Myelodysplastic Syndrome with Ph Negative Monosomy 7 Chromosome following Transient Bone Marrow Dysplasia during Imatinib Treatment for Chronic Myeloid Leukemia

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Abstract

We describe a 60-year-old Japanese patient with chronic myeloid leukemia (CML) who developed myelodysplastic syndrome (MDS) with Ph negative monosomy 7 chromosome following transient bone marrow dysplasia during imatinib treatment. Most cases that developed chromosomal abnormality in Ph negative cells during imatinib therapy were reported to have less clinical implications, while rare cases developed MDS/AML. The present case suggested that metaphase karyotype analysis and bone marrow examination should be performed for the long term follow-up under imatinib treatment in cases showing cytopenia. The results also suggested that monosomy 7 in Ph negative cells may be an indicator of a poor prognosis.

Key words: CML, MDS, monosomy 7, Ph negative cells


Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic disorder characterized by the presence of Philadelphia chromosome (Ph) resulting in translocation t (9; 22) (q34; q11), which leads to the formation of the BCR-ABL1 fusion gene (1). The BCR-ABL1 fusion gene encodes a chimeric protein which increases tyrosine kinase activity and plays a central role in the leukemogenesis of CML (2). Imatinib mesylate is a potent tyrosine kinase inhibitor which binds to the ATP-binding site of BCR-ABL1. It induces a complete cytogenetic response (CCyR) in more than 90% of newly diagnosed CML patients, therefore it is now the first-line therapy for CML patients, replacing the role of interferon-α (3, 4). Recently, second-generation tyrosine kinase inhibitors, such as nilotinib and dasatinib, have become available for patients who are intolerant or resistant to imatinib (5). Therefore, the assessment and management of the adverse effects and efficacy are important to improve the prognosis of CML patients.

Cytopenia is one of the common adverse effects of imatinib. In the early phase of imatinib therapy, neutropenia is associated with the elimination of Ph clones, and recovery according to normal hematopoiesis is observed. In the late phase under normal hematopoiesis, myelosuppression including grade 3/4 neutropenia, anemia, and thrombocytopenia occur in about 10% of patients (6). Most such patients, improve on the withdrawal or dose reduction of imatinib. Some patients with cytopenia show myelodysplastic change in Ph-negative blood cells, but the clinical course of such patients is not well-recognized.

Several reports showed that CML patients develop chromosomal abnormality in Ph-negative cells during imatinib therapy (7-13). The clinical implications of such a phenomenon are still unclear. Clinical courses in such patients were reported to usually be similar to patients without chromosomal aberration, and some are transient (14). However rare

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Received for publication September 3, 2010; Accepted for publication October 21, 2010
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cases with chromosomal abnormality developed myelodysplastic syndrome (MDS) or acute myeloblastic leukemia (AML) (15-18). We report a CML patient who developed MDS with Ph-negative monosomy 7 chromosome following transient bone marrow dysplasia without chromosomal abnormality during imatinib treatment.

### Case Report

A 60-year-old Japanese man was referred to our hospital because of marked leukocytosis and thrombocytosis in May 2001. He had been pointed out as showing leukocytosis on medical check-ups from 1997. Peripheral blood analysis revealed a white blood cell count of 20,670/μL with 0.5% myeloblast, 7.5% myelocytes, 3.0% metamyelocytes, 9.5% stab-form neutrophils, 51.0% segmented form neutrophils, 13.5% lymphocytes, 0.5% monocytes, 2.0% eosinophils, 12.5% basophils. The hemoglobin concentration was 14.5 g/dL and the platelet count was 113.8×10^4/μL. The neutrophil alkaline phosphatase stain (NAP) score was 72 and rate was 40%. Bone marrow analysis revealed hyperplastic marrow with myeloid hyperplasia. G-band karyotype analysis of bone marrow cells showed 46XY, t (9; 22) (q34;q11) in all of the 20 analyzed metaphase cells. FISH analysis of bone marrow cells using a bcr/abl translocation DNA probe showed that 97.3% of cells were positive for a fusion signal. Quantitative RT-PCR using peripheral blood cells showed an increase to 970 copies/μg RNA. So, he was re-started on treatment with 200 mg of imatinib.

In November 2007, his platelet count decreased again to 4.5×10⁴/μL. This time, the hemoglobin concentration was 11.3 g/dL and the white blood cell count was 2,420/μL with 0.5% myeloblasts, 1% myelocytes, 5% stab-form neutrophils, 12.5% segmented-form neutrophils, 62.0% lymphocytes, 19.0% monocytes, 0% eosinophils, and 0% basophils. MCV and MCHC were 109.6 fL, and 34.9 pg, respectively. We discontinued imatinib again, but platelet counts showed no recovery. Bone marrow analysis showed dysplasia in three lineages without blast proliferation (Fig. 2). Karyotype analysis revealed that Ph chromosome presence was negative, but monosomy 7 was observed in 16 of 20 analyzed cells (Fig. 3). FISH analysis revealed that the bcr/abl fusion

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**Figure 1.** Morphology of bone marrow cells in May, 2005, May-Giemsa stain. a.) ×400. b.) ×600. Dysplasia in erythroblasts as a megaloblastic change without the proliferation of myeloblasts is shown.
signal was negative although 83.0% of bone marrow cells had monosomy 7 (Fig. 4a, b). Quantitative PCR of bcr/abl in peripheral blood showed 99 copies/μg RNA. We diagnosed him with MDS (RCMD: refractory cytopenia with multilineage dysplasia). Four months after the termination of imatinib, FISH analysis showed that 88.0% of peripheral blood cells were monosomy 7 positive and negative for bcr/abl. Because quantitative PCR showed elevation up to 5,500 copies/g RNA, we re-started 100 mg of imatinib. His MDS progressed to AML, and he died of AML in CCyR of CML after 2.5 years.

Discussion

Several reports have described the occurrence of clonal chromosomal abnormality in Ph-negative cells (7-14). Previous studies reported an incidence of chromosomal abnormality of 2-17%. The majority of abnormalities are trisomy 8, monosomy 7, and 20q-, which are often present in MDS. However, most cases with chromosomal abnormality were not associated with myelodysplasia or AML development and some seemed to be transient. Also, the prognosis of cases with chromosome abnormality was similar to that of those without an abnormality. This suggested that chromosomal abnormality during imatinib therapy may have different clinical implications from those associated with other cytotoxic chemotherapies. Only rare cases showing chromosomal abnormality during imatinib therapy developed MDS/AML (15-18). In the revised recommendations of European LeukemiaNet chromosomal abnormality in Ph negative cells at any time is categorized into warning category (19). However, it is not clear whether or not each kind of chromosomal abnormality has different implications regarding the clinical course. The present case suggested that monosomy 7 in Ph-negative cells should be borne in mind as a risk factor for MDS/AML development.

The mechanisms of MDS development during imatinib treatment remain unclear. Because most cases of MDS during imatinib treatment have been reported in CML patients, imatinib has been generally considered to have no direct mutagenic effect on Ph-negative cells, and Ph-negative cells themselves show genetic instability in CML patients (16). However, it was recently reported that a gastrointestinal stromal tumor (GIST) patient developed MDS with monosomy 7 during imatinib treatment, suggesting that imatinib plays a direct role in causing MDS (20). Imatinib is a potent tyrosine kinase inhibitor which binds to the ATP-binding site of BCR-ABL as well as c-kit and the PDGF receptor. Deficiency of the c-kit signal led the impaired hematopoietic reconstitution of hematopoietic stem cells in myeloablated animals. Also, the mice with mutant c-kit develop severe macrocytic anemia (21). Taken together, the inhibition of signal transduction in molecules other than BCR-ABL in normal hematopoietic stem cells may cause MDS during imatinib treatment. Chromosomal abnormality has also been reported in patients treated with nilotinib or dasatinib (22-24). Fur-

Figure 2. Morphology of bone marrow cells in November, 2007. May-Giemsa stain. ×400. a.) Multinucleated erythroblast b.) Multinucleated megakaryocyte c.) Pseudo Pelger abnormality in neutrophils.
Further study is needed to elucidate the cause of chromosomal abnormality during treatment with tyrosine kinase inhibitors.

Cytopenia is one of the common adverse effects of imatinib. In the late phase under normal hematopoiesis, myelosuppression, including grade 3/4 neutropenia, anemia, and thrombocytopenia occurs in about 10% of patients (6). Most patients improve on the transient withdrawal of imatinib, and can restart imatinib treatment. Some patients with cytopenia show dysplastic changes in Ph-negative bone marrow cells, but few reports have described the long term clinical course of such patients. The transient cytopenia with marked megaloblastic change in the present patient may reflect genetic damage to Ph-negative bone marrow cells, and the subsequent development of MDS with monosomy 7 could be caused by a second hit in normal hematopoietic stem cells. During treatment with imatinib, bone marrow morphological examination and metaphase karyotype analysis should be conducted even after achieving CCyR over a long-term follow-up in CML patients showing cytopenia.

The authors state that they have no Conflict of Interest (COI).
References