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Original Research Article

A study on clinical, immunophenotypic pattern in pediatric acute leukemias in a teaching hospital

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ABSTRACT

Background: Acute leukemia contributes to nearly one third of the pediatric malignancies. For effective management of a curable malignancy, the epidemiology of childhood leukemias and audit of previously treated patients would be required. The objective was to study the clinical and immunophenotypic pattern of acute leukemia in children <12 years of age admitted in a tertiary centre.
Methods: Prospective study done on 31 children, diagnosed as leukemia and treated over a period of 3 years in GRH, Madurai. Detailed history analysis, clinical examination, lab investigations including flowcytometry were done.
Results: ALL was the most common acute leukemia in children (90.3%). 85.7% were identified as B-cell and 14.3% as T-cell. Of the B-ALL, 87.5% was pre-B, 8.3% pro-B and 4.2% mature B ALL. Myeloid antigen co-expression was seen in 35.7%. Fever was the most common symptom (87%) and hepatosplenomegaly was the most common sign (>90%). Poor outcome was noted in 42.3%. T-cell appeared to have worse prognosis than B-cell but did not retain independent prognostic significance in univariate analysis.
Conclusions: B-ALL was more common than T-ALL. Extra medullary organ involvement indicates increased tumor burden and poor outcome. None of the clinical or laboratory parameters appeared to predict poor outcomes in our study and this may be due to small sample size. This study provides an insight into the data regarding the epidemiology, clinicopathologic feature and outcome of acute leukemia in a center with low resource settings.

Keywords: Acute lymphoblastic leukemia, Flowcytometry, Immunophenotype, Myeloid antigen

INTRODUCTION

Acute leukemias are one of the most common malignancies in children aged <15 years, accounting for nearly 30%. Though several risk factors have been proposed, a specific etiology has not been determined till date. Fortunately, it is one of the curable malignancies in children and hence early diagnosis is essential.

Studies from India have reported variable outcomes, with few specialized centers showing a favourable outcome in more than 70%.[1] Not all children have access to the regional Cancer Institutes of India. Children managed at other centers must also receive a minimum standard of care. Multiple poor prognostic factors are described in ALL such as age <1 year or >10 years, male sex, very high leukocyte count, mature B-cell type and T-cell type of ALL, chromosomal abnormalities {ex: t (9;22) or t (4;11)}, which when present have a high chance of relapse and mortality. Whether the risk factors in our population are similar or any other unique risk factor operates in our patients, has to be confirmed.

Flowcytometry has now become a standard tool for diagnosing and monitoring acute as well as chronic leukemia. Immunophenotyping by flow cytometry enables accurate diagnosis and treatment on the basis of which further treatment is planned. Immunophenotyping

also enables risk stratification. Therefore, there is an emerging need to create a leukemia database in the respective population. Establishing a national registry would address many of these issues. However, in the absence of such a system in place as of now, studies from regional/district hospitals can act as a reasonable substitute.

Risk Stratification by Immunophenotype: CD 34+ is a poor prognostic factor when it is associated with Multi-drug resistant gene (MDR1). CD7, CD56 which is associated with extramedullary disease are prognostically unfavorable. CD19 does not have prognostic significance. Detection of residual or recurrent blasts by multi parameter flow-cytometry following therapy predicts outcome.

Immunophenotyping of ALL

Precursor B-cell ALL

Diagnosis of precursor B-ALL by FCM is primarily based on the following antigen expression: CD19, CD34, HLA-DR and CD10. Detection of cytoplasmic CD79a, CD22 and TdT characterize B-lineage.

T- Cell ALL

The T-cell phenotypes corresponding to early stages of differentiation are CD34+/CD7+/CD2+ and some of them are also CD10+. The latter represents the pre-T cell, a precursor detected in the bone marrow. More mature phenotypes lack CD34 and CD10 and through a transitional stage, which is negative for CD4 and CD8 (stage II). In stage III the cell normally becomes double positive (CD4 and CD8). The cells are also TdT+. Cytoplasmic CD3 is a characteristic marker for T-cell lineage. CD7 is the composite phenotype essential for the diagnosis of T-cell ALL. As it is evident that, in the absence of CD7 expression, T-ALL diagnosis cannot be entertained.

METHODS

This study aims to analyse the clinical and immunophenotypic pattern of acute leukemias in children <12 years of age admitted in Govt. Rajaji Hospital, Madurai using a structured proforma which includes history, clinical examination, lab investigations.

It is a prospective, observational study. Carried out in pediatric hemato-oncology ward, ICH and RC, GRH, Madurai, from September 2012 – August 2014.

Leukemia is defined by the presence of >25% leukemic blasts in bone marrow in ALL and >20% in AML. All newly diagnosed cases of acute leukemia, in children <12 years of age are included in the study. The ethical clearance is obtained from Institutional ethics committee, Madurai Medical College and Govt. Rajaji Hospital, Madurai. All patients (<12 years) diagnosed as acute leukemia in pediatric hemato-oncology ward in ICH and RC, GRH, Madurai were included as subjects of the study. Informed consent was obtained from the parents of the children included. All patients underwent detailed history analysis, clinical examination and investigations as per structured proforma.

The investigations like complete blood count, peripheral smear, bone marrow aspiration, CSF analysis, flowcytometric analysis, RFT, LFT, Chest X ray, ECG, ECHO, USG abdomen, microbiological investigation, serum Uric acid, amylase, CT Brain, chest (if indicated) were done in all patients.

Patients diagnosed as ALL were treated with MCP-841 protocol, considering all patients as high risk. AML patients were treated with Cytarabine (7 days) and Doxorubicin (3 days) cycles. Relapsed cases were treated with BFM-Relapse protocol.

Age, sex, initial WBC count, hemoglobin, platelet count, hepatomegaly, splenomegaly, lymphadenopathy, parotid enlargement, presence or absence of mediastinal lymphadenopathy, renomegaly, sub-type of ALL based on immunophenotyping were analysed. EGIL scoring system was applied to find any biphenotypic leukemia.

Failure to achieve remission in 28th day bone marrow aspiration is termed as induction failure. Poor outcome patients include those who had expired, induction failure, relapsed even before the completion of treatment. Analyzing the clinical and immunophenotypic profile of poor outcome group of patients with the rest of the patients.

Sample collection and processing

In suspected cases of leukemia, peripheral blood smear and bone marrow aspirates taken from iliac crest of patients was sent to pathology department for immediate staining and analysis. Slides were stained with PAS, Sudan Black B and MPO stains and reports were given accordingly.

5 ml of heparinized venous blood sample were taken for immunophenotype analysis. The cells were gated according to percent viability, processed in a flow cytometer by indirect immunofluorescence technique using single color method.

B-lineage markers - CD19, CD79a, CD22, CD20, CD10 (>20% of total cells). Among B-ALL, If CD10+, it is pre-B cell and if negative, it is pro-B cell. If IgM (surface) +, it is mature B-cell. T-lineage markers include CD2, CD3, CD5, CD7, CD4, CD8.Myeloid markers are CD13, CD14, CD15, CD33, CD117, MPO. Multipotent stem cell markers are CD34, CD45, TdT, HLA-DR. Myeloid antigen co-expression was defined as > 30% leukemic cells positive for myeloid markers. All the data were

entered in Excel sheet and statistical analysis done using Epi Info 7 software. Random variables were expressed in mean ± SD, non-random variables in median and inter-quartile range. For categorical variables, chi square or Fisher exact test was used. P value < 0.05 was considered to be significant.

RESULTS

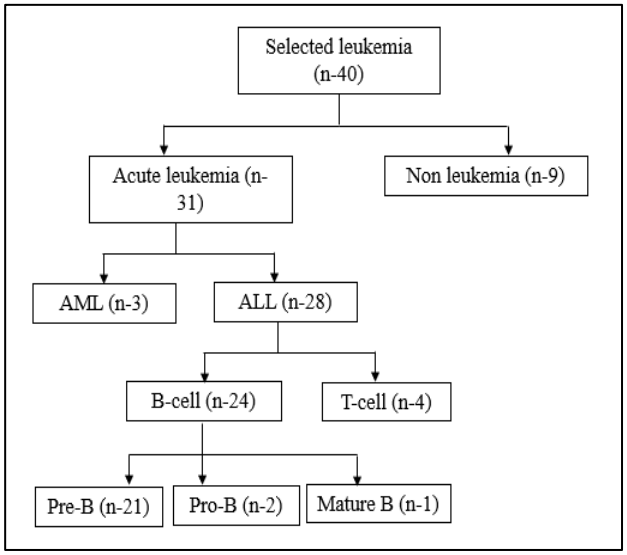

Figure 1: Overview of the study.

Acute Lymphoblastic Leukemia (ALL) was the commonest (n-28,90.3%) and the remaining three patients had Acute Myeloid Leukemia (AML) (9.7%) The leukemia patients were aged 1.5 to 12 years with a mean age of 6.13 years and standard deviation of ±3.25 years. No significant difference in sex distribution among ALL, whereas AML shows male predilection. Common symptoms during presentation were shown in Figure 2.

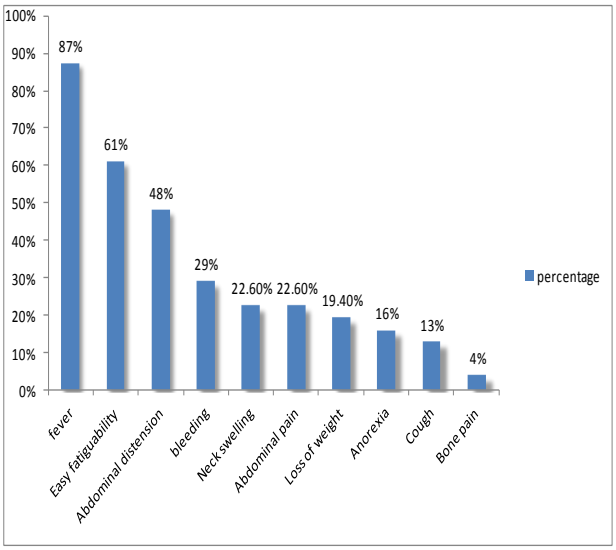

Figure 2: Clinical symptoms in acute leukemia patients at presentation.

Common clinical signs during presentation were revealed in Table 1.

Table 1: Clinical signs in acute leukemia patients at presentation.

Clinical signs	No. of patients (n-31)	%
Hepatomegaly	30	96.8
Splenomegaly	28	90.3
Pallor	24	77.4
Lymphadenopathy	16	51.7
Petechiae/ Purpura	7	22.6
Bone tenderness	5	16.1
Parotid enlargement	3	9.7
CNS manifestation	1	3.2

Serum creatinine with mean±SD-0.71±0.16 and bilirubbin levels with mean±SD –0.78±0.12 were within normal limits in all these individuals. Chest radiograph was routinely performed, and it was abnormal in three patients (9.7%).

Two of them had pleural effusion and one had mediastinal widening. Two patients in T-ALL group and one in B-ALL group had renomegaly in USG abdomen. Other imaging investigations were performed when clinically indicated. The hemoglobin value ranged from 2.6 g/dL to 15 g/dL with a mean±SD of 6.48±2.79 g/dL. 89.3% of ALL cases have HB <10 g%.

The total leukocyte count in our patients ranged from 2600 to 2,91,000 cells/cu.mm. Median is 9100 cells/cu.mm. Four patients had total leukocyte count >1,00000 cells/ cu.mm (14.3%), as shown in Figure 3.

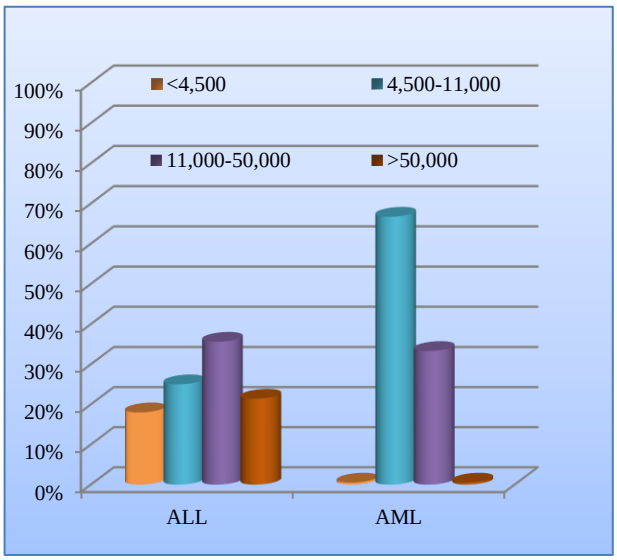

Figure 3: Total leukocyte count analysis.

Platelet counts ranged from 4000 to 2,50000 cells/cu.mm with a median of 28000 cells/cu.mm. CD13, CD15, CD33, CD117, MPO are positive in all the three cases of AML (100%). CD123 in two cases and CD56 in one of

the three cases. CD19 was a consistent marker in B-ALL (96%) followed by CD10 (91.7%).

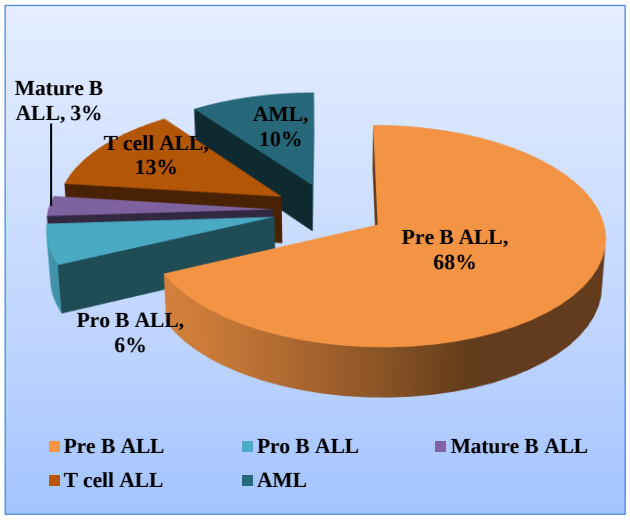

Figure 4: Distribution of types of leukemia.

Table 2: Commonly co-expressed myeloid markers in ALL.

CD marker	No. of cases (n-24)	%
CD 19	23	96
CD 22	21	87.5
CD 79a	13	54.2
CD 10	22	91.7
IgM (surface)	1	4.1
CD 34	10	41.6
CD 45	8	33.3
HLA-DR	11	45.8
CD 13	9	37.5
CD 15	7	29
CD 33	1	4.1
TdT	5	20.8
MPO	0	00

9 out of the total 21 patients of pre-B cell ALL had myeloid co-expression. CD13 and CD15 were the commonly co-expressed myeloid markers in ALL, as shown in Table 2. CD3 positive in all 4 cases of T-ALL (100%). CD5 and CD7 were positive in three of the four T-cell ALL patients (75%). One patient had positive myeloid markers such as CD13, CD33, CD15 and was labelled as T-cell ALL with aberrant myeloid expression, as shown in Table 3.

Among 28 cases, 4 were T-cell ALL, remaining 24 cases were B-cell ALL (pre-B cell -21, pro B cell – 2, Mature B cell–1).10 cases showed myeloid co expression (35.7%), as shown in Table 4. Most cases of B-cell and T-cell ALL were in the age group of 3-10 years, as shown in Table 5. Overall male female ratio in ALL was 1.3:1. None of the subtypes of ALL had any significant relationship with a particular gender as evident from the non-significant p value.

Table 3: T-cell ALL with aberrant myeloid expression.

CD marker	No. of cases (n-4)	%
CD 2	2	50
CD 3	4	100
CD 4	1	25
CD 5	3	75
CD 7	3	75
CD 8	0	00
CD 45	1	25
CD 13	1	25
CD 15	1	25
CD 33	1	25
MPO	0	00

Table 4: All sub-types based on immunophenotype.

ALL subtype	Number of patients (n-28)	%
B cell ALL	24	85.7
Pre-B cell ALL	21	87.5
Pro-B cell ALL	2	8.3
Mature-B cell	1	4.2
T cell ALL	4	14.3
Myeloid Ag+	10	35.7

Table 5: Age distribution.

Age (in years)	B-ALL (n-24)	T-ALL (n-4)
<1	-	-
1-2	5 (21%)	1 (25%)
3-10	17 (71%)	2 (50%)
>10	2 (8%)	1 (25%)

Neck swelling, bleeding, cough appeared to be more common in T-cell than B-cell clinically but not statistically significant, as shown in Table 6. Hepatomegaly and splenomegaly were the most common signs in both B-cell and T-cell ALL. Parotidomegaly was noted in 2 T-cell patients and one mature B-cell patient, as shown in Table 7.

Table 6: Presenting symptoms of ALL.

Symptoms	B- ALL (n-24) (%)	T- ALL (n-4) (%)	p value
Fever	20 (83.3)	4 (100)	0.91
Abdominal distension	15 (62.5)	3 (75)	0.93
Easy fatigue	13 (54.2)	3 (75)	0.81
Anorexia/ weight loss	8 (33.3)	2 (50)	0.93
Neck swelling	6 (25)	3 (75)	0.16
Bleeding manifestation	5 (20.8)	2 (50)	0.60
Bone /Joint pain	5 (20.8)	1 (25)	0.58
Cough breathlessness	4 (16.7)	2 (50)	0.39

Of the total 28 ALL cases, 20 were alive, 6 died and 2 cases lost to follow up. Induction failure was noted in 3 out of 28 patients (alive-2; death-1). 3 out of 28 patients (10.7%) relapsed. All the three are alive and under follow up (2 – Pre-B cell and 1-T-cell). The site of relapse was bone marrow. No CNS, testicular or any other site relapse was noted in the present study.

Table 7: Presenting signs in ALL.

Signs	B-ALL (n-24)	T-ALL (n-4)	p value
Hepatomegaly	23 (96)	4 (100)	0.298
Splenomegaly	23 (96)	4 (100)	0.298
Pallor	20 (83.3)	3 (75)	0.762
Lymphadenopathy	14 (58.3)	3 (75)	0.937
Bleeding	3 (12.5)	2 (50)	0.267
Bone tenderness	5 (21)	00	0.762
Parotidomegaly	1 (4)	2 (50)	0.059
Renomegaly	1 (4)	2 (50)	0.059
Mediastinal widening	0	1 (25)	0.298
CNS manifestation	0	1 (25)	0.298
Testicular enlargement	Nil	Nil	

On analysing the cause of death, 2 cases died of severe pneumonia, 3 cases had sepsis with UGI bleed and 1 case died of CNS hemorrhage. The 2 cases which were lost to follow up was excluded from the final outcome analysis(n-26). 11 out of 26 (42.3%)cases had poor outcome. These patients (n-11) were compared with the rest of the population (n-15). Among those with age <2 years, CNS involvement, myeloid antigen coexpression, clinically poor outcome was noted. None of them with T-cell or renomegaly had good outcome. But statistically no significant difference was made. Renomegaly in ultrasound was noted at the time of diagnosis in two T-cell ALL and one Pre-B cell ALL.

Table 8: Analysing the factors with poor outcome.

Clinical/lab feature	Poor outcome group (n-11)	Others (n-15)	p value
Age ≤ 2, 10	5	2	0.168
Male gender	6	9	0.934
Lymphadenopathy	7	8	0.901
Mediastinal lymphadenopathy	1	0	0.878
Parotidomegaly	1	1	0.606
Renomegaly	3	0	0.06
Bleeding	4	3	0.629
CNS involvement	1	0	0.878
Hb (≤5)	5	5	0.826
TLC (>50000)	3	2	0.690
Platelet count (≤20000)	5	6	0.496
CALLA +	10	6	0.496
My Ag +	5	5	0.826
T-cell	3	0	0.06

One of the two T-cell ALL patient expired and the other relapsed. The B-cell ALL patient also relapsed. On follow up during treatment kidney and also parotid enlargement decreased in size which indicates tumor infiltration and late presentation of the patient. The details are shown in Table 8.

DISCUSSION

Studies from India report variable outcomes in pediatric acute leukemias, with few specialized centers showing a favorable outcome of more than 70%.[1] But given the vast differences in access to and standard of health care across the country the same good results are not reproducible in all centers. Among the various factors affecting the outcome, bulky disease, mediastinal widening, increased white count, thrombocytopenia and age <3 years are known to have poor outcomes.[2-5]Over the study period of two years, 35 cases of acute leukemia were diagnosed. Acute lymphoblastic leukemia (90.3%) was the most commonly diagnosed acute leukemia, a data which is comparable to studies from the west as well as from other parts of India.[6] In accordance with the literature, the most common age group is 3- 9 years.[7] No infantile leukemia was noted In the present study as opposed to 3-5% in other studies (Table 9).[8]

Table 9: Correlation with median age of onset.

	Median age
Present study	6 years
Tata Memorial Hospital [5]	7.2 years
AIIMS [4]	7.6 years

No male or female preponderance was noted, analogous to the data from a referral institute in Pakistan, but studies from the west and other parts of India however suggested a male preponderance in ALL.[9] Kulkarni et al noted a significant male preponderance of 2.5:1 after an analysis of data from India.[10]

Table 10: correlation of presenting clinical signs.

Signs	Present study	AIIMS study	Tata memorial study
Hepatomegaly	96.8	95	80
Splenomegaly	90.3	90	78
Lymphadenopathy	51.7	87	79
Mediastinal mass	3.6	7.8	1.8
Parotidomegaly	10.7	-	-
Renomegaly	10.7	-	-

Fever was the commonest presenting feature (87%), followed by easy fatigability in 57.6%. In our present study, bone pain was present in 6.4% patients, whereas certain other series report bone pain in 21% to 38% of the patients with ALL.[11-13] Most of the cases in our population present very late as is evident by the extra-medullary organ involvement which indirectly indicates

tumor burden. The presence of parotidomegaly and renomegaly and its significant association with T-cell leukemia is noted. Enlargement of parotid glands as well as kidneys have been reported in acute lymphoblastic leukemia.[14-16]

Anemia and thrombocytopenia are much more common, found in up to two thirds of the patients. Anemia of less than 10 g/dL hemoglobin was found in 90% of our patients. Leukocytosis >50,000 cells/cu.mm was found in up to 21.4% patients of ALL. A normal or below normal count was present in 45% patients. Our data was no different from the existing literature.

Table 12: Prevalence of various types of leukemia.

ALL subtype	Present study (n-28)	Japanese study
B-cell ALL	85.7	87
B cell subtype		
Pre-B cell ALL	83.3	81
T cell ALL	14.3	13

Apart from being a common feature of ALL, thrombocytopenia also bears prognostic significance, and has been shown to affect outcomes.[18] However, this was not replicated in the present study and there seemed to be a poor statistical correlation of platelet count with outcome.

Bleeding seen in leukemia patients appear to be multifactorial, and not related to thrombocytopenia alone. For example, gum bleeding was present in children with platelet count of one lakh cells and few patients had no bleed despite a platelet count of few thousand cells only. Other factors like leukocytosis leading to leukostasis may play a role in these bleeding tendencies. Extreme degree of leukocytosis (1,00,000 cells/cu.mm) was seen in 6 cases of ALL (14.3%) which coincides with studies done in Tata Memorial Hospital (14.6%), AIIMS (18%).[4,5]

Among the acute lymphoblastic leukemia, T cell ALL flowcytometry accounted for 14%, and the remaining 86% being B cell ALL. Diagnosis of ALL by flowcytometry done in 1774 Japanese children yielded a similar result. Here T-cell and B-cell ALL were responsible for 13% and 87% cases respectively.[19]

The B-cell ALL were further characterized and more than 81% of these cases were found to be pre-B cell type. In our series of 24 B-cell ALL patients, 83.3% (n-20) were Pre-B cell ALL. CD 13 and CD 33 which are markers of myeloid lineage are occasionally noted in ALL, both B and T cell. In our series one out of the four T-cell ALL and eight of the twenty B-cell ALL had markers of myeloid lineage.

Statistically significant difference in myeloid expression between T and B-cell ALL was reported in a study of Japanese children with ALL.[19]

Factors associated with poor outcome

Though a prognostic value of age in predicting outcome could not be established clearly from our study, the proportion of patients with poor outcome were more in the age group less than two years as opposed to those more than two years of age.

This is consistent with the national and international data where younger age has been associated with poor outcomes.[17,18]

In the present study, no statistically significant difference in outcome was observed between those with myeloid co-expression and those without myeloid co-expression.

Out of the three cases with either T-cell or renomegaly, none of them had good outcome. But a statistical significance was not obtained. Smaller sample size and varying duration of follow up of each of these patients could possibly affect this analysis in the present study.

Six patients (21.4%) of the total 28 ALL patients succumbed to the disease prior, in contrast to well developed nations where a treatment success of more than 80% has been already achieved.

A study from Adyar cancer institute showed that the completeness of treatment and the type of hospital emerged as one of the most important factor affecting the survival in paediatric cancers, especially acute lymphoblastic leukemia6. Poor outcome (death, induction failure and death) in our series was 42.3%. Relapse in central nervous system and testes are known, but all the three of our patients had bone marrow relapse only.

Our study has certain limitations, the main ones being a small sample size. A larger sample size would have found more significant factors which affected outcome in these children.

This study provides a baseline data which can guide further planned data collection. Also, it provides an insight into observation of T-cell leukemia and myeloid co-expression in immunophenotype results and look carefully for organ enlargement including kidneys. Further it should be emphasized that establishing a national and regional cancer registry will enable systematic data collection. Discrepancies in health care resource allocation can be sorted out only if there is clear data on the epidemiology of all pediatric cancers (the commonest being ALL) from various regions of the country.

CONCLUSION

In summary, ALL (90%) is the most common acute leukemia in children <12 years of age. Mean age of 6±3.25 years with no sex predilection was noted. Fever was the most common symptoms (87%) and

hepatosplenomegaly was the most common sign(>90%). Parotidomegaly and renomegaly had significant association with T- ALL. B-cell (85.7%) was more common than T-cell (14.3%). Myeloid antigen co-expression was seen in 35.7%. CD13 was the most commonly associated myeloid marker (35.7%).

None satisfy the criteria for biphenotypic acute leukemia. T-lineage ALL carries worse prognosis than B-cell but did not serve as a statistically significant prognostic factor. Poor outcome was noted in 42.3% of children even before the completion of treatment. Infection was the commonest cause of death. It is still difficult to treat complications in low resource settings.

Recommendations

Immunophenotyping should be done in all cases of leukemia, even in resource limited settings for accurate diagnosis, prognostication and tailoring of treatment.

Presence of extra-medullary organ involvement including renal enlargement should be looked for carefully at the initial presentation.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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