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# Evaluation of the significance of mutation and expression of the specific chimeric oncogene Bcr-abl p210 in chronic myeloid leukemia in the Uzbek population

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**Abstract:** The use of tyrosine kinase inhibitors (TKI) considerably improved the prognosis for most patients with chronic myeloid leukemia (CML). However, the issue of resistance to TKI therapy remains a challenge. At present, much attention is paid to the study of molecular genetic profile of tumor cells in CML patients and the role of somatic mutations in various genes, beyond *BCR-ABL1*, in the development of resistance to TKI therapy. New data emerge on the frequency of somatic mutations in various genes by the time of primary diagnosis of CML, commonly in the chronic phase, and on clonal changes during treatment, also when the disease progresses. Of particular interest is the role of somatic gene mutations in the transformation of CML into accelerated phase and blast crisis. Special importance is attributed to the time between the detection of somatic mutations and the registration of disease progression. This review focuses on the results of recent and most relevant studies of molecular genetic profile of CML patients at various disease stages. These studies aim to reveal the associations between somatic mutations in genes and a response to TKI therapy, as well as to assess the prognostic value of the mutations detected upon primary diagnosis and CML therapy.

**Keywords:** tyrosine kinase inhibitors, *BCR-ABL1*, chronic myeloid leukemia.

**Аннотация:** Применение ингибиторов тирозинкиназы (ИТК) значительно улучшило прогноз у большинства пациентов с хроническим миелоидным лейкозом

(ХМЛ). Однако проблема резистентности к терапии ИТК остается актуальной. В настоящее время большое внимание уделяется изучению молекулярно-генетического профиля опухолевых клеток у больных ХМЛ и роли соматических мутаций в различных генах, помимо BCR-ABL1, в развитии резистентности к терапии ИТК. Появляются новые данные о частоте соматических мутаций в различных генах к моменту первичной диагностики ХМЛ, как правило, в хронической фазе, и о клональных изменениях в процессе лечения, в том числе при прогрессировании заболевания. Особый интерес представляет роль мутаций соматических генов в трансформации ХМЛ в фазу акселерации и бластный криз. Особое значение придается времени между обнаружением соматических мутаций и регистрацией прогрессирования заболевания. В обзоре рассматриваются результаты последних и наиболее актуальных исследований молекулярно-генетического профиля больных ХМЛ на различных стадиях заболевания. Целью этих исследований является выявление связей между соматическими мутациями в генах и ответом на терапию ИТК, а также оценка прогностической ценности мутаций, обнаруженных при первичной диагностике и терапии ХМЛ.

**Ключевые слова:** ингибиторы тирозинкиназы, BCR-ABL1, хронический миелоидный лейкоз

**Annotatsiya:** Tirozin kinaz inhibitörlerini (TKI) qo'llash surunkali miyeloid leykemiya (KML) bo'lgan bemorlarning ko'pchiligi uchun prognozni sezilarli darajada yaxshiladi. Biroq, TKI terapiyasiga qarshilik masalasi muammo bo'lib qolmoqda. Hozirgi vaqtda CML bilan kasallangan bemorlarda o'simta hujayralarining molekulyar genetik profilini o'rganishga va TKI terapiyasiga qarshilikni rivojlantirishda BCR-ABL1 dan tashqari turli genlardagi somatik mutatsiyalarning roliga katta e'tibor qaratilmoqda. KML ning birlamchi diagnostikasi vaqtida, odatda surunkali bosqichda, turli genlardagi somatik

mutatsiyalar chastotasi va davolash paytida, shuningdek, kasallik kuchayganida klonal o'zgarishlar haqida yangi ma'lumotlar paydo bo'ladi. KMLni tezlashtirilgan fazaga va portlash inqiroziga aylantirishda somatik gen mutatsiyalarining roli alohida qiziqish uyg'otadi. Somatik mutatsiyalarni aniqlash va kasallikning rivojlanishini qayd etish o'rtasidagi vaqt alohida ahamiyatga ega. Ushbu sharh kasallikning turli bosqichlarida CML bemorlarining molekulyar genetik profilining so'nggi va eng dolzarb tadqiqotlari natijalariga qaratilgan. Ushbu tadqiqotlar genlardagi somatik mutatsiyalar va TKI terapiyasiga javob o'rtasidagi bog'liqlikni aniqlashga, shuningdek, birlamchi tashxis va CML terapiyasi natijasida aniqlangan mutatsiyalarning prognostik qiymatini baholashga qaratilgan.

**Kalit so'zlar:** tirozin kinaz inhibitorlari, BCR-ABL1, surunkali miyeloid leykemiya

**Introduction.** Chronic myelogenous leukemia (CML) is characterized by uncontrolled proliferation of myeloid-derived cells [1]. The pathogenesis of the disease is caused by impaired DNA repair, which leads to the formation of an abnormal Philadelphia chromosome (Ph), a reciprocal translocation between chromosomes 9 and 22 [2, 3]. At the time of primary diagnosis, approximately 90–95% of patients with CML are in the chronic phase (CP) [4–6]. Without treatment, CML progresses from CP to the acceleration phase (AP) and blast crisis (BC). Before the advent of BCR-ABL1 kinase inhibitors, the median survival of patients with CP of CML ranged from 3 to 5 years. With the advent of tyrosine kinase inhibitors (TKIs), survival rates in patients with CML have improved, especially when a complete cytogenetic response (CCR) is achieved. In this group of patients, overall survival became comparable to that in the general population [7].

The BCR-ABL1 fusion gene is detected in more than 95% of patients with CML, ~20%–25% of adult patients and 5% of children patients with acute lymphoblastic leukemia [8]. It is occasionally found in acute myeloid leukemia and acute mixed lineage

leukemia. Therefore, in most cases, BCR-ABL1 measurement is applied for diagnosis and detection of patients with CML in clinical practice and classification of disease types. The tyrosine kinase activated by fusion gene changes the level of protein phosphorylation and inhibits cell apoptosis, responsible for occurrence of neoplastic disorders. Tyrosine kinase inhibitor (TKI) effectively inhibits the activity of the BCRABL1 protein in patients with CML by binding to the adenosine triphosphate-binding pocket of tyrosine kinase [9].

**Objective.** To assess the significance of the specific Bcr-abl p210 chimeric oncogene mutation and its expression in chronic myeloid leukemia.

Method: The materials of our scientific research work were based on the results of clinical (morphological) analyses, standard cytogenetic and molecular genetic studies, and diagnostics of CML patients who were treated in the Republican Specialized Scientific and Practical Medical Center of Hematology (RIGIATM) Molecular Genetics, Cytogenetics and FISH Laboratory in 2023-2024 in inpatient (120 patients) and outpatient (22 patients). Of the 142 patients in the main group, 68 (47.9%) were women, and 74 (52.1%) were men. The age range of patients included in the main group was from 7 to 80 years. We divided the patients into 5 groups by age. The age range was 7-17 years - 2 (1.4%); 18-44 age range 58 (40.8%); 45-59 age range 46 (32.4%); 60-74 age range 33 (23.2%); 75-90 age range 3 (2.1%).

After blood biomaterials were collected, patients' RNA was isolated using QIAGEN reagents (USA) on a NanoDrop 2000 spectrophotometer (NanoDropTechnologies, USA) with a wavelength of A260/280 nm and an RNA concentration of 1.7/1.

Detection of the BCR-ABL p210 chimeric oncogene was performed by PCR in RT mode using a RotorGene 6000/Q thermal cycler (Corbett Research). The amplification process was carried out with initial DNA denaturation at 50 ° C for 30 minutes; 1 cycle of denaturation at 95 ° C for 15 minutes; selection of primers at 95 ° C for 15 seconds; DNA

synthesis was carried out in 45 cycles at 62 ° C for 1 minute. The results obtained were distributed in subgroups of the main group and summarized.

**Result.** The expression of the BCR-ABL p210 chimeric oncogene in chronic myeloid leukemia (CML) is of great importance in the molecular diagnosis and pathogenesis of the disease. According to the results of standard cytogenetic methods in our study, among all 142 patients diagnosed with CML, positivity for the "Ph" chromosome was detected in 132 (92.8%) cases, while the "Ph" chromosome was not detected in the remaining 10 (7.0%) patients with CML. At the same time, based on the use of a newly developed panel of test systems using PCR, the chimeric oncogene BCR/ABL P210 was detected in 142 (100.0%) cases. We studied 142 patients in our main group, divided into 2 groups. The first group was primary CML patients (22 - 15.5%), and the second group was CML patients with ongoing follow-up (120 - 84.5%), which allowed us to analyze the molecular profile differentiation and clonal evolution processes. Ph chromosome was detected in 95.5% of primary CML patients, and BCR-ABL p210 expression was recorded in all of these patients (100%). The presence of BCR-ABL p210 (100%) was also confirmed in 7.0% of patients who did not have a Ph chromosome (see Table 1).

**Table 1**

**Analysis of the BCR-ABL p210 chimeric oncogene in primary CML patients**

| | Ph+ | | Ph- | | Bcr-Abl p210 + | |
|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** |
| **primary CML** n=22 | 21 | 95.5 | 1 | 4.5 | 22 | 100.0 |

BCR-ABL p210 expression was performed to assess the effect of the tyrosine kinase enzyme in CML patients under long-term follow-up.

The results indicate that the BCR-ABL p210 oncogene may be present even in patients without Ph chromosome detection in cytogenetic analysis, which increases the importance of molecular tests in the diagnosis of CML. Therefore, the detection of BCR-ABL p210 by PCR should be used as an important molecular marker for the diagnosis of CML and effective patient monitoring. Quantitative measurements of BCR-ABL p210 expression serve as a reliable marker for assessing the effectiveness of therapy, the level of minimal residual disease, and potential resistance mechanisms. These data are necessary to determine the prognosis of response to treatment and progression, especially during the period of tyrosine kinase inhibitor (TKI)-based therapy. Also, the expression levels obtained using molecular diagnostic methods reflect the genetic diversification and clonal recombination processes of individual patients, which creates an additional scientific basis for the development of individualized treatment strategies.

**Conclusion.** Based on the results obtained, quantitative assessment of the BCR-ABL p210 oncogene helps to identify minimal residual disease, early identification of mechanisms of sensitivity and resistance to TKI therapy. This plays an important role in the formation of individual treatment plans and determining the prognosis of the disease. The combination of molecular diagnostics and cytogenetic analysis allows for a deeper study of the pathogenesis of CML and accurate monitoring of patients. The results of the study show that assessment of BCR-ABL p210 expression is crucial not only for diagnosis, but also for determining the effectiveness of therapy and detecting resistance at an early stage. Therefore, a comprehensive diagnostic strategy that includes molecular tests is an important tool in clinical practice for CML patients.

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