تم تدقيق البحث من قبل
الاستاذ:
بتاريخ:
وقد تم تصحيح كافة الاخطاء وكان البحث وفق متطلبات النشر
توقيع الاستاذ:

SERUM CONCENTRATION OF INTERLEUKIN -1α AND INTERLEUKIN-8 ASSOCIATED WITH ABSOLUTE MONOCYTE COUNT IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)*

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Abstract

Interleukin-1α(IL-1α) and interleukin 8 (IL-8) have a major role in initiation of immune response. These two cytokines are secreted mainly by monocyte. This study aimed to evaluate the initiation of immune response in patients with acute lymphoblastic leukemia. Blood samples were collected from 36 patients with ALL (26 treated and 10 untreated). Other 10 blood samples were collected from healthy individuals as control group. Enzyme linked immunosorbent assay (ELISA) was used to estimate serum concentration of IL-1 and IL-8. Absolute monocyte count in each blood sample was determined. The study showed a significant decrease in serum concentration of IL-1α in treated and untreated patients, whereas, serum concentration of IL-8 and blood absolute monocyte count showed significant increase in untreated patients. Dropping in IL-1α and elevation of IL-8 with increasing absolute monocyte count may indicate suppression of gene expression for IL-1 but not for IL-8.

التراكيز المصلية لبين ابيضاض ١ الفا (IL-1α) وبين ابيضاض ٨ (IL-8)المقترنة مع الاعداد المطلقة للخلايا الوحيدة في مرضى ابيضاض الدم اللمفي الحاد

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الخلاصة

كل من بين ابيضاض ١ ألفا وبين ابيضاض ٨ دور أساسي في المراحل الأولية للاستجابة المناعيـــة ، ويفرز كلا من هذين المحركين الخلويين بشكل رئيسي من الخلايا الوحيدة . استهدفت الدراسة تقييم المراحل الأولية للاستجابة المناعية في مرضى ابيضاض الدم اللمفي الحاد . جمعت عينـــات دم مـــن ٣٦ مريـــضا بابيضاض الدم اللمفي الحاد (٢٦ معالجون و ١٠ غير معالجين) بالإضافة إلى ١٠ عينات مـــن أشـــخاص

أصحاء مثلوا مجموعة سيطرة . استخدمت تقنية الاليزا لتقدير التراكيز المصلية لبين ابيضاض ١ و ٨ وتم حساب العدد المطلق للخلايا الوحيدة في كل عينة دم .أظهرت النتائج انخفاضا معنويا في التراكيز المصلية لبين ابيضاض ١ ألفا في المرضى المعالجين وغير المعالجين فيما أظهرت التراكيز المصلية لبين ابيضاض ٨ والعدد المطلق للخلايا الوحيدة ارتفاعا معنويا في المرضى غير المعالجين . إن انخفاض تراكيز بين ابيضاض ١ ألفا وارتفاع تراكيز بين ابيضاض ٨ مع زيادة العدد المطلق للخلايا الوحيدة ربما يشير إلى تثبيط التعبير الجيني لبين ابيضاض ١ ألفا وليس بين ابيضاض ٨ .

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Introduction

Cytokine is the general term for a large group of soluble molecules involve in the signaling between cells during immune response [1]. The vast majority of cytokines have a pleiotropic action influencing cells from different systems by various mode of action [2, 3]. IL-1 is a cytokine secreted by monocyte, macrophage, large granular lymphocyte and some other body cells. There are two distinct molecular forms of IL-1 called IL-1α and IL-1β [4] which are encoded by the same gene on chromosome 2 [5]. This cytokine has a major role in initiation of immune response [6], hematopoiesis, and removal of myeloid suppression in leukemic patients after cessation of chemo and radiotherapy [7]. Some studies showed dropping in both molecular forms of this cytokine in ALL patients [8].

The cytokine IL-8 is a secreted mainly by monocyte, fibroblast as well as many other body cells. It is encoded by a gene on chromosome 4 and acts as a chemo-attractant factor for macrophage, T lymphocyte and other inflammatory cells [9]. Some studies revealed that serum levels of this cytokine elevated in treated and untreated patients with ALL [10, 11], however, Mazur *et al* [12] reported dropping in serum levels of this cytokine after cessation of chemotherapy. This study aimed to evaluate immune response initiation through estimation of serum concentrations of IL-1α and IL-8 associated with absolute monocyte count in treated and untreated patients with ALL.

Materials and Methods

Patients:

A total of 36 in and outpatients with ALL from both sexes in Baghdad teaching Hospital during the period from December 2004 to August 2005 were used for this study . These patients were divided into two groups: twenty-six (14 – 53 years old, 13 males and 13 females) treated patients with ALL, and ten (14 – 68 years old, 5 males and 5 females) untreated patients with ALL (newly diagnosed).

Additionally, ten (25 -49 year old, 6 males and 4 females) healthy individual from outside the hospital were used as a healthy control group. All study population didn't receive blood transfusion for more than one month before the time of sampling.

Samples:

Five mL of venous blood were collected from each individual. Each blood sample was divided into two parts: one in EDTA tube for total leukocyte count and absolute monocyte count and the other in plain tube for serological tests.

Immunological assays :

Enzyme-Linked immunosorbent assay (Immunotech, France) was used to estimate the serum levels of IL-1α and IL-8 in each sample.

Absolute Monocyte Counts (AMC):

Blood films were used for differential leukocyte count (TLC), and AMC was obtained by multiplying monocyte percentage by TLC.

Statistical analysis:

Mean values and standard deviation (SD) of the parameters recorded were calculated. Statistical package for the social sciences was used to find least significant differences between means of group. Statistical probability of $p< 0.05$ was considered significant.

Results and Discussion

Serum levels of IL-1α :

The highest serum concentration of IL-1α was recorded in healthy control group which was 15.43± 3.1 pg/mL and it differed significantly from both untreated (8.32± 0.48 pg/mL) and treated group (9.18 ± 1.68 pg/mL) with no significant difference between treated and untreated group.

Serum levels of IL-8 and absolute monocyte count : The study revealed that the highest concentration of IL-8 and AMC (31.1± 4.2

pg/mL and 1344 ± 669 × 10^9 /L respectively) were in untreated group which differed significantly from both treated group (23.32 ± 2.36 pg/mL and 208.57 ± 37.62 ×10^9/L respectively) and healthy control group (21.13 ± 2.36 pg/mL and 298.5 ± 71.27 × 10^9 respectively) with no significant difference between treated and healthy control group Figure (1 and 2).

Cytokines microenvironment plays an important role in determining the nature of any response generated, and any defect in this environment will affect the nature of immune response. IL-1α and IL-8 are considered among most important cytokines that participate in the initiation of immune response, and as they supposed to be produced mainly by monocyte and macrophage, it is expected that serum levels of these two cytokines will be elevated in association with increased absolute monocyte count especially in untreated patients. This is almost true for IL-8 but not for IL-1α as monocyte is not the sole source of these cytokine, besides, there are many other factors which interfere with secretion of cytokines from monocyte as well as other body cells.

It is well known that tumor cells produce various cytokines, chemokines, angiogenic and growth factors which enable these cells to survive and grow with the presence of natural immune system. Among these cytokine is IL-10 [13]. It is a potent immunosuppressive factor that plays a major role in protecting tumor cells from immune-mediated destruction [14]. Serum levels of this cytokine was found to be increased in patients with ALL [15] . Many studies have pointed out that IL-10 inhibits production of IL-1 and IL-8 from polymorphonuclear leukocyte and monocyte and up-regulate IL-1 receptors antagonist [16, 17].

Another factor which produce by tumor cell and can influence production of IL-1α and IL-8 is TGF-β1. Dubois *et al* [18] revealed that this factor is a potent inhibitor of IL-1 receptor expression in lymphoid and myeloid progenitor. More recently, Qi *et al* [19] showed that TGF-β1 induces production of IL-8 and macrophage chemo-attractant protein 1 (MCP-1) via tissue growth factor. This may explain partially elevation of IL-8 but not IL-1 in untreated patients.

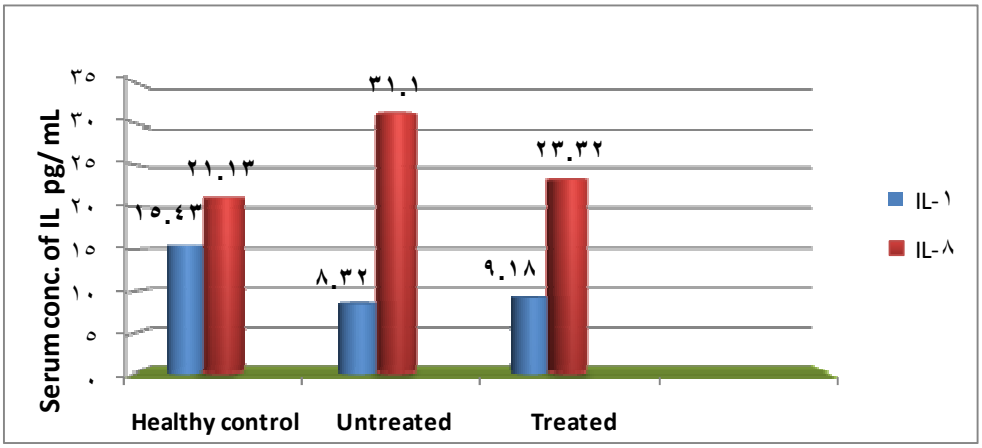

Figure 1: Serum concentration of IL-1α and IL-8 in the three studied groups

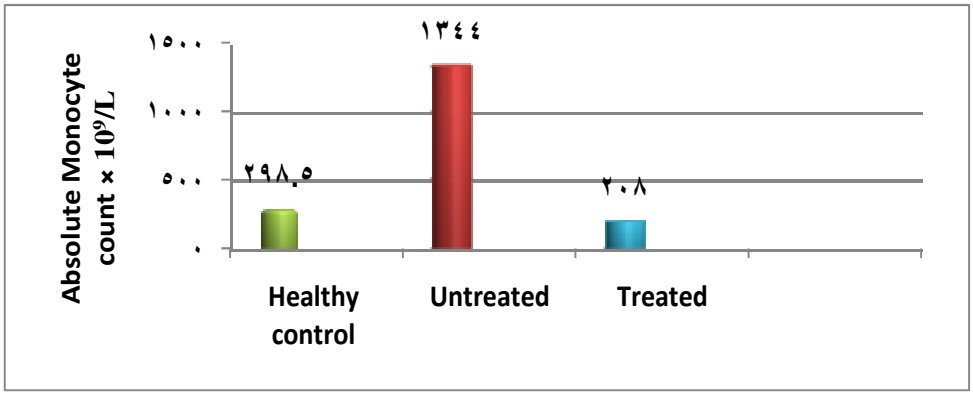

Figure 2: Absolute monocyte count in the three studied groups

Some cytokines from normal body cells, may do also, influence serum levels of IL-1α and IL-8. The fact that high concentration of IFN-α could inhibit IL-1 production has been already noted [20, 21] and defective in IFN-α production has been associated with active disease in patients with rheumatoid arthritis due to relatively high concentration of IL-1 [21], however, IFN-α was showed to down-regulate production of IL-8 in human monocyte [22], so, the elevation of IL-8 and dropping of IL-1 cannot be attributed to concentration of IFN-α. The other cytokine which influence IL-1α and IL-8 production is IL-4. This cytokine, which recently found to be secreted from basophil [23], can dramatically block the release of IL-1 from monocyte or macrophage [24]. Nevertheless, IL-4 inhibits IL-8 gene expression in monocyte [25]; therefore, we cannot attribute the divergence in serum levels of IL-1 and IL-8 to this cytokine Although chemotherapy has a direct effects on immune system and can influence the production of various cytokines [26], there were no significant differences in serum levels of IL-1α between treated and untreated groups, whereas serum levels of IL-8 in untreated group differed significantly from treated and healthy control groups. This may be indicate that chemotherapy has an effect on the production of IL-8 but not IL-1. Supporting this point of view, Shibakura *et al* [27] have shown that doxorubicin increased the production of IL-8 and MCP-1 in human small cell lung cancer lines while serum levels of IL-8 had dropped after cessation of chemotherapy in ALL patients [11].

Alteration in monocyte kinetics have been measured after short-term and long-term administration of adrenal corticoids in human. Profound monocytopenia develops promptly and its duration and degree depend on the amount, stability, and route of steroid administration [28]. This can clearly explain the significant increase in absolute monocyte count in untreated group and insignificant difference between treated and healthy control groups.

Collectively, these data indicate that there is a defect in gene expression of IL-1 in monocyte in ALL patients. This defect may be partially caused by INF-α and/or TGF-β or may be some other factors. In any case, as IL-1α is important for initiation of immune response, it may be helpful to use this cytokine clinically to overcome the myeloid suppression caused by chemotherapy

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