

Letter to the Editor

Disappearance of Both the *BCR/ABL1* Fusion Gene and the *JAK2V617F* Mutation with Dasatinib Therapy in a Patient with Imatinib-Resistant Chronic Myelogenous Leukemia

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Keywords: JAK2V617F, CML, dasatinib

TO THE EDITOR

A single point mutation within the non-receptor tyrosine kinase Janus Kinase 2 (*JAK2*) leading to the substitution of phenylalanine for valine at amino acid 617 (*JAK2V617F*) was reported to be present in more than 95% of patients with polycythemia vera (PV). *JAK2V617F* has been considered to be absent in chronic myelogenous leukemia (CML) patients with the *BCR/ABL1* fusion gene.¹ However, recent findings have identified the coexistence of both the *BCR/ABL1* fusion gene and the *JAK2V617F* mutation.²⁻⁵ Here, we present a patient with CML in whom the coexistence of the *JAK2V617F* mutation and *BCR/ABL1* was detectable from the time of the initial diagnosis until the termination of seven years of imatinib therapy. The first part of this patient's clinical course has already been reported.⁶ Here, we report the latter part of the patient's clinical course, from imatinib to dasatinib therapy. Treatment with dasatinib following imatinib was molecularly successful, as a complete hematologic response was obtained and the major molecular response for the *BCR/ABL1* fusion gene and tests for the *JAK2V617F* mutation each became negative.

The patient was a 43-year-old man with a diagnosis of chronic-phase CML who had a hematocrit (Ht) value of 49%. Cytogenetic analysis revealed a karyotype of 46, XY, t(9;22)(q34;q11) in all metaphases [20/20]. After five years of interferon α and hydroxyurea therapy, treatment with imatinib was initiated, as shown in Fig. 1.⁶ One month after the commencement of imatinib therapy, hematological remission was

achieved, and a complete cytogenetic response was obtained at 33 months. Although imatinib was effective for his CML, his red blood cell count gradually increased. As the Ht value exceeded 50% (red blood cells, 512 μL ; white blood cells, 6,500 μL ; platelet count, 19.2 μL), intermittent phlebotomy was subsequently performed. During the clinical course of the patient's disease over a 13-year period, bone marrow cells with the *JAK2V617F* mutation were present at a constant level of about 20%. These findings have been previously reported.⁶ After 12-13 years, the number of copies of *BCR/ABL1* mRNA increased to 16,000 copies/ μg of total RNA, and three out of every 100 bone marrow cells were positive for *BCR/ABL1* on a fluorescence *in situ* hybridization (FISH) analysis, despite the administration of 400 mg of imatinib per day. Dasatinib (100 mg/day) was started at year 13 (Fig. 1). The patient's erythrocytosis did not subsequently require phlebotomy. Intriguingly, both the *JAK2V617F* mutation and *BCR/ABL1* mRNA were not detectable 15 years after the initial detection. At year 18, the patient's Ht value was 47.2% (red blood cells, 483 μL ; white blood cells, 7,600 μL ; platelet count, 17.4 μL).

At the time of diagnosis, coexisting aberrations (100% *BCR/ABL1* and 20% *JAK2V617F*) were detected in the bone marrow cells.⁶ During the clinical course, the rate of *BCR/ABL1* positivity in the bone marrow cells varied with the clinical response, but the rate of positivity for *JAK2V617F* remained steady at about 20%. We therefore speculated that the *BCR/ABL1* and *JAK2V617F* mutations might be secondary to an initial, as yet unknown, stem cell defect that induced clonal hematopoiesis (Fig. 2). Two different subclones might have evolved from the same initial clonal stem cell proliferation.²⁻⁷ Some published case studies have described coexisting aberrations, with the *BCR/ABL1*-positive clone predominating over the *JAK2V617F* clone and requiring treatment with imatinib.^{2,3}

After 13 years, the patient became resistant to imatinib treatment, as shown by the presence of 3 of the 100 cells that

Received : April 2, 2012

Revised : April 21, 2012

Accepted : May 7, 2012

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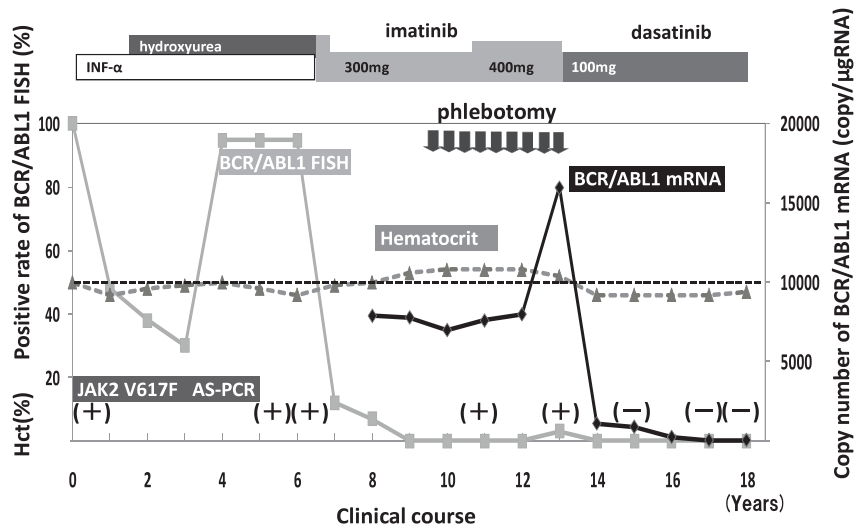


Fig. 1. Positivity for sequential *JAK2V617F* mutations and the rate of positivity for *BCR/ABL1* mRNA and *BCR/ABL1* FISH during the clinical course.

were analyzed as being positive for *BCR/ABL1* FISH and the detection of 16,000 copies/ μ g of RNA on an RQ-PCR analysis. Tests for secondary point mutations within the tyrosine kinase domain of *BCR/ABL1* were negative, and additional chromosomal abnormalities were not detected at this time.

Although imatinib is not known to inhibit the *JAK2V617F* mutation, imatinib has been shown to be a potent inhibitor of the growth of endogenous, erythroid progenitor cells *in vitro* and to demonstrate some clinical benefits in PV patients.^{8,9} Imatinib may also have had a partial effect on the *JAK2V617F*-positive clone in the present case. Dasatinib exhibits increased potency but reduced selectivity compared

with imatinib. However, dasatinib is also not known to inhibit *JAK2*. If dasatinib is found to down-regulate the proliferation of the abnormal clone, dasatinib may act against the unknown molecular lesion postulated to precede the *JAK2V617F* mutation in PV^{10,11} and to inhibit endogenous erythroid colony growth in PV (Fig. 2).¹² Given the powerful inhibitory effect of dasatinib on PV progenitors, dasatinib could affect PV by targeting the consequences of an as-yet-unknown molecular abnormality.

Dasatinib inhibits ABL tyrosine kinase as a target molecule and may have been able to inhibit *JAK2V617F* as an off-target molecule in the present case.

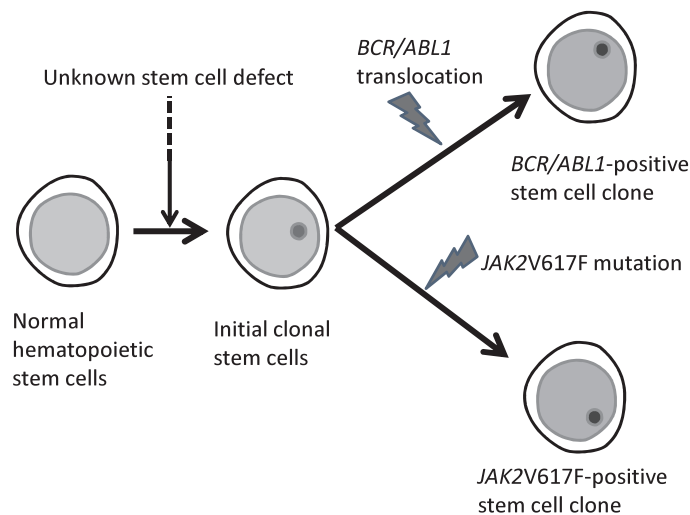


Fig. 2. The postulated clonal evolution in the present CML case based on the clinical course during dasatinib therapy following imatinib therapy.

In the present case with imatinib-resistant CML, dasatinib exerted an inhibitory effect on coexisting *BCR/ABL1*- and JAK2V617F-positive malignant cells.

Conflict of interest : None.

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