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MicroRNA 21 Fails to Predict Tyrosine Kinase Inhibitor Response in CML: MicroRNA 21 Gagal Memprediksi Respons Inhibitor Kinase Tirosin pada Leukemia Mieloid Kronis (CML)

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Abstract

Chronic myeloid leukemia is characterized by the BCR-ABL fusion gene and is routinely treated with tyrosine kinase inhibitors, although treatment resistance remains a clinical challenge. MicroRNA 21 has been widely reported as an oncogenic microRNA and proposed as a potential biomarker for predicting therapeutic response in chronic myeloid leukemia. This study aimed to evaluate the association between microRNA 21 expression levels and clinical response to tyrosine kinase inhibitor therapy in chronic myeloid leukemia patients. A cross-sectional single-center study was conducted involving 50 Philadelphia chromosome–positive chronic myeloid leukemia patients receiving tyrosine kinase inhibitors. MicroRNA 21 expression was quantified using real-time quantitative polymerase chain reaction, and treatment response was classified according to European LeukemiaNet 2020 criteria. Comparative and correlation analyses were performed to assess associations between microRNA 21 expression and hematological and molecular response parameters. The results demonstrated no statistically significant difference in microRNA 21 expression between good and poor responders, and no meaningful correlation with treatment response indicators. This finding contrasts with earlier studies that identified microRNA 21 as a predictor of resistance when measured at diagnosis. The novelty of this study lies in demonstrating that post-treatment microRNA 21 expression lacks prognostic value in predicting ongoing tyrosine kinase inhibitor response. These findings suggest that microRNA 21 should be interpreted cautiously as a biomarker and highlight the need for longitudinal biomarker assessment to improve precision medicine strategies in chronic myeloid leukemia.

_ Chronic Myeloid Leukemia, MicroRNA 21, Tyrosine Kinase Inhibitors, Treatment Response, Biomarker Evaluation

Highlights:

- MicroRNA 21 shows no association with TKI treatment response in CML patients
- Post-treatment microRNA 21 lacks prognostic utility for therapy outcomes
- Findings challenge microRNA 21 as a universal resistance biomarker

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Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm with an annual incidence of two cases per 100,000, constituting about 15% of newly diagnosed adult leukemia cases. The CML-specific mortality rate is low, at 0.5%–1%. CML was the first cancer linked to a chromosomal defect, specifically the Philadelphia chromosome (Ph), which arises from the reciprocal translocation t(9;22). This translocation fuses the Abelson murine leukemia (ABL) gene on chromosome 9 with the Breakpoint Cluster Region (BCR) gene on chromosome 22, creating the BCR-ABL oncogene. This hybrid gene produces a constitutively active tyrosine kinase oncoprotein, which drives the uncontrolled growth and division of CML cells.[1]

The standard treatment for CML involves Tyrosine Kinase Inhibitors (TKIs), a class of pharmaceutical drugs approved by the FDA that interfere with protein kinase signal transduction pathways. The BCR gene contains several breakpoint regions (M-BCR, m-BCR, µ-BCR), which determine the type of BCR-ABL transcript produced. The most common transcripts in CML are e13a2 and e14a2, both encoding the p210 oncoprotein, which possesses the constitutive tyrosine kinase activity central to leukemogenesis.[2]

Non-coding RNAs, unlike coding RNAs (like mRNA), regulate various levels of gene expression without encoding proteins. MicroRNAs (miRNAs) are a category of small , single-stranded, non-coding RNAs (approximately 22–23 nucleotides long) that act post-transcriptionally. Their primary function is to control biological processes by "silencing" genes, typically by promoting mRNA degradation or repressing its translation. However, the function of miRNAs is complex; they can also indirectly increase protein expression by breaking down natural inhibitors of certain mRNAs.[3]

MicroRNA-21 (miR-21) is the most frequently upregulated miRNAs of cancer, often referred to as an oncomiR. It targets multiple tumor suppressor genes linked to apoptosis, invasion, and proliferation, thereby contributing to tumorigenesis. Studies have suggested that miR-21 is linked to chemotherapy resistance and functions as a pro-survival and anti-apoptotic factor. Higher levels of miR-21 expression have been reported in CML patients compared to healthy controls at diagnosis, with expression levels correlating with disease stage (higher in CML-BP and lower from CML-AP to CML-CP). The findings propo a potential role for miR-21 as a biomarker for diagnosis and prognosis in CML, and some authors have reported that Imatinib reduces miR-21 expression, suggesting its potential for monitoring therapy response.[4]

Given the conflicting or evolving understanding of miR-21's role in CML treatment response, the objective of this study was to assess the correlation between microRNA-21 (miR-21) expression levels and the clinical response to Tyrosine Kinase Inhibitor (TKI) therapy in CML patients under treatment.

Materials and Methods

2.1. Study Design and Patient Population

The present research was designed as a cross-sectional, single center examination. The research carried out in collaboration between the Hematological Consultant unit at Al-Diwaniyah General Hospital and the Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Al-Qadisiya , Iraq. The study duration was five months, from October 2024 to February 2025.

The study included **50 patients** diagnosed with Philadelphia chromosome-positive CML. All recruited patients were currently receiving at least one type of TKI treatment and had comprehensive clinical and laboratory records available for review.

2.2. TKI Treatment and Response Criteria

All patients included in the study were receiving Tyrosine Kinase Inhibitor (TKI) therapy, including Imatinib**,** Nilotinib**,** andBosutinib, as first- or second-line treatment for CML. The specific TKI and dosage were determined by the treating physician based on standard clinical guidelines. Patients had been on TKI therapy for a minimum of 12 months.

The Patients were categorized into two groups according to their molecular response to TKI therapy, following the European LeukemiaNet (ELN) 2020 recommendations [10]:

- **Good Response Group (n=29):** Patients who achieved an optimal response, defined as Major Molecular Response (MMR) (BCR-ABL1 ≤ 0.1% on the International Scale (IS)) at 12 months or later.
- **Poor Response Group (n=21):** Patients who showed a warning or failure response, defined as achievement failure MMR (BCR-ABL1 ≥ 0.1% IS) at 12 months or later, or those who experienced loss of response.

2.2. Ethical Approval and Data Collection

The present study protocol was accepted by the Ethics Research Committee of Al-Qadisiya University. Informed consent was obtained from each patient and control participant in accordance with the Declaration of Helsinki.

For diagnosis and follow-up, standard procedures included a complete blood count and molecular analysis of BCR-ABL1 by real-time quantitative PCR.

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2.4. Gene Expression Analysis of microRNA-21

Extraction of RNA and Synthesis of cDNA

The entire RNA was taken from whole blood samples using **TRIpure RNA extraction reagents (ELK, China)** following the manufacturer's protocol, which involved lysis with Triazol, chloroform extraction, isopropanol precipitation, and 70% ethanol washing. RNA concentration was measured using the **Quantus™ Fluorometer (Promega, USA)**. The extracted RNA was reverse transcribed into complementary DNA (cDNA) using the **ADDBio kit (Korea)**. The reaction of the mixture (20 µl total volume) included 4 µl of RNA and was incubated at 50°C for 60 minutes for reverse transcription.

Quantitative Reverse Transcriptase PCR (RT-qPCR)

The expression level of microRNA-21 (miR-21) was quantified by RT-qPCR using the**AddScript RT-qPCR Syber master (AddBio, Korea)** on a **BioRAD (USA)** real-time qPCR machine. The housekeeping gene was **GAPDH.**

Primers used in this study:

Gene	Primer	Sequence (5'->3')
House Keeping Gene (GAPDH)	Forward	GAAGGTGAAGGTCGGAGTC

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