The Management of Second Generation Thyrosine Kinase Inhibitors Treatment: Case Report

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ABSTRACT

The current management of chronic myeloid leukemia (CML) is dependent upon chronic thyrosine kinase inhibition (TKI). Several drugs have been developed for tyrosine kinases during the last decade. Imatinib mesylate (IM) is the first molecular targeting TKI. IM is the current 'standard- of -care' in CML patients to obtain cytogenetic remission. Patients refractory to IM can be treated with second generation TKI including dasatinib. The aim of this case report is to assess the efficacy of dasatinib treatment in the basis of IM failure.

Keywords: CML, Imatinib failure, Dasatinib, Cytogenetic remission

ÖZET

İkinci Nesil Tirozin Kinaz İnhibitör Tedavi Yönetimi: Olgu Sunumu

Günümüzde kronik myeloid lösemi (KML) tedavisi, kronik tirozin kinaz inhibisyonuna (TKI) dayanır. Son 10 yılda tirozin kinazlar için çeşitli ilaçlar geliştirilmiştir. İmatinib mesilat (IM) TKI amaçlı ilk hedefe yönelik moleküldür. KML hastalarında sitogenetik remisyon elde etme amaçlı standart tedavi IM olarak tanımlanır. IM yetmezliği olan hastalar ikinci nesil TKI ilaçlarla, örneğin dasatinib ile, tedavi edilir. Bu olgu sunumunun amacı IM yetmezliği temelinde dasatinib tedavisinin etkinliğini incelemektir.

Anahtar Kelimeler: KML, İmatinib yetmezliği, Dasatinib, Sitogenetik remisyon

INTRODUCTION AND CASE REPORT

A 57-year old chronic alcoholic man was admitted to hematology clinic with weight loss and malaise in April 2007. Blood count showed leucocytosis and thrombocytosis, afterwards, cytogenetics and molecular tests from bone marrow aspiration and biopsy confirmed the diagnosis of Chronic Myeloid Leukemia (CML). Hematological, cytogenetical and complete molecular responses were achieved at the first, third and sixth month of treatment, respectively with imatinib 400 mg once daily treatment regimen. Following two years imatinib therapy, liver enzyme levels elevated (AST: 117 U/L, ALT: 170 U/L, GGT: 220 U/L) and > 10^6 copies of HBV DNA detected by PCR. The patient was diagnosed with acute hepatitis B, and thus lamivudine 100 mg/day treatment was initiated. In September 2009, the loss of cytogenetic response were observed on routine bone marrow aspiration with sustained hematological and molecular responses and normal hepatic function tests and negative HBV DNA results.

QUESTIONS AND ANSWERS

Question: *Which therapy should be considered in the case of cytogenetic response loss?*

***Answer*:** The targeted second generation TKIs dasatinib and nilotinib, are available for imatinib resistant or intolerant CML patients[1,2] and therefore, dasatinib 100 mg once daily treatment was started.

Question: *What should you consider in terms of adverse events?*

***Answer*:** The most common adverse events are cytopenias (neutropenia, leukocytopenia, and thrombocytopenia) and non-hematologic adverse events like fluid retention, headache, diarrhea, nausea, fatigue, rash, and dyspnea. Dasatinib treatment, causes mild-to-moderate elevation in serum aminotransferase levels. Severe acute hepatitis including acute liver failure requiring transplantation[5] or fatal hepatic necrosis[6,7] have been reported rarely.

The patient developed dry cough and dyspnea in the second month of dasatinib 100 mg/ day treatment. The hematological parameters were within the normal range. A massive pleural effusion was confirmed by chest X-ray. AST and ALT levels were increased to three times of normal level.

Question: *How do you manage the adverse events?*

Answer: Dasatinib related fluid retention events were managed by drug interruption and supportive care measures that include diuretics and short courses of steroids. Grade 3 or 4 elevations of transaminases or bilirubin were reported in ≤ 5% of patients with chronic or accelerated phase CML.

Pleural effusion was successfully managed with dasatinib dose interruption and diuretics. The pleural effusion demonstrated regression after 10 days on chest X-ray. Because of acute hepatitis B history and abnormal liver function, PCR anlaysis were repeated to evaluate HBV-DNA. HBV-DNA PCR results were negative and the liver function test were in normal range. After dasatinib dose interuption, dasatinib 50 mg once daily was re-introduced and diuretic treatment were stopped. Dasatinib treatment dose was increased from 50 mg/ day to 100 mg/day after fifteen days.

Question: *What do you suggest about the treatment of imatinib resistant CML patients?*

***Answer*:** In follow-up, the patient achieved complete cytogenetic and molecular response at the 6th month of dasatinib treatment after a bone marrow aspiration. Dasatinib 50 mg/ day treatment is still ongoing.

DISCUSSION

Imatinib has revolutionized the treatment of patients with CML. However, some patients may have resistance or intolerance to imatinib over time. For these patients, two alternative therapeutic options are available. Dasatinib, approved in 2006 for imatinib resistant or intolerant patients with chronic, accelerated or blastic phase CML, has displayed significant efficacy, with a 2-year follow-up showing durable hematologic and cytogenetic responses, as well as prolonged progression-free and overall survival. Nilotinib approved in 2007 for imatinib resistant or intolerant patients with chronic or accelerated phase CML based on strong effi-

cacy as well as a favorable safety profile. Several factors including mutation status, patient history, and existing comorbidities can impact the decision to use dasatinib or nilotinib[8] Dasatinib is a broad-spectrum tyrosine kinase inhibitor (TKI) which inhibits *BCR-ABL* activity more potently than imatinib and also an inhibitor of platelet derived growth factor receptor (PDGFR) and c-Kit.

Adverse events related to dasatinib treatment are less common with 100 mg once daily versus 70 mg BID use. Shah N, et al. showed that grade $^{3}/_{4}$ pleural effusion with dasatinib 100 mg once daily treatment is 2%.[4]

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