CASE REPORT

Imatinib-Related Bone Marrow Aplasia After Complete Cytogenetic Response in Chronic Myeloid Leukemia

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ABSTRACT

Imatinib mesylate is a BCR-ABL tyrosine kinase inhibitor used in the management of chronic myeloid leukemia. It is a safe and well-tolerated agent with a few manageable side effects. We are reporting a case of imatinib-related fatal bone marrow aplasia after complete cytogenetic response.

Key words: *Imatinib. Chronic myeloid leukemia. Bone marrow aplasia.*

INTRODUCTION

Imatinib mesylate is a small molecule tyrosine kinase inhibitor that has revolutionized the treatment of chronic myeloid leukemia.[1] Most of these patients are likely to require life-long therapy. It is pretty well-tolerated by majority of the patients with very few side effects, which may be hematological and non-hematological. Among the latter category, bone marrow aplasia is a rare but life-threatening side effect.[2] We are reporting a case of this fatal complication of imatinib therapy in a patient treated for chronic myeloid leukemia.

CASE REPORT

A 51 years old male was reffered with the diagnosis of Chronic Myeloid Leukemia (CML) in chronic phase. Cytogenetic studies reported that 70% metaphases were Philadelphia chromosome positive (Ph^+). Patient was asymptomatic and clinically there was neither viceromegaly nor lymphadenopathy. Baseline investigations included complete blood picture, which showed leukocytosis with WBC counts 56000/mm^3. Blood chemistry values, ultrasound of abdomen, and chest X-ray turned out to be essentially normal. Patient was prescribed capsule imatinib mesylate at a dose of 400 milligrams per day (mg/d) and advised to attend the CML clinic monthly. Patient came on follow-up visit after one month with complaints of dizziness off and on and mild to moderate joint pains. Complete Blood Picture (CBC) along with differentials was normal. Serum uric acid level was also within normal limits. RA factor was negative. Patient was prescribed tablet diclofenac sodium 50 mg three times a day and imatinib was continued in the same dose with monthly follow-up. On the next follow-up, dizziness and joint pains were improved. Diclofenac was stopped and patient was continued with monthly follow-up. Four months after original referral (in June 2004) bone marrow biopsy was done to evaluate treatment response. Cytogenetic studies showed that 50% metaphases were Ph^+. Patient was continued with same therapy at the same dose of 400 mg/day and scheduled monthly visits. He remained asymptomatic and tolerated the treatment very well. Bone marrow biopsy was done for the third time in January 2005 with cytogenetic studies for evaluation of response to imatinib. Only 10% of metaphases were Ph^+. Patient was asymptomatic again and tolerating the therapy very well, which was continued.

In July 2005, routine investigations revealed, for the first time, hemoglobin levels of 9.9 g/dl and platelet counts 89000/mm^3. White cell counts were within normal limits. Patient was, however, asymptomatic, clinically. Imatinib was reduced to 300 mg/d. Next month i.e. August 2005, there were still no symptoms with platelet counts 78000/mm^3. Hemoglobin level and white cells were within normal range. Clinical impression was probably imatinib-related thrombocytopenia but the possibility of disease progression could not be ruled out. Therefore, dose was further reduced to 200 mg/d and bone marrow biopsy was repeated along with cytogenetic studies. It

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showed overall slightly depressed cellularity. Karyotype was normal along with complete cytogenetic response with no detectable Ph^+ cells.

In September 2005, patient developed fever along with productive cough. CBC showed hemoglobin at 8.6 g/dl, platelets at 60000/mm^3, and white cell count of 4200 / mm^3. X-ray chest was unremarkable. Patient was referred to infection specialist who prescribed Azithromycin for suspected respiratory tract infection. Patient reported one week later with continued high-grade fever. CBC revealed further deterioration of blood counts with white cells at 1900/mm^3, hemoglobin at 7.3 g/dl, and platelets were 42000/mm^3. Imatinib was stopped and patient was admitted in isolation for investigations and treatment. Blood and urine cultures were sent and intravenous broad-spectrum antibiotics were started. Patient did not respond to the therapy and fever remained high-grade even after 72 hours of antibiotics. On the 3rd day of admission, infection specialist also added Amphotericin B to the regimen. Patient was still febrile after 48 hours of additional anti-fungal therapy. Blood and urine cultures did not reveal any growth.

General condition of the patient deteriorated rapidly and he developed cough along with dyspnea. Chest x-rays showed bilateral basal, ill-defined densities along with blunting of cardio-phrenic angles. PCR showed detection of *Mycobacterium tuberculosis* (MTB) DNA. A diagnosis of MTB bacteremia was made and Anti-Tuberculosis Therapy (ATT) was started. After two weeks of ATT, temperature of the patient started touching the baseline and dyspnea slightly improved. The thrombocytopenia and anemia, however, were persisting.

Two days later, general condition of the patient deteriorated again with complaints of dyspnea, yellow discoloration of conjunctiva, and distention of abdomen. Clinically, there was icterus of conjunctiva, splenomegaly, and ascities. Liver function tests revealed serum bilirubin levels of 5.2 mg/dl and ALT levels of 320 U/L. This was attributed to ATT, which was then stopped. Ultrasound scan of abdomen showed grossly enlarged spleen as well as para-aortic lymphadenopathy and moderate ascites. CBC showed worsening of pancytopenia with white cells 2900/mm^3, hemoglobin 4.4 g/dl, and platelet count 15000/mm^3. Patient was continued with supportive therapy in the form of growth factors, platelet transfusions and packed red cells along with modified doses of ATT and broad-spectrum antibiotics. Patient did not respond and expired on the 35th day of admission.

DISCUSSION

Chronic Myeloid Leukemia (CML) accounts for 15% of all leukemias.[3] Cytogenetically, it is characterized by a balanced, reciprocal translocation between the long arms of chromosome 9 and 22. This characteristic translocation, termed as Philadelphia chromosome (Ph^+), is observed in 95% of patients with CML.[4] Imatinib is a highly effective therapy for the treatment of Ph^+ chronic myeloid leukemia. In CML, fusion of BCR and ABL (Philadelphia chromosome) results in a 210 kilo Dalton chimeric protein (p210). This p210 acts as signal transduction via tyrosine kinase pathway resulting in uncontrolled growth of transformed myeloid cells. Imatinib mesylate acts by disrupting this abnormal signalling pathway.

Therapy with imatinib is generally well-tolerated. In minority of the patients, side effects like nausea, vomiting, fatigue, muscle cramps, edema, and myelosuppression have been reported.[5] Severe hematological complications are extremely rare. That patient was one of those exceptions who developed bone marrow aplasia after complete cytogenetic response to imatinib therapy. Jiang *et al.* in their study of 54 CML patients, treated with imatinib, reported Grade 3 neutropenia or thrombocytopenia in about 10%.[6] Sneed *et al.* reported imatinib-related grade III/IV neutropenia and thrombocytopenia in 45% and 22%, respectively, of their 143 patients of CML.[7] Lokeshwar *et al,* reported a 46-year-old women with chronic phase CML who was treated with imatinib. Six weeks later, she developed severe pancytopenia associated with fever, chest infection and bleeding. A bone marrow biopsy revealed hypoplasia (cellularity < 5%). She died of pulmonary mucormycosis.[8] Sumi *et al.* reported a 73-year-old woman with chronic myeloid leukemia who was treated with interferon-alpha, hydroxyurea, and busulfan before imatinib mesylate treatment. She received 400 mg of imatinib mesylate for 17 days before the agent was discontinued because of pancytopenia. A bone marrow biopsy on the 87th day after the last imatinib mesylate administration demonstrated severe hypocellularity. She needed many packed red cells and platelet transfusions and filgrastim administration. Grade IV neutropenia continued for 35 days and Grade III thrombocytopenia continued for over 122 days.[9]

The presently reported patient was treated with full supportive therapy but he did not respond. *Mycobacterium tuberculosis* bacteremia as well as complications of reduced platelets and hemoglobin levels were the key factors responsible for causing death. CML patients on imatinib therapy need close monitoring. Those pre-treated with busulfan and interferon-alpha may be at a higher risk of developing bone marrow aplasia.

REFERENCES

1. Hernandez-Boluda JC, Cervantes F. Imatinib mesylate (Gleevec, Glivec): a new therapy for chronic myeloid leukemia

and other malignancies. *Drugs Today* (Barc) 2002; **38**: 601-3.

2. Schmitt-Graeff A, Hochhaus A. Hematological side effects of tyrosine kinase inhibition using imatinib. *Pathologe* 2006; **27**: 40-6.
3. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, *et al.* (edi). SEER cancer statistics review, 1975-2000. Bethesda: *National Cancer Institute;* 2003.
4. Mitelman F. The cytogenetic scenario of chronic myeloid leukemia. *Leuk Lymphoma* 1993; **11** (Suppl 1): 11-5.
5. Turkina AG, Khoroshko ND, Druzhkova GA, Zingerman BV, Zakharova ES, Chelysheva Elu, *et al.* Therapeutic efficacy of imatinib mesylate (Glivec) in chronic phase of myeloid leukemia. *Ter Arkh* 2003; **75**: 62-7.
6. Jiang H, Chen SS, Jiang B, Jiang Q, Lu DP. Treatment of 54 chronic myelogenous leukemia with Gleevec. *Zhongua Xue Ye Xue Za Zhi* 2003; **24**: 281-5.
7. Sneed TB, Kantarjian HM, Talpaz M, O'Brien S, Rios MB, Bekele B, *et al.* The significance of myelosuppression during therapy with imatinib mesylate in patients with chronic myelogenous leukemia in chronic phase. *Cancer* 2004; **100**:116-21.
8. Lokeshwar N, Kumar L, Kumari M. Severe bone marrow aplasia following imatinib mesylate in a patient with chronic myelogenous leukemia. *Leuk Lymphoma* 2005; **46**: 781-4.
9. Sumi M, Tauchi T, Shimamoto T, Sshida G, Nakajima A, Ito Y, *et al.* Chronic myeloid leukemia associated with sustained severe pancytopenia after imatinib mesylate therapy. *Rinsho Ketsueki* 2002; **43**: 868-70.