Research Article

Effectiveness of Modified UKALL protocols in Children with Acute Lymphoblastic Leukemia; an experience of Children Welfare Teaching Hospital.

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Abstract

Background: Acute Lymphoblastic Leukaemia (ALL) is the most common diagnosis in childhood cancer. Cure is possible and even likely. **Aims of study:** To evaluate the effectiveness of modified UKALL protocols in a setting with limited resources and to define an event free survival of Acute Lymphoblastic Leukemia in children aged 1 -15 years who were committed to finish treatment.

Methods: This is a retrospective study that reviewed 559 children with newly diagnosed ALL between 1 and 15 years of age during the period: January 1st, 2000 to December 31st, 2009 who were committed to finish treatment protocol. All patients were treated with regimens modified from Medical Research Council protocol (United Kingdom Acute Lymphoblastic Leukemia- UKALL- protocols). The Event Free Survival (EFS) was measured using Kaplan – Meier method with a total duration of observation till December 31st 2011 (a minimum of two years post starting treatment) and data were processed and tabulated using SPSS (Statistical Package for the Social Sciences) .

Results: The majority of treated children (348, 62.2%) were standard risk group; remission induction was achieved in 461(82.4%) patients. Eleven patients (1.9%) were poor responders. Death during first 60 days from treatment was reported in 87 (15.5%) patients and death in complete remission (CR) was reported in 49 (8.7%) patients. The major presumptive causes of death were infection/sepsis followed by bleeding. Of 559 patients; 302(54%) remained in continuous complete remission with a median follow up time of 52.5 months (range from 23.9 months- 11.6 years). There was a significant difference in EFS between Standard Risk group (61.2%) and High Risk group (42.2%) after induction (P=0.02) and in later phases of therapy (P=0.0002). Increased relapse rate in high risk group was the reason behind the difference in EFS (P=0.0004) between two groups. Relapses were documented in 110(19.6%) patients and the bone marrow (51.8%) was the main site of relapse followed by CNS (27.2%).

Conclusion: The study showed lower ALL EFS than that of recognized cancer centers.

Keywords: Acute Lymphoblastic Leukemia, Childhood, Outcome, UKALL protocols

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy in most parts of the world, however its proportional representation varies in different regions, ranging from 15% to over 40%. Over the years there has been a remarkable improvement in the outcome of the childhood ALL as a result of serial clinical trials conducted by pediatric oncology cooperative groups who studied the disease biology and followed risk directed combination therapy with better supportive care [(1)].In low- and middle-income countries, outcomes have been worse than in high income countries [(2)].

The aim of this study is to evaluate the effectiveness of Modified UKALL protocols in a setting with limited resources, to assess the institutional standards of management and define an Event Free Survival (EFS) of Acute Lymphocytic Leukemia in children who were committed to finish treatment.

PATIENTS AND METHODS

The study is a retrospective analytic study. Between January 1st, 2000 to December 31st, 2009; 559 patients between 1 and 15 years age with newly diagnosed ALL were reviewed at the oncology unit of Children Welfare Teaching Hospital (CWTH) were studied. For these patients, all available medical records, notes, laboratory data were reported. A chart review was performed to determine age, gender, residence, duration of onset, clinical presentation, date of diagnosis and results of investigations. The total duration of observation extended from January 1st 2000 till December 31st 2011(a minimum of 2 years post starting treatment). In all patients the diagnosis of ALL was established by bone marrow aspirate. Patients with ALL-L3 morphology were excluded from the study because they were treated with different protocols. Morphological classification of the blast cells according to FAB system was carried out in most of the patients. Immunophenotyping and karyotyping facilities were not available. Most of the patients underwent lumbar puncture within the first two weeks from induction, and the cerebrospinal fluid was examined. The definition of central nervous system (CNS) involvement was based on the presence of any number of white blood cells (WBCs) per microliter of cerebrospinal fluid (CSF) with leukemia cells on a cytocentrifuged smear, or the presence of cranial nerve palsies[3]. All patients had also been evaluated by radiological examination (Chest X-Ray) for the presence of mediastinal mass. Patients were assigned to a Standard or High risk group on the basis of their age and leukocyte count at initial presentation. Patients were considered to have Standard Risk (SR) ALL if they were 1-9 years old with a presenting leukocyte count of less than $50x10^9$/L, otherwise the patients are classified as High Risk (HR). Treatment used was regimen modified from Medical Research Council, United Kingdom Acute Lymphoblastic Leukemia (MRC 97 Modified 1999 - UKALL) Protocol.Response to treatment was measured by the number of blasts in bone marrow aspirate on day 21 or day 28 of induction therapy[3]. **Event free survival** (EFS) was defined as all events leading to remission failure (early death or non-responders) or the end of a first remission period (relapse, second malignancy and death from any cause). Patient who didn't attain a complete remission were considered failures at time zero[4]. Patient data were tabulated and processed using SPSS (Statistical package for the social sciences) version 18.0 for windows. Chi-square test was used to identify the associations between the event free survival and studied independent variables. Kaplan-Meier method was used to show the survival curves. P-values equal or less than 0.05 were considered significant[5].

RESULTS

Patient characteristics: The study identified 559 patients that met the diagnosis of ALL who were 1-15 years age. Most of the patients in the study were from Baghdad 264 (47.2%) patients, followed by Diala 50 (8.9%), Babil 40 (7.1%), Karbala 35 (6.2%) and Wasit 34 (6.0%).

The detailed demographic and clinical data of the 559 patients are presented in table 1.The median age was 5.4 years (range 13 months to 14.5 years), 313 (56.0%) males & 246 (44.0%) females forming Male: Female ratio of 1.2:1. The median duration of onset of symptoms was 38 days (range 2 days to 12 months).

Initial Laboratory and Radiological features: Table (1) shows the profile of laboratory and radiological findings;the hemoglobin level ranged between 2.2-14.6 g/dl with a median of 6.6 g/dl. Initial leukocyte count ranged from 1-990$\times10^9$/L with a median of 14.6 $\times10^9$/L. 148 (26.4%) patients had an initial leukocyte count of ≥ 50 $\times10^9$/L. The median Platelets count was 36×10^9/L (range 1-1,000 $\times10^9$/L). Morphological classification using the FAB system had showed L2 subtype in 372 (66.5%) patients, L1 in 88 (15.7%), presumptive T-cell morphology in 44 (7.8%) cases, and in 55 (9.8%) cases, the pathological reports mentioned only ALL without the subtype. CSF cytospin analysis of 146 patients was missed either because of non-availability of the test or the sample was traumatic and improper for analysis. Of 413 patients; 399 (96.6%) samples were normal, 14 (3.4%) samples were positive, another 2 patients had clinical signs of CNS disease while their CSF cytospin was negative forming a total of 16 (3.8%) patients with CNS disease at presentation. Mediastinal mass was detected by chest x-ray in 94 (16.8%) patients.

Treatment outcome: Based on age and initial highest WBCs; 348 (62.2%) patients were classified as having standard risk and 211 (37.7%) as high risk. All 559 patients received induction chemotherapy according to Modified UKALL protocols and 461 (82.4%) achieved a

complete remission (CR) as shown in table (2). Ninety-eight (17.5%) patients failed to achieve remission during induction either because they died because of treatment related complications within 30 days from starting treatment, including 10 patients in whom the evaluation of remission was not assessed and they died between 30-60 days from induction, to have a total deaths of 87 (15.5%) patients or of being poor or non-responders in 11 (2%) patients. Of the 461 patients who achieved CR following induction chemotherapy; 302 (54%) remained in CCR with a median follow up time of 52.5 months (range,23.9 months-11.6 years) as shown in table (2) and figure (1). The adverse events that occurred during post induction phases till the end of analysis period were 159 (28.4%); of which 49 (8.7%) treatment related deaths, and 110 (19.6%) relapses as shown in table (2).The common site for relapse was the bone marrow in 51.8% followed by CNS relapse in 27.2% followed by combined bone marrow and CNS relapse in 12.7%; isolated testicular relapse was noted in 2.7% of cases. Table (3) shows the summary of adverse events of 559 children aged 1-15 years. The main presumptive cause of death was infection during both induction and post induction phases (44/87 (50.5%) and 31/49 (63.2%) respectively), followed by bleeding as shown in table (4). There was a significant statistical difference between the EFS of Standard Risk group (61.2%) and High Risk group (42.2%), P value of (0.001) as shown in table (2) and figure (2). Comparing the standard risk with high risk groups; there was a significant statistical difference in survival after induction phase (p=0.02) and high statistical difference in post remission phases of therapy (p=0.0002). With further evaluation, the difference was mainly in the relapses (p=0.0004) rather than in death as an event (p=0.4) in later phases of treatment, as shown in table (2).

DISCUSSION

Male to Female ratio was almost equal which is comparable to the developed nations [6-11]. In the Indian study by Kulkarni [12] and several areas of North India where parents often seek medical advice and treatment preferentially for male siblings, they observed a definite bias towards males with M:F ratio of 3.2:1. Hyperleukocytosis (WBC count $\geq 50 \times 10^9$/L) was present in (26.4%) of the patients, this figure was comparable to Al attar study (28.4%)[13]. It was higher than the figures mentioned in other studies like Schrappe et al study (19.7% to 22.3%)[14], Silverman et al study (18.3%)[6], Karimi study from Iran (20%)[15], Gaynon et al study (21% to 22.8%)[16], Indian study (14.6%) by Kulkarni[12] and other Indian centers (15.3% to 24.2%) [17,18] but less than Hussein et al study from Egypt (39.6%) which included an older age group as an upper limit (0-18 years)[19].The literature described Approximately 20 percent of children with ALL are seen with leukocyte counts greater than 50,000 cells [20], This higher incidence of high-risk features may represent different biologic factors in childhood ALL in Iraq which need further evaluation or due to late presentation because of delay in diagnosis. These patients are at a high risk for developing tumor lysis syndrome, the management of which requires hydration, allopurinol, packed red cell transfusions and close clinical and investigational monitoring. Primary CNS involvement was seen in 3.6 % of our patients with ALL which is comparable to other studies in western countries (2.4% to 5.3%) [14,16] and lower than Hussein et al study (9%) and higher than Al-Attar study (2.3%). A significant number of patients were not analyzed for CNS manifestation and even those for whom CSF were analyzed, the corrected analysis of CNS status was not feasible and the reports were limited to the presence or absence of primitive cells. In spite of improvement in supportive care that decreased the mortality rate during induction therapy to approximately 3% or less in the recognized cancer centers, our results showed higher Induction mortality rate (15.6%) compared with other studies done in Egypt (5.8%) [19], Iran (1.3%) [15] and El Salvador 7.9% [21]. This cohort group of patients has EFS of 54%, this figure can't represent the true outcome of patients treated in CWTH but it reflects the exact figure for patients who were committed to the whole period of treatment. A previous attempt done by Advani et al [18] to assess their institutional standard of management and the best cure rates from India in childhood ALL have been reported by this assessment, the investigators had a pre-selection policy wherein patients coming from a local area and willing to comply with an expensive treatment protocol were included in the study. Accrual was therefore biased towards the richer section of the society with a positive impact on loss to follow up and toxic death rates.

Table 1: Demographic Data, Clinical Data,Initial Laboratory & Radiological results of 559 children (Age 1 to 15 years) treated at the CWTH from 2000-2009:

Datum	No.	% (valid %)
Overall	**559**	**100**
Age (years)		
1-9	470	**84.0**
10-15	89	**15.9**
Sex		
Males	313	**56.0**
Females	246	**44.0**
Duration of symptoms		
<6weeks	402	**71.9**
6weeks-6months	154	**27.5**
>6months	3	**0.5**
Fever	391	**69.9**
Bleeding tendency	149	**26.6**
Lymphadenopathy	404	**72.2**
Hepatomegaly ≥ 5cm BCM*	261	**46.7**
Splenomegaly ≥ 5cm BCM*, **	206	**36.8(36.9)**
Hemoglobin (g/dl)		
<6g/dl	202	**36.1**
6-10g/dl	288	**51.5**
>10g/dl	69	**12.3**
WBC ($\times 10^9$/L)		
<10	231	**41.3**
10-49.99	180	**32.2**
≥50	148	**26.4**
Platelets ($\times 10^9$/L)		
<20	109	**19.5(30.5)**
20-99.99	188	**33.6(52.6)**
≥100	60	**10.7(16.8)**
Unknown***	202	**36.1**
Bone marrow		
ALL-L1	88	**15.7(17.4)**
ALL-L2	372	**66.5(73.8)**
T- cell (L1 or L2)	44	**7.8(8.7)**
ALL (undetermined)	55	**9.8**
CSF cytospin		
CSF cytospin positive	14	**2.5(3.4)**
CSF cytospin negative	399	**71.3(96.6)**
NR	146	**24.3**
Mediastinal mass (CXR)		
Present	94	**16.8(16.9)**
Absent	459	**82.1(83.0)**
NR	**6**	**1.0**

*** BCM: below costal margin**

****One patient had splenectomy 1 month before presentation (Thalassemia).**

*****The platelets were counted roughly or not recorded.**

NR: Not Recorded.

Table 2: Treatment Results of 559 children (Age 1 to 15 years) treated at the CWTH from 2000-2009:

Treatment Phase	Total	Standard risk	High risk	P
Induction Phase				
Total No.	**559(100%)**	**348(62.2%)**	**211(37.7%)**	
Failures	98(17.5%)	51(14.6%)	47(22.2%)	0.02
Poor responders*	11	6	5	
Died within 30 days	77	40	37	
Died 30-60 days without evaluation	10	5	5	
Complete remissions	461(82.4%)	297(85.3%)	164(77.7%)	
Post Induction Phases				
Total No.	**461**	**297**	**164**	
Events	159(28.4%)	84(24.1%)	75(35.2%)	0.0002
Relapse	110(19.6%)	55	55	0.0004
Deaths during remission	49(8.7%)	29	20	0.43
Continuous complete remission (CCR)	302(54%)	213(61.2%)	89(42.2%)	0.001

***Poor responders= including partial and non-responders**

Table 3: Summary of adverse events of 559 children (Age 1 to 15 years) treated at the CWTH from 2000-2009:

Event	No.	% from total
Total Events	**257**	**45.9**
Death	136	**24.1**
Relapse	110	**19.6**
Poor responders*	**11**	**2**

***Poor Responders=including partial and non-responders**

Table 4: Presumptive causes of death as an event in 136 children with ALL:

Cause	No. (%)
Overall	**136**
During Induction	**87 (63.9%)**
Infection	**44 (50.5%)**
Infection/Bleeding	**19 (21.8%)**
Bleeding	**15 (17.2%)**
Tumor lysis syndrome/Renal failure	**5 (5.7%)**
Procedure complication*	**2 (2.3%)**
Asparginase side effects	**2 (2.3%)**
Post Induction Phases	**49 (36.0%)**
Infection	**31 (63.2%)**
Bleeding	**11 (22.4%)**
Hepatic decompensation	**3 (6.1%)**
Unknown**	**4 (8.1%)**

*** One patient died with complication of chest tube; the other one died with complication of anesthesia after BMA.**

**** Three patients died at home; one patient died with liver masses (secondaries).**

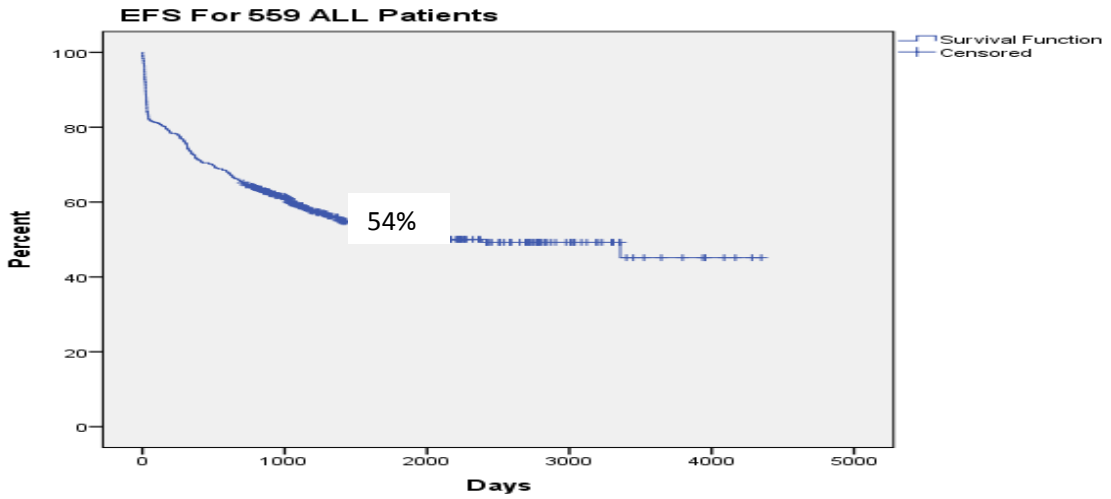

Figure 1: Event Free Survival for 559 children (Age 1 to 15 years) treated at the CWTH from 2000-2009.

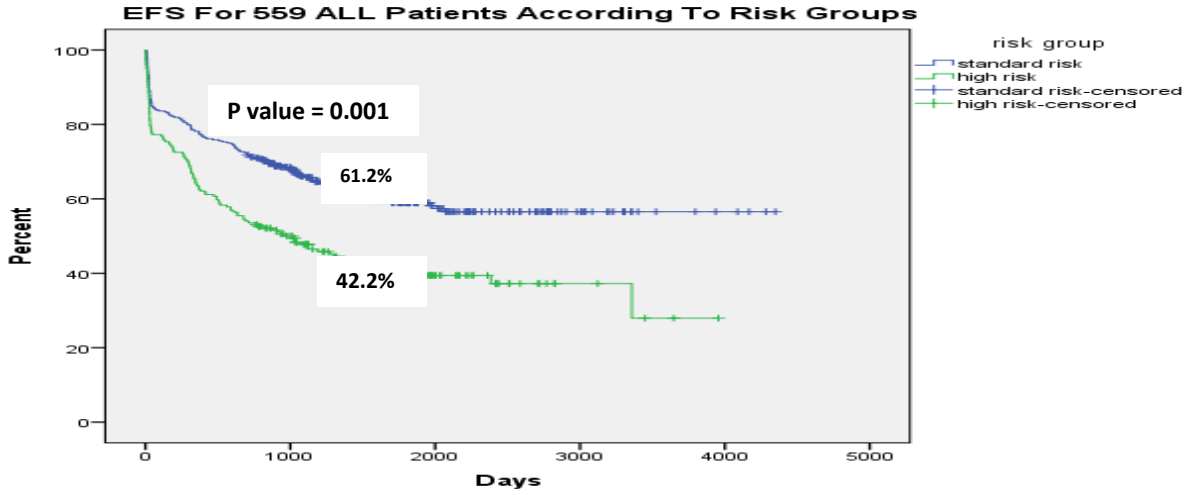

Figure 2: Comparison EFS between risk groups for 559 children (Age 1 to 15 years) treated at the CWTH from 2000-2009.

In this manner; we can compare our study with the results of developed countries were abandonment is not a factor in the treatment failure. Death was the main reason of treatment failure in this cohort group (24.1%); The high death rates are likely to be a consequence of bulky disease at diagnosis, inter-current infections, malnutrition, differences in level of hygiene achievable at home or in the hospital and poor access to acute care. Although our classification of risk groups depends only on age and WBC count because immunophenotyping and karyotyping procedures were not feasible in Iraq, there was a statistically significant correlation between risk groups and EFS (P=0.001). Relapse was documented in 19.6% cases. The rate of relapse in our patients was lower than 24.3% in Kulkarni study and other Indian centers but was significantly higher in comparison to figures reported by investigators from resource rich nations [3,7,18,22]. The estimated 5-year EFS in this study was inferior to the cure rates reported from the developed countries [3,7,9,23-25]. These results could be attributed to the several fold higher number of toxic deaths, higher relapse rates and poor nutritional status. There was a statistically significant

difference in EFS between risk groups during induction and post remission phases of therapy; this was related to death during induction phase but to relapse in the later phases of treatment. This signify that in post induction phases; both groups are facing the same problems that leads to death while still high risk group is still at risk of relapse in spite of intensive treatment during the first 10 weeks of protocols, the high relapse rate and high incidence of CNS relapse indicate the need for re-evaluation of our treatment protocols.

RECOMMENDATIONS:

Multicentric trials in different parts of Iraq are required to determine risk factors, pattern of relapsed disease and survival outcome.

CONCLUSIONS:

Event Free Survival of 54% was inferior to the results of the recognized cancer centers. There was statistically significant difference regarding EFS between Risk groups during induction phase and post remission phases of treatment. The commonest cause of death was infection/sepsis while the commonest site of relapse was bone marrow.

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