Case Report

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Successful Treatment of a Chronic-Phase T-315I-Mutated Chronic Myelogenous Leukemia Patient with a Combination of Hydroxyurea and Interferon-Alfa

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Abstract

Mutations of BCR-ABL1 are observed in 50% of patients with Imatinib-resistant chronic myeloid leukemia (CML). The T315I mutation is resistant to imatinib and second-generation tyrosine kinase inhibitors (TKIs). We report the case of a 42-year-old male diagnosed with CML who acquired the T315I mutation while on Imatinib therapy. He was treated sequentially with combination therapy, comprising of interferon alpha and hydroxyurea which led to disappearance of the mutation and sustained haematological and major molecular response (MMR). To our knowledge, this is the first case report with a 12 year follow up showing the effectiveness of hydroxyurea/IFNα combination therapy for CML patients bearing the T315I BCR-ABL mutation.

Keywords: Imatinib; CML; Mutation

Introduction

The disease burden in chronic myeloid leukemia (CML) is linked to the activity of its chimeric oncoprotein, the BCR-ABL1 tyrosine kinase. Tyrosine kinase inhibitors (TKIs) are standard therapy for patients with chronic myeloid leukemia (CML), with durable responses noted in most cases.[1] Mutations of *BCR-ABL1* are observed in 50% of patients with Imatinib-resistant chronic myeloid leukemia (CML). Of these mutated patients, 10% to 15% harbour T315I mutations. This results in a substitution of Isoleucine for Threonine in position 315, causing a conformational change in the binding site occupied by all TKIs, and portends universal resistance to TKI therapy.[2] Patients who carry the T315I mutation in BCR-ABL are unresponsive to Imatinib (IM) as well as second-generation TKIs; this mutation might, therefore, represent an important pathway for CML cells.[3] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only established salvage option for patients harboring the T315I BCR-ABL mutation.[4] However, allo-HSCT can be performed only in eligible patients.[5] Hence, patients harboring the T315I BCR-ABL mutation, who are not eligible for allo-HSCT, require treatment with combinations of already approved drugs. We report here the clinical outcome for chronic myeloid leukemia (CML) patient who acquired the T315I mutation while on Imatinib and was treated successfully, with a combination of Interferon alpha (IFNα) and hydroxyurea.

Case report

A 42-year-old male was diagnosed with CML in 2007. The patient initially received treatment

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with hydroxyurea 500 mg/day and Imatinib 400 mg/day was started there after with favourable tolerability. He achieved a complete hematologic response (CHR) within 3 months and major molecular response (MMR) within 6 months. He maintained an adequate response for five years followed by progressive increase in BCR-ABL transcripts (24.5%). The dose of Imatinib was increased to 600 mg/day. Six months later he complained of increasing fatigue, abdominal girth, and easy bruisability. A bone marrow aspirate at this time showed accelerated-phase CML with raised total leukocyte count (TLC). BCR-ABL transcripts measured by real time quatitative polymerase chain reaction (RQ-PCR) was 29.25% at this time. Imatinib dose was further escalated to 800 mg/day; however, despite increased dose therapy for six months, there was no hematologic response. The patient had complains of low appetite, bone pain and weakness. T315I mutation was found positive by Allele specific Oligonucleotide (ASO)-PCR in Feb 2015. As the patient had not shown response to Imatinib and could not be switched to Dasatinib due to finanacial constraints, he was started IFNα 80 µg/week and hydroxyurea 500 mg/day. During this therapy, the patient had rebound increased TLC whenever hydroxyurea was stopped (Figure 1). In Oct 2016, twenty months after initiation of IFNα, RQ-PCR revealed a two log reduction of BCR-ABL transcripts and the patient was found negative for T315I BCR-ABL mutation by ASO-PCR. The hydroxyurea/ IFNα combination therapy is being continued without any dose reduction and the patient's TLC continued to be within normal range 45 months after initiation this therapy without any evidence of a recurrence of the T315I BCR-ABL mutation.

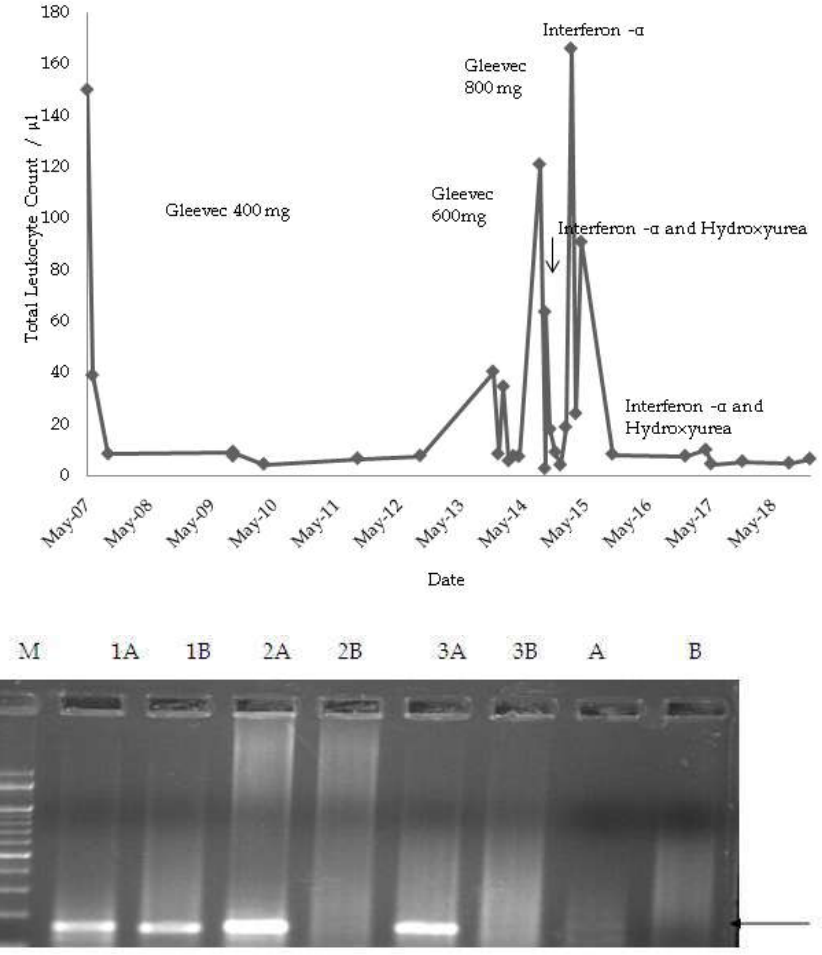

Fig. 1: Agarose gel electrophoresis of T315I mutation by ASO-PCR. Lane A is showing amplification for wild band and lane B is showing amplification for mutant band for patient. Lane M, 100 bp marker, lane 1B is patient samples showing amplification of heterozygous mutant of 158 bp (Imatinib 800 mg/day), Lan2B and 3B is patient's samples is negative for 315 mutation (after 30 and 45 months of interferon and hydroxyurea treatment) and showing amplification of only wild type of 158 bp. Lane A and B is negative control for this reaction.

Discussion

Resistance to TKI therapy is multifactorial and includes both BCR-ABL dependent and independent mechanisms. Kinase domain (KD) mutations represent a clinically relevant subset of resistant disease. T315I mutation in the BCR-ABL gene is associated with clinical resistance to Imatinib and other TKIs.[6] Strategies for eradicating KD mutations, such as T315I, that confer poor prognosis and resistance to monotherapy, include sequential and combination therapies with drugs having different mechanisms of actions.[7]

IFNα is known to stimulate the turnover and proliferation of hematopoietic stem cells in vivo and T315I BCR-ABL mutated clone is more susceptible to IFNα. Therefore it has been suggested that the recruitment of dormant CML stem cells into the cell cycle by pegylated IFNα may increase the efficacy of TKIs.[8]

Only two cases have been reported in literature where the successful treatment of T-315I-mutated chronic myelogenous leukemia patient with IFNα alone or in combination with with Imatinib has been achieved.[9,10] Our patient did not respond to Imatinib even after dose escalation, found to have T315I mutation and was started on combination therapy with IFNα and hydroxyurea. During this treatment regimen, whenever an attempt was made to stop hydroxyurea, the patient's TLC became high, hence we continued both drugs. The hydroxyurea/IFNα combination therapy resulted in MMR, suggesting its effectiveness in patients harbouring the T315I BCR-ABL mutation.

In conclusion, although our experience is limited to one patient, hydroxyurea/IFNα combination therapy could be a viable treatment option for CML patients with a T315I BCR-ABL mutated patients with resistance to Imatinib who are transplant ineligible. Further large scale studies would be required to see the efficacy and applicability of hydroxyurea/IFNα combination therapy in the Imatinib unresponsive patients harbouring T315I mutation.

References

1. Jabbour E, Kantarjian H, Jones D, et al. Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. Leukemia 2006;20(10):1767–73.
2. Apperley JF. Part I. mechanisms of resistance to imatinib in chronic myeloid leukaemia. Lancet Oncol. 2007 Nov;8(11):1018–29.
3. Branford S, Melo JV, Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? Blood. 2009 Dec 24;114(27):5426–35.
4. Nicolini FE, Basak GW, Soverini S, et al. Allogeneic stem cell transplantation for patients harboring T315I BCR-ABL mutated leukemias. Blood. 2011 (pii:2011-07-367326).
5. Nicolini FE, Mauro MJ, Martinelli G, et al. Epidemiologic study on survival of chronic myeloid leukemia and Ph(?) acute lymphoblastic leukemia patients with BCR-ABL T315I mutation. Blood. 2009 Dec 17;114(26):5271–8.
6. Legros L, Hayette S, Nicolini FE, et al. BCR-ABL(T315I) transcript disappearance in an imatinib-resistant CML patient treated with homoharringtonine: a new therapeutic challenge? Leukemia. 2007 Oct;21(10):2204–6.
7. Shah NP, Tran C, Lee FY, et al. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004 Jul 16;305(5682):399–401.
8. Peudhomme C, Guilhot J, Nicolini FE, et al. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. N Engl J Med. 2010 Dec 23;363(26):2511–21.
9. Itonaga H, Tsushima H, Hata T, et al. Successful treatment of a chronic-phase T-315I mutated chronic myelogenous leukemia patient with acombination of imatinib and interferon-alfa. Int J Hematol. 2012 Feb;95(2):209–13.
10. De Lavallade H, Khorashad JS, Davis HP, et al. Interferon-alpha or homoharringtonine as salvage treatment for chronic myeloid leukemia patients who acquire the T315I BCR-ABL mutation. Blood. 2007 Oct 1;110(7):2779–80.