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RESEARCH ARTICLE

CD30 EXPRESSION VERSUS SERUM SOLUBLE CD30 (SCD30) LEVEL AS A PROGNOSTIC MARKERS IN ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Objectives: As we noted that CD30 is a valuable molecule in regulation of growth and death of lymphocytes in malignant lymphomas, we decided to analyze CD30 expression and serum soluble CD30 (sCD30) molecule level in patients with acute lymphocytic leukemia (ALL) to assess their role as a prognostic markers and to examine the possibility of anti-CD30 to be a targeted therapy in these patients.

Methods: We studied CD30 expression by multicolor flow cytometry immunophenotypic analysis on bone marrow aspirates of 90 ALL patients (51 T-ALL and 39 B-ALL). Serum sCD30 level was measured by Enzyme Linked Immunosrbent Assay (ELSA). We correlate CD30 and sCD30 values with all of white blood cell counts, Hemoglobin, platelets, bone marrow blasts and cytogenetics.

Results: Our study conducted on 90 ALL patients. The 90 ALL patients included 51 patients with T-ALL and 39 with B-ALL. Of the 51 T-ALL patients, 29 (56.8%) were males and 22 (43.2%) were females. Mean age was 42.4±19.1 years old (10-78 years), and of 39 B-ALL patients, 23(59%) were males and 16 (41%) were females. Mean age was 44.4±18.6 years old (9-70 years). In T-ALL, 33.3% (17 out of 51 patients) have high CD30-expression and 27.4% (14 out of 51 patients) have elevated serum sCD30.We found that there was a significant correlation between both CD30 expression and sCD30 level with WBCs count, BM blasts, Adverse risk cytogenetics, BCR/ABL and with relapse for CD30 expression, complete remission failure with elevated serum sCD30 level. While in B-ALL, CD30 expression (>20%) was detected in 20.5% (8 out of 39 patients) and elevated sCD30 was detected in 15.4% (6 out of 39 patients). However, we did not found significant relation between both CD30 expression and sCD30 level and BCR/ABL, relapse and failure of treatment.

Conclusions: CD30 is expressed by lymphoblasts in ALL patients. We found that high CD30 expression and elevated sCD30 level can be used as prognostic markers for relapse and complete remission failure respectively in only T-ALL subtype not in B-ALL subtybe. Furthermore, these patients with adverse risk cytogenetics have not too many treatment options, so the use anti-CD30 targeted therapy may be a possible alternative for this patient group.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is determined in both adults and children, but its incidence be at height between ages 2 and 5 years (Smith *et al*., 2011). ALL in Children 10 years or older and children younger than 1 year, with mature B-cell (Burkitt) leukemia mainly do bad than those with common, pre-B or early pre-B-cell ALL, with very high WBC counts (more than 50,000 cells per cubic millimeter), with hypodiploidy and those with a translocation between chromosomes 9 and 22 (the Philadelphia chromosome), 4 and 11, 1 and 19, or responds poorly to conventional therapy. Refractory or relapsed ALL is frequently noticed as an untreatable disease (Smith *et al*., 2011). The survival rate of ALL has enhanced to almost 90% in recent treatment. However new applications are wanted to extra advance survival while contracting adverse effects (Hiroto Inaba, 2013). Monoclonal antibodies conducted at cell surface antigens display a targeted access for treating leukemia and other cancers. In B-cell acute lymphoblastic leukemia (BALL), anti-CD20 monoclonal antibodies have been proved to advance survival when used in the first line treatment (Thomas *et al*., 2010). Antibodies directed at CD22 (Topp *et al*., 2011) and CD19 (Kantarjian *et al*., 2012) attempt a low toxic and highly useful access to eliminate minimal residual disease (MRD), lengthen relapse-free survival and have displayed potency in patients with relapse. In precursor T-cell acute lymphoblastic leukemia (T-ALL), treatment is based

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usually on accelerated chemotherapy which followed by stem cell transplantion (Fielding *et al*., 2012). Antibody targeted treatment in T-ALL is lesser intensively researched than B-ALL. With the exclusion of anti-CD52 (Tibes *et al*., 2006), total practice with monoclonal antibody-targeted therapy in T-ALL is very restricted. CD30 molecule was first off distinguished in 1982 as the antigen of the monoclonal antibody Ki-1 (Schwab *et al*., 1982) and appears as a 120 kDa transmembrane glycoprotein be a member of the tumor necrosis factor receptor (TNF-R) superfamily (Smith *et al*., 1994), frequently expressed by Hodgkin and Reed-Sternberg (H-RS) cells in Hodgkin's disease (HD) and by malignant cells of some types of non-Hodgkin's lymphomas, such as human T-lymphotropic virus type 1-positive (HTLV-1+), CD30 anaplastic large-cell lymphoma (ALCL) and adult T-cell leukemia lymphoma (ATLL) (Oran and Weisdorf, 2012). Soluble form of CD30 (sCD30), the extracellular part of the membrane bound CD30 can be cleaved by the action of a zinc-metalloprotease (Hansen *et al*., 2000). This produces a soluble form of CD30 (sCD30) with a molecular mass of 85-90 kDa. Shedding of CD30 occurs as an active process of viable CD30 positive cells. Soluble CD30 can interfere with signaling by membrane bound CD30 through binding to CD30L and blocking its interaction with CD30 on the cell membrane (Kennedy *et al*., 2006). To be effective. Alternatively, soluble CD30 could interfere with transmembrane signaling by associating with membrane-bound CD30 to form complexes that cause dominant negative interference. It has been suggested that sCD30 provides a mechanism by which CD30 positive tumors can escape immunosurveillance and the apoptosis induced activity of CD30L (Smith *et al*., 2011). In patients with HL and ALCL sCD30 appears to be a reliable tumor burden marker. Several reports have identified correlations between serum sCD30 levels and poor prognosis in CD30-positive lymphomas (Nadali *et al*., 1995). An anti-CD30 chimeric antibody conjugated by a protease-cleavable linker to monomethylauristatin E, an agent that disrupts microtubules (Katz *et al*., 2011). Has been shown to induce durable responses in patients with refractory and relapsed Hodgkin lymphoma and relapsed anaplastic large cell lymphoma with well tolerated side effects (Younes *et al*.,). The current research aims to analyze CD30 expression and serum soluble sCD30 molecule level in patients with acute lymphoblastic leukemia (ALL) to assess their role as a prognostic markers.

Patients and Methods

Patients

Ninety patients with de novo ALL (51 patients with TALL and 39 with BALL) were involved in this study. These patients were admitted to Hematology unit, clinical pathology department and south Egypt cancer institute, Assiut university, Egypt, and were grouped depending on morphology and immunophenotyping (FAB classification). The clinical and laboratory data consisted of age; sex, white blood cell count, hemoglobin level, platelets count, BM Blasts, cytogenetics, BCR/ABL mutation, FAB classification and the improvement after induction chemotherapy were obtained from patients' medical records.

Flow cytometric Immunophenotyping analysis

BM aspirates were collected in EDTA-anti-coagulated tubes and processed within 24 hours of collection. Routine flow cytometry immunophenotyping confirmed the presence of lymphoblasts in all cases. Routine flow cytometry immunophenotypic analysis for T-ALL and B-ALL including: CD2, CD3, CD4, CD7, CD8, CD10, CD14, CD19, CD20, CD22, CD25, CD34, CD38, CD36, CD45, CD79a, CD81, CD123, HLADR, TdT, cytoplasmic CD3 and cytoplasmic IgM (BD Biosciences, San Jose, CA, USA). Distinct mixtures of these markers were used according to the disease status either as initial diagnosis or follow-up; and according to B- or T-cell lineage of the ALL. In addition to, CD30-FITC (BD Biosciences, San Jose, CA, USA) were analyzed on 4 color BD FACSCALIBUR.

Molecular Analysis

RNA extraction

Total RNA was extracted from peripheral blood samples at diagnosis using ABIOpure™ Total RNA Blood Extraction Kit (version 2.0), USA, using manufacturer's protocol. cDNA synthesis from RNA by (RT-Kit plus, Nanogen, Italy), using manufacturer's protocol.

For BCR/ABL mutation detection: by PHILADELPHIA P210 Q-PCR Alert AmpliMIX for detection and measurement of the cDNA of P210 BCR-ABL. The PCR consisted of decontamination step at 50°C for 2 minutes followed by initial denaturation at 95°C for 10 minutes, then 35 cycles at 94°C for 15 seconds, 60°C for 60 seconds. PCR products were analyzed on 7500 Fast Real Time PCR.

Cytogenetic Analysis

Depending on the recommendations of the International System for Human Cytogenetic, cytogenetic analysis was done using short term cultures (Smith *et al*., 2011). At least 20 metaphases were examined. Cytogenetic risk prognosis was categorized as follows: In children: Favorable, High hyperdiploidy, t(12;21)(p13;q22) and t(1;19)(q23;p13.3); Adverse, Hypodiploidy(< 45 chromosome), t(9;22)(q34;q11.2) and t(4;11)(q21;q23) and t(8;21). In Adults: Favorable, High hyperdiploidy, t(1;19)(q23;p13.3, t(10;14)(q24;q11), abnormal 9p and abnormal 12p; Adverse, Hypodiploidy, t(9;22)(q34;q11.2) and t(4;11)(q21;q23).

Enzyme Linked Immunosorbent Assay

Serum sCD30 Assay

Serum samples were withdrawn from each patient and stored at –70ºC until tested. Serum sCD30 concentrations were measured using enzyme-linked immunosorbent assay (The Thermo Scientific™ Pierce™ CD30 (TNFRSF8) ELISA Kit. USA). Optical density was checked at 450 nm using an ELISA microplate reader. We interpreted sCD30 concentrations from the standard curve created using the recombinant human sCD30 standards supplied with the kit.

Statistics

The Fisher's exact test or chi-square was used for comparison of categorical variables and the t test or one-way analysis of variance (ANOVA) was applied for numerical comparisons using Statistical Package for Social Science, Version 20 (SPSS Inc., Chicago, IL, USA). Spearman correlation coefficient was used to examine the correlation among different studied parameters. A p value of <0.05 was considered to be statistically significant.

RESULTS

The 90 ALL patients included 51 patients with T-ALL and 39 with B-ALL. Of the 51 T-ALL patients, 29 (56.8%) were males and 22 (43.2%) were females. Mean age was 42.4±19.1 years old (10-78 years), and of 39 B-ALL patients, 23(59%) were males and 16 (41%) were females. Mean age was 44.4±18.6 years old (9-70 years) in our study, in cases of T-ALL high CD30 expression (>20%) (Figure 1) was detected in 33.3% (17 out of 51 patients). High CD30 expression was found in all FAB classifications of ALL. No significant correlation was found between CD30 positivity and clinical data of patients including age and sex, laboratory data including Hb level and platelets count (Table 1). However, there was a significant correlation between CD30 expression and WBCs count, BM blast count and adverse cytogenetics (r=0.488, P=0.025), (r=0.411, P=0.030) and (r=0.501, P=0.002) respectively (Table1). Among the 17 patients with high CD30 expression there were 7 patients with favorable risk cytogenetics and 10 patients with adverse risk cytogenetics (P= 0.015). Additionally, we found that there was a significant relationship between CD30 expression and BCR/ABL mutation in ALL patients (58.8% of positive CD30 expressed patients had BCR/ABL mutation compared to 18.2% of negative CD30 expressed patients) (P= 0.034) (Table 2).

Table 1. Correlation between Clinical and laboratory characteristics in T- ALL patients to CD30 expression and serum sCD30 level

	CD30 %		sCD30 pg/ml	
	r	P	r	p
Age	-0.057	0.639	-0.264	0.068
WBCs	0.488	0.025	0.521	0.034
RBcs	0.123	0.497	0.134	0.481
HGB	0.077	0.667	0.108	0.392
PLT	-0.092	0.589	-0.081	0.600
BM Blasts	0.411	0.030	0.400	0.033
Cytogenetics	0.501	0.002	0.413	0.009
FAB	-0.237	0.088	-0.219	0.154

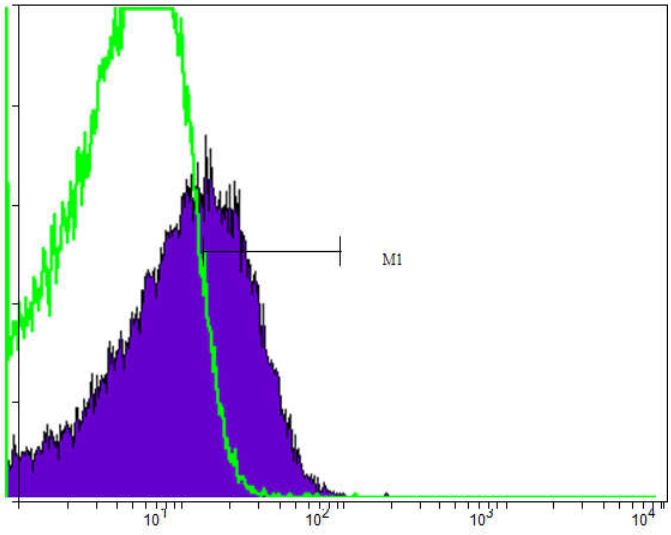

Figure 1. Flow cytometric histogram shows Positive CD30 expression. The green line indicates the negative control, filled line indicates a positive case

We also found that 8(47.1%) of the highly expressed CD30 patients relapsed after completion of the treatment compared to only 9(26.5%) of the negative expressed CD30 (P=0.013) (Table 2) (Figure 2). In multivariate analysis high CD30 expression in T-ALL patients with adverse risk cytogenetics was predictor for relapse in patients showed increased WBCs (leucocytosis>20 10^3/µl) and increased BM Blasts(> 20%) (Table 3), the results given as odds ratio {95% Confidence interval}: 2.7{1.71-5.0}P= 0.003, 2.8{1.23-3.9}P= 0.010 respectively (Table 4). For sCD30 assay, elevated sCD30 were detected in 27.4% (14 out of 51 patients). With Regards to sCD30, we analyzed the relationships between the level of sCD30 expression and clinical data (age, sex), laboratory (WBCs count, Hb level, platelets count and BM blast count at diagnosis), FAB classification, cytogenetic risk groups, BCR/ABL and the outcome in patients with de novo T-ALL. Regarding the clinical data there was no significant relationship with elevated sCD30, But the patients with elevated sCD30 had elevated WBCs count, BM blast count and adverse cytogenetics (r=0.521, P=0.034), (r=0.400,P=0.033) and (r=o.413, P=0.009) respectively(Table1). 8(57.1) patients with elevated sCD30 had BCR/ABL mutation (0.005). With regards to FAB classification and cytogenetic risk groups, there was no significant relationship between elevated sCD30 and FAB T-ALL subtypes, however 9 of 14(64.3) patients with elevated CD30 (>100pg/ml) had adverse risk cytogenetics (P= 0.009). Furthermore, 9 of these patients did not get complete remission after completion of treatment (P=0.012) and from the 5 patients that assumed CR, 3 patients relapsed (Table 3). In multivariate analysis high serum sCD30 (>100 pg/ml) in AML patients with adverse cytogenetics was predictor for treatment failure in patients showed increased WBCs count (leucocytosis>20 10^3/µl), the results given as odds ratio {95% Confidence interval}: 3.4{1.71-5.3} P= 0.004 (Table 4). For cases of B-ALL high CD30 expression (>20%) was detected in 20.5% (8 out of 39 patients). High CD30 expression was found in all FAB classifications of ALL. No significant correlation was found between CD30 positivity and clinical data of patients including age and sex, laboratory data including Hb level and platelets count (Table 5).

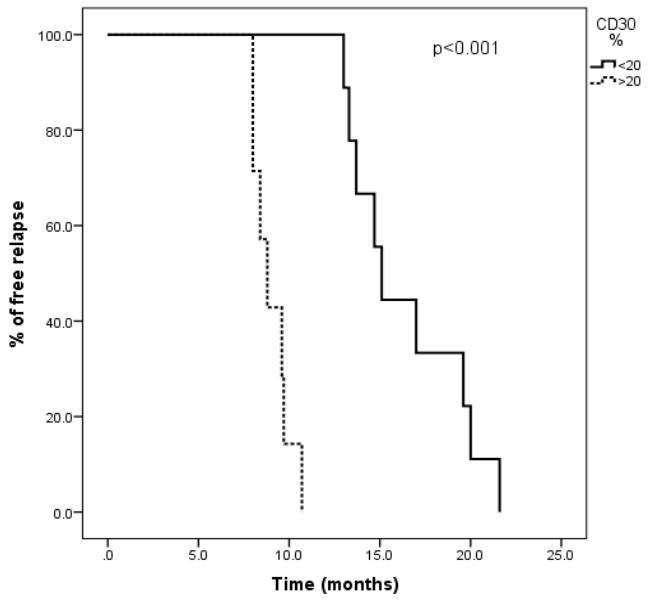

Figure 2. Kaplan-Meier Analysis for % Free Relapse in T-ALL patients. Solid line indicates patients negative for CD30 expression, Dashed line indicates patients with positive CD30 expression

Table 2. Clinical and laboratory characteristics in ALL patients in relation to CD30 expression

Parameters	CD30 >20%			
	T-ALL	P	B-ALL	P
Number of patients,%	17(33.3)		8(20.5)	
Age(years),(Mean±SD)	45±15.7		40.4±16.2	0.582
Sex,n(%)				
Male	9(52.9)	0.108	3(37.5)	0.071
Female	8(47.1)		5(62.5)	
WBCs(Mean±SD)10^3/µl	171.28±110.11	0.025	168.64+88.642	0.042
Hb level(Mean±SD)g/dl	5.93±1.50	0.211	6.58+1.23	0.391
Platelet(Mean±SD) 10^3/µl	46.56±27.72	0.675	50.91+34.22	0.963
B.M Blasts	69.54±14.90	0.030	74.12+15.4	0.030
FAB,n(%)				
L1	4(23.5)		2(25)	
L2	5(29.4)	0.601	4(50)	0.125
L3	8(47.1)		2(25)	
Karyotype,n				
Favorable	7(41.2)	0.015	3(37.5)	0.071
Adverse	10(58.8)		5(62.5)	
BCR/ABL, n(%)	10(58.8)	0.034	3(37.5)	0.093
Outcome, n(%)				
CR	9(52.9)	0.024	6(75)	0.082
Relapse	8(47.1)	0.001	2(25)	

Table 3. Clinical and laboratory characteristics in ALL patients in relation to serum sCD30 level

Parameters	sCD30 >100pg/ml			
	T-ALL	P	B-ALL	P
Number of patients,%	14(27.4)		6(15.4)	
Age(years),(Mean±SD)	46±16.2		39.9±15.4	0.660
Sex,n(%)				
Male	6(42.9)	0.117	3(50)	0.567
Female	8(57.1)		3(50)	
WBCs(Mean±SD)10^3/µl	166.14±109.72	0.034	166.74+87.54	0.047
Hb level(Mean±SD)g/dl	6.15±1.22	0.323	6.69+1.34	0.275
Platelet(Mean±SD) 10^3/µl	47.11±28.64	0.665	51.01+33.39	0.860
B.M Blasts	72.54±15.11	0.030	74.09+15.9	0.038
FAB,n(%)				
L1	2(14.3)		1(16.7)	
L2	5(35.7)	0.214	2(33.3)	0.244
L3	7(50)		3(50)	
Karyotype,n				
Favorable	5(35.7)		3(50)	
Adverse	9(64.3)	0.009	3(50)	0.064
BCR/ABL, n(%)	8(57.1)	0.005	2(33.3)	0.100
Outcome, n(%)				
CR	5(35.7)	0.072	4(66.6)	0.064
Relapse	3(21.4)		3(27.3)	

Table 4. Multivariate analysis for relapse in patients with high CD30 expression and adverse cytogenetics in T-ALL patients, Multivariate analysis for treatment failure in patients with elevated serum sCD30 level and adverse cytogenetics in T-ALL patients

Parameters	Relapse					
	High CD30 expression			Elevated sCD30 level		
	Odds Ratio	95%Cl	P	Odds Ratio	95%Cl	P
Age	0.32	0.29-1.2	0.822	0.30	0.28-1.2	0.832
WBCs	2.7	1.71-5.0	0.003	3.4	1.71-5.3	0.004
HB	0.56	0.38-1.8	0.794	0.44	0.32-1.3	0.777
Platelets	0.49	0.34-1.5	0.663	0.55	0.47-1.8	0.601
BCR/ABL	-	-	-	-	-	-
BM Blasts	2.8	1.23-3.9	0.010	0.9	0.79-1.8	0.065

Table 5. Correlation between Clinical and laboratory characteristics in B- ALL patients to CD30 expression and serum sCD30 level

	CD30 %		sCD30 pg/ml	
	r	P	r	p
Age	-0.067	0.646	-0.246	0.073
WBCs	0.392	0.042	0.488	0.047
RBcs	0.112	0.476	0.120	0.441
HGB	0.068	0.600	0.120	0.365
PLT	-0.079	0.564	-0.088	0.666
BM Blasts	0.340	0.030	0.400	0.038
Cytogenetics	0.307	0.086	0.234	0.097
FAB	-0.233	0.099	-0.206	0.137

Additionally there was no significant correlation with either adverse cytogenetics or BCR/ABL mutation. However, there was a significant correlation between CD30 expression and WBCs count, BM blast count (r=0.392, P=0.042) and (r=0.340, P=0.030) respectively (Table 5). We found that only 2(25%) of the highly expressed CD30 patients relapsed after completion of the treatment with no significant value (Table 2). For sCD30 assay, elevated sCD30 was detected in 15.4% (6 out of 39 patients). With Regards to sCD30, we analyzed the relationships between the level of sCD30 expression and clinical data (age, sex), laboratory (WBCs count, Hb level, platelets count and BM blast count at diagnosis), FAB classification, cytogenetic risk groups, BCR/ABL and the outcome in patients with de novo B-ALL. Regarding the clinical data there was no significant relationship with elevated sCD30, But the patients with elevated sCD30 had elevated WBCs count and BM blast count (r=0.488, P=0.047) and (r=0.400, P=0.038) respectively (Table5). With regards to FAB classification, cytogenetic risk groups and BCR/ABL there was no significant relationship between elevated sCD30 and FAB B-ALL subtypes, adverse cytogenetics and BCR/ABL mutation. Furthermore, only 2 of these patients did not get complete remission after completion of treatment (Table 3).

DISCUSSION

CD30 antigen is a trans-membrane glycoprotein particle which is a part of the tumor necrosis factor receptor super family (20). After stimulation, CD30 employs pleiotropic actions on cell survival and growth, which mainly depend on the NF-κB pathway activation (Buchan and Al-Shamkhani, 2012). In our study, we analyzed the both CD30 expression and sCD30 in 90 ALL patients (51 T-ALL and 39 B-ALL) and its correlation with WBCs count, BM blasts, cytogenetics, BCR/ABL mutation, complete remission and relapse (bone marrow blast ≥5%, reappearance of blasts in peripheral blood and/or extramedullary disease and death). In this study we reported that high CD30 expression and elevated sCD30 in serum occurs with a percentage of 33.3% (17 out of 51 patients) and 27.4% (14 out of 51 patients) in T-ALL patients, respectively and 20.5% (8 out of 39 patients) and 15.4% (6 out of 39 patients) in B-ALL patients, respectively. Zheng *et al* repored that Using a 20% cutoff, CD30 was expressed more frequently in TALL, 38%, than in B-ALL, 14% (Zheng *et al*., 2014). Durkop *et al* reported that after the earliest detection of CD30 expression on RS cells of HL, CD30 was also recognized in different lymphoid neoplasms of T-, B-, and NK-cell origin (Durkop *et al*., 2000). Nadali *et al* reported that CD30 is also detected on non-lymphoid germ cells neoplasms, and can be found sometimes in mesenchymal tumors and nasopharyngeal carcinoma (Durkop *et al*., 2000; Latza *et al*., 1995). For serum sCD30 levels, high levels have been reported in different neoplasms (HL, ALCL, nasopharyngeal carcinoma, embryonal carcinoma of the testis) characterized by strong T-cell or B-cell activation (Deutsch *et al*., 2011). In this study we reported that there was a significant correlation between both high CD30 expression and elevated sCD30 and WBCs count, BM blasts, adverse risk cytogenetics, BCR/ABL mutation in T-ALL (That in contrast to Zheng *et al* that found that no correlation between CD30 expression and cytogenetic data in T-ALL (Zheng *et al*., 2014). We also observed that high CD30 expression in T-ALL has a poor prognostic factor for relapse in 60 years and younger patients with adverse risk cytogenetics. Moreover, elevated sCD30 at diagnosis was a predictor of complete remission failure 9(64.3%) patients with elevated sCD30 (>100pg/ml) had not get complete remission compared with 8(21.6%) patients with low serum sCD30 (P= 0.012). Nadali *et al* reported that in patients with HL and ALCL sCD30 appears to be a predictable tumor burden marker (26). Various reports have detected correlations between serum sCD30 levels and poor prognosis in CD30-positive lymphomas (Leoncini *et al*., 2013). Marshall stated that serum levels of sCD30 are high in almost untreated patients with HL and correlate with tumor burden, event-free survival and response to therapy (Marshall, 2000). In a multivariate analysis of risk factors, serum sCD30 levels more than 100 U/ml were predictor of a poor outcome for patients with HL (Marshall, 2000). Serum sCD30 values recurred to the normal level when patients accomplished complete remission, and returned to high values again at relapse, indicating that serum sCD30 can be used efficiently for monitoring disease activity in patients with positive CD30 ALCL (Nadali *et al*., 1995). However, for a bad luck we did not found any significant correlations between both CD30 expression and serum sCD30 level and adverse risk cytogenetics or BCR/ABL in B-ALL that is with Zheng *et al* who reported that CD30 expression showed no difference between cases of B-ALL with and without BCR-ABL (Zheng *et al*., 2014). After all, estimation of serum levels of sCD30 should be used as a non-invasive method for prognosis evaluation and disease activity monitoring in CD30 positive T-ALL patients. Furthermore, these patients could have a magic benefit of therapy by using anti-CD30 antibodies (which need further studies) instead of starting the conventional chemotherapy which will not give the optimal response.

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