Archives of Razi Institute, Vol. 77, No. 5 (2022) 1895-1899

DOI: 10.22092/ARI.2022.359504.2435

Original Article

Evaluation of Serum Interleukin-15 in Acute Lymphoid and Myeloid Leukemia Patients

Wadai, G. M. A[1]*

1. College of Biotechnology, University of Al-Qadisiyah, Al Diwaniyah, Iraq

Received 19 July 2022; Accepted 9 August 2022
Corresponding Author: ghasoun.wadai@qu.edu.iq

Abstract

The interleukin-15 is a unique proinflammatory cytokine associated with immune response regulation and the growth, survival, and biological behavior of leukemic cells. This study assesses the effect of both types of acute malignancies, lymphoid and myeloid, on the interleukin-15 serum levels for Acute Lymphoid Leukemia and Acute Myeloid Leukemia patients. The interleukin-15 serum levels were measured for 21 acute lymphoid leukemia patients and 21 acute myeloid leukemia patients compared to healthy people (24) as a control group using the ELISA Peprotech Company (USA), a protocol kit. The research data explain a significant decrease in interleukin-15 serum level for acute lymphoid leukemia (ALL) patients (99 pg/ml)compared with the healthy group (126 pg/ml) at level (*P* value=0.009), while the acute myeloid leukemia (AML) (141 pg/ml) patients recorded a nonsignificant increase in IL-15 serum level from the healthy group at (*P*>0.05). The data outcome clarified an important effect of acute lymphoid leukemia in reduced proinflammatory interleukin-15 serum level due to impairment in T and B lymphocyte production, which is correlated with immunosuppression response toward leukemia, while acute myeloid leukemia non-significantly increases the interleukin-15 serum level.

Keywords: Proinflammatory cytokine, Immune system, blood

1. Introduction

Interleukin-15 (IL-15) is a unique proinflammatory cytokine (1). It is known as a member of the γc family cytokines, which act on regulating the development, proliferation, survival, and differentiation of immune cells (2); as a result, it has the same immune-enhancing properties as IL-2 (3), excepting the stimulation of immunosuppressive Treg (4, 5). It mediates the immunity response interaction between innate and adaptive immune cells (6). Chiefly, this cytokine is secreted as a matured protein by macrophages, monocyte, and dendritic cells (DCS) in addition to stromal cells (7), and so produced by skeletal muscle as a myokine, which affects adipose tissue and muscle cells (8). So, It acts to reject and destroy cancer cells by increasing and stimulating innate and adaptive cells such as the natural killer cells (NK), natural killer T cells (NKT), memory T helper, and cytotoxic CD+T cells (1, 9). In addition, proliferating human T and B cells lead to enhance innate and adaptive antitumor response (2, 10) and so has an important effect on homeostasis development (11), though it is a member of the immunoregulatory cytokines family by inducing several mechanisms of the antitumor immunity, and so-known as a perfect application for tumor therapy without severe toxicity (12). Also, it is a member of hematopoietic cytokines, which is crucial for the production of most blood cell types (13). Hematopoietic homeostasis depends on these cytokines and growth factors to regulate the balance between cell growth, proliferation, differentiation,

and apoptosis (13). Rots and his colleagues observed that the single nucleotide variations (SNVs) of IL-15 may well stimulate the development of acute lymphoid leukemia (ALL)-dependent on the gene variation; they might activate the pre-B leukemia cell proliferation. So this variation is associated with the treatment (14).

Leukemia formation arises in the bone marrow and changes the environment surrounding the cancer cell to maintain the pathogenic progression and abnormality proliferation of the standard hematopoiesis processes (15).

Acute lymphoid leukemia is a proliferation of abnormal B or T lymphoblast due to irregular chromosome variation, including the uncontrolled production of undeveloped precursor cells of lymphocytes, which affects the composition of the bone marrow (16). While acute myeloid leukemia (AML) is a type of cancer in which the bone marrow makes many abnormal blood cells (17).

The bone marrow environment was developed in both acute leukemia cases to alter the cytokine expression profile (18). Recently published data describe the effect and variations of IL-15 regulation during the progress and development of leukemias (1). Therefore, this study was designed to spotlight the relationship between serum levels of IL-15 and the two types of acute leukemia (myeloid & lymphoid) in Iraqi patients due to the poorly knowledge of the antitumor immune response for leukemia.

2. Materials and Methods

2.1. Subject

Sixty-six individuals diagnosed with acute leukemia were used in this study before undergoing chemotherapy treatment. The participant's ages ranged from 19 to 71 years. The participants were classified into 2 groups: the first group was ALL (n=21), the second group was AML (n=21), and the healthy group was composed 24 individuals.

2.2. IL-15 Assessment

Interleukin-15 was measured using an ELISA kit from Peprotech Company (USA). 5 ml of the vein blood sample were collected from all the participants and kept in a vacuum tube containing a clot activator. To separate serum, the collected blood samples were centrifuged at 1500 g for 15 min, and the separated serum was stored at -20 ℃ until use. The levels of IL-15 were determined according to a kit Peprotech Company procedure.

2.3. Statistical Analysis

The differences among study group median values were determined using Excel Microsoft office 16. The result data was documented as (median±SD) and used one-way ANOVA to test the serum level data for ALL and AML compared with the healthy (control) group. This data calculation recorded a significant decrease in IL-15 serum level for ALL at the ($P \leq 0.01$) for ALL groups and a nonsignificant increase in IL-15 serum level for the AML group.

3. Results

This study depends upon 42 acute leukemia Iraqi patients who participated in this experiment, ALL (n=21) and AML (n=21), compared with a healthy matching group composed of 24 healthy volunteers. The result of the study is described below in table 1 and clarifies the comparison of the IL-15 serum level between both leukemia-type groups before starting treatment with the healthy control group. The recorded data showed a significant decrease in the level of IL-15 for ALL patients (99±25.2 pg/ml) compared with the healthy group (126±31.8pg/ml) at ($P \leq 0.01$), whereas a nonsignificant increasing recorded for the median level of IL-15 for AML patients (141±43.1pg/ml) compared with a healthy group (126±31.8 pg/ml) (Figure 1).

Table 1. Explain the comparison of the median IL-15 serum level between the (ALL and AML) patients and the healthy group

Groups	No.	Median (pg/ml)±SD	(range) (pg/ml)	*P*-value Compare with healthy
ALL	21	99±25.2	70-149	0.001 **
AML	21	141±43.1	29-215	0.7 NS
Healthy	24	126±31.8	77-190	1

NS=non-significant ,**= ($P \leq 0.01$)

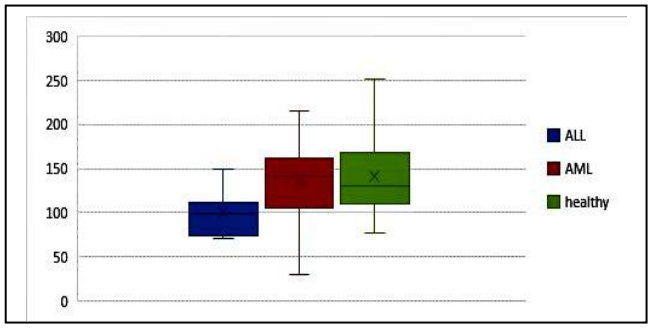

Figure 1. Explain the comparison of IL-15 serum levels among 3 study groups (ALL, AML, and healthy groups)

The relation between IL-15 serum level and patients' age is nonsignificant, where the correlation coefficient between them is equal to 0.20, as explained in table 2.

Table 2. Explain the relation between the IL-15 serum concentration and the age of acute leukemia patients

Parameters	Correlation coefficient (r)	Level sig. (*P*-value) *P*-value
IL-15 level& patients' ages	0.20	1.8 NS

NS: Nonsignificant

4. Discussion

Hematopoietic homeostasis depends on the interaction of several growth factors that regulate cell growth, proliferation, differentiation, and apoptosis (13). This process depends on cytokines produced by various cell types (1), so the cytokine and chemokines have both therapeutic and pathogenic effects in leukemia (19). The proinflammatory cytokine IL-15 promotes T-lymphocyte, B-lymphocyte, and NK cell production in addition to their cytolytic activity (16), without causing considerable damage (4, 12). Consequently, it is essential to the survival and proliferation of malignant hematopoietic cells regardless of their surroundings (20). That may be related to the pathogenesis of leukemic cells due to the oncogenic modification in tumor cells and their stromal environment that happens during tumor growth, such as the loss of immunogenic tumor antigen and the induction of immunosuppressive characteristics in cancer cells. These changes act to evade the immune defines system (21).

The result of this research clarified a significant decrease in IL-15 serum levels for ALL patients compared with the healthy group; this result agrees with another study, which confirms the low.

According to the findings of the previously published studies (22, 23), their findings suggested that the drop in IL-15 serum levels in ALL patients is attributable to impaired T and B lymphocyte generation, which correlates with an immunosuppressive response to leukemia. We can only express disagreement with Wenjian, Hua (24), who found significantly elevated IL-15 levels in adult ALL and AML patients. Another study explains that both types of acute leukemia (ALL and AML) had elevated IL-15 serum levels compared to the control group (25); in addition, both previous studies found a correlation between the lower IL-15 serum level for ALL and high-risk cytogenetics for ALL patients compared to patients with non-high-risk cytogenetics for ALL. Whereas the current study refers to the nonsignificant increasing IL-15 serum level recorded for patients compared to the healthy group, these results may be due to the small sample size. In addition, the previous studies recorded a negative relation between survival and IL-15 serum amounts, where the reduction in IL-15 serum amount related to a high survival degree compared with those with high IL-15 serum levels (24, 25). The earlier studies correlated the genetic variation in IL-15 genes with ALL development and specifically increased the risk of childhood ALL, which is related to hyperdiploid in the population of Lativian because of the effect on the tumor microenvironment (14).

Even with the plenty of IL-15 expression by tumor microenvironment cells, the amount of IL-15 complexes recorded significantly decreased in advanced tumors (23).

Due to the functional loss of hematopoietic stem cells, the aging process reduces the function of the hematopoietic system and increases geriatric hematological disease (HSCs) (26). Our result explains a nonsignificant

association between the age of patients and their serum concentration of IL-15, which may be due to attenuated secretion of IL-15 for younger and older patients.

Another study described that low plasma-15 levels were associated with sarcopenia, which is associated with elderly healthy people, due to changes in the production of IL-15by muscle mass (8). This clarified that the decrease in the production of IL-15 by muscle cells is a result of the attenuated weakness of muscle in more aged people, and this feature is shared.

This study record that acute leukemia is related to decreasing serum levels of IL-15 for acute lymphoid leukemia patients, whereas there is a nonsignificant increase in acute myeloid leukemia patients.

Authors' Contribution

Study concept and design: G. M. A. W.
Acquisition of data: G. M. A. W.
Analysis and interpretation of data: G. M. A. W.
Drafting of the manuscript: G. M. A. W.
Critical revision of the manuscript for important intellectual content: G. M. A. W.
Statistical analysis: G. M. A. W.
Administrative, technical, and material support: G. M. A. W.

Ethics

The current research was accepted by the Ethics of Helsinki 1975 declaration as revised in 1983, which agreed with the ethics committee of the Clinical Haematology Department–medical city hospital. All patients signed written informed consent, and all members of the study groups gained the informed agreement.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgment

We want to acknowledge Dr. Hind Mizher and Dr. Kifah al-Jacobi, who critically reviewed this article's content.

References

1. Zhang S, Zhao J, Bai X, Handley M, Shan F. Biological effects of IL-15 on immune cells and its potential for the treatment of cancer. Int Immunopharmacol. 2021;91:107318.
2. Leonard WJ, Lin J-X, O'Shea JJ. The γc family of cytokines: basic biology to therapeutic ramifications. Immunity. 2019;50(4):832-50.
3. Yang Y, Lundqvist A. Immunomodulatory effects of IL-2 and IL-15; implications for cancer immunotherapy. Cancers. 2020;12(12):3586.
4. Knudson KM, Hodge JW, Schlom J, Gameiro SR. Rationale for IL-15 superagonists in cancer immunotherapy. Expert Opin Biol Ther. 2020;20(7):705-9.
5. Meghnem D, Morisseau S, Frutoso M, Trillet K, Maillasson M, Barbieux I, et al. Cutting edge: Differential fine-tuning of IL-2–and IL-15–dependent functions by targeting their common IL-2/15Rβ/γc receptor. J Immunol. 2017;198(12):4563-8.
6. Briukhovetska D, Dörr J, Endres S, Libby P, Dinarello CA, Kobold S. Interleukins in cancer: from biology to therapy. Nat Rev Cancer. 2021;21(8):481-99.
7. Kubo H, Mensurado S, Gonçalves-Sousa N, Serre K, Silva-Santos B. Primary Tumors Limit Metastasis Formation through Induction of IL15-Mediated Cross-Talk between Patrolling Monocytes and NK CellsAntimetastatic Innate Response to Primary Tumors. Cancer Immunol Res. 2017;5(9):812-20.
8. Yalcin A, Silay K, Balik AR, Avcioğlu G, Aydin AS. The relationship between plasma interleukin-15 levels and sarcopenia in outpatient older people. Aging Clin Exp Res. 2018;30(7):783-90.
9. Waldmann TA, Dubois S, Miljkovic MD, Conlon KC. IL-15 in the Combination Immunotherapy of Cancer. Front Immunol. 2020;11:868.
10. Robinson TO, Schluns KS. The potential and promise of IL-15 in immuno-oncogenic therapies. Immunol Lett. 2017;190:159-68.
11. Waldmann TA, Miljkovic MD, Conlon KC. Interleukin-15 (dys) regulation of lymphoid homeostasis: Implications for therapy of autoimmunity and cancer. J Exp Med. 2020;217(1).
12. Guo J, Liang Y, Xue D, Shen J, Cai Y, Zhu J, et al. Tumor-conditional IL-15 pro-cytokine reactivates anti-tumor immunity with limited toxicity. Cell Res. 2021;31(11):1190-8.
13. Miao R, Lim VY, Kothapalli N, Ma Y, Fossati J, Zehentmeier S, et al. Hematopoietic stem cell niches and

signals controlling immune cell development and maintenance of immunological memory. Front Immunol. 2020;11:600127.

14. Rots D, Kreile M, Nikulshin S, Kovalova Z, Gailite L. Influence of IL15 gene variations on the clinical features, treatment response and risk of developing childhood acute lymphoblastic leukemia in Latvian population. Pediatr Hematol Oncol. 2018;35(1):37-44.
15. Wang A, Zhong H. Roles of the bone marrow niche in hematopoiesis, leukemogenesis, and chemotherapy resistance in acute myeloid leukemia. Hematology. 2018;23(10):729-39.
16. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J. 2017;7(6):577.
17. Kantarjian H, Kadia T, DiNardo C, Daver N, Borthakur G, Jabbour E, et al. Acute myeloid leukemia: current progress and future directions. Blood Cancer J. 2021;11(2):1-25.
18. Çelik H, Lindblad KE, Popescu B, Gui G, Goswami M, Valdez J, et al. Highly multiplexed proteomic assessment of human bone marrow in acute myeloid leukemia. Blood Adv. 2020;4(2):367-79.
19. Rubio-Jurado B, Sosa-Quintero LS, Carrasco-Martinez IL, Norato-Delgado A, Garcia-Luna E, Guzmán-Silahua S, et al. New biomarkers in non-Hodgkin lymphoma and acute leukemias. Adv Clin Chem. 2020;96:19-53.
20. Fiore PF, Di Matteo S, Tumino N, Mariotti FR, Pietra G, Ottonello S, et al. Interleukin-15 and cancer: some solved and many unsolved questions. J Immunother Cancer. 2020;8(2).
21. Sugimura R, Chao Y. Deciphering Innate Immune Cell-Tumor Microenvironment Crosstalk at a Single-Cell Level. Front Cell Dev Biol. 2022;10.
22. Cierna Z, Smolkova B, Cholujova D, Gronesova P, Miklikova S, Cihova M, et al. Decreased levels of circulating cytokines VEGF, TNF-β and IL-15 indicate PD-L1 overexpression in tumours of primary breast cancer patients. Sci Rep. 2021;11(1):1-11.
23. Santana Carrero RM, Beceren-Braun F, Rivas SC, Hegde SM, Gangadharan A, Plote D, et al. IL-15 is a component of the inflammatory milieu in the tumor microenvironment promoting antitumor responses. roc Natl Acad Sci. 2019;116(2):599-608.
24. Wenjian L, Hua W, Weida W, Mengyuan Z, Chengcheng L, Yue L. High serum level of interleukin-15 predicts poor prognosis in adult standard-risk acute lymphoblastic leukaemia. American Society of Hematology Washington, DC; 2017.
25. Moussa MM, Sheeba M, Mohsen EA, Elshazly M, Hussein NE. Assessment of serum interleukin-15 in adult acute leukemia patients (Egyptian sample). Egypt J Haematol. 2020;45(2):68.
26. Verovskaya EV, Dellorusso PV, Passegué E. Losing sense of self and surroundings: hematopoietic stem cell aging and leukemic transformation. Trends Mol Med. 2019;25(6):494-515.