

Successful Dasatinib Treatment in Chronic Myeloid Leukemia after Long-term Imatinib Failure: Case Report

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ABSTRACT

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disease almost always caused by a genetic defect known as the Philadelphia (Ph) chromosome. Ph chromosome is associated with a BCR/ABL fusion gene expressed as an oncoprotein, which is generally considered as the initiator for the chronic phase of CML. Tyrosine kinase inhibitors (TKI) are target-specific therapeutic agents that has successful results for obtaining complete responses for the majority of patients with this disease. Imatinib mesylate has been accepted as standard of care for the newly diagnosed chronic phase patients with CML. Although imatinib mesylate has been successful in most of patients by providing complete hematological and cytogenetical response and also major molecular response, imatinib resistance could be seen in some of the patients detected as loss of the response or never obtained optimal response. The response criteria for CML patients treated with imatinib, definition of the optimal response, suboptimal response and failure were defined and published as ELN recommendations. Dasatinib is approved for imatinib resistant and intolerant CML patients. In this report, we have presented a case with chronic phase CML who lost hematological and cytogenetical response and successfully treated with dasatinib.

Keywords: Chronic myeloid leukemia, Imatinib, Dasatinib, Resistance

ÖZET

Kronik Myeloid Lösemide Uzun Dönem İmatinib Yetmezliği Sonrası Dasatinib tedavi Başarısı: Olgu Sunumu

Kronik myeloid lösemi (KML) hemen daima Philadelphia (Ph) kromozomu olarak bilinen bir genetik defect ile oluşturulan kronik bir myeloproliferatif hastalıktır. Ph kromozomu bir onkoprotein eksprese eden BCR/ABL füzyon geni ile ilişkilidir ve bunun kronik faz KML'nin başlatıcısı olduğu düşünülür. Tirozin kinaz inhibitörleri (TKI) hedefe yönelik terapötik ajanlardır ve KML'li hastaların önemli kısmında tam yanıt sağlarlar. İmatinib mezilat, yeni tanı kronik faz KML hastalarının tedavisinde standart seçenektir. İmatinib mezilat ile çoğu hastada tam hematolojik, tam sitogenetik ve major moleküler yanıt elde etmek başarılmalıdır. İmatinib ile tedavi edilen hastalar için yanıt kriterleri, optimal yanıt, suboptimal yanıt ve başarısızlık kavramları çok iyi tanımlanmış ve ELN kılavuzu olarak yayınlanmıştır. Dasatinib, imatinib direnci ya da intoleransı olan hastaların tedavisinde onaylanmış bir ilaçtır. Bu yazıda, imatinib tedavisi altında hematolojik ve sitogenetik yanıt kaybı ortaya çıkan ve dasatinib ile başarılı şekilde tedavi edilen bir olgu sunulmaktadır.

Anahtar Kelimeler: Kronik myeloid lösemi, İmatinib, Dasatinib, Direnç

INTRODUCTION AND CASE REPORT

A 35-year-old man admitted to the hematology unit with leukocytosis and splenomegaly findings in July 1996. He had also fatigue, abdominal disturbance, low-grade fever and 3 kg weight loss in the last 3-4 months. Physical examination revealed splenomegaly (9 cm below the costal margin) and hepatomegaly (3 cm below the costal margin) and no lymphadenopathy. Hemogram analysis showed white blood cells (WBC); 329.000/mm³, hemoglobin (Hb); 13 g/dL, platelets (plt); 429.000/mm³. Differential analysis of WBC was as follows: neutrophil 46%, basophil 4%, eosinophil 4%, blastic cells 2%, monocyte 4%, promyelocyte 10%, myelocyte-metamyelocyte-stab 30%. Bone marrow aspiration and biopsy revealed hypercellular bone marrow with prominent myeloid hyperplasia. At the time of diagnosis, due to some technical reasons, classical cytogenetic analysis from bone marrow aspiration could not be performed, but based on the clinical and laboratory data, the diagnosis of the patient was accepted as chronic myeloid leukemia (CML).

Question: *What should be the treatment option for this patient in 1996?*

Answer: Before the tyrosine kinase inhibitor (TKI) era, the optimal therapy for young patients with CML was allogeneic stem cell transplantation (Allo-SCT). Before Allo-SCT procedure (donor screening and preparation), hydroxyurea or busulphan could be started to decrease the WBC counts and splenomegaly. Also, interferon was the only drug providing minimal or partial cytogenetical response at that date, so it could be considered for treatment of CML after achieving reduction of WBC counts.

Treatment was initiated with oral busulphan and continued with hydroxyurea. The dose regimen was adjusted based on the regular WBC counts. Sibling donor screening and HLA-typing was proposed but the patient refused to have Allo-SCT. When the WBC counts decreased < 10.000/mm³, interferon-alpha-2b was initiated with the dose of 3 MU/day three times in a week. In May 1997, interferon dose was increased up to 9 MU/day. Hematological parameters were almost normal except WBC counts which was around 24.000/mm³.

The patient was followed-up until 2002 with the same interferon dose and intermittent use of hydroxyurea. G-banding karyotype analysis confirmed the positivity of *Ph* chromosome in 20 metaphases from bone marrow aspiration sample. In February 2002, imatinib mesylate was approved and released to market in Turkey and the treatment of the patient was switched from interferon to imatinib mesylate (IM) 400 mg/day. At that time, the qualitative PCR was performed for the detection of *bcr/abl* transcript and the reported as positive. Patient was followed up with regular hematological parameters and RT-PCR for quantitative analysis of *bcr/abl* transcript levels. In April 2007, the leukocyte count was found to be as 19.500/mm³ and *bcr/abl* level increased (Figure 1). The patient was again offered to have sibling donor screening and HLA-typing, but the patient refused to have Allo-SCT one more time.

Question: *What should be the intervention for this patient in 2007?*

Answer: Since the only approved and available tyrosine kinase inhibitor in 2007, in Turkey was imatinib mesylate, the appropriate way was to increase imatinib mesylate 600 mg/day. By the way, BMS Company had started dasatinib compassionate use program (CUP) for patients with CML who were resistant or intolerant to imatinib mesylate treatment in Nov 2006. Dasatinib CUP was also another option in 2007.

IM dose was increased to 600 mg/day and followed up with 15 day intervals until August 2007. Leukocyte count was still 26.500/mm³ in August 2007 and then differential analysis from peripheral blood smear revealed the presence of myelocyte, metamyelocyte and promyelocyte in peripheral blood. Bone marrow aspiration and biopsy were performed and cytogenetical status of the patient was reassessed. Karyotype analysis showed 100% *Ph* (+) cells in 20 metaphases. The RT-PCR results showed increased ratio of *bcr/abl* gradually (Figure 1). The loss of hematological and cytogenetical response (unconfirmed) were demonstrated with IM 600 mg/day.

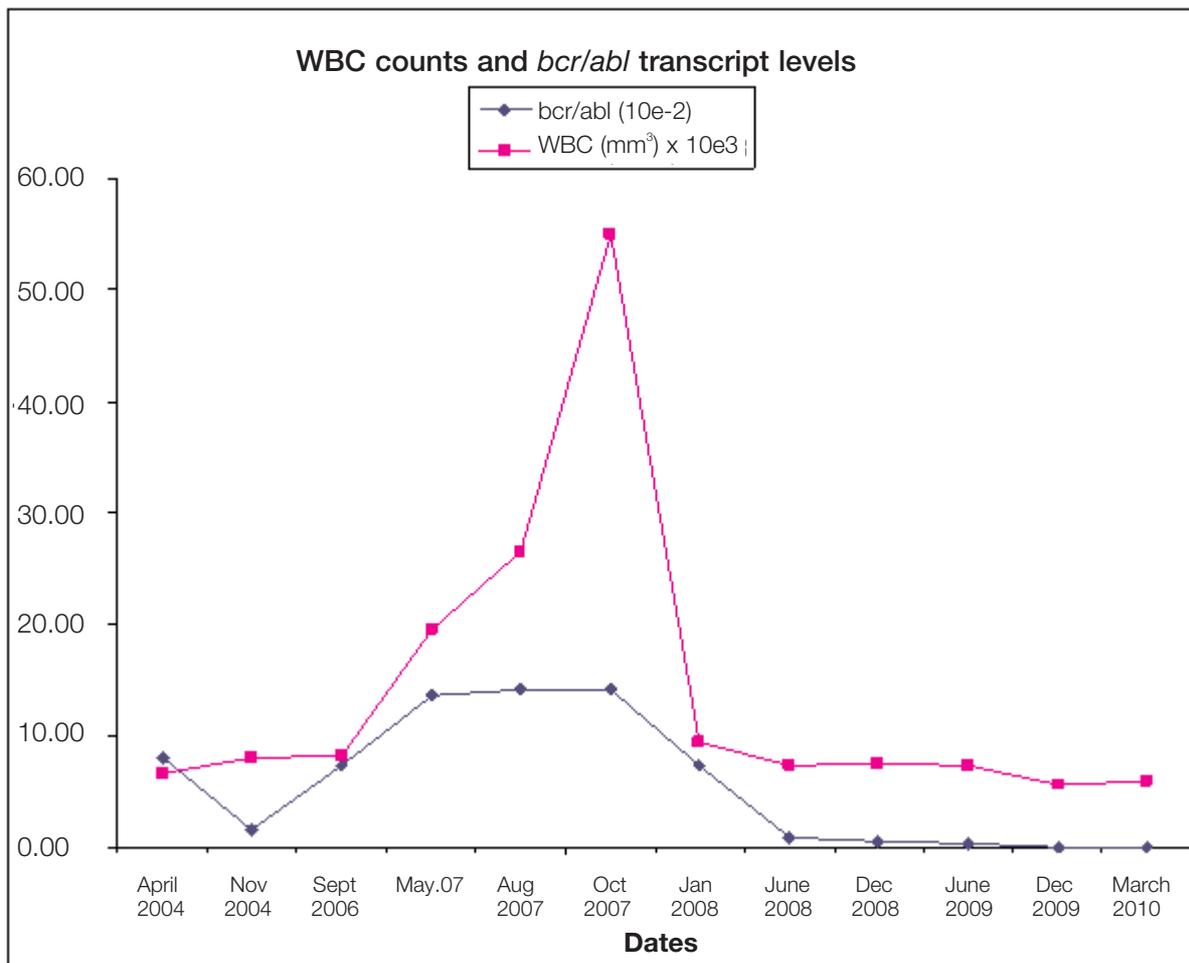


Figure 1. The WBC and *bcr/abl* measurements of patient as a time dependent manner. *Bcr/abl* levels were represented as laboratory results in numerical values and not illustrated as international scale (IS) or calculated with correction factor (CF) since the laboratory providing these results has not had yet its own CF. *Bcr/abl* transcript levels were measured by RT-PCR with the reference gene of GAPDH.

Question: What should be done for this patient in this situation?

Answer: Since the patient refused to have Allo-SCT, the best option for this patient is to switch the therapy to second- generation TKI.

The dasatinib treatment was performed for CUP in August 2007. Leukocyte count was found to be as 55.000/mm³ at the end of Sept 2007 and dasatinib 70 mg BID was initiated in October 2007. One month after initiating dasatinib treatment, hematological parameters were evaluated with two-week intervals. WBC count were found to be as 1150/mm³ with 400/mm³ neutrophil. After dasatinib was stopped, WBC count was evaluated we-

ekly. Two weeks later, leukocyte count was found to be as 4000/mm³ with 50% of neutrophil, and dasatinib 70 mg once daily was initiated and increased up to 100 mg QD gradually. By means of dose management, hematological adverse events were under control and treatment continued with dasatinib 100 mg QD. Peripheral blood analysis revealed slow but significant decrease *bcr/abl* transcript level. Classical G-banding of metaphases from bone marrow aspiration which was performed in June 2008 documented no *Ph*⁺ cells and confirmed complete cytogenetic response (CCyR) in 20 metaphases. *Bcr/abl* transcript level at that time was measured below the starting point of dasatinib. The patient was followed up with three-monthly inter-

vals and persistent complete hematological response (CHR) was observed. The patient complained of shortening in breathing and left chest pain for the last 2 weeks at Oct 2008 and hospitalized in local center. Chest X-ray showed the minimal pleural effusion in left side. We decided to interrupt dasatinib treatment and managed the pleural effusion with supportive treatments with furosemide and low dose steroid. After three-weeks, pleural effusion and symptoms were completely disappeared. Dasatinib 100 mg QD was re-initiated and regular chest X-rays showed no pleural effusion. Cytogenetical analysis from bone marrow aspiration in June 2009 showed that there were no Ph + metaphases. These results confirmed persistent and stable CCyR. Bcr/abl ratio was reported as negative, hematological parameters, physical findings were normal and also CCyR maintained in March 2010. The patient achieved CHR, CCyR and newly CMR.

DISCUSSION

Chronic myeloid leukemia (CML) has been defined as the clonal hematological malignancy which is characterized by the presence of unique chromosomal abnormality. This chromosomal abnormality has been known as Philadelphia chromosome (*Ph*) resulted in reciprocal translocation between chromosome 9 and 22 producing new fusion gene.¹ This novel fusion gene is named as *bcr/abl*, which encodes a constitutively active protein tyrosine kinase.² *Bcr/abl* contributes to uncontrolled and increased proliferation; genetic instability and blocking of apoptosis in malignant CML clone.³ Imatinib mesylate blocks the ATP-binding site of *bcr/abl* tyrosine kinase activity and the downstream signaling pathways activated by *bcr/abl* activation.⁴ A randomized trial, the International Randomized Study of Interferon vs STI571 (IRIS) was initiated to compare imatinib with the previous standard of care for chronic phase CML, interferon- α (IFN) plus cytarabine in newly diagnosed patients with chronic phase CML. According to the 5-years results of IRIS study, only 68% of the patients in CCyR still remained on imatinib therapy.⁵ Also, the long term follow-up of patients treated with imatinib has created a new terminology like "imatinib intolerance" or "imatinib resistance" which need to switch the therapy with new generation TKIs. The main mec-

hanism for imatinib resistance has been clearly documented as the mutations occurred under the treatment of imatinib.⁶

Dasatinib is one of the second generation TKI and has an activity against many signaling kinases including *bcr/abl* and SRC family and structurally different from imatinib.⁷ It has been approved by FDA in June 2006 and by Turkish Ministry of Health in December 2007 for the treatment of all phases of *Ph(+)* CML and ALL with resistance or intolerance to prior therapy including imatinib.⁸ It has activity against many of the mutant forms of *bcr/abl* and, its ability to bind both the inactive and active forms of *bcr/abl* provides broader spectrum. The results of START Phase II trials showed that dasatinib is an effective treatment regimen in CML and *Ph(+)* ALL diseases with relatively low and tolerable side effects.^{8,9} A prospective randomized study of four different doses and schedules identified a dose of 100 mg once daily as effective and better tolerated than other doses and schedules.¹⁰

Dasatinib has some side effects including neutropenia, thrombocytopenia, nausea, muscle cramps, bone pain, arthralgias, skin rash, edema and fluid retention and pleural effusion. Grade 3-4 neutropenia and thrombocytopenia are common and potentially serious complications of dasatinib treatment. The frequency of myelosuppression depends on the disease stage.¹¹ For chronic phase CML patients, standard advice is to interrupt dasatinib at the first episode of grade 3-4 neutropenia. Treatment can be resumed at the same dose when absolute neutrophil count (ANC) has increased above $1 \times 10^9/L$. The dasatinib dose should be reduced if thrombocytopenia or neutropenia recurs.¹¹ Pleural effusion, which occurs in 20% of the patients, is perhaps the most troublesome complication of dasatinib and can develop in patients with no other signs of fluid retention.⁹⁻¹¹ Pleural effusion can develop at any time during the therapy but is slightly more frequent at first months of treatment. Often, pleural effusions are bilateral and are more frequent in accelerated phase patients and in patients who take higher dose of dasatinib.¹² Regular surveillance chest radiographs are not recommended, however patients should be examined frequently, and a chest radiograph should be performed promptly according to clinical judgment. The etiology of dasatinib-induced pleural ef-

fusion is unclear, but inhibition of PDGFR is a possible mechanism. The pleural effusion generally resolves rapidly after discontinuation of dasatinib, but this process can be accelerated by the addition of diuretics or steroids. Generally 1-2 weeks interruption of dasatinib is sufficient duration for disappearance of pleural effusion. After complete resolution of pleural effusion, dasatinib can be resumed with the same dose.⁹

Achieving CCyR and CMR would provide a long time for the patient without any sign of active disease in patients with CML. Dasatinib can successfully induce cytogenetic and molecular response in patients who experienced long lasting disease and resistant to imatinib therapy. Side effect management can be succeeded by short term interruption of the drug or helpful medications.

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