Soluble carcinoembryonic antigen cell adhesion molecule 1,6 and 8 in acute myeloid leukemia: their relation to survival and prognosis

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Abstract: Background: The carcinoembryonic antigen cell adhesion molecules (CEACAM) play important roles in cell adhesion as well as cancer cell invasion and metastasis. Objectives: to study the soluble CEACAM 1,6 and 8 in acute myeloid leukemia (AML) and to determine if they had an impact on the survival and prognosis. Methods: 102 subjects were included. They were 53 with AML and 49 healthy persons. All were subjected to the measurement of soluble CEACAM 1,6 and 8 by ELISA. The patients were divided into the high and low group by using median of each parameter in patients as a cut off value. Results. Significant increase of sCEACAM1,6 and 8 was found in their high group when compared to the control group. No significant difference was found in the low group of both sCEACAM1 and 6 when compared to the control. In contrast, a significant increase of sCEACAM8 was found. There were significantly positive and negative correlation of the high sCEACAM1 with lactic dehydrogenase and each of the surface CD66a, sCEACAM6 and 8 respectively. Significant positive correlations were found between sCEACAM6 and 8. There was a Significant increase of the relapse-free survival (RFS) in the highest group of sCEACAM6. Also, it was associated with increased overall survival (OS) 6.2 times when compared to the low group. Soluble CEACAM8 had a significant good impact on induction remission. Conclusion: The high group of sCEACAM6 and sCEACAM8 are independent good prognostic factors for overall survival and induction remission. sCEACAM1 is a poor prognostic factor.

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1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease. It has the potential to invade locally and infiltrate a variety of different tissues other than bone marrow. The mechanisms of invasion are related to angiogenesis, endothelial adhesion and cell migration (1,2).

The carcinoembryonic antigen cell adhesion molecules (CEACAMs) play important roles in cell adhesion as well as cancer cell invasion and metastasis. The CEACAMs family belongs to the immunoglobulin (Ig) supergene family (3). The CEACAM family is divided into two groups: the first is carcinoembryonic antigen (CEA) and the classic non-specific cross-reacting antigens (NCA). The CEA consist of 12 which are 1,3,4,5,6,7,8,16,18,19,20,21. The second includes the pregnancy-specific glycoproteins (3-5). CEACAM1 is the most widely distributed protein within the gene family, being present in different epithelia, on endothelial cells, as well as in lymphoid and myeloid cells in normal tissues. The CEACAM1 has 12 different isoforms of which 3 are secreted versions. The secreted forms play significant role in the inhibition of intercellular adhesions (6) or in diseased situations such as obstructive jaundice (7) and it is a marker of melanoma, pancreatic, and urothelial bladder cancer progression (8-10).

CEACAM6 is distributed, with significant expression in many epithelia, as well as in granulocytes and monocytes (11). Its deregulation was first noticed in leukocytes of chronic myeloid leukemia (12), in childhood acute lymphoblastic leukemia (of B cell origin) (13) and in acute myeloid leukemia (14,15). CEACAM6 is overexpressed in several epithelial carcinomas. In addition, it is involved in many crucial cellular events such as migration, invasion and tumorigenicity (16-17). It now appears that CEACAM6 might be the most specific marker for a number of aggressive cancers and could

be valuable in the follow-up of patients with pancreatic carcinoma after surgery (18).

CEACAM8 is present on the surface of granulocytes as well as stored in the secondary granules of granulocytes. Upon activation, CEACAM8 can be translocated to the plasma membrane from the storage pools within granulocytes. Both CEACAM8 versions comprise an identical amino acid sequence except for a leader sequence labeling the designated membrane-bound CEACAM8. So far, no ultimate biological function could be identified to the released, soluble CEACAM8 in human (19).

No studies have been focused on soluble CEACAM1, 6 and 8 in acute myeloid leukemia and their relation to prognosis and survival of patients.

Aim of this study

The aim of this work was to study the soluble CEACAM 1,6 and 8 in AML. To detect if they had a relation to the survival and prognosis of patients and if they can be used as predictive markers in AML.

2. Subjects and Methods

Subjects

The analytical methods of this study were carried out in the Hematology lab of the King Abdullah city, Makkah, Saudi Arabia. The Umm AlQura University ethics committee approved the protocol of this study. Written informed consent was obtained according to the Declaration of Helsinki. This study was carried out from May 2014 to May 2016; it included 53 newly diagnosed AML patients and 49 healthy persons as a control group. The diagnosis of AML was based on WHO classification (20-21). The patients were divided into high and low group by using the median of each parameter in patients as a cut off value. All AML cases received intensive, response- adapted double induction and consolidation therapy as previously described (22-23).

Sample collection

5 ml of blood sample were collected from each participant under complete aseptic conditions. 2ml for performing complete blood count (CBC) and the other 3 ml was used for biochemical studies and determination of soluble CEACAM 1,6 and 8. A 2ml of the bone marrow aspiration sample was collected for examination, immunophenotyping and cytogenetic analysis.

Inclusion criteria

All newly diagnosed cases of de novo and secondary AML were taken.

Exclusion criteria

Patients with AML on chemotherapy were excluded. In addition, patients with obstructive jaundice and or any types of solid tumors were excluded from the study.

Methods

All participants were subjected to the followings:

CBC on Sysmex XT-2000, Siemens diagnostic-Germany and examination of peripheral blood film.

Measurement of soluble CEACAM1, CEACAM6 and CEACAM8 by enzyme - linked immuno Sorbent assay (ELISA) according to the manufacturer's instructions. The kits were provided by Cusabio Biotech Co (China). The sensitivity for CEACAM1,6,8 were less than 0.195ng/ml, 0.33ng/ml and 0.156 ng/ml respectively. The CV% of the intra-assay precision of both CEACAM1 and 8 was less than 8, whereas the CV% of the interassay precision was less than 10%. The CV% of the intra-assay precision of CEACAM 6 was less than 10, whereas the CV% of the interassay precision was less than 15%.

Measurement of surface CD66a, CD66b and CD66c on BD-FACS-Canto II System (BD- Bio Science). The CD66a from R & D. The CD66 b and c from BD.

Determination of liver enzyme and lactic dehydrogenase on COBAS INTEGRA® 6000 analyzers (Roche Diagnostics-Germany).

The following tests were done to the patients only: -

Examination of bone marrow aspiration and biopsy films.

Immunophenotyping for patients: it was performed using BD-FACS-Canto II System (BD- Bio Science) and reagent system (BD- FACS Setup) as previously described (24).

Conventional karyotype analysis and fluorescence in situ hybridization were performed (25).

Statistical analysis

The statistical analysis of this study was done using SPSS program version 20. Quantitative data were described in the form of mean ± SD for the normally distributed data. The median and range was used for the data that were not normally distributed. The comparison between the groups was performed by using the student t test. The Mann–Whitney U test and Kruskal Wallis were used for the data that was not normally distributed. The chi -square test or Fisher exact test was used for comparison between qualitative data. The Kaplan- Meier method, the log- rank test and Tarone -Ware were used to compare the overall survival (OS) and relapse free survival (RFS) of the patients in different group studied (26-27). A logistic regression model was used to analyze the associations between variables and response to induction therapy. A Cox proportional hazards model was used to identify the independent prognostic factors with respect to the OS and RFS. The significance level was set at 0.05.

3. Results

The results of this study are summarized in tables from 1 to 6 and figures1-3

This study included 53 patients with AML and 49 healthy subjects as a control group. All the AML patients were de novo, except 3 cases, one on top of myelodysplastic syndrome, the second was a blastic crisis of chronic myeloid leukemia and the third had a history of cancer breast. The distributions of AML patients were as follow: M1 = 14, M2 = 17, M3=8, M4 = 4, and M5= 10. They were 31 men and 22 women with a male to female ratio of 1.4:1. Their mean age was 43.94± 16.8 years. Their median age was 42 years and ranged from 15 to 81 years. No significant difference was found between the patients and control with regards to age and sex. 19 of our patients (35.8%) were presented with fever and 17 (32.1%) with bleeding manifestation. One case only with organomegaly (1.9%). The cytogenetic abnormalities of our patients were, 10 (19.5%) favorable, 34 (63.4%) intermediate, 8 (14.6%) unfavorable and 1 (2.4%) not done. The favorable profiles include cases with [t (8;21), t (15;17), and inv 16], the intermediate profiles include cases with [normal karyotype, +8,+4, +11q23, t (9;11), and t (1;9;22)], and the unfavorable include cases with [complex abnormality, inv 17, t (7;11), monosomy 7, hypodiploidy and t (9;22)]. The clinical data are shown in table1.

Table 1: Comparison between AML patients and control with regards to clinical, hematological and chemical parameters

Parameters studied	AML (n=53)	Control (n=49)	P and significance
Age/y	*43.85± 16.83	38.7 ±11.5	0.085 NS
Median	42	41	
Range	15-81	20.0-58.0	
Sex Male	31.0	21	
Female	22.0	28	0.117 NS
Ratio	1.4:1	1.0:1.3	
FAB classification			
M1, M2	14;17		
M3	8		
M4, M5	4;10		
TLCX109/l	*43.8±66.0	6.2±1.3	<0.001HS
Median	20.0	5.8	
Range	0.8-381.7	4.5-9	
Hemoglobin g/dl	*8.3±1.9	12.9±1.1	<0.001 HS
Median	8.0	13	
Range	3.8-12.7	12.0-16.0	
Platelets X109/l	*64.9±71.9	280.0±79.0	<0.001 HS
Median	42.0	256.0	
Range	2.0-374.0	150.0-400.0	
Peripheral blood blast %	*40.9±31.9		
Median	40		
Range	0.0-95.0		
Bone marrow blast %	*58.3±23.6		
Median	62.0		
Range	20.0-95.0		
LDH u/l	*591.5±411	200.0± 43.9	
Median	481.0	189.0	<0.001 HS
Range	131.0-1795.0	140.0-280.0	
SGOT u/l	*48.0±144.7	25.2±5.7	
Median	25	25.0	0.735NS
Range	5.6- 1075.0	11.0-37.0	
SGPT u/l	*37.9±31.9	26.2±8.2	0.020 S
Median	30	26	
Range	8.0-220.0	11.0-53.0	

* mean ± SD NS= not significant, S= significant, HS= highly significant, LDH= lactic dehydrogenase, SGOT= serum glutamic oxaloacetic transaminase, SGPT= serum glutamic pyruvic transaminase.

The comparisons between the different groups studied, with regards to the soluble CEACAM1, 6,8 are shown in Table 2.

The soluble CEACAM 6 and 8 had higher significant values in AML patients when compared to the control group p<0.001. Whereas, the soluble CEACAM1showed no significant difference between the patients and the control group p>0.05. Table 2.

Due to the wide range of our data in the 3 sCEACAM, we split each of sCEACAM1,6 and 8 into groups (high and low) using median of the patients in each parameter as a cutoff value.

In the sCEACAM1groups, a significant increase of sCEACAM1 was found in the high group when compared to the low one and to the control group p<0.001 & p=0.006 respectively. No significant difference was found between the low group and the control group p=0.154. In the sCEACAM 6 groups, significant increase of sCEACAM 6 was found in the high group when compared to the low one and to control group p<0.001. Whereas, no significant difference was found between the low group and the control group p=0.926. In the sCEACAM 8 groups, the high group had significant higher values than the lower one p<0.001. In addition, both group had significant higher values when compared to the control group p<0.001and 0.002. table 2.

Table 2: Comparison between different group with regards to the soluble CEACAMs

Parameters studied	High ≥ cut off	Low <cut off	Whole group	Control (n=49)	P and significance
s CEACAM1 ng/ml					P1 <0.001
Cut off	1.8				P2 0.006
Median	7.8	0.71	1.8	2.1	P3 0.154
Min-max	1.9-39.3	0.33-1.75	0.33-39.3	0.15-19.48	P4 0.221
s CEACAM6 ng/ml					P1 <0.001
Cut off	2.5				P2 <0.001
Median	5.27	0.71	2.54	0.74	P3 0.926
Min-max	2.5-6.63	0.15- 2.44	0.15-6.63	0.2-2.0	P4 <0.001
s CEACAM8 ng/ml					P1 <0.001
Cut off	18.9				P2 <0.001
Median	28.66	11.7	18.98	7.4	P3 0.002
Min-max	18.9-36.97	3.1-18.8	3.1-36.97	0.77-21.8	P4 <0.001

P1 between high and low group; p2 between high and control; p3 between low and control; p4 between whole group and control.

Table 3: The relationship between the 3 sCEACAM

Parameters studied	s CEACAM1		s CEACAM6		s CEACAM8		control
	High ≥ cut off	Low <cut off	High ≥ cut off	Low <cut off	High ≥ cut off	Low <cut off	
s CEACAM1 ng/ml							
Median				6.57		2.7	
Min-max				0.33-39.3		0.33-38.4	
P1	--------	---------	0.929	0.011	1.09	0.173	2.1
P2			0.4-4.93	0.123	0.35-39.3	0.395	0.15-19.48
P3				0.192		0.559	
s CEACAM6 ng/ml							
Median		5.0				0.97	
Min-max		0.31-6.63				0.16-5.58	
P1	0.900	0.002	--------	--------	4.8	0.005	0.74
P2	0.15-6.31	0.084			0.15-6.63	<0.001	0.2-2.0
P3		<0.001				0.030	
s CEACAM8 ng/ml							
Median		22.7		13.79			
Min-max		9.2-36.97		3.1-32.05			
P1	15.6	0.011	22.7	0.002	---------	---------	7.4
P2	2.98-34.6	<0.001	10.8-36.97	<0.001			0.77-21.8
P3		<0.001		<0.001			

P1 between high and low; p2 between control and high; p3 between control and low.

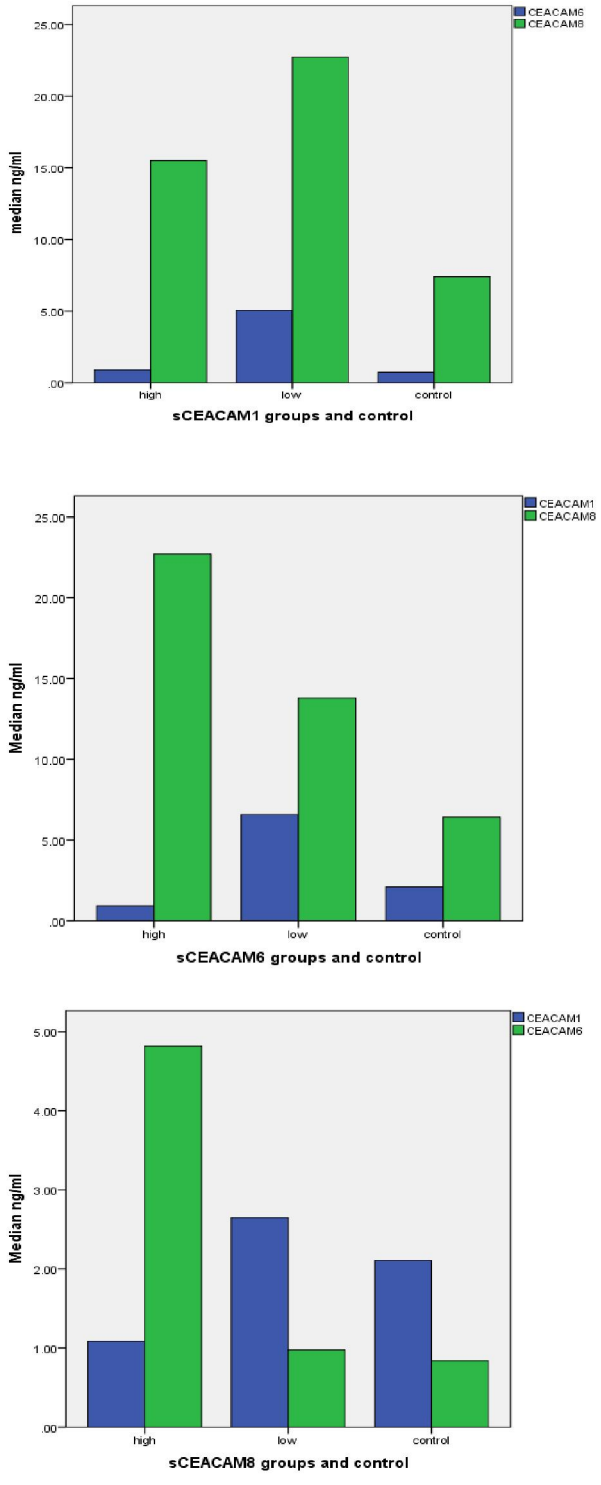

Figure 1: The relationship between the different soluble CEACAM

The relationship between the 3 sCEACAM Table3 and figure 1:

The values of sCEACAM6 and 8 in the high group of sCEACAM1 showed a significant decrease when compared to their values in the low group of sCEACAM1. sCEACAM6 in the high group of sCEACAM1 showed no significant difference when compared to the control group. whereas, sCEACAM6 in the lowest group of sCEACAM1 had significantly higher values when compared to the control group. The sCEACAM8 in both groups of sCEACAM1 was significantly increased when compared to the control group.

In the high group of s sCEACAM6, a significant decrease of sCEACAM1 was found when compared to their values in the low group of sCEACAM6. Moreover, no significant difference was found between both groups of sCEACAM1 and control group. The sCEACAM8 in both groups of sCEACAM6 had higher significant values when compared to the control group and when compared to each other. The values of sCEACAM1 in both groups of sCEACAM8 showed no significant difference when compared to each other and to the control. The concentration of sCEACAM6 in both groups of sCEACAM8 had significantly higher values versus control and versus each other.

The correlations between soluble CEACAMs and different parameters studied in AML are shown in table 4.

In the high group of sCEACAM1, there was a significant negative correlation of sCEACAM1 with each of sCEACAM6, 8, surface CD66a, the duration of the OS and the duration of the RFS. Significant positive correlation with LDH. In the low group of sCEACAM1, significant positive correlations of sCEACAM1 with each of myeloperoxidase (MPO) and CD13 $p<0.05$.

In the high group of sCEACAM6, there was a significant positive correlation with sCEACAM8, $r=0.707$, $p<0.001$.

In the high group of sCEACAM8, there was a significant positive correlation with sCEACAM6, $p=0.012$. No significant correlations were found with their surface counterpart and with other markers studied. No significant correlation was found in the low groups of both parameters. Table 4.

The comparisons between the high and low group of each soluble CEACAMs in AML are shown in Table 5.

The high group of sCEACAM1 showed a significant increase of SGOT and a significant decrease in the duration of RFS. The high group of sCEACAM6 had a significant increase in the duration of OS and RFS. No other significant differences were detected with regards to the age, sex, organomegaly,

FAB subtypes, type of AML, WBC count, hemoglobin concentration, platelets count, peripheral blood blast, bone marrow blast, LDH and the cytogenetic analysis.

Table 4: Correlation between different parameters studied

	sCEACAM1		sCEACAM6		sCEACAM8	
	r	p	r	p	r	p
sCEACAM1	---------	----------	-0.220	0.325	-0.217	0.319
sCEACAM6	-0.472	0.023	----------	----------	0.544	0.012
sCEACAM8	-0.432	0.035	0.707	0.001	----------	---------
Age/year	0.071	0.748	-0.010	0.965	0.092	0.676
Sex	-0.278	0.200	0.079	0.726	0.013	0.935
TLC X109/l	0.001	0.996	-0.374	0.086	0.289	0.182
PBB X109/l	-0.163	0.457	-0.052	0.818	0.082	0.711
BMB X109/l	-0.041	0.852	0.190	0.396	0.076	0.730
CD66a %	-0.595	0.007	-0.213	0.340	0.069	0.753
CD66b%	0.081	0.751	-0.330	0.134	-0.100	0.650
CD66c%	0.075	0.766	-0.050	0.824	0.090	0.683
CD13%	0.169 *0.450	0.440 0.036	0.214	0.339	-0.091	0.679
CD33%	0.242	0.266	0.204	0.363	-0.130	0.555
CD14	-0.235	0.280	-0.291	0.283	-0.224	0.304
CD64	-0.032	0.892	-0.064	0.779	-0.180	0.410
MPO%	0.175 *0.458	0.424 0.032	0.195	0.384	-0.080	0.716
LDH IU/l	0.472	0.036	-0.263	0.250	-0.229	0.319
Duration of O S/month	-0.565	0.004	-0.088	0.717	0.398	0.067
Duration of RFS/month	-0.728	0.001	-0.306	0.249	0.209	0.422

TLC= total leukocytic count; PBB= peripheral blood blast; BMB= bone marrow blast; MPO= myeloperoxidase; LDH= lactic dehydrogenase; OS= overall survival; RFS= relapse free survival.
*Indicate correlation in the low group. Only the significant correlation was added.

Table 5: comparison between high and low group of soluble CEACAM 1,6 and 8 in AML

	sCEACAM1		**sCEACAM6**		**sCEACAM8**	
	High≥ 1.8 no=27	Low<1.8 no=26	high≥2.5 no=27	Low<2.5 no=26	high≥18.9 *no=27	Low<18.9 no=26
WBC **median** **range** **p**	14.4 3.1-381.7	11.7 0.8- 14 0.453	10.3 0.8-117	22.3 1.0-381.7 0.331	10.3 0.8-148	26.5 1.0-381.7 0.630
Hemoglobin median **range** **p**	8.1 3.8-12.0	7.9 5-12.7 0.466	8.3 5.9-12.1	7.9 3.8-12.7 0.268	7.8 3.8-12.0	8.4 5-12.7 0.335
Platelets median **range** **p**	36.3 2-229.0	43 11-297 0.231	46 11-150	30.5 2.0-297.0 0.152	42 9-150	31.5 2-297 0.503
PBB **median** **range** **p**	48.0 0-95.0	23.5 0.0-92 0.213	27 0.0-90	52 0.0-95.0 0.193	28 0.0-92.0	52 0-95 0.466
BMB **median** **range** **p**	57.5 20-95.0	66.5 20-94 0.341	66 20-91	65.5 20-95 0.961	70 20-92	57.5 20-95 0.466
LDH **median** **range** **p**	535 213-1890	419 139-1334 0.390	419 181-1451	558 139-1795 0.223	442 182-1495	534 139-1795 0.652
SGOT **median** **range** **p**	28 13-74	20.5 5.6-62 0.027	23.5 5.6-74	25.5 11.0-109.0 0.424	21 5.6-74	26 11.0-109.0 0.724
†OS **median** **range** **p**	3.8 0.7-20.3	6.2 0.4-16.8 0.365	8.0 0.4-20.3	2.2 0.7-14.5 0.012	5.3 0.7-14.8	2.8 0.4-20.0 0.279
†RFS **median** **range** **p**	3 0.1-19.1	6.6 1.0-15.9 0.019	7.7 3-19.1	1.8 0.1-13.6 0.001	4.4 0.8-14.6	3.7 0.1-19.1 0.326

PBB= peripheral blood blasts; OS= overall survival; RFS= relapse free survival
† duration only

Table 6: multivariate analysis for overall survival in AML patients (Cox regression model)

	B	Sig.	Exp (B)	95.0% CI for Exp (B)	
				Lower	Upper
age	.053	.019	1.054	1.009	1.102
Bone marrow blast	.032	.062	1.032	.998	1.068
sCEACAM6group	1.836	.027	6.270	1.230	31.964

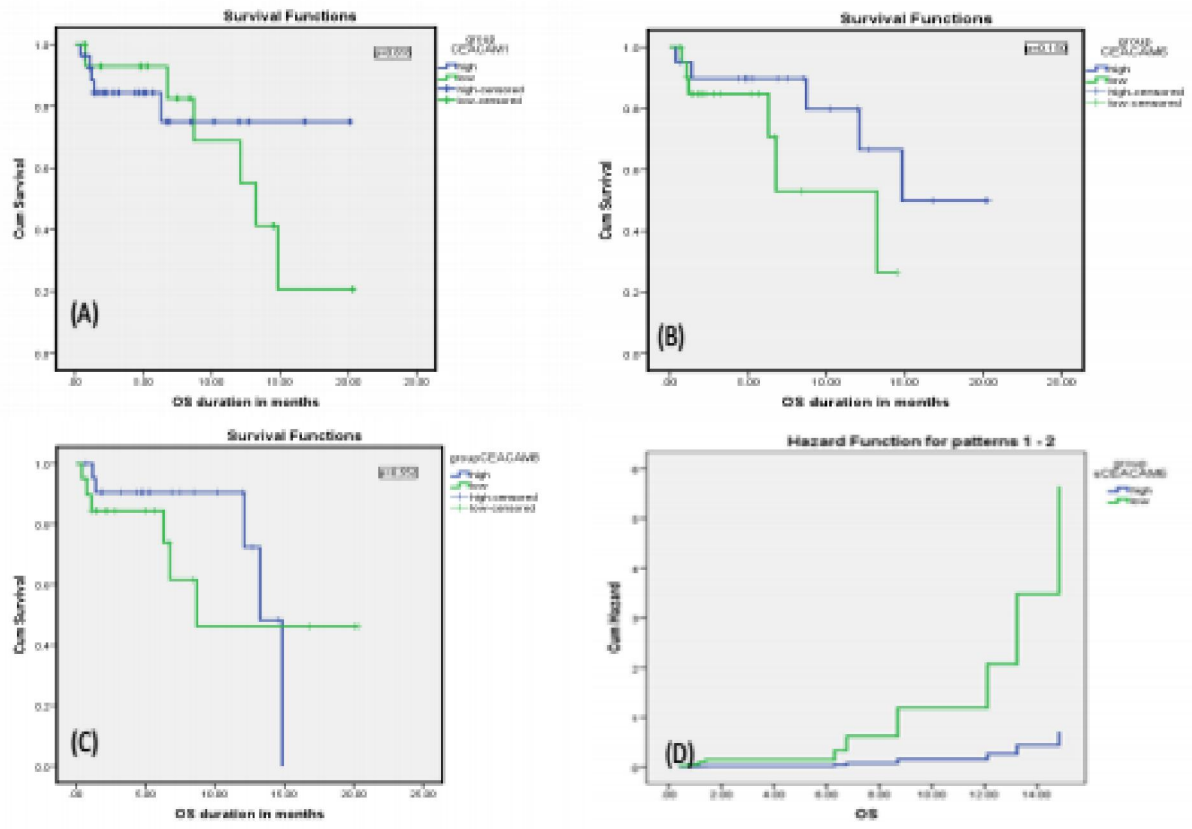

Figure 2: impact of sCEACAM1,6 and 8 on overall survival (OS) studied by Kaplan Meier test. (A) impact of sCEACAM1 on OS. (B) impact of sCEACAM6 on OS. (C) impact of sCEACAM8 on OS. (D) hazards function of sCEACAM6 on OS

The Prognostic impact of soluble CEACAM 1,6,8:

Response of patients to first induction complete remission (CR):

In AML, out of 53 patients, 37 (69.8%) responded to induction remission and achieved complete remission at day 28 to 39. 13 patients (24.5%) did not respond to induction remission, 2 cases missed (3.8%) and 1 (1.9%) new case did not take the result of it at the first induction remission as we finished the study. In addition, no significant differences were found in the values of CEACAM1, 6,8 in those who enter a complete remission or not p=0. 292,0.166,0.238 respectively.

Effect of CEACAM1, 6,8 on induction remission: -

At first, we compared all the parameters studied with induction remission as a grouping variable. These factors were sCEACAM1, sCEACAM6, sCEACAM8 with their groups, total leukocyte count, hemoglobin, platelets, peripheral blood blasts, bone marrow blasts, LDH, sex, age, organomegaly, type of AML, FAB subtype and cytogenetic abnormalities. It was found that, both the sCEACAM8 and the number of bone marrow blast had effect on induction remission, p=0. 048 and p= 0.011 respectively. Then the logistic regression model (forward LR stepwise) was done to assess whether the soluble CEACAM 8 and bone marrow blast is affecting the achievement of complete remission. It was found that, the soluble CEACAM8 was statistically significant p=0. 047, beta = - 0.087, odd ratio or exponential beta = 0.917, confidence interval= 0.842- 0.999. The hazard of not achieving a complete remission decreased by (1 – 0.917) X100 =

8.3%. So, the sCEACAM8 was an independent prognostic factor for the achievement of complete remission. The bone marrow blast lost its significance when introduced into the model.

The survival analysis and the effect of sCEACAMs on the OS and RFS. Figure 2 and 3:

In this study, the median OS was 4.8 months and it ranged from 0.03 to 20.3 months. The median RFS was 4.3 months and it ranged from 0.1 to 19.0 months.

The Kaplan Meier analysis showed a significant increase on the RFS in the high group of sCEACAM 6 using Tarone Ware test p=0.05. No other significant effects of the sCEACAM on the survival functions were found. Figure 2 and 3.

The effect of CEACAM1, 6,8 on OS and RFS using Cox proportional hazard test table 6 and figure 2.

The Cox regression model (backward stepwise) was done to determine their effects on OS and RFS. Variables with a P value of 0·3 or less in univariate analysis were included in the model which are age, hemoglobin, peripheral blood blast, bone marrow blast, and sCEACAM6 and its groups. The high sCEACAM6 group had 6.2 times decrease hazard of death and increase OS than the lowest group of it. In addition, age was significantly associated with the increased hazard of death and the decreased OS. No other significant parameters were obtained.

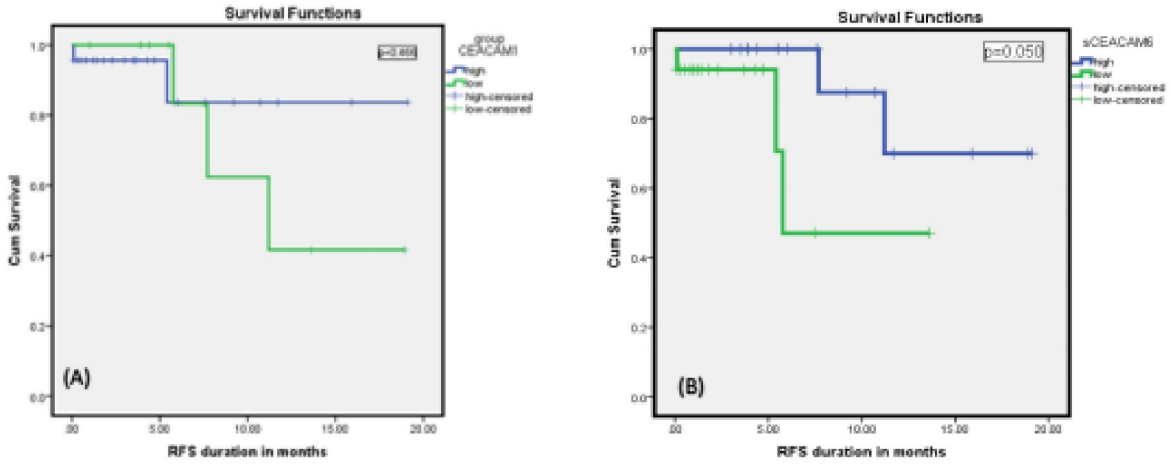

Figure 3: impact of sCEACAM1 and 6 on relapse free survival (RFS) studied by Kaplan Meier test. (A) impact of sCEACAM1 on RFS. (B) impact of sCEACAM6 on RFS.

4. Discussion

Prognostic factors in AML are heterogeneous, and new ones are still likely to be found. The aim of this study was to measure the soluble CEACAM 1,6 and 8 in AML and to detect their relation to the prognosis and survival of patients. To our knowledge, this is the first time to measure sCEACAM1, 6 and 8 in AML patients. The high group of sCEACAM1 was significantly increased when compared to the control group. The origin of sCEACAM1 in AML remains unclear. Previous reports about the origin of sCEACAM1 in solid tumors demonstrated that it was originated from shedding of cells or dead cells in addition to active secretion (26). The positive significant correlation between sCEACAM1 and each of CD13 and MPO in the low group of sCEACAM1 in our work make us suggest that it was released from the blast cells via active synthesis and not via shedding from the surfaces of the blast cells as only 6% of the cases express CD66a on their surface (15). In addition, the significant negative correlation between soluble and surface CEACAM1 may indicate a suppressive effect of sCEACAM1 on the surface expression of CEACAM1. The functions of sCEACAM1 are not entirely elucidated, although it has been shown that sCEACAM1 can inhibit intercellular homophilic adhesion so increase metastasis and spread of the tumor (6). High sCEACAM1 was associated with poor prognosis in the different solid tumors (8-10). In our study, the high sCEACAM1group had a significant positive correlation with LDH which is a poor prognostic factor and higher levels of it associated with early relapse (29). In addition, it had a negative correlation with the duration of OS and RFS which again indicates a poor prognosis. Moreover, significantly higher values of SGOT were found in the high group of sCEACAM1 which indicates infiltration of the liver and liver cell injury (30). From all these results, we suggested that high sCEACAM1 had an impact on the prognosis and survival of patients.

In our work, both high and low group of sCEACAM8 had higher significant values when compared to the control group. Whereas, only the high group of the sCEACAM6 showed a significant increase when compared to the control group. CEACAM6 is distributed in granulocytes, monocytes and epithelial cells and the CEACAM8 is expressed on the surface of granulocytes and stored in specific vesicles of granulocytes in the secondary granules of it. On activation, sCEACAM8 can be translocated to the plasma membrane from the storage pools within granulocytes (11,19,31). No previous reports were found about the sources of sCEACAM6 and 8 in AML. The significant positive correlation between sCEACAM6 and 8 in all groups studied in our work denote that the sources of both molecules are the same. In this study, the absence of a significant correlation between both sCEACAM6 and 8 and each of surface CEACAM6, surface CEACAM8, CD13, CD33, CD14, CD 64 and myeloperoxidase make us suggest that the blast cells are not the source of soluble CEACAM6 and 8 in the circulation. Factors that increase concentrations of sCEACAM 8 with the release from granulocytes are the granulocytes macrophage colony stimulating factor, cytokines from T lymphocytes and acute inflammation; all these factors are present in AML and may lead to the release of sCEACAM 8 from granulocytes and increased its concentration in the circulation (20,32). The sCEACAM8 can bind and interact with all CEACAM1 and 6 cell types such as epithelial, endothelial and all hematopoietic cells to do their functions (19). We suggested that this binding may stimulate the sCEACAM6 to be released from granulocytes or monocytes or epithelial cells.

In this study, it was obvious that there was a relationship between the 3 sCEACAM1, 6,8 in AML. In the high group of sCEACAM1, the sCEACAM6 had insignificant difference when compared to the control group. In addition, the sCEACAM1 in the high group of sCEACAM6 was insignificant from the control. This may indicate that when the parameter is high, it suppresses or decrease secretion of the second parameter. This was confirmed in our work by the significant negative correlation between both parameters in the high group of sCEACAM1. The relationship between sCEACAM1 and 8 was different. The sCEACAM8 in the high group of sCEACAM1 was significantly higher than the control group and this may indicate no effect of high sCEACAM1 on the values of sCEACAM8. In contrast, sCEACAM1 in the high group of sCEACAM8 had insignificant difference from the control and this may denote a decrease in the secretion of sCEACAM1 by sCEACAM8. In a previous study of human epithelial cells, the workers demonstrated that soluble CEACAM8 dampened the TLR2-triggered immune response of CEACAM1-expressing human pulmonary epithelial cells. This may be the same with our work that sCEACAM8 decrease or suppress the release of sCEACAM1 (33). From these results, we suggest that the injections of recombinant sCEACAM 6 in those patients with high sCEACAM1 can be used to counteract the undesired effect of it in AML patients and to improve the prognosis of patients.

In this study, when comparing the high versus low group of different sCEACAMs, there was a significant increase in the duration of OS and RFS in the high group of the sCEACAM6 and a decrease in the RFS in the high group of sCEACAM 1. This again proves our suggestion that sCEACAM1 is a poor prognostic factor, whereas, sCEACAM6 is a good prognostic factor. Moreover, when the Kaplan- Meier analysis was done to confirm these findings. Only a significant increase in the RFS in the high group of sCEACAM 6 when compared to the low one was found. This confirms that the high group of sCEACAM6 was a good prognostic factor as it was associated with higher relapse free survival. The significant was obtained by using the Tarone Ware test p=0. 05 and not by the log rank test which was insignificant p=0. 065. The discrepancy between the 2 tests may be explained by the fact that there are other factors which influence the performance of the log - rank test. The factors may be a number of events ≤ 5, may be the range of data and may also be the difference between the sizes of two groups (34). In our work, the number of events was 5 and we depend on the results of Tarone -Ware test.

To detect the role of sCEACAM1, 6 and 8 as independent prognostic factors. Both the multiple regression analysis and cox regression tests were done. The sCEACAM8 was an independent good prognostic factor for the achievement of complete remission and the hazard of not achieving complete remission decreased by 8.3%. The high group of sCEACAM6 showed higher overall survival and decreased hazard of death 6.2 times when compared to the lower one. This indicates that sCEACAM8 and the high group of sCEACAM6 are independent good prognostic factors.

Conclusion:

sCEACAM1 is a poor prognostic factor. The high group of sCEACAM6 is a good independent prognostic factor, whereas sCEACAM8 could predict a good response to induction remission. High values of sCEACAM6 and sCEACAM8 can suppress or decrease the secretion of sCEACAM1. Recombinant sCEACAM 6 and 8 could be used to counteract the undesired effect of sCEACAM1 and to improve the prognosis of the AML patients.

Recommendation

The measurement of sCEACAM1 and 6 at diagnosis is essential to identify those with poor prognostic factors. More studies are needed to clarify the role of sCEACAM1, 6 and 8 in AML and to prove our results.

Disclosure of interest: the authors report no conflict of interest

Geolocation Information:

This study was carried on Makkah, Saudi Arabia

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Author Contributions

A. Z.: share in the design of the study, did the statistical analysis, preparing tables and figures, writing and revising of the main manuscript text. HM: Did the ELISA technique, calculated the concentration of the markers, helped in the preparation of the master table for statistical analysis and critical reviewing of the manuscript. MI: share in the design of the study, helped in the selection of cases, performance of lab work, preparation of the master table for statistical analysis and critical reviewing of the manuscript. ST: collection of control samples and sharing in the reviewing and writing of the manuscript. NA: helped in the selection of cases, preparation of the master table for statistical analysis and critical reviewing of the manuscript.

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The authors report no conflict of interest.

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Additional information.

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