Clinical Case Report

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Recurrent chronic myeloid leukemia with t (9;22;16) (q34; q11; p13) treated by nilotinib

A case report

Yefei Shu, MD, Wei Yang, MD, Xuejin Zhang, MD, Xiaofeng Xu, MD*

Abstract

Rationale: Variant Philadelphia chromosome translocations involving chromosomes other than chromosomes 9 and 22 have been reported in 5% to 10% of patients with chronic myeloid leukemia (CML). Here, a case of CML with a t (9, 22, 16) (q34; q11; p13) translocation, which has never been described, is reported.

Patient concerns: A 59-year-old female with dry cough, referred to our hospital, exhibited hepatosplenomegaly, high basophil count, and high platelet count at admission without any other known chronic diseases.

Diagnoses: The patient was diagnosed with CML with the translocation t (9;22;16) (q34; q11; p13). The patient was treated with imatinib, a first-generation tyrosine kinase inhibitor (TKI), discontinuously, achieving a complete hematological response for 7 years. Since November 8, 2017, the patient had recurrent fever, and her platelet count rose to 1422×10^9/L. Subsequently, the E279K mutation in the BCR-ABL kinase region was detected.

Outcomes: According to a previous report, this mutation confers sensitivity to nilotinib, a second-generation TKI. In the end, the patient received treatment with nilotinib and showed a complete hematological response.

Lessons: The present study reports a rare case of CML with Ph chromosome and a t (9;22;16) (q34; q11; p13) translocation. For such cases about CML with variant Philadelphia chromosome translocations or BCR-ABL kinase region mutation, TKI may still be valuable.

Abbreviations: ACAs = additional cytogenetic aberrations, CML = chronic myeloid leukemia, OS = overall survival, Ph = Philadelphia, TKI = tyrosine kinase inhibitor.

Keywords: chronic myeloid leukemia, nilotinib, t (9 ;22 ;16) (q34, q11, p13)

1. Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease that is characterized by the Philadelphia (Ph) chromosome with the reciprocal translocation t (9;22) (q34; q11).[1] The chromosome 9 and chromosome 22 transposal t (9; 22) (q34; q11) causes the cancer gene C-ABL at 9q34 to link with the BCR gene at 22q11, forming the BCR-ABL gene on chromosome 22.[2] Around 95% of chronic myelogenous leukemia patients show t (9;22) (q34; q11).[3]

Around 5% to 10% of these patients show complex translocations involving a third chromosome in addition to chromosomes 9 and 22.[4,5] Extra Ph, +8, i(17q) and +19, have been described as the most common secondary changes (known as the major route), whereas others infrequent changes are considered the minor route.[6] Here, we report a recurrent, complicated, differentiated case of CML with t (9,22,16) (q34; q11; p13) which was treated by nilotinib, a second-generation tyrosine kinase inhibitor (TKI).

2. Case report

In May 2010, a 59-year-old female with dry cough was referred to our hospital for examination and treatment. The patient exhibited hepatosplenomegaly at admission without any other known chronic diseases. Laboratory results were as follows: white blood cells, 9.3×10^9/L (normal range, 4.0–10.0×10^9/L); basophils 1.3×10^9/L (normal range, 0–0.15×10^9/L); hemoglobin, 12.2 g/dL (normal range, 11.5–15.5 g/dL); platelets, 519×10^9/L (normal range, 100–300×10^9/L); promyelocytes 2%. Physical examination found splenomegaly (3 cm below the costal margin).

The bone marrow routine exam indicated the following: original granulocytes 6.5%, promyelocytes 1.0%, basophilic cells 7%; leukemia immune typing: primitive myeloid cell populations 7.16%; basophilic cell group 15.10%, M-bcr-abl/abl 50%; JAK2 mutation (−). A complex karyotype t (9;22;16) (q34; q11; p13) was determined by G-banding and fluorescence in situ hybridization (FISH) using a commercially available probe specific for BCR and ABL revealed that the typical Ph-chromosome with BCR/ABL-translocation was present, accompanied with other abnormalities. Thus, the patient was diagnosed with chronic phase CML.

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YS and WY contributed equally to this study.

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Department of Hematology, Hangzhou Red Cross Hospital, Hangzhou, Zhejiang, PR China.

* Correspondence: Xiaofeng Xu, Department of Hematology, Hangzhou Red Cross Hospital, East 208 Huancheng Road, Hangzhou, Zhejiang 310003, PR China (e-mail: hhxuxiaofeng@126.com).

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The patient was treated with 400 mg/d imatinib (a first-generation TKI) discontinuously; routine blood examination results were stable. The patient was under follow-up since 2010, and responding well to treatment. In February 2012, the patient stopped treatment because the white blood cell count decreased significantly. To control the disease, she started long-term treatment with hydroxyurea (1 and 2 g on alternate days) until 2014, and then discontinued the drug due to intolerance. Since August 20, 2014, she started taking imatinib (400 mg/d) again. With these treatments, the patient achieved a complete hematological response and stopped coming to the hospital for consultation until 2017. On November 8, 2017, her platelet count rose to 1422×10^9/L, accompanied with recurrent fever. Bone marrow puncture was performed again, and the bone marrow smear report showed 2.5% of the original cells; however, the bone marrow flow was negative. A complex karyotype t (9;22;16) (q34; q11; p13) was identified by G-banding again. Evaluation of the BCR-ABL kinase region showed the E279K mutation. On November 22, 2017, platelet separation was performed and platelet count decreased further to 800×10^9/L; on November 22, 2017, she started taking nilotinib (400 mg, twice a day); on November 25, 2017, mild adverse events, including the whole body aches, fever, and vomiting were observed and these immediate adverse events were relieved gradually in the next 2 weeks. On November 30, 2017, the platelet count rose to 900×10^9/L. On December 13, 2017, white blood cell count was 3.2×10^9/L, hemoglobin was 9.4 g/dL, and platelet count was 311×10^9/L. On April 7, 2018, white blood cell count was 2.1×10^9/L, hemoglobin was 11.9 g/dL, and platelet count was 184×10^9/L. As of September 10, 2018, the patient is still receiving nilotinib and continues to show a complete hematological response without side effects.

Ethical approval was given by the medical ethics committee of Hangzhou Red Cross Hospital to publish this study. The patient has consented for the publication of the present case report.

3. Discussion

Variant Ph translocations have been divided into simple variant translocations involving chromosome 22 and another chromosome, and complex variant translocations involving chromosomes 9 and 22 and 1–3 other chromosomes.[7,8] Two different mechanisms are known to generate variant 3-way translocations, a one-step mechanism in which chromosomal breaks occur simultaneously on 3 different chromosomes and a two-step mechanism involving 2 sequential translocations in which a standard t (9;22) translocation is followed by a second translocation involving additional chromosomes.[4] A case with a 3-way Ph translocation variant involving 16p13 associated with CML, which has only been observed in our hospital, in addition to t (9,22,16) (q34; q11.2; p13) is reported.[9]

In CML patients, additional cytogenetic aberrations (ACAs) in Ph-positive cells affect the progression and response to treatment depending on the chromosomal aberration and time of appearance. ACAs are usually detected during disease progression into the accelerated phase or blast crisis.[10] At diagnosis, ACAs have been observed in ~5% of cases and are associated with clonal evolution, resistance, and adverse prognosis under imatinib treatment.[11] Imatinib is still effective because of the presence of BCR-ABL. The European Leukemia Net guidelines suggest that the presence of ACAs at diagnosis may represent a 'warning', requiring careful monitoring.[12] A previous study showed that the presence of ACAs in the early chronic phase was one of the independent predictors for CML progression within a year. While several studies have shown worse overall survival (OS) with imatinib treatment in patients with a variant Ph translocation, there are also many reports showing less impact on OS.[13] For patients with TKI resistance, mutation and ACA screening may play a role in identifying patients with poorer prognoses.[14] However, the impact of t (9;22;16) (q34; q11; p13) at diagnosis and its prognostic significance are issues worthy of discussion.

Imatinib, as a first-line drug, achieves 85% to 90% of the 10-year survival rate of CML patients.[15] Imatinib acts by blocking BCR-ABL gene expression and inducing apoptosis of CML cells, playing a vital role in continued survival and better quality of life.[5] Although initial response is high, therapy fails in up to 40% of patients and initial response is lost within 2 years in approximately 25% of patients with t (9;22) (q34; q11) translocation.[16] In another study, it was found that the patients with complicated differentiated disposal Ph positive CML showed a poorer prognosis after treatment with imatinib.[7]

The present study reports a rare case of CML with Ph chromosome and a t (9;22;16) (q34; q11; p13) translocation at diagnosis, with unfavorable responses, even though the patient received appropriate treatment. Although a long overall survival time (>8 years) was observed in the present study, the patient progressed to an accelerated phase of CML. During treatment with imatinib, the patient developed resistance. One of the most important mechanisms of acquiring resistance is via mutations in the tyrosine kinase domain of ABL1. The E279K mutation was detected in the present patient during the last year of follow-up. Based on a previous report,[17] showing the sensitivity of the E279K mutant to nilotinib, the patient received treatment with nilotinib. After failure of the treatment with imatinib, nilotinib induced a more rapid reduction in the expression of BCR-ABL transcripts, even in the hematopoietic stem cell population.[18] Nilotinib can achieve a faster and better molecular response, and gradually become one of the first-line treatment options for CML patients.[19,20]

The acceleration period of the patient was characterized by increased platelets and recurrent fever. Platelets are significantly affected during CML progression and treatment; however, currently there is no literature available on the role that platelets play in CML progression, despite reports of platelet count and size being affected.[21,22] Moreover, it has been confirmed that high platelet count is an independent predictor of response to imatinib in myeloid blast crisis of CML.[23]

This is a rare CML case with t (9;22;16) (q34; q11; p13), treated by imatinib discontinuously without cytological mitigation for 7 years. After entering the acceleration periodcharacterized by increased platelets and recurrent fever, once the E279K mutation was detected, the treatment was shifted to nilotinib, and complete hematological response was achieved. For such cases about CML with variant Philadelphia chromosome translocations or BCR-ABL kinase region mutation, TKI may still be valuable.

Author contributions

Conceptualization: Xuejin Zhang.
Project administration: Xiaofeng Xu.
Writing – original draft: Yefei Shu.
Writing – review & editing: Wei Yang.

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