

Correlation of Interleukin-8 Level with Chronic Myeloid Leukemia (Cml) in Iraqi Patients Treated With Imatinib Therapy

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ABSTRACT

Cancer cells can evade immune surveillance effectively through many mechanisms. In chronic myeloid leukemia (CML), although the immune system is dysfunctional in newly diagnosed patients, tyrosine kinase inhibitor (TKI) therapy may be able to restore the immune system function through suppressing the cloned cells. Several clinical trials on cancer showed a correlation between the elevated level of IL-8 with either poor prognosis or poor response to some therapies. Here, the level of IL-8 among different responders CML patients on imatinib therapy was tested. The blood samples from failed responses and optimal responses CML patients were used to measure IL-8 levels by sandwich ELISA. The results of this study were as follow: IL8 level showed a significant increase in median level for failure responses CML patients 102.53 pg/mL in comparison to control group 2.50 pg/mL and optimal CML patients 4.22 pg/mL, while there was no significant difference between optimal and control groups from one side and different molecular responder CML patients. The immune responses by IL8 level looks unrelated to depth of molecular response and BCR-ABL transcripts level among the optimal responders CML patients.

Keywords: Chronic myeloid leukemia (CML), Imatinib mesylate, IL-8.

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INTRODUCTION

Leukemia is a cancer of the early blood-forming cells. Most often, leukemia is a cancer of the white blood cells, but some leukemias start in other blood cell types. Several types of leukemia are divided based mainly on whether it is acute (fast-growing) or chronic (slower growing) and whether it starts in myeloid or lymphoid cells. Different types of leukemia have different treatment options and outlooks.¹ There are four major types of leukemia Acute Lymphocytic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), Acute Myelogenous Leukemia (AML),² and Chronic Myeloid Leukemia (CML). Chronic myeloid leukemia is a myeloproliferative neoplasm associated with t(9;22) (q34;q11), the so-called Philadelphia chromosome. This chromosomal rearrangement creates the BCR-ABL fusion gene, which encodes BCR-ABL, a constitutively active tyrosine kinase.³ CML is characterized by a period of immune dysfunction present in patients at diagnosis before the commencement of tyrosine kinase inhibitor (TKI) therapy. This facilitates tumor progression

and self-preservation by preventing host development of anti-leukemia immune responses.

Interleukin 8 (IL-8), the first chemokine to be characterized, was discovered in 1987.⁴ IL-8, known as a pro-inflammatory chemokine, induces the accumulation of neutrophils along the vascular wall. The release of this cytokine is triggered by special inflammatory signals from different types of cells. IL-8 has a key role in the defense mechanism through the effects on neutrophil activity but continued and prolonged presence of IL-8 in circulation in response to inflammatory conditions may cause variable degrees of tissue injuries. Like most of peptide hormones or mediators, IL-8 transmits its signals through proper cell surface heptahelical receptors. In addition, IL-8 stimulates the mitogen activating protein kinase (MAPK) and tyrosine phosphorylation of cellular proteins. Blocking of IL-8 actions could be considered for therapeutic purposes.⁵ The primary receptor-binding domain of all chemokines is near terminal NH₂, and its antagonists can be obtained by truncation or substitutions in this region.⁴

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In this study, an assessment of immune response status by analysis of IL-8 level through different types of CML responses on imatinib treatment.

MATERIALS AND METHODS

Subjects

This study was conducted between November 2020 till March 2021 at Baghdad Teaching Hospital/Medical City. Sixty patients with CML were enrolled in the present study on imatinib mesylate therapy for more than 1 year duration. The response assessment of imatinib mesylate therapy for the studied groups followed the European Leukemia Net (ELN) 2020 criteria, 6 confirmed by blood film indices, and qRT-PCR results for BCR-ABL transcript. Thirty cases were with the major molecular response (p210 BCR-ABL transcript levels \leq 0.1% IS) and classified as optimal response group to imatinib therapy and another 30 case were with loss their molecular response (p210 BCR-ABL transcript levels $>$ 1% IS) with or without the hematological response and were classified as failure response group to therapy. The recent molecular data were taken from the patient's records within the maximum duration results of 3 months from sampling time. Twenty-eight apparently healthy volunteers, age and gender-matched samples were taken as a control group in the current study. At the time of sampling, blood count indices were obtained and calculated for subjects by an automated blood count analyzer and IL8 level assessment by ELISA test.

Statistical Analysis

Data were analyzed using SPSS software (v. 24). Descriptive statistics (means, median, and frequency) were conducted for the participants' parameters. Analysis of variance (ANOVA) and post-hoc (Tukey) test were used to compare the means of biomedical markers between the groups when the continuous variables having normal distribution. Kruskal Wallis test were used to measure the difference between the three groups. Mann-Whitney U test was used to measure the difference in the biomedical parameters between two groups. Spearman's correlation was used to measure the relationships among biomedical markers within each group.

RESULTS

The Characteristics of the Studied Groups

Sixty CML patients on imatinib mesylate therapy in this study were enrolled, 30 patients have an optimal response (MMoR) were registered with a mean duration of imatinib therapy (73.70 ± 37.64) months; mean age (45.70 ± 14.06) years; Male: Female ratio (1.7:1). The other 30 patients have a failure molecular and/or failure hematological response) were enrolled with a mean duration of imatinib therapy (63.80 ± 43.87) months; mean age (45.00 ± 14.31) years; Male: Female ratio (0.7:1). Twenty-eight matched age and gender healthy volunteers were considered as a control group with a mean age (45.75 ± 9.24) years; Male: Female (1:1).

Quantitative Genetic Data Analyses

Assessment of the degree of TKI response in all CML patients was done according to the results of qRT-PCR for p210 BCR-ABL transcript levels. The results of P210 BCR-ABL% differ significantly ($p < 0.001$) between the optimal and the failure responder CML patients with the highest P210 BCR-ABL transcript levels in the failure responder CML group (29.66 ± 24.89)%. All patients with optimal response were with a major molecular response (MMoR) (p210 BCR-ABL transcripts \leq 0.1% IS).

All optimal response patients had demonstrated a major molecular response (BCR-ABL \leq 0.1%), 63.33% of them had BCR-ABL levels ranged between (0.1–0.0032%). There was 46.67% of failure response patients group had failure molecular response, other 53.33% had both failure molecular response (FMR) and failure hematological response (FHR) and BCR-ABL levels were ($>$ 1%).

IL-8 levels in CML patients and control groups were measured using sandwich ELISA. Results showed that the median level of IL-8 in serum was higher among CML patients with failure response (102.53 pg/mL) that ranged between (6.09–376.09) pg/mL compared to the control samples

Table 1: IL-8 level distribution among different studied groups

Parameter	Control	Optimal response to TKI	Failure response to TKI	p-Value
IL-8 (pg/mL) (Range)	2.50 (0.16-9.22)	4.22 (0.16-13.28)	102.53 (6.09-376.09)	<0.001

* Values are presented as median (Interquartile range) using the Kruskal-Wallis test.

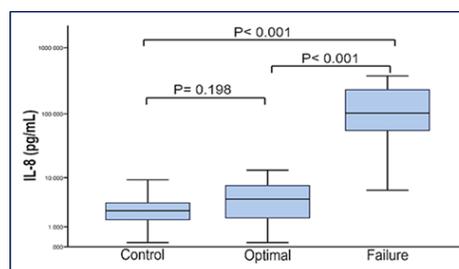


Figure 1: The difference in the median IL-8 level among different CML patients and control groups.

Table 2: The relationship P210 BCR-ABL percentage levels according to CML patients with IL-8

Parameter	P210 BCR-ABL level %	
	Optimal response to TKI	Failure response to TKI
IL-8 (pg/mL)	ρ -0.147	0.372
	p-Value 0.438	0.043

*Statistical significance at $p < 0.05$ according to spearman's correlation.

Table 3: The difference in IL-8 levels for CML patients with the different results P210 BCR-ABL transcript

Parameter		P210 BCR-ABL level%			
		0.1-0.0032% MMR	<0.0032% MMR	>1% FMR	>1% FMR & FHR
IL-8 (pg/mL)	Median (Range)	2.97 (0.16-9.84)	6.41 (0.16-13.28)	61.56 (6.09-239.84)	214.37 (24.22-376.09)
	p-Value	0.053		0.002	

*statistical significance at $p < 0.05$ according to the Mann-Whitney test.

(2.50 pg/mL) with a range of (0.16–9.22) pg/mL and optimal response CML patients (4.22 pg/mL), which ranged between (0.16–13.28) pg/mL, with a significant difference ($p < 0.001$) among the three groups, as shown in (Table 1).

There was no significant difference between optimal response CML patients compared to the control group with ($p = 0.198$), while the study showed a significant difference between failure responders CML patients and the control group with ($p < 0.001$) from one side and the optimal responders CML patients from the other side, as shown in (Figure 1).

Correlation Analysis

The correlation analysis showed a significant direct relationship between P210 BCR-ABL transcript and IL-8 levels ($p=0.043$) in the failure response CML patients group. While in the optimal response, CML patients had no significant relationship ($p=0.438$) (Table 2).

Depending on qRT-PCR results that are expressed as BCR-ABL % in a log scale, the optimal and failure responder CML patients were divided into four groups: the first group was considered if BCR-ABL levels ranged from (0.1 to 0.0032% IS) (log 3, log 4 and log 4.5 reduction level), whereas the second group BCR-ABL levels were less than 0.0032% IS (log 5 reduction level), the third and fourth group with $\geq 1\%$ IS BCR-ABL levels with or without failure hematological response (Table 3).

The IL-8 analysis in CML patients among FMR groups or FMR and FHR groups with clinical and pathological parameters illustrated a significant difference. While showed no significant differences in the optimal responders' patients with different molecular responses (log 3 reduction or log 4 or other deeper log 4.5 and 5 reduction levels) (Table 3).

Discussion

TKIs have a dual mode of action with a direct inhibitory effect on BCR-ABL tyrosine kinase and immuno-modulatory or suppressive effects. Sanmamed *et al.* reported that the chemokine IL-8 is an important biomarker in many types of cancer.⁷ Contradictory results have been observed between in vitro and *in vivo* studies.

Several in vitro studies have demonstrated the inhibitory effects of imatinib on immune responses.^{8,9}

IL-8 levels were increased in patients with various cancers, and higher circulating IL-8 levels seem to correlate with higher stage, grade and tumor burden.^{10,11} Furthermore, Ciracia *et al.*

mentioned that the treatment of CML patients with imatinib causes IL-8 down-regulation in comparison to untreated patients.¹² Results in this study are related to an increase of early myeloid progenitor among the failure group and loss of the molecular response.

It was also revealed that the expression of IL-8 indicated that it may serve as an important predictor for monitoring TKI efficacy.¹³ This study showed a lower IL-8 level in the optimal responders CML patients compared to failure responders groups with a significant difference ($p < 0.001$), while the IL8 level among different of BCR-ABL transcripts levels for the optimal response CML patients was insignificant different making the MMR at 0.1% fair enough to induce good and stable immune response regardless the deeper response.

Conclusions

IL-8 assessment as a pro-inflammatory response was important immunological biomarker in CML patients among different responses on imatinib therapy. Also, the significant high level of IL-8 level in CML patients with failure response versus the optimal response in CML patients might play an important role in the immunological body response and pathogenesis of uncontrolled progression of CML; while 0.1% of BCR-ABL might be enough to make an ideal immune response for disease control mimic to deep molecular response in CML patients.

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