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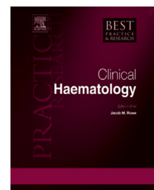

Making the diagnosis, the tools, and risk stratification: More than just BCR-ABL

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A B S T R A C T

The implementation of cytogenetic and molecular techniques into standard clinical practice has improved our ability to more accurately diagnose and monitor CML. Routine peripheral blood *BCR-ABL* transcript testing can help monitor response, predict outcome, and detect early resistance or poor adherence to TKI therapy. The widely-used Sokal, Hasford and EUTOS clinical risk stratification scores were developed in patients receiving chemotherapy, interferon and imatinib, respectively; their predictive ability in patients receiving next-generation tyrosine kinase inhibitors (TKIs) remains to be established. Newer more sensitive molecular techniques are being developed that may aid in the expanding emphasis on discontinuing therapy in patients with a deep and consistent molecular response.

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Introduction

Chronic myeloid leukemia (CML) is perhaps the most famous example of a specific, acquired genetic abnormality causing disease. The reciprocal translocation of genetic material from the breakpoint cluster region (*BCR*) gene on chromosome 22 with the Abelson (*ABL*) gene on chromosome 9 forms the Philadelphia chromosome (Ph) [1,2]. This unique genetic event codes for the abnormal fusion protein, BCR-ABL, and this constitutively active tyrosine kinase drives the pathogenesis of the disease. Both the translocation and *BCR-ABL* transcript are detectable through the use of various laboratory techniques,

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allowing the accurate diagnosis of CML, as well as sensitive monitoring of therapeutic response. Thus, the Ph is a unique biomarker, as it is the target for both therapy (with tyrosine kinase inhibitors), and diagnostic tests.

Making the diagnosis: understanding the CML "toolkit"

Patients who present with an elevated, left-shifted, white blood cell count that is not better explained by infection or inflammatory response should be suspected as having CML. Other hallmarks of the disease include an enlarged spleen, basophilia, and presence of such constitutional symptoms as fever, rigors, sweats and anorexia. Review of the peripheral blood smear shows myelocytes, metamyelocytes, and bands, as well as varying degrees of eosinophils, basophils and nucleated red blood cells. Often the diagnosis of CML can be inferred on clinical grounds, but prior to instituting therapy, laboratory studies to determine the presence of either the Philadelphia chromosome (Ph) or *BCR-ABL* fusion must be performed. As will be discussed below, patients with clinical features of CML, but without detectable Ph or *BCR-ABL*, should undergo alternative diagnostic testing (e.g. *JAK2* V617F, *CSF3R*, etc.) for consideration of alternative diagnoses, including atypical CML or a myelodysplastic/myeloproliferative (MDS/MPN) overlap disorder.

There is considerable heterogeneity that exists between patients in regards to the exact locations of the involved chromosomal breakpoint regions. However, in the vast majority of cases, a portion of the breakpoint cluster region (*BCR*) gene on chromosome 22, band q11 has been fused with the tyrosine kinase domain of the Abelson (*ABL*) gene on chromosome 9, band q34 [3]. There are, thus, three primary methods the clinician must use in the diagnosis and monitoring of CML: cytogenetics, fluorescence *in situ* hybridization, and molecular testing with polymerase chain reaction (PCR) techniques.

Cytogenetic testing

Conventional metaphase cytogenetics require dividing cells, and thus are most often performed from bone marrow as opposed to peripheral blood [4]. Two weeks are usually required for results to be obtained. Since generally only 20 cells are visualized, the lower level of detection of the Ph is roughly 5% (one Ph with 19 negative cells). Most translocations resulting in the juxtaposition of *BCR* and *ABL* are readily detected by conventional cytogenetics, but a small proportion of cases may involve complex changes that still result in formation of a *BCR-ABL* transcript but without detectable Ph. The advantage of cytogenetics is that it can detect other structural chromosomal changes, which can be indicative of advanced phase disease. Therefore, all patients suspected of having CML should undergo bone marrow cytogenetic testing to both make the diagnosis as well as determine the stage of disease. The disadvantage of cytogenetics is that typically only 20 cells are sampled, and thus it is not as informative in monitoring ongoing disease burden during treatment as other methods such as FISH and RT-PCR (below).

Fluorescence in situ *hybridization (FISH)*

As opposed to conventional cytogenetic testing, analysis by FISH uses fluorescently-labeled probes for the *BCR* and *ABL* genes to detect co-localization of genetic material that should be found on separate chromosomes in normal cells. For rapid clinical decision-making, FISH has certain advantages over cytogenetics, including the speed of the assay (generally 1–2 days), and the fact that the technique can be performed on both dividing and static cells (thus, cells in metaphase or interphase), allowing for analysis of either peripheral blood or bone marrow specimens [4]. Because 200–500 cells are routinely assayed, FISH has a superior limit of detection for the *BCR-ABL* translocation compared to cytogenetics. However, the propensity for false-positive signals (due to chance co-localization of probes in three-dimensional space, for example) means that borderline or low-level positive fluorescence signals must be interpreted with caution [5]. Notably, since probes specific for *BCR* and *ABL* are used, other important chromosomal rearrangements that might be present will go undetected unless cytogenetic testing is performed concurrently.

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