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Clinicolaboratory Characteristics and Outcome of Pediatric Acute Lymphoblastic Leukemia in a Resource-Limited Setting: A Study from South Egypt

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Abstract

Background: Remarkable progress has been made in the treatment of pediatric acute lymphoblastic leukemia (ALL), with survival rates reaching > 80% in high-income countries. In Egypt, the outcome of treatment of ALL has been less favorable.
Aim: To evaluate the clinicolaboratory characteristics in patients admitted at Sohag Cancer Center and to assess the outcome and the prognostic factors affecting it.
Methods: This retrospective study included 79 pediatric ALL patients, from January 2010 to December 2014, who were treated according to modified Total therapy study XIIIB high-risk ALL of St. Jude Children's Research Hospital (SJCRH).
Results: 52% were males with a median age of 6 years. 58.2% were stratified as HR, 69.6% had precursor B-ALL, 39.2% presented with total leucocytic count (TLC) (≥ 50x109/L), and 11.3% had CNS leukemia. Complete remission (CR) was achieved in 87.3%. Regarding treatment outcome, induction failure was reported in 5.1%, relapse in 24.1%, deaths in CR in 7.2%, and continuous complete remission in 59.5%. The median follow-up was 42 months, 4 years OS, EFS, and DFS were 64.1 ± 5.6, 57 ± 5.7, and 63.3 ± 5.8% respectively. TLC and bone marrow aspirate postinduction were the only significant prognostic factors affecting EFS.
Conclusions: The modified TXIIIB of SJCRH was effective in improving ALL outcomes in our center, however, survival rates were much lower than internationally reported results with only initial TLC and response postinduction having a significant effect on EFS and DFS.

Keywords: Acute lymphoblastic leukemia, Egypt, Limited resources, Pediatric, Outcome
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Introduction

Acute lymphoblastic leukemia (ALL), the most common childhood cancer worldwide, is an aggressive hematologic malignancy treated with intensive multiagent chemotherapy [1]. The outcome of childhood ALL has dramatically improved over the last 50 years with the current cure rates approaching 90% in high-income countries. This is attributed to the introduction and gradual intensification of combination chemotherapy with contemporary regimens, alongside the improvement of prognostic factors [2, 3]. In developing countries, the outcome of ALL has been less favorable due to socio-cultural factors, financial constraints, inadequate supportive care, and may be genetic heterogeneity [4, 5].

This study aimed to describe the clinicolaboratory pattern of pediatric ALL patients at an emerging tertiary center in Upper Egypt, to study the outcome of modified total therapy study XIIIB for high-risk ALL protocol of St. Jude Children's

Research Hospital (SJCRH), and to evaluate prognostic factors that affect patients' survival, faced with the challenge of limited health resources.

Methods

This retrospective study included newly diagnosed pediatric (age: 2-18 years) patients with ALL (L1, L2) who had been treated at the Pediatric Oncology Department of Sohag Cancer Center (SCC) which is a tertiary center in Upper Egypt in the period from January 2010 to December 2014. Patients were followed up until January 2018. Causes of exclusion were mature B-ALL (Burkitt's Leukemia or L3) diagnosis, early death at presentation (in the first week) before starting chemotherapy, pretreatment, and missing medical records.

Data collected

Clinical data including patient demographics, diagnosis, treatment response, and outcome, were retrieved from medical records.

Diagnosis: Included history and physical examination at presentation, laboratory studies include morphological, cytochemical examination, and immunophenotyping of leukemic blasts on bone marrow aspirate (BMA) or peripheral blood (PB). Minimal residual disease (MRD) or cytogenetic studies were not done. Cerebrospinal fluid (CSF) was considered positive if contains >5 nucleated cells/mm3 with morphologically identified blasts by cytocentrifugation [6]. Routine imaging studies done included: chest X-ray, abdominopelvic and testicular sonography.

Risk assessment and treatment: Patients were classified according to the National Cancer Institute (NCI)/Rome criteria into standard risk (SR) (age 1–9 years, initial WBC < 50 × 10^9/L and patients without central nervous system [CNS] involvement) and high risk (HR) (all other patients) [6]. All patients were treated according to the modified Total therapy study XIIIB for high-risk ALL of SJCRH [7].

Response assessment and its definitions: Early response was assessed by the presence of peripheral blasts on D8 induction therapy instead of BMA on D15 induction because of our limited resources, good responder (GR) was considered when there was < 1 × 10 blasts ^{9}/L and poor responder (PR) ≥ presence of 1 × 10 blasts ^{9}/L or more in PB on day 8 [8]. BM morphologic criteria post induction was based on blast content in BM: M1 (<5% blasts), M2 (<25% blasts) or M3 (≥25% blasts) remaining in the bone marrow [9]. Complete remission (CR) was defined as the absence of leukemic blasts in peripheral blood and CSF and less than 5% blasts on BMA smears (M1), together with hematopoietic regeneration and no evidence of extramedullary disease after induction phase [9]. Patients who were alive and in CR until January 2018 were considered in continuous complete remission (CCR). Induction failure was defined as either morphological persistence of leukemic blasts in BM or extramedullary site after the completion of the induction therapy [10]. The refractory disease was considered in patients who do not attain CR after remission induction and consolidation phases. Relapse was defined as M3 marrow after achieving initial CR [9]. Treatment failure included induction deaths, refractory disease, relapse, secondary malignancy, abandonment of therapy, or deaths in CR [10].

Assessment of toxicity: Toxicity of treatment was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [11].

Statistical analysis

Data were analyzed using STATA 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Quantitative data were represented as mean and standard deviation (SD) or median and range. Qualitative data were presented as numbers and percentages. Survival analysis was done using the Kaplan-Meier method and a comparison between survival curves was done using the log-rank test. *P-value* was considered significant if it was ≤ 0.05. Overall survival (OS), event-free survival (EFS), and disease-free survival (DFS) were considered as the treatment outcomes in this study. Overall survival was defined as the time from date of diagnosis to the date of death from any cause or last date of follow-up, EFS as the time from the date of diagnosis to the date of first treatment failure of any kind (relapse, absence, death or major treatment toxicity that required cessation of chemotherapy) and DFS for patients who achieved CR to the time of relapse or death (excluding induction deaths).

Results

After reviewing the medical records of 87 ALL patients, 79 patients were eligible for this study, 8

patients were excluded due to very early deaths (6 patients) and missing medical records (2 patients).

Table 1 shows the clinical and laboratory characteristics of included patients in relation to immunophenotyping. Twenty-four patients (30.4%) had T-lineage ALL subtype and 55 patients (69.6%) had B-lineage ALL. The median (range) age of all patients was 6 (2-17) years and differed significantly between B-precursor and T-ALL patients (4[2-17] vs. 10 [3-17], respectively; p <0.0001). The mean (SD) age was 4.19 (4.49), 5.8 (3.8), and 10.4 (4.2) years for all patients, B-precursor and T-ALL patients, respectively. The male-to-female ratio was 1.1:1 for the whole group, 0.9:1 for B-precursor ALL patients, and 1.3:1 for T-ALL.

Hyperleukocytosis were more observed in patients with T-cell ALL (29.25%) in comparison to B-precursor cell (7.3%) (p = 0.035). The high-risk group represented the majority of patients (58.2%) and differed significantly according to immunophenotyping being higher in T cell ALL patients.

On D8, most of the patients (69/79, 87.4%) were GRs, while 10 patients (12.7%) were PRs. Three out of ten (30%) of the PRs failed to achieve CR post-induction versus only 1/69 (1.4%) of GRs (p=<0.001).

Table 1: Patients and disease characteristics and their distribution according to immunophenotyping

Characteristics	All patients (n=79)	B-precursor ALL (n =55)	T-ALL (n =24)	p-value
	n (%)	n (%)	n (%)	
Age (years)				
1-10	59 (74.7)	46 (83.6)	13 (54.1)	0.007
>10	20 (25.3)	9 (16.4)	11 (45.8)	
Gender				
Male	41 (52)	27 (49.1)	14 (58.3)	0.450
Female	38 (48)	28 (50.9)	10 (41.7)	
Fever	63 (79.7)	47 (85.5)	16 (66.7)	0.057
Lymphadenopathy	65 (82.3)	45 (81.8)	20 (83.3)	0.573
Hepatosplenomegaly	61 (77.2)	47 (85.5)	14 (58.3)	0.008
Mediastinal mass	14 (17.7)	0 (0)	14 (58.3)	<0.0001
Total leukocytic count ($\times 10^9$/L)				
< 50	48 (60.7)	36 (65.5)	12 (50)	0.035
50-100	20 (25.3)	15 (27.3)	5 (20.8)	
>100	11 (13.9)	4 (7.3)	7 (29.2)	
Hemoglobin (g/dl)				
< 6	11 (13.9)	9 (16.4)	2 (8.3)	0.496
6-10	59 (74.7)	39 (70.9)	20 (83.3)	
>10	9 (11.4)	7 (12.7)	2 (8.3)	
Platelets ($\times 10^9$/L)				
< 50	38 (48.1)	31 (56.4)	7 (29.2)	0.03
50-100	27 (34.2)	17 (30.9)	10 (41.7)	
>100	14 (17.7)	7 (12.7)	7 (29.2)	
Bone marrow morphology				
L1	52 (65.8)	37 (67.5)	15 (62.5)	0.681
L2	27 (34.2)	18 (32.7)	9 (37.5)	
Central nervous system infiltration				
Positive	9 (11.3)	5 (9.1)	4 (16.4)	0.330
Negative	70 (88.6)	50 (90.9)	20 (83.3)	
Risk stratification				
Standard risk	33 (41.8)	32 (58.2)	1 (4.2)	<0.0001
High risk	46 (58.2)	23 (41.8)	23 (95.8)	

Of 79 patients, 6 (7.5%) died during induction (5 sepsis, 1 tumor lysis syndrome). Induction remission was reported in 69/79 (87.3%) patients. Four (5.1%) patients failed induction but achieved CR after the consolidation phase. The number of patients who achieved CR was 73 (92.4%).

Treatment failure was documented in 32 (40.5%) patients including induction deaths (6 patients), abandonment of therapy (one patient), relapse (19 patients), and deaths in remission (6 patients) with no second malignancies recorded in our study. Continuous CR (CCR) was documented in 47 (59.5%) patients. Relapse occurred in 19/79 (24.1%) patients and included 12 (15.2%) late relapses and 7 (8.9%) early relapses. The relapse was medullary in 7 (8.9%) patients, isolated CNS in 4 (5.1%), and combined in 8 (10.1%). All relapsed cases died (2 died from sepsis and 17 from disease progression).

The most common toxicity that occurred among our patients was BM suppression grade II-III in 34 patients (43%) and mucositis grade III to IV in 30 patients (37.9%). Hepatotoxicity grade II-III was observed in 15 patients (18.9%) which occurred post-infectious (hepatitis virus B and C) and chemotherapy-induced, while grade IV toxicity was detected in 5 patients (6.3%) due to MTX toxicity.

The median follow-up period of all evaluable cases was 42 months, ranging from 8 to 72 months. 4-years OS rate (SE) was 64.5% (5.5) for all patients, 68.8% (7) for the SR group, and 57.7% (9.2) for the HR group. 4-years EFS ± SE was (57 ± 5.7%) for all patients, (57.6 ± 8.6%) for the SR group, and (57.5 ± 7.5%) for the HR group. 4-years DFS ± SE was (63.3 ± 5.8%) for all patients, (59.8 ± 8.5%) for the SR group, and (65.4 ± 7.6%) for the HR group.

Table 2 summarizes the effect of prognostic factors on patients' survival, none had a significant statistical effect on OS. While for EFS; TLC was highly significant (*P*=0.004) as well as BMA post-induction (*P*=<0.0001). For DFS, BMA post induction was still having a highly significant effect (*P*=<0.001).

Table 2: Survival rates in relation to different risk factors

Variable	Overall survival			Event-free survival			Disease-free survival		
	n	4-year rate (%[SE])	*p-value*	*n*	4-year rate (%[SE])	*p-value*	*n*	4-year rate (%[SE])	*p-value*
Whole group	79	64.1 (5.6)		79	57.1 (5.7)		73	63.3 (5.8)	
Age (years)									
1-10	59	67.4 (6.4)	0.34	59	61.8 (6.7)	0.11	57	62.9 (4.2)	0.851
≥10	20	54.2 (11.3)		20	45(11.1)		16	64.9 (7.9)	
Gender									
Male	41	71.9 (7.2)	0.23	41	61.8 (7.9)	0.20	38	67.7 (4.6)	0.061
Female	38	55.2 (8.5)		38	51.9 (8.2)		35	58.6 (5.7)	
Total leukocytic count ($\times 10^9$/L)									
< 50	48	71.4 (6.8)	0.06	48	69.8 (6.8)	0.004	48	67.1 (4.3)	0.519
50-100	20	58.4 (11.3)		20	38.6 (11.2)		17	54.4 (6.7)	
>100	11	45.5 (15)		11	36.4 (14.5)		8	61.3 (11.8)	
Immunophenotyping									
T-ALL	24	57.7 (10.2)	0.48	24	53.5 (10.3)	0.58	22	61.5 (4.6)	0.474
B-ALL	55	67.1 (6.6)		55	58.7 (6.9)		51	60.3 (5.2)	
Risk stratification									
Standard risk	33	68.6 (7)	0.49	33	57.6 (8.6)	0.87	31	59.8 (5.6)	0.418
High risk	46	57.5 (9.2)		46	57.5 (7.5)		42	65.4 (4.7)	
Early response, D8									
Good responder	69	66.8 (5.8)	0.33	69	58.3 (6.1)	0.55	63	78.5 (6.4)	0.084
Poor responder	10	45 (17.4)		10	50 (15.8)		10	59.4 (4.1)	
BMA on the 36th day of induction									
M1	69	72 (5.4)	0.12	69	65.9 (5.8)	<0.0001	69	67.4 (3.8)	<0.001
M2	3	66.7 (27)		3	66.7 (27)		3	29.9 (3.1)	
M3	1	0		1	0		1	0	

SE: standard error; **ALL:** Acute lymphoblastic leukemia; **BMA:** Bone marrow aspirate

Discussion

Management of children with cancer in Egypt is offered mainly through general and university hospital services, which are only partially covered by health insurance. Most of the patients suffer from shortages of chemotherapy and supportive medications, which may only be provided through personal charitable donations or non-profit organizations. Indeed, there is a lack of infection control programs or awareness of hygiene practices either by the patient's families or hospital staff. Despite all these difficulties, cancer-treating centers are following international protocols; however, modifications may be done to reduce toxicities and/or increase the cost-effectiveness of therapy [12].

According to patients' criteria and NCI/Rome criteria risk classification system, the majority of the patients 46 (58.2%) were classified as HR. This was the same as the study of Hussein et al. (58.4%) but it was higher than the results of SJCRH (44%), Lustosa de Sousa et al. (46%), and Shibl et al. (47%) [7, 10, 13, 14]. This higher incidence of HR features may be due to different biologic factors in childhood ALL in Egypt, late onset of presentation in many patients or it could be due to unavailability of diagnostic tools such as cytogenetics which can precisely stratify patients into a lower risk group.

Immunophenotyping studies revealed that most of the patients had B precursor ALL (69.6%), while T-ALL represented (30.4%), which is markedly different from the results of SJCRH with (82%) for B-precursor ALL and (17.5%) for T-ALL and nearly similar to results of Sidhom et al. (75.8%) for B-ALL and (24.2%) for T-ALL [10, 15]. The proportion of T-cell ALL has been reported as high (up to and even beyond 50%) in all childhood ALL in developing countries, and in particular within patients from lower socioeconomic strata [16].

In studying the relation between IPT and risk groups, 23 (95%) patients of T-All were stratified as HR, while the majority of B precursor ALL (58%) were stratified as SR with a significant difference between (P=<0.0001) which is consistent with Tantawy et al. and Shibl et al. [7, 12].

The age at presentation ranged between (2-17 years), the median age at the time of diagnosis was 6 years, and it showed wide variation between B and T-ALL; (4 years versus 10 years) (P=<0.0001), which was nearly similar to the results of NCI; (5years. for all patients, 4.5years for B precursor ALL and 8 years for T-ALL) [13]. The majority of the patients (74.7%) had a favorable age group (1-10 years), which was consistent with Abdelhamid et al. in Egypt and Shen et al. in Shanghai Children's Medical Center [17, 18]. Of those, 83.6% had B precursor ALL while 45.8% of T-ALL patients belonged to the unfavorable age group ≥10 years (P=0.007), this was consistent with the results of [12, 14].

Regarding gender, there was male predominance (51.9%) with a male to female ratio of 1.1:1. This ratio was lower than previously reported in SECI (1.5:1) and exactly similar to the results of SJCRH which was (1.1:1) [10, 18]. Male gender also predominated among the HR group and T-ALL (58.3%), this is because the incidence of the male gender is more common in the T-ALL subtype and usually they were stratified as HR [19].

Concerning clinical data at presentation; features of bone marrow and lymphoid system infiltration in our study were detected as follows: (79.7%) for fever, (86%) for pallor, (25.3%) for bleeding, (8.9%) for bone pain, (82.3%) for lymphadenopathy, (77.2%) for HSM and (17.7%) for mediastinal involvement this was in agreement with many reports from the Middle East and neighboring countries [20, 21] and much higher than internationally reported results by [22]. These relatively higher results in our developing countries may be due to the late onset of presentation and delayed diagnosis of the disease. Lymphomatous features such as (HSM and lymphadenopathy) were more common among B precursor ALL than T-ALL patients with the significant impact of HSM on IPT (P=0.008) which was consistent with many reported studies as [13].

Features of CNS infiltration were also considered as an HR criterion. The internationally published results reported CNS disease in less than (5%) with predominance among the HR group [22, 23]. While for the patients in the current study, we found CNS disease in 9 patients (11.3%) most of them were of B precursor ALL subtype, which is approaching the results of Hussein et al. [13] who reported CNS disease in 14/154 patients (9%) and was strikingly higher than results of Lustosa de Sousa et al. (6.5%) and Tantawy et al. (5.8%) which may be due to the difference in the percent of HR group between these studies [12, 14]. This lower incidence of CNS leukemia in developed countries may be due to the inclusion of a larger sample size used in the international studies and higher accuracy of techniques used in the diagnosis of CNS disease.

Initial TLC (<50x109/L) was reported in the majority of patients (60.7%), but unfortunately, this

was less than Shibl et al. (69%) and much lower than Shen et al. (83%) [7, 17]. Leukocytosis (50-100x109/L) and hyperleukocytosis (>100x109/L) were recorded as 25.3% and 13.9% respectively which is similar to the results of the Multi-Institutional International Collaborative Study (CALLME1) by the Middle East Childhood Cancer Alliance (MECCA) 21 but it was higher than reported by SJCRH, Berlin-Frankfurt-Munster (BFM-95) and Nordic Society of Pediatric Hematology and Oncology (NOPHO ALL2008) studies [10, 23, 24]. This difference may be due to delayed diagnosis as long as a higher percentage of the HR group in our study. B precursor ALL predominated among patients presented with TLC (<50x10^9/L) and (50-100x10^9/L) by (65.5%) and (27.3%), but T-ALL constituted the majority of patients with hyperleukocytosis (>100x10^9/L) (29.2%) with significant difference (P=0.035), similar to the study of [13].

Regarding the response post-induction, induction remission was reported in 87.4% of patients, which was slightly higher than the results of Shen et al. in which CR was reported to be 86% [17]. Induction failure was recorded in 5% of the patients, which was slightly lower than Hussein et al. (6.5%) and much higher than SJCRH (2%) [10, 13], this relatively higher incidence of induction failure in our study and NCI may be due to modifications done to the original protocol.

Early response was assessed as one of the prognostic factors, by CBC with differential count on D8 induction, as there was no ability to perform BMA d15 or MRD to all patients during the induction phase which was carried out and reported in the original protocol. The majority of our patients were GR (87.4%). On studying the relation between early response on D8 and remission induction, 30% of PR did not achieve CR post-induction versus only 1.6 % of GR with a significant difference (*P*= 0.001) which was consistent with [25].

Treatment failure was reported in 40.5% of the patients, which is the same as the study of Shibl et al. in Upper Egypt and lower than Abdelmabood et al. and Alecsa et al. [7, 26, 27], and higher than reported in SJCRH, BFM-95 and NCI [10, 15, 24]. This higher percentage of relapse may be due to the higher percentage of HR group in our patients.

Deaths encountered 39% of patients which was greatly higher than reported in developed countries [14, 20]. Induction deaths occurred in 6 patients (7.6%), and deaths in CR were encountered in 6/79 patients (7.6%), which was slightly higher than Sidhom et al [15]. These higher induction and remission mortality rates of patients in the current study could be attributed to the increased rates of infections, sepsis, and MTX toxicity due to defective infection control programs and supportive care facilities.

Unlike Pui et al., Winter et al. and Surapolchai et al. [28-30], no second neoplasms were reported in our study, which may be due to the reduction of the dose of vepesid used in the modified TXIIIB ALL protocol adopted from SJCRH in our institution or due to short period of follow up and small sample size.

About 60% of the patients achieved CCR, this was comparable with many reports [18, 26], but it was much lower than the results of European and North American studies [10, 23, 31].

The median follow-up for our patients was 42 months ranging between 8-72 months. The 4-years OS, EFS and DFS were 64.1 ± 5.6%, 57.0 ± 5.7% and 63.3 ± 5.8% respectively. These low survival rates can be explained by high relapse and death rates in our study which was comparable with many reports from developing countries (Mexico, sub–Saharan Africa, India) and also from Egypt [26, 32-35] but it much lower than SJCRH (5-year EFS was 80.8% ± 2.6%), BFM-95 (6-year EFS was 79.6% ± 0.9%), Medical Research Council United Kingdom (MRC UK) (5-year EFS was 87.3% ± 1.2%) and Children Oncology Group (COG) (6-year EFS was 79.6% ± 1.6%) [10, 24, 36].

Univariate analysis of the prognostic factors showed that leukocytosis and response to induction were the only factors that showed significant unfavorable effects on EFS and DFS. This is nearly similar to Lustosa de Sousa et al. [14] who also found that TLC and age have significant effects on EFS. Also, it was consistent with Al-Sudairy et al. [37] who found hyperleukocytosis to have a significant effect on EFS.

Conclusions

The modified TXIIIB protocol of SJCRH was effective in improving ALL outcomes in our center, however, survival rates were much lower than internationally reported results with only initial TLC and response postinduction having a significant effect on EFS and DFS. Also, the majority of the patients were diagnosed as HR, with high relapse and death rates. Our recommendations are to improve our health care facilities, regarding diagnostic tools, supportive care measures, and infection control programs.

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Authors' contribution
Conception or design: All authors; Acquisition, analysis, or interpretation of data: All authors; Drafting or revising the manuscript: All authors; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest
The authors declare that they have no conflict of interest to disclose.

Data availability
The deidentified datasets used and/or analyzed during the current study are available from the corresponding author (AMO) on reasonable request.

Ethical considerations
This study was approved by the Institutional Review Board of South Egypt Cancer Institute, Assiut, Egypt (Approval No. 233).

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Study registration
Not applicable.

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