ORIGINAL ARTICLE

RESPONSE OF INDUCTION THERAPY IN DIFFERENT IMMMUNOLOGICAL SUBTYPES OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

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ABSTRACT

Objective: To analyse response of induction chemotherapy in different immunological subtypes of acute lymphoblastic leukemia in children.

Material and Methods: This cross sectional study was conducted at the Department of Pathology, Pakistan Institute of Medical Sciences (P.I.M.S), Islamabad, Pakistan from June 2014 to September 2015. A total of 51 children ranging from 1-13 years of age, and diagnosed with ALL were included in the study. Immunophenotyping was recorded. All patients were given chemotherapy according to the BFM (Berlin-Frankfurt-Münster) protocol in the Oncology Department P.I.M.S. During induction therapy, 10 patients died. Remaining 41 patients received a complete course of induction therapy. Response to induction therapy was determined in these 41 patients by counting blast cells in the bone marrow at the end of induction therapy. Patients having <5% blasts are said to have achieved complete remission, while those having >5% blast cells are said to be in remission failure. Remisson pattern was used to assess the response of induction chemotherapy in different immunophenotypes of ALL and conclusions were drawn accordingly.

Results: Out of 51 patients , 10 patients died during induction therapy. Remaining 41 patients received complete course of induction therapy. These 41 patients were analysed for response of induction therapy. Out of 41 patients, there were 27 (65.9%) males and 14 (34.1%) females. Out of 41 patients of ALL, 36 (87.8%) patients had Precursor B-cell ALL, 3 (7.3%) patients had T-cell ALL, while 2 (4.8%) patients had Precursor T-cell ALL. So, 36 (87.8%) patients had B-lineage ALL, while 5 (12.2%) patients had T-lineage ALL. Out of 41 patients, 37 (90%) patients showed complete remission at the end of induction therapy, while 4 (10%) patients were not in complete remission. Out of 36 patients of Precursor B-cell ALL, 33 (91.7%) were in complete remission, while 3 (8.3%) were not in remission. There were 2 patients of Precursor T-cell ALL and both of them achieved complete remission. There were 3 patients of T-cell ALL. Two of them achieved complete remission, while 1 faced induction failure. Out of 10 patients who died during induction therapy, 5 (50%) patients died due to intracranial bleeding, and 4 (40%) patients died due to sepsis. Tumor lysis syndrome was observed in 1 (10%) patient. Bleeding was the common cause of death.

Conclusions: The present study showed that response to induction therapy is better in Precursor B-cell ALL as compared to T-cell ALL. It was also found that the rates of complete remission are lower in our setup. Induction death rate is high in our setup due to delayed platelet and blood transfusions, poor socioeconomic status,and lack of knowledge about the disease in population.

Key Words: Leukemia, immunophenotyping, chemotherapy, remissioin induction, precursor cell, lymphoblastic leukemia-lymphoma.

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common cancer in children[1-5]. The world wide incidence of ALL is about 3 per 100,000 population[2]. About 3 out of 4 cases occur in children who are below 6 years of age[2]. ALL constitutes 80% of childhood leukemias[6]. It is more common in males. About 85% of cases have B-cell ALL, and 15% have T-cell ALL[1].

In Pakistan, various studies have been done on Acute Lymphoblastic Leukaemia[7-12]. According to one study done by Yasmeen N in 2009, ALL is the most com-

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mon malignancy in children in Pakistan[12]. The median age of ALL patients in Pakistan is 6 years[7,12]. Male to female ratio of ALL in Pakistan is 1.7:1[12]. Another study done by Khwaja MR and collegues in 2005 suggested that 17% patients of ALL are T-cell ALL[11]. According to another study done by Fadoo Z et al, mean age of Pakistani children with ALL was 6 years[7]. Treatment of ALL consists of chemotherapy, which is given in three phases i.e remission induction phase, consolidation phase and maintenance phase[13]. Remission induction is the first phase of chemotherapy[14,15].

Drugs given in induction phase are Prednisone or Dexamethasone, Vincristine, Asparaginase, with or without Daunorubicine[1,13]. Consolidation therapy consist of Vincristine, Etoposide, Cytosine arabinoside and Cyclophosphamide. Maintenance therapy (also called continuation therapy) include methotrexate and mercaptopurine[1].

The response to remission induction therapy is an important prognostic factor in ALL. The standard method to assess response to chemotherapy is by counting the percentage of blast cells in the bone marrow at the end of induction therapy[16]. If there are less than 5% blast cells in the bone marrow, patient is said to have achieved complete remission[1,17]. If there are more than 5% blasts, induction failure is considered[18]. At the end of induction therapy, 98-99% of children with ALL achieve a complete remission, while 2-3% children have induction failure[16,18]. Response to induction therapy is different in different immunological subtypes of ALL. Overall, precursor B-cell ALL has a better cure rate than T-cell ALL[3,19].

MRD analysis monitors response more accurately as compared to conventional methods, and has higher prognostic value[1]. Therefore, in addition to bone marrow analysis MRD assay is increasingly being used to assess response to induction therapy in ALL patients. As MRD is more accurate specific and sensitive technique, its use is highly recommended in tertiary care centers of the country. However, in our setup where financial constrain is a big hurdle, microscopy is still a quite helpful tool for quick assessment and helping clinicians to make early diagnosis.

The data regarding rates of complete remission and induction death rate in the developed countries may not be representative of our population. Therefore, the present study was done to analyse the response of induction therapy in ALL patients in our setup.

MATERIAL AND METHODS

This cross sectional descriptive study was conducted at the Department of Pathology, Pakistan Institute of Medical Sciences (P.I.M.S), Islamabad. The study was conducted from June 2014 to September 2015. Total of 51 patients were included in the study by consecutive sampling technique. Newly diagnosed cases of ALL who have been given the induction chemotherapy, from 1 year age to 13 years age, and both sexes were included in the study. Patients who had relapsed ALL, infantile leukemia, and ALL patients already on chemotherapy elsewhere were excluded from the study. Out of these 51 patients, 10 patients died during the course of induction therapy and could not complete the induction treatment. The remaining 41 patients received a complete course of induction therapy. The remission response was assessed in these 41 patients.

Diagnosis of ALL was made on the basis of detailed history, clinical examination and detection of blast cells on peripheral blood film, and bone marrow aspirate. Immunophenotyping was recorded to know the subtype of ALL. All patients were given chemotherapy according to the BFM (Berlin-Frankfurt-Münster) protocol i.e a four-drug induction chemotherapy consisting of vincristine, prednisolone, L-asparaginase and daunorubicin for period of 28 days in the Oncology Department P.I.M. Bone marrow biopsy was done one weak after induction therapy ended (i.e at day 33±2). Remission status was determined by counting the percentage of blast cells in the bone marrow at the end of induction therapy. Remission pattern was noted as complete remission (<5% blasts in bone marrow) or induction failure (>5% blasts in bone marrow).

All data was analysed by using SPSS version 18.0. Continuous variables like age, TLC count , were measured in Mean and Standard deviation. Categorical variables like sex, remission pattern were measured in frequency and percentage. The response to induction therapy was stratified according to subtypes of ALL.

RESULTS

A total of 51 newly diagnosed cases of ALL were included in the study. Out of these, 10 patients died during the course of induction therapy. The remaining 41 patients received a complete course of induction therapy. The remission response was assessed in these 41 patients.

The characteristics of 41 patients who completed the induction therapy are given in Table 1. Age of the study sample ranged from 2 year to 13 years (mean age of 6.6 years ± 2.67 SD). Male to female ratio was 1.9:1. Ratio of B-lineage to T-lineage ALL in the study sample was 7.2:1. Table 2 and 3 shows remission status in different immunological subtypes of ALL. The clinical charasteristics of 10 patients who died during induction therapy, and their cause of death are given in table 4 and 5 respectively.

DISCUSSION

The cure rate of ALL has reached almost above 80% due to present treatment strategy and better supportive care of patients[13]. The response to the chemotherapy is one of an important prognostic factors in ALL[1,16]. Patients who achieve complete remission have a better prognosis. Children with precursor-B cell ALL

Table 1: characteristics of Patient who received complete course of induction therapy (N=41)

Variables	n (%)
Age	
1-5 years	14 (34.1%)
6-10 years	24 (58.5%)
11-13 years	3 (7.3%)
Gender	
Male	27 (65.9%)
Female	14 (34.1%)
TLC at presentation	
$<50x10^9/L$	31 (75.6%)
$>50x10^9/L$	10 (24.4%)
Chief complaints at presentation	
Fever	35 (85.3%)
Weight loss	15 (36.5%)
Nausea/vomiting	1 (2.4%)
Cough	1 (2.4%)
On examination	
Pallor	38 (92.7%)
Hepatomegaly	36 (87.8%)
Splenomegaly	28 (68.3%)
Lymphadenopathy	26 (63.4%)
Testicular swelling	1 (2.4%)
Petechial rash	11 (26.8%)
Mediastinal involvement	4 (9.7%)
CNS involvement	1 (2.4%)
Immunophenotype	
Precursor-B cell	36 (87.8%)
Precursor-T cell	2 (4.8%)
T cell ALL	3 (7.3%)

Table 2: Remission status in 41 patients of ALL at end of induction therapy (day 33)

Remission status	N (%)
Complete remission	37 (90%)
Not in remission (Induction failure)	4 (10%)

have better cure rate than that of T-cell ALL[1,3,13]

In the present study, out of a total of 41 cases of ALL, 37 (90%) patients showed complete remission at the end of induct in therapy, while 4 (10%) patients faced induction failure. This shows a lower rate of complete remission as compared to local and international studies. According to a local study done by Mushtaq N at Aga Khan University Hospital, Karachi, children

Table 3: Remission status in different immunological subtypes of ALL

Remission status	Immunophenotypes		
	Precursor B-cell ALL n (%)	Precursor T-cell ALL n (%)	T-cell ALL n (%)
Complete remission	33 (91.7)	2 (100)	2 (66.7)
Not in remission Inducton failure)	3 (8.3)	—	1 (33.3)
Total	36 (100)	2 (100)	3 (100)

Table 4: Characteristics of 10 patients who died during induction chemotherapy

Variables	N (%)
Age	
1-9 years	6 (60%)
>9 years	4 (40%)
Gender	
Males	5 (50%)
Females	5 (50%)
TLC at presentation	
$<50x10_9/L$	8 (80%)
$>50x10_9/L$	2 (20%)
Immunophenotype	
Precursor-B cell ALL	9 (90%)
Precursor-T cell ALL	1 (10%)

Table 5: cause of death in 10 patients during induction therapy

Cause of death	N (%)
Bleeding	5 (50%)
Infection	4 (40%)
Tumour lysis syndrome	1 (10%)

less than 15 years of age were evaluated for response to induction therapy. It was found that a complete remission was achieved in 97% cases[8]. In another study done by Khalid S in Karachi, data of children with ALL over a period of 17 years was analysed. It was found that 97.8% of patients achieved complete remission by the end of induction therapy[20].

In another local study done by Idris M at Armed Forces Institute of Pathology, Combined Military Hospital, Rawalpindi; response to induction therapy was evaluated in a total of 33 patients less than 15 years of age. At the end of induction, complete remission was achieved in 31 out of 33 (94%) patients while 2 (6%) pa-

tients did not achieve remission 21. However , one of the local studies done by Fadoo Z in Karachi showed results somewhat closer to that reported in the present study[4]. Out of 646 patients, 489 completed induction therapy, and in them 450 (92%) achieved complete remissin while 39 (8%) did not achieve complete remission[7].

International studies show a higher rate of complete remission and lower rates of induction failure as compared to the present study. Schrappe M et al reported that induction failure occurred in 2.4% of patients[18]. Pui CH and colleagues published the treatment data of 10 clinical trials involving children with ALL. The data showed a complete remission rate of 98-99% in all the trials, including ALL-BFM trial[22]. Complete remission rate of 97% was reported in study of Starry J[23]. Cooper SL reported that in Western population, induction failure occurs in 3-5% ALL patients[1].

The response to induction chemotherapy in the present therapy (90%) is much lower than that reported in the regional and the Western literature. In the present study, it was found that out of 36 patients of Precursor B-cell ALL, 33 (91.7%) achieved complete remissin, while 3 (8.3%) faced induction failure. Out of 3 patients of T-cell ALL, 2 (66.7%) patients with T-cell ALL achieved complete remission, while 1 (33.3%) patient with T –cell ALL faced induction failure. This data suggested that complete remission rates were higher in B-lineage ALL as compared to T-lineage (91.7% for B-lineage versus 66.7% for T-lineage), and that induction failure is commonly seen in T-cell ALL as compare to B-cell ALL (33.3% versus 8.3%).

These findings were consistent with different local and international studies done so far. In a local study done by Fadoo Z in Karachi, complete remissin rate in B-lineage ALL was 92.4% and in T-lineage was 88.2%[7]. Schrappe M et al reported in their study that induction failure occurred most commonly in patients with T-lineage ALL[18]. Cooper SL also reported the similar finding of high rate of induction failure in T-cell ALL[1]. Lauten M et al reported in their study a higher rate of remission in precursor B-cell ALL as compared to T-cell ALL, which is consistent with the present study[24]. So, better remission rates in Precursor B-cell ALL as compared to T-cell ALL in the present study were quite consistent with local and international studies.

In the present study, out of 51 patients treated for ALL, 10 patients died during the induction therapy, while remaining 41 patients had completed induction therapy. So, the induction death rate in the present study was 19.6%. Out of 10 patients, 5 (50%) died due to bleeding in the form of intracranial bleeding, 4 (40%) died due to sepsis (infection), and 1 (10%) died due to tumor lysis syndrome. High mortality rate of 19.6% in our population was mainly due to haemorrhage and infections during the chemotherapy. Similar data has been reported by Mulatsih and Mostert from Indonesia who reported high mortality rate of 29% and 23%[25,26]. The incidence of treatment related mortality in the developed countries is about 2-3%.[1,27,28]. This shows that there is a need to improve the supportive care for children receiving treatment for ALL in the developing countries. Poor socioeconomic status, poor knowledge of the patient and attendants about the disease; the belief of the attendants that the disease is uncurable and resultant delay in platelets and blood products arrangement are the contributing factors for high mortality rate in our setup.

Limitations of the study:

1. At the time of study, immunophenotyping was not available in P.I.M.S. So, we had to rely on other institutions for immunophenotyping.
2. The study was conducted in a single Tertiary care center in the capital. Further studies are required to be done on larger population sample to generate more significant figures.

CONCLUSION

The results of the present study showed that the response of the induction therapy was better in Precursor B-cell ALL as compared to T-cell ALL. Hence there is a correlation between treatment response and immunophenotype in our setup in line with international studies.

The mortality rate during induction therapy is high in our setup. Its main causes are bleeding and infections .Timely platelet and blood transfusions along with infection control needs to be ensured to decrease the mortality rate.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Khan MI:	Main idea.
Yasmeen N:	Result, compilation data analysis
Khan SA:	Data collection.
Rahman-SU:	Discussion & proof reading.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.