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Serum level of human transforming growth factors β3 in Iraqi patient with chronic myeloid leukemia

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Abstract:

BACKGROUND: The Philadelphia chromosome serves as the molecular marker for chronic myeloid leukemia (CML) result from fusion oncogene, leading to genetic instability including chromosomal aberrations and common altered genes that regulate cell proliferation and apoptosis. Transforming growth factor-β (TGF-β) signaling pathway is an important regulator of cellular functions, such as proliferation, differentiation, migration, and cell survival.

OBJECTIVES: The objective of this research was to investigate the role of TGFs-β3 as predictive biomarker on disease progression.

MATERIALS AND METHODS: This study includes three groups (50) individuals: newly diagnosed CML patients (male: 28 and female: 22), (50) CML chronic phase (male: 25 and female: 25), and (50) apparently healthy volunteers (male: 30 and female: 20). The National Center of Hematology at Mustansiriyah University admitted the patients. An analysis of each patient was diagnosed using a complete blood count, a bone marrow test, and a BCR-ABL gene test. ELISA technique was applied to assess the serum level of TGFs-β3.

RESULTS: the results displayed high significant differences among patients (newly diagnosed) compared to the chronic phase, it was 59.7517 and 39.9167 pg/mL, respectively, and high significant differences among patients (newly diagnosed) compared to control, it was 59.7517 and 36.8861 pg/mL, respectively, as well as the serum level of TGF-β3, was elevated with some hematological marker.

CONCLUSION: Elevated TGF-β levels can promote the development of myelofibrosis and some hematologic malignancies by influencing the immune system.

Keywords:

chronic myeloid leukemia, enzyme-linked immunosorbent assay, transforming growth factor beta-3

Introduction

A cancer of the hematopoietic stem cells is called chronic myeloid leukemia (CML) known for having chromosomes 9 and 22 translocated; the translocated chromosome is also known as the Philadelphia chromosome.[1] Through the activation of several intracellular signal transduction pathways, including Ras/Raf/MAPK, JAK/STAT3, and PI3K/AKT through its protein tyrosine kinase, BCR/ABL is necessary for the pathogenesis of CML. This interference with the formation of hematopoietic stem cells or progenitor cells occurs.[2]

Tyrosine kinase inhibitors (TKIs), which block the chimeric oncoproteins (p210BCR-ABL1), are the fundamental of CML treatment.[3] The average age of the population is reflected in the 50–60-year median age of onset[4] CML is divided into three phases: chronic phase, accelerated phase, and blast phase, TKIs a targeted treatment that has been shown to improve CML patients' quality of life and have significant response rates.[5]

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There are many studies in Iraq to predictive biomarkers for CML progression and development.[6-9]

Transforming growth factor (TGF) beta-3 is a protein that the TGF-β3 gene encodes, known as a cytokine, which is involved in cell differentiation, embryogenesis, and[10] cytokines that play a significant role in controlling a range of cellular functions, including immune response, bone morphogenesis, motility, adhesion, differentiation, cell cycle progression, and development in multi-organ systems.[11] Tumorigenesis is one of the many diseases that could result from TGF-β3 and its downstream mediators becoming more or less functional. In particular, TGF-β serves as a tumor suppressor in the initial phases of cancer and is essential in eradicating cancerous cells by inhibiting the proliferation and differentiation of cells, which in turn initiates the apoptotic process.[12] The signaling mechanism of TGF-β plays a pivotal and dual role in the advancement of cancer in humans. TGF-β not only stimulates autophagy, apoptosis, and cell cycle arrest in cancerous cells, but it also increases the stemness, tumor cell motility, angiogenesis, the bone morphogenetic proteins epithelial-mesenchymal transition (EMT), and invasion, indicating that it has a dual effect of supporting and suppressing tumor growth.[13]

TGF-β is an important regulator of the innate and adaptive immune systems, suppressing inflammation and serving as a general upholder of immune tolerance.[14] TGF-β deficiency can lead to inflammation and fibrosis, while excess TGF-β activity suppresses the immune system and promotes tumor growth. Tumorigenesis is supported by TGF-β-induced immunosuppression, while its deficiency can lead to inflammation and fibrosis. To reduce excessive adaptive immunity in the early postnatal period, TGF-β directly affects T cells.[15]

Materials and Methods

This study consists of three groups with CML. The patients' ages ranged from 35 to 62 years, first group includes 50 newly diagnosed CML patients (males: 28 and females: 22), second group consist of 50 CML patients treated with TKI where the p210 BCR-ABL transcript levels were < 0.1% IS, indicating the full molecular response (male: 25 and female: 25). Third group includes another 50 apparently healthy volunteers (male: 30 and female: 20). The personal information such as age, sex, duration of disease, and reverse transcription-quantitative polymerase chain reaction result for BCR-ABL1 IS (%) were also included in the study. All patients are diagnosed according to BCR-ABL gene testing, bone marrow assessment, and complete blood count (CBC).

The samples were admitting from the National Center of Hematology/Mustansiriyah-University, this study was conducted in Baghdad during the period of March 2023 to November 2023.

The study's design was accepted by the Institute of Genetic Engineering and Biotechnology for Postgraduate Studies/University of Baghdad. Written informed consents were obtained from all patients and apparently healthy control group.

Patients exclusion criteria

Persons under the age of 18, patients suffering from liver or kidney disease along with those who suffer from hepatitis B and C, and patients with HIV were also excluded from the study.

Collecting of blood samples

A 5 mL sample of blood was taken from each individual in each group, 3 mL blood was maintained in tubes of EDTA for the CBC, and 2 mL for ELISA.

For determining the level of TGFB3 in serum of CML patients and apparently healthy by using ELISA kit (SUNLONGBIOTECH/ China).

Statistical analysis

The results used one-way ANOVA. $P \leq 0.05$ was used to determine statistical significance. Using Pearson correlation to determine the correlation between two quantitative variables, receiver operating characteristic (ROC) was used.

Results

The concentration of the serum level of TGF-β3 in newly diagnosed CML patients significant than in chronic phase CML patients was 59.7517 and 39.9167 pg/mL, respectively, while newly diagnosed CML patients was highly significant than in control was 59.7517 and 36.8861 pg/mL, respectively, it is shown in Table 1.

TGF-β3 (pg/mL) levels showed high significant differences among patients (newly diagnosed) compared to chronic phase and control in the current study [Figure 1].

The receiver operating characteristic curve

The two patients state that the ROC analysis may distinguish between "diseased" and "nondiseased".[16] The

Table 1: Serum level of Human transforming growth factors β3

Groups	Mean	SD	SEM	*P*
Control	36.8861[c]	3.19981	1.53996	0.001**
Chronic phase	39.9167[b]	2.65492	0.41463	
Newly diagnosed	59.7517[a]	4.19598	0.59340	

[a,b,c]Different leter mean significant. **High significant when $P \leq 0.01$ between three groups, CP=Chronic phase, SD=Standard deviation, SEM=Standard error of mean

Table 2: Receiver operating characteristic curve data of the transforming growth factor-β3

Parameters	AUC	Explanation	*P*	The best cutoff	Sensitivity (%)	Specificity (%)
TGF	0.99	Excellent	0.001	50.66	100	98

TGF=Transforming growth factor, AUC=Area under the curve

area under the curve is a useful metric that characterizes the intrinsic validity of diagnostic tests by combining measures of sensitivity and specificity.[17]

Results in Table 2 revealed that the cutoff point between sensitivity (100) and specificity (98) for TGF-β3 was 50.66. Result revealed that the area under the curve for TGF-β3 was 0.99 and gives significant differences $P \leq 0.05$. When the value of the area under the curve equals 0.001.

Correlations between transforming growth factor-β3 serum level and hematological markers

This finding indicated a strong association between the TGF-β3 serum level it was observed just with the hemoglobin and also showed there was a high significant correlation between white blood cells and platelets and also high significant between platelets and hemoglobin will no significant correlation between white blood cell and hemoglobin shown in Table 3.

Table 3: Correlations between transforming growth factor-β3 serum level and clinical marker hematology

	TGF	WBC	HB	PLT
TGF				
Pearson correlation	1	−0.098	0.170*	−0.140
Significant (two-tailed)		0.235	0.037	0.087
WBC				
Pearson correlation		1	−0.164*	0.347**
Significant (two-tailed)			0.045	0.000
HP				
Pearson correlation			1	0.400**
Significant (two-tailed)				0.000
PLT				
Pearson correlation				1
Significant (two-tailed)				

*Correlation is significant at the 0.05 level (two-tailed), **Correlation is significant at the 0.01 level (two-tailed). WBC=White blood cell, HP=HB hemoglobin, PLT=Platelets, TGF=Transforming growth factor

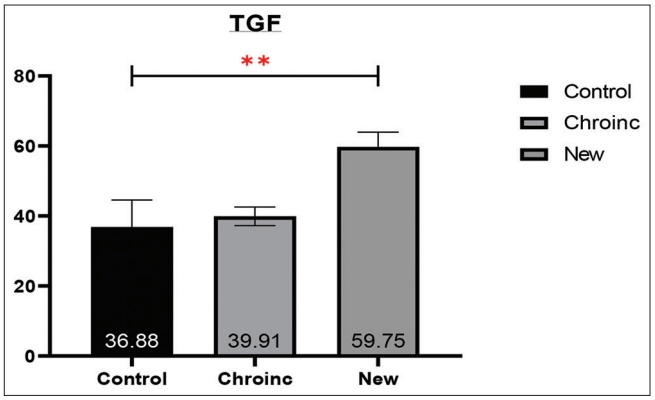

Figure 1: The serum level of transforming growth factor-β3 in patient's groups compare with apparently healthy control. TGF: Transforming growth factor

Discussion

Current research, agrees with research by Mtashar for AML patients, that found significant statistical differences in serum levels of interleukin-15, TGF-β, and AML at diagnosis and control subjects[18] while TGF-β3 inhibits chronic myelogenous leukemia hematopoiesis by inducing Fas-independent apoptosis.[19]

Cytokine dysregulation has been connected to the etiology of several hematological malignancies, including AML, and plasma cytokine levels have been connected to the course and prognosis of the disease.[20]

For hematopoietic progenitor cells, the TGF-β signaling pathway is a key antiproliferative and differentiation signal, successfully inhibiting cell cycle progression and encouraging differentiation (Dong and Blobe 2006).[21] TGF-β suppresses tumors, however, in tumor cells, it loses its anti-proliferative effect and turns into an oncogenic factor.[12,22] TGF-β inhibits the advancement of the cell cycle through controlling the transcription of cell cycle regulators. During cell cycle division, anti-proliferative responses can be produced at any point; however, they are only effective during the G1 phase. TGF-β3 mRNA expression was decreased in a Double-Hit Model of Neonatal Mice with Bronchopulmonary Dysplasia.[23]

TGF-β3 gene upregulation in patients with bone marrow fibrosis, targeting up-regulated fibrosis-associated genes, like TGF-β3, may enhance the therapeutic response to CAR19.[24]

Cytokines or what is known as motorized cells are dissolved molecules that the body produces from its cells, from tissue injury, or from a specific illness such as cancer.[25,26]

Conclusion

Through their impact on the immune system, increased levels of TGF-β can facilitate the progression of certain hematologic malignancies and myelofibrosis.

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Conflicts of interest

There are no conflicts of interest.

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