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Original Article

Assessment of Expression and Prognostic Significance of Interleukin 3 Receptor Alpha Subunit (CD123) in Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is a malignant expansion of immature lymphoid cells that results from multi-step genetic changes in a single lymphoid progenitor cell. Flowcytometric Immunophenotyping of childhood acute lymphoblastic leukemia (ALL) plays an important role not only in the diagnosis and classification of B and T cell lineages, but also in predicting the outcome. B-lymphoid blasts from acute lymphoblastic leukemia (ALL) have been shown to express functional CD123 and the CD40 ligand stimulates proliferation of precursor-B (pre-B) ALL by upregulating CD123 expression.

Aims of the study: 1. Detect expression of interleukin 3 receptor (alpha chain) CD123 in childhood acute lymphoblastic leukemia cases (ALL).
2. Correlate the expression of CD123 with hematological parameters and to the induction chemotherapy.

Patients and Methods: Thirty three patients under 15 years of age admitted to the Children's Welfare Teaching Hospital (CWTH) for diagnosis and treatment. Haematological parameters including Hb, WBC count, and platelet count were obtained from the file records of the patients. Flowcytometry Immunophenotyping was done for interleukin 3 receptor alpha subunit (CD123),CD19 and CD3 were investigated in those ALL patients by using four –color Cyflow® Cube 6 flow cytometry device (PartecCyflow®, German).

Results: In B-ALL CD123 expression was positive in 21 out of 23 patients (91.3%), while in T-ALL no patient express CD123. There was 95.6% of B-ALLs had achieved complete remission after first course of induction therapy, versus 80% of T-ALL. In B-ALLs all 21 patients who were CD123 positive had responded to induction remission, moreover the only one case who did not respond to therapy was CD123 negative and PAS negative; p-value < 0.05.

Conclusion: CD123 is frequently expressed in pediatric ALLs blasts. CD123 was exclusively expressed in B-lineage with absent expression in T-lineage ALLs. CD123 is significantly associated with good prognostic indicators and good treatment response to initial induction therapy.

KEYWORDS: Acute lymphoblastic leukemia (ALL), CD3, CD19, CD123, Flowcytometry, Immunophenotyping, Interleukin 3 receptor.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant expansion of immature lymphoid cells that results from multi-step genetic changes in a single lymphoid progenitor cell. Its incidence peaks between the ages of 2 and 4 years; rates are lower during later childhood, adolescence and young adulthood. It is the most common leukemia in children representing 23% of cancer diagnosis among children younger than 15 years.[1]

The French-American-British (FAB) morphologic classification of ALL was based largely on morphology where cases of ALL were categorized as L1, L2 and L3. And contained little prognostic or therapeutic information[2].

Leukemic cells from patients with ALL express a variety of different antigens that are also found on normal lymphocyte precursors at discrete stages of maturation.

Because leukemic lymphoblasts lack specific morphologic and cytochemical features, immunophenotyping by flow cytometry and genetic analyses are essential for diagnosis[3].

Flowcytometric Immunophenotyping of childhood acute lymphoblastic leukemia (ALL) plays an important role not only in the diagnosis and classification of B and T cell lineages, but also in predicting the outcome[2]. The World Health Organization (WHO) classification was revised in 2008 and has changed the classification to reflect increased understanding of the biology and molecular pathogenesis of the diseases.

The WHO classification divides these heterogeneous lymphoid diseases into 2 major categories: precursor lymphoid neoplasms and mature lymphoid neoplasms. The precursor lymphoid diseases include both B lymphoblastic leukemia/lymphoma and T lymphoblastic leukemia/lymphoma. The distribution of the immunophenotypic subsets in adult and pediatric ALL is similar, with precursor B-cell ALL accounting for the majority (70%–85%) of all cases, precursor T-cell ALL accounting for approximately 15% to 25% of cases; B-cell ALL cases are terminal.[4]

Deoxynucleotidyltransferase (TdT) positive, human leukocyte antigen (HLA)-DR positive and almost always positive for CD19 and CD79a. CD10 and CD22 are positive in most cases. The lymphoblasts in precursor T-cell ALL are TdT positive and most often express CD7 and cytoplasmic CD3; CD4 and CD8 are frequently co expressed on the blasts.[5]

Interleukin 3 (IL-3) is a potent hemopoietic growth factor which stimulates multipotential hemopoietic stem cells; it stimulates the formation of multilineage colonies in vitro and also maintains spleen colony forming units (CFU-S) in vitro. In addition, it serves as a growth factor for committed cells, including mast cells, megakaryocytes, eosinophils, erythroblasts, pre-B cells, and potentially pre-T cells.

CD123 is a subunit of a heterodimer IL-3 receptor, a member of the cytokine receptor superfamily. It is a 70 kDa protein, which binds IL-3 with high specificity but with low affinity. CD123 is encoded by the IL-3 alpha gene, located in the pseudoautosomal region (PAR) at the ends of the short arms of the X and Y chromosomes (Xp22.3 and Yp11.3). B-lymphoid blasts from acute lymphoblastic leukemia (ALL) have been shown to express functional CD123 and CD40 ligand stimulates proliferation of Precursor-B (pre-B) ALL by upregulating CD123 expression[6].

MATERIALS AND METHODS

This cross sectional prospective study was conducted on 33 pediatric patients with newly diagnosed ALL (23 B-ALLs and 10 T-ALLs), randomly selected in relation to sex. All patients were below 15 years old, were newly diagnosed morphologically as ALL and confirmed diagnosis by cytochemical stains and sub-typing by Immunophenotyping and with no history of steroid or chemotherapy absence of prior malignancy. ALL (L3 FAB was excluded). All patients who died before induction phase and all patients who missed from follow up were excluded.

Thirty three patients who were 21 male and 12 female under 15 years of age with mean age (6.3 ± 3.5) admitted to the Children's Welfare Teaching Hospital (CWTH) in Baghdad for diagnosis and treatment. The Patients' PB and BMA samples were analyzed in Teaching Laboratories of the Medical City in Baghdad.

For each patient a questionnaire form was done, haematological parameters including Hb, WBC count, and platelet count were obtained from the case file of the patients where they were done by hematology analyzer (Cell-DYN, RUBY list) Peripheral blood and bone marrow aspirate had been obtained, blood films was stained with leishman stain and examined by consultant hematologist for diagnosis.

Special stains with Sudan black B and PAS were recommended to confirm the diagnosis. Flow cytometry Immunophenotyping was done at Private Laboratory in Baghdad. For any case in the study morphology, cytochemistry, CD123, cCD3 and CD19 expression detection by flow cytometry were carried out to confirm the diagnosis as ALL and further subtypes whether B or T-cell lineage.

All patients were re-evaluated for complete remission achievement after one cycle of chemotherapy. Patients were assigned as 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 less than 10 years old with a presenting leukocyte count of less than 50x109/L, otherwise the patients were considered as High Risk (HR) ALLs. Response to treatment was measured by the number of blasts in bone marrow aspirate on day 28 of induction therapy.

Induction failure was defined as Failure to achieve remission after 1 month of therapy. Complete remission (CR) is defined by Cheson et al (< 5% bone marrow blast cells of normal cellularity and restoration of normal peripheral blood values of at least 1500/μL neutrophils and 100,000/μL platelets).[7]

BLOOD SAMPLING

A total venous blood sample of 2.5 ml and /or bone marrow aspirate sample of 0.5 ml was obtained from each patient included in this study, bone marrow aspirate was obtained from posterior superior iliac crest under aseptic technique, and the sample was collected in EDTA tubes for subsequent diagnosis depending on morphology, cytochemistry and immunophenotyping study by flow cytometry.

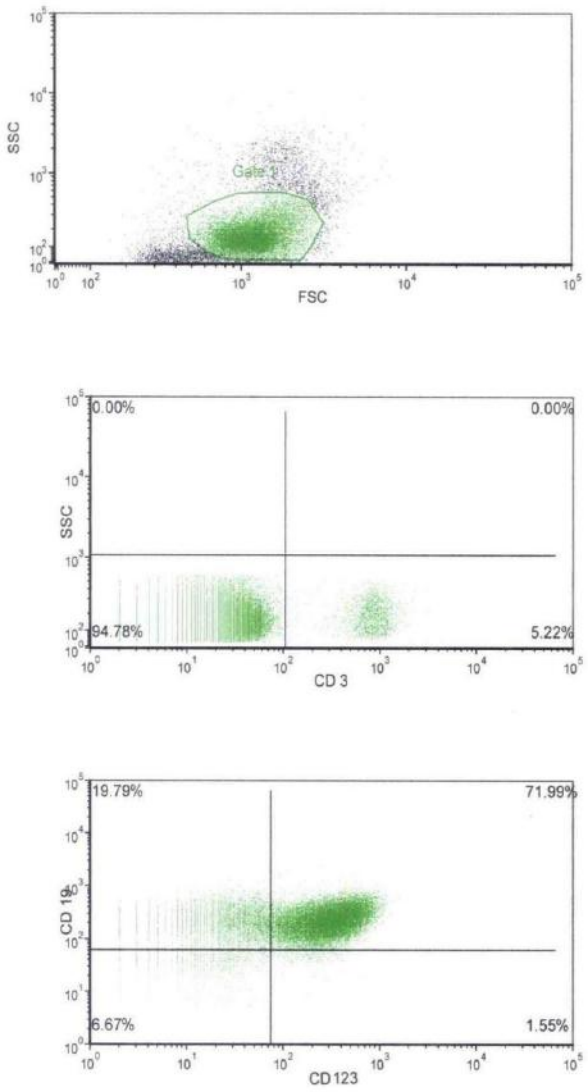


Fig 1: B-ALL shows positive CD123 expression

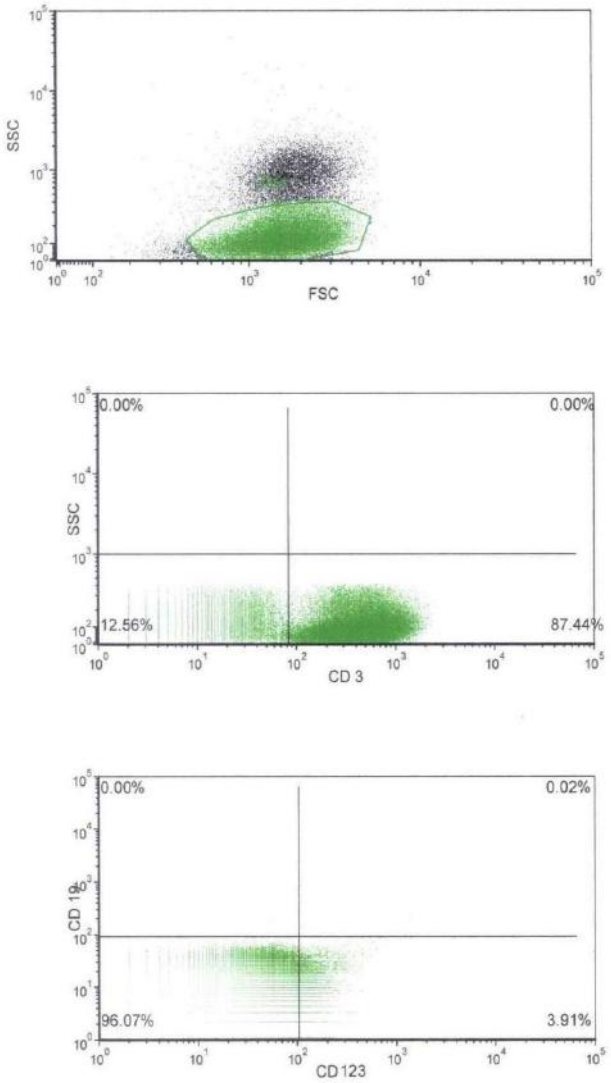


Fig 2: T-ALL shows negative CD123 expression.

SPECIAL STAINS

Sudan Black B

Which stains the granules of some AML blasts to appear as black spots under the microscope (≥ 3% positive), while ALL blasts do not react with this stain.

Periodic Acid–Schiff (PAS)

Cases of ALL show positive blocks or granules of bright red PAS material in clear cytoplasm.[8]

FLOW CYTOMETRY IMMUNOPHENOTYPING

Immunophenotypic analysis was performed on BM and/or PB samples freshly collected on EDTA tubes. Cells were stained using direct immunofluorescence mAbs and analyzed using four-color CyFlow® Cube 6 flow cytometry device (CyFlow® ,Partec, Germany).

The device software is based on the WindowsTM operating system for multi-parametric data acquisition, display, data analysis, and instrument control. Flow cytometry (Cyflow® Counter) is used as a fully-equipped portable / desktop FC with laser excitation in blue and red, it analyses up to three optical parameters (SSC and 2 fluorescence channels).[9]

REAGENTS

Permeabilizing reagent

Permeabilizing Solution 2 (BD FACSTM) is a premixed concentrate formulated specifically for use in flow cytometry. It is intended for the permeabilization of cell membranes prior to intracellular immunofluorescence staining with monoclonal antibodies. It is provided as a buffered solution containing <15% formaldehyde and <50% diethylene glycol and a proprietary permeabilizing agent.[3]

Lysing Reagent

Cylyse, which is an erythrocyte lysing reagent kit for wash and no wash procedures with a complete preservation of the surface proteins and practically no loss of cells, was used for lysis. Residual debris does not need to be removed by centrifugation due to properties of the lysing reagent buffer. Fixative reagent A fixes and stabilizes the leukocytes. The fixed samples can be stored for up to 24 hours at 2 C to 8 C before analysis.[10]

In this study immunophenotyping for interleukin 3 receptor alpha subunit CD123,CD19 and CD3 were investigated in those ALL patients by using four –color

Cyflow® Cube 6 flow cytometry device (PartecCyflow®, German). The technique with the principle of Stain–Lyse–No Wash was used.

For gate the cells of interest we depend on FSC/SSC gate, identification of blast cells was performed using forward scatter (FSC) versus side scatter (SSC) parameters.[10]

For CD123 and CD19 antigens included in the study, antigen expression was considered to be positive when the percentage of positive blast cells was equal or greater than 20% because they were surface Ags, while cytoplasmic CD3 was considered to be positive when the percentage of positive blast cells was equal or greater than 10%.[11]

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS version 18. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means +/- SD. Independent (t-test) was used to find mean differences between two variables. Pearson's chi square (*X2*) test was used to find the association between dependent and independent variables. *P-value* of ≤ 0.05 was considered as statistically significant.

RESULTS

A total number of 33 pediatric patients with de novo acute lymphoblastic leukemia [(23) B-ALLs & (10) T-ALLs] diagnosed by consultant hematologists cytomorphologically by Lieshmen stain and cytochemically by SBB and PAS stain on PB and/or BM aspirate smears. Immunophenotyping was done by Flowcytometry to detect the expression of CD123, CD19, and cCD3.

The mean age of all patients included in this study was 6.3 ± 3.5 SD, with a median of 5.3 years old. No case below 1-year-old had been recorded, according to risk stratification the age of patients was grouped into 2 intervals, less than 10 years and equal or more than 10 years.

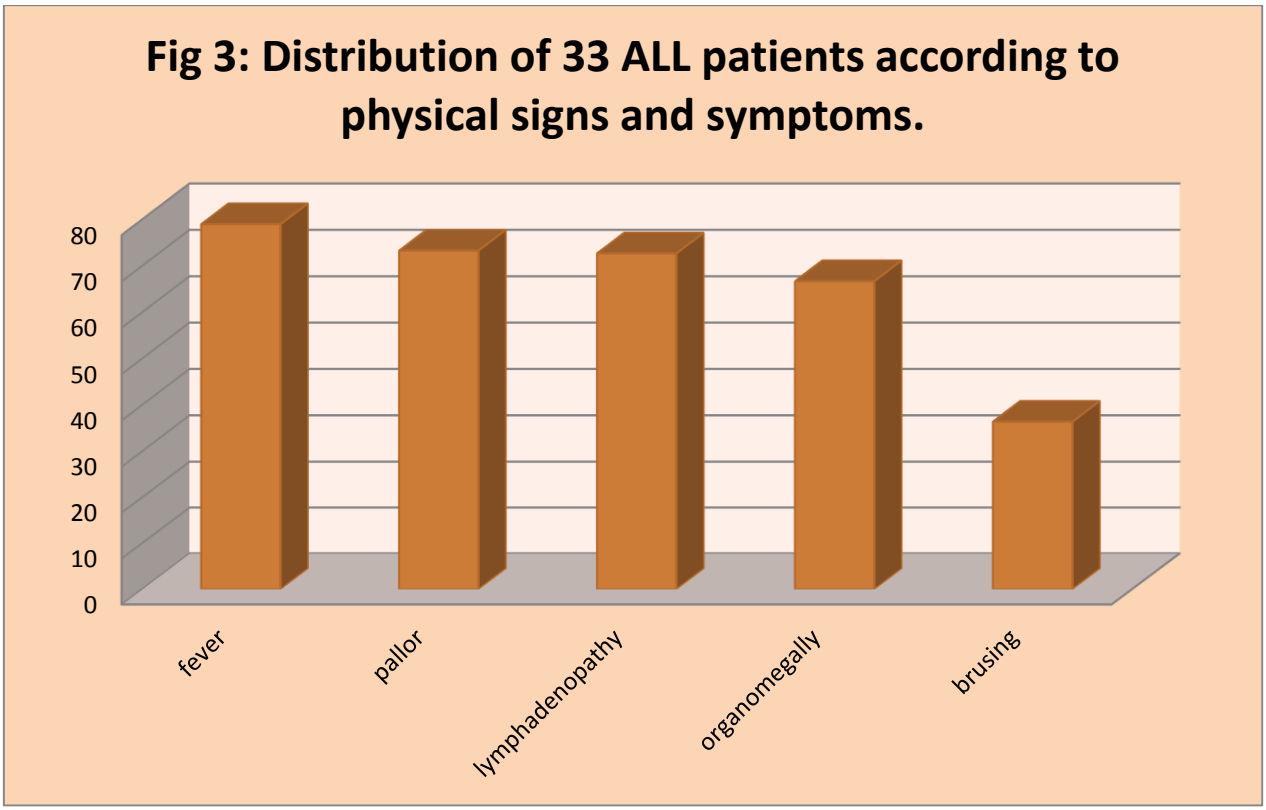
Moreover the age of 20 out 23of B-ALL patients 87% was less than 10 years interval, the mean age was 5.23 and median was 4.60, where as in T-ALL patients there were 6 out of 10 patients (60%) more than 10 years interval, the mean age was 8.95 and median was 9.

The gender of patients; ALL was observed more in male where 63.63% (21/33) of patients were male and 36.37% (12/33) were female, with a male to female ratio of 1.75:1. Moreover the male to female ratio in B-ALL was 1.3: 1, while in T-ALL there was obvious male predominance with male to female ratio of 4: 1.

Clinical Features

Clinical features of all ALL patients included in the study were represented in Fig 3. Which revealed that the most frequent signs and symptoms for all patients included in this study was fever, followed by pallor, lymphadenopathy, hepatosplenomegaly, whereas bruising was the least frequent sign.

Mediastinal widening only was shown in T-ALLs, lymphadenopathy was more frequently encountered in T rather than B-ALLs, in addition to the resting signs and symptoms.



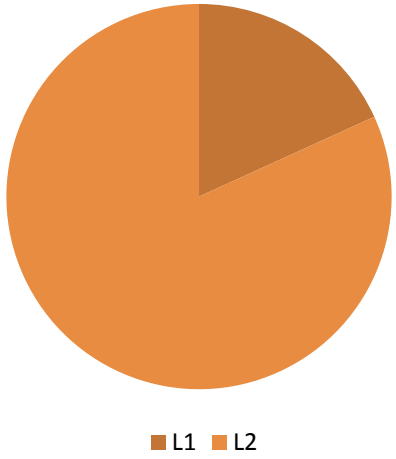


Fig 4: Distribution of patients according to FAB classification

Table 1: Distribution of CD123 expression in B & T-ALL

	CD123		
	$+ve$ No.	$-ve$ No.	Total
B-ALL	21	2	23
T-ALL	0	10	10
	21	12	33

Table 2: expression of CD123 in 23 B-ALL patients

CD123	FREQUENCY	PERCENT
$-ve$	2	8.7
Moderate $+ve$	12	52.2
Bright $+ve$	9	39.1
Total	23	100

Hematological parameters

Many patients were anemic with Hb of less than 7 g/dl in both ALL subtypes; in B-subtype the median Hb was 7.24 g/dl, only one B-ALL patient was with Hb of more than 11 g/dl, while in T-subtype the median Hb was 7.20 g/dl.

Majority of T-ALL patients 80% initially presented with leukocytosis of more than 50x 109 /L with median WBCs count of 122 x 109/L, while majority of B- ALL patients 79.3 % were initially presented with white blood cells count of less than 50x 109/L, with median WBCs of 10 x 109/L.

Most patients were thrombocytopenic and only 21.7% (5/23) of B-ALL were with platelet count of more than 100 x109/L, their median platelet count of 63.43 x 109/L, while no T-ALL patient had platelet count of more than 100 x 10/L and their median platelet count of 40 x 109/L.

Distribution of ALL Subtypes according to FAB Classification

In current study only 6 out of 33 patients (18.2%) were morphologically diagnosed as L1 subtype, the remaining 27 patients (81.8%) were diagnosed as L2 FAB. (Fig 4)

Interleukin 3 receptor alpha subunit CD123 expression

In B-ALL CD123 expression was positive in 21 out of 23 patients (91.3%), while in T-ALL no patient express CD123, moreover in B-ALL there was 9 out of 23 had been with bright expression, while 12 were with moderate intensity, no dim expression cases. (Table 1, 2)

Relationship between the CD123 expression and the Clinical parameters in B-ALL

Age

Within age group < 10 years old interval period, CD123 was positively expressed in 20 out of 20 patients (100%); from those patients 9 had bright intensity, while in the interval period of ≥ 10 years old CD123 show positive expression in 1 out of 3 patients (33.3%) who showed moderate intensity. By applying chi-square test, there was statistically significant relation of the CD123 expression in age group in B-ALL.

Gender

CD123 was positively expressed more in male where 12 out of 13 patients (92.3%), were positive for the marker, while it was positively expressed in 9 out of 10 female patients (90%), however there was no statistically

significant association between gender and CD123 expression in B-ALL

Relationship between the CD123 antigens expression and the clinical signs and symptoms in B-ALL

There was no significant correlation between CD123 expression in B-ALL and the main clinical signs and symptoms.

Relationship between the CD123 antigen expression and the hematological parameters in B-ALL

All anemic patients with Hb less than 7 g/dl presented with positive CD123 expression, the only one patient who had Hb above 11 g/dl had positive CD123 expression, p-value > 0.05, Moreover from five patients who had platelet count above 100 x 109/L four of them had positive CD123 expression, p -value > 0.05.

All patients who had WBCs below 50 x 109/L had positive CD123 expression, while from five patients who had WBCs above 50 x 109/L only two were negative for CD123 expression, thus only WBCs showed a significant association with CD123 expression by applying chi-square test see table 3.

Table 3: The relation of the CD123 expression to hematological Parameters.

Parameter	Class	CD123 No.		P-value
		+ *ve*	-ve	
Hb(g/dl)	<7	15	0	0.132
	7-11	5	2	
	>11	18	0	
WBCs *10^9/L	<50	18	0	0.034
	>50	3	2	
PLT *10^9/L	<100	17	1	0.106
	>100	4	1	

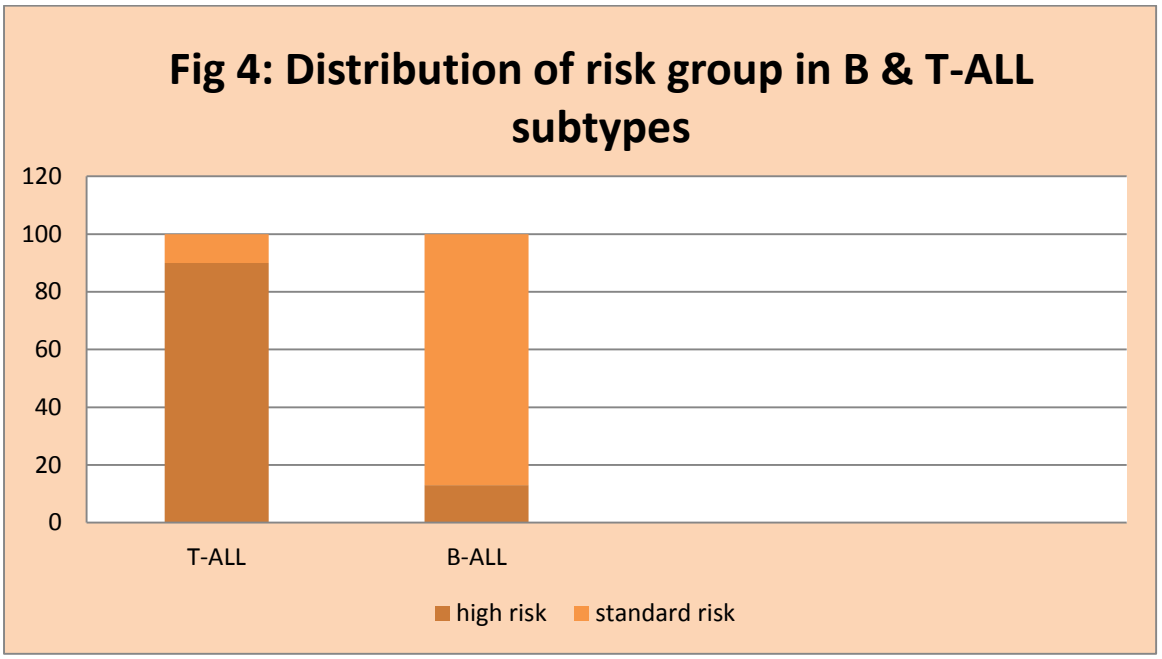


Table 4: Distribution of CD123 expression in risk groups in B-ALLs

CD123	STANDERD RISK (No.)	HIGH RISK (No.)	p- value
negative	0	2	0.001
moderate	11	1	
bright	9	0	
total	20	3	23

Table 5: The correlation of CD123 and induction remission in B-ALL.

Induction remission	CD123 +VE (No.)	CD123-VE (No.)	TOTAL (No.)	P-VALUE
YES	21	1	22	0.004
NO	0	1	1	
TOTAL	21	2	23	

Induction remission

- **Risk stratification:** According to risk stratification which was adapted by NCI[12] there was either standard risk or high risk groups depending on age and WBCs count on initial presentation. There was large different distribution of risk groups between B & T- ALL subtypes as shown in Fig 4.
- **Correlation of CD123 with risk group in B-ALL**: All cases that showed bright intensity of CD123 were classified in the standard risk group, and no case with bright expression of CD123 was detected in the high risk group, moreover the only two negative CD123 expression cases were considered

as high risk according to risk stratification, p-value < 0.05, see table 4.

- **Response to treatment:** Complete remission during first cycle of induction remission treatment was achieved in 30 out of 33 ALL patients (90.9%) while only 3 patients (9.1%) failed to respond. Comparing T-ALLs to B-ALLs patients 95.6% of B-ALLs had achieved complete remission after first course of induction therapy versus 80% of T-ALL.
- **Correlation of CD123 with treatment response in B-ALL:** All 21 patients who were CD123 positive had responded to induction remission, the only one patient who did not respond to induction remission was CD123 negative; p-value < 0.05 table 5.

DISCUSSION

Clinical Presentation

The most frequent signs and symptoms for ALLs patients included in this study was fever, whereas bruising was the least frequent, this was comparable with Al- Mulla et al[13] study while it is not in line with Settin et al[14] and Harpani PT et al[15] studies which showed different distribution of the clinical signs and symptoms, this can be related to sample size.

Haematological parameters

This study was in concordance with many studies that focus on the importance of WBCs count as continuous prognostic variable in determining the risk strategies in ALL management.

Hyperleukocytosis (WBC count $\geq 50 \times 10^9$/L) was presented in (39.4%) of ALL patients, this result was comparable with Hussein et al study from Egypt[16] (39.6%), however it was much higher than many other studies[17]. this can be explained by the fact that in this study there was large relative proportion of T- subtype which characterized by high WBCs counts.

Interleukin 3 receptor alpha subunit (CD123) expression

Regarding diagnosis and sub-typing of ALL cases; all cases were diagnosed morphologically and cytochemically by PAS and SBB by 2 specialist hematologists as ALL, CD19 and cCD3 markers were applied for sub typing of ALLs to B or T- ALLs respectively this was similarly adapted by Moroccan study. This can be explained by high sensitivity and specificity of these markers particularly cCD3.[18]

In present study: CD123 was expressed in 21 out of 23 B-ALLs (91.3%), while in T-ALL no patient had expressed CD123, those results were comparable pioneered study by Munoz and his coworkers, which had similarly found that all B-ALLs (100%) express CD123, while all T-ALLs did not express CD123.[19]

Moreover 9 out of 23 B-ALLs patients (39.1%) showed bright expression, while 12 patients (52.2%) showed moderate intensity, those results were comparable with Djokic and his coworkers study.[6] In 2009, which showed 93% of B-ALL express CD123: 59% intermediate expression and 34% high expression and only one case from 10 T-ALLs show positive intermediate expression. Djokic and his coworkers had reported that there was a close correlation between CD123 expression and hyperploid genotype, a frequent genetic abnormality in childhood ALLs associated with favorable outcome; in contrast, B-ALLs associated with other genetic abnormalities, such as ETV6/RUNX1, BCR/ABL1, PBX1/TGF3 translocations or a normal karyotype, did not display CD123 over expression.

So CD123 is a favorable marker since:

- All CD123 positive cases with bright expression were within standard risk category, while the only two B-ALLs with negative CD123 were within high risk group. P-value < 0.05 and
- The only one case who failed to response to therapy was CD123 negative. P-value < 0.05.

Risk stratification:

In current study, the patients were classified according to NCI/Rome criteria[20] accordingly the standard risk in this study which included patients with age < 10 years and initial WBC $<50x10^9$/l; and high risk which included all other patients.

In this study 90% of T-ALLs versus 13% of B-ALLs were within high risk group those results were compared with Uckun et al study[21]which revealed 40% of B- ALLs versus 70% of T-ALLs were at high risk, however when larger sample size is adapted and other advanced prognostic tools were included all T-ALLs patients were detected within high risk group such as in Indonesian and Le Clerk et al studies.[22]

CONCLUSION

- CD123 is frequently expressed in pediatric ALLs blasts.
- CD123 is exclusively expressed in B-lineage with absent expression in T- lineage ALLs.
- CD123 is significantly associated with good prognostic indicators and good treatment response to initial induction therapy.
- Pattern and positivity results of PAS stain could be of prognostic value, but not independently of other prognostic factors.

RECOMMENDATIONS

- Further studies with larger numbers of patients and longer time of follow- up are recommended to confirm our results.
- CD123, together with other markers may be used for a tentative flow cytometric identification of hyperdiploid B-ALLs.
- Cytogenetic study may be recommended for further explanations of the association between CD123 and hyperdiploidy or other cytogenetic abnormalities.
- The expression pattern of CD123 remained constant after chemotherapy so aberrant CD123 expression in

ALL is a good marker for minimal residual disease monitoring.

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