Concomitant L248V with E225V mutation in BCR-ABL gene associated with rapid CML lymphoid blast crisis

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Case Report

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Abstract

Background

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome (Ph), resulting from the t(9;22)(q34;q11.2) translocation. Imatinib, a tyrosine kinase inhibitor, has revolutionized the treatment of CML. However, despite the initial response, some patients may progress to an advanced stage, such as a blast crisis.

Case Presentation:

We report a 40-year-old female who presented with CML chronic phase taking imatinib 400 mg/day and achieved a complete hematological response (CHR) after one month of treatment. She achieved suboptimal response in the third month (BCR-ABL positive 10.29% IS). However, five months into therapy, she developed a sudden lymphoid blast crisis with chromosomal aberrations involving chromosome 10 and 12. Molecular analysis detected concomitant L248V with partial exon 4 deletion and E225V mutations within the BCR-ABL1 fusion gene. The patient received intensive chemotherapy and dasatinib.

Conclusion

We report the first case of concomitant mutation of L248V with partial exon 4 deletion and E255V on BCR-ABL1 gene mutation which contributes to a sudden precursor B-cell lymphoid blast crisis.

Introduction

Chronic Myeloid Leukemia (CML) is a clonal myeloproliferative disorder characterized by the unregulated proliferation of myeloid precursor cells within the bone marrow. This leads to the accumulation of abnormal white blood cells, primarily granulocytes, in the peripheral blood and bone marrow. The disease is driven by the BCR-ABL1 chimeric gene product, that codes for a constitutively active tyrosine kinase, resulting from a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34.1;q11.2), known as the Philadelphia chromosome (Ph)\(^1\).

CML accounts for 15–20% of adult leukemia cases. The worldwide incidence is approximately 0.6 to 2.0 cases per 100,000 persons, which are more common in males than females, with ratios ranging between 1.3 and 1.8.\(^2\)

According to European LeukemiaNet (ELN) definition \(^3\), CML is categorized into different stages based on the progression of the disease, comprising the chronic phase, accelerated phase, and blast phase. (Table 1) The chronic phase usually lasts several years. The accelerated phase lasts 4 to 6 months. The blast phase, terminal phase of CML, lasts only a few months.\(^4,5\) The majority of CML cases (> 90%) are
diagnosed in chronic phase, while a minority (2.2%) may present with *de novo* blast crisis. Patient with blast transformation from chronic phase or accelerated phase can either be myeloid or lymphoid blast crisis. Lymphoid blast crisis accounts for around 30% of CML blast crisis cases. 

Table 1

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Accelerated phase</th>
<th>Blast phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blast cells: &lt;15% of total in blood</td>
<td>• Blast cells: ≥15% of total in blood or bone marrow</td>
<td>• Blast cells: ≥30% of total in blood or bone marrow</td>
</tr>
<tr>
<td>• Blast cells and promyelocytes: &lt;30% of total in blood and bone marrow</td>
<td>• Blast cells and promyelocytes: ≥30% of total in blood or bone marrow</td>
<td>• Extramedullary disease with immature blast cells</td>
</tr>
<tr>
<td>• Basophils: &lt;20% of total in blood and bone marrow</td>
<td>• Basophils: ≥20% of total in blood or bone marrow</td>
<td></td>
</tr>
<tr>
<td>• Platelets: &gt;100 × 10^9 cells per L</td>
<td>• Persistent thrombocytopenia (&lt; 100 × 10^9 platelets per L) unrelated to therapy</td>
<td></td>
</tr>
<tr>
<td>• No additional chromosomal abnormalities at the time of diagnosis</td>
<td>• Clonal chromosomal abnormalities in Philadelphia chromosome-positive cells, major route, on treatment</td>
<td></td>
</tr>
</tbody>
</table>

The first-line treatment is a Tyrosine-kinase inhibitor (TKI). A short course of hydroxyurea may be given in symptomatic patients with high white blood cell or platelet counts while molecular and cytogenetic confirmation of the CML diagnosis is pending. Currently, four FDA-approved TKIs that are commercially available to use as a first-line treatment for chronic phase CML are first-generation imatinib and second-generation dasatinib, nilotinib, and bosutinib.

It is essential to regularly monitor the patient’s response to TKI drug therapy in CML to assess the response. (Table 2)
### Table 2
**Response definition**

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematologic response (CHR)</td>
<td>Leukocyte count $&lt; 10 \times 10^9$/L; platelet count $&lt; 450 \times 10^9$/L; normal differential with no early forms; no splenomegaly</td>
</tr>
<tr>
<td>No cytogenetic response</td>
<td>$&gt; 95%$ Ph positive cells</td>
</tr>
<tr>
<td>Minimal cytogenetic response</td>
<td>$66 - 95%$ Ph positive cells</td>
</tr>
<tr>
<td>Minor cytogenetic response</td>
<td>$36 - 65%$ Ph positive cells</td>
</tr>
<tr>
<td>Major cytogenetic response</td>
<td>Complete and Partial cytogenetic responses</td>
</tr>
<tr>
<td>- Partial cytogenetic response (PCyR)</td>
<td>$1 - 35%$ Ph positive cells</td>
</tr>
<tr>
<td>- Complete cytogenetic response (CCyR)</td>
<td>$0%$ Ph positive cells</td>
</tr>
<tr>
<td>Major molecular response (MMR)</td>
<td>$BCR-ABL1$ IS $\leq 0.1%$</td>
</tr>
<tr>
<td>- MR4.0</td>
<td>$BCR-ABL1$ IS $\leq 0.01%$</td>
</tr>
<tr>
<td>- MR4.5</td>
<td>$BCR-ABL1$ IS $\leq 0.0032%$</td>
</tr>
<tr>
<td>Complete molecular response (CMR)</td>
<td>Undetectable $BCR-ABL1$</td>
</tr>
</tbody>
</table>

The European LeukemiaNet (ELN) has defined a treatment milestones base on quantity of $BCR-ABL1$ during treatment.$^3$ (Table 3)
Table 3
Treatment milestones base on European LeukemiaNet (ELN) definition

<table>
<thead>
<tr>
<th></th>
<th>Optimal response</th>
<th>Warning or suboptimal response</th>
<th>Intolerance or resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Not applicable</td>
<td>High-risk ACA, high-risk ELTS score</td>
<td>Not applicable</td>
</tr>
<tr>
<td>3 months</td>
<td>BCR-ABL1 ≤10%</td>
<td>BCR-ABL1 &gt;10%</td>
<td>BCR-ABL1 &gt;10% confirmed within 1–3 months</td>
</tr>
<tr>
<td>6 months</td>
<td>BCR-ABL1 ≤1%</td>
<td>BCR-ABL1 &gt;1–10%</td>
<td>BCR-ABL1 &gt;10%</td>
</tr>
<tr>
<td>12 months</td>
<td>BCR-ABL1 ≤0.1%</td>
<td>BCR-ABL1 &gt;0.1–1.0%</td>
<td>BCR-ABL1 &gt;1%</td>
</tr>
<tr>
<td>Any time after 12 months</td>
<td>BCR-ABL1 ≤0.1%</td>
<td>BCR-ABL1 &gt;0.1% to 1.0% and loss of major molecular response</td>
<td>BCR-ABL1 &gt;1%; emergence of resistance mutations; high-risk ACA</td>
</tr>
</tbody>
</table>

Following imatinib treatment, early molecular response rates at 3 months (BCR-ABL1 ≤ 10% IS) range between 60 and 80%. At one and 5 years, MMR rates range between 20–59% and 60–80%, respectively.8–10

Sudden blast crisis (SBC) is categorized as a rapid onset of blast crisis after a documented optimal response to TKI and within 3 months of a normal complete blood count. Incidence was 0.7% of CML chronic phase patients who were treated with imatinib.11 Though SBC is rare during the TKI therapy era, it was reported in a patient who, previously achieved MMR, discontinue TKI due to restricted access to health services during COVID-19 pandemic.12

Although persistent expression of BCR-ABL leads to genomic instability, there is a report that deletions of the derivative chromosome 9 in CML can lead to rapid progression to blast crisis by loss of one or more tumor suppressor genes(TSG).13 Chromosomal abnormalities involving chromosome 8,17,19 and 22 were reported, whether they were associated with genomic stability or not, with duplication of the Ph chromosome or trisomy 8 being the most frequent in CML blast crisis.14

There are two reports of L248V BCR-ABL mutation in imatinib-resistant CML patients.15 Both cases developed disease progression between 15 to 17 months. While the E255V mutation reported in Korea was a relatively more aggressive clinical course in just three months, the patient developed to an accelerated phase, not a blast crisis.16

This report presents an adult woman with CML sudden lymphoid blast crisis from concomitant L248V with partial exon deletion and E255V mutation developed in a patient who previously responded to imatinib and had good compliance with medication.

Case Report
A 40-year-old female with no known underlying diseases presented to the hospital with a two-day history of high-grade fever. Upon examination, her temperature was 36.6 C, her blood pressure measured 130/80 mmHg, and her respiratory rate was 20/min. General examination revealed no pallor. Abdominal examination indicated mild hepatomegaly and splenomegaly 4 FB BLCM.

Initial investigations revealed Hb 11.3 g/dL, WBC 92790 cells/mm³, Neutrophils 67% Lymphocytes 14%, Monocyte 3%, Eosinophil 3%, Basophil 3%, Band form 2%, Blast 1%, Metamyelocyte 3%, Promyelocyte 3%, Platelet count 737000/mm³. BCR-ABL by reverse transcription PCR (RT-PCR) from blood was positive > 55% IS. Bone marrow biopsy showed 95% cellularity, marked myeloid predominance, and increased megakaryocytes. Bone marrow aspiration revealed markedly hypercellular marrow, M:E ratio of 10:1, and myeloblast 2%. Chromosome study showed 46, XX,t(9;22)(q34;q11.2)[20]. She was diagnosed with the CML chronic phase, intermediate risk Sokal score. Imatinib 400 mg oral per day was started in December 2023.

**Management and outcome**

One month after starting imatinib, the patient achieved CHR, which Hb 10.0 g/dL, WBC 2760/mm³ with normal differential counts and platelet count 288,000/mm³. Physical examination showed no hepatomegaly and no splenomegaly. She reported good compliance with imatinib.

Three months after starting imatinib, CBC was normal. Hb 10.7, WBC 7370, N66%, L28%, Eo1%, Monocyte3%, platelet 268000. BCR-ABL was positive 10.29% IS, compatible with suboptimal response, according to ELN definition. After discussing it with the patient, she decided to continue with imatinib 400 mg/day.

Five months after starting imatinib, the patient developed fatigue, dyspnea, and gum bleeding. Physical examination was body temperature 36.5 C, blood pressure 167/94 mmHg, pulse rate 97/min, respiratory rate 20/min, mild hepatomegaly, splenomegaly 2 FB BLCM. Her CBC revealed Hb 10.2, Hct 31.6%, WBC 269490/mm³ with 94% of lymphoblast and platelet count of 52,000/mm³. Peripheral blood smear showed markedly increased lymphoblasts. (Figs. 1 and 2) Bone marrow biopsy showed small foci of atypical large cells with blastic nuclear appearance infiltration. Bone marrow aspiration revealed markedly hypercellular marrow, 90% lymphoblast. Flow cytometry showed CD10+, CD19+, CD34+, HLA-DR+, TdT + blasts with aberrant CD33 expression compatible with precursor B acute lymphoblastic leukemia (ALL). Chromosome study was 46,XX,t(9;22)(q34;q11.2),del(12)(q22q24.1)[8]/ 46,XX,t(9;22)(q34;q11.2),ins(10;12)(q22;q22q24.1)[3]. BCR-ABL1 protein p210 (b2a2) was positive, p190 was negative. BCR-ABL mutation gene assay with peripheral blood sample (by RT-polymerase chain reaction) detected **L248V with partial exon 4 deletion and E225V mutation.** She was diagnosed with CML with lymphoid blast crisis.

The patient received Pediatric-adapted Ph-positive-ALL treatment protocol due to age 40 years old. She received vincristine [2 mg/week intravenously for 4 doses], doxorubicin [30 mg/m² weekly for 3 doses].
prednisolone [60 mg/m² for 28 days], and asparaginase [5,000 U/m² for 10 days], together with switching the TKI from imatinib to dasatinib 140 mg/day. Due to intensive chemotherapy, she developed two episodes of Candida tropicalis septicemia and Stenotrophomonas septicemia. She died from septic shock nonresponsive to multiple antibiotics 7 months after the initial CML diagnosis.

**Discussion**

Imatinib is one FDA-approved, first-line treatment for chronic phase CML. Although the patient has responded to imatinib by achieving CHR before, mutations within the tyrosine kinase domain of the ABL gene are a significant contributor to resistance against tyrosine kinase inhibitors in individuals with chronic myelogenous leukemia (CML). These mutations are observed in a substantial portion of CML patients who experience resistance, with prevalence ranging from 30–90%, depending on the studies. These mutations encompass over 40 distinct amino acid changes, each imparting varying degrees of resistance to imatinib, a commonly used TKI.

Based on current knowledge, it is not advisable to routinely conduct mutation screening unless there are specific reasons to do so, such as a loss of treatment effectiveness. Identifying mutations in the ABL gene during the chronic phase (CP) of CML treatment may potentially improve treatment outcomes. Nevertheless, it’s important to note that regular ABL mutation screening is not generally recommended for CML patients.

In this study, we found a concomitant mutation of L248V with partial exon 4 deletion and E255V on the BCR-ABL1 gene mutation and chromosomal aberrations involving chromosome 10 and 12 which contributes to not only resistance to tyrosine kinase inhibitors but also a sudden lymphoid blast crisis.

**Conclusion**

This case describes mutations in the BCR-ABL1 gene, specifically the L248V with partial exon 4 deletion and E255V variants, and chromosomal aberrations involving chromosome 10 and 12 which impact the response to imatinib treatment and a sudden lymphoid blast crisis in a patient who previously responded to imatinib.

**Declarations**

ST wrote the first draft of the manuscript. PW researched literature and revised the manuscript. SU participated in data collection and analysis. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Informed Consent

The patient and her family were informed about this publication and consent form was signed.
References


Figures
Figure 1

peripheral blood smear

Figure 2

peripheral blood smear