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The role of miRNA -150 between different BCR-ABL p210 transcript levels and between different levels of imatinib optimal response in CML patients

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ABSTRACT

The dysregulation of miRNA expression patterns is one of the many effects developments of cancer, miRNA has been found to express abnormally in hematological neoplasia such as chronic myeloid leukemia and solid malignancies. Resistance and the degree of response following tyrosine kinase inhibitor treatment are correlated with miRNA expression. Hence, in this study we tried to study the relationship of miRNA-150 between different breakpoint cluster region–Abelson (BCR- ABL) P210 transcript levels and the role miRNA- 150 between different levels of imatinib optimal response in chronic myeloid leukemia (CML). Our study included sixty chronic myeloid leukemia (CML) patients they were divided into two groups based on response to imatinib therapy, thirty samples of the optimal molecular response of chronic myeloid leukemia (CML) patients, and thirty samples of failure molecular response chronic myeloid leukemia (CML) patients. Thirty samples of apparently healthy volunteers were included and evaluated as control. According to the P210 BCR-ABL%, the results showed a significant difference (P= < 0.0001) between the responder and the failure response CML patients. Assessed the result of miRNA-150 showed a significant difference between both CML patients (P = < 0.0001), assessed miRNA-150 level among different response groups, and failure response of CML patients (P = 0.0002). A cutoff value of response vs. failure response (1.784) with high sensitivity can be a diagnostic value to differentiate between response and failure response. Changing gene expression with different amounts of miRNAs had an impact on drug-gene interactions, with consequences for cell growth and death. Gene expression of different levels miRNA-150 among of CML patients of imatinib therapy showed high expression in response patients than failure response patients. The gene expression level of miRNA-150 differs through different responses in CML patients.

KEYWORDS: CML; Imatinib mesylate; miRNA; miRNA-150.

الخلاصة

خلل التنظيم في أنماط التعبير للحمض التووي الريبي واحد من التطورات العديدة للسرطان، وقد وجد أن الحمض التووي الريبي يعبر بشكل غير طبيعي في الأورام الدموية مثل سرطان الدم النخاعي المزمن والأورام الخبيثة الصلبة. ترتبط المقاومة ودرجة الاستجابة بعد علاج TKI بتعبير الحمض التووي الريبي. ومن ثم، في هذه الدراسة، حاولنا دراسة العلاقة بين miRNA- 150 ومستويات نسخ مختلفة من p210 BCR-ABL ودور miRNA- 150 بين مستويات مختلفة من الاستجابة المثلى لإيماتينيب في سرطان الدم النخاعي المزمن. الطريقة: تضمنت دراستنا ستين مريضًا بسرطان الدم النخاعي المزمن تم تقسيمهم إلى مجموعتين بناءً على الاستجابة للعلاج بإيماتينيب، ثلاثين عينة من الاستجابة الجزيئية المثلى لمرضى سرطان الدم النخاعي المزمن وثلاثين عينة من مرضى سرطان الدم النخاعي المزمن. تم تضمين ثلاثين عينة من المتطوعين الأصحاء على ما يبدو وتقييمها كمجموعة تحكم. النتائج: وفقًا لنتائج P210 BCR-ABL٪، كان هناك فرق كبير (P = <0.0001) بين المستجيبين وفشل الاستجابة لمرضى سرطان الدم النخاعي المزمن. أظهرت نتيجة تقييم ميرنا **-150** فرقًا كبيرًا بين مرضى سرطان الدم النخاعي المزمن (P = <0.0001). تم تقييم مستوى miRNA-150 بين مجموعات الاستجابات المختلفة واستجابة فشل مرضى سرطان الدم النخاعي المزمن (P = 0.0002). يمكن أن تكون قيمة القطع للاستجابة مقابل استجابة الفشل (**1.784**) ذات الحساسية العالية ذات قيمة تشخيصية للتمييز بين الاستجابة واستجابة الفشل. الخلاصة: تغيير التعبير الجيني بكميات مختلفة من miRNAs له تأثير على تفاعلات الجينات الدوائية، مع عواقب على نمو الخلايا وموتها. كان التعبير الجيني بمستوى مختلف من miRNA-150 بين مرضى سرطان الدم النخاعي المزمن الذين عولجوا بإيماتينيب تعبيرًا عاليًا في مرضى الاستجابة مقارنة بمرضى استجابة الفشل. يختلف مستوى التعبير الجيني لـ miRNA-150 باختلاف الاستجابة لمرضى سرطان الدم النخاعي المزمن.

INTRODUCTION

Hematopoiesis is described as the ability of self-renewing cells to form mature blood cells, [1]. Abnormal hematopoiesis is characterized by an increase of immature cells in the bone marrow, hematological cancer known as leukemia comes in a wide range of forms [2]. Between January 2018 and December 2019, the Iraqi Center for Hematology in the Medical City complex of Baghdad recorded 3102 eligible leukemia cases. For all types of cancer, 1402 cases were registered in 2018 and 1700 in 2019 [3]. Chronic myeloid leukemia (CML) is a rare disease worldwide and its incidence is estimated to be 1-2 cases / 100,000 presence of people, accounting for around 15% of newly diagnosed adult leukemia cases [4] . CML diagnosed in 8,450 persons in the United States in 2020, with 1,130 people dying from the disease [5]. Men are more likely than women to be diagnosed with CML, and the disease usually occurs in their sixth or seventh decade of life [6]. Agranulocytosis, marrow hypercellularity, and splenomegaly are all symptoms of CML, which is caused by a mutation in a pluripotent stem cell [7]. This myeloproliferative neoplasm is a clonal hematopoietic stem cell (HSC) neoplasm marked by an increase in myeloid linage cells at all stages of development [4] . The increase of Philadelphia chromosome-positive (Ph+) myeloid cells is a defining feature of CML patients. A reciprocal translocation between the Abelson (ABL) protooncogene on chromosome 9 and the breakpoint cluster area (BCR) on chromosome 22 results in the Ph chromosome, t (9;22) (q34; q11). [8]. This results in the production of an abnormal mRNA product, p210 BCR-ABL, a fusion protein with constitutive ABL tyrosine kinase (TK) activity [9]. This kinase regulates several downstream substrates, including A serine threonine kinase also known as protein kinase B (Akt), Myelocytomatosis MYC and c-Jun N-terminal kinase (JNK), which are all required for normal cell proliferation and survival. The hyperactivity of the BCR-ABL kinase, on the other hand, breaks this delicate balance and drives cells to uncontrolled proliferation and survival, both of which provide a growth advantage to malignant cells with this mutation, ultimately leading to CML pathogenesis [10]. For the efficient treatment of CML, tyrosine kinase inhibitors (TKIs) are required to suppress the kinase activity of the BCR-ABL protein [11]. Imatinib mesylate is a tyrosine kinase inhibitor TKI that inhibits downstream BCR-ABL signaling by blocking the ATP binding site of the protein [10]. Although imatinib, a tyrosine kinase inhibitor TKI, works for the great majority of CML patients, resistance can develop either spontaneously or during treatment [4]. MicroRNAs (miRNAs) are short noncoding RNAs that affect cell survival and development after transcription. Overexpression of oncogenic miRNAs (oncomiRs) or reduced expression of tumor suppressor miRNAs have been found in malignancies, and miRNAs have been proven to induce carcinogenesis [12]. Over 30% of basic genes, which are involved in key biological processes such as proliferation, differentiation, survival, invasion, and programmed cell death, are found in the human genome, have been demonstrated to be regulated by miRNAs [13]. Although the role of miRNA in leukemia pathogenesis remained unclear, some research has suggested that miRNA expression profiles could be used as biomarkers for leukemia diagnosis, prognosis, and treatment response [14]. Lineage commitment and differentiation are influenced by a set of miRNAs present in hematopoietic cells [15]. In hematological malignancies, aberrant miRNA expression has been reported, with distinct expression patterns compared to normal equivalents [11]. Changes in transcription regulation may potentially cause changes in microRNA expression during carcinogenesis. Transcription factors encoded by oncogenes or suppressor genes regulate some microRNAs [16]. For numerous miRNAs, functional validation of unregulated miRNAs in hematopoiesis has been demonstrated miRNAs have been linked to leukemogenesis and have been implicated in important hematological processes [17].

MATERIALS AND METHODS

This study was carried out between September 2021- July 2022 at Baghdad Teaching Hospital/ Medical City. The current study included 60 CML patients who were over the age of 18 and had been on imatinib mesylate therapy for over a year. Based on treatment response and BCR-ABL transcript levels, patients were divided into groups. The European Leukemia-Net (ELN) guidelines were used to define treatment response criteria The results were taken from the previous examinations of the patients depended Real-time quantitative (RQ-PCR) gene expert machine [18]. Thirty

samples were determined to be optimal responders (p210 BCR-ABL transcript levels less than 0.1%) and thirty samples as failure molecular responders (p210 BCR-ABL transcript levels greater than 1%). Thirty samples of apparently healthy volunteers were used as controls. At the time of sampling, blood count indices were obtained using an automated blood count analyzer This study was approved by the scientific ethics committee/ All the study experiments were performed at the University of Mustansiriyah University - College of Science - Department of biology. Excretion criteria: <12-month treatment, CML on other TKI, Chronic illness and malignance, Chronic illness, and malignance. Inclusion criteria: Age≥18-year-old, CML patients on imatinib therapy for at level 12 month, no other malignance, no other chronic diseases.

ANALYSIS OF DATA

1. Analysis of the results as shown by Rotor-Gene Q Series Software which included:

a. Recording Ct values of each amplification reaction

b. Amplification plots.

c. Dissociation curves.

2. The expression ratio was calculated without a calibrator sample according to the following equation:

   DCT (test)=CT gene of interest (target, test) – CT internal control.

3. Finally, the expression ratio was calculated according to the formula (Schmittgen and Livak 2008).

   DCt=Normalized expression ratio folding.

STATISTICAL ANALYSIS

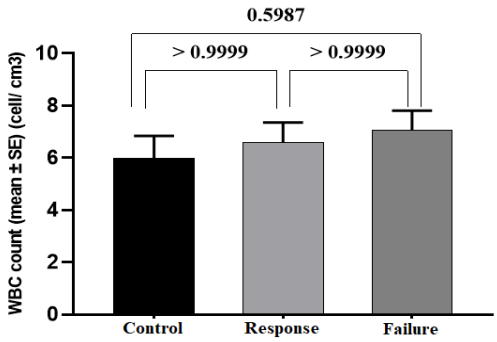
GraphPad Prism 7.0 was used for statistical analysis, to detect the effect of different parameters in study, discrete variables presented using their number and percentage, chi square test was used to analyze. For non-parametric data such variables analyzed by Kruskal-Wallis test for comparison between different groups (response, and failure response and control). The probability was calculated for Variables that followed normal distribution One way ANOVA used for their analysis. For post Hoc analysis, Tukey U test used for those analyzed by One way ANOVA, while Dunn's multiple comparison test for those analyzed by Kruskal-Wallis test. We performed a receiver operator curve (ROC) analysis to look at how miRNA expression levels differed between instances of optimum and failure responses, with a significance threshold of P 0.05.

RESULTS

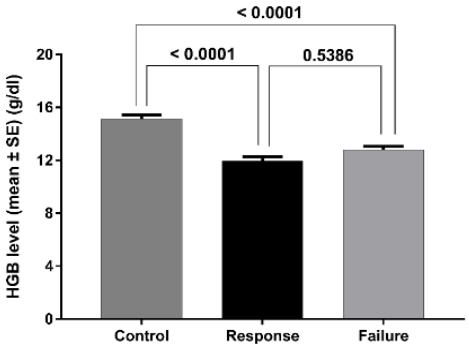
General features of both patients and controls: Response to imatinib treatment was used to split 60 individuals with CML into two groups, thirty samples were with optimal response with (mean age 45.97±2.23 years, M:F ratio 12:18) and thirty samples were with failure response with (mean age 49.87±2.25 years, M:F ratio 18:12) As a control, thirty samples of apparently healthy volunteers were included and evaluated (mean age 30.93±1.75 years, M:F ratio 24:6). The following patient characteristics were included based on a complete blood count: The median white blood cells count (cell/cm^3) for the response, failure response CML patients and control group was (6.6×10^3) (3.9-15.3), (7.05×10^3), (3.1-12.6), (6.15×10^3), (0.8-18.3) respectively, they showed no significant difference between all studied groups as shown in Figure 1A. While the median hemoglobin level g/dl to µL for the response, failure response CML patients and control group was (12.15 g/dl) (6.8-15.3), (13.1 g/dl) (9.6-15.9), (15.8 g/dl) (10.2-17.3) respectively, showed no significant difference (P=0.5386) for both patients CML groups, but showed a significant difference among patients groups and control group according to the hemoglobin level (P=<0.0001) showed reduced hemoglobin levels than the control, as shown in Figure 1B. The median platelets count ×103/µL for the response, failure response CML patients and control group was (235×103) (17-391), (210.5×103) (48-1237), (237×103) (159-450) respectively showed no significant difference between all student groups, as shown in Figure 1C. Quantitative polymerase chain reaction analysis of p210 BCR-ABL transcripts and peripheral blood indices, all CML cases were classified based on imatinib therapy response there was a significant difference (P= <0.0001), between the response and the failure responder CML patients with a highest transcript level in failure responder CML group with mean (7.463±3.345%) and optimal response group with mean (0.0145±0.03%) in terms of BCR-ABL transcript levels, as shown in Figure 2.

distribution of mean BCR-ABL p-210 level among different responses of CML patients groups. the mean BCR-ABL1 (< 0.0032), (0.01-0.0032), (0.1-0.01) and (>1), the result showed in this study, the mean ±SE BCR-ABL p-210
level different response groups and failure response group=(0.0019±0.0005, 0.0056±0.0007, 0.0271±0.0036, 7.463±3.345) respectively, shown high significant difference between all studied patients (p=<0.0001). Assessed of mean miRNA expression level among response group and failure response group of CML patients, the mean folding miRNA-150 expression (391.8±349.3 and 1.919±0.4081), for both response and failure response respectively, the result showed high significant difference between both patients groups (P=<0.0001), as shown in Figure 3.

(A)



(B)



(c)

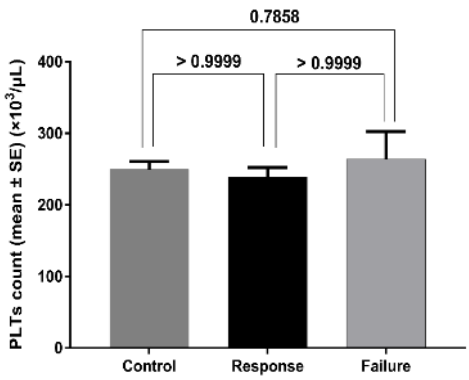


Figure 1. Patients' characteristics based on complete blood count in both CML and control groups (A) white blood cells count (B) hemoglobin level (C) Platelet count.

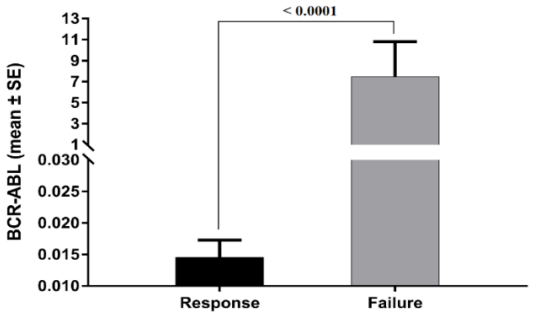


Figure 2. Shown P-value BCR-ABL P-210 level between response and failure response of CML patients.

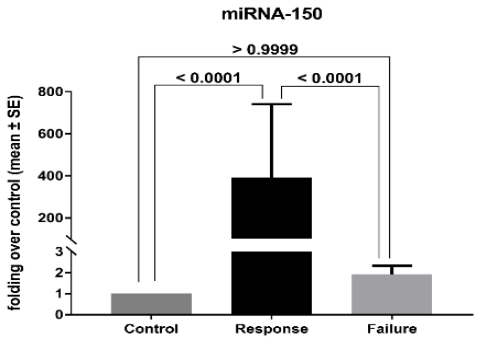


Figure 3. Shown P-value of miRNA-150 expression with BCR-ABL level through response and failure response of CML patients.

Assessed of mean miRNA-150 expression level among different responses groups and failure response group of CML patients showed significant difference result in the mean BCR-ABL1 (<0.0032), (0.01-0.0032), (0.1-0.01) and (>1), were expression (1203±1164, 14.17±8.502, 59.16±24.35 and 1.919 ± 0.4081) respectively, as shown in Figure 4.

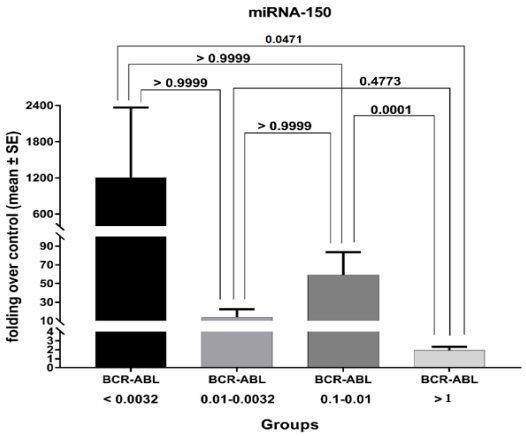


Figure 4. MiRNA -150 expression level among different responses groups and failure response of CML patients.

Shown in Table 1 to determine cutoff value and miRNA-150 expression levels were analyzed using a receiver operating characteristic (ROC) curve

(1.784) with high sensitivity that can be used to distinguish between response and failure response, as shown in Figure 5 and 6.

Table 1. The ROC analysis for miRNA-150 expression.

Comparison groups	Control vs. Response	Response vs. Failure response
AUC	0.819	0.819
95% CI of AUC	0.715-0.922	0.715-0.922
P-value	<0.0001	<0.0001
SN (%)	70	70
SP (%)	73.3	73.3

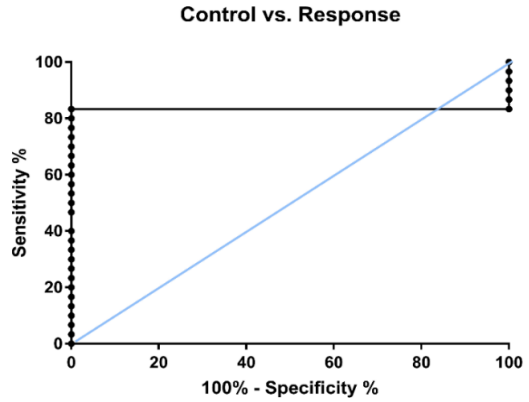


Figure 5. ROC analysis for miRNA-150 expression for control vs. response.

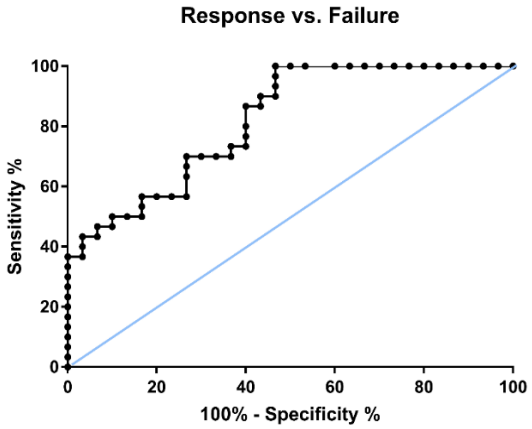


Figure 6. ROC analysis for miRNA-150 expression for response vs. failure response.

DISCUSSION

When comparison differential expression of microRNAs in CML patients who responded to TKI therapy ("responders") versus those who did not ("non responders"), as well as between normal control bone marrow cells and CML patients' leukemic cells The goal is to identify microRNAs as predictive biomarkers of TKI sensitivity as well as to aid in the investigation of potential microRNA mediated TKI resistance mechanisms for therapeutic use [19]. MiRNA levels in the blood were shown to alter considerably in newly diagnosed CML patients before and throughout the first two weeks of Imatinib treatment, suggesting the possibility of identifying easily detectable biomarkers to track TKI response. These findings show that miRNA signatures could be used as biomarkers in CML research, allowing for CML staging and predicting patient response to TKI therapy [20]. MYB mRNA stability and translation efficiency are both affected by miR-150, MYB has been shown to be a top predicted target of miR-150, furthermore, miR-150 can target MYB in chronic myeloid leukemia (CML) and limit the production of a number of oncogenes, preventing CML cells from proliferating [19]. MYB is a confirmed target of miR-150. MYB expression was dramatically enhanced at Dg in AP/BC, with a significant negative association of MYB with miR150 expression and a significant positive correlation between MYB expression and BCR-ABL transcript level in contrast to controls [20]. At the molecular level, BCR-ABL and miRNA-150 had a positive connection. This means that once patients on imatinib have achieved molecular remission from chronic myeloid leukemia, miRNA-150 can be used to predict remission outcome [21]. TKI inhibit BCR-ABL oncoprotein phosphorylation by blocking the ATP-binding site of the kinase domain of ABL, the activity of this compound results in the transcriptional modulation of various genes involved in the control of the cell cycle, cell adhesion, and cytoskeleton organization, leading the Ph-positive cell to an apoptotic death. Tyrosine kinases are a part of many cell functions, including cell signaling, growth, and division. These enzymes may be too active or found at high levels in some types of cancer cells, and blocking them may help keep cancer cells from growing. Some tyrosine kinase inhibitors are used to treat cancer [22].

Our study included 60 CML patients with mean age was (45.97± 2.23, 49.87 ± 2.25, 30.93 ± 1.75) years for both response, failure response CML patients and control group, respectively, without significant statistical differences between both patients groups. With a younger average age than the general population, this is akin to a review of the ELN in 2020. the people were typical; a diagnosis is made around the age of 50, which reflects the population's lower median age [18]. Our studied groups showed significant difference of age between the control from one side and different groups of CML patients from the other

side (P=<0.0001). Chronic myeloid leukemia (CML) affects people of all ages, and its prevalence rises with age. Prior to the introduction of imatinib, older age was a risk factor. Since then, CML patients' outcomes have improved, and older age appears to have lost its negative impact [21]. white blood cells count they showed no significant difference between both patients group, also between patients different response groups and control group, our studied failure response CML patients were with failure molecular response. While the median hemoglobin level g/dl to µL showed no significant difference for both patients CML groups, but showed a significant difference between patients groups and control group. (P=<0.0001) showed reduction of hemoglobin levels than the control, in CML patients group proliferation of granulocytes inhibit hematopoiesis in erythrocytes, or which might be related to the long-term use of imatinib treatment [22]. Anemia increases gradually with the prolongation of medication [23]. The median platelet count was within the normal range in all studied groups, but this does not rule out the presence of CML at various stages in this study. According to European Leukemia Net recommendations, achieving CHR within 3 months of starting therapy is an optimal response. With TKI therapy, nearly all patients with chronic CML achieve a CHR [24]. In our study, we compared the expression level of miRNA with the degree of response achieved after treatment for CML patients with failure response. Assessment miRNA-150 expression levels in different responses and failure response of CML patients, the result significant differences appeared between (<0.0032 vs. >1) and (0.1-0.01 vs. >1), (P=0.0471) (P=0.0001) respectively, without significant difference among other studied patients groups. MiRNA -150 expression in CML showed a significant inverse connection with the levels of the MYB and BCR-ABL transcripts [25]. MYB, an oncogenic transcription factor that controls hematopoiesis at the early progenitor levels, is inhibited by the miRNA -150, and treatment with TKIs affects these levels reciprocally [26]. When neoplasia develops, progresses, or responds to treatment, miRNA-RNA expression, which is a dynamic process, reflects changes at the cellular level [27]. BCR-ABL and miRNA-150 have a strong association in this study's molecular remission data. This suggests that miRNA -150 may be helpful in predicting outcomes once patients using imatinib for chronic myeloid leukemia have achieved molecular remission, high expression of miRNAs targeting BCR-ABL sensitized the CML cells to imatinib treatment, suppressed proliferation and induced apoptosis. Relapse or full molecular remission could be the results of this association [28].

CONCLUSIONS

Changing gene expression with different amounts of miRNAs has an impact on drug-gene interactions, with consequences for cell growth and death The miRNA functions as a guide by base-pairing with target mRNA to negatively regulate its expression. The level of complementarity between the guide and mRNA target determines which silencing mechanism will be employed; cleavage of target messenger RNA (mRNA) with subsequent degradation or translation inhibition, whose main role is to regulate mRNA by leading to its degradation and also to adjust the protein levels. Gene expression different level miRNA-150 among of CML patients of imatinib therapy were high expression in response patients than failure response patients. The gene expression level of miRNA-150 difference among different level BCR-ABL-210 transcript in optimal response CML patients. By the different miRNA-150 gene expression level among CML patients we can predict response or failure response to therapy.

Disclosure and conflict of interest: The authors declare that they have no conflicts of interest.

Ethical Clearance: This study was approved by the scientific ethics committee. All the study experiments were performed at Mustansiriyah University, College of Science, Department of biology.

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