

CD44 and CD44 Variant 6 in Children with Acute Lymphoblastic Leukemia

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Abstract

Background and objectives: Acute lymphoblastic leukemia (ALL) is a malignant disorder of lymphoid progenitor cells. Many prognostic factors are important for therapeutic assignment. The cell adhesion molecule CD44 is involved in pathologic activities of tumour cells and hematological malignancies. CD44v6 is an important isoform of CD44 family. It plays an important role in the growth and metastasis development in some hematological malignancies. The aim of this study is to detect CD44 and CD44v6 expression in children with acute lymphoblastic leukemia and to correlate them with prognosis and other standard prognostic factors for ALL.

Subjects and methods: The study carried out on 57 children divided into: group I included 40 newly diagnosed children with acute lymphoblastic leukemia who were followed up for one year and group II 17 apparently healthy children of matched age and sex (as control group). Each child was subjected to complete history taking, clinical examination, laboratory investigations in the form of routine investigations; CBC, Leishman-stained peripheral blood smears, LDH. Bone marrow aspiration, Myeloperoxidase-stained peripheral blood, bone marrow smears, Immunophenotyping on BM/PB samples determined by Flowcytometer for routine panel of acute leukemia. Special investigations in the form of; flowcytometric analysis of CD44 and CD44v6 mRNA expression by quantitative RT-PCR were done for all children.

Results: CD44 expression was significantly higher in group I than group II ($P=0.001$) while there was no significant difference between CD44v6 in group I and group II. Significant positive correlation between CD44% and LDH level, total leucocytic count and bone marrow blast cell ($r=0.64$, $P=0.001$ & $r=0.62$, $P=0.001$ & $r=0.92$, $P=0.001$) respectively, However there was statistically significant negative correlation between CD44%, hemoglobin(HB) level and platelet count ($r=-0.93$, $P=0.001$ & $r=-0.92$, $P=0.001$) respectively. CD44%, white blood cell count, Percentage of cases with lymphadenopathy and/or splenomegaly was significantly higher in children with unfavorable outcome. There was non significant difference between favorable and those with unfavorable outcome as regards CD44v6 ($P=0.1$) and there was no correlation between CD44 v6, HB level, platelet count, WBCs count, LDH level and B.M. blast cells in ALL patients.

Conclusion: CD44 but not CD44v6 expression can serve as a powerful prognostic marker in childhood ALL associated with bad prognosis. CD44 high expression identifies high risk subgroup.

Keywords: Acute lymphoblastic leukemia (ALL); Prognostic factors; CD44; CD44v6

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disorder of lymphoid progenitor cells that proliferate and replace the normal hematopoietic cells of the bone marrow. These lymphoblasts replace the normal bone marrow elements resulting in marked decrease in the production of normal blood cells [1].

A number of clinical and biological features at the time of presentation are relevant to the prognosis and affect the response to treatment [2]. These prognostic factors include age, gender, number of bone marrow blasts, white blood cell (WBC) and platelet number, cytogenetic abnormalities, extramedullary involvement (EMI), and immune phenotype. The prognostic relevance of immune phenotype and the expression of various markers in ALL have been documented and provide important information as regards classification, diagnosis and treatment [3,4].

CD44 is an adhesion molecule, a glycoprotein, which is expressed by B and T lymphocytes, that mediates cell attachment to extracellular matrix components and adhesion to endothelial cells. Its levels of expression vary between cell types and their activation state [5].

CD44 variants (CD44v) are mainly expressed on epithelial cells, encoding amino acids with extensive glycosylation sites and chondroitin acid-binding sites. Splicing in continuous or septal way, different variable region exons combination encode different CD44 molecules. At present, there are more than 10 kinds of CD44v in many cell lines detected by polymerase chain reaction. Alternative splicing is the basis for the structural and functional diversity of this protein, and may be related to tumor metastasis [6].

CD44v6 is found to confer metastatic behavior of tumor cells and plays an important role in pathophysiology and prognosis. In hematopoietic malignancies increased gene expression of exons v6 and v9 is associated with poor prognosis in non-Hodgkin lymphoma and

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myeloma, and exon v6 with poor prognosis in acute myeloid leukemia [7].

Subjects and Methods

The study population included 57 children; Group I included 40 newly diagnosed children with acute lymphoblastic leukemia (their ages ranged from 3 to 12 years and included 21 males and 19 females) selected from oncology out-patient clinic of Minia Oncology Center, Minia University hospital and South Egypt Cancer Institute during the period from December 2012 to June 2013 and followed up for one year. Group II included 17 apparently healthy children matched for age and sex with the patient group as a control group (their ages ranged from 4 to 12 years and included 9 males and 8 females).

Both patients and control groups were subjected to the following: complete history taking, clinical examination and laboratory investigations in the form of: Complete blood count determined by automated cell counter sysmex kx-21N (TAO Medical Incorporation, Japan), Examination of Leishman-stained peripheral blood smears for differential leucocytic count. Abdominal ultrasonography, bone marrow aspiration and, assessment of blast cell number and morphology and myeloperoxidase-stained peripheral blood were done for patients only. Bone marrow aspiration was done by marrow puncture needles (Klima type) either from anterior or posterior superior iliac spine and examination of leishman-stained smears. Immunophenotyping was done on BM/PB samples determined by Flowcytometer (FACS Calibur BD bioscience, USA) for routine panel of acute leukemia, LDH determined by Elitech Clinical Systems, Puteaux France. Flow cytometric analysis for CD44 and CD44v6 mRNA expression by quantitative RT-PCR(using Light Cycler Roche, Germany) .

All analyses were performed with version 19 of Statistical Package of Social Science (SPSS). Qualitative data were expressed as proportions, while quantitative data were expressed as mean \pm standard deviation (SD). Qualitative data were analyzed by Chi square (χ^2) test. Comparisons between groups for normally distributed quantitative data were performed by Student's t-test. Correlations between variables were obtained by Pearson's test. For all analyses, statistical significance was defined as p values less than 0.05.

Results

According to immunophenotyping (Table 1-3)

Group I subdivided into: (T- Lineage ALL (Ia included 4 patients) and B-lineage ALL (Ib included 36) which subdivided into: "Early pre-B (Ib1 included one patient), Common B (Ib2 included 14 patients), Pre-B (Ib3 included 20 patients) and B-ALL (Ib4" included one patient). There were no statistically significant differences between group Ib2 (n=14) and group Ib3 (n=20) except for WBCs count which was significantly higher in group Ib3 (p= 0.04*).

According to expression of CD44

Group I subdivided into: (Negative (Ix), Weak positive (Iy), Strong positive (Iz)).

There were no statistically significant differences between patient subgroups regarding age, sex, splenomegaly and hepatomegaly. However there was border line statistically significant increase in percentage of cases with lymphadenopathy in group Iz compared to group Ix and in group Iz compared to group Iy.

Concerning the outcome, there was statistically significant increase in relapsed and died patients in group Iz, group Iy when compared to group Ix.

Variables		Group I N=40	Group II N=17	P-value
Age	Range	3-12	4-12	0.3
	Mean \pm SD	8.2 \pm 3.5	7.9 \pm 3.3	
Sex	Male	22(55%)	9(52.9%)	0.8
	Female	18(45%)	8(47.1%)	
HB "g/dl"	Range	4.2-10.9	11.7-13.4	0.001**
	Mean \pm SD	7.6 \pm 1.9	12.5 \pm 0.5	
Plat. "/cmm"	Range	5000-99000	201000-397000	0.001**
	Mean \pm SD	41150 \pm 28008	321117.6 \pm 61856.5	
WBCs "/cmm"	Range	2200-190000	5600-10200	0.01*
	Mean \pm SD	31685 \pm 36631.9	8400 \pm 1300.9	
LDH (IU/L)	Range	392-3503	215-318	0.001**
	Mean \pm SD	1180.7 \pm 743.9	266.8 \pm 40.3	
CD44 "%"	Range	10.7-100	0-7.6	0.001**
	Mean \pm SD	65.2 \pm 35.9	2.5 \pm 2.5	
CD44v6	Range	0 - 4.8	0-1.55	0.3
	Mean \pm SD	0.48 \pm 0.97	0.26 \pm 0.54	

*=significant

**= highly significant

Table 1: Demographic and laboratory data of studied groups.

Variables	Favorable N=16	Unfavorable N=24	P
Age (year)	6.7 \pm 3.6	7.1 \pm 3.4	0.7
Sex	Male 7(43.8%)	15(62.5%)	0.2
	Female 9(56.2%)	9(37.5%)	
Lymphadenopathy	6(37.5%)	18(75%)	0.008*
Hepatomegaly	6(37.5%)	14(58.3%)	0.09
Splenomegaly	6(37.5%)	20(83.3%)	0.001**
HB (g/dl)	7.4 \pm 1.5	7.7 \pm 2.2	0.6
Plat. Count (/cmm)	51187.5 \pm 28407.1	34458.3 \pm 26213.1	0.06
WBCs count (/cmm)	13375 \pm 10157.3	42633.3 \pm 42294.7	0.01*
CD44%	28.4 \pm 26.5	89.7 \pm 12.4	0.001**
Immunophyontyping	T- ALL 0	4(16.7%)	0.3
	Early pre B 0	1(4.2%)	
	Common B 7(43.8%)	7(29.2%)	
	PreB 9(56.3%)	11(45.8%)	
	B-ALL 0	1(4.2%)	
CD44 V6	0.19 \pm 0.4	0.6 \pm 1.2	0.1

Table 2: Comparison between favorable & Unfavorable outcome in ALL patients.

Variables	r	P
Age (years)	-0.13	0.4
LDH (IU/L)	0.64	0.001**
Hb(g/dl)	-0.93	0.001**
Plat.(/cmm)	-0.92	0.001**
WBCs(/cmm)	0.62	0.001**
Bone marrow blast%	0.92	0.001**
CD44 V 6	0.25	0.1

*=significant

**= highly significant

Table 3: Correlation between CD44 and studied parameters in ALL patients.

There was no statistically significant differences between patient subgroups regarding HB level, WBCs count, CD44v6 and Immunophenotyping, however there was statistically significant decrease in platelet count and increase in LDH level in group Iz compared to group Ix .

According to expression of CD44v6

Group I subdivided into: (Negative (In), positive (Io)).

There was no statistically significant differences between patient subgroups except for increase percentage of cases with splenomegaly in group Io than in group In ($P=0.01^*$).

Discussion

Acute leukemia is the commonest cancer affecting children, with acute lymphoblastic leukemia (ALL) being more common than acute myeloid leukemia (AML). The overall outcome of childhood ALL is generally favorable, with cure rates now exceeding 80% [8]. Despite this improvement, however, about 20-25 % of the patients still relapse [9].

The majority of patients experiencing disease relapse cannot be adequately assessed for their chance of experiencing relapse at diagnosis. Immunophenotypic and cytogenetic prognostic markers for these patients offers the possibility to reassign them to a lower or higher risk grouping [10].

In the present study there were 22 (55%) males and 18 (45%) females, these results are compatible with Wu et al. [11], Reichard et al. [12] and Stacy and Patrick [13] who reported increase percentage of male than female in ALL patients.

LDH level in this study was significantly higher in ALL patients compared to control group. The results agreed with Hafiz and Mnnan [14], and Hunger et al. [15] who reported that early measurement of serum LDH could be useful in identifying response to chemotherapy.

The majority of patients, both children and adults, with ALL are of B-lymphoid origin. The B lymphoblastic leukemia is classified as precursor B leukemia (B-ALL) since the blast cells are neoplastic counterparts of normal B-cell precursors [16]. The classification into B- and T-ALL is important for risk stratification and treatment [17].

Immunophenotyping in the present study showed that 50% of patients were pre-B-ALL, 2.5% were mature B-ALL, early pre B 2.5%, Common B 35% (total: 90%) and 10% were T-ALL. This agreed with the study done by Zhang et al. [18] who found on their study on 139 ALL children, there were 103 cases (74.1%) of B-ALL, 24 cases (17.3%) of T-ALL as it was previously reported in other populations in studies done by Bachir et al. [19] who found on their study on 279 patients below the age of 18 years with newly diagnosed ALL that 78.85% of patients have B-cell acute lymphoblastic leukemia "B-ALL" and 21.15% of patients with acute lymphoblastic leukemia have "T-ALL" and also Supriyadi et al. [20] found in their study on 381 children with acute lymphoblastic leukemia of them 83% were B-lineage ALL and 17% T-lineage ALL .

Shrestha et al. [21] and Shushma et al. [22] reported that common ALL is a large group, which represents the majority of childhood ALL which was in disagreement with this study, this may be due to different number of cases or a variation in age range in the patient group.

It was found that there was no significant difference between B-ALL subtypes except in relation to leucocytic count which was higher in pre-B-ALL patients. This data was in line with Ramyar et al. [23] who reported an unfavorable prognosis for the pre-B group.

In this study, 82.5% of ALL patients positively expressed CD44, these was slightly higher than those reported by Guoqiang et al. [24] who encountered CD44 expression in 77% and 76.8% of ALL patients respectively, but slightly lower than Ulrike et al. [5] who reported CD44 expression in 90.3% of ALL patients .

According to the relationship between CD44 expression and various studied standard prognostic factors, there were significant positive

correlations between CD44 level and LDH level, white blood cells, bone marrow blast cells in ALL patients. However there were significant negative correlations between CD44 level and both of hemoglobin level and platelet count .

This was in agreement with Ahmed and Hassab [25] who made their study on 30 newly diagnosed ALL pediatric patients for CD44 expression by flow cytometry and correlated it to age, sex, TLC, HB, platelet count, blast % in peripheral blood and bone marrow, immunophenotyping and LDH.

These results came in contrast to Kamazani et al. [26] who reported that the expression of CD44 had no statistical association with any of standard prognostic markers.

It was found that CD44 was significantly higher in ALL patients with lymphadenopathy. Similarly it was found that CD44 was significantly higher in ALL patients with splenomegaly. These results were in agreement with those reported by El-sharkawy et al. [27] and Lubomir et al. [28] who found that the high expression of CD44s was associated with high tumour burden (i.e lymphadenopathy and organomegally). Williams et al. [6] explain that by the assumption that CD44 being an adhesion molecule , may be involved in the pathogenesis of a high tumor burden .

Khan et al. [10] presented the first large study examining the predictive value of CD44 protein expression on the outcome of treatment for children with ALL and its expression may serve as a new prognostic factor in childhood ALL, and that analysis for its expression may contribute to improve the management of ALL patients who lack prognostic cytogenetics.

Follow up of all patients showed that the percentage of CD44 expression in patients who had favorable outcome complete remission (CR) was (28.4%) while in patients who had unfavorable outcome (incomplete remission, relapse and death) were (89.7%). This was confirmed by a study done by Khan et al. [10].

The present study showed a highly significant association between the CD44 expression and unfavorable prognosis This observation was noticed by Theodora and Evangelia [29] who demonstrated that CD44 induce tumor growth, survival as well as cancer cell invasion.

In this study, according to expression of CD44, 65% of patients were strongly positive while 17.5% patients were weak positive and the remaining patients 17.5% showed negativity for CD44 and when comparing these groups with each other's it was found that there was statistically significant decrease in platelet count, increase in LDH level, increase in percentage of lymphadenopathy and unfavorable outcome in strongly positive cases. Zac et al. [30] also showed the association between the high +ve CD44 expression with poor clinical outcome.

In contrast to this study Kamazani et al. [4] reported no significant correlation between CD44 expression and well-established risk factors such as age, WBC count, central nervous system involvement and chromosomal abnormalities.

Concerning CD44V6, the present study reported that there was no significant difference concerning CD44v6 expression between patients and controls and there was non-significant correlation between CD44v6 and CD44 level in ALL patients and that there was no significant difference between favorable and unfavorable prognosis as regard expression level.

These results agreed with Khan et al. [10] who reported that no

correlation between total CD44 protein expression levels and CD44v6 protein or mRNA expression levels, and that CD44V6 expression was not associated with poor outcome.

This was in disagreement with Bendall et al. [31], Kyueng et al. [32] and Todaro et al. [33] who reported That CD44v6 expression is correlated directly with poor survival. The discrepancy between these studies is likely due to different number of cases.

Conclusions

In conclusion, strong CD44 expression appears to be a powerful prognostic indicator in children with ALL while CD44 Variant 6 had no role in these children. CD44 is correlated well with the standard poor prognostic markers. Analysis of CD44 expression in addition to other standard prognostic markers at diagnosis may pave the way to improve the outcome.

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