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Subsets of natural killer cells in chronic myeloid leukemia and their relation with some inflammatory cytokines

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Abstract:

BACKGROUND: As in other malignancies, different subsets of natural killer (NK) cells play a crucial role in the recognition and lysing of malignant cells in chronic myeloid leukemia (CML).

OBJECTIVES: This study aims to identify two subsets of NK, cytotoxic (cluster of differentiation [CD] 16+^{bright}) and cytokine-producing NK (CD56+^{bright}) in newly diagnosed CML patients.

MATERIALS AND METHODS: This study is conducted on 20 newly diagnosed Iraqi patients (12 males and 8 females) with CML, in chronic phase, at the age range of 17–55 years. Along with patients, 20 healthy subjects (with matched age and gender) were enrolled to act as a control group. To identify NK cells and their subsets in peripheral blood samples, the expression of CD45, CD3, CD56, and CD16 markers was evaluated by flow cytometry technique. Furthermore, the serum level of interferon gamma (IFN-γ) and interleukin (IL)-18 was determined by the enzyme-linked immunosorbent assay technique.

RESULTS: The age of patients at the diagnosis of disease is (35.6 ± 12.2 years) and the male: female ratio was 1.5:1. The serum level of IL-18 in newly diagnosed CML patients (30.3 ± 6.5 pg/mL) was significantly ($P < 0.0001$) higher than those in control group (18.3 ± 7.8 pg/mL), while the serum levels of IFN-γ in newly diagnosed patients are significantly ($P = 0.006$) dropped down to (89.1 ± 7.2 pg/mL from that in control group (109.4 ± 30.3 pg/mL). The percentage of NK cells in newly diagnosed CML patients is significantly lower than in control group. There is a significant elevation in the cytotoxic NK cells (CD16+^{bright}) subset, and a significant decrease in the cytokine-producing NK subset (CD56+^{bright}) in newly diagnosed patients when compared to those in control group.

CONCLUSION: Although there is an elevation in the percentage of cytotoxic NK cells (CD16+^{bright}) subset of CML patients at the first diagnosis, these cells are not able to recognize and attack malignant cells, which may be due to low expression of their activating receptors and needs more investigation. Furthermore, present results found a low percentage of cytokine-producing NK cells (CD56+bright) and a low level of IFN-γ in CML patients, although there is an elevation in IL-18, which indicates that IL-18 may be not the main stimulator to these cells, so activation pathway of this subset of NK cells needs further investigation.

Keywords:

Chronic myeloid leukemia, cluster of differentiation 16+, cluster of differentiation 56+, interferon-gamma, interleukin-18, natural killer

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Introduction

Chronic myeloid leukemia (CML) is a hematological malignancy characterized by upregulation and uncontrolled proliferation of myeloid cells in the bone marrow due to the fusion of ABL1 gene sequence "9q34" downstream of BCR gene sequence "22q11." This fusion is described as the "Philadelphia chromosome" resulting in an active tyrosine kinase, this enzyme instigates and stimulates

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a number of signaling pathways, ultimately inducing the transformation of normal cells into a cancerous state.[1-3] In the realm of leukemia, CML holds a notable position accounting for approximately 15% of newly diagnosed cases in adults.[4] Predominantly, this form of leukemia manifests itself in individuals within the fifth and sixth decades of life in developed and Western countries with increasing concomitantly with age.[5] Furthermore, there is a slight male predominance with the ratio of male-to-female ranges from 1.3:1 to 1.8:1.[6]

Natural killer (NK) cells are large granular lymphocytes arising from the lymphoid origin that is considered the third largest population of lymphocytes following T and B cells, including 10%–15% of all peripheral blood lymphocytes involved in defense against certain malignant and virus-infected cells.[7] In numerous clinical studies, NK cells have been employed to inhibit tumor growth, NK cells also lyse target cells by antibody dependent cell-mediated cytotoxicity (ADCC), a critical mode of action for many therapeutic antibodies that are used for treating cancer.[8] NK cells evoke a rapid response against tumor cells based on "signals from activating and inhibitory receptors" on the cell surface. Accordingly, these receptors are capable to recognize the modified protein expression on target cells and quickly attack malignant cells without prior sensitization.[9] Like active cytotoxic T cells, NK cells also produce cytotoxic granules that include perforin and granzymes to directly lyse tumor cells after activation. Moreover, NK cells are crucial for controlling adaptive immune responses since they are also powerful makers of chemokines and cytokines including tumor necrosis factor-alpha "TNF-α" and interferon-gamma "(IFN-γ)."[10] NK cells are "identified by the expression of the surface markers cluster of differentiation (CD) 56 and CD16 and the lack of CD3" (CD56+CD16+CD3-).[11] Those with the higher density of lytic granules constitute about 90%–95% of NK cells which are abbreviated as $CD16^{bright}CD56^{dim}$ and have cytolytic properties, whereas the rest 5%–10% of NK cells are abbreviated as $CD56^{bright}CD16^{dim}$ subset that has specialized proliferative potential and secretes a number of immunoregulatory chemokines and cytokines such as interferon-gamma "IFN-γ," tumor necrosis factor "TNF-α/β," and interleukin (IL)-10.[12] IFN-γ is an important immunoregulatory protein produced mainly by T cells and NK cells in response to different signals, it increases the susceptibility of NK-mediated killing, and it has been shown to play a role in apoptosis by activating and upregulating genes or proteins that inhibit cell growth.[13] IL-18, originally named as "IFN-γ-inducing factor," is an immunostimulatory cytokine that regulates both innate and adaptive immune responses.[14]

Therefore, this study is designed to identify the two main subsets of NK cells in newly diagnosed CML patients at chronic phase and their relation with IL-18 and IFN-γ.

Materials and Methods

Twenty newly diagnosed Iraqi patients (12 males and 8 females) in the age range of 17–55 years with CML in chronic phase, who agreed to participate in this study, were involved in this study. They were referred to the National Center of Hematology (NCH), Mustansiriyah University in Baghdad between May 2022 and December 2022. Along with patients, 20 healthy subjects (with matched age and gender) were enrolled to act as control group. About 5 mL of blood were aspirated from all subjects using peripheral vein punctures and dispensed into two aliquots; the first one was prepared by transferring 2 mL of whole blood into anticoagulant tubes containing ethylenediaminetetraacetic acid and processed within 24 h of collection for flowcytometry from Biolegand Company/USA. Peripheral blood NK cells of CML patients and normal individuals have been investigated based on gating parameters (forward scatter and side scatter) and expression of specific surface markers (CD45, CD56, CD3, and CD16). However, the second aliquot was prepared by transferring 3 ml of whole blood into a nonheparinized gel tube and left for 15 min at 4°C to clot, then centrifuged at 4100 rpm for 10 min to separate serum, which was dispended into two aliquots in Eppendorf tubes and stored in −80°C until being used to determine the serum level of IFN-γ and IL-18 from Sunlong company/China, by means of enzyme-linked immunosorbent assay technique.

Statistical analysis

Data were expressed as mean ± standard deviation and/or percentage, then statistically analyzed to determine the difference between the two groups by *t*-calculator, Chi-square, and matrix correlation by using Vassar stats program).

Ethical consideration

Written informed consent was provided by all patients before entry into the study, and the study protocol was approved by Review ethical committee of college of Dentistry / Mustansiriyah university.

Results

Nonsignificant difference between the patient and control group in their average age and gender [Table 1]. Patients are presented to NCH in the fourth–fifth decades of their age (35.6 ± 12.2 years) with male dominance (male: female ratio = 1.5:1).

The serum level of IL-18 in newly diagnosed CML patients (30.3 ± 6.5 pg/mL) is significantly higher ($P < 0.0001$) than those in control group (18.3 ± 7.8 pg/mL) [Figure 1], while the serum

levels of IFN-γ in newly diagnosed patients are significantly (*P*=0.006) decreased to (89.1 ± 7.2 pg/ml from that in control group (109.4 ± 30.3 pg/ml) [Figure 2].

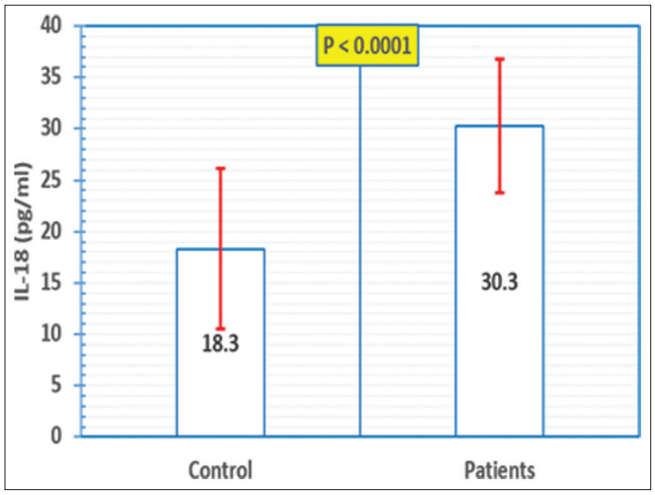

Figure 1: Serum level of IL-18 in patients and control groups. IL = Interleukin

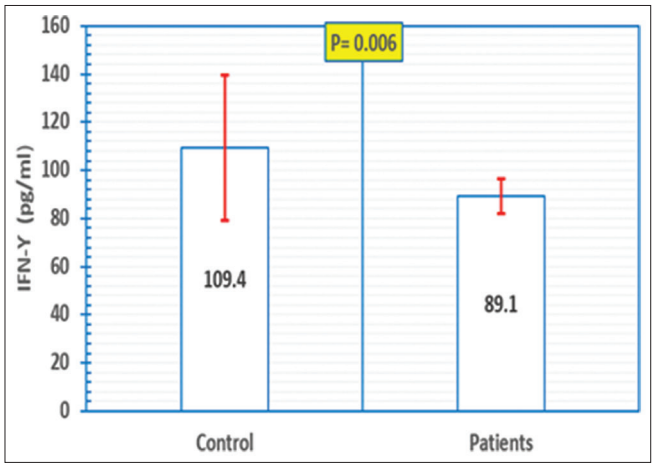

Figure 2: Serum level of IFN-γ in patients and control groups. IFN-γ = Interferon gamma

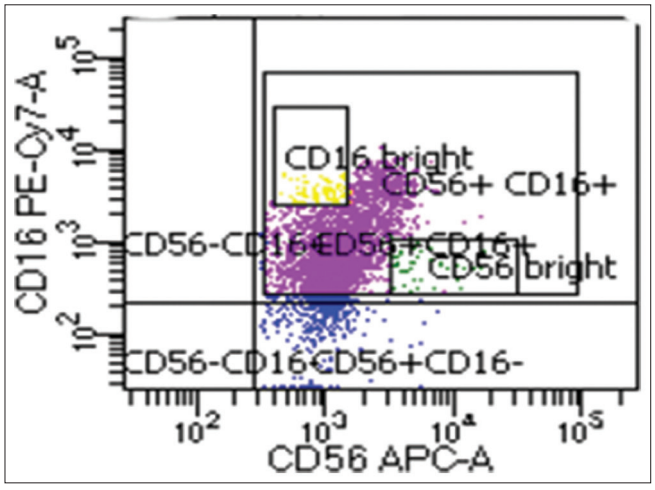

Figure 3: Natural killer subsets in blood samples of patient and control groups

In addition to the expression of CD56, NK cells also expressed CD16 which is illustrated in the large box located on the upper right quadrant of the scattered flow cytometer and represents CD56+CD16+ [Figure 3]. These cells are subdivided into two subsets based on their expression of the surface markers "CD16 and CD56." The two major subsets are CD56+^{bright}CD16+^{dim} (Cytokine producing NK) which are located in the small box with green color. However, CD16+^{bright}CD56+^{dim} (Cytotoxic NK) are located in small box with yellow color.

To estimate the percentage of total NK cells, Table 2 shows NK cell population (CD16+CD56+) constitutes about 76.7% ± 10.1% in newly diagnosed patients which is significantly lower than 84.5% ± 5.2% in the control group. Furthermore, this table shows that the cytotoxic NK cells (CD16+^{bright}) subset constitutes about 7.22% ± 4.08% of all NK cell populations in newly diagnosed CML patients which is significantly higher than 1.66% ± 0.78% in the control group. However, the percentage of cytokine-producing NK subset (CD56+^{bright}) in newly diagnosed CML patients constitutes about 0.72% ± 0.39% from all NK cell populations, which is significantly lower than 1.43% ± 1.1% in the control group. By calculating the ratio between cytotoxic and cytokine-producing NK cells, this ratio in newly diagnosed patients constitutes 10.4:1, which is significantly higher than 2.6:1 in the control group about 4 times.

Discussion

According to the findings of this study, the mean age of patients at the diagnosis of the disease was 35.6 ± 12.2 years. This aligns closely with a prior study

Table 1: Matched age and gender in patients and control group

Character	Controls (*n*=20)	Patients (*n*=20)	*P*
Age (years)			
Range	19–61	17–55	0.399
Mean±SD	39.2±12.1	35.6±12.2	
Gender			
Male, *n* (%)	12 (60)	12 (60)	1.0
Female, *n* (%)	8 (40)	8 (40)	
Male:Female ratio	1.5	1.5	

SD=Standard deviation

Table 2: Percentage of natural killer subsets in blood samples of chronic myeloid leukemia patients and control groups

NK (%)	CD expression	Control (*n*=20)	Patients (*n*=20)	*P*
Total	CD16+, CD56+	84.5±5.2	76.7±10.1	<0.0001
Cytotoxic	CD16+^{bright}	1.66±0.78	7.22±4.08	<0.0001
Cytokine-producing	CD56+^{bright}	1.43±1.1	0.72±0.39	0.019
Cytotoxic/cytokine ratio		2.6:1	10.4:1	0.012

NK=Natural killer, CD=Cluster of differentiation

in Iraq conducted between 2002 and 2006 which reported that the median age at the onset of the disease was 37 years.[15] A recent Iraqi study indicated that 216 CML patients visited the NCH between 2005 and 2020; their average age at diagnosis was in the final years of the fourth decade of life.[16] In contrast, the median age at diagnosis of CML patients in developed countries such as the USA was setting at 65 years which is notably higher than in developing countries.[17] In addition, the present study determined a male-to-female ratio of 1.5:1 among CML patients, this finding is consistent with multitude previous studies which indicating a higher incidence of CML among males.[15,17,18]

In concerning to IL-18, the significant increase of IL-18 serum level in newly diagnosed CML patients compared with the control group [Figure 1] is compatible with another study done by Floridi in 2023 who demonstrated that IL-18 is significantly increased in CML patients and could be considered a prognostic factor and also might be involved in the progression and resistance to therapy of CML.[19] Regardless increment in IL-18 as a potent stimulator for the production of gamma interferon, the present study found a significant decrease in the serum level of IFN-γ in CML patients [Figure 2]. This controversial result can be interpreted under two categories: first, this reduction may be resulted from the decreasing in the percentage of cytokine-producing NK cells subset as illustrated in Table 2, which indicates that IL-18 is not a key inflammatory mediator to stimulate CD56 expression and subsequently the production of IFN-γ. Second, the total amount of peripheral IFN-γ can be originated from several sources rather than NK cells alone because an early study indicated that the reduction in IFN-γ was due to decreasing its production by T cells of patients with untreated CML.[20] Moreover, IL-18 was originally discovered as an enhanced factor for IFN-γ production from T helper-1 cells in the presence of IL-12 in response to IL-18 stimulation.[21]

In concerning with NK cells, Table 2 shows a significant decrease in the total percentage of NK cell population (CD16+CD56+) in newly diagnosed patients, and significant enlargement of the cytotoxic NK cells ($CD16^{bright}$) subset in newly diagnosed CML patients, and lower expression of cytokine-producing NK subset ($CD56+^{bright}$) in newly diagnosed CML patients in comparison with those in the control group. The decrease in the total number of NK cells suggests that, overall, the immune system of the CML patients is obstructed and unable to supply enough number of effector cells which are able to kill cancer cells.[22] Some studies reported severely decreased counts of NK cells in untreated CML patients.[23] Many other studies demonstrated that AML patients are characterized by a decreased in the median number and percentages of peripheral blood NK cells in comparison with normal values.[24,25] Comparable to results of previous studies, Pierson and Miller found that the $CD56+^{bright}$ NK subset is significantly reduced in all patients with CML although NK is not derived from the cancerous clone, rather they are affected inherently by their malignant microenvironment.[26] Furthermore, it has been suggested that the number of NK cells in patients with leukemia appears to gradually decrease as the disease progresses from the chronic phase to blast crisis, and their activity against malignant cells in different types of leukemia at an advanced stage of the disease shows reduced cytotoxicity.[27]

Although the two major subsets of NK cell markers "CD56 and CD16" are present in human cells, and induce different functions in NK cells,[12,28] the elevated number of cytotoxic NK cells ($CD16+^{bright}$) reported in this study could not recognize and attack the tumor cells in newly diagnosed patients with CML. To interpret this condition, NK cells in "newly diagnosed CML patients" may have lost their recognition capability or their cytotoxicity. However, NKs in patients with AML, MDS, and CML sometimes are dysfunctional.[8,29] Several previous studies reported that NK cells can recognize tumor cells through their receptors or surface markers to activate the functions of NK cells by one of the two tumor-recognizing models: "Missing-self recognition" and "stress-induced recognition." The missing-self recognition model includes the loss of inhibitory effect of NK cell resulting from the absence of MHC-class-I molecule on the tumor cell. In the "stress-induced recognition model," the damaged protein on tumor cells bind to the activating receptors of NK cell and stimulate NK cells cytotoxic functions.[30,31] On the other hand, direct activation of NK cells facilitates the killing of tumor cells either by direct or indirect mechanisms. In direct means, they induce apoptosis in tumor cells by releasing perforin and granzymes, antibody dependent cell-mediated cytotoxicity (ADCC), or death receptor-dependent apoptosis.[32-34] However, the indirect model of NK cell activation involves the secretion of chemokines and cytokines, which enhance immune cell proliferation and activation, such as macrophages, monocytes, dendritic cells, cytotoxic T-lymphocytes, and B-cells. These cells are cytotoxic toward tumor cells, which die as a result of the immune response associated with apoptosis and necrosis.[28,31,35] Moreover, Binelli *et al*., observed that patients are presented with an immature noneffective deficient cytotoxicity NK cell profile, particularly those who are nonresponded to treatment with first and second tyrosine kinase inhibitor generations.[36] Therefore, since NK cells serve an important role in the immune response and have the ability of killing cancer cells, NK cell immunotherapy development in hematological malignancies and research into strategies to enhance NK cell function for CML treatment needs more investigation.[37]

Conclusion

Although there is an elevation in the percentage of cytotoxic NK cells (CD16+^{bright}) subset of CML patients at the first diagnosis, these cells are not able to recognize and attack malignant cells, which may be due to low expression of their activating receptors and needs more investigation.

Furthermore, present results found a low percentage of cytokine-producing NK cells (CD56+bright) and a low level of IFN-γ in CML patients, although there is an elevation in IL-18, which indicates that this cytokine may not be the main stimulator to these cells, so activation pathway of this subset of NK cells needs further investigation.

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Conflicts of interest

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