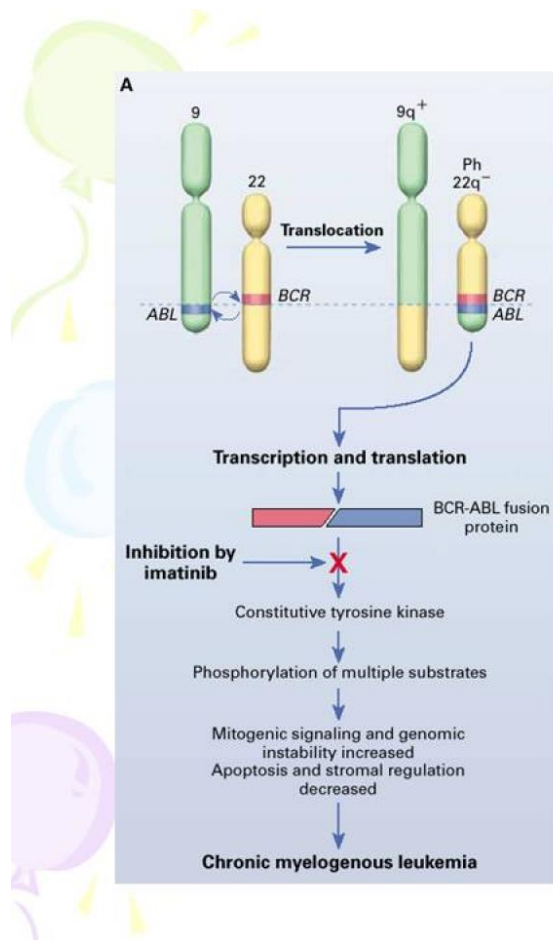


Chronic Myelogenous Leukemia BCR-ABL1 by PCR



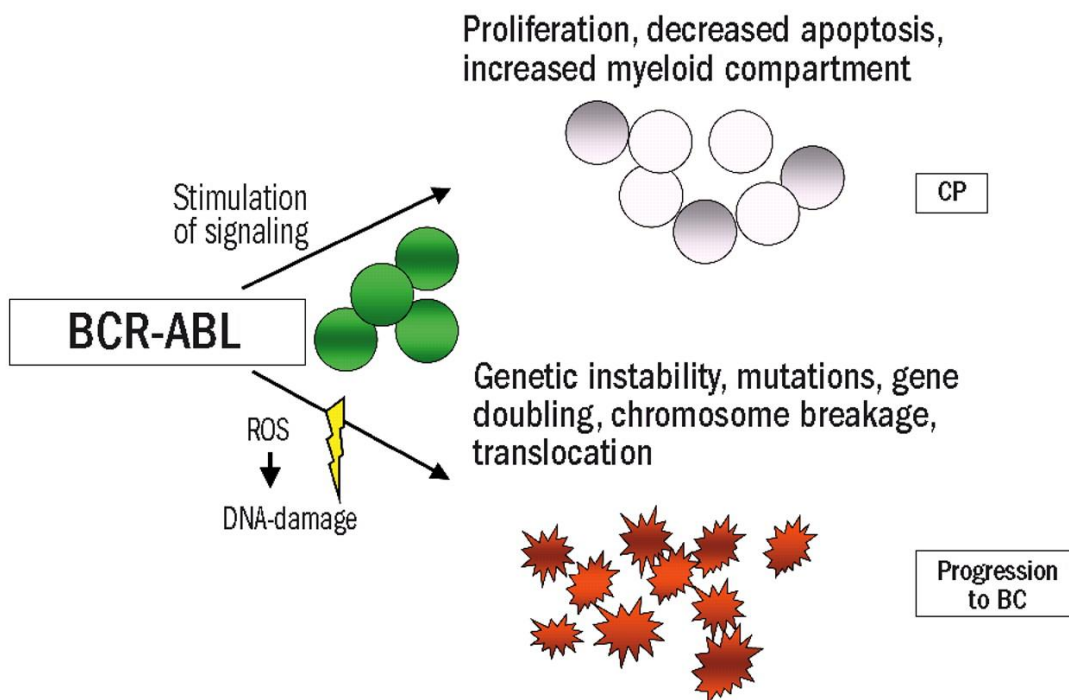
Philadelphia Chromosome

- A shortened chromosome 22 resulting from the translocation between chromosome 9 and chromosome 22
- Produces BCR-ABL oncogene

Introduction

In the 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms, MPNs include: chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia, mastocytosis, and unclassifiable MPNs. CML is the only MPN that is characterized by the chromosomal translocation t(9;22), BCR-ABL fusion gene.

In most cases, diagnosis of CML is based on blood counts (leukocytosis and frequently also thrombocytosis) and differential immature granulocytes, from the metamyelocyte to the myeloblast, and basophilia). Splenomegaly is present in >50% of cases of CML in the initial chronic phase (CP), but about 50% of patients are asymptomatic. Proof of diagnosis is attained by demonstration of the Philadelphia (Ph) chromosome (22q-) resulting from the balanced translocation $t(9;22)(q34;q11)$, and/or the BCR-ABL rearrangement in peripheral blood or bone marrow cells.



Clinical Background

The BCR-ABL1 fusion gene is formed by a translocation between chromosomes 9 and 22 [$t(9;22)$], which also results in an abnormally short chromosome 22 (the Philadelphia chromosome; Ph). The fusion gene is present in virtually all individuals with CML and is the hallmark diagnostic feature of the disease. The BCR-ABL1 rearrangement results in the production of a fusion protein with constitutive tyrosine

kinase activity, which is thought to play a role in the development of leukemia.

Methodology

The Method used in this assay is reverse transcription polymerase chain reaction (RT-PCR) - GeneXpertDx System. The amount of BCR-ABL transcript is quantified as the ratio of BCR-ABL/ABL.

Clinical Use of BCR-ABL1 RT-PCR

- Diagnose chronic myelogenous leukemia (CML)
- Monitor the effectiveness of therapy
- Monitor minimal residual disease (MRD)
- Predict disease progression

Interpretive Information

Diagnosis

Along with characteristic cell morphology findings, presence of the P210 BCR-ABL transcript is consistent with CML.

Typical testing strategy

At diagnosis: BM cytogenetic studies and quantitative measurement of BCR-ABL1 transcript levels are recommended before treatment initiation

Monitoring Progress

The quantity of transcript detected in the initial test serves as a baseline for serial monitoring. An increasing BCR-ABL1/ABL1 percent ratio over time suggests an increase in tumor burden, while a decreasing ratio suggests a favorable response to therapy. For P210 transcription, a BCR-ABL1/ABL1 ratio of 0 represents a complete

molecular response to therapy. BCR-ABL1/ABL1 % (IS) values $\leq 0.1\%$ correspond to a 3-log or greater reduction from the baseline, indicating a major molecular response (MMR) in CML patients and thus excellent progression-free survival.

Monitoring response to TKI therapy in CML

The goal of TKI therapy is to achieve a complete cytogenetic response within 12 months of initiation of therapy with goal of eventual major molecular response. A subset of individuals will eventually achieve a complete molecular response. The favorable prognosis is measured as a 3-log decrease in the level of BCR-ABL1 fusion transcripts (major molecular response) within 18 months of beginning TKI therapy is an indicator of favorable outcome

The recommended strategy of monitoring using quantitative RT-PCR

- 1- Every 3 months when treatment response is evident
- 2- After complete cytogenetic response has been achieved and every 3 months for 3 years, and every 3-6 months thereafter
- 3- More frequent monitoring may be required in individuals with rising BCR-ABL1 transcripts to detect early relapse

Sample Precautions

- Specimen Required: 5.0 mL EDTA Blood
- Storage/Transport Temperature: Refrigerated
- Unacceptable Conditions: Bone marrow samples, Ambient temp or Frozen storage condition - Sample volume < 1.0 mL
- Samples exceeds 48 hour transport.

Ordering Information

Test Code	Test Name
1565	Major BCR-ABL Detection by Real Time PCR
1579	Major BCR-ABL Monitoring by Real Time PCR

References:

1. Vardiman JW, Melo JV, Baccarani M, et al.(2008)
2. Borowitz MJ & Chan JKC. (2008)
3. Jones D, Rajyalakshmi L, Cortes J, et al. (2008)
- 4.Serpa et al. (2010)