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ORIGINAL ARTICLE

Clinical significance of sCD86 levels in patients with acute myelogenous leukemia

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Abstract *Introduction:* CD86 (B72) molecules are surface glycoproteins and members of Ig superfamily that are expressed only on professional APCs and are important in the early interactions between APCs and T cells during the induction of immune response. It is well established that mCD86 is expressed by AML blasts in a considerable proportion of patients. The release of soluble forms of membrane molecules provides a powerful means by which leukocytes can either inhibit or enhance the biological effects relative of their membrane-bound counterparts, and there is now considerable evidence to support the possibility that the release of a soluble form of CD86 (sCD86) has an immunoregulatory role *in vivo*. The observation that sCD86 levels are highest in the FAB subtypes with the highest AML blast levels, together with the observation that high levels of sCD86 are associated with poor prognosis, strongly suggests that sCD86 is derived from the malignant cells in these patients.

The aim: The present study was to assess levels of sCD86 in de novo acute myeloid leukemia patients and to determine any possible correlation with outcome following induction chemotherapy.

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The study was carried out on 30 patients with de novo acute myeloid leukemia and 20 healthy controls.

Method: Levels of soluble CD86 (sCD86) in the serum was measured using ELISA technique at presentation and after one cycle of induction chemotherapy.

Conclusion: We found that sCD86 was detected in both patients and controls. Levels of sCD86 were higher than the cut-off value in 36.6% of patients. There was a significant difference between levels of sCD86 before and after treatment. Patients (54.5%) with high sCD86 levels had monocytic morphology. Patients with high levels of sCD86 had a lower rate of complete remission.

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1. Introduction

Acute myelogenous leukemia represents a group of clonal hematopoietic stem cell disorders that result from genetic alterations in normal hematopoietic stem cells. These alterations induce differentiation arrest and/or excessive proliferation of abnormal leukemic cells or blasts.^{1,2}

The generation of both humoral immune responses (by B cells) and cell mediated cytotoxicity (by cytotoxic T (T_C) cells) depends on the activation of $CD4^+$ T helper cells (T_H). Initial T_H cell activation is initiated by the interaction of the TCR–CD3 complex with the processed antigenic peptide bound to class II MHC molecule on the surface of an APC (antigen presenting cell).³

Activation of resting T_C involves first of all TCR stimuli and then secondly stimulation with cytokines, especially IL-2, most probably from activated T_H cells.⁴

All naïve T cells require two signals to initiate an immune response. Signaling through the T cell-antigen receptor in the absence of a costimulatory signal may or may not affect T cells. The principal costimulatory molecule is CD28, a receptor that is constitutively expressed on the surface of nearly all $CD4^+$ T_H cells and the majority of $CD8^+$ T_C cells. When both the TCR and CD28 bind to their ligands at the same time, their respective intracellular signals act synergistically to activate the cell's replicative machinery and secretory apparatus.^{5,6}

Successful delivery of signal 2 implicates migration of a coinhibitory receptor called CTLA-4 from its subcellular Golgi compartment to the T cell plasma membrane. CTLA-4 is normally not present to any significant degree in the inactive T cell membrane, competes with CD28 for its ligands (B7.1 and B7.2), and sends a turn off signal to the T cell. Therefore, the newly activated T cell has to manage two contradictory communications: an early activation/proliferation message from CD28 and a delayed deactivation/nonproliferation message from CTLA-4. Evidence suggests that when B7.1 and B7.2 bind to their receptors, signals are generated in both directions: into the APC and into the T cell, affecting both cells.^{7,8}

The expression of the B7 antigens, B7.1 (CD80) and B7.2 (CD86), is tightly regulated.⁹

Unstimulated antigen presenting cells are largely B7.2 negative and B7.1 negative.^{10–12}

After activation, dendritic and epidermal Langerhans' cells, B cells, and macrophages upregulate the expression of B7.2 and B7.1. In addition to their expression on MHC class II-bearing cells, B7.2 is expressed on granulocytes, B7.1 on fibroblasts, and both molecules are present on activated murine and human T cells.^{10,11,13}

This pattern of expression raises the possibility that B7 molecules may have other functions in addition to the costimulation of T cells. Several cytokines modulate the expression of B7.1 and B7.2, including IL-10, IL-4, granulocyte-macrophage colony stimulating factor, and interferon- γ .¹⁰

Some investigators have suggested that CD80 and CD86 provide similar costimulatory signals for T cell proliferation and cytokine production,^{14,15} others demonstrated that they produce contrasting effects.^{16,17}

While other studies found that CD80 could negatively regulate T cell activation induced by either mitogens or specific antigens, while CD86 can positively regulate T cell activation through CD28-mediated signals.^{18–20}

The reasons for the differences seen in costimulatory signals initiated by CD80 and CD86 are not fully known. One critical determinant could be the differences in the peak expression of CD80/CD86/CD28/CTLA-4. Both CD86 and CD28 are constitutively expressed in high levels, whereas CD80 and CTLA-4 expression is induced, and their surface expression peaks 24–48 h after induction.^{21,22}

Because of their various modulatory functions, probably for and against tumor immunity, the pathologic roles of B7 family molecules expressed by human tumor cells are of great interest. Serum levels of sCD86 were found to be significantly elevated in patients with multiple myeloma and were associated with a shorter survival.²³

In acute myeloid leukemia, it was reported that leukemic cells from a substantial number of patients expressed B7.2.^{24–27} However, conflicting results exist whether such patients are associated with poor prognosis. There are a number of mechanisms by which tumors may actively evade or silence/suppress an immune response. Direct deletion of immune effector cell by expression of death-inducing ligands. (B) Direct tolerization of tumor-reactive T cells. (C) Suppression of tumor-reactive T cells by regulatory T cells. (D) Ignorance of tumor as a result of spatial separation of T and tumor cells. (E) Tolerization of host T cells by cross-presentation of tumor-derived antigens.²⁷

The aim of the study is to assess the level of soluble CD86 level (sCD86) in patients with de novo AML and determine any possible correlation with treatment outcome.

2. Methods

The study was carried out on 50 subjects:

Thirty adult patients with de novo acute myeloid leukemia. Their ages ranged between 16 and 55 years with a mean value of 31.7 ± 13.76 years selected from patients admitted to the

Hematology Unit, Alexandria Main University Hospital and 20 healthy adult persons (volunteers) age and sex matched as controls.

The study was approved by the Research Ethics Committee (REC) of Alexandria University and a written informed consent was obtained from all patients participating in the study.

On admission, patients included in the study were subjected to the following:

1. Full history taking
2. Thorough clinical examination
3. Routine investigations:
 - A. Biochemical tests including:
 - Liver function tests, renal function tests, LDH, uric acid.
 - B. Radiological Imaging:
 - Echocardiography before starting chemotherapy.
 - Plain X-ray chest, ultrasound abdomen.
4. Hematological assessment:
 - Complete blood picture.
 - Bone marrow examination with morphological examination and immunophenotyping for diagnosis.
 - Peripheral blood samples were taken before and after chemotherapy for assessment of sCD86 from AML patients and from control.

All patients received induction chemotherapy in the form of cytosine arabinoside (100 mg/m²) for seven days and doxorubicin (25 mg/m²) for 3 days.

2.1. Exclusion criteria

All patients with the following criteria were excluded from the study:

- Patients aged < 16 years or > 60 years.
- Patients with significant renal, hepatic or cardiac impairment that prevented them from receiving full dose of induction chemotherapy.
- Patients with FAB subtype M₃ (patients did not receive the standard 3 + 7 chemotherapy protocol).

2.2. Assessment of sCD86

Peripheral blood samples were taken before starting chemotherapy. Control samples were obtained from 20 healthy individuals who volunteered to give their samples. 2 ml of venous blood were withdrawn into plain vacutainer tubes, allowed to clot for 10 min at room temperature. Samples then were centrifuged for 10 min. Sera were removed and stored at -20 °C until processed for estimation of the serum soluble CD86 by enzyme linked immunosorbent assay (ELISA).^{33,34}

2.3. Cut-off value for sCD86

The cut off value was 40 µ/ml. Patients with levels equal to or above cut off value were defined as sCD86 positive, while patients with levels of sCD86 below cut off value were defined as sCD86 negative.

2.4. Statistical methods

Data (expressed as mean and standard deviation) entry to the computer was done followed by tabulation and analysis. Analysis was done using SPSS-15 (Statistical Package for Social Sciences version 15).

Correlation between sCD86 and other parameters was done using Pearson correlation. Comparison of sCD86 levels before and after treatment was done using paired *t*-test.

3. Results

The study was focused on 30 adult patients with de novo AML admitted to the Hematology department, Alexandria Main University Hospital. Their ages ranged between 16 and 55 years with a mean value of 31.7 ± 13.76 years. They were 15 males (50%) and 15 females (50%) and 20 healthy adult persons as a control group, their ages ranged between 16 and 50 years with a mean of 32.5 ± 9.89 years. They were 11 males (55%) and nine females (45%).

As regards the distribution of FAB subtypes among patients; two patients were M₀ representing 6.7%, 12 patients were M₂ representing 40%, four patients were M₁ representing 13.3%, seven patients were M₄ representing 23.3%, five patients were M₅ representing 16.6%, with no cases M₆ or M₇.

As regards the clinical outcome after the first cycle of chemotherapy, 11 patients achieved CR (36.7%) and 19 patients did not achieve CR (63%).

Soluble CD86 WAS DETECTED in the plasma of all normal controls and patients included in the study. Levels of SCD86 in the patients ranged from 6.6 to 96.1 µL/ml with a mean of 39.44 ± 27.08. In control Levels of SCD86 ranged from 3 to 29.4 µL/ml with a mean of 14.46 ± 8.49. There was significant difference between the levels detected in normal control and patients *p* = 0.001. (Table 1)

As regards the positivity for soluble CD86, 19 patients (63.3%) were negative and 11 patients (36.7%) were positive (Fig. 1).

Among 30 AML patients (2 were FABM₀ 6.7%, 4 FABM₁ 13.3%, 12 FABM₂ 40%, 12 FABM₄ and M₅ 40%). Complete remission was achieved in (one patient FABM₀ 9.1%, 1 FABM₁ 9.1%, 2 FABM₂ 27.3%, 6 FABM₄ & M₅ 54.5%) (Table 2).

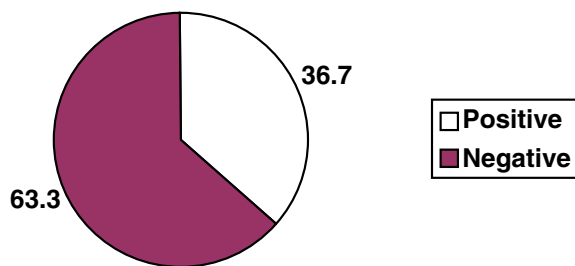
Soluble CD86 (sCD86) was detected in the plasma of all normal controls and patients included in the study. In AML patients: Levels of sCD86 ranged from 6.6 to 96.1 U/ml with a mean of 39.44 ± 27.08. While in the control group, levels of sCD86 ranged from 3 to 29.4 U/ml with a mean 14.46 ± 8.49. There was a significant difference between the levels detected in normal controls and levels detected in patients (*P* = 0.001). There was also a significant difference between sCD86 levels in patients before and after treatment (*P* = 0.0001) (Fig. 2).

Distribution of sCD86 positivity among the different FAB subtypes demonstrated that 54.5% of sCD86 positive patients (6 of 11) had monocytic morphology (M₄ and M₅) and 45.5% (5 of 11) had non monocytic morphology.

There was a significant positive correlation between levels of sCD86 before treatment and white blood cell counts (*P* < 0.05) (Table 3).

Table 1 Levels of sCD86 in AML patients.

Case number	sCD86 (U/ml)		Control
	Before	After	
1	61	11	29.4
2	20	14.1	23.4
3	39	13.6	21.4
4	9.2	4.8	20.2
5	15.8	7.6	23.4
6	19.4	18	19
7	31	18.4	10
8	66.3	23.6	27.6
9	61	24	3
10	29	15	9.4
11	31	12	5.4
12	39	13	5.2
13	32	12.4	3.8
14	52	21	5
15	96.1	5.4	6.6
16	96	14.6	11.6
17	22.8	13	8.4
18	35.4	27	18
19	40	10.2	19.4
20	89.6	79	19
21	48.8	15	
22	6.6	6.4	
23	87.3	26.4	
24	9.4	5	
25	26	14.2	
26	20	16.6	
27	62	3.4	
28	7.2	5	
29	11.6	6.4	
30	18.6	6	
Range	6.6 – 96.1	3.4–79	3–29.4
Mean	39.44	15.4	14.46
S.D	27.08	13.7	8.49

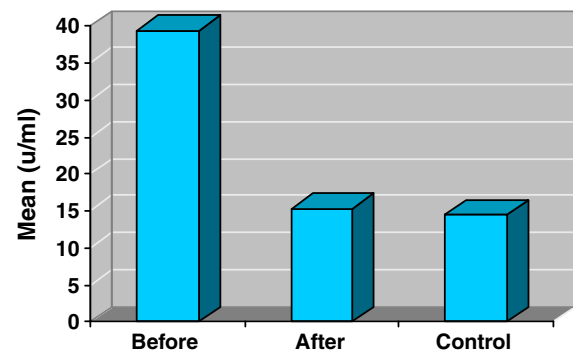
**Figure 1** Distribution of AML patients according to the positivity for sCD86 before treatment.

On comparing the outcome in relation to sCD86 levels: in sCD86 positive patients 27.3% (3 of 11) achieved complete remission while 72.7% (8 of 11) did not achieve complete remission. While among sCD86 negative patients, 42% of patients (8 of 19) achieved complete remission and 57.9% (11 of 19) did not achieve complete remission.

The one year overall survival among CD86 positive patients seven survived (63.6%) and four died (36.4%), while CD86 negative patients 14 died (73.7%) and five survived (26.3%).

Table 2 Relation between outcome and FAB subtype.

FAB			Outcome		Total
			CR	No CR	
M ₀	No.	1	1	2	
	%	9.1%	5.3%	6.7%	
M ₁	No.	1	3	4	
	%	9.1%	15.8%	13.3%	
M ₂	No.	3	9	12	
	%	27.3%	47.4%	40%	
M ₄ and M ₅	No.	6	6	12	
	%	54.5%	31.6%	40%	
Total	No.	11	19	30	
	%	100%	100%	100%	

**Figure 2** Comparison between levels of sCD86 (before and after treatment) and control group.

4. Discussion

The aim of the present study was to evaluate the levels of soluble CD86 (sCD86) levels in patients with de novo acute myeloid leukemia and whether this may be correlated with treatment outcome.

The study was performed on thirty adult patients with de novo acute myeloid leukemia (and 20 healthy controls, age and sex matched).

Levels of sCD86 were determined in AML patients, levels were measured again after the first cycle of induction chemotherapy for follow up in an attempt to find any possible correlation with outcome.

In the current study, sCD86 levels were detected in the sera of patients with de novo AML before and after administration of induction chemotherapy as well as in the sera of normal controls.

Levels of sCD86 in patients before chemotherapy ranged from 6.6 to 96.1 U/ml with a mean 39.44 ± 27.08 U/ml. Levels of sCD86 in controls ranged from 3 to 29.4 U/ml with a mean value of 14.46 ± 8.49 U/ml.

The majority of patients (63.3%) had sCD86 levels similar to that of normal controls. Our observations were consistent with Hock et al. who found that 75% of their patients having sCD86 levels within the range observed in normal donors.²⁸

Levels of sCD86 were significantly higher in patients before treatment in comparison to controls ($p = 0.0001$).

Table 3 Correlation coefficient between level of sCD86 before and after treatment and white blood cells.

		sCD86 before	sCD86 after
WBCs	<i>r</i>	0.374*	-0.121
	<i>p</i>	0.042	0.525

* Denotes significant correlation.

Level of sCD86 was significantly higher in patients before treatment than after treatment ($p = 0.001$).

Level of sCD86 in patients in remission was normal. This result is in agreement with that achieved by Hock et al.²⁹ in their study suggesting that at least in some AML patients, sCD86 levels may reflect disease status. Hock et al. also analyzed the changes in sCD86 levels during treatment and found that levels of sCD86 steadily declined following commencement of chemotherapy becoming normal by the time of first remission.

With respect to CD86, the release of a soluble form provides a potentially powerful mechanism by which cells may modulate the co-stimulatory signals delivered through mCD86.²⁸ Both APC and AML blasts express sCD86 transcript and mCD86 protein; thus both cell types provide a potential source of the elevated sCD86 levels observed in some patients. The observation that sCD86 levels are highest in the FAB subtypes with the highest AML blast levels of mCD86 expression, together with the observation that high levels of sCD86 are associated with poor prognosis, strongly suggests that sCD86 is derived from the malignant cells in these patients.^{29,30}

Hollberg and Kapsogeorgou et al. reported that a number of cell types express functionally distinct forms of CD86 probably as a result of changes in glycosylation status. It is therefore possible that sCD86 generated by APC and AML blasts may differ functionally.^{31,32}

In the current study, distribution of sCD86 levels among the different FAB subtypes showed that 54.5% of sCD86 positive patients had monocytic morphology (M_4 and M_5) and 45.5% had non monocytic morphology. These results are similar to the results observed by Hock et al. in their study demonstrating that 76% sCD86 positive patients had monocytic morphology.

APC expression of CD40, adhesion molecule, and (most importantly) B7 molecules is critical for the induction of immune responses. This led to the concept that tumor cells escape immunosurveillance because they lack expression of these molecules. However, in AML, many of the blast cells, particularly those of the FAB M_4 - M_5 subtype, have an APC-like phenotype, and a number of studies have now reported that high expression of CD40, adhesion molecule, or CD86 molecules is associated with poor prognosis. These findings suggest APC and malignant cells and/or that other mechanisms regulate the function of these molecules in a malignant setting.³³⁻³⁵

White blood cell counts in sCD86 negative patients had a mean of 32.337 ± 56.2202 ($\times 10^9/L$), while in sCD86 positive patients, white blood cell counts had a mean of 70.509 ± 74.5899 ($\times 10^9/L$). Although white blood cell counts in sCD86 positive patients were higher than in sCD86 negative patients, this difference was not statistically significant. However, levels of sCD86 in AML patients before treatment were significantly positively correlated with leukocyte counts.

Tamura et al.³⁶ reported in their study that sCD86 positive AML patients had a significantly higher leukocyte count compared with the sCD86 negative patients ($p = 0.026$), these results suggesting that sCD86 may be related to the increase in leukemic cells in the hosts. The finding that sCD86 (B7.2) was associated with hyperleukocytosis in their patients suggested that expression of these molecules might contribute to the proliferation of AML cells by helping them evade anti-tumor immune responses.

On comparing the outcome in relation to sCD86 in the current study, 27.3% of sCD86 positive patients had achieved complete remission following induction chemotherapy. In sCD86 negative patients, 42% had complete remission. CR rate was lower in positive sCD86 patients than sCD86 negative patients; however these differences were not statistically significant.

This observation was similar to that demonstrated by Hock et al.²⁸ who found that in patients younger than 60 years, sCD86 levels provided a prognostic marker independent of cytogenetics and leukocyte count. However, Tamura et al.³⁶ did not find B7.2 expression an independent prognostic factor in their study.

These results were different from those reported by Hock et al.²⁸ They demonstrated that AML patients 60 years and younger with high levels of sCD86 tended to have a shorter survival compared with patients with normal sCD86, although this difference was not significant. Their analysis indicated that increased sCD86 levels were associated with poor survival. Although the presence of elevated sCD86 levels was associated with FAB M_4 - M_5 subtypes, these patients did not have a significantly different survival compared with patients who had non-FAB M_4 - M_5 subtypes. However, as the number of patients was small, this result must be treated with caution until it is validated in a larger patient group.

In their study, Hock et al. demonstrated that in patients older than 60 years, there was no significant difference in the survival of patients with normal sCD86 levels and patients with high sCD86 levels. This finding does not preclude a role for sCD86 in these patients but may reflect the presence of other independent factors that have a stronger influence on outcome.

The difference between results of the current study and the other studies regarding the possible correlation between levels of sCD86 and survival could be attributed to the fact that the major cause of death in our patients was sepsis and some patients died during aggressive consolidation cycles after achieving complete remission. Also in some patients, the non-compliance of the patients themselves in follow up caused some of them to be delayed in receiving their consolidation with subsequent relapse or death due to the complications of relapse without enough time for them to receive consolidation.

Antitumor T cell mediated specific immune responses require well organized, multiple steps of molecular interaction of MHC molecules on APCs (professional APCs and/or tumor cells), presentation of tumor specific peptides in optimal amounts by MHC molecules, optimal costimulatory signals, intact T cell-receptor associated signal mechanisms, and the presence of an appropriate cytokine milieu. When one of these steps becomes deranged, the immune response against tumor cells may become insufficient. In patients who have developed a malignancy, the malignant cells have evaded

antitumor immunity using mechanisms that are probably diverse even among patients with the same malignant disease.

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