from another center	5(2.1 %)
referred to other center	1(0.4%)
Started induction therapy	221(92.1%)

RESULTS

Of (240) children diagnosed with ALL (L1&L2) over a period of 3 years, only 221 of those ALL patients participated in the study and underwent to the analysis. All participated patients were Iraqi children who referred from different parts of Iraq; most of them were from Baghdad (Table 2).There is no significant different between male and female, the mean age was (4.4) at presentation. About two third of the patients were standard risk group. (Table3). 91% of patients with PreB cell ALL with slightly higher percent of ALL-L1 than ALL-L2. The T cell ALL accounts 9% of all "ALL" cases. (Table4). Of 221 ALL patients, 189 of them did cytospin analysis, the remaining 32 patient didn't do it because traumatic sample or unavailability of cytospin, 4.8% (n=9) of ALL patients present with initial CNS involvement (table5). Of a total 221 ALL patients who received induction, 14.5% of them did not complete induction therapy, the remaining 85.5% of patients completed induction therapy and reached 1st complete remission (CR1) (Table 6)

The outcome of 221 ALL patients by day 30 of induction were 25 of them died by day 30, the induction death accounted (11%). The remaining 196 patients (89%) were alive by day 30 with either remission (n=189), abandonment (n= 4) or induction failure (n=3 patients) as show in table (6) and figure (1). The most common cause for death during induction phase of therapy was infection 20/25 (80%), the detail description of induction death show in (Table7). The remission status at day 28 had no so significant different in related to multiple variables like gender, age and risk groups with slightly higher rate of remission among Precursor B cell than T cell ALL. The limited number of other induction outcome

including poor response and Abandonment lead to statistically difficult to calculate the significant different in related to multiple variables.(Table8)

Table 2: Geographical distribution of 221 ALL patients.

Governorate	Number	Percent %
Baghdad	83	37.6
Babylon	37	16.7
Najaf	23	10.4
Diwaniya	22	10
Anbar	19	8.6
Karbala	18	8.3
Muthana	15	6.8
others	4	1.8

Table3: Demographic Characteristics of 221 ALL Patients at Presentation

Characters	Number	Percent %
Gender	221	
M	126	57%
F	95	43%
		M:F ratio =1.3:1
Age	221	Mean 4.4
<1 y	8	3.6
1-9.9 y	193	87.3
≥10 y	20	9.1
Risk group.	221	100
Standard Risk(WBC <50 × 10^9/L, age 1-9.99 years)	151	68.3
High Risk (WBC ≥50 × 10^9/L, Age<1, ≥ 10 years, T cell ALL)	70	31.7

Table4: Bone Marrow morphology and immunophinotype results of (221) ALL Patients at presentation.

Subtypes	No.		%	
Bone Marrow Morphology	221		100	
Precursor B-cell ALL-L1	103	Pre B cell	46.6	91.4
	99		44.8	
Precursor B-cell ALL-L2				
ALL-L1/L2 ?T-cell	19		8.6	
Flow Cytometry	21			
Precursor B cell ALL	12			
T-cell ALL	9			

Table5: CSF cytospin analysis of 189 ALL patients at presentation.

	Number	%
Cytospin analysis	189	100
normal	180	95.2
positive	8 (9)	4.8
Fascial pulsy with negative cytospin	1	

Table6: Outcome of induction therapy of 221 ALL patients.

Outcome of induction Phase	Number		%	
Induction death	25		11.3	
Abandonment during induction	4	32	1.8	14.5
Induction failure(PR/NR)	3		1.4	
Achieved CR1	189		85.5	
Total	221		100	

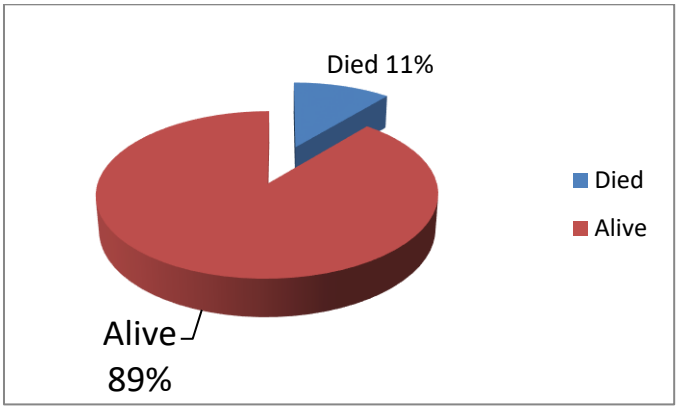

Figure 1: Induction mortality of ALL patients during (2013-2015)

Table7: describe induction death of 221 ALL patients.

		Death No./ total No.	%
Died on			
	1st week	5/25	20
	2nd week	5/25	20
	3rd week	6/25	24
	4th week	9/25	36
Age group	<1y	1/8	12.5
	1-9.99 y	20/193	10.4
	≥10 - <15y	4/20	20
Gender	M	14/126	11.1
	F	11/95	11.6
ALL- subtype	PBC(L1,L2)	22/202	11
	(L1/L2)T cell	3/19	15.9
Risk Group	SR	15/151	10
	HR	10/70	14.3
Cause of death	Infection	18/25	72
	Bleeding	4/25	16
	Both	2/25	8
	Others(tumor lysis syndrome)	1/25	4

Table8: Induction outcome of 196 ALL patients alive by day 30 in related to different variables

variables	CR1(189) NO/total NO (%)	NR(3) NO/total NO (%)	Abandonment(4) NO/total NO (%)
Age groups	189/221 (85.5)	3/221 (1.4)	4/221 (1.8)
<1 y	7/8 (87.5)	0/8	0/8
1-9.99 y	166/193 (86)	3/193 (1.5)	4/193 (2.1)
≥10-<15 y	16/20 (80)	0/20	0/20
Gender M	109/126 (86.5)	2/126 (1.6)	1/126 (0.8)
F	80/95 (84.2)	1/95 (1)	3/95 (3.2)
ALL- subtype			
PBC ALL	174/202 (86)	2/202 (1)	4/202 (2)
T cell ALL	15/19 (78.9)	1/19 (5.2)	0/19
Risk Group SR	130/151 (86)	2/151 (1.3)	4/151 (2.7)
HR	59/70 (84.3)	1/70 (1.4)	0/70

DISCUSSION

This prospective study evaluated pediatric ALL patients who were attending oncology unit of CCTH, M: F ratio was approximately equal (1.3:1) and this result was comparable to another Iraqi study at oncology unit of children welfare teaching hospital/Baghdad by *Ghali H.H*[11] *who reported M:F Ratio 1.2:1.* While other Asian countries,[12,13,14] have reported higher males proportion. It's difficult to estimate a real male preponderance because there are no population-based registries for gender distribution in Iraq. The predominant age group in this study and other studies reported by Fadoo. Z et al,[12] was 1-9.9 years. The median age of patients at diagnosis was 4.4 years (range 0.25-13.75 years), in Western countries study, the peak incidence is between 3–5 years [15] and Ghali H.H study,[11] the median age was 5.4 while it was lower than Fadoo, Z et al [12] and *Gao C* et al[16] that reported, the mean presenting age of the patients (6.87 years) And that different is probably due to each center has upper limit of age for children accepted, where the upper limit of age in our center and another Iraqi centers is <15 years, while in other comparable centers, the upper limit is 18 years. In this study, approximately two third (68.3%) of patients were standard risk and one third (31.7%) with high risk ALL and these findings nearly were consistent with those reported in Ghali H.H study [11] (62.2%) patients were standard risk and (37.7%) were high risk.

, and Fadoo, Z et al,[12] who reported that high risk ALL accounted for 35%. In this study, the majority of patients were Precursor B cell ALL subtype(91%) , presumptive T-cell morphology constituted (9%) , and it is approximately similar to slightly higher than that found by Ghali H.H,[11] while slightly lower than ALL in the developed countries[13 ,16, 17] *and* Gaynon PS et al,[18] *that* are seen predominant B cell Precursor ALL subtype type with the T subtype constituting between 10 -15%, Fadoo, Z et al,[12] study found that the proportion of B cell Precursor ALL was the predominant subtype (78.5%) while T-cell subtype was constituted 17.5%. In contrast, to other studies by *Magrath I.* et al[19] and *Siraj AK et al*[20] that has reported a higher proportion of the T-cell subset (20–50%), This slightly lower percent of T cell ALL in compared to other studies could be due to under estimation of T cell subtype due to unavailability of flow cytometry. 4.8% of ALL patients were CNS positive at presentation; this result approximately consists to result of Ghali H.H,[11] that found (3.8%) patients with CNS disease at presentation, Gaynon PS et al,[18]and Laningham FH et al,[21] showed that only 3% of ALL patients demonstrated overt CNS involvement at diagnosis. Fadoo, Z et al,[12] study reported 6.6% of ALL patients had CNS involvement at presentation, CNS2 5.8 and CNS3 0.8%, Induction Outcome of ALL patients over 3 years experience at our oncology center found that 85.5% of them completed induction therapy and achieved first complete remission (CR1). Precursor B cell ALL was slightly higher percent of remission status than T cell ALL, which is approximately consist with Ghali H.H study,[11] who reported(82.4%) of patients achieved

CR1 and higher than Rana ZA et al,[14] study that found only 74% of patients went into complete remission, While lower than Li CK et al[22], Schrappe M et al,[23]and Fadoo, Z et al,[12] studies that reported the induction remission rate were 95.3%, 95% and 92% respectively, with slightly higher among Pre B cell (92.4%) than T (88.2%) by Fadoo, Z et al study,[12] The rate of induction death was 11.3%, one third of them died at last week of induction, the gender was independent predictors of an enhanced risk for death but induction death was slightly higher among patients≥10 years, those with T cell subtype and to leaser extend high risk patients. Two third of ALL patient died during induction were due to infection, these result was comparable to that of Ghali H.H,[11] study, induction death rate was (13.7%), and the death was more among high risk ALL patients than standard risk, the infection as presumptive cause of death present in (50.5%) while bleeding in 17.2% of them and both infection and bleeding in 21.8% of them. Cohort study of Fadoo, Z et al,[12] found , 8.6% of the children died during the induction phase with slightly higher among T cell than Precursor B cell ALL (15.3% and 11.8%) and The majority (n = 49; 72%) died of infectious causes . Another study by *Asim M et al* [24] had reported 12.8% deaths in children with ALL during induction. Rana ZA et al *[14] study found that* Seven (18%) patient died due to febrile neutropenia and sepsis during the course of induction therapy. Our result are remarkably higher than that reported from developed countries by Harrison *CJ* et al,[25] where induction mortality rate is less than 2%, and Prucker C et al,[26] study that reported induction death 0.78% (n=7/896) with 57% (n=4/7) of them died during first two weeks of induction phase, and 57% (n=4/7) died due to infection, *The high number of ALL patients that incompatible to limited number of beds that lead to overcrowded of patients which could be contributed to increase risk of transmitted infection and increment in induction death especially when there is no isolated room in addition to that, poor laboratory facility with limited amount of many antibiotic and antifungal might be consider as another contributory cause for increase risk of induction death .The BMA result at day 28 of induction found that 1.4% of patient did not achieved remission, with more percent among T than PreB cell ALL (5.2% reverse 1%) but no different between standard and high risk patients, and this result approximately consist to that reported by Ghali H.H study[11] 1.9% of patient were no response(1.7% among standard risk patients and 2.3 among high risk),Suzuki N et al,[27] found that 2.2% of leukemic patents failed to achieve Complete Remission(CR), also* Schrappe M et al,[23] reported that 5% of ALL patient who do not achieve complete induction remission half(2.5%) of them suffer induction failure and another half(2.5%) due to induction mortality, while Fadoo, Z et al,*[12]* study found Day 28 Bone marrow,M2/M3 (>5% blasts) in (3.8%), Rana ZA et al [14]study found (5%) into partial remission (5-25% blast cells in bone marrow) and (3%) was not in remission (> 25% blast cells in the bone marrow), In this study (3.8%) n=9/240 abandoned before started induction therapy, and (1.8%) n= 4/221 abandoned after started induction therapy as a total 5.4% n=13/240 of patients abandonment of treatment. Fadoo, Z et al,[12] study reported that over 10% of patients, abandonment of treatment within the first month of therapy. The abandonment of treatment is of critical concern, the reasons for abandonment is not exactly detected but these are likely due to multiple possibility, we think the important reason is that residence of many patients is a hot area in Iraq because of the war, that make them face many difficulties in reaching for oncology center in Baghdad for treatment in addition to personal suggestion that malignancy is incurable disease and there is no benefit of treatment, and possible some of them could be travel outside the country for treatment .

Conclusion:

- The early outcome for children with ALL at end of induction therapy was suboptimal, while slightly high percent of induction death with some patients abandoned treatment; only 85.5% survived the induction phase.
- Infection was the most common cause of deaths observed in children with ALL during the induction.

Recommendation

- Outcome of patients with ALL is related not only to the leukemia itself, but also to infectious and toxic morbidities and mortality, so improvement of outcome and reduction of death rates may be by improved supportive and intensive care with effective control of infection as well as focusing on the causes and solutions for abandonment and late referral.
- It's important to focus on the causes of failed induction and try to identify the solutions for infection, abandonment and late referral.

REFERENCES

1. Gurney J.G, Bondy M.L . Epidemiology of childhood cancer. In: Pizzo PA, Poplack DG, Adamson PC, eds. Principles and Practice Of Pediatric Oncology. 6th edition. Philadelphia, Lippincott Williams and Wilkins; 2011; 1: 5-62.,
2. Kaatsch P, Sikora, E, Pawelec G . "Epidemiology of childhood cancer". Cancer treatment reviews June 2010; 36 (4): 277–85.
3. Pan IJ, Daniels JL, Zhu K. Poverty and childhood cancer incidence in the United States. Cancer Causes Control. 2010; 21:1139-1145.)
4. James A. W, Paul S.G . Acute Lymphoblastic Leukemia in Children. In: Greer JP, Foerster J, Rodgers GM, eds. Wintrobe's Clinical Hematology. 12th Edition. Philadelphia, Lippincott Williams and Wilkins; 2009; 80: 1892-1893.
5. Moricke A, Reiter A, Zimmermann M, Gadner H, Stanulla M, Dordelmann M *et al*. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood 2008; 111: 4477 4489.
6. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med 2006; 354: 166–178.
7. Pui CH, Sandlund JT, Pei D, Campana D, Rivera GK, Ribeiro RC *et al*. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood 2004; 104: 2690–2696.
8. Silverman LB, Declerck L, Gelber RD, Dalton VK, Asselin BL, Barr RD *et al*. Results of Dana-Farber Cancer Institute Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1981–1995). Leukemia 2000; 14: 2247–2256.
9. Redner A. Leukemias. In: Lanzkowsky P. Manual of Pediatric Hematology and Oncology.5th edition. Elisevier Inc; 2011; 17: 535-536.
10. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009;360:470–480.
11. *Ghali HH.* Effectiveness of Modified UKALL protocols in Children with Acute Lymphoblastic Leukemia; an experience of Children Welfare Teaching Hospital. Mustansiriya Medical Journal. December 2014; 13: 53-60.
12. Fadoo Z, Nisar I, Yousuf F, et al . Clinical features and induction outcome of childhood acute lymphoblastic leukemia in a lower/middle income population: A multi-institutional report from Pakistan. Pediatric Blood & Cancer. October 2015; 62: 1700–1708.
13. *Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer 2009; **46**:264–273.*
14. Rana ZA, Rabbani MW, Sheikh MA, et al. Outcome of childhood acute lymphoblastic leukaemia after induction therapy- 3 years experience at a single paediatric oncology centre.Pubmed 2009;21(4):150-153.
15. *Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the children's oncology group. J Clin Oncol 2011; **2037**:8018.*
16. *Gao C, Zhao XX, Li WJ, et al. Clinical features, early treatment responses, and outcomes of pediatric acute lymphoblastic leukemia in China with or without specific fusion transcripts: A single institutional study of 1,004 patients. Am J Hematol 2012; **87**:1022–1027.*
17. *Stiller C. Childhood cancer in Britain: Incidence, survival, mortality. Oxford, UK: Oxford University Press; 2007.*
18. *Gaynon PS, Angiolillo AL, Carroll WL, et al. Long-term results of children's cancer group studies for childhood acute lymphoblastic leukemia 1983-2002: a Children's Oncology Group Report.Leukemia.2010;24(2):285-97.*
19. *Magrath I, Shanta V, Advani S, et al. Treatment of acute lymphoblastic leukaemia in countries with limited resources; lessons from use of a single protocol in India over a twenty year peroid. Eur J Cancer 2005; **41**:1570–1583.*
20. *Siraj AK, Kamat S, Gutiérrez MI, et al. Frequencies of the major subgroups of precursor B-cell acute lymphoblastic leukemia in Indian children differ from the West. Leukemia 2003; **17**:1192–1193.*
21. Laningham FH, Kun LE, Reddick WE, Ogg RJ, Morris EB, Pui CH. Childhood central nervous leukemia: historical perspectives, current therapy, and acute neurological sequelae. Neuroradiology 2007;49:873–88.
22. Li CK , Chik KW, Ha SY et al. Improved outcome of acute lymphoblastic leukaemia treated by delayed intensification in Hong Kong children: HKALL97 study. Hong Kong Med J. 2006 Feb;12(1):33-9.
23. Schrappe M, Hunger SP, Pui CH, et al. Outcome after induction failure in childhood acute lymphoblastic leukemia.N Engl J Med. 2012;366(15):1371-81.
24. *Asim M, Zaidi A, Ghafoor T,et al. Death analysis of childhood acute lymphoblastic leukaemia; Experience at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan. J Pak Med Assoc 2011; **61**:666–670.*
25. *Harrison CJ, Moorman AV, Broadfield ZJ, et al. Three distinct subgroups of hypodiploidy in acute lymphoblastic leukaemia. Br J Haematol 2004; 125:552–559.*
26. Prucker C, Attarbaschi A , Peters C, et al. Induction death and treatment-related mortality in first remission of children with acute lymphoblastic leukemia: a population-based analysis of the Austrian Berlin-Frankfurt-Münster study group. *Leukemia* 2009; 23: 1264–1269.
27. Suzuki N, Yumura-Yagi K, Yoshida M, et al. Outcome of childhood acute lymphoblastic leukemia with induction failure treated by the Japan Association of Childhood Leukemia study(JACLS) ALL F-protocol. Pediatric Blood Cancer. 2010;54(1):71-8.