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# Dilemmas in the Diagnosis and Management of CML in Pakistan

Pakistan'daki KML Olgularının Tanı ve Tedavi Yönetimindeki İkilemler

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# To the Editor,

The *BCR::ABL1* fusion gene causes chronic myeloid leukemia (CML), leading to the abnormal activation of the ABL1 kinase and enhancing leukemic cell proliferation. Patients with CML are categorized into three phases: the chronic phase, accelerated phase, or blast phase [1]. Several biomarkers have been employed in diagnosing and confirming the disease. CML can be effectively controlled with the use of tyrosine kinase inhibitors (TKIs) [2]. Pakistan is the fifth largest country in the world with a population of more than 240 million and is classified as a middle-income nation. The majority of CML patients are from Punjab (67.6%) and Khyber Pakhtunkhwa (20.2%), including both rural and urban areas of these provinces [3]. CML, being a somatic cancer, involves various environmental, nutritional, and genetic factors.

Despite notable advancements in the treatment of CML in recent years, imatinib remains the primary therapy initially utilized, acting to inhibit the relevant oncoprotein. Second-generation TKIs such as nilotinib offer increased effectiveness compared to imatinib, targeting a broader array of pathways. In cases of imatinib resistance, patients often transition to nilotinib. However, for those resistant to nilotinib, ponatinib emerges as a preferred strategy. Nevertheless, the effectiveness of TKIs is limited, and managing a blast crisis is a formidable challenge in CML treatment. In this progressed stage of the disease, there is evidence of a complex mix of clonal, genomic, and molecular variations, frequently involving additional abnormalities in chromosomes and mutations within the BCR::ABL1 kinase domain, as well as other genes associated with leukemia. For patients failing multiple TKIs, including third-generation ponatinib, outcomes remain unsatisfactory with limited treatment options available [4]. In addition, management of the disease in older individuals, pregnant women, TKI-resistant

patients, and those with comorbidities presents additional hurdles in both diagnosis and treatment. This complexity often leads to adverse outcomes, with mortality being a frequent consequence.

Difficulties are encountered in both the management and diagnosis of CML. The Pakistani government provides access to imatinib and nilotinib, but third-generation TKIs are not widely available. The primary obstacle lies in the cost of diagnostic tests, which are crucial for CML patients. Hematological, cytogenetic, and molecular tests are recommended to assess the disease status. Additionally, a fresh complete blood count test is conducted at each follow-up appointment. Some patients show resistance and a mutational analysis test is recommended, which involves advanced techniques like next-generation sequencing, whole-exome sequencing, Sangar sequencing, or panel sequencing to evaluate the changes in the genome and plan the best strategy for therapy. However, these tests are too costly for middle-class individuals to afford as each test costs more than half of a laborer's monthly income. Furthermore, the government of Pakistan does not provide testing facilities.

There are few oncology departments in government hospitals. The Pakistan Atomic Energy Commission (PAEC) has 19 PAECmanaged Atomic Energy Cancer Hospitals spread across the country, significantly contributing to alleviating the cancer burden in the country and handling almost 80% of cancer cases in Pakistan [5]. Timely improvement in the diagnosis and management of CML is a pressing issue in Pakistan. The government of Pakistan should take measures to establish cancer care hospitals in every district of the country. Diagnostic facilities and genetic screening should be available in hospitals. Facilities for third-generation advanced TKIs and combination therapies should be provided to enhance treatment options and improve patient outcomes. Keywords: Chronic myeloid leukemia, TKI resistance, CML management, CML diagnostic techniques, CML therapies in Pakistan

Anahtar Sözcükler: Kronik myeloid lösemi, TKI direnci, KML vönetimi, KML tanısal teknikler, Pakistan'da KML tedavisi

#### Ethics

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### Footnotes

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