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Estimation of plasma soluble interleukin-2 receptor alpha chain level in adults with acute myeloid leukemia

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Abstract:

BACKGROUND: Acute myeloid leukemia (AML) is a clonal malignant condition of immature hematopoietic cells, characterized by clonal proliferation of abnormal cells (blasts) in the marrow leading to impairment of the normal blood cell production giving rise to failure of the bone marrow. Soluble interleukin-2 (IL-2) receptor alpha chain is a protein that is involved in the assembly of the high-affinity IL-2 receptor, and it has a critical role in controlling immune system homeostasis. The overexpression of sIL-2RA was investigated in many hematopoietic malignancies, and it was correlated with poor outcome.

OJECTIVES: The aim of this study was to assess the sIL-2RA level as a prognostic factor and assess its impact on survival and if it can be used as a targeted treatment for a better outcome.

MATERIALS AND METHODS: Sixty newly diagnosed adults with AML before starting therapy were included in the study, and they were followed up for 6 months to document survival status. Thirty healthy adults were taken as a control group. Using an enzyme-linked immunosorbent assay, the plasma sIL-2RA level was measured. Statistical analysis was done using Microsoft Excel 2019 and version 26 SPSS statistical software. P <0.05 was considered statistically significant.

RESULTS: A considerable difference in the plasma sIL-2RA level between AML patients and controls also was more elevated in patients who died after 6-month follow-up. According to the blast percentage, total white blood cell count, and M0-M2 subgroups, the sIL-2RA level correlated positively. Irrelevant association was found regarding the patients' age, the count of platelet, and the hemoglobin.

CONCLUSIONS: Plasma sIL-2RA level is higher in AML patients than the control group at the time of diagnosis. Patients with a high level of plasma sIL-2RA have an inferior (overall survival) and poor outcome. SIL-2RA level is higher in M0-M2 subgroups than other subtypes. There is a significant association between sIL-2RA level and the absolute count of leukemic blasts.

Keywords:

Acute myeloid leukemia, enzyme-linked immunosorbent assay, plasma soluble interleukin-2 receptor alpha chain

Introduction

Acute myeloid leukemia is a malignant disorder of immature cells in the hematopoietic system. The leukemic stem cell proliferative advantage together with apoptosis inhibition and diminishing the ability to differentiate leads to the accumulation of immature or blast cells in the bone marrow. Eventually normal hematopoiesis will be suppressed by the blasts which lead to marrow failure and organ and tissue infiltration.[1,2] In adults, it is the most common form of acute leukemia with the shortest survival (5-year survival = 24%) with incidence that increases with age with a median age at diagnosis of 68 years in the United States.[3]

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Soluble interleukin-2 receptor alpha chain (~40 kDa), which is termed as sIL-2R or sCD25, are found profusely in the circulation of healthy people, but the levels of these receptors increase with inflammation, infection, and autoimmune diseases. By a process of proteolytic cleavage, it will be shed from the membrane-bound IL-2Rα ectodomains.[4] Alpha chain (CD25) is one of the key elements of the IL-2 receptor. This chain has a crucial function in T-cell growth, along with the functions of both regulatory and effector T-cells.[5-10] Soluble IL-2R is part of the IL-2 membrane receptor and can be localized on the cell surface of various lymphocyte lineages, including activated T and NK cells, eosinophils, monocytes, and some tumor cells.[11] Elevated sIL-2R levels were found in most types of hemolymph tumors, including Hodgkin lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma.[12] In acute myeloid leukemia (AML), overexpression of IL-2RA is associated with poor outcome and chemotherapy resistance, leading to promoting its multiplying capacity, arresting the differentiation of cells, and preventing apoptosis.[13] The aim of this study was to assess the level of sIL-2RA as a prognostic factor and assess its impact on survival and if it can be used as a future target of treatment for a better outcome and to correlate the level of sIL-2RA/CD25 with other prognostic factors.

Materials and Methods

Sixty AML adult patients who were recently diagnosed from September 2022 to September 2023 were included in this cross-sectional study at Baghdad Teaching Hospital in Medical City. According to patients' blood film morphology, immunophenotyping, and bone marrow aspirates, the diagnosis was established.

AML patients were followed up for 6 months from diagnosis time to document their survival status.

In this study, written informed consent was taken from all of the individuals who were included in the study, and it was approved by the Ethical Committee of the Scientific Council of Pathology at the Iraqi Board. The patients were included before starting therapy and recently diagnosed. The patients' age in this study was equal to and above 14 years old and below 82 years old. Thirty healthy adults were included in this study as a control group. Their age was matched to the patient's group; they were 19 males and 11 females.

Measuring the plasma soluble IL-2 receptor alpha chain level for the control individuals and patients' group was done using a double-sandwich enzyme-linked immunosorbent assay (ELISA) technique with the use of the IL-2sRα ELISA kit from SUNLONG.

Results

The mean age of the newly diagnosed AML patients' group was 46.57 ± 18.93 years, and the median age for the patients' group was 45 [Table 1]. The number of males in patients and controls was 32/60 (53.3%) and 19/30 (63.3%) correspondingly, and there was no substantial differences.

Distribution of acute myeloid leukemia cases according to hematological and clinical features

The mean Hb concentration of the newly diagnosed AML patients was 8.08 ± 2.11 g/dl (range: 4.3–16.4 g/dl). The mean total leukocyte count was 43.7 ± 55.83 × 10^9/L (range: 1–200 × 10^9/L).

The mean absolute neutrophilic count was 3.83 ± 6.02 × 10^9/L (range: 0.04–33 × 10^9/L).

The mean absolute lymphocytic count was 4.71 ± 6.31 × 10^9/L (range: 0.2–44.4 × 10^9/L).

The mean platelet (PLT) count was 52.09 ± 34.43 × 10^9/L (range: 15–186 × 10^9/L). The mean blast percentage in peripheral blood was 48.27 ± 27.6% (range: 5%–96%) and bone marrow percentage was 68.88 ± 22.8% (range: 20%–98%) [Table 1].

Table 1: Hematological characteristics of the patient's group

Parameter	Patients (*n*=60)
Hb (g/dL)	
Mean±SD	8.08±2.11
Median (range)	7.8 (4.3–16.4)
WBC (×10^9/L)	
Mean±SD	43.7±55.83
Median (range)	20.5 (1–200)
Platelets (×10^9/L)	
Mean±SD	52.09±34.43
Median (range)	45 (15–186)
RDW CV (%)	
Mean±SD	16.37±2.32
Median (range)	16.05 (12.2–24)
ANC (×10^9/L)	
Mean±SD	3.83±6.02
Median (range)	1.23 (0.04–33)
ALC (×10^9/L)	
Mean±SD	4.71±6.31
Median (range)	2.75 (0.2–44.4)
Blast% in PB	
Mean±SD	48.27±27.6
Median (range)	43 (5–96)
Blast% in BM	
Mean±SD	68.88±22.8
Median (range)	75 (20–98)

Hb=Hemoglobin, WBC=White blood cell, RDW=Red cell distribution width, ANC=Absolute neutrophilic count, ALC=Absolute lymphocyte count, PB=Peripheral blood, BM=Bone morphogenetic, SD=Standard deviation

Fever was the most common presentation (66.6%), followed by pallor (63.3%) and then extramedullary disease (55%).

Plasma soluble interleukin-2 receptor alpha chain concentration and the relation with other prognostic factors

The median and range values of sIL-2RA in the patients were 567.66 pg/ml and 463.35–808.66 pg/ml, respectively, whereas the median and the range values for the controls were 62.14 pg/ml and 43.65–135.3 pg/ml, respectively. Statistically, a major difference was found in the median level among patients and controls, $P < 0.001$ [Table 2].

The plasma sIL-2RA level didn't show a positive correlation with age, Hb, PLT, and cytogenetic risk groups but showed a significant correlation with blast count in PB and BM [Table 3]. Furthermore, a positive association was shown regarding the total count of white blood cells (WBCs). Regarding FAB classification, the median plasma sIL-2RA level was higher in M0-M2 subgroups in comparison with M4-M7 subgroups at the time of diagnosis [Table 4]. According to gender, plasma sIL-2RA level showed a positive correlation with the male gender [Table 5].

Relation of plasma sIL-2RA levels and patients' prognosis

Patients were followed up for 6 months from diagnosis time, 36 patients with AML (60%) were dead, and 24 patients (40%) were still alive. There were significant positive correlations between plasma sIL-2RA level and death in AML patients. The mean value of the sIL-2RA level in the patients who died was (614 ± 88.99) with a median (range) 590.07 (507.05–808.66), while the mean value was (539.21 ± 340.77) with a median(range) 543.24 (463.35–593.54) for the patients who were still alive. The P value < 0.001 [Table 6].

Table 2: Evaluation of plasma sIL-2RA levels in patients and controls

Parameters	Control (n=30)	Patients (n=60)		P*
sIL-2RA (pg/mL)	Median	62.14	567.66	<0.001
	Range	(43.65–135.3)	(463.35–808.66)	

*P value by Mann–Whitney test

Table 3: Associations of plasma sIL-2RA with the hematological parameters in the patient's group

Parameters	SIL2RA	
	Patients	Control
Age (years)		
r	−0.203	0.015
P	0.120	0.936
Hb (g/dL)		
r	0.228	−0.214
P	0.079	0.255
WBC (×10⁹/L)		
r	0.714	0.286
P	<0.001	0.126
Platelets (×10⁹/L)		
r	0.032	0.192
P	0.806	0.309
Blast% in PB		
r	0.346	-
P	0.007	-
Blast% in BM		
r	0.464	-
P	<0.001	-

Hb=Hemoglobin, WBC=White blood cell, PB=Peripheral blood, BM=Bone morphogenetic

Table 4: The comparison of plasma sIL-2RA levels in the patient's group in relation to French-American-British classification

Parameter	M0-M2 (n=41)	M4-M7 (n=19)	P*
sIL-2RA			
Mean±SD	602.57±89.14	544.2±36.07	0.010
Median (range)	572.03 (499.65–808.66)	548.95 (463.35–593.54)	

*P value by Mann–Whitney test. SD=Standard deviation

Table 5: Comparison of sIL-2RA in the patient's group according to gender

Parameter	Male (n=32)	Female (n=28)	P*
sIL-2RA			
Mean±SD	612.65±97.64	551.43±35.48	0.011
Median (range)	590.4 (496.29–808.66)	564.52 (463.35618.41)	

*P value by Mann–Whitney test. SD=Standard deviation

Discussion

Acute myeloid leukemia is a poor prognostic hematopoietic malignancy. It was detected in 21,450 cases and gave rise to 10,920 deaths in 2019 in the United States.[14] In adults, it is considered to be the most common type of acute leukemia with a prevalence that increases according to age. AML is clinically and genetically miscellaneous, and current improvements have enhanced our understanding of the cytogenetic abnormalities and molecular mutations of this disease.

The mean age of newly diagnosed acute myeloid leukemia in the developing countries was lower than in the developed countries. The mean age of newly diagnosed AML patients results were comparable with studies reported from Iraq that was prepared by Tawfiq *et al.*,[15] Muhsin and Al-Mudallal,[16] and Mohammad *et al.*,[17] whereas the highest prevalence of AML was informed in old patients in the Europe and United States.[18,19] The discrepancy might be clarified due to the influence of geographical, ethnic, and environmental factors in Western countries in comparison with Iraq. AML cases were observed more in males than in females,

Table 6: Comparison of sIL-2RA in the patient's group according to prognosis

Parameter	Alive (*n*=24)	Dead (*n*=36)	*P**
SIL2RA			
Mean±SD	539.21±34.77	614±88.99	<0.001
Median (range)	543.24 (463.35–593.54)	590.07 (507.05–808.66)	

**P* value by Mann–Whitney test. SD=Standard deviation

the result of this study is comparable to a local Iraqi studies,[15,17,20,21] and to studies were done in United States and Europe,[17,18] while it disagreed with Muhsin and Al-Mudallal[16] and Jahic *et al*.[22] The reason why AML is more common in males than females is still unidentified.

This study showed that AML-M2 was the most common subtype, and this was related to previous Iraqi studies done by Alwan *et al*.[23] and Pouls *et al*.[24] Nevertheless, this result differs from previous local studies reported by Tawfiq *et al*.[15] and Mohammad *et al*.,[17] whereas in the international reports, M2 and M4 subgroups were the most prevalent.[25,26]

Fever and pallor were the most frequent signs in patients. The results go with Muhsin and Al-Mudallal.[16]

The extra medullary signs (splenomegaly, lymphadenopathy, hepatomegaly, and central nervous system disease) were less prevalence than fever at presentation and this study goes with Muhsin and Al-Mudallal.[16]

At diagnosis time, the mean WBC count was higher than the Egyptians and other Iraqi reports[15,27] but similar to Pouls *et al*.[24] The mean PLT count result was comparable to local Iraqi studies.[15,24,28] The mean hemoglobin level result was close to an Egyptian study with an 8.4 g/dl median level[27] and to studies that were done in Iraq.[15,24]

Plasma sIL-2RA level in AML patients in this study was evaluated using ELISA. In this study, the increased plasma sIL-2RA level was shown to be a common incidence in patients with AML and the sIL-2RA level in the patients was considerably greater than that of the controls ($P < 0.001$), which is in covenant with two other studies.[29,30] Other studies proved identical outcomes in other solid and hematological tumors.[31,32]

After 6 months of follow-up from the time of diagnosis to evaluate the OS, 60% of patients were dead and 40% were still alive. The mean plasma level of sIL-2RA at diagnosis was significantly higher in patients who had died than in those who were still alive. The correlation of sIL-2RA with inferior OS in our study goes with other studies.[33,34] Furthermore, additional studies have found that high levels of sIL-2RA correlate with adverse disease progression, poor response to chemotherapy, and inferior OS.[35,36]

An elevated sIL-2RA level was related to lymphocyte activation, though in hematological malignancies, the sIL-2RA is thought to be released by the tumor cells and binding to interleukin-2 resulting in suppressing the host immune response by increasing the regulatory T-cell generation and suppressing the intratumoral effector T-cells granule production. Consequently, the increased levels of sIL-2RA have been suggested to suppress the host antitumor immunity state in patients with malignancy resulting in neoplastic growth enhancement.[12,37]

According to FAB classification of AML, sIL-2RA was found to be correlate considerably with M0-M2 group than M4-M7 group ($P = 0.010$), and this correlated with another study.[29]

Unlike the other subgroups of leukemia, M0-M2 subgroups show the IL-2 receptor expression. Moreover, the interleukin-2 receptor alpha chain(IL-2Rα) on the cell surface of the AML (M0-M2) will be shed in a soluble form by proteolytic processing, this leads to increase the soluble IL-2Ra level in these subgroups.[30,38] While this study disagrees with Nakase *et al*.[34] regardin the difference in soluble IL-2 receptor alpha chain level among AML subgroups.

SIL-2RA was correlated significantly with blast count ($P < 0.001$). This result is comparable to another study.[39]

Regarding gender, sIL-2RA level was found to be correlated significantly with gender. In males, the level was higher.

Plasma sIL-2RA level showed no significant correlation with hemoglobin ($r = 0.228$, $P = 0.079$) and PLT count ($r = 0.032$, $P = 0.803$). It showed that the level sIL-2RA does not correlate with Hb and PLT count at the time of diagnosis.

Conclusions

Plasma sIL-2RA level is higher in AML patients than the control group at the time of diagnosis. Patients with a high level of plasma sIL-2RA have an inferior (OS) and poor outcome. SIL-2RA level is higher in M0-M2 subgroups than other subtypes. There is a significant association between sIL-2RA level and the absolute count of leukemic blasts. The sIL-2RA level does not correlate with PLT count and hemoglobin level at the diagnosis time.

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Conflicts of interest
There are no conflicts of interest.

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