Received: 17 September 2017 | Accepted: 1 November 2017

DOI: 10.1002/pro6.31

CASE REPORT

WILEY

Imatinib resistance was reversed by nilotinib in the acute transformation of chronic myeloid leukemia: A case report

Meng Xiao* | **Hongjing Zhou*** | **Shuguo Li*** | **Chunlei Xin** | **Tongfeng Zhao** | **Yunliang Hao** | **Shumei Li** | **Yanyan Liang**

Jining NO.1 People's Hospital, Jining, China

Correspondence
Tongfeng Zhao, Jining NO.1 People's Hospital, Jining 272000, China.
Email: zhaotongfeng@126.com

*These authors contributed equally to this work.

Abstract

Chronic myeloid leukemia (CML) is a clonal malignant hematopoietic disorder that arises in a hematopoietic stem cell. Its characteristic cytogenetic abnormality is an abnormal chromosome 22 called the Philadelphia (Ph) chromosome. The *BCR-ABL1* fusion gene in this chromosome can encode a tyrosine protein kinase and is the molecular basis of CML pathogenesis. The tyrosine kinase inhibitor (TKI) imatinib is the 'gold standard' therapy for the treatment of CML. However, around 30% of the patients develop imatinib resistance. In this report, we will illustrate a case of an adult female with acute transformation of CML whose imatinib resistance was reversed by nilotinib and has had a long-term survival.

KEYWORDS

chronic myeloid leukemia, imatinib, nilotinib, tyrosine kinase inhibitors

1 | INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal malignant hematopoietic disorder that arises in a hematopoietic stem cell. Its characteristic cytogenetic abnormality is a reciprocal translocation between chromosomes 9 and 22, t (9;22)(q34;q11), which gives rise to an abnormal chromosome 22 called the Philadelphia (ph) chromosome. The *BCR-ABL1* fusion gene in this chromosome can encode and express tyrosine protein kinase, activate the downstream signaling pathway, and lead to excessive proliferation, the blocked apoptosis of myeloid progenitor cells, and the decreased adherence of bone marrow stromal cells, creating a large number of immature myeloid cells that are released into the peripheral blood circulation, which causes CML.[1] A tyrosine kinase inhibitor (TKI) is a pharmaceutical drug that inhibits the *BCR-ABL* tyrosine kinase, and is the first-line treatment for most patients with CML. In the present report, we illustrate a case of a woman with an acute transformation of CML whose imatinib resistance was reversed by nilotinib and has had a long-term survival.

2 | CASE REPORT

XX Man, a 29-year-old woman, was admitted to Qingdao Municipal Hospital, Qingdao, China, due to epistaxis 9 years previously, which had been diagnosed with CML based on a routine blood test, bone marrow morphology, detection of fusion genes, and chromosome analysis. The patient was treated with imatinib (400 mg/day, oral administration) for 4 years. During this course, she occasionally rechecked her routine blood test, with results of white blood cell count (WBC) 9×10^9/L, platelets (PLT) 300×10^9/L, and hemoglobin (HGB) 140 g/L, but she did not undergo cytogenetic and molecular biological monitoring. She was initially admitted to Jining No.1 People's Hospital, Jining, China, because of fever accompanied by fatigue 3 years previously. On examination, she showed an anemic appearance, splenomegaly, and bleeding points scattered on her lower limbs. Laboratory tests revealed pancytopenia (HGB 52 g/L, leucocytes 2.83×10^9/L, neutrophils 0.3×10^9/L and PLT 23×10^9/L) and that a few immature cells were found on the blood smear, the hepatorenal function and coagulogram were normal, and abdominal ultrasound showed splenomegaly. A bone marrow cell morphology test suggested that a CML blast crisis myelogram be carried out. A bone marrow biopsy showed apparent fibrous hyperplasia, hematopoietic depletion, and reticular fiber staining. The quantification of *BCR-ABL* P210 in peripheral blood was 0.54%. DNA sequencing of ABL kinase (mutation) was negative. Flow cytometry analysis of peripheral blood suggested that 63.6% of the cell subsets showed abnormal expression in karyocytes, including CD34, HLA-DR, CD33, CD123, CD9 expression, partial CD38, CD7, CD36 expression, and low

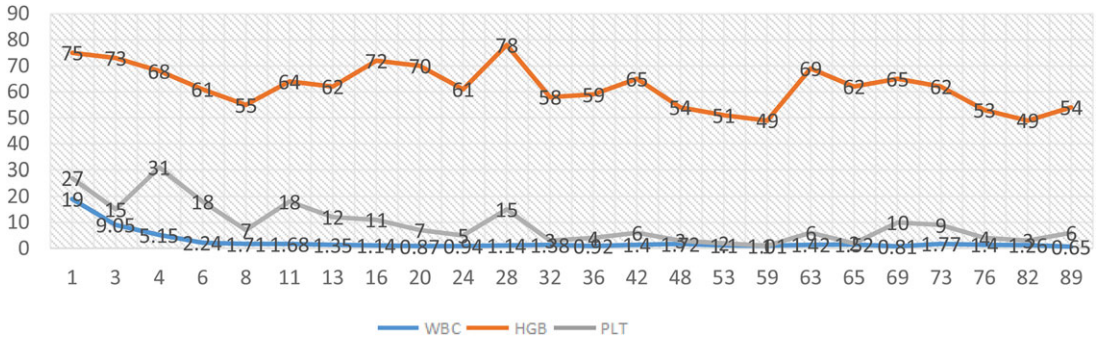

FIGURE 1 Three months of routine blood monitoring

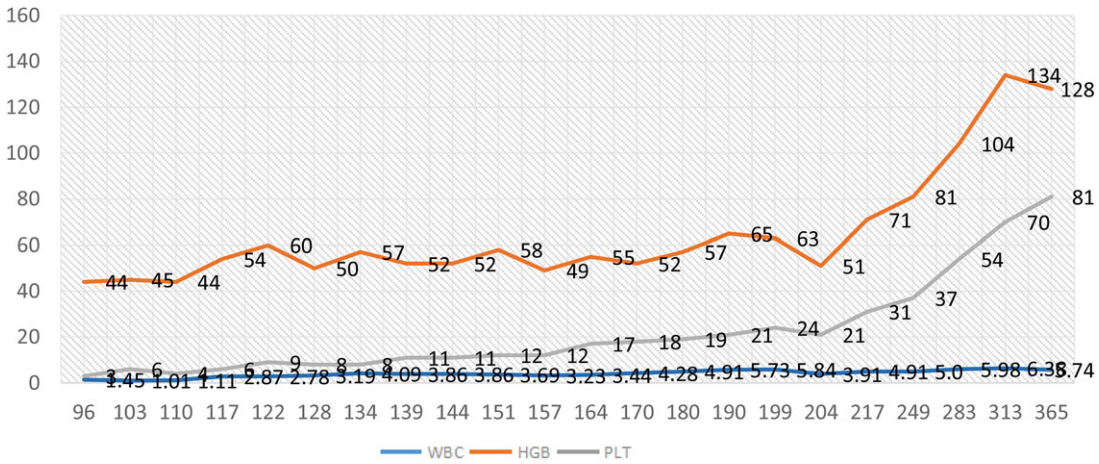

FIGURE 2 Nine months of routine blood monitoring

CD11 expression; however, CD13, CD56, CD19, TdT, cCD9, MPO, and cCD3 were negative, which matched the AML phenotype. Chromosome examination showed three kinds of clonal abnormalities, including +8, i(17), t(9;22); +8, i(17), t(9;22), ph and +8 × 2, i(17), and t(9;22), +20, +ph. Based on the above findings, the patient was diagnosed as chronic myeloid leukemia-blast crisis (*BCR/ABL* P210-positive, with myelofibrosis).

The patient was treated with daunorubicin 40 mg q.d. on days 1–2 and Ara-c 100 mg q.d. on days 1–4 in combination with nilotinib 400 mg oral administration to enhance the induced relieving rate. On the 45th day, a routine blood test showed a WBC of 1.1×10^9/L, N 0.21×10^9/L, HGB 51 g/L, and PLT 2×10^9/L, and bone marrow cell morphology showed that the bone marrow hyperplasia had diminished, and that the myeloblasts had decreased significantly (from 41% to 4%). She continued to take nilotinib orally, supplemented with anti-infection and blood transfusion therapies.

Blood tests always showed pancytopenia (WBC 1.0×10^9/L, HGB 60 g/L, PLT 5×10^9/L) throughout the first 3 months (Figure 1), which suggested that complete hematological remission was not achieved. Bone marrow cell morphology showed that the granulocyte series, erythron series, and megakaryocytic series hyperplasia were slightly lower after the CML blast crisis had been treated. Flow cytometry analysis of bone marrow suggested that the myeloid blast cell subsets were just 1.4%. The quantification of *BCR-ABL* P210 in bone marrow was 29.74%. DNA sequencing of ABL kinase (mutation) was negative. Chromosome examination showed clonal abnormalities, including +8, i(17q), t(9;22), and +ph.

Blood routine tests were monitored for 9 months, and the results showed that the blood counts increased gradually; first, the WBCs increased (4 months), followed by the PLTs (5.5 months), and, finally, HGB (Figure 2). The patient's symptoms and signs disappeared, the spleen was untouched, and there were no immature cells in peripheral blood smears. One year later, the bone marrow cell morphology showed a granulocyte series, erythron series, and megakaryocytic series hyperplasia myelogram after the CML had been treated. Detection of residual leukemia in bone marrow showed that the CD34, CD17, HLA-DR, CD33, CD13, and CD33 myeloid blast cell subsets were <0.01% in karyocytes. The quantification of *BCR-ABL* P210 in bone marrow was 0.05%. Based on the aforementioned findings, the major molecular response had been achieved.

The patient continued to take nilotinib orally (400 mg b.i.d.) after leaving the hospital; 18 months later, the routine blood test results had returned to normal (WBC 4.0×10^9/L, HGB 142 g/L, PLT 117×10^9/L). The quantification of *BCR-ABL* P210 in peripheral blood was 0.03%. Two years later, the routine blood test results remained almost normal (WBC 3.98×10^9/L, HGB 124 g/L, PLT 203×10^9/L). The quantification of *BCR-ABL* P210 in peripheral blood was 0.01%. The patient has remained stable until now.

3 | SUMMARY AND PROSPECT

The *BCR-ABL* protein encoded by the *BCR-ABL* fusion gene is the molecular basis of CML pathogenesis, but it is not expressed in normal cells, which makes it a target for CML treatment.[2]

The TKIs currently on the market include the first-generation TKI, imatinib; the second-generation TKIs, dasatinib, nilotinib, and bosutinib; and the third-generation TKI, ponatinib. In the present report, we illustrated a case of a woman with an acute transformation of CML, whose imatinib resistance was reversed by nilotinib, and has had a long-term survival; adverse reactions included slightly increased transaminase and bilirubin, and abdominal distension, which improved after symptomatic treatment. Studies have shown that the ability of nilotinib to inhibit cell line growth is 60-fold as potent as that of imatinib; nilotinib could reverse imatinib resistance caused by *BCR-ABL* mutations, except for E255K/V, F359C/V, T3135I, and Y253H.[3] They have shown that nilotinib is a more active and a more effective *BCR-ABL* inhibitor than imatinib. We are looking forward to the advent of a new generation of TKIs that will bring higher remission rates and longer survivals or even long-term disease-free survival.

CONFLICT OF INTEREST

The authors declare that they had read the article and there are no competing interests.

REFERENCES

1. Jain P, Kantarjian H, Cortes J, Chronic myeloid leukemia: overview of new agents and comparative analysis [J]. *Curr Treat Options Oncol*. 2013;14(2):127–143.
2. Wei G, Rafiyath S, Liu D, First-line treatment for Chronic myeloid leukemia: dasatinib, nilotinib or imatinib. *J Hematol Oncol*. 2010;3:47.
3. Kelly K, Swords R, Mahalingam D, et al. Optimizing outcomes in patients with Chronic myeloid leukemia in chronic phase: comparative safety profiles of Newer agents. *Leuk Lymphoma*. 2010;51(8):1399–1413.

How to cite this article: Xiao M, Zhou H, Li S, et al. Imatinib resistance was reversed by nilotinib in the acute transformation of chronic myeloid leukemia: A case report. *Prec Radiat Oncol*. 2017;1:134–136. https://doi.org/10.1002/pro6.31