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IDENTIFICATION OF ADDITIONAL CHROMOSOMAL ABNORMALITIES IN Ph-POSITIVE CHRONIC MYELOID LEUKEMIA

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Summary

Keywords: *chronic myeloid leukemia; Philadelphia chromosome; additional chromosomal abnormalities; tyrosine kinase inhibitor*

Purpose: *The study consisted of analyzing the spectrum of karyotype changes in Ph-positive CML patients.*

Methods of the study. The biomaterial for the study was bone marrow and peripheral blood of 142 patients with CML (68 men, 74 women) hospitalized for diagnosis and treatment at the Republican Scientific and Practical Medical Center of the Ministry of Health of the Republic of Uzbekistan for the period 2023-2024. Genetic diagnostics of CML was carried out using the methods of standard cytogenetic study (STS) of G-stained metaphase chromosomes, fluorescent in situ hybridization (FISH) and quantitative PCR with reverse transcription.

Conclusion. The results of the study showed that additional chromosomal abnormalities were detected in 20% of Ph-positive CML patients, and the spectrum of karyotype changes is represented not only by high-risk ACA, but also by other clonal cytogenetic abnormalities. Evaluation of the clinical significance of such ACA requires an in-depth study of their relationship with the clinical course of CML and response to TKI therapy.

Abstract. Chronic myeloid leukemia (CML) is an oncohematological disease of the hematopoietic system, characterized by the presence of the Philadelphia (Ph) chromosome in tumor cells, containing the BCR::ABL1 oncogene, and disease progression from the chronic phase to the acceleration phase and blast crisis. The derivative chromosome 22 (Ph chromosome) is the result of a reciprocal translocation t(9;22)(q34;q11). The aberrant BCR::ABL1 oncogene encodes the BCR-ABL1 protein with constantly increased tyrosine kinase activity. Kinase activity leads to disruption of physiological signaling pathways, causes uncontrolled proliferation, inhibition of differentiation and apoptosis [1,2].

Ph chromosome is found in 90-95% of patients with CML and is the main target for treatment with targeted drugs - tyrosine kinase inhibitors (TKIs). However, approximately 15-20% of patients with CML have additional chromosomal abnormalities (ACA), which have a significant impact on the course of CML, treatment

efficacy and prognosis, since they are associated with the risk of CML progression [5]. Thus, high-risk ACA, including additional Ph chromosome, i(17)(q) +8, +19, +21, +17, -7/7q-, 3q26.2, 11q23 and complex karyotypes can be associated with a longer time to complete cytogenetic remission (CCR) and major molecular response (MMR), as well as with a shorter progression-free survival and overall survival for patients treated with imatinib, which requires an individual approach to the treatment of such patients [3,4]. However, other chromosomal abnormalities may be detected in Ph-positive CML cells, the significance of which has not yet been sufficiently studied. Therefore, the study of additional chromosomal changes in CML is an urgent task.

Results. The Ph chromosome was detected in 139 patients (97.9%) with CML diagnosis based on clinical and laboratory data. In 3 patients (2.1%) the Ph chromosome was not detected by cytogenetic methods. In 28 (20.0%) Ph-positive patients, additional chromosomal abnormalities were detected, including: trisomy 8 (+8) – in six patients (21.4%); isochromosome [i(17)(q)] – in four patients (14.3%); additional Ph chromosome (+der22) – in four patients; trisomy 19 (+19) – in one patient (3.6%); trisomy 17 (+17) – in one patient (3.6%); trisomy 15 (+15) – in one patient (3.6%). monosomy 21 (–21) – in one patient (3.6%); deletion of the long arm of chromosome 13 [del(13q)] – in two patients (7.1%). Four patients (14.3%) had additional derivative chromosomes of unknown origin (+der?). Five patients (17.9%) had hypodiploid karyotypes (2n<46) with unidentified chromosome losses, two more patients (7.1%) had hyperploid karyotypes (4n~10n). The obtained data indicate that the spectrum of chromosomal changes occurring in patients with CML goes beyond the list of additional high-risk anomalies. Occurring in Ph-positive cells as a result of genomic instability and clonal evolution, additional anomalies may be a consequence of the ineffectiveness of ITC treatment due to primary or acquired resistance to therapy. If the high-risk chromosomal abnormalities identified in this study (+der22, +8, i(17)(q), +17, +19) are known predictors of the disease transition to the acceleration stage and blast crisis, then other cytogenetic changes (+15, –21, del(13q), etc.) have an uncertain prognostic status due to the rare occurrence of each individual rearrangement. Evaluation of the clinical significance of extraordinary ACA requires accumulation of data on cases with such abnormalities and a more detailed study of their relationship with clinical and laboratory parameters of hematological, cytogenetic and molecular response to ITC therapy, the course and outcome of CML.

Conclusion. The results of the study showed that additional chromosomal abnormalities were detected in 20% of Ph-positive CML patients, and the spectrum of karyotype changes is represented not only by high-risk ACA, but also by other clonal cytogenetic abnormalities. Evaluation of the clinical significance of such ACA requires an in-depth study of their relationship with the clinical course of CML and response to TKI therapy. Early detection of these abnormalities allows choosing a more appropriate

therapeutic approach. However, larger multicenter studies are needed to more clearly determine the clinical significance.

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