The Influence of ADAR1 enzyme on BCR-ABL1 mutation in Chronic Myeloid Leukemia patients

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Abstract:

Background: Chronic Myeloid Leukemia is driven by the BCR-ABL fusion protein, a potent tyrosine kinase that arises from the Philadelphia chromosome. While tyrosine kinase inhibitors have revolutionized Chronic Myeloid Leukemia treatment, resistance remains a challenge. Recent research highlights the role of adenosine-to-inosine (A-to-I) RNA editing, mediated by ADAR1 enzymes, in various cancers. Aberrant ADAR activity has been implicated in hematological malignancies, suggesting potential new therapeutic avenues for Chronic Myeloid Leukemia.

Aim of study: Estimation of ADAR1 enzyme among Chronic Myeloid Leukemia patients and correlation with BCR-ABL1 ratio.

Materials and methods: This case-control study examined 120 Chronic Myeloid Leukemia patients (including newly diagnosed and treated) and 30 healthy controls, investigating the relationship between BCR-ABL1 gene, ADAR1 enzyme levels, and treatment outcomes (response vs. failure) in Chronic Myeloid Leukemia. The study analyzed blood samples from all participants, including those receiving imatinib or other tyrosine kinase inhibitors. Detection of BCR-ABL1 by conventional PCR as well as estimation of ADAR1 enzyme using sandwich ELISA.

Results: ADAR1 enzyme levels are elevated in Chronic Myeloid Leukemia patients, especially those with treatment relapses and BCR-ABL1 mutations. ADAR1 enzyme elevated among CML patients with a BCR-ABL1 mutation

Conclusion: ADAR 1enzyme levels are higher in Chronic Myeloid Leukemia patients with relapses compared to those responding to treatment. This suggests a potential role for ADAR 1 enzyme in disease progression and resistance to therapy.

Keyword: ADAR1, CML, BCR-ABL, Philadelphia, TKIs

Introduction:

The clonal myeloproliferative disease known as Chronic Myeloid Leukemia (CML) is caused by multipotent hematopoietic stem cells (HSCs). The distinctive cytogenetic anomaly that distinguishes CML is the translocation of t(9;22)(q34;q11) between the long arms of chromosomes 9 and 22, which produces a derivative 22q- that is commonly referred to as the" Philadelphia chromosome**"** [1,2] which results in the constitutive activation of the BCR-ABL oncoprotein is a potent tyrosine-kinase signaling protein that drives cell proliferation and reduces apoptosis, which causes leukemia. [3]

Tyrosine Kinase Inhibitors TKIs, such as imatinib, have dramatically improved CML outcomes by targeting BCR-ABL. However, resistance mechanisms, including mutations in BCR-ABL and alterations in cellular signaling pathways, can lead to treatment failure. [4]

A-to-I editing is a common editing RNA process in humans which is mediated by ADARs. These enzymes, which are responsible for the editing, are located in the nucleus and/or cytoplasm in physiological conditions, where they convert adenosines (A) to inosines (I) on double stranded mRNA. Some tumors show abnormal ADAR-mediated-editing which is perhaps the most widely recognized form of ADAR dysfunction. Recently, the biology of ADARs especially in the context of their functional implications in hematological malignancies was uncovered.[5]

ADAR1 plays a critical role in maintaining cellular homeostasis by editing a wide range of RNA transcripts. It has been shown to regulate innate immune responses, RNA splicing, and protein translation.[6] In cancer, ADAR1 can promote tumorigenesis by editing oncogenes, tumor suppressors, and immune checkpoint genes. For example, ADAR1-mediated editing of the interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) gene can inhibit its antiviral function, promoting tumor growth.[7] Recent studies have highlighted the role of RNA editing in cancer pathogenesis, with adenosine deaminase acting on RNA 1 (ADAR1) being a key regulator.[8] The potential role of ADAR1 in CML pathogenesis has not been extensively studied. However, recent findings suggest that ADAR1 may contribute to BCR-ABL-mediated leukemogenesis. ADAR1 has been shown to be upregulated in CML cells, and its expression correlates with disease progression. Furthermore, ADAR1 inhibition has been shown to induce apoptosis in CML cells.[5,8,9]

Several mechanisms could underlie the impact of ADAR1 on BCR-ABL activity: **Direct Editing of BCR-ABL mRNA,** ADAR1 could directly edit the BCR-ABL mRNA,

leading to changes in protein structure or function. This could alter BCR-ABL kinase activity, substrate specificity, or sensitivity to TKIs. **Editing of BCR-ABL Signaling Pathways,** ADAR1 could edit mRNAs encoding proteins involved in BCR-ABL signaling pathways, such as growth factor receptors, transcription factors, or cell cycle regulators. This could indirectly modulate BCR-ABL activity and contribute to leukemogenesis.[9] **Regulation of Cellular Stress Responses,** ADAR1 has been shown to regulate cellular stress responses, such as the unfolded protein response and DNA damage response.[10]

These pathways can be activated in CML cells due to BCR-ABL-induced cellular stress. ADAR1 could modulate these responses, impacting CML cell survival and proliferation. [10]

This study aimed to investigate the association between genetic factors (BCR-ABL1), treatment outcomes, and ADAR enzyme in CML patients

Materials and methods:

This case-control study examined 120 chronic myeloid leukemia (CML) patients from the National center of Hematology / Mustansiryiah university /Baghdad, over the period between January 2021 and February 2023., including 20 newly diagnosed individuals and 80 undergoing treatments. Among the treated patients, 65 received imatinib, while 35 were treated with other tyrosine kinase inhibitors (TKIs). Treatment response was observed in 69 out of 80 treated patients, while 31 experienced treatment failure. The study also included 30 healthy individuals as controls, matched to the patients by age and gender, CBC, Peripheral blood smear and bone marrow aspiration and BCR-ABL ratio data obtained from CML patients undergoing treatment. Blood samples were collected from all participants: 2 mL for analyzing BCR-ABL1 gene and 3 mL for measuring serum levels ADAR enzyme.

Inclusion criteria, new diagnosis and treated CML patients of any sex. The age of patients from 18 to 65 years and the treated patient on TKIs.

Exclusion criteria, the age under 18 years old, pregnant, or lactating women, and patients ongoing active systemic infection.

Detection of BCR-ABL1 gene: The process involve to key steps: DNA extraction from blood sample used the G-spin™ Total DNA extraction kit (Intron / Korea) following this step Polymerase chain reaction (PCR) is employ to amplified a specific target region from a DNA template. This is achieved by specific designed

oligonucleotides that bind to target sequence, enable to replication of that particular DNA segment.

The detection of BCR-ABL1 gene (429bp) by specific primer (IDT/Korea) final concentration 10 pmol/µl, the primers were designed by the NCBI Primer-BLAST tool.

Forward :CTGAATGTCATCGTCCACTCA

Reverse :CGCGTCTTTGCTTTATTCACA

PCR amplification was performed using a standard thermal cycler (Biometra- Germany). A volume of 2 µl of template DNA was supplied to PCR master mix tubes. followed by the addition of 1 µl each of forward and reverse primers to the same PCR master mix tubes. A volume of 25 µl of distilled water was added to the PCR-premixed tubes using conventional PCR method.

PCR amplification was conducted using a typical thermal cycler (Biometra - Germany) according to the following protocol: Approximately 4 µl of a DNA sample was introduced into PCR master mix tubes (12µl) . Two microliters of forward and reverse primers were added to each PCR master mix tube. A volume of 5 µl of distilled nuclease-free water was introduced into the PCR master mix tubes, resulting in a final volume of 25 µl.

Thermal Cycles Conditions: The amplification of the target regions of BCR-ABL1 gene was performed using primers, according to mentioned conditions in the following table. Annealing temperature provided by manufacture instruction (IDT/Korea).

Amplification conditions ***BCR-ABL1*** **gene in patients with CML.**

Gene	Initial denaturation Tm*	Denaturation Tm*	Annealing Tm*	Extension Tm *	Final extension Tm*	No. of cycles
BCR-ABL1	95C^0 /5 min.	95C^0 /1 min.	53 C^0 /1 min.	72 C^0 /2 min.	72 C^0 /5 min.	40
Tm: Temperature						

PCR products of target regions **BCR-ABL1 gene** were electrophoresed on 1.5 % agarose at 85 V for 1h and visualized by red safe stain. Image

were capture using a gel documentation system.

Estimation of *ADAR1* enzyme Concentration in Serum of Patients and control group using experimental kit based on quantitative sandwich enzyme-linked Immunosorbent assay (ELISA) (Sandwich ELISA **)** (MyBioSource Biotechnology Inc.\USA**)**

Ethical considerations; All participants provided written informed consent prior to joining the study, and the research protocol received approval from the Ethics Review Committee of the College of Dentistry at Mustansiriyah University.

Statistical analysis: To evaluate the significance of the variables studied, the Chi-square test was used. All statistical analyses were performed using SPSS version 28 software (IBM, Delaware, Chicago, USA). A p-value of less than 0.05 was considered statistically significant.

Results:

Age and sex distribution among study CML patients' groups were matching with the control group (P = 0.62). The sex ratio among the new diagnosis group and treated group was 1.5 and 1.08, respectively, which was match with control group ratio 1.5 (P = 0.565) [Table 1].

Table 1. Age and Sex distribution between patients with CML groups and controls groups.

Parameters		Patients (n=120)		Controls (n=30)	p-value
		New diagnosis (n=20)	Treated (n=100)		
Age Mean±SD		35±12.1	51±11.89	44±13.7	0.62
Gender	Male	12(60%)	52(52%)	18 (60%)	0.565
	Female	8(40%)	48(48%)	12 (40%)	
Gender	Ratio	1.5:1	1.08	1.5	

In the current study the 20 cases were new diagnosis CML. At the time of diagnosis, White blood cell (WBC) count average 173.5x10⁹/. Leukocytosis more than 100x10⁹/L was noted in 80% of cases. Mean Hb was 12.1g/l. The platelets count mean was of 283x10⁹/L. Among a group of CML patients undergoing treatment, 65 out of 100 were receiving imatinib, while the remaining 35 were treated with other tyrosine kinase inhibitors, such as nilotinib and bosutinib. White blood cell (WBC) count means

173.5x10⁹/. Mean Hb was 12.3g/l. The platelets count mean was of 323x10⁹/L. BCR -ABL1 was found in 68% of cases table (2).

Table 2. Hematological and molecular changes in CML groups in comparison to control groups.

Parameters		Patients (n=120)		Controls (n=30)
		New diagnosis (n=20)	Treated (n=100)	
WBC x10^9 /L mean ±SD		173.5±88.13	7.7±5.47	6.6±0.75
Platelets x10^9 /L mean ±SD		283±138	323±312	246.6±56.3
Hb g/dl mean ±SD		12.1±1.65	12.3±1.65	13.1±1.4
PCV mean ±SD		36.9±5.21	37.5±6.9	40.1±4.5
BCR-ABL1 ratio mean ±SD		20.6±6.8	6.3±12.6	0
BCR-ABL1 mutation	Positive	20 (100%)	68(68%)	0
	Negative	0	32(32%)	30(100%)
SD: standard deviation				

Comparison between CML groups, controls group according to BCR-ABL1 gene expression, and ADAR1 enzyme level:

There are statistically significant differences among groups according to BCR-ABL 1gene expression (p value < 0.001). According to The (ADAR) enzyme level, there are significant differences between new diagnosis CML and control group), p value (< 0.001) and there are significant differences between treated group and control group p value (<0.001). while there are no significant differences between new diagnosis CML and treated group p value (0.326) table (3).

Table 3. Comparison between new CML, treated patients and control groups according to BCR-ABL1 gene expression and ADAR1 enzyme level.

Parameters	Patients (n=120)		Controls (n=80)	p-value
	New diagnosis (n=20)	Treated (n=100)		
BCR-ABL1 ratio Mean±SD	20.6±6.8	6.3±12.6	0	*<0.001 **<0.001 ***<0.001
ADAR enzyme Mean±SD	9.3±5.8	10.7±7.4	2.9±1.88	*0.326 **<0.001 ***<0.001

*** Comparison between New diagnosis CML and treated patients.**
**** Comparison between New diagnosis CML patients and control group.**
***** Comparison between treated patients with cml and control subjects.**
SD: standard deviation

Comparison between newly diagnosis CML, treated patients with respond to treatment and relapse in BCR-ABL1 gene expression level and ADAR1 enzyme level.

To BCR-ABL1 gene expression there are statistically significant differences between new diagnosis group and response to treatment group (p-value: <0.001) also between new diagnosis group and relapse patients' group (p-value: 0.03) while non-significant differences between respond to treatment and relapse group (p-value: 0.59).

In order to ADAR1 enzyme level, there are statistically significant differences between new diagnosis CML and relapse group as well as with control group, p value (< 0.001) while there are no statistically differences between new diagnosis group and response to treatment group p value (<0.73)table (4).

Table 4. Comparison between new diagnosis CML, treated patients respond to treatment and relapse in BCR-ABL1 gene expression and ADAR1 enzyme level.

Parameters	New diagnosis (n=20)	Treated (n=100)		p-value
		Response to treatment (n=69)	Relapse (n=31)	
BCR-ABL1 ratio Mean±SD	20.6±11	4.7±12.6	9.8±14.1	*<0.001 **0.03 ***0.59
ADAR enzyme Mean±SD	9.3±5.8	9.17±7.95	14.4±4.71	*0.73 **<0.001 ***<0.001

The distribution of BCR-ABL1 mutations across study groups

BCR-ABL mutation was found in all new diagnosis CML patients (100%) while in treated patients was found in 68 patients (68%) out of 100 patients. The p-value associated with the correlation between BCR-ABL1 mutation, and the groups is less than 0.001, indicating a highly significant association. Table (5).

Table 5 Distribution of BCR -ABL 1 mutation between CML patients' groups

Mutations		New diagnosis (n=20)	Treated (n=100)	p-value
BCR-ABL1	Positive	20(100%)	68(68%)	<0.001**
	Negative	0	23(23%)	
	Negative	13(65%)	64(64%)	
**Significant p-value at 0.01				

The BCR-ABL1 mutation among respond and not respond patients with CML, 37 (53.6%) were positive out of 69 (100%) in response to treatment patients while among not respond patients BCR-ABL1 mutation was positive in all group. The p-value associated with the correlation between BCR-ABL 1mutation and treatment response is less than 0.001, indicating a highly significant association table 6.

Table 6. Distribution of BCR -ABL mutation CML patients' response to treatment and not respond.

Mutations		CML patients on treatment (n=100)		p-value
		Respond (n=69)	Not respond. (n=31)	
BCR-ABL	Positive	37(53.6%)	31(100%)	<0.001**
	Negative	32(46.4%)	0	
**Significant p-value at 0.01				

Comparison between BCR-ABL 1 mutation and ADAR 1enzyme level

The table 7 presents data on mutations in CML (Chronic Myeloid Leukemia) patients and their corresponding values ADAR enzyme, along with p-values:

BCR-ABL 1mutation:
Positive (n=88): CML patients with a BCR-ABL1 mutation have a mean ADAR1 enzyme value of 15.5±9.44.
Negative (n=32): CML patients without a BCR-ABL1 mutation have a mean ADAR 1enzyme value of 10.55±5.8.

The p-values 0.02 for ADAR1 enzyme suggest that there is statistically significant difference in the ADAR1 enzyme levels between patients with and without a BCR-ABL1 mutation.

Table 7. Comparison between BCR-ABL mutations and ADAR enzyme

Mutations		CML patients (n=100) ADAR1 enzyme mean ±SD	p-value
BCR-ABL1	Positive(n=88)	15.5±9.44	0.02*
	Negative(n=32)	10.55±5.8	
*Significant p-value at 0.05 SD; Standard deviation			

Correlation between BCR-ABL ratio before and after treatment in CML patients

Table 8 shows a positive correlation between ADAR 1enzyme activity and BCR-ABL1 ratio in chronic myeloid leukemia (CML) patients, both at diagnosis and after treatment. The correlation coefficient (r) was 0.185 at diagnosis (p = 0.043), indicating a weak but statistically significant association. After treatment, the correlation strengthened to 0.309 (p = 0.002), suggesting a more pronounced link between ADAR 1enzyme activity and BCR-ABL1 ratio levels. This suggests that ADAR 1enzyme activity may play a role in the response to treatment in CML patients.

Table 8: Correlation between BCR-ABL ratio before and after treatment

Parameters		BCR-ABL1 ratio at diagnosis	BCR-ABL 1ratio after treatment
ADAR 1enzyme	r	0.185*	0.309**
	p	0.043	0.002

Discussion:

Chronic myeloid leukemia is described as a condition of the clonal progenitor of the hemopoietic tissue in which the production of new myeloid blast cells is accelerated while the rate of apoptosis is decreased. The Philadelphia (Ph) chromosome is formed as a result of a translocation between chromosomes 9 and 22 long arms (t (9; 22) (q34; q11.2), which causes the abnormal gene known as BCR-ABL1 to form. BCR-ABL1 is

responsible for the pathology of the disease. [11]

In a current study, the average age of patients with a new diagnosis is 35 years, group has an average age of 51 years. However, the p-value of 0.62 suggests that the difference in age between the groups is not statistically significant. In terms of gender, the data indicates a slightly higher proportion of males in the patient groups compared to the control group, although this difference is not statistically significant. The result are compatible with epidemiological data that sows that the CML patient's age differs at the time of analysis depicts the median age ranges among 52–64 year[12], another study shows that CML usually presents at a median age (35–45 years) in Asians and the global incidence rate of CML is 15/1,000,000 per year with a male to female ratio of 1.34. [13,14]

The ADAR protein level among new diagnosis CML, treated group and control group there was no significant differences between new diagnosis and treated cml group. And there were significant differences between control groups and other CML groups. This finding aligns with previous studies indicating that ADARs have significant implications in both developmental processes and disease pathogenesis, with an emerging association with cancer advancement. The involvement of ADAR1 in many cancer types has been extensively studied, and it has been shown to mostly exhibit pro-oncogenic properties. The contribution of ADAR1 to cancer development has been linked to a wide range of pathways, as discussed by Baker *et al.* [15] The presence of aberrant ADAR-mediated editing is a notable characteristic seen in several types of malignancies. Significantly, the biological activities of ADARs and their functional significance in haematological malignancies have been recently elucidated. [5,16]

The mechanism of ADAR-mediated RNA editing has the capacity to influence a wide range of biological events, ADAR-mediated RNA editing plays a critical role in various post-transcriptional regulatory mechanisms, including RNA interference, "microRNA function, RNAstability, localization, nu clear retention, degradation, and alternative splicing.[17] Furthermore, elevated levels of ADAR-mediated RNA editing activity may indicate a reversion to a primitive transcriptional program characteristic of embryonic stem cells, suggesting a potential link between RNA editing and the regulation of pluripotency or cellular differentiation. This highlights the broader implications of ADAR activity in maintaining cellular identity and function. [18]

ADAR enzyme levels show significant differences between newly diagnosed CML patients and treated patients. Additionally, within the treated patients the RNA editing enzyme ADAR1 catalyzed the conversion of adenosine two inosine within double- stranded RNA (dsRNA)

substrates. As a multifunctional protein, ADAR1 plays a critical role in regulating diverse physiological processes, such as embryonic developments, cell differentiation, and immune regulation. Additionally, it's functional versatility has significant implications for the advancement of gene editing technologies, highlighting its potential as a tool for precision genetic modification and therapeutic applications, [19] ADAR1 may promotes therapeutic resistance of a broad array of human malignancies. [20] The research conducted by Jiang et al. (2013) provided evidence that ADAR-1-mediated RNA editing contributes to the transformation of myeloid progenitor cells into leukemia (LSC) in chronic myeloid leukaemia (CML). This transformation is facilitated by the upregulation of the myeloid transcription factor PU.1 and the generation of aberrantly spliced variants of GSK3β.[9]

ADAR enzyme and BCR-ABL ratio at diagnosis: They exhibit a weak positive correlation ($r = 0.185$, $p = 0.043$), suggesting a potential link between ADAR enzyme levels and the BCR-ABL ratio at CML diagnosis this result agreement with Jiang and their colleges that showed ADAR 1 found in both respond and not respond patients which is agreement with study that showed ADAR 1 may ,be detection in chronic phase, crisis phase of CML. [9]

BCR-ABL ratio at diagnosis and BCR-ABL ratio after treatment: A strong positive correlation ($r = 0.469$, $p < 0.001$) implies that the BCR-ABL ratio at diagnosis is related to the ratio after treatment, indicating its predictive value and this result agree with many studies that showed there were relationship between BCR-ABL at diagnosis and response or not respond to treatment. [21,22]

Conclusion:

ADAR enzyme levels are elevated in CML patients, particularly those experiencing relapse. This suggests a potential link between ADAR activity and disease progression. Furthermore, ADAR activity may be associated with BCR-ABL mutations, suggesting that it could play a role in the development or maintenance of CML. While the exact mechanisms are still under investigation, these findings suggest that targeting ADAR1 could be a promising avenue for CML treatment.

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