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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE ROLE OF CYTOGENETIC AND MOLECULAR GENETIC ANALYSIS IN MONITORING AND PROGNOSIS OF TARGETED THERAPY IN CHRONIC MYELOID LEUKEMIA

Specialty:	2409.01 Genetics
Field of science:	Biology
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GENERAL CHARACTERISTICS OF THE WORK

Relevance of the problem. Chronic myeloid leukemia (CML) is a hematological malignancy caused by the BCR/ABL1 fusion gene, characterized by the excessive proliferation of immature granulocytes, which accumulate in the bone marrow and interfere with normal hematopoiesis. According to epidemiological data, this condition accounts for approximately 15–20% of all leukemia cases diagnosed in adults. Characteristically, CML follows a biphasic or triphasic clinical course and is most commonly identified in the chronic phase (CP) in the majority of patients.[1]

This phase may persist for 3 to 6 years; however, if left untreated, the disease typically progresses to the accelerated phase (AP) or eventually to blast crisis (BC).[2] CML is the first cancer in which a specific chromosomal abnormality enabling the identification of leukemic tumor cells was described. In 1961, P.S. Nowell and D.A. Hungerford were the first to identify an abnormally shortened chromosome 22, which was later named the Philadelphia chromosome (Ph chromosome) in honor of the city where it was discovered. It was only in 1973, following the implementation of differential chromosome banding techniques in cytogenetic practice, that a critical discovery was made in elucidating the pathogenesis of CML. Specifically, J. Rowley demonstrated that the Philadelphia chromosome does not result from a chromosomal deletion, but rather from a reciprocal translocation between chromosomes 9 and 22.[3-4] It was not until the

[1] Soverini, S., De Benedittis, C., Mancini, M., & Martinelli, G. Best Practices in Chronic Myeloid Leukemia Monitoring and Management. Oncologist. 2016. – p. 626–633.

[2] Mughal TI, Goldman JM. Chronic myeloid leukemia: STI 571 magnifies the therapeutic dilemma. Eur J Cancer 2001. – p. 561–568.

[3] Nowell P.C., Hungerford D.A. A minute chromosome in human chronic granulocytes leukaemia // Science. 1960. – p. 1497–1501.

[4] Rowley J.D. Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia indentified by quinacrine fluorescence and Giemsa staining. Nature. - 1973. – p. 290–-293.

end of the 20th century that the pathogenic mechanisms underlying the development of CML were fully elucidated, leading to the formulation and development of targeted therapeutic strategies for this disease. The study of the characteristics of the BCR/ABL1 hybrid protein led to the discovery of Imatinib Mesylate (IM), a BCR/ABL1 tyrosine kinase inhibitor (TKI), marking the beginning of successful therapeutic strategies for CML.[5] IM is a selective TKI that has emerged as a prototype in targeted therapy for hematologic malignancies. It was specifically developed not only to inhibit the BCR/ABL1 fusion gene, but also to suppress the proliferation of cells expressing stem cell factor receptors, c-KIT tyrosine kinases, and platelet-derived growth factor (PDGF) receptors.[6]

Although IM is considered the gold standard for the treatment of CML, resistance to the drug emerges in a proportion of patients, posing a significant therapeutic challenge. Recent studies have demonstrated that more than 25% of CML patients may develop resistance to IM at least once during their lifetime.[7]

Several mechanisms underlying resistance have been described; however, mutations within the BCR/ABL1 tyrosine kinase domain (KD) remain the most extensively studied. One of the primary causes of treatment failure is the emergence of mutations within the ABL1 kinase domain that disrupt the binding of the drug. In patients with additional chromosomal aberrations (ACAs) beyond the Philadelphia chromosome, as well as those harboring various gene mutations, the therapeutic response to IM is significantly reduced. Notably, the involvement of the cytochrome P450 (CYP) enzyme family must also be considered.[8]

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[5] Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. Blood. 2008. – p. 4808–4817.

[6] Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. Am J Hematol 2020. – p. 691–709.

[7] Yaghmaie M, Yeung CC. Molecular mechanisms of resistance to tyrosine kinase inhibitors. Curr Hematol Malig Rep. 2019. – p. 395–404.

[8] Verma D, Kantarjian H, Shan J. et al.: Survival outcomes for clonal evolution in chronic myeloid leukemia patients on second generation tyrosine kinase inhibitor therapy. Cancer. 2010. – p. 2673–2681.

Different mutations exhibit varying levels of sensitivity to TKIs. The detection of such mutations can guide the selection of appropriate TKIs and influence the prognosis of CML patients by enabling therapy to be tailored based on the identified mutation. This is particularly critical in cases involving the T315I mutation, where the use of next-generation TKIs or consideration of hematopoietic stem cell transplantation may be necessary. The results of mutation analysis can help guide subsequent treatment decisions in accordance with the recommendations of the European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN).[9]

Currently, several next-generation TKIs including Nilotinib (Tasigna®), Dasatinib (Sprycel®), Bosutinib (Bosulif™), Ponatinib (Iclusig™), and Omacetaxine (Synribo™) are available and are used in patients who do not respond to IM therapy.

Therefore, investigating the mutations characteristic of the local population alongside BCR/ABL1 translocation, ACAs, gene mutations, ABL1 KD mutations, cytochrome P450 gene polymorphisms, and response levels to IM therapy is critically important for the diagnosis, monitoring, and prognosis of the disease.

The adoption of the "Action Program for Combating Hematologic Malignancies for 2017-2021" in our country has played a significant role in enabling, for the first time in Azerbaijan, a comprehensive study of CML patients and in achieving the outlined objectives.

Object and subject of the study. The study's subject was 699 CML patients receiving treatment in the clinical departments of the Scientific Research Institute of Hematology and Transfusiology. The study consisted of control and experimental groups. The 699 study participants were subsequently stratified into five groups: the first experimental group (n=242), which aimed

[9] Aypara Hasanova, Chingiz Asadov, Nigar Karimova, et al. Spectrum of BCR-ABL mutations in Azerbaijanian imatinib-resistant patients with chronic myeloid leukemia. Pathology & Oncology Research. 2023. – p. 1–11.

to determine the initial diagnosis and response to IM therapy (1187 tests, Real-Time Polymerase Chain Reaction-RT-PCR), the second experimental group (n=163) focused on identifying ACAs (163 tests, Standard Cytogenetics-SC), the third experimental group (n=141) aimed at detecting gene mutations (564 tests, Fluorescence *in situ* Hybridization-FISH), the fourth experimental group (n=163) concentrated on identifying ABL1 KD mutations (564 tests, Pyrosequencing), and the fifth experimental group (n=153) was dedicated to identifying the CYP3A4*18 and CYP3A5*3 polymorphisms of the cytochrome P450 gene (459 tests, Restriction Fragment Length Polymorphism-RFLP). A total of 3025 tests were conducted during the study. Various mutations were identified in the study cohorts using cytogenetic and molecular-genetic methods, and the role of these mutations in the diagnosis of CML patients, determining the response to IM therapy, as well as in monitoring and prognosis, was investigated.

Aim of the study. Determining the levels of response to IM therapy in Azerbaijani CML patients, identifying the most common mutations in the local CML patient population, and investigating the role of these mutations in the pathogenesis of CML, disease progression, as well as primary and secondary resistance to IM, are essential for determining the prognosis and selecting timely and appropriate treatment strategies.

Research objectives:

1. Evaluation of response levels to IM therapy in a cohort of Azerbaijani patients with CML;
2. İnvestigation of the most common ACAs in Azerbaijani patients with CML and their impact on overall survival (OS);
3. Investigation of P53, RB1, and ASS1 gene deletions, chromosome 8 hyperdiploidy, and BCR/ABL1 fusion copy number in CML patients and their role in disease progression;
4. Screening of ABL1 KD mutations in a cohort of CML patients and determination of their role and mechanisms in disease progression, OS, and resistance to IM therapy;
5. Study of cytochrome P450 polymorphisms in CML patients and the impact of these polymorphisms on the risk of

developing CML, as well as the development of resistance to IM therapy;

6. To investigate the role of the identified mutations in the development of primary and secondary resistance, disease progression, and prognosis in patients with CML.

Research Methods. To obtain the results, standard cytogenetic, molecular cytogenetic, and molecular genetic methods, (including PCR, Pyrosequencing, and RFLP), were used.

Main findings presented for the defense:

1. For the first time, a comparative analysis of cytogenetic, FISH, and molecular genetic methods (PCR, pyrosequencing, RFLP) was conducted in the local population of CML patients, and their significance in diagnosis, monitoring, and prognosis of the disease was established.

2. For the first time, response levels to IM therapy were determined in a cohort of Azerbaijani CML patients, and the reasons for the low level of major molecular response (MMR) in local patients were identified.

3. For the first time, the most common ACAs were investigated in Azerbaijani patients with CML, and their role in the development of resistance to IM and disease progression was identified.

4. For the first time in the local CML patient population, deletions in the P53, RB1, and ASS1 genes, hyperdiploidy of chromosome 8, and the copy number of BCR/ABL1 fusions were identified and analyzed to evaluate their role in disease progression and the development of resistance to IM therapy.

5. For the first time in a cohort of Azerbaijani CML patients, screening of ABL1 KD mutations was performed, the most common mutations were identified, and their significance in the development of primary and secondary resistance, disease progression, and prognosis was established.

6. For the first time in local CML patients, an association was identified between cytochrome P450 polymorphisms and both the risk of disease development and the response level to IM therapy.

Originality. For the first time, mutations and polymorphisms

at the genomic, chromosomal, gene, single nucleotide, and restriction fragment length polymorphism levels have been investigated in Azerbaijani patients with CML. For the first time, cytogenetic, FISH, PCR, pyrosequencing, and RFLP methods were applied in a cohort of Azerbaijani CML patients to identify the spectrum and frequency of ACAs, gene mutations, ABL1 KD mutations, and cytochrome P450 gene polymorphisms (CYP3A4*18 and CYP3A5*3), as well as their role in IM response and resistance. In addition, response levels to IM were analyzed across different time intervals. The study also conducted a comprehensive evaluation of the significance of cytogenetic, molecular cytogenetic, and molecular genetic analyses in the diagnosis of CML, identification of primary and secondary resistance during targeted therapy, therapy monitoring, and disease prognosis.

Therefore, the research work is original.

Theoretical and practical value. As a result of the study, in addition to BCR/ABL1 translocation, the identification of ACAs, gene mutations, ABL1 KD mutations, cytochrome P450 gene polymorphisms, and response levels to IM therapy in the Azerbaijani CML patient cohort enabled the prediction of disease progression, informed the selection of more effective next-generation TKIs, and guided critical clinical decisions such as hematopoietic stem cell transplantation. Based on the findings, a patient-specific prognostic assessment and corresponding treatment and monitoring algorithm were developed. The implementation of this algorithm has contributed to timely and appropriate therapeutic decision-making, increased treatment efficacy, improved OS, and enhanced patient recovery.

Approbation and presentation of the work. The main objectives and results of the dissertation were presented at the following scientific conferences and events:

- “Hematologiyanın Aktual Problemləri”, Bakı, Azərbaycan, 2024
- “The 2nd Annual Meeting of the İnternational Academy for the Clinical Hematology (IACH)”, Paris, France, 2019

- “24 Congress of the European Hematology Association”, Amsterdam, The Netherlands, 2019
- “Xth Eurasian Hematology Oncology Congress”, Istanbul, Turkey, 2019
- “Hematologiyanın Aktual Problemləri”, Bakı, Azərbaycan, 2019
- “IXth International Eurasian Hematology Oncology Congress”, Istanbul, Turkey, 2018.

Affiliation. The work was performed at the National Hematology and Transfusion Center (*prev.* the Scientific-research Institute of Hematology and Transfusiology).

Publications. The results of the work have been summarized in 25 publications: 15 articles, 7 abstracts, and 3 Methodical Manuals. 5 articles were published as single-authored, and 4 articles as first-author publications. Among these, 4 were published in international journals, 6 in reputable Scopus-indexed journals with an Impact Factor, and 15 in local journals. The author's scientific publications indexed in Scopus and Web of Science have been cited, and their h-index is currently 2.

The structure and content of the dissertation. Dissertation was compiled on 188 A4 pages (217369 characters), including introduction (8 p., 13903 chac.), literature review (52 p., 89900 chac.) materials and methods (26 p., 27999 chac.), results of the study (48 p., 50282 chac.), conclusion (12 p., 22341 chac.), results and practical recommendations (4 p., 5693 chac.), and a list of abbreviations (2 p., 1351 chac.). It includes 308 literature sources (32 p.) and is illustrated with 35 tables and 38 figures.

MATERIALS AND METHODS

The study population was selected from individuals treated in the clinical departments of the Scientific Research Institute of Hematology and Transfusiology. The study population included both control and experimental groups. The control group comprised healthy individuals who had applied to the Blood Bank, while the experimental group was stratified into five subgroups.

The first subgroup, consisting of CML patients, was used to determine initial diagnosis and response to IM therapy. The second subgroup was evaluated to identify ACAs. The third subgroup was analyzed to detect deletions in the P53, RB1, and ASS1 genes, hyperdiploidy of chromosome 8, and the number of BCR/ABL1 fusion gene copies. The fourth subgroup was used to identify ABL1 KD mutations, and the fifth subgroup was analyzed for CYP3A4*18 and CYP3A5*3 polymorphisms in the Cytochrome P450 gene (Fig. 1).

A total of 699 CML patients treated between May 2014 and December 2019 were analyzed both retrospectively and prospectively. At the time of analysis, 594 patients were in the chronic phase, 73 in the AP, and 32 in the BC phase. In total, 3,025 examinations were conducted on these patients. Disease phases were determined in accordance with the ELN recommendations.

The study included patients belonging to an ethnic group that has been residing in Azerbaijan for at least three consecutive generations. Patients with a history or clinical evidence of other chronic or acute diseases, other types of cancer, hepatic or hematological abnormalities, or infections such as hepatitis B, hepatitis C, or HIV were excluded from the study.

Five research methods were employed during the execution of the dissertation study. Blood and bone marrow samples were collected into LH and EDTA-containing test tubes.

ACAs were investigated using the standard cytogenetic method. Peripheral blood and bone marrow cells were cultured for 24 and 48 hours to obtain metaphase spreads, and chromosomes were stained using the GTL banding technique. Karyotyping was performed using the Axio Imager A2 microscope (Carl Zeiss) and IKAROS software (Metasystems).

Gene mutations were examined using the FISH method. Analyses were conducted on interphase nuclei and metaphase chromosomes from peripheral blood and bone marrow samples. Preparations were analyzed using the Imager A2 microscope (Carl Zeiss), ISIS software (Metasystems), and DAPI/TexasRed/FITC filters.

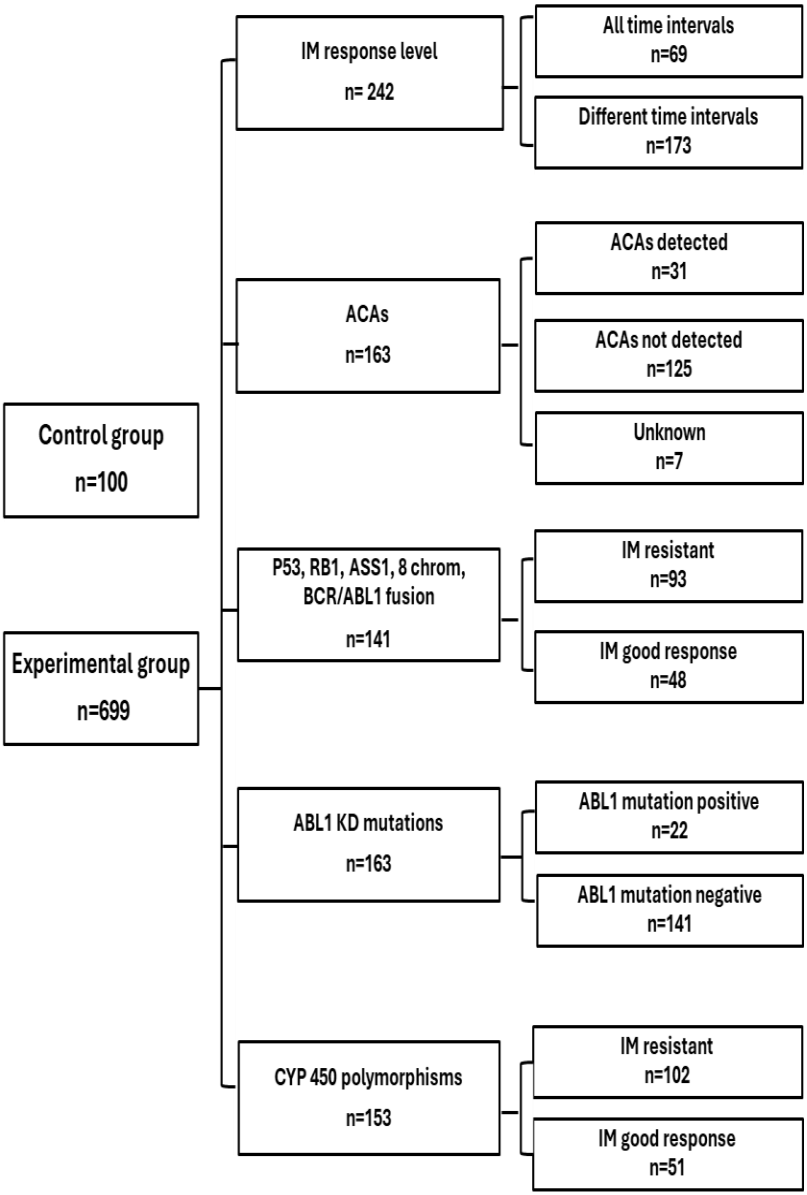

Figure 1. Design of the study.

Real-time PCR (RT-PCR) method. The evaluation of p210 BCR/ABL1 chimeric oncogene expression consisted of several stages: RNA isolation, synthesis of cDNA via reverse transcription, and real-time PCR amplification. RNA purity and concentration were measured using a NanoDrop spectrophotometer (NanoDrop 2000, Thermo Scientific). Reverse transcription was performed using the T100™ Thermal Cycler (Bio-Rad), and detection of the BCR-ABL1 Mbcr transcript was carried out using real-time PCR with the Rotor-Gene Q system (Qiagen).

Screening for ABL KD mutations was performed using the pyrosequencing method. Following RNA extraction from peripheral blood samples, complementary DNA (cDNA) was synthesized using the T100™ Thermal Cycler (Bio-Rad). Subsequently, two rounds of PCR amplification were conducted using the PyroMark PCR Kit (Qiagen, Germany) and the Rotor-Gene Q system (Qiagen). Finally, pyrosequencing was carried out using the PyroMark Q24 platform (Qiagen), and data analysis was performed with the PyroMark Q24 software.

RFLP method. Following DNA isolation, restriction fragment length polymorphisms were studied using the PCR reaction Fırepol DNA Polymerase (Solis Biodyne) kit, restriction enzyme (New England BioLabs), and Veriti Dx Thermal Cycler (Applied Biosystems).

To evaluate the association between two categorical variables, the χ^2 test and Fisher's exact test were applied. The strength of risk association was assessed by calculating the odds ratio (OR) and 95% confidence intervals (CI). All statistical tests were two-sided, and a P-value of <0.05 was considered statistically significant. The Kaplan-Meier method was used to generate survival curves. The data were collected using **Microsoft Office Excel**, and statistical analyses were conducted using both Excel's built-in statistical functions and the **IBM SPSS (Statistical Product and Service Solutions)** software (versions 22 and 24).

RESULTS AND DISCUSSION

Analysis of the Response to first-line therapy with IM in Azerbaijani patients with chronic myeloid leukemia. The study included 242 patients in the chronic phase of CML. A total of 1,187 samples were collected from these patients after the initiation of IM treatment, across predefined time intervals: 3–5 months, 6–11 months, 12–17 months, 18–23 months, and ≥24 months. Of the patients, 115 (47.5%) were male and 127 (52.5%) were female. The median age was 44.2 years (range, 19–81). The samples were grouped into five predefined time intervals according to ELN guidelines to evaluate the response to IM therapy.[10]

Within the study cohort, only 69 patients (411 samples) had available samples across all time intervals. In the first-time interval, 76.8% of patients (53/69) achieved BCR/ABL1^{IS} transcript levels of ≤10%, and all of them maintained this response in the last two intervals. Between 6 and 11 months, 63.7% (44/69) had BCR/ABL1^{IS} transcript levels of ≤1%. By 12–17 months, 43.4% (30/69) had levels of ≤0.1%, and during the 18–23 month interval, 40.5% (28/69) reached ≤0.0032%. In the ≥24-month group, BCR/ABL1^{IS} transcripts were undetectable in 17.4% of patients (12/69).[11]

In a larger cohort without complete sample data across all time intervals (173 patients /776 samples), 83.3% of patients (144/173) had BCR/ABL1^{IS} transcript levels ≤10% in the first time interval, increasing to 90.1% (156/173) in the final interval. In the second time interval, 68.7% (119/173) had BCR/ABL1^{IS} levels ≤1%. In the third interval, 46.8% (81/173) achieved results consistent with MMR (≤0.1%).

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[10] Aypara Həsənova. Azərbaycanlı XML Xəstələrdə İmatiniblə Birinci Xətt Terapiyasına Verilən Cavabın Təhlili. "Hematologiyanın Aktual Problemləri" Beynəlxalq Konfransının materialları. Bakı. 2024. – s. 178–179.

[11] Chingiz Asadov, Ayten Shirinova, Aypara Hasanova, Zohra Alimirzoeva. Evaluation of CML Distribution, Diagnostics and Treatment in Azerbaijan. The 2nd Annual Meeting of the İnternational Academy for the Clinical Hematology (IACH), Paris, France \ September 19-21, 2019. Poster presentation.

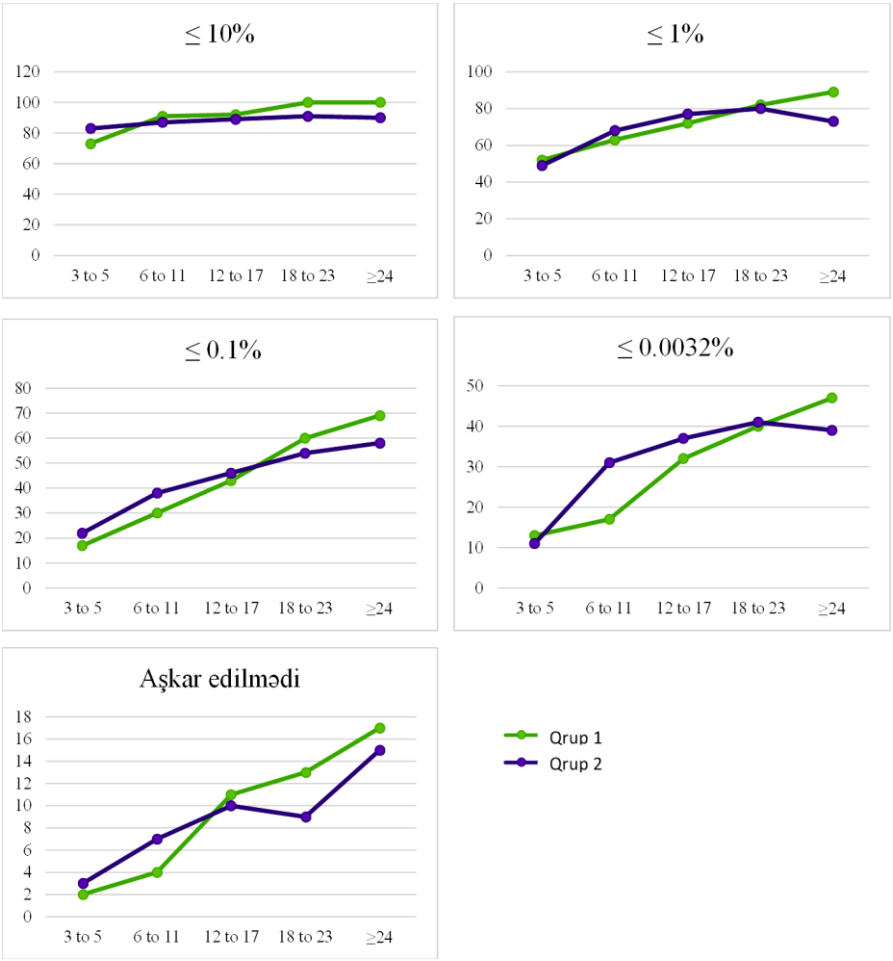


Figure 2. IM therapy response of the chronic phase CML patients obtained at five predetermined intervals: 3–5 months, 6–11 months, 12–17 months, 18–23 months, and ≥24 months following the initiation of treatment. Group 1 represents the data of the patients with samples available in all time intervals (n=69); group 2 is the data of a larger group of patients with samples missing in some intervals (n=173). Diagrams depict BCR-ABL1^{IS} transcript levels ≤10%, ≤1%, ≤0.1% ≤0.0032%, and nondetected levels. The data is represented as percentages.

During the fourth time interval, 41.6% (72/173) of patients had BCR/ABL1^{IS} levels ≤0.0032%. In the final time interval, BCR/ABL1^{IS} transcripts were undetectable in 15.0% of patients (26/173).

The molecular response of the 69 patients with samples analyzed at all time intervals was generally consistent with the response observed in the 173 patients who lacked consecutive interval data up to the 12–17 month period (Fig. 2). However, the first group demonstrated better responses during the 18–23 month and ≥24-month intervals.

In the 18–23 month interval, all patients demonstrated at least a 1-log reduction in BCR/ABL1IS transcript levels, and 82.6% (57/69) achieved at least a 2-log reduction.

The IRIS study reported these response rates as 93.7% and 83.8%, respectively. MMR was achieved in 60.8% (42/69) of patients. This level of detail was not assessable in the second group, as some patients had their first molecular test only at 12–18 months or later following initiation of IM therapy. Evaluation at ≥24 months after initiation of IM treatment showed that MMR was achieved in 69.5% (48/69) and deep molecular response (DMR) in 47.8% (33/69) of patients. Among those who did not achieve MMR by 24 months (30.5%, 21/69), treatment with IM was continued.

The results demonstrated that the treatment response of Azerbaijani patients with chronic phase CML receiving IM (400 mg/day) was comparable to the responses reported in randomized international studies.

Suboptimal response may be attributed to non-adherence to treatment, lack of timely monitoring, or the development of secondary resistance to the drug. These findings underscore the importance of regular follow-up monitoring every 3 to 6 months.

Characteristics of additional chromosomal aberrations in Azerbaijani patients with chronic myeloid leukemia. This retrospective study analyzed 163 patients diagnosed with CML. At the time of assessment, 119 patients were in the CP, 26 in the AP, and 18 in the BC phase.

Among the 31 patients in whom ACAs were detected, ABL1 KD mutations were present in 9 cases. Of the 22 patients (13.4%) with

identified mutations, various ACAs were detected in 9 cases (41%). Among the 141 patients (86.6%) without detected mutations, various ACAs were found in 22 cases (15.6%) (Fig. 3).

During the analysis, additional Philadelphia chromosomes (+Ph), other chromosomal aberrations, and several structural abnormalities were identified in metaphases, including: (-3), (+7), (-7), (+8), (-8), (-9), (+13), (+14), (-16), (+19), i(17)(q10), t(11;18), t(5;7), (+20), (+21), (+22), +der(22), (-X), (+Y), and (-Y).[12]

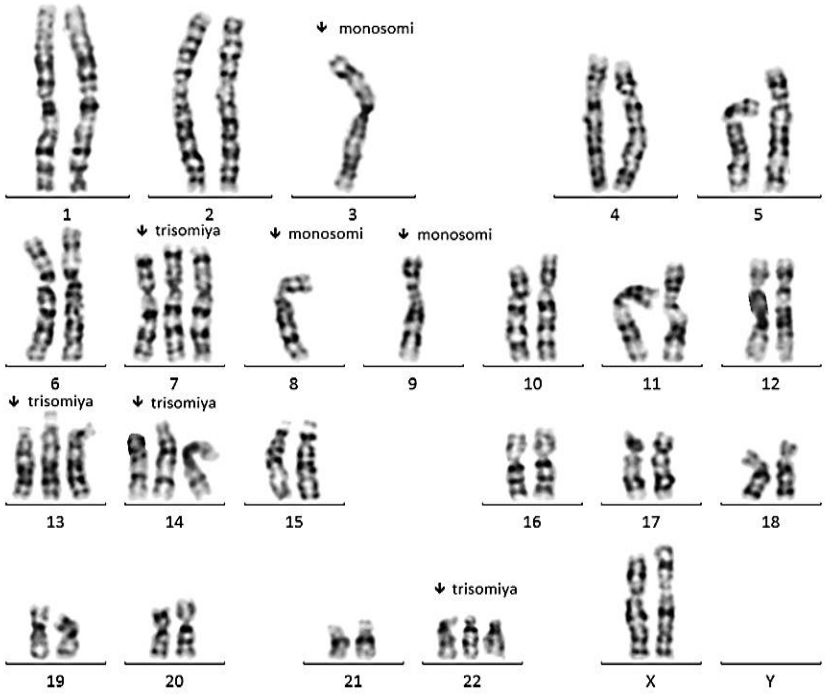


Figure 3. Karyotype identified in a patient with a negative Ph chromosome clone who did not achieve MMR following IM therapy: 47, XX, -3, +7, -8, -9, +13, +14, +22.

[12]Aypara Həsənova. Azərbaycanda imatinibə rezistent xroniki mieloid leykozlu pasiyentlərdə BCR/ABL1 kinaz domeni mutasiyaları ilə əlavə xromosom aberrasiyalarının assosiasiyası. SAĞLAMLIQ.az, 2024, – s. 72–86.

In the Azerbaijani CML patient cohort, the most frequently observed ACAs were trisomy 8 (+8) in 10 patients, an additional Philadelphia chromosome (+Ph) in 7 patients, and an isochromosome of chromosome 17q [i(17q)] in 3 patients, corresponding to 32%, 22%, and 10%, respectively. Among the 8 patients with the T315I mutation, ACAs were detected in 5 cases.

In this study, a significant association was identified between ABL1 KD mutations and ACAs in CML patients (P = 0.006).

Over a 5.5-year follow-up period, the progression-free survival (PFS) rate was 0% in the group with both TKD mutations and ACAs, whereas it was 70% in the group with TKD mutations but without ACAs (P = 0.004). The estimated median OS for the BP groups was 33 months (Fig. 4).

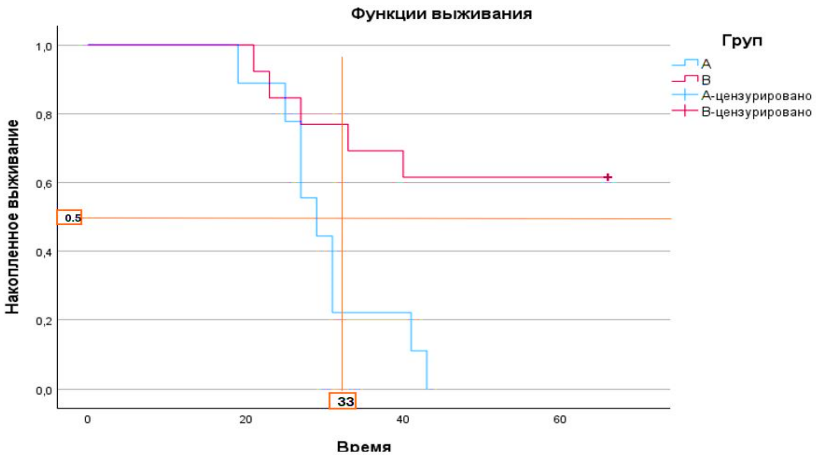


Figure 4. OS in 22 CML patients based on TKD mutation and ACAs status: (A) TKD mutation positive, ACAs positive; (B) TKD mutation positive, ACAs negative. P = 0.004.

Over a 5.5-year follow-up period, the OS rate was 0% in the group with both ACAs and positive TKD mutations, whereas it was 63.6% in the group with ACAs but negative TKD mutations (P = 0.001). The estimated median OS for both groups A and B was 58 months. Thus, this study confirms that patients with ACAs have

poorer progression-free survival outcomes compared to those without ACAs.

Based on my research, such systematic analyses have rarely been conducted previously. In earlier studies, the frequency of mutations among patients resistant to IM ranged from 12% to 63%. This wide range may be attributed to differences in the proportion of patients in advanced disease phases.

In our study, the relatively low frequency of mutations (13.4%) may be related to the higher proportion of patients in the CP compared to those in the AP or BC phases. Consistent with previous studies, when stratified by disease phase, a similar frequency of TKD mutations was observed in our patient cohort.

Screening for mutations and ACAs in patients with TKI resistance may enable the identification of those with a poorer prognosis. In TKI-resistant patients, screening for BCR/ABL1 TKD mutations is recommended prior to switching TKIs, as detection of these mutations can aid in the appropriate selection of therapy and provide prognostic insights. The results of mutational analysis may guide subsequent treatment decisions in accordance with ELN and NCCN recommendations.

Characteristics of gene mutations. A total of 141 CML patients were included in the study for retrospective analysis. Patients were divided into 2 groups, 93 of whom were resistant to IM treatment and 48 of whom were good responders to IM treatment. Of the CML patients in the study group, 62 were male and 79 were female. The age of the patients was ≤49 in 81 patients and ≥50 in 60 patients. The median age was 45.

The deletion of P53, RB1, and ASS1 genes, hyperdiploidy of chromosome 8 and the number of BCR/ABL1 fusion genes were investigated in CML patients who showed resistance to IM treatment and failed to achieve MMR after 12, 18, and 24 months, as well as in patients who responded well to IM treatment (Fig. 5).

A strong association was identified between the initial blast cell count and resistance to IM treatment ($P = 0.00004$). Additionally, a correlation was found between the disease phase and resistance to IM treatment ($P = 0.0016$) (Table 1).

P53 deletion was detected in 7 patients. Among them, 6 were identified in patients with poor response to IM treatment, and 1 was in a patient with a good response. No association was found between this mutation and resistance to IM treatment. However, two patients with P53 mutation accompanied by hyperdiploidy of chromosome 8 and three gene fusions (including amplification of the BCR/ABL1 gene), as well as one patient with P53 mutation and three gene fusions, had died by the end of the study. All three patients were in blast crisis phase and showed no response to combination chemotherapy or second-line TKIs.

No RB1 gene mutations were detected in any of the 141 patients examined. Based on the results of this study, it can be suggested that the RB1 gene does not play a role in the molecular pathogenesis of CML progression or the development of resistance to IM treatment.

Table 1
Mutation characteristics

Variable	N (141)	IM resistant (n=93)	IM good response (n=48)	P-value ($\chi 2$)
P53 Deletion				
Normal	134	87	47	0.2578
Deletion	7	6	1	$\chi 2$=1.2804
RB1 Deletion				
Normal	141	93	48	0.6419
Deletion	0	0	0	$\chi 2$= 0.2161
ASS1 Deletion				
Normal	120	80	40	0.6709
Deletion	21	13	8	$\chi 2$= 0.1805
8 chromosomes Hyperdiploidy				
Normal	108	62	46	**0.0001**
Hyperdiploidy	33	31	2	$\chi 2$=15.02
Fusion BCR/ABL1 gene				
1F	79	68	11	**0.00001**
2F	58	22	36	$\chi 2$=33.60
3F	4	3	1	
[a]P <0.05. IM, Imatinib				

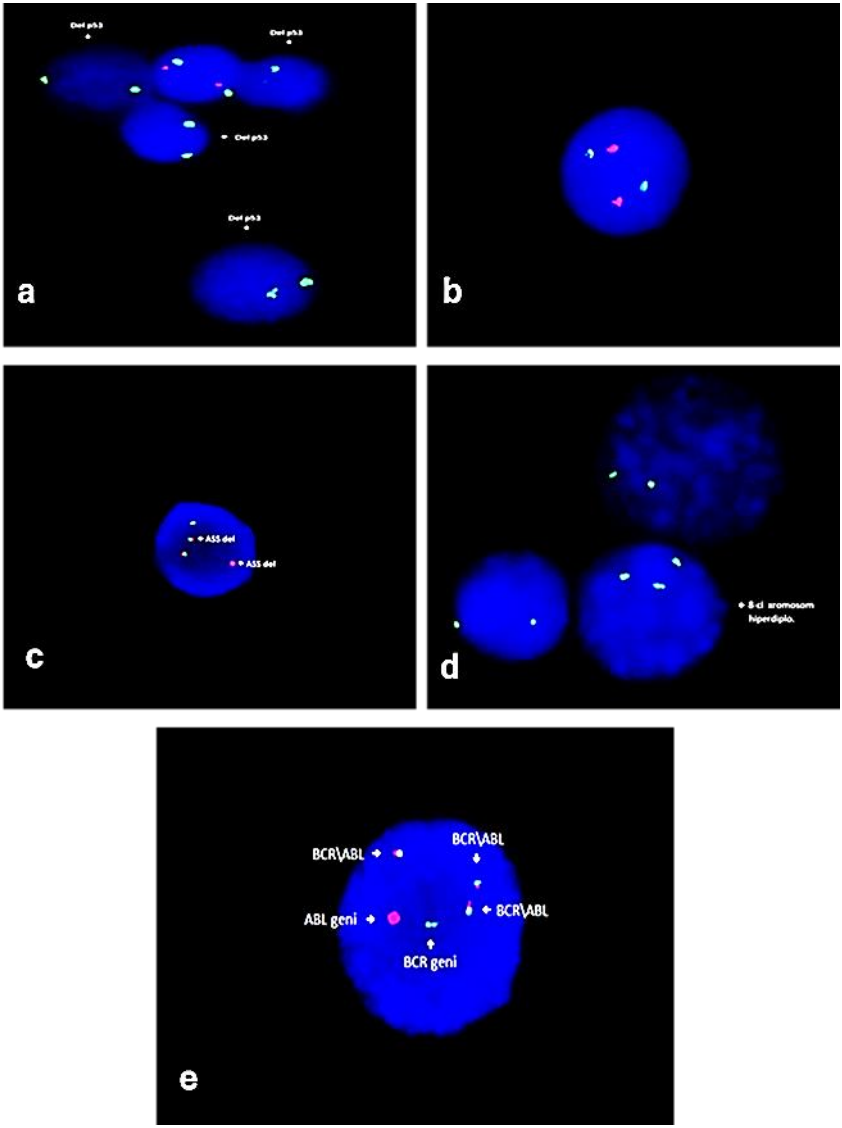


Figure 5. FISH images of select patients with identified mutations. a. P53 gene deletion (2G0R) (2G0R). b. Normal RB1 gene (2R2G). c. ASS1 gene deletion (1G, 1R0B, 1F, 1F0B). d. Trisomy of chromosome (+8) (3G). e. Three BCR/ABL fusion genes (1R1G3F).

ASS1 gene deletion was detected in 21 patients. However, no direct correlation was found between ASS1 gene deletion and the development of resistance to IM treatment.

Hyperdiploidy of chromosome 8 was detected in 33 of the patients examined. The study revealed a strong correlation between chromosome 8 hyperdiploidy and resistance to IM treatment ($P = 0.0001$).[13]

A significant association was observed between fusion signal count and poor response to IM treatment ($P = 0.00001$). Based on the results, it can be suggested that both decreased and increased fusion signal counts may contribute to the development of resistance to IM treatment and disease progression.

Frequency of ABL1 KD point mutations and their impact on TKI resistance in Azerbaijani patients with chronic myeloid leukemia. A total of 163 CML patients were included in the study for retrospective analysis.

During the analysis, 119 patients were in the XF phase, 26 in the AF phase, and 18 in the BC phase. KD mutation screening was performed in CML patients who showed resistance to IM treatment and failed to achieve MMR after 12, 18, and 24 months (Table 2).

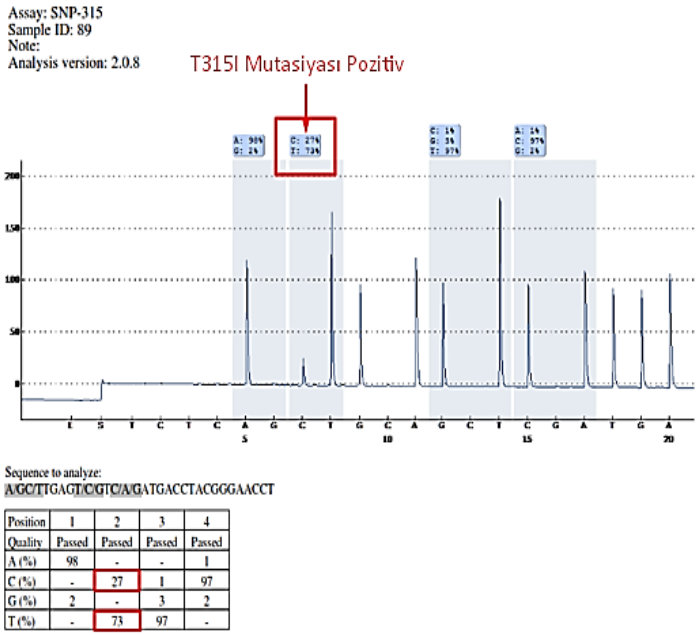
A strong association was identified between ABL1 KD mutations and disease phases ($P = 0.00001$). In addition, a correlation was found between KD mutations and gender ($P = 0.004$). Overall, 8 out of 14 mutations screened were detected in 22 of the 163 patients (13.4%).

In the Azerbaijani CML patient cohort, the most frequently observed mutations associated with IM resistance were T315I, F359C, F359V, and F317L (Fig. 6). The OS rates in the ABL1 KD mutation-positive and mutation-negative groups were 50% and 93%, respectively ($P = 0.00001$). After 43 months, the OS rate was 0% in the T315I mutation-positive group and 92% in the mutation-

[13]Aypara Hasanova, Chingiz Asadov, Aytan Shirinova, Gunay Aliyeva, Zohra Alimirzoyeva. Genetic Factors Associated with Imatinib Resistance in Chronic Myeloid Leukemia: Role of P53, RB1, ASS1 Gene Deletions, and Chromosome 8 Hyperdiploidy. Pathology - Research and Practice. 2025. – p. 1-5. PubMed ID: 40156964; Impact Factor: 2.9

negative group (P = 0.00001).[14]

The estimated mean OS for the BX group was 26 months. These findings indicate that the OS rate is significantly lower in patients with the T315I mutation.



Position	1	2	3	4
Quality	Passed	Passed	Passed	Passed
A (%)	98	-	-	1
C (%)	-	27	1	97
G (%)	2	-	3	2
T (%)	-	73	97	-

Figure 6. Detection of the T315I mutation by the pyrosequencing method in patient 89 (C=27% → T=73%).

Multiple mutations were identified in four patients: F359V/F359C mutations were detected in three patients, and T315I/Y253H mutations in one patient. However, due to the retrospective nature of this study, it was not possible to confirm whether these mutations were compound or polyclonal.

[14]Aypara Hasanova, Chingiz Asadov, Nigar Karimova, Aytan Shirinova, Gunay Aliyeva, Zohra Alimirzoyeva. Spectrum of BCR-ABL mutations in Azerbaijanian imatinib-resistant patients with chronic myeloid leukemia. Pathology & Oncology Research, 2023. – p. 01–11. PubMed ID: 38188610; Impact Factor: 2.3

Table 2

Clinical, hematological, and epidemiological characteristics of the patients

		BCR/ABL1 Mutation		
Variable	**N (163)**	**Positive (n=22)**	**Negative (n=141)**	**P-value**
Sex				
Male	80	17	63	**<0.004[a]**
Female	83	5	78	χ^2=8.08
Age, years				
Mean, 43 (range, 12-79)	163	53 (24-79)	42 (12-78)	0.231
≤49	86	9	77	χ^2= 1.43
≥50	77	13	64	
Disease phase at screening				
CP	119	5	114	**0.00001**
AP	26	5	21	χ^2= 53.12
BC	18	12	6	
Risk group				
Low	48	3	45	0.126
Mean	94	17	77	χ^2=4.13
High	21	2	19	
Spleen				
Normal	10	1	10	0.811
Medium (growth up to 8 cm)	118	17	100	χ^2= 0.41
Massive (>8 cm)	35	4	31	
HB				
Normal (120-160 g/l)	13	3	10	
Mild anemia (100-119 g/l)	49	4	45	<0.480
Mean anemia (80-99 g/l)	57	9	48	χ^2= 2.47
Severe anemia (65-79 g/l)	42	6	38	
WBC				
Normal 3.9-9 (109/l)	2	0	2	0,843
Leukopenia <3.9 (109/l)	0	0	0	χ^2= 0,34
Leukocytosis >9 (109/l)	161	22	139	

PLT				
Normal 180-400 (109/l)	92	12	81	0.920
Thrombocytopenia <180 (109/l)	23	3	21	χ^2= 0.16
Thrombocytosis >400 (109/l)	46	7	39	
Blast cell				
0	62	3	59	**0.017**
1-10	99	18	81	χ^2= 8.12
>10	2	1	1	
Eosinophil Basophil Association				
Eosinophils superiority	118	16	101	0.187
Basophilic superiority	20	4	16	χ^2= 4.79
Without superiority	23	1	23	
No Association	2	1	1	
Additional chromosome aberrations				
Present	31	9	22	**0.006**
Absent	125	11	114	χ^2=10.13
Missing	7	2	5	
Blood group				
O(I)	49	6	43	0.645
A(II)	76	10	66	χ^2=1.66
B(III)	24	5	19	
AB(IV)	14	1	13	
Rh-factor				
Rh+	155	21	134	0.932
Rh-	8	1	7	χ^2=0.007
Seasons				
Spring	38	3	35	
Summer	50	10	40	0.394
Autumn	16	2	14	χ^2=2.98
Winter	57	6	51	
Missing	2	1	1	

[a]P <0.05. CP, chronic phase; AP, acceleration phase; BC, blast crisis; Missing, loss of observation; TKI, tyrosine kinase inhibitor; HB, hemoglobin; PLT, platelet; WBC, white blood cells.

In the current study, it was also not feasible to analyze the impact of compound mutations on progression-free survival due to the limited number of patients.

The development of resistance to TKIs can be classified into BCR/ABL1-dependent and BCR/ABL1-independent mechanisms. BCR/ABL1-dependent mechanisms include overexpression of the BCR/ABL1 kinase and mutations within the BCR/ABL1 domain. BCR/ABL1-independent mechanisms involve the activation and overexpression of alternative signaling pathways (e.g., JAK/STAT), as well as impaired regulation of efflux systems that lead to decreased intracellular TKI levels. Among these mechanisms, ABL1 KD mutations represent the most critical contributors to resistance.

Investigation of CYP3A4*18 and CYP3A5*3 polymorphisms of the cytochrome P450 gene in Azerbaijani patients with chronic myeloid leukemia. The study included 153 patients (102 IM-resistant and 51 with a good response to IM). Among the CML patients, 129 were in the CP, 13 in the AP, and 11 in the BC phase, and all had received at least 12 months of first-line IM treatment (Fig. 7).[15]

Analysis of the CYP3A5*3 polymorphism in CML and control groups revealed that the frequency of the G/G genotype was significantly higher in the CML patient group (99.35%) compared to the control group. This suggests that the presence of the CYP3A5*3 allele may be associated with an increased risk of developing CML (P = 0.016). However, no correlation was found between this polymorphism and the response to IM treatment (Table 3).

In contrast, CYP3A4*18 SNPs were significantly associated with response to IM treatment and indicated an increased risk of developing resistance to IM therapy (P = 0.013). Additionally, the frequency of the CYP3A4*18 allele was significantly higher in poor responders (100%) compared to good responders (97.1%) (P = 0.036).

[15] Chingiz Asadov, Nigar Karimova, Aypara Hasanova, Bayram Bayramov, Ayten Shirinova, Zohra Alimirzoyeva. Association of CYP3A5*3, CYP3A4*18 & CYP2B6*6 polymorphisms with imatinib treatment outcome in Azerbaijani chronic myeloid leukaemia patients. Indian J Med Res 158, August 2023, – p. 151– 160. PubMed ID: 37706370; Impact Factor: 4.2

Table 3
Distribution of CYP3A5*3 and CYP3A4*18 polymorphisms in the case CML and control groups

Genotype	Range				P value
	N (n=153)	IM resistant (n=102)	IM good response (n=51)	Control group (n=100)	
CYP3A5*3					
Homozygous wild-type (AA)	1/0.65	1 / 0.98	0/0	0/0	$\chi 2$ =0.5, P=0.47 (IMR-IMGR)
Heterozygous (AG)	0/0	0/0	0/0	5/5	-
Homozygous mutant (GG)	152/99.35	101/99.02	51/100	95/95	$\chi 2$=8.3, **P=0.016** (all pat.-cont. gr.)
CYP3A4*18					
Homozygous wild-type (TT)	150/98	102/100	48/94.12	100/100	$\chi 2$=6.0, **P=0.013** (IMR-IMGR)
Heterozygous (TC)	3/2	0/0	3/5.9	0/0	$\chi 2$=1.96, P=0.38 (all pat.-cont. gr.
Homozygous mutant (CC)	0/0	0/0	0/0	0/0	-

Despite the lack of correlation with response to IM treatment, the presence of the CYP3A5*3 allele appears to be associated with an increased risk of developing CML. In contrast, CYP3A4*18 SNPs were significantly associated with response to IM treatment and indicate an increased risk of developing resistance to IM therapy.

Based on the findings of this study, it can be concluded that investigating the aforementioned mutations contributes to a better understanding of the molecular mechanisms underlying CML. Furthermore, the identification of these mutations and their association with IM treatment response facilitates disease prognosis,

guides the selection of more effective next-generation TKIs, and supports critical clinical decision-making, such as bone marrow transplantation. In line with the results obtained, a prognosis-based treatment and monitoring algorithm has been developed for each patient.

The findings of this study further underscore the importance of cytogenetic and molecular genetic analyses not only in CML patients, but also in the diagnosis, monitoring, and prognosis of all oncohematological diseases.

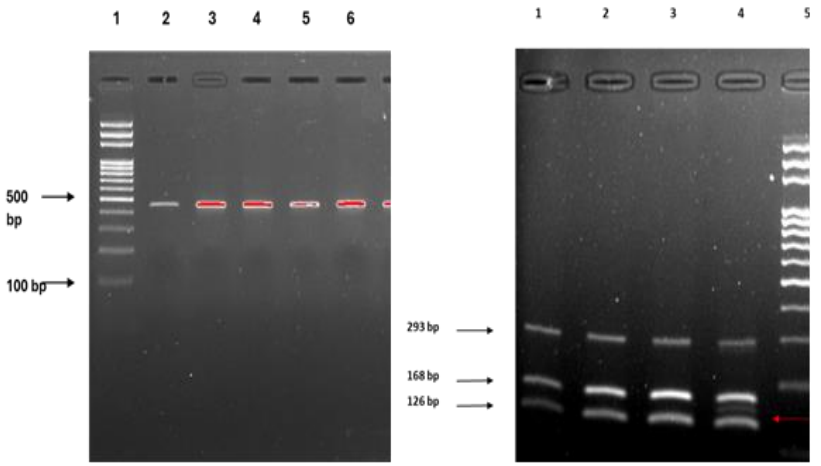


Figure 7. Gel electrophoresis after RFUP analysis for CYP3A4*18.

Gel electrophoresis after RFUP analysis for CYP3A5*3.

CONCLUSION

1. For the first time, the molecular response levels to IM in Azerbaijani CML patients were investigated. It was determined that the molecular responses of 69 patients with sample analyses available across all time intervals were generally consistent with the responses of 173 patients who lacked consecutive interval

assessments between 12–17 months. However, patients in the first group exhibited better responses between 18–23 months and at ≥24 months. All patients in this group achieved at least a 1-log reduction after 18 months, and 82.6% (57/69) achieved at least a 2-log reduction. Such outcomes could not be confirmed in the second group, as initial molecular testing in some patients was performed only after 12-18 months or later following IM initiation. These findings underscore the critical importance of consistent molecular monitoring at 3- to 6-month intervals.

2. For the first time in the Azerbaijani CML patient cohort, various ACAs were identified with differing frequencies. The most commonly observed ACAs were trisomy 8 (+8), an additional Philadelphia chromosome (+Ph), and isochromosome 17q [i(17q)]. A significant association was found between ABL1 KD mutations and the presence of ACAs (P = 0.006). Over a 5.5-year follow-up period, the OS rate was 0% in patients with both TKD mutations and ACAs, whereas it was 70% in those with TKD mutations but without ACAs (P = 0.004). Among patients with ACAs, OS was 0% in the TKD-positive group compared to 63.6% in the TKD-negative group (P = 0.001). These findings confirm that the presence of ACAs is associated with significantly poorer OS outcomes in CML patients."

3. For the first time in the local CML patient population, no direct correlation was found between the deletions of P53, RB1, and ASS1 genes and resistance to IM therapy. However, a strong correlation was observed between hyperdiploidy of chromosome 8 and IM resistance (P = 0.0001). A significant correlation was also found between the number of fusion events and poor response to IM therapy (P = 0.00001). These findings suggest that both low and high fusion signal counts may contribute to the development of resistance to IM and the progression of the disease.

4. For the first time in Azerbaijan, the mutation spectrum of ABL1 KD was investigated, and it was found that the most commonly observed mutations associated with IM resistance in the local CML patient cohort were T315I, F359C, F359V, and F317L mutations. The OS rates for patients in the BCR/ABL1 mutation-positive and mutation-negative groups were 50% and 93%,

respectively (P = 0.00001). For the T315I mutation-positive and negative groups, the OS rates were 0% for the T315I-positive group and 92% for the negative group after 43 months (P = 0.00001). These results indicate that the OS rate is significantly lower in patients with the T315I mutation.

5. For the first time in the local patient population, a statistically significant association was observed between the most commonly found CYP3A5*3 gene polymorphism of the cytochrome P450 family and the risk of CML development (P = 0.016). Furthermore, it was found that the CYP3A4*18 polymorphism significantly affected resistance to IM therapy in CML patients (P = 0.013).

6. As a result of a comprehensive, multi-faceted study, an individualized treatment and monitoring algorithm was developed for the first time based on personal prognoses for each patient within the Azerbaijani chronic myeloid leukemia (CML) cohort.

PRACTICAL RECOMMENDATIONS

1. Considering that continuous monitoring of patients is essential for proper clinical management, I would like to emphasize the importance of including such laboratory tests in the list of services covered by the Medical Insurance System in Azerbaijan. Furthermore, the quantitative measurement of BCR/ABL1 transcripts at different time intervals in patients receiving IM therapy should be mandated by both public and private healthcare systems. These measures will ensure accurate monitoring of treatment responses in all CML patients and enable the timely implementation of alternative therapeutic strategies when necessary**.**

2. In addition to the BCR/ABL1 translocation, the identification of ACAs and gene mutations may be useful in identifying patients with poor prognosis who do not respond well to IM therapy. This information is clinically significant for predicting the disease progression in CML patients, selecting more effective next-generation TKIs and making critical decisions such as bone marrow transplantation.

3. The identification of ABL1 KD mutations can play a crucial role in elucidating the molecular mechanisms of drug resistance during treatment with TKIs. Screening for ABL1 KD mutations in CML patients with both primary and secondary resistance to IM will allow for the proper selection of TKIs, determination of prognosis, and the implementation of personalized treatment. Specifically, alternative treatment options should be considered for patients with the T315I mutation.

4. It is recommended to perform a comparative analysis of CYP3A5*3 and CYP3A4*18 polymorphisms together with other genetic alterations in order to determine the progression tendencies of CML, predict disease prognosis, and improve disease monitoring. Additionally, investigating the spectrum and frequency of these polymorphisms in Azerbaijani CML patients and healthy individuals may provide valuable insights into the risk of other oncohematological disorders and the metabolism of targeted therapies.

5. In cases of resistance to IM and second-line TKIs, the identification of ACAs, gene mutations, ABL1 KD alterations, and cytochrome P450 polymorphisms should be integrated into treatment and monitoring algorithms. This approach will support early therapeutic intervention and timely decision-making regarding hematopoietic stem cell transplantation in resistant patients.

6. The development of personalized algorithms based on genetic and pharmacokinetic markers is recommended for evaluating treatment response and disease prognosis. Such algorithms will facilitate timely selection of optimal therapeutic strategies, enhance treatment efficacy, improve OS, and contribute to better patient outcomes.

LIST OF PUBLICATIONS ON THE SUBJECT OF THE DISSERTATION

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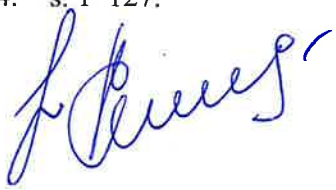

The defense will be held on 26 September 2025, at 11⁰⁰ at the meeting of the FD 1.37 Dissertation Council operating under the Genetic Resources Institute of the Ministry of Science and Education of the Republic of Azerbaijan.

Address: AZ1106, 155 Azadlig Avenue, Baku (conference hall)

The dissertation is available for review at the library of the Genetic Resources Institute of the Ministry of Science and Education of the Republic of Azerbaijan.

The electronic versions of the dissertation and abstract are available on the official website of the Genetic Resources Institute of the Ministry of Science and Education of the Republic of Azerbaijan (https://www.genres.az).

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