# Assessment of the Serum Level of Interleukin-6 and Interleukin-10 in Newly Diagnosed Acute Myeloid Leukemia Patients and the Response to Induction Chemotherapy

ZAINAB A. ABD EL-HAFEZ, M.D.*; MADLEEN A. ABDOU, M.D.*; TAREQ S. AHMED, M.D.** and MAI M. SALAH EL-DIN, M.Sc.*

*The Departments of Clinical Pathology\* and Clinical Oncology & Nuclear Medicine\*\*, Faculty of Medicine, Assiut University, Egypt*

## Abstract

*Background:* Acute leukemia is the most common hematological malignancy in adults, characterized by distorted proliferation of immature bone marrow-derived cells (BM blasts) that may also involve peripheral blood or solid organs. Blood cells and their marrow based progenitors are exquisitely responsive to their environment, and cytokines are an essential part of it. The overexpression of cytokines in leukemia patients declines in complete remission suggesting that these events are dependent on AML activity, possibly due to autonomous blast cytokine secretion.

*Methods:* Using ELISA kit, serum levels of IL-6, IL-10 were estimated before and after induction chemotherapy in 30 patients with AML from February 2015 to May 2016 from Clinical Oncology Department, Hematological Diseases Unit in Internal Medicine Department, Assiut University Hospital and Medical Oncology Department, South Egypt Cancer Institute and 20 age and sex matched healthy controls were also enrolled.

*Results:* IL-6 and IL-10 levels were significantly higher in newly diagnosed AML patients than in control group and their levels decreased when patients responded to induction chemotherapy (the blast cell count in their BM fall to >5%).

*Conclusion:* Our study demonstrated the decrease in the serum level of two markers (IL-6 and IL-10) in AML patients after induction chemotherapy, suggesting that assessment of their levels may be used as a prognostic markers and beneficial in the evaluation of the therapy making them highly applicable to routine clinical laboratories.

*Key Words:* *AML – Induction chemotherapy – ELISA – IL-6 – IL-10.*

## Introduction

**ACUTE** Myeloid Leukemia (AML) represents a group of hemopoetic stem cell disorders in which both failure to differentiate and proliferation in the stem cell compartment results in accumulation of non-functional myeloid cells termed myeloblasts and loss of normal hematopoietic function frequently resulting in fatal complications [1].

The etiology of AML is heterogeneous and complex, but it is widely accepted that both environmental and genetic factors play significant roles in the development of the disease. Immune system disorders have increased the understanding of leukemogenesis [2].

Little is known about the pathogenic events leading to initiation and progression of this disease, elevated regulatory T (Treg) cells in a variety of hematological malignancies including AML have been reported [3]. Patients with a lower Treg cell frequency at diagnosis have a better response to induction chemotherapy and a favorable diagnosis [4].

Considerable efforts have been spent in identifying prognostic markers that might predict clinical outcomes in AML patients and several characteristics including older age, cytogenetics and performance status are commonly used as predictors of survival. Prognosis in AML patients has been related to the frequently observed defective function of their immune system that hampers the development of effective response against leukemic blasts [5,6].

Normally, Cytokines are secreted by different types of cells in response to a variety of stimuli such as tissue damage or infection and regulate the immune response and other biologic process.

In AML patients, cytokines can be produced by both leukemic blasts and cells of the immune

system and the role of cytokines in the pathogenesis of acute leukemia has not been fully clarified [7]. Thus, aberrant cytokine signaling is a feature of leukemia that may contribute to proliferation, blast survival, resistance to chemotherapy and patients" prognosis [8].

Interleukin-6 (IL-6) is a cytokine with pleiotropic inflammatory effects, has demonstrated different effects on the growth of leukemic blasts [4]. It may also exert anti-inflammatory biological activity by enhancing plasma interleukin-1 receptor antagonist (IL-1ra), interleukin-10 (IL-10) and cortisol in humans [9].

IL-10 is the most important anti-inflammatory cytokine found within the human immune response. It is a potent inhibitor of Th1 cytokines, including both IL-2 and IFN-$\gamma$. This activity accounts for its initial designation as cytokine synthesis inhibition factor [10]. In addition to its activity as a Th2 lymphocyte cytokine, IL-10 is also a potent deactivator of monocyte/macrophage proinflammatory cytokine synthesis [11]. The function of it has been detected in the leukemic cells of most ALL and AML cases and it suppresses the immune reactions, suggesting that IL-10 could be associated with escape of leukemia cells from immune surveillance [12].

Interactions between pro-inflammatory and anti-inflammatory cytokines regulate cytokine response. Thus, tumour necrotic factor-alpha (TNF-$\alpha$) and IL-1 $\beta$ can stimulate their own and each other's production and also IL-6 secretion [13].

On the other hand, IL-6 and TNF-$\alpha$ may induce IL-10 secretion with potential to inhibit IL-6, TNF-$\alpha$ and IL-1 $\beta$ production. Changes in one of these cytokines lead to compensatory mechanisms that alter the cytokine network [14].

*Aim of the work:*

- To assess the serum levels of IL-6, IL-10 in newly diagnosed acute myeloid leukemia patients and after induction chemotherapy.

- To determine the relationship of the levels of these cytokines and the laboratory finding especially the bone marrow blast cells.

## Material and Methods

This is a prospective case control study. It was carried out on patients from Clinical Oncology Department, Hematological Diseases Unit in Internal Medicine Department, Assiut University Hospital and Medical Oncology Department, South Egypt Cancer Institute. This study included 30 patients with AML diagnosed by WHO classification and sub-classified (M1-M7) by FAB classification from February 2015 to May 2016. Age of the patients ranged from 20-68 years. Regarding gender, 12 cases were males and 18 were females as well as 20 age and sex matched healthy controls were also enrolled. The study was approved by the Ethical Committee of Faculty of Medicine, Assiut University. Consents were obtained from the patients before enrollment in this study.

*The studied groups:*

- *First group:* Included 30 newly diagnosed patients (ND) i.e. Before induction.

- *Second group:* Included the same 30 patients after ten days of induction chemotherapy with cytarabine (ara-C) and anthracycline (most often daunorubicin) (after induction).

- *Third group:* Included 20 apparently healthy individuals as control group.

*Exclusion criteria:*

• No medically unstable conditions (e.g., unstable diabetes, uncontrolled arterial hypertension, infection or ischemic heart disease).

• Not pregnant or nursing.

• No other previous or current malignant disease likely to interfere with protocol treatment or comparisons.

• No prior chemotherapy or radiotherapy.

*Blood samples:*

- Venous blood (5ml) was collected from patients prior and after induction of chemotherapy, also from control group.

- 2ml of venous blood was withdrawn into K3 EDTA tube for CBC.

*Method:*

For each patient, the following laboratory processes were done:

- Complete Blood Count (CBC) was done using CELL DYN (1700).

- Bone Marrow Aspiration (BMA) according to Dacie and Lewis Practical Hematology.

- Flow cytometry for immunophenotyping that was needed for the diagnosis of all cases by using FACS (fluorescence activated cell sorting) Caliber multicolor flow cytometry (BECTON DIKINSON, USA).

- Cytochemical tests.

**- *Interleukin-6 ELISA assay by using:***

Wuhan ELAab Science Co for Human inter-leukin-6 ELISA kit, Catalog No.: E00079h from China according to manufacturer instructions.

**- *Interleukin-10 ELISA assay by using:***

Wuhan ELAab Science Co for Human inter-leukin-10 ELISA kit, Catalog No.: E00056h from China according to manufacturer instructions.

*Statistical analysis:*

Data collected and analyzed by computer pro-gram SPSS" Ver. 20" Chicago. USA. Data ex-pressed as mean, Standard deviation, number and percentage. ANOVA test and Chi. Square were used to determine significance for categorical variable.

**Results**

This study included 30 newly diagnosed AML patients with age ranged from 20-68 years (Mean ± SD, 40.76±16.75). According to sex, 12 cases were males (40.0%) and 18 were females (60.0%). Twenty healthy individuals were examined as control group with age ranged from 22-62 years (Mean ± SD, 32.55±10.74), 9 cases were male (45.0%) and 11 were female (55.0%).

*Tables (1,2):* Showed differences in peripheral heamogram elements between the patients and control group before and after induction chemo-therapy. With significant difference ( $p$=0.00) be-tween the two groups regarding WBCs, Hb and platelets, where they were lower in the patients than control group except WBCs which was higher in the newly diagnosed patients (ND/before induc-tion) than control group.

*Table (3):* Showed blast cells count in bone marrow before and after induction in the study group. With highly significant reduction in blast cells count after induction (mean ± SD, 24.69± 10.87; range, 1-78%) than before induction (mean ± SD, 58.10±23.10; range, 20-93%) ( $p$=0.000).

*Table (4) and Fig. (1):* Showed differences in IL-6 and IL-10 mean values of serum levels in newly diagnosed patients and control groups. With significantly higher values of IL-6 in the study group (mean ± SD, 42.46±28.10; range, 21.3-140.6 pg/ml) than the control group (mean ± SD, 1.53± 1.42; range 0.0-4.5pg/ml) ( $p$=0.000*) and IL-10 was higher in the study group (mean ± SD, 177.68 ±103.46; range, 26-432pg/ml) than the control group (mean ± SD, 19.24±15.41; range, 4.1-58.2 pg/ml) ( $p$=0.000*).

*Table (5) and Fig. (2):* Showed differences in IL-6 and IL-10 mean values of serum levels in in patients after induction and control groups. With significantly higher values of IL-6 in the study group (mean ± SD, 37.02±26.36; range, 10.7-125.3 pg/ml) than the control group (mean ± SD, 1.53± 1.42; range 0.0-4.5pg/ml) ( $p$=0.000*) and IL-10 was higher in the study group (mean ± SD, 135.60 ±87.62; range, 16.0-270.5pg/ml) than the control group (mean ± SD, 19.24±15.41; range, 4.1-58.2 pg/ml) ( $p$=0.000*).

*Table (6) and Fig. (3):* Showed differences in IL-6 and IL-10 mean values of serum levels in in newly diagnosed patients and after induction. There was significant lower difference in serum level of IL-6 after induction chemotherapy (mean ± SD, 37.02±26.36; range, 10.7-125.3pg/ml) than before induction (ND) (mean ± SD, 42.46±28.10; range, 21.3-140.6pg/ml) ( $p$=0.001) and also IL-10 was lower in after induction (mean ± SD, 135.60± 87.62; range, 16.0-270.5pg/ml) than before induc-tion (mean ± SD, 177.68±103.46; range, 26-432 pg/ml) ( $p$=0.006).

*Table (7) and Fig. (4):* Showed correlations between serum levels of IL-6 and IL-10 concen-trations and some of the laboratory parameters [age, White Blood Cells (WBCs), Hemoglobin level (Hb), Platelets count (PLT), peripheral blast cells (P. blast) and bone marrow blast (B.M blast)] were analyzed in AML patients after induction chemotherapy. There were significant positive correlations between IL-6 and BM. blasts ( $r$=0.745, $p$=0.000*). There were no correlations between any of the other laboratory parameters and the cytokines concentrations.

Table (1): Profile of peripheral hemogram elements in newly diagnosed patients (before induction) and control groups.

| Item | Study group "n=30" | Control group "n=20" | $p$-value* |
|---|---|---|---|
| I- HB (g/dl) | 7.07±1.88 | 12.80±0.955 | $p$=0.000*** |
| | (3.6-11.7) | (12.0-15.0) | |
| II- Platelets (X 10⁹/L) | 54.66±11.84 | 256.60±54.29 | $p$=0.000*** |
| | (10.0-204.0) | (150.0-340.0) | |
| VIII- WBCs (X 10⁹/L) | 22.90±4.80 | 7.64±1.91 | $p$=0.002** |
| | (1.1-103.0) | (4.0-11.3) | |
| IV- P. Blast (%) | 40.89±29.50 | – | – |
| | (2.0-91.0) | | |

Table (2): Profile of peripheral hemogram elements in patients after induction and control groups.

| Item | Study group "n=30" | Control group "n=20" | *p*-value* |
|------|------|------|------|
| I- HB (g/dl) | 8.26±1.39 (6.0-11.90) | 12.80±0.955 (12.0-15.0) | *p*=0.000*** |
| II- Platelets (X 10⁹/L) | 88.74±39.87 (7.0-355.0) | 256.60±54.29 (150.0-340.0) | *p*=0.000*** |
| VIII- WBCs (X 10⁹/L) | 4.12±1.51 (0.40-20.0) | 7.64±1.91 (4.0-11.3) | *p*=0.001** |
| IV- P. Blast (%) | 11.58±6.75 (1.0-68.0) | – | – |

Table (3): Blast cells count in bone marrow before and after induction in study group.

| Item | Before "n=30" | After "n=20" | *p*-value* |
|------|------|------|------|
| *Blasts (%):* | | | |
| Mean ± SD | 58.10±23.10 | 24.69±10.87 | *p*=0.000*** |
| Range | (20.0-93.0) | (1.0-78.0) | |

Table (4): Differences in IL-6 and IL-10 serum levels in newly diagnosed patients and control groups.

| Item | Newly diagnosed "n=30" Mean ± SD Median (range) | Control groups "n=20" Mean ± SD Median (range) | *p*-value* |
|------|------|------|------|
| 1- IL-6 (pg/ml) | 42.46±28.10 33.0 (21.3-140.6) | 1.53±1.42 1.3 (0.0-4.5) | *p*= 0.000* |
| 2- IL-10 (pg/ml) | 177.68±103.46 162.8 (26.0-432.0) | 19.24±15.41 13.1 (4.1-58.2) | *p*= 0.000* |

Table (5): Differences in IL-6 and IL-10 serum levels in patients after induction and control groups.

| Item | After induction "n=30" Mean ± SD Median (range) | Control groups "n=20" Mean ± SD Median (range) | *p*-value* |
|------|------|------|------|
| 1- IL-6 (pg/ml) | 37.02±26.36 29.1 (10.7-125.3) | 1.53±1.42 1.3 (0.0-4.5) | *p*= 0.000* |
| 2- IL-10 (pg/ml) | 135.60±87.62 130.5 (16.0-270.5) | 19.24±15.41 13.1 (4.1-58.2) | *p*= 0.000* |

Table (6): Differences in IL-6, IL-10 and TGF-β serum levels in newly diagnosed patients (before induction) & after induction.

| Item | Before induction "n=30" Mean ± SD Median (range) | After induction "n=30" Mean ± SD Median (range) | *p*-value* |
|------|------|------|------|
| 1- IL-6 (pg/ml) | 42.46±28.10 33.0 (21.3-140.6) | 37.02±26.36 29.1 (10.7-125.3) | *p*= 0.000* |
| 2- IL-10 (pg/ml) | 177.68±103.46 162.8 (26.0-432.0) | 135.60±87.62 130.5 (16.0-270.5) | *p*= 0.006* |

Table (7): Correlations between serum levels of IL-6 and IL-10 concentrations and some of the laboratory parameters after induction chemotherapy.

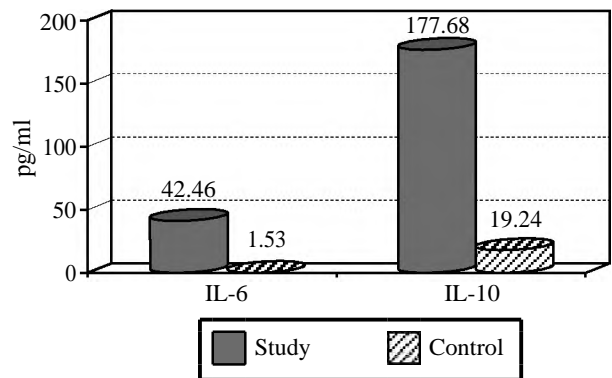| | IL-6 | | IL-10 | |
|------|------|------|------|------|
| | *r*-value | *p*-value | *r*-value | *p*-value |
| Age | 0.090 | 0.635 | –0.012 | 0.948 |
| HB | –0.125 | 0.511 | –0.112 | 0.557 |
| WBCs | –0.057 | 0.766 | –0.259 | 0.167 |
| PLT | –0.299 | 0.108 | –0.211 | 0.263 |
| P. Blast | 0.265 | 0.157 | –0.036 | 0.850 |
| BM. Blast | 0.745 | 0.000* | 0.304 | 0.103 |



Fig. (1): Differences in IL-6 & IL-10 mean values of serum levels in newly diagnosed patients and control groups.
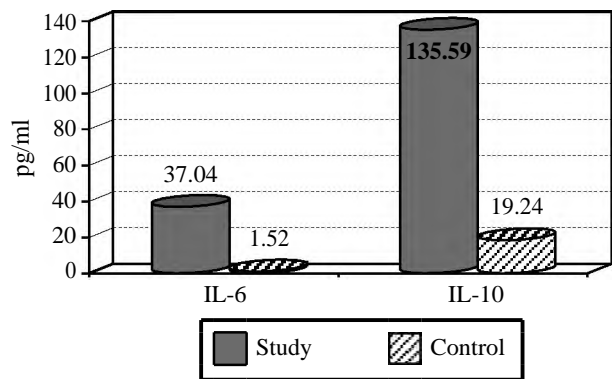


Fig (2): Differences in IL-6 & IL-10 mean values of serum levels in patients after induction and control groups.
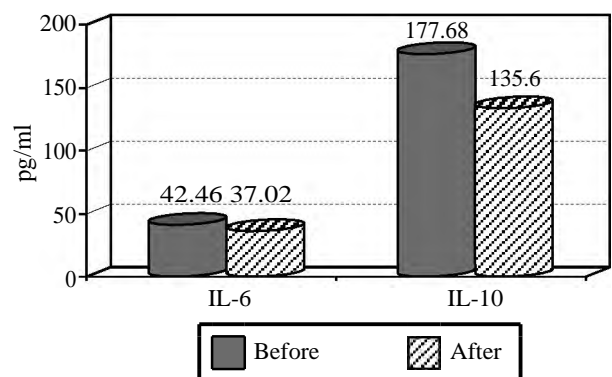


Fig. (3): Differences in IL-6 & IL-10 mean values of serum levels in patients before induction & after induction.
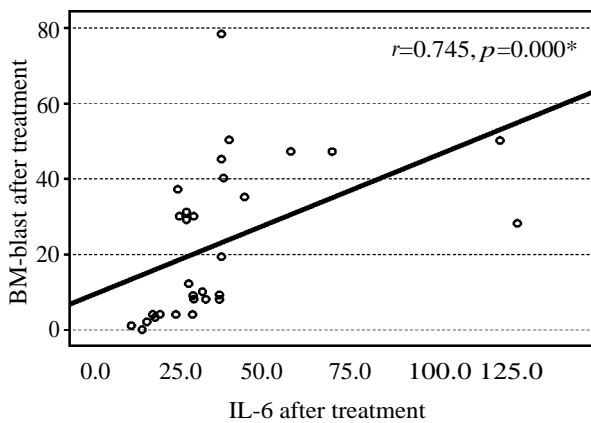
Fig. (4): Correlation between IL-6 and BM blast after induction chemotherapy.

## Discussion

Acute Myeloid Leukemia (AML) is a life-threatening hematopoietic stem cell neoplasm characterized by an increase in the number of myeloid cells in the bone marrow and an arrest in their maturation, frequently resulting in fatal infection, bleeding or organ infiltration, with or without leukocytosis [1,15].

The etiology of AML is heterogeneous and complex, but it is widely accepted that both environmental and genetic factors play significant roles in the development of the disease. Immune system disorders have increased our understanding of leukemogenesis. However, little is known about the pathogenic events leading to the initiation and progression of this disease [2].

Cytokines are soluble molecules secreted by different types of cells in response to a variety of stimuli such as tissue damage or infection. In AML patients, cytokines can be produced by both leukemic blasts and cells of the immune system and the role of cytokines in the pathogenesis of acute leukemia has not been fully clarified [7,16].

Thus, aberrant cytokine signaling is a feature of leukemia that may contribute to proliferation, blast survival, resistance to chemotherapy and patients' prognosis [8,16]. They regulate the immune response and other biologic processes, acting through a surface receptor, they provide target cells with specific information about conditions inside the organism, and cause a specific response. Under abnormal conditions, this physiological role of cytokines is maladaptive. The influence of inflammation and altered cytokine signaling on oncogenesis, leading to tumour progression, has been documented [17].

Interleukin-6 is produced mainly by monocytes and macrophages and in a smaller percentage by fibroblasts, endothelial cells, lymphocytes T and B, chondrocytes and amnion cells. The production of interleukin-6 is stimulated by interleukin-1 (IL-1) and interferon (INF), Tumor Necrosis Factor (TNF), lipopolysaccharide, DNA viruses and RNA viruses [18].

Interleukin-6 is a multifunctional cytokine with pleiotropic effects. Its importance lies in the stimulation of lymphocytes B differentiation and induction of permanent differentiation of lymphocytes B into plasma cells which produce different classes of immunoglobulin. Interleukin-6 stimulates lymphocytes T to the production of interleukin-2 (IL-2) and the synthesis of its receptors. It can be constitutively expressed and markedly increased in AML cells [19].

The present study was carried out on the serum samples of 30 patients with AML and 20 controls which aimed to determine the role of two cytokines (IL-6 and IL-10) in the pathogenesis and outcome of AML before and after induction chemotherapy in the same patient group.

In this study, we found that the serum levels of IL 6 before the induction chemotherapy in the study group (newly diagnosed) were significantly higher than those after chemotherapy and the control group. Increased IL-6 levels decreased when patients responded to induction chemotherapy, suggesting that the measurement of IL-6 concentrations may be valuable in the evaluation of therapeutic effect.

These results were in agreement with Abd El Maksoud et al., who demonstrated that the serum concentrations of IL-6 in AML Newly Diagnosed (ND) and relapsed patients were significantly higher compared to control group and the concentration fall in remission [20].

Dawood also agreed with our results as they found that there was a significant increase in the serum level of IL-6 concentration in the ND and relapsed patient group, while in remission group, serum IL-6 fall within the normal range when compared with control group. And also, found that there was inverse correlation between serum level of IL-6 in ND and relapsed patients with AML and heamoglobin percent and positive correlation with total leukocyte count [21].

Sun agreed with our results however they used plasma from bone marrow samples as they found elevated level of IL-6 in bone marrow of AML-

ND patients which is consistent with what Wu and Fredly et al., had reported [22-24].

Also, Tian et al., agreed with our study as they demonstrated markedly elevated concentration of IL-6 in ND AML patients but in their BM plasma samples [25].

On the other hand, Alizadeh et al., didn't confirm these results as they found that IL-6 serum level in the AML patient group was lower than control group [26].

Treg cells, a subpopulation of CD4 + T cells, inhibit the immune response by influencing the activity of other cell types. Typically, Treg cells are classified into naturally occurring CD4 + CD25 + Treg cells, IL-10 secreting Treg cells, and TGF-0 secreting Treg cells based on the types of cytokines they produce [27].

Previously, elevated levels of regulatory T (Treg) cells in a variety of hematological malignancies including AML have been reported [3,4]. Patients with a lower Treg cell frequency at diagnosis have a better response to induction chemotherapy and a favorable prognosis [4,28].

Interleukin-10 is known to inhibit cytokine production by T cells, and exerts anti-inflammatory and immunosuppressive activities. It inhibits the production of IL-2, IFN gamma and granulocyte macrophage colony stimulating factors as well as the proliferative response to T helper 1 cells [29].

As regard our results concerning IL-10 we found that the serum level of IL-10 before the chemotherapy in the study group (newly diagnosed patients) were significantly higher than those after chemotherapy and control group. Increased IL-10 levels decreased when patients respond to induction chemotherapy.

These results were in accordance with Sun et al., as they found that the peripheral serum level of IL-10 in AML ND patients was much higher than that in complete remission patients or controls and similar elevated level of IL-10 in bone marrow plasma of AML-ND patients [24].

Wu et al., agreed with our study and demonstrated that AML ND patients also had increased plasma IL-10 levels compared with complete remission patients and control group [30].

Musuraca et al observed a significantly higher increase in the frequency of IL-10 + secreting cells in AML ND patients than the healthy controls [31].

Yao et al., [34] agreed with our study but they used gene expressing IL-10 mRNA from the BM samples of the AML patients. They revealed that the IL-10 expression in the newly diagnosed AML patients was higher than the non-tumor controls, this indicated the leukemic cells in bone marrow could secret IL-10 in an autocrine way as the local secretion of IL-10 in the tumor growth process, may cause the loss of the sensitivity to cytotoxic T lymphocytes and make the growth of tumor cells easier. This result was similar to the published paper [32], IL-10 mRNA of remission group (by chemotherapy) was significantly decreased when compared with the newly diagnosed AML group, but still higher than the non-tumor controls. They concluded that this may be due to the chemotherapy which inhibits the growth and activity of the leukemic cells and affects the function of the patients' immune system [33,34].

*Conclusion:*

We have demonstrated that AML patients before induction chemotherapy had increased serum concentrations of IL-6 and IL-10 and their levels start to decrease after the induction. These results open a new avenue in the study of tumor immunotherapy.

*Conflicts of interest:* There are no conflicts of interest.

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# تقييم مستوى الإنترليوكين ٦ والإنترليوكين ١٠ فى مرضى سرطان الدم النخاعى (الميلودى) الحاد حديثى التشخيص والإستجابة للعلاج الكيميائى الحثى

سرطان الدم الحاد هو الآورام الخبيثة الدموية الآكثر شيوعا لدى البالغين، والتى تتميز بالإنتشار المشوه للخلايا المستمدة من نخاع العظام غير الناضجة والتى قد تصيب آيضا الدورة الدموية الطرفية آو الآعضاء الصلبة. خلايا الدم وإسلافها تستجيب بشكل رائع مع بيئتها، والسيتوكينات تشكل جزءا آساسيا منه. مستويات السيتوكينات الشاذة فى مرض سرطان الدم النخاعى (الميلودى) الحاد والإستجابة الغير طبيعية له موثقة جدا. هبوط مستوى تلك السيتوكينات المرتفع فى مرضى سرطان الدم بعد تحقيق خمول كامل للمرض يرجع إعتماد السيتوكينات على الخلايا الجزعية الآولية المفرزة آثناء نشاط المرض. فى هذه الدراسة قمنا بإستخدام مجموعة (الايلايزا)، لتقدير مستويات الإنترليوكين-٦ والإنترليوكين-١٠ قبل وبعد العلاج الكيميائى الحثى فى ٣٠ مريضا بمرض سرطان الدم النخاعى (الميلودى) الحاد من فبراير ٢٠١٥ إلى مايو ٢٠١٦ من قسم علاج الآورام ووحدة آمراض الدم فى قسم الطب الباطنى بمستشفى جامعة آسيوط وقسم الآورام الطبية، بمعهد جنوب مصر للسرطان. كما تم تسجيل ٢٠ شخص مطابق لعمر وجنس المرضى تقريبا كمجموعة ضابطة.

بعد الحصول على النتائج وجدنا آن مستوى الإنترليوكين-٦ والإنترليوكين-١٠ آعلى بكثير فى المرضى الذين تم تشخيصهم حديثا بمرض سرطان الدم النخاعى (الميلودى) الحاد مقارنة بالمجموعة الضابطة وإنخفضت مستوياتهم عندما إستجاب المرضى للعلاج الكيميائى الحثى (عدد خلايا الجزعية الآولية إنخفضت إلى آقل من ٥٪).

الخلاصة:ظهرت دراستنا إنخفاضا فى مستوى الإنترليوكين-٦ والإنترليوكين-١٠ فى مرضى سرطان الدم النخاعى (الميلودى) الحاد بعد العلاج الكيميائى الحثى، مما يشير إلى آن تقييم مستويات تلك الإنترليوكينات يمكن آن تستخدم كعلامات تنذيرية ومفيدة فى تقييم تأثير العلاج المستخدم مما يجعلها قابلة للتطبيق بشكل كبير كإختبارات روتينية داخل المعامل.