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Case Report

Rare *BCR::ABL1* Fusion Gene in Chronic Myeloid Leukaemia: A Case Report

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Abstract

Chronic myeloid leukemia with a *BCR::ABL1* b2a3 transcript is difficult to detect by conventional polymerase chain reaction (PCR). This can result in an incorrect diagnosis. We report a man with typical features of chronic myeloid leukemia but with a negative conventional PCR test for *BCR::ABL1* in whom we identified a *BCR::ABL1* fusion gene by fluorescence *in situ* hybridization and PCR with custom *BCR* and *ABL1* primers.

Introduction

Three intronic chromosome breakpoint regions in *BCR,* when joined with *ABL1,* are associated with the development of chronic myeloid leukemia (CML) including: (1) major (M-*BCR*); minor (m-*BCR*); and (3) micro (u-*BCR*). The M-*BCR* region consists of *BCR* introns downstream of exon 13 (e13, previously b2) or 14 (e14, previously b3) linked to exon 2 (a2) of *ABL1*. *BCR::ABL1* fusions e13a2 (b2a2) and e14a2 (b3a2) result in a P210$^{BCR::ABL1}$ chimeric protein. m-*BCR* and u-*BCR* have uncommon breakpoints in the intronic region between *BCR* exon 2 and exons 19 and 20 which encode 190-kDa$^{BCR::ABL1}$ (e1a2) and 230-kDa$^{BRC::ABL1}$ (e19a2), resulting in P190$^{BCR::ABL1}$ and P230$^{BCR::ABL1}$. Several atypical *BCR::ABL1* transcripts (e1a3, e13a3, e14a3, e19a3, e6a2 and e8a2) are reported resulting from breakpoints outside *ABL1* intron 1 *or BCR* introns 1, 13 or 14 and may be missed using standard *BCR* and *ABL1* primers in polymerase chain reaction (PCR).

We report the case of a young man with clinical and laboratory features of CML and a *BCR::ABL*1 b2a3 transcript. Despite a negative PCR test for *BCR::ABL1* transcripts using conventional *BCR* and *ABL1* primers a translocation was detected by fluorescence *in situ* hybridization (FISH) and confirmed using novel PCR primers. He responded rapidly to nilotinib.

Case report

In 2015 a routine blood test of an asymptomatic 19-year-old man showed leukocytosis and thrombocytosis; exact values are unknown. He was referred to a hematologist but demurred. In 2017, a blood study performed in an emergency department because of ethanol intoxication showed a hemoglobin concentration of 155 g/L, white blood cell (WBC) and platelet concentrations of 17 × 10E+9/L and 475 × 10E9/L with 72% granulocytes. Again, there was no follow-up. Six months later he saw a physician complaining of nausea, weight loss and palpitations. There was no lymph node, spleen or liver enlargement on physical exam. The hemoglobin concentration was 145 g/L, WBC concentration, 15.9 × 10E+9/L with 67% granulocytes and platelets, 599 × 10E+9/L. A computed tomography scan showed no abnormalities. He refused a bone marrow examination and no cytogenetic studies were done. A multiplex qualitative and quantitative PCR test using e14a2 and e13a2 primers for *BCR::ABL1* transcripts was negative. FISH analyses with *BCR* and *ABL1* probes were consistent with t(9; 22), leading to a presumptive diagnosis of CML. He received nilotinib, 800 mg/d. An RNA sample using an e13a3 qualitative primer confirmed CML. After 1 month, his hemoglobin concentration and WBC and platelet concentrations were normal. A bone marrow exam in late 2018 revealed a 46,XY karyotype in 20 metaphases studied. FISH was not repeated. Two years after starting nilotinib, he had a hemoglobin concentration of 151 g/L and WBC and platelet concentrations of 5.9 × 10E+9/L and 276 × 10E+9/L with 52% granulocytes. In early 2019, PCR was done using primers designed to detect the b2a3 transcript. A *BCR* exon 13 region-targeting forward primer (5′-CATCCGGGAGCAGCAGAAGAA-3′) and

Keywords: Chronic lymphocytic leukemia; *BCR::ABL1*; Polymerase chain reaction; Ph-chromosome.

Abbreviations: CML, chronic myeloid leukemia; FISH, fluorescence *in situ* hybridization; PCR, polymerase chain reaction; TKIs, tyrosine kinase-inhibitors; WBC, white blood cell.

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ABL1 exon a3 region-targeting reverse primer (5′-GTGTTTCTC-CAGACTGTTGGCT) were used. A reverse transcription PCR test was negative indicating a > 4.5-log reduction in BCR::ABL1 transcripts on the International Scale (<$MR^{4.5}$). The subject is well without symptoms or adverse events from nilotinib.

Discussion

BCR::ABL1 transcripts with intronic breakpoints downstream of *ABL* a2 are rare. *ABL* a2 encodes part of Src homology 3 (SH3) domain which inhibits the SH1 kinase domain required for the activation of signal transducer and activator of transcription-5 by $P210^{BCRABL1}$. This might result in a milder leukemia phenotype. Although the *ABL* a3 breakpoint does not affect the ATP/imatinib binding site sequence it potentially alters the tertiary structure of $P210^{BCR::ABL1}$ and could increase (tyrosine kinase-inhibitor) TKI binding. We are testing this hypothesis by computer modeling and *in vitro* experiments.

There is considerable controversy regarding whether the specific *BCR::ABL1* transcript correlates with the prognosis of people with CML, especially those receiving TKIs. Several studies have reported correlations between *BCR::ABL1* transcript type and response to TKIs.[1–15] We recently reported that the e14a2 *BCR::ABL1* transcript was associated with a higher rate of therapy-free remission.[13] Another study reported that the e14a2 transcript correlated with an increased response to imatinib, and conversely, the e13a2 transcript was associated with a worse response.[14] A 3rd study reported higher rates of a 4.5-log reduction in *BCR::ABL1* transcripts, better event-free survival and less risk of transformation to the acute phase in subjects with an e14a2 than in those with an e13a2 transcript, regardless of initial TKI therapy.[15] Lower response rates to TKIs were reported in subjects with an e13a2 transcript. A registry of 45,503 newly diagnosed patients from 45 countries suggested that the transcript type may correlate with therapy-response and the likelihood of therapy-free remission.[16] Another study of subjects receiving imatinib found that those with atypical *BCR::ABL*1 transcripts are younger, respond better to TKI therapy and have a better prognosis than those with CML with typical *BCR* breakpoints. Structural and laboratory analyses of the mechanism of action of TKIs in this setting are underway.

In conclusion, individuals with clinical and laboratory features of CML and a *BCR::ABL1* b2a3 transcript may not be detected by routine PCR testing with conventional *BC*R and *ABL1* primers. Cytogenetic FISH or PCR testing with specialized primers should be performed for individuals with suspected CML and a negative conventional PCR-test for *BCR::ABL1*.

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Conflict of interest

RPG is a consultant to Antengene Biotech LLC, Ascentage Pharma Group and NexImmune, Inc.; Medical Director, FFF Enterprises, Inc.; A speaker for Janssen Pharma and Hengrui Pharma; Board of Directors: Russian Foundation for Cancer Research Support; and Scientific Advisory Boards, Nanexa AB and StemRad Ltd. The other authors have no conflict of interest to declare.

Author contributions

RD and DGT conceived the typescript. DdOT, IB and LN did the laboratory studies. RPG revised the typescript. The authors approved the content, accepted responsibility for the content and agreed to submit the typescript for publication.

Ethical statement

The study was approved by the Ethics Committees of the respective institutions consistent with precepts of the Declaration of Helsinki (2013). The subjects gave written informed consent to publish the article.

Data sharing statement

All data are in the typescript.

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