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CD30 Expression *vs.* Serum Soluble CD30 (sCD30) Level: Role in Prognosis and Treatment of Acute Myeloid Leukaemia

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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 analyzed CD30 expression and serum soluble CD30 (sCD30) molecule level in patients with acute myeloid leukemia (AML) 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 50 AML patients. 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. 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 SPSS version 20. A p value of <0.05 was considered to be statistically significant.

Results: Our study conducted on 50 AML patients, the mean patients' age was 47.4 ± 18.1 years (range, 17-77), 11 (22%) were males and 39 (78%) were females. 16 (32%) patients have high CD30-expression and 11 (22%) 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, FLT3/ITD and with relapse for CD30 expression, complete remission failure with elevated serum sCD30 level.

Conclusions: CD30 is expressed by myeloblasts in AML patients. We found that high CD30 expression and elevated sCD30 level can be used as prognostic markers for relapse and complete remission failure respectively. 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 which need further studies.

Keywords: CD30; sCD30; Acute myeloid leukemia; Relapse; CD30 targeted therapy

Introduction

Acute myeloid leukemia (AML) is a clonal hematopoietic illness accompanied by atypical regeneration of hematopoietic stem cells, discrimination arrest at blast cells, infiltration of peripheral blood by blasts [1]. AML in old age [2], secondary to myeloproliferative neoplasms (MPN) or myelodysplastic syndromes (MDS), accompanied with high-risk cytogenetics responds unwell to routine treatment. Relapsed or refractory AML is usually anticipated as an untreatable illness [3]. High-risk AML sets up a biologically different group of disease and involves a vast percent of cases of adult AML [2-4].

Till now the adverse risk group of AML patients have no perfect treatment, so we study CD30 molecule expression in these patients to assess its prognostic role and in turn the possibility of the use of ani CD30 targeted therapy in treatment of these bad luck patients.

CD30 molecule was first off distinguished in 1982 as the antigen of the monoclonal antibody Ki-1 [5,6] and appears as a 120 kDa transmembrane glycoprotein be a member of the tumor necrosis factor receptor (TNF-R) superfamily [7], 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) [8,9].

An 88-kd soluble form of the CD30 molecule (sCD30) is separated from the surface of $CD30^+$ cells by the use of cell surface metalloproteinase TNF-α converting enzyme (TACE) [10]. However the mechanisms that conducting to the separation of sCD30 has not been researched in detail it might be a result of proper activation signals in feedback to interaction with $CD30L^+$cells [11]. Release of CD30 takes place as an active mechanism of viable CD30 positive cells. Soluble CD30 can obstruct the signaling by membrane-bound CD30 by way of attaching to CD30L and impeding its interaction with CD30 on the cell membrane. More readily, soluble CD30 could prevent transmembrane signaling by combining with membrane-bound CD30 to form complexes that lead to effective negative impedance. It has been submitted that sCD30 gives a mechanism by which CD30-positive tumor cells can bypass immunosurveillance and the CD30L activity induced apoptosis [12].

New drugs, for example inhibitors of FLT3, nucleoside analogues, histone deacetylase farnesyl-transferase, and DNA methyltransferase

taken alone or in combination, afford therapeutic options for high risk AML patients. Although, the long-term survival of these patients persists disappointing [13].

Unique antibody-based target treatment, such as anti-CD20 [14] and anti-CD22 [15] has shown hopeful results in adult acute lymphoblastic leukaemia [16].

Anti-CD30 chimeric antibody conjugated by a protease-cleavable linker to monomethylauristatin E, a factor that disorganizes microtubules. It has been shown to cause persistent responses in patients with relapsed anaplastic large cell lymphoma and with refractory and relapsed Hodgkin lymphoma [17,18].

The current research aims to analyze CD30 expression and serum soluble sCD30 molecule level in patients with acute myeloid leukemia (AML) to assess their role as prognostic markers.

Materials and Methods

Patients

Fifty patients with *de novo* AML were included in this work. These patients were admitted to Hematology unit, clinical pathology department and south Egypt cancer institute, Assiut University, Egypt, and were divided into groups according to morphology and immunophenotyping (FAB classification). The patients' written consent was obtained according to the declaration of Helsinki and the study has been approved by local ethics committee prior to their inclusion in the study.

The clinical and laboratory data consisted of age, sex, white blood cell count; haemoglobin level, platelets count, BM Blasts, cytogenetics, FAB classification, FLT3/ITD and the improvement after induction chemotherapy were obtained from patients' medical records.

Flow cytometric immunophenotyping analysis

Bone marrow aspirate samples were collected in EDTA tubes and handled within 24 h of aspiration. A panel of monoclonal antibodies was designed against myeloid lineage specific antigens including CD13, CD33, MPO, Cyto MPO, CD15, CD14, CD41 and non-specific antigens including CD45, CD34, CD 11C, CD 117 and HLA-DR. In addition to, CD30 were analysed on 4 color BD FACSCALIBUR.

Cytogenetic analysis

Cytogenetic analysis was done using short term cultures, depending on the recommendations of the International System for Human Cytogenetic [15]. We examined at least 20 metaphases. Cytogenetic risk groups were classified as follows: high risk, –7/del (7q), –5/del (5q), abn 3q, complex aberrations (X3 independent aberrations), t (6;9) and t (9;22); inter- mediate risk, normal karyotype or all other karyotypic abnormalities. Low risk, inv (16) and t (8;21).

Molecular analysis

DNA extraction: Genomic DNA was extracted from peripheral blood samples at diagnosis using an Invitrogen PureLink™ Genomic DNA Mini Kit: USA, by QIA cube Extractor.

For FLT3-internal tandem duplication (FLT3/ITD) mutation analysis. PCR products were analyzed on standard 3% agarose gels. Normal amplification produced a 330 bp product; whereas, FLT3 ITD mutations showed longer PCR products.

Enzyme linked immunosorbent assay

Serum sCD30 assay: Serum samples were withdrawn from each patient and stored at –70°C 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 SPSS version 20. A p value of <0.05 was considered to be statistically significant.

Results

Of the 50 AML patients, 20 (40%) were males and 30 (60%) were females. Mean age of the patients was 47.4 ± 18.1 years old with the range being 17-77 years.

In our study, using a traditional 20% cutoff (24), high CD30 expression (>20%) (Figure 1) was detected in 32% (16 out of 50 patients).

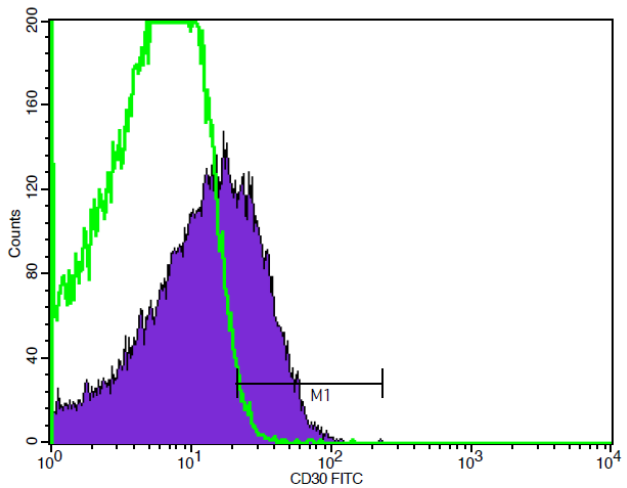

Figure 1: Flowcytometric histogram shows Positive CD30 expression. The green line indicates the negative control; filled line indicates a positive case.

High CD30 expression was found in all FAB classifications of AML, except for M0 and M5. 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 1a and b).

Parameters	CD30>20%	P	sCD30>100 pg/ml	P
Number of patients,%	16 (32)		11 (22)	
Age (years), (Mean ± SD)	45 ± 15.7		39.3 ± 15.1	0.671
Sex, n (%)				
Male	9 (56.3)	0.108	4 (36.4)	0.06
Female	7 (43.8)		7 (63.6)	
WBCs (Mean ± SD)103/µl	146.23 ± 108.92	<0.001	166.74+87.54	<0.001
Hb level (Mean ± SD) g/dl	6.64 ± 1.24	0.233	6.69+1.34	0.284
Platelet (Mean ± SD) 103/µl	48.61 ± 29.83	0.755	50.91+34.22	0.951
B.M Blasts	73.56 ± 15.81	<0.001	74.09+15.9	<0.001
FAB, n (%)				
M0	0 (0)		0 (0)	
M1	2 (12.5)		1 (9.1)	
M2	6 (37.5)		4 (36.4)	
M3	3 (18.7)		3 (27.3)	
M4	1 (6.3)	0.204	1 (9.1)	0.113
M5	0 (0)		0 (0)	
M6	2 (12.5)		1 (9.1)	
M7	2 (12.5)		1 (9.1)	
Karyotype, n				
Favorable	3 (18.8)		1 (9.1)	
Intermediate	4 (25)	0.017	3 (27.3)	0.004
Adverse	9 (56.3)		7 (63.6)	
Flt3/ITD, n (%)	9 (56.3)	0.023	8 (72.7)	0.001
Outcome, n (%)				
CR	9 (56.3)	0.09	4 (36.4)	0.004
Relapse	7 (43.8)	0.002	3 (27.3)	

Table 1a: Clinical and laboratory characteristics in AML patients in relation to CD30 expression and serum sCD30 level.

However, there was a significant correlation between CD30 expression and WBCs count, BM blast count and adverse cytogenetics (r=0.429, P=0.034), (r=0.366, P=0.032) and (r=0.509, P=0.001) respectively (Table 2).

Among the 16 patients with high CD30 expression there were 3 patients with favourable risk cytogenetics, 4 patients with intermediate risk cytogenetics (2 of 4 patients with normal cytogenetics), and 9 patients with adverse risk cytogenetics (P=0.017).

We also found that 7 (43.8%) of the highly expressed CD30 patients relapsed after completion of the treatment compared to only 9 (26.5%) of the negative expressed CD30 (P=0.002) (Table 1 and Figure 3).

Parameters	CD30<20%	P	sCD30<100 pg/ml	P
Number of patients, %	34 (68)		39 (78)	
Age (years), (Mean ± SD)	44 ± 15.5		41.3 ± 16.1	0.763
Sex, n (%)				
Male	15 (44.1)	0.312	20 (51.3)	0.869
Female	19 (55.9)		19 (48.7)	
WBCs (Mean ± SD) 103/µl	25.16 ± 29.45	0.456	34.9+60.76	0.679
Hb level (Mean ± SD) g/dl	6.22 ± 1.13	0.253	6.26+1.12	0.368
Platelet (Mean ± SD) 103/µl	53.15 ± 54.05	0.665	50.91+34.22	0.871
B.M Blasts	47.32 ± 12.01	0.087	74.09+15.9	0.083
FAB, n (%)				
M0	1 (2.9)		1 (2.6)	
M1	2 (5.9)		2 (5.1)	
M2	5 (14.7)		6 (15.4)	
M3	4 (11.8)		5 (12.8)	
M4	6 (17.7)	0.334	7 (17.9)	0.225
M5	13 (38.2)		15 (38.5)	
M6	2 (5.9)		2 (5.1)	
M7	1 (2.9)		1 (2.6)	
Karyotype, n				
Favorable	16 (47.1)		19 (48.8)	
Intermediate	11 (32.3)	0.179	13 (33.3)	0.094
Adverse	7 (20.6)		7 (17.9)	
Flt3/ITD, n (%)	8 (23.5)	0.165	9 (23.1)	0.123
Outcome, n (%)				
CR	28 (82.4)	0.07	29 (74.4)	0.087
Relapse	10 (29.4)	0.081	11 (28.2)	

Table 1b: Clinical and laboratory characteristics in AML patients in relation to CD30 expression and serum sCD30 level.

	CD30%		sCD30 pg/ml	
	r	P	r	p
Age	-0.068	0.638	-0.263	0.065
WBCs	0.429	0.034	0.500	0.041
RBcs	0.101	0.485	0.114	0.430
HGB	0.073	0.615	0.129	0.372
HCT	0.119	0.411	0.131	0.366
PLT	-0.081	0.575	-0.072	0.617
BM Blasts	0.366	0.032	0.422	0.035
Cytogenetics	0.509	0.001	0.443	0.008
FAB	-0.239	0.095	-0.208	0.148

Table 2: Correlation between Clinical and laboratory characteristics in AML patients to CD30 expression and serum sCD30 level.

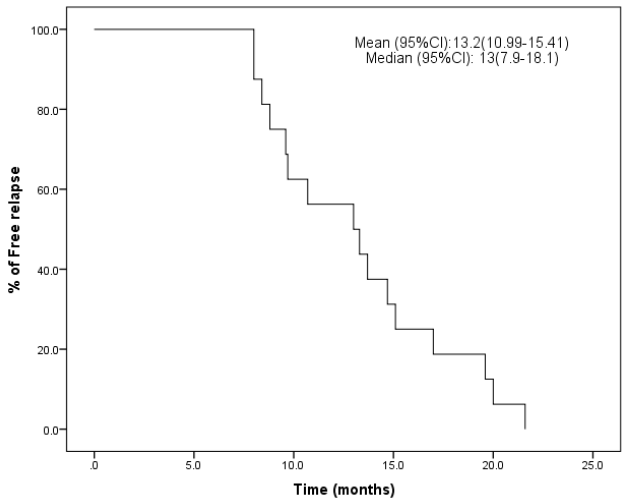

Figure 2: Kaplan-Meier analysis for overall percent of relapse in the fifty AML patients.

Additionally, we found that there was a significant relationship between CD30 expression and FLT3/ITD mutation in AML patients (56.2% of positive CD30 expressed patients had FLT3/ITD mutation compared to 14.7% of negative CD30 expressed patients) (P=0.023) (Table 1a, b and Figure 2).

In multivariate analysis high CD30 expression in AML patients with 60 years and less was predictor for relapse in patients showed increased WBCs (leucocytosis>20 X 10^3/µl) and increased BM Blasts (>20%), the results given as odds ratio {95% Confidence interval}: 2.9 {1.88-5.4}, P=0.002, 2.3 {1.43-4.2}, P=0.008 respectively (Table 3).

For sCD30 assay, elevated sCD30 were detected in 22% (11 out of 50 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, FLT3/ITD and the outcome in patients with *de novo* AML.

Parameters	Relapse		
	Odds Ratio	95%CI	P
Age	-	-	-
WBCs	2.9	1.88-5.4	0.002
HB	0.45	0.33-1.4	0.785
Platelets	0.56	0.49-1.9	0.543
FLT3/ITD	0.39	0.28-1.3	0.709
BM Blasts	2.3	1.43-4.2	0.008

Table 3: Multivariate analysis for relapse in patients with high CD30 expression and adverse cytogenetics in patients with 60 years and young.

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=0.500, P=0.041), (r=0.422, P=0.035) and (r=o.443, P=0.008) respectively (Table 2). 8 (72.7) patients with elevated sCD30 had FLT3/ITD mutation (0.001). With regards to FAB classification and cytogenetic risk groups, there was no significant relationship between elevated sCD30 and FAB AML subtypes, however 7 of 11 (63.6) patients with elevated sCD30 (>100 pg/ml) had adverse risk cytogenetics (P=0.004). Furthermore, 7 of these patients did not get complete remission after completion of treatment (P=0.004) and from the 4 patients that assumed CR, 3 patients relapsed (Table 1a and b).

In multivariate analysis high serum sCD30 (>100 pg/ml) in AML patients with 60 years and less was predictor for treatment failure in patients showed increased WBCs count (leucocytosis>20 X 10^3/µl) and FLT3/ITD mutation (Table 3), the results given as odds ratio {95% Confidence interval}: 3.1 {1.91-5.8}, P=0.001, 3.3 {1.96-6.3}, P=0.001 respectively (Table 4).

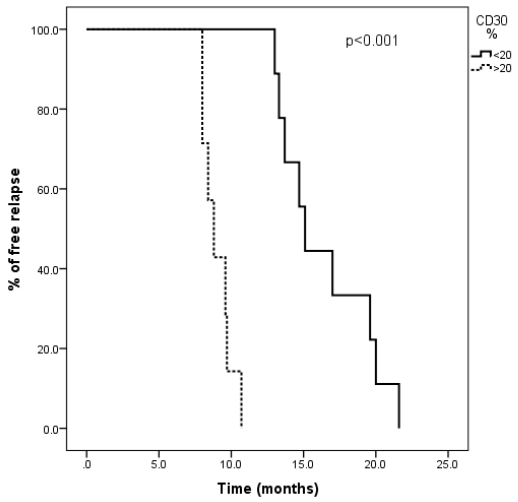

Figure 3: Kaplan-Meier Analysis for % Free Relapse. Solid line indicates patients negative for CD30, Dashed line indicates Patients with positive CD30 expression.

Parameters	Relapse		
	Odds Ratio	95%CI	P
Age	-	-	-
WBCs	3.1	1.91-5.8	0.001
HB	0.55	0.41-1.5	0.785
Platelets	0.67	0.69-1.8	0.543
FLT3/ITD	3.3	1.96-6.3	0.001
BM Blasts	0.9	0.35-1.9	0.071

Table 4: Multivariate analysis for treatment failure in patients with elevated serum sCD30 and adverse cytogenetics in patients with 60 years and young.

Discussion

CD30 antigen is a trans-membrane glycoprotein particle which is a part of the tumor necrosis factor receptor superfamily [19]. After stimulation, CD30 employs pleiotropic actions on cell survival and growth, which mainly depend on the NF-κB pathway activation [20].

In our study, we analyzed the both CD30 expression and sCD30 in 50 *de novo* AML patients and its correlation with WBCs count, BM blasts, cytogenetics, FLT3/ITD, complete remission and relapse (bone marrow blast ≥ 5%, reappearance of blasts in peripheral blood and/or extramedullary disease and death).

In this study we stated that high CD30 expression and elevated sCD30 in serum occurs with a percentage of 32% (16 out of 50 patients) and 22% (11 out of 50 patients) in *de novo* AML patients, respectively. Durkop H 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 [21]. Nadali et al. stated that CD30 is also detected on non-lymphoid germ cells neoplasms, and can be found sometimes in mesenchymal tumors and nasopharyngeal carcinoma [21,22]. 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 [23]. 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, FLT3/ITD mutation (That in contrast to Zheng W et al. that found that CD30 expression did not associate with NPM1, FLT3 ITD, D835, or RAS mutation state [24].

We also observed that high CD30 expression 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 7 (63.6%) patients with elevated sCD30 (>100 pg/ml) had not get complete remission compared with 4 (36.4%) patients with low serum sCD30 (P=0.004). Nadali et al. reported that in patients with HL and ALCL sCD30 appears to be a predictable tumor burden marker [25]. Various reports have detected correlations between serum sCD30 levels and poor prognosis in CD30-positive lymphomas [26]. 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 [27]. 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 [27]. 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 [25]. Also Zheng W et al. showed that CD30 expression is commonly found in AML patients who were refractory to different current treatment in comparison to *de novo* AML patients with no treatment [24]. Additionally, AML Patients with adverse cytogenetic risk, refractory to treatment were displayed high CD30 expression as found by the median percent of positive cells, but not by utilizing a 20% cut-off [24].

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 AML 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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