

A Unique Three-Way Variant Philadelphia Chromosome $t(6;9;22)(p21.3;q34;q11.2)$ in a Newly Diagnosed Patient with Chronic Myeloid Leukemia Responded to Flumatinib

Lili Chen¹, Junling Zhang^{1,2}, Na Yang¹, Ningping Tan¹, Di Meng¹, Fei Zhang¹, Yuyang Qi¹, Guangqi Wu¹, Zhenyu Li³

¹Department of Hematology, The Affiliated Suqian Hospital of Xuzhou Medical University, Suqian, People's Republic of China; ²The Medical Department, 3D Medicines Inc., Shanghai, People's Republic of China; ³Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, People's Republic of China

Correspondence: Zhenyu Li, Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, 221002, People's Republic of China, Email lizhenyumd@163.com; Guangqi Wu, Department of Hematology, The Affiliated Suqian Hospital of Xuzhou Medical University, Suqian, 223800, People's Republic of China, Email wgqjssq@163.com

Background: Chronic myeloid leukaemia (CML) is a clonal malignant disorder of a pluripotent hematopoietic stem cell characterized by the presence of Philadelphia (Ph) chromosome in more than 90% of patients. However, about 5–10% of CML patients show a variant Ph translocation, involving one or more chromosomes in addition to 9 and 22. The treatment and prognostic impact of such additional abnormalities is not known. Herein, we report a unique case of a three-way translocation variant in CML and responded to flumatinib.

Case Presentation: A 22-year-old Asian female who presented with leukocytosis was diagnosed with CML. Cytogenetic karyotyping analysis showed $46,XX,t(6;9;22)(p21.3;q34;q11.2)$. She was treated with flumatinib, and MR5.0 ($BCR-ABL1$ IS $\leq 0.001\%$, international scale) was achieved after three months of continuous treatment.

Conclusion: This was the 5th case of $t(6;9;22)$, in particular, a new variant Ph translocation, and the first successful case treated with flumatinib in the world.

Keywords: $t(6;9;22)(p21.3;q34;q11.2)$, CML, Philadelphia chromosome, flumatinib, case report

Introduction

Chronic myeloid leukemia (CML) is a malignant tumor formed by clonal proliferation of pluripotent hematopoietic stem cells, which accounts for about 15% of adult leukemia.¹ It is characterized by the presence of a translocation between chromosomes 9 and 22, $t(9;22)(q34;q11)$, known as the Philadelphia (Ph) chromosome, leads to the generation of *BCR-ABL* oncogenic fusion gene.² The gene encodes a chimeric BCR-ABL protein with constitutive kinase activity, which affects the proliferation and apoptosis of bone marrow cells.³ Although more than 90% of CML patients are associated with typical $t(9;22)(q34;q11)$, but about 5–8% of newly diagnosed CML patients are associated with complex variant Ph (vPh) chromosome, involving one or more chromosomes in addition to 9 and 22.⁴ The mechanism of vPh chromosome translocations generation and its effect on prognosis is unclear, but may further classify CML in specific subsets requiring different therapeutic approaches. However, some previous studies have suggested that CML patients with vPh chromosome may have a worse prognosis than patients with typical translocations, including 3 cases with CML with three-way complex vPh $t(6;9;22)$ chromosome translocations.^{5–8}

For CML patients with Ph chromosome-positive and *BCR-ABL1*-positive, the emergence of tyrosine kinase inhibitors (TKIs) such as imatinib significantly improved the prognosis of patients.⁹ However, CML was associated with vPh t

(6;9;22) whether patients could benefit from other TKI therapy has not been reported. Herein, we report a unique case of a three-way vPh chromosome translocation in CML and responded to flumatinib.

Case Presentation

A 22-year-old female patient presented to a local hospital in August 2020 due to left abdominal distention and discomfort. Color ultrasound of abdomen showed splenomegaly (thickness: 57mm). Hematological analysis revealed white blood cell (WBC) was $330.08 \times 10^9/L$, neutrophils $295.65 \times 10^9/L$, lymphocytes $8.24 \times 10^9/L$, eosinophils $2.07 \times 10^9/L$, basophils $14.30 \times 10^9/L$, a hemoglobin level of 84 g/L, and platelet count of $229 \times 10^9/L$. Peripheral blood smear showed 3.0% lymphocytes, 0.5% monocytes, 1.0% eosinophils, 4.0% basophils, 4.0% promyelocytes, 20.0% mesogranulocyte, and 15.0% metamyelocytes, 48% band granulocyte, 5% segmented neutrocyte. In addition, the nucleated red cells were 2 per 100 cells (Figure 1). Aspartate aminotransferase is 47.5U/L, lactate dehydrogenase is 1903.3U/L. Genetic analysis results indicated that no obvious mutations on JAK-2 V617F, CALR, and MPL were observed. Cytogenetic analysis was performed utilizing bone marrow culture cells, and all analyzed cells showed a complex, three-way t(6;9;22)(p21.3;q34;q11.2) Ph chromosome translocation (Figure 2). Therefore, she was diagnosed with CML-CP, and her Sokal and EUTOS long-term survival (ELTS) score were 0.59 (low risk) and 1.577 (low risk), respectively.

Initially, she was treated with orally administered hydroxyurea at a daily dose of 1.0g bid on August 6, 2020. However, during the course of treatment, the WBC count dropped to $18 \times 10^9/L$. Therefore, hydroxyurea was discontinued, and flumatinib at a daily dose of 600 mg was administered on August 14, 2020. Her BCR-ABL/ABL international scale (IS) levels at 3, 6, 9 and 12 months were 0.249%, 0.000%, 0.000% and 0.000%, respectively. Molecular response (MR) of *BCR-ABL1* gene was assessed by RT-PCR using *ABL* gene as reference gene in our central laboratory. Blood counts were measured during treatment. Three months after flumatinib treatment, molecular remission 5 (MR5) (BCR-ABL/ABL $\leq 0.001\%$ IS) was achieved, and complete MR (CMR) remained until December 2021. Blood counts were normal (Table 1).

Discussion

CML was associated with clone stem cell syndrome, and cytogenetic abnormality was acquired abnormality. Ph chromosomes, presented in more than 90% of cases, were later responsible for the production of the protein BCR-ABL gene fusion. More importantly, this fusion gene would interfere with WBC and weaken the immune system.¹⁰ However, 5–8% of CML patients' present variant and complex translocation, in addition to chromosomes 9 and 22, known as vPh. Despite the genetically heterogeneous nature of these alterations, available data indicate that CML patients displaying complex variant translocations do not exhibit a less favorable outcome as compared to individuals presenting conventional Ph-positive CML.¹¹ Di Raimondo et al found that two CML patients with complex variant

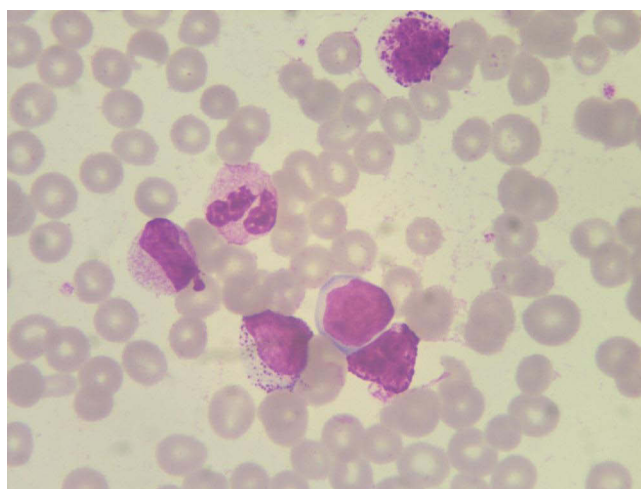


Figure 1 Peripheral blood smear result.

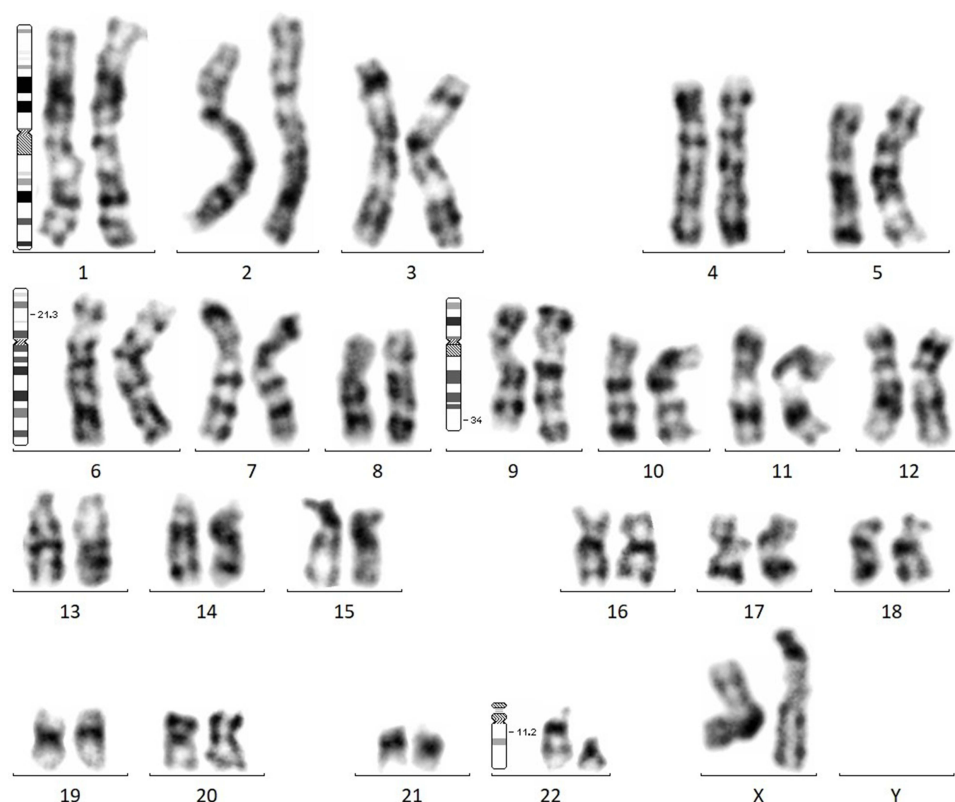


Figure 2 Cytogenetic analysis shows a variant three-way translocation 46,XX,t(6;9;22)(p21.3;q34;q11.2).

translocations achieved an optimal response to tyrosine kinase inhibitors (TKI) treatment.¹² In a retrospective study, 693 CML chromosomes were identified by conventional and molecular cytogenetics, of which 5% (32/693) had vPh chromosomes, and the most common variation was t(1;9;22) (p36;q34;q11.2), t(1;9;22)(q21;q34;q11.2), t(2;9;22)(p13;q34;q11.2), t(5;9;22)(q31;q34;q11.2), t(5;9;22)(q35;q34;q11.2), t(9;22;11)(q34;q11.2;q13), t(9;22;12)(q34;q11.2;p13) and t(9;22;15)(q34;q11.2;q22).¹³

The clinical significance and mechanism of vPh chromosome formation were still not clear. Some researchers predict a one-step mechanism, while others predict a two-step or multi-step mechanism.¹⁴ However, existing results suggested that the vPh translocation in CML patients may affect the response to imatinib treatment, thereby affecting the prognosis of patients.¹⁵ At the same time, the proportion of patients with vPh translocation CML in accelerated phase was higher than that of patients with classical translocation CML (56% vs 38%).¹⁶ Various side effects have been reported in patients treated with imatinib.¹⁷ Therefore, how to choose treatment for patients with complex karyotypes is a pain point in

Table I The Hematological Analysis Result of the Patient During the Therapy

	2020/9/14	2020/9/28	2020/10/12	2020/10/26	2020/11/23	2020/12/7	2020/12/21
WBC ($\times 10^9/L$)	7.12	6.8	4.95	6.68	7.76	6.17	6.48
Neutrophils ($\times 10^9/L$)	3.99	3.15	1.91	3.21	3.8	2.57	2.68
Lymphocytes ($\times 10^9/L$)	2.22	2.81	2.36	2.72	3.09	2.81	3.08
Eosinophil ($\times 10^9/L$)	0.09	0.13	0.11	0.1	0.17	0.14	0.09
Basophils ($\times 10^9/L$)	0.11	0.06	0.03	0.03	0.02	0.02	0.02
RBC ($\times 10^{12}/L$)	3.31	3.53	3.78	4.03	4.09	3.85	4.14
Hemoglobin (g/L)	103	107	112	119	130	119	126
Platelet ($\times 10^9/L$)	151	165	172	181	179	168	190

Abbreviations: WBC, white blood cell; RBC, Red blood cells.

clinical treatment. At the same time, these patients may need to be closely monitored for treatment side effects and disease progression.

Flumatinib, a novel oral *BCR-ABL1* TKI currently marketed in China, has better efficacy than imatinib in the treatment of newly diagnosed chronic phase CML. In the FESnd study, the rate of major molecular response at 6 months and 12 months was significantly higher with flumatinib than with imatinib (33.7% vs 18.3%; $P = 0.0006$; 52.6% vs 39.6%; $P = 0.0102$, respectively). At 3 months, the rate of early molecular response was also significantly higher in patients receiving flumatinib than in those receiving imatinib (82.1% vs 53.3%; $P < 0.0001$). More patients receiving flumatinib achieved MR4 at 6, 9, and 12 months (8.7% vs 3.6%, $P = 0.0358$; 16.8% vs 5.1%, $P = 0.0002$; and 23.0% vs 11.7%, $P = 0.0034$, respectively). No patients had progression to accelerated phase or blast crisis in the flumatinib group vs 4 patients in the imatinib group by 12 months.¹⁸ Whether flumatinib is effective in CML patients with vPh chromosomes has not been reported in the literature.

In the present study, we report the first case of a complex three-way vPh chromosome t(6;9;22)(p21.3;q34;q11.2) successfully treated with flumatinib, which has not been described previously. This case provides a broader treatment for CML patients with vPh chromosomes, but whether it is effective for more complex vPh chromosomes needs to be verified by prospective clinical studies, and further explore the mechanism of vPh occurrence.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of The Affiliated Suqian Hospital of Xuzhou Medical University.

Consent for Publication

The patient provided written informed consent for the case details to be published.

Funding

There is no funding to report.

Disclosure

Junling Zhang is employee of 3D Medicines Inc. The authors report no other conflicts of interest in this work.

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