Single BCR/ABL1 Fusion Isoform Testing Based on Prior Results Proven Insufficient in Monitoring CML Patient Due to Mutation Co-Expression

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Abstract

A hallmark of Chronic Myelogenous Leukemia (CML) is the translocation of part of chromosome 9 with chromosome 22, "swapping" DNA across the chromosomes and leading to the formation of oncogene BCR/ABL1. Various molecular methods can be used to detect the specific (isoform) oncogene fusions, information that is critical to informing prognostic and therapeutic decisions. Once a specific isoform is identified in a patient, laboratories typically narrow their testing to monitoring only that fusion, to follow patient response and further inform treatment decisions. However, these established fusion isoforms can change over time[1,2]. Consequently, narrowly focused monitoring of a single isoform can lead to missed changes in the patient's oncogene profile, delaying critical care and fast therapeutic intervention.

Here we present a case study of a patient tested using a more comprehensive approach to CML patient monitoring by Precipio's clinical lab that identifies an otherwise-missed isoform change from previous tests, enabling the physician to act quickly to adjust the patient's treatment plan.

Case Presentation

A 64-year-old African American male previously diagnosed with chronic myelogenous leukemia (CML) with a p210 isoform fusion, presented for routine check-up with neutrophilic leukocytosis and pain due to shingles. His past medical history revealed shingles, hypertension, and cardiac problems. His vital signs were within normal ranges and the physical exam was normal. The patient was obese (BMI 4279 kg/m2). He was on Hydrocodone-Acetaminophen (7.5 – 325mg) oral tablets. Blood analysis confirmed the neutrophilic leukocytosis with high eosinophils and neutrophils.

Table 1 Blood work up

Test	Normal Range	Results
WBC (x10³/µL)	4.5 – 10.5	48.27
RBC (x10⁶/µL)	4 – 6	4.75
HGB (g/dL)	11 – 18	13.9
HCT	35 – 60	42.4
MCV (µm³)	80 – 99.9	89.2
MCH (pg)	27 – 31	29.3
MCHC (g/dL)	33 – 37	32.8
RDW%	11.5 – 13.7	17.5
PLT (x10³/µL)	150 – 450	3.2.1
MPV (µm³)	7.8 - 11	8.8
LYM%	18.94 – 46.71	8.48
MON%	4.88 – 12.81	3.25
NEU%	40.62 – 71.65	85.05
EOS	4.5 – 10.5	48.27
BAS	4 – 6	4.75

Discussion

HemeScreen BCR/ABL1 panel testing which detects p190, p203, p210, and p230 isoforms was performed to monitor the patient's fusion isoform status to detect p210 expression as well as isoform changes and co-expressions. Precipio's lab detected an elevated level of p210 expression, as well as a co-expression of fusion isoform p190 that was previously undetected. BCR/ABL1 translocations in the major breakpoint cluster region resulting in fusion protein are seen in nearly all cases of chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) and myeloproliferative neoplasms (MPN/MDS). p190 BCR/ABL1 fusion encodes micro transcripts e19a2 common in Philadelphia-positive B-ALL and has been reported in 1% of CML cases.

Clinical monitoring for p210 expression status alone would have been insufficient for monitoring this patient due to the rise in isoform transformation and co-expressions. In a simple workflow, the HemeScreen panel-based approach with broad isoform coverage supports routine monitoring of mutation status as well as detecting isoform transformations and co-expressions when they occur.

[1] Elias Jabbour, Hagop M. Kantarjian, Giuseppe Saglio, et. al.. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood 2014; 123 (4): 494–500. doi:10.1182/blood-2013-06-511592

[2] Soverini S, De Benedittis C, Papayannidis C, et al. Drug resistance and BCR-ABL kinase domain mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia from the imatinib to the second-generation tyrosine kinase inhibitor era: The main changes are in the type of mutations, but not in the frequency of mutation involvement. Cancer. 2014;120(7):1002-1009. doi:10.1002/cncr.28522