ORIGINAL ARTICLE

Induction-remission response in peadiatric acute lymphoblastic leukaemia, Lahore protocol versus UKALL 2011 interim guidelines

Safia Khan,[1] Saadia Anwar,[2] Muhammad Farooq Latif,[3] Ayesha Farooq,[4] Mahwish Faizan[5]

Abstract

Objective: To compare the outcome of induction-remission in acute lymphoblastic leukaemia patients treated according to two different guidelines.

Methods: The descriptive retrospective cohort study was conducted at The Children's Hospital Lahore, Pakistan, and comprised clinical information sheets of acute lymphoblastic leukaemia patients from September 2014 to August 2015. Data regarding demographics, risk categorisation, rapid early response and induction-remission assessment was collected separately for Group 1 patients treated with Lahore protocol and Group 2 patients using United Kingdom acute lymphoblastic leukaemia-2011 interim guidelines. Data was analysed using SPSS version 20.0.

Results: Of the 98 patients who had a median age of 6.4 years (interquartile range: 1.5-16 years), 48(49%) were in Group 1 and 50(51%) in Group 2. There were 14(29%) patients with standard risk in Group 1 while 34(71%) were high-risk. The corresponding numbers in Group 2 were 30(60%) and 20(40%) in Group 2. Rapid early response was noted in 18(37.5%) patients in Group 1 and 11(28%) in Group 2. Remission was achieved in 38(79%) patients in Group 1 and 36(72%) in Group 2. There was significant association of rapid early response with induction-remission in Group 2 ($p<0.05$) but not in Group 1 ($p>0.05$).

Conclusion: Induction-remission rate was comparable in the two treatment groups, but significant association of rapid early response with induction-remission was observed only in patients treated using United Kingdom acute lymphoblastic leukaemia-2011 interim guidelines.

Keywords: Induction-remission, Lahore Protocol, UKALL Interim Guidelines. (JPMA 70: 591; 2020)
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Introduction

Acute lymphoblastic leukaemia (ALL) represents 20-30% of paediatric malignancies under the age of 15 years.[1] Approximately 85% of ALL patients have Pre-B cell ALL (PB-ALL) with cure rate of around 80%.[2] Incidence of childhood leukaemia varies widely across the world with 36 cases per million in whites and 41 cases per million in Hispanics compared to 16 cases per million in low-income countries.[3,4] These variations may be due to differences in diagnostic techniques and reporting procedures.[5] Age at the time of diagnosis, initial white blood cell (WBC) count, rapid early response (RER), cytogenetic changes and central nervous system (CNS) involvement are independent prognostic ALL markers.[6-10] Based on age and WBC count, patients can be categorised into standard risk and high-risk groups with 5-year event free survival (EFS) >95% in standard risk patients.[11,12] Risk categorisation aims at reducing treatment-related toxicity in low-risk patients while ensuring intensive therapy in patients with high risk of disease recurrence. Induction chemotherapy is the first phase of treatment of acute leukaemia aimed at achieving complete remission. Percentage of malignant cells (blasts) in bone marrow at the end of induction therapy can help to predict outcome. Ten-year overall survival (OS) is around 26% and 41% in patients with M3 (25% or more blast cells) and M2 (5-24 % blast cells) bone marrow at the end of induction therapy respectively.[19,20] Studies report end of induction-remission rate of 95% in ALL patients in developed countries with failure rate of up to 5%.[13] However, the outcome of ALL is relatively poor in developing countries like India, Pakistan and Bangladesh probably due to delay in diagnosis and extent of disease at presentation, higher infection rates, suboptimal post-treatment care, lack of resources and supportive care.[14] Various treatment protocols, including Children's Oncology Group Acute Lymphoblastic Leukaemia (COG-ALL), United Kingdom Acute Lymphoblastic Leukaemia (UKALL) 2011 interim guidelines, and Burlin-Frankfurt-Munster-90 (BFM-90), are used to treat ALL in clinical practice.[11,12,16,24,25] The induction phase of the treatment in most protocols is based on four chemotherapeutic agents, including

[1]Pediatric Hematology Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [2,5]Pediatric Hematology Oncology, The Children Hospital and Institute of Child Health, Lahore, Pakistan, [3]Department of Medical Oncology, Dubai Hospital, Dubai, UAE, [4]Burnley General Hospital, Burnley, UK.

Correspondence: Safia Khan. Email: dr.safiakhan80@yahoo.com

vincristine, asparaginase, daunorubicin and steroids. The induction treatment for patients with standard risk disease comprises three drug combinations, including vincristine, asparaginase and steroids (prednisone or dexamethasone), while high-risk patients are usually treated with four-drug therapy with the addition of daunorubicin to the above three. In the past, clinicians used different treatment protocols and chemotherapy doses for ALL patients in Pakistan. This led to inconsistency in clinical practice and outcome data. In 1990, few oncologists and paediatricians agreed on a unified treatment regime called the Lahore group (LG) protocol to ensure better compliance, uniformity in practice and data acquisition for audits. LG protocol is local unpublished protocol based on BFM-90 and UKALL XI with some modifications in chemotherapy doses to minimize toxicity, like reduction of asparaginase and methotrexate during the consolidation and the re-induction phases while keeping them intact in the induction phase.[9,25] The current study was planned to evaluate and compare the outcome of induction therapy, including RER and end-of-induction remission, in ALL patients treated with LG and UKALL protocols.

Patients and Methods

The descriptive retrospective cohort study was conducted in the Paediatric Haematology Oncology Department of The Children's Hospital and Institute of Child Health, Lahore, Pakistan, and comprised medical records of diagnosed PB-ALL patients aged 1-16 years, admitted in the ward for management during between September 2014 and August 2015. The cases and their records were identified from the hospital database after approval from the institutional board. Clinical case notes, patient records and treatment charts were reviewed to collect data regarding demographics, clinical presentation, risk stratification, early response assessment and end-of-induction remission assessment. Records of patients with T-Cell leukaemia, mixed or bi-lineage leukaemia and relapsed leukaemia were excluded.

Based on the protocol used, the patients were divided into LG and UKALL groups. Diagnosis of PB-ALL was made on the basis of leukaemia cell-specific morphology, immunological and biochemical features either on bone marrow aspiration and trephine biopsy or flow cytometry on peripheral blood with high WBC count. Chest X-ray (CXR) and cerebrospinal fluid (CSF) analysis were performed for each patient at the time of diagnosis to assess mediastinal widening and central nervous system (CNS) involvement respectively. CNS involvement on the basis of CSF analysis was classified as CNS-1, CNS-2 and CNS-3.[10,15] CNS-1 was defined as no blast cells in CSF regardless of WBC count, while patients with blast cells in CSF and <5 WBC/ul were classified as CNS-2. CSF sample containing ≥5 WBC/ul with unequivocal blast cells was defined as CNS-3. Early response assessment was carried out by bone marrow biopsy on day 8 of the induction therapy in the LG group and on day 8 or 15 in the UKALL group depending upon risk stratification. RER was defined as <5% blast cell in bone marrow (M1).[15] Patients with 5-24% blast cells (M2) or ≥25% blast cells (M3) on bone marrow examination were categorised as slow early responders and were upgraded to high-risk group during the induction phase of the treatment in both the groups.[19,20,22] End-of-induction remission assessment was performed on day 29 of the induction therapy in both the groups. Remission was defined as normal cellular bone marrow with <5% blast cells in the presence of neutrophil count of $>1x10^9$/L and platelet count of $>100x10^9$/L in the peripheral blood with no extra-medullary disease. Minimal residual disease (MRD) assessment was not available for the study population.[16,20]

Patients in the LG group received prednisolone for 7 days and one dose of intrathecal methotrexate prior to the induction phase of chemotherapy. Response to prednisolone was assessed prior to the induction chemotherapy (Day zero) by peripheral blast cell count.

Statistical analysis was performed using SPSS version 20.0. Descriptive statistics were used to express the findings as frequencies and percentages, and median and interquartile range (IQR) and mean and standard deviations (SD), as appropriate. The two groups were compared in terms of demographic data, presentation, early response assessment and end-of-induction remission. Univariate and multiple regression analysis were performed on risk groups, early response assessment and end-of-induction remission assessment. Chi square and Fisher's exact tests were used to compare the groups with $p<0.05$ being statistically significant.

Results

Of the 98 patients, 60(61%) were males and 38(39%) were females. The overall median age at presentation was 6.4 years (IQR: 1.5-16 years). Of the total, 48(49%) were in LG group and 50(51%) in UKALL group. Fever was the commonest clinical presentation in 96(98%) patients, followed by pallor in 71(72%). In the LG group, hepatosplenomegaly and lymphadenopathy was found in 36(75%) and 6(12.5%) patients, and in the UKALL group the corresponding numbers were 36(72%) and 20(40%). In the LG group,

Table-1: Demographics and clinical features.

	Number of patients	Lahore Protocol [n=48] N (%)	Number of Patients	UKALL 2011 Guidelines [n=50] N (%)
Gender	48		50	
Male		38 (79.2 %)		22 (44 %)
Female		10 (20.8 %)		28 (56 %)
Age	48		50	
1 to 10 years		43 (89.6 %)		41 (82 %)
>10 years		05 (10.4 %)		09 (18 %)
Mean (Std. deviation)		6.4 (0.42)		6.4 (0.53)
Median (range)		6 (2.0 – 13.5)		5.8 (1.5 – 16)
Fever	48		50	
Yes		47 (98 %)		49 (98 %)
Pallor	48		50	
Yes		34 (70.8 %)		37 (74 %)
Bone Pains	48		50	
Yes		22 (45.8 %)		13 (26 %)
Superficial bleeds (petechiae, bruises, epistaxis)	48		50	
Yes		12 (25 %)		14 (28 %)
Seizures	48		50	
Yes		0 (0 %)		09 (18 %)
Altered Sensorium	48		50	
Yes		2 (4.2 %)		0 (0 %)
Hepatosplenomegaly	48		50	
Yes		36 (75 %)		36 (72 %)
Lymphadenopathy	48		50	
Yes		06 (12.5 %)		20 (40 %)
Testicular involvement	38		22	
Yes		01 (2.6 %)		0 (0 %)

UKALL: United Kingdom acute lymphoblastic leukaemia-2011 interim guidelines.

Table-2: Baseline laboratory workup.

	N	Lahore Protocol [n=48] N (%)	N	UKALL 2011 [n=50] N (%)
WBC at presentation	48		50	
Mean (Std. deviation)		33.0 (7.76)		40.6 (11.0)
Median (Range)		14.8 (1.0 – 250.0)		12.0 (0.6 – 475.6)
Hb	48		50	
Mean (Std. deviation)		8.1 (0.34)		7.8 (0.42)
Median (Range)		8.3 (2.9 – 12.6)		7.6 (2.5 – 15.6)
Platelet	48		50	
Mean (Std. deviation)		76.6 (14.8)		64.6 (13.6)
Median (Range)		49.0 (6.0 – 635.0)		30.0 (5.0 – 477.0)
CNS Status	48		50	
CNS 1		48 (100 %)		48 (96 %)
CNS 2		0 (0 %)		01 (02 %)
CNS 3		0 (0 %)		01 (02 %)

UKALL: United Kingdom acute lymphoblastic leukaemia-2011 interim guidelines. WBC: White blood cell; Hb: Haemoglobin; CNS: Central nervous system.

1(2.10%) patient had testicular involvement (Table-1).

On diagnostic investigations, 7(15%) LG patients had WBC >50,000 and 9(19%) had platelets <20,000. In the UKALL group, high WBC count and thrombocytopenia were found in 9(18%) and 18(36%) patients. Mediastinal widening on CXR was reported in 2(4.2%) patients in LG group. CNS involvement was reported in 2(4%) patients (CNS-2=1, CNS-3=1) in the UKALL group, while there was none in thr LG group (Table-2).

Table-3: Risk Group stratification and Induction response by Lahore Protocol and UKALL 2011.

	N	Lahore Protocol [n=48] N (%)	p Value	N	UKALL 2011 [n=50] N (%)	p Value
BMF Risk Factor	48			50		
< 1.2		15 (31.2 %)			NA	
>1.2		33 (68.8 %)			NA	
Risk Group	48			50		
Standard Risk		14 (29.2 %)	1		30 (60 %)	0.353
High Risk		34 (70.8 %)			20 (40 %)	
Early response assessment						
(Day 8 or 15 bone marrow)	48		0.282	50		0.005
Rapid Early Response (M1)		18 (37.5 %)			14 (28 %)	
Slow Early Response (M2 or M3)		30 (62.5 %)			36 (72 %)	
Remission Assessment						
(Day 29 Bone marrow)	48			50		
Remission (M1)		38 (79.2 %)			36 (72%)	
No Remission (M2 or M3)		10 (20.8 %)			14 (28%)	

* M1: <5% blast cell in bone marrow, M2: 5% to 24% blast cells in bone marrow, M3: ≥25% blast cells in bone marrow.
UKALL: United Kingdom Acute Lymphoblastic Leukaemia - 2011 interim guidelines.
BMF: Burlin-Frankfurt-Munster.

In terms of risk profile, 15(31%) LG patients and 30 (60%) UKALL patients were stratified as standard risk, while the remaining in both the groups were high-risk. RER was observed in 18(37.5%) patients in the LG group of whom 7(14.5%) were standard risk and 11(23%) had high risk. In the UKAAL group, 14(28 %) patients achieved RER; 10(20%) standard risk and 04(08%) high risk. End of induction-remission was achieved in 38(79%) LG patients; 11(29%) standard risk and 27(71%) high risk. In the other group, 36(72%) patients, including 20(40%) standard risk and 16(32%) high risk, achieved end-of-induction remission. All 14(100%) patients with RER in UKALL group and 16(89%) in LG group achieved remission at the end of induction therapy (Table-3).

Risk group was not a significant prognostic factor (p=0.349), but RER was significantly associated with rate of end-of-induction remission (p=0.003). RER was significantly associated with end-of-induction remission rate in patients in the UKALL group (p=0.005).

Discussion

Paediatric ALL is a curable disease with long-term survival rate of 80-90% in the developed countries due to advanced systemic treatments, development of specialist paediatric oncology units and biomedical research. However, survival rates in the developing countries remain low. Failure to achieve end-of-induction remission in many patients and disease relapse is a major concern in low-income countries, like Pakistan, India and Bangladesh, due to inadequate treatments and paucity of post-treatment and supportive care. The current retrospective study reviewed the outcome of induction-remission in patients with standard or high-risk ALL treated as per LG protocol and UKALL 2011 interim guidelines. It compared rates of RER and end-of-induction remission in both the groups. Overall end-of-induction remission rate was found to be 76%. In LG group, 79% patients achieved end-of-induction remission compared to 72% in the UKALL group. Fadoo et al. did a prospective multi-institutional study in Karachi, reporting that 489 of 646 (75.6%) enrolled patients completed the therapy and 70% achieved remission.[15] In a retrospective study from Bangladesh, induction-remission was reported to be 86% (n=137).[16] The results of these studies are comparable to overall remission rate of the current study, but patients treated with LG protocol had relatively higher induction-remission rate of 79%.

In the current study, overall induction failure rate was 24%; 21% in LG group, and 28% in the UKALL group. This is consistent with the results of a study from Pakistan in which the induction failure rate was 30%.[15] In contrast, data from high-income countries showed higher induction-remission rates.[17,18] The induction failure rates in both treatment groups in the current study was also higher than the data from clinical studies in the United States and Europe where it was 5-10%.[19-21]

The ALL BFM 95 trial reported induction-remission rate of 100% in patients with RER.[22] In the current study, a statistically significant association was observed between RER and induction-remission in the UKALL group. All patients with RER in the UKALL group achieved end-of-induction remission. However,

remission rate was 89% in early responders in LG group. Among patients who had slow early response, 43% eventually achieved remission in the current study. The rate of remission in slow responders was equal in both treatment groups. However, Gaynon et al. observed that in patients with slow early response, only 13% later achieved remission.[23] Results of our study support existing data from developing countries indicating lower induction-remission rates in ALL patients with no significant variation between the two treatment groups. However, induction-remission rates are significantly better in high-income countries. A number of factors can be responsible for this variation. Due to lack of education and public awareness, patients usually present late with advanced disease. Access to specialised paediatric cancer treatment centres, support services and trained healthcare professionals is difficult due to limited resources in low-income countries. Many patients cannot afford costly and prolonged course of treatment. Moreover, difference in patient population, treatment regimens and definition used for induction failure may also be contributing factors for inconsistency in results. Risk categorisation by using cytogenetic tests and molecular analysis can help better stratify standard and high-risk patients to aid management decisions.

The current study has some limitations. The data was collected retrospectively from single treatment centre and the sample size is small. The results may not reflect treatment outcomes across the country. However, the findings highlight relatively low rates of induction outcome in developing countries, like Pakistan. A prospective randomised multi-centre study with larger sample size in needed to produce robust data in this regard.

Conclusion

There was no significant difference in end-of-induction remission rate between LG protocol and UKALL 2011 interim guidelines. RER was significantly associated with remission in overall study population. In UKALL group, significant association was seen between RER and remission.

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