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Case Report

Safety and Efficacy of Asciminib in Chronic Myeloid Leukemia Patient with Chronic Kidney Diseases: A Case Report

Awni Alshurafa[a] Afshan Adil[b] Mohamed A. Yassin[a]

[a]Hematology Department, Hamad Medical Corporation, Doha, Qatar; [b]Internal Medicine Department, Hamad Medical Corporation, Doha, Qatar

Keywords
Chronic myeloid leukemia · Chronic kidney disease · Asciminib · Deep molecular response · *BCR::ABL1*

Abstract
Introduction: Chronic myeloid leukemia (CML) is characterized by the presence of the *BCR::ABL1* fusion gene, and the advent of tyrosine kinase inhibitors (TKIs) has revolutionized its therapeutic landscape. Asciminib, a STAMP inhibitor, emerges as a promising option for patients unresponsive or intolerant to multiple conventional TKIs. However, the safety and efficacy of asciminib in individuals with chronic kidney disease remain understudied. ***Case Presentation:*** In this report, we detail the case of a 62-year-old patient with CML and stage 3 chronic kidney disease, who faced intolerance to traditional TKIs primarily due to fluid retention. The transition to asciminib therapy resulted in a profound molecular response and did not exacerbate renal function, effectively addressing the fluid retention issue. ***Conclusion:*** This case highlights the potential of asciminib as a viable therapeutic alternative for CML patients with chronic kidney disease, particularly those intolerant to standard TKIs. Further research is warranted to establish the broader safety and efficacy profile of asciminib in this patient population.

Introduction

Chronic myeloid leukemia (CML) is a neoplasm of hematopoietic stem cells. It is distinctly marked by the presence of the *BCR::ABL1* fusion gene, often arising from a balanced translocation connecting chromosomes 9 and 22. This chromosomal alteration gives rise to

Correspondence to:
Awni Alshurafa, dr.a.shurafa@gmail.com

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the Philadelphia chromosome. CML constitutes a significant proportion of adult leukemia, accounting for 15–20% of cases. The global annual incidence is approximately one to two cases per 100,000 individuals [1, 2].

Tyrosine kinase inhibitors (TKIs) have transformed CML care by directly inhibiting *BCR::ABL1*, leading to remission and replacing older treatments with more effective and targeted treatments. Choosing a TKI is influenced by multiple factors including disease phase, CML risk score (low/intermediate vs. high), side effects and safety profile, drug interactions, patient's preferences, and medical comorbidities among other factors. Chronic kidney disease is diagnosed when renal damage or decreased kidney function is observed for 3 months or longer, irrespective of the underlying cause. TKIs can affect kidney function due to their metabolism and potential accumulation in renal impairment [3–5].

Asciminib is a targeted ABL inhibitor that interacts with the myristoyl pocket of *BCR::ABL1*. It is indicated for adult patients with CML who have not responded to or tolerated two or more TKI treatments [6]. However, the data about the safety and efficiency of asciminib in chronic kidney disease are limited. Herein, we present a case of CML with chronic kidney disease stage III, where the patient achieved both stable kidney function and a deep molecular response as a result of asciminib therapy. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535958).

Case Presentation

We present a 62-year-old gentleman, a known case of type 2 diabetes mellitus, dyslipidemia, and poorly controlled hypertension for more than 20 years. Also, he is obese with a body mass index of 36 kg/m^2 and has fatty liver disease. He is following up with nephrology for grade 3 chronic kidney disease, with baseline creatinine between 150 and 180 μmol/L, with eGFR 30–40 mL/min/1.73 m^2. His cause of chronic kidney disease is assumed to be longstanding diabetes (kidney biopsy not done). Physical examination was unremarkable apart from hepatomegaly due to fatty liver disease. The patient was referred to the hematology clinic due to persistent leukocytosis. He was asymptomatic.

His complete blood count showed WBCs: 20.6 × 10^9/L, hemoglobin: 15.5 gm/dL, platelets: 280 × 10^9/L, absolute neutrophil count: 11.5 × 10^9/L (56%), lymphocytes: 4.7 × 10^9/L (23%), eosinophils: 0.6× 10^9/L (3%), basophils: 1.85 × 10^9/L (9%). A peripheral smear was done which showed neutrophil leukocytosis with a mild shift to the left, leucoerythroblastic picture, basophilia, mild eosinophilia, and few circulating blasts. The recommendation was to rule out myeloproliferative disorders including CML.

Abdomen ultrasound showed mild hepatomegaly secondary to fatty liver disease and no splenomegaly. Further investigations were done which demonstrated no evidence of the V617F missense mutation within the JAK2 gene and no evidence of an insertion/deletion mutation within exon 9 of the CALR gene, however positive for an e13a2 *BCR::ABL1* gene fusion by single-step RT-PCR. Interphase FISH analysis was reported at diagnosis to show an abnormal signal pattern involving a *BCR::ABL1* rearrangement and the presence of *t*(9;22) Philadelphia chromosome translocation consistent with a diagnosis of CML. He also underwent a bone marrow biopsy which further confirmed it. The karyotype did not show any additional chromosomal abnormalities. The EUTOS long-term survival (ELTS) score was 1.31 which corresponds to low risk.

The decision was made by the primary hematologist to start him on imatinib 400 mg daily in February 2021. Follow-up laboratories showed that he achieved a complete homological response, complete cytogenetic response, and deep molecular response (*BCR::ABL1* value of ≤0.01% IS), and his kidney function remained stable. However, the main adverse effect was

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an interval increase in weight due to fluid retention, with clinical complaints of periorbital puffiness, lower limbs swelling, and significant shortness of breath which limit his daily activities. He was started on regular oral doses of furosemide by his nephrologist without significant improvement. Considering the patient's medical history, which includes diabetes, dyslipidemia, uncontrolled hypertension, and stage 3 kidney disease, and in view of how other TKIs like nilotinib, dasatinib, and ponatinib might worsen these preexisting conditions, as an alternative, asciminib at a dose of 40 mg twice daily (BID) was offered. The patient was counseled that there is no evidence that shifting to asciminib will protect his kidney since it is a new medicine and there is no study to prove or disprove; however, he agreed to start asciminib with close monitoring of kidney function which remains stable with maintaining deep molecular response (Fig. 1).

Discussion

TKIs have revolutionized CML treatment by specifically targeting the *BCR::ABL1* fusion protein, which drives leukemia. These drugs are offering higher response rates and fewer side effects. They transformed CML into a manageable condition, enhancing patient outcomes and longevity. As successful targeted therapy restored life expectancy in many cases, the prevalence of CML has been on the rise. Consideration of various factors such as individual characteristics of the CML patients, adherence to TKI drug therapy, lifestyle choices, existing health conditions, the specific toxicity profile of the TKI drug, and the expertise of physicians and clinical centers is essential when determining the most suitable initial treatments for individuals newly diagnosed with CML. However, some patients do not tolerate or respond adequately to this treatment. Consequently, there is a demand for novel TKIs with distinct mechanisms to address this challenge [7–10].

Asciminib has gained approval for treating patients with chronic-phase CML who do not tolerate or respond to TKIs. It functions by binding to the myristoyl site of the *BCR::ABL1* protein, emulating myristate, and reinstating kinase activity inhibition. However, the long-term efficacy and safety of asciminib still require careful monitoring. From a pharmacokinetic standpoint perspective, asciminib is mainly eliminated through the feces, with just 11% being eliminated through urine [11].

The data about the safety and efficiency of asciminib in chronic kidney disease are limited. A phase 1 study describing the pharmacokinetic profile of a single dose of asciminib (40 mg) in individuals with impaired renal function shows that patients with severe kidney disease demonstrated 49–56% higher exposure (area under the curve), with similar maximum plasma concentration than matched healthy individuals. This result suggests that the exposure or safety profile of asciminib remains unaffected by renal impairment in a clinically significant manner. This supports the usage of asciminib in patients with different levels of renal dysfunction [12]. In a recently published case report, the authors presented a 63-year-old patient diagnosed with CML who underwent a kidney transplant and faced issues with tolerating TKIs. Subsequently, the patient was transitioned to asciminib treatment, which not only successfully attained a deep molecular response but also the use of asciminib did not result in any worsening of the patient's renal function [13].

In our patient, who had been diagnosed with CML and initially treated with imatinib, the therapy was effective in achieving a deep molecular response. However, the patient experienced intolerance to imatinib due to side effects of fluid retention, which did not respond adequately to diuretics. Given the patient's medical history, including diabetes, dyslipidemia, uncontrolled hypertension, and stage 3 kidney disease, it is important to consider how other TKIs (nilotinib, dasatinib, ponatinib) may worsen these conditions [14]. Consequently, the

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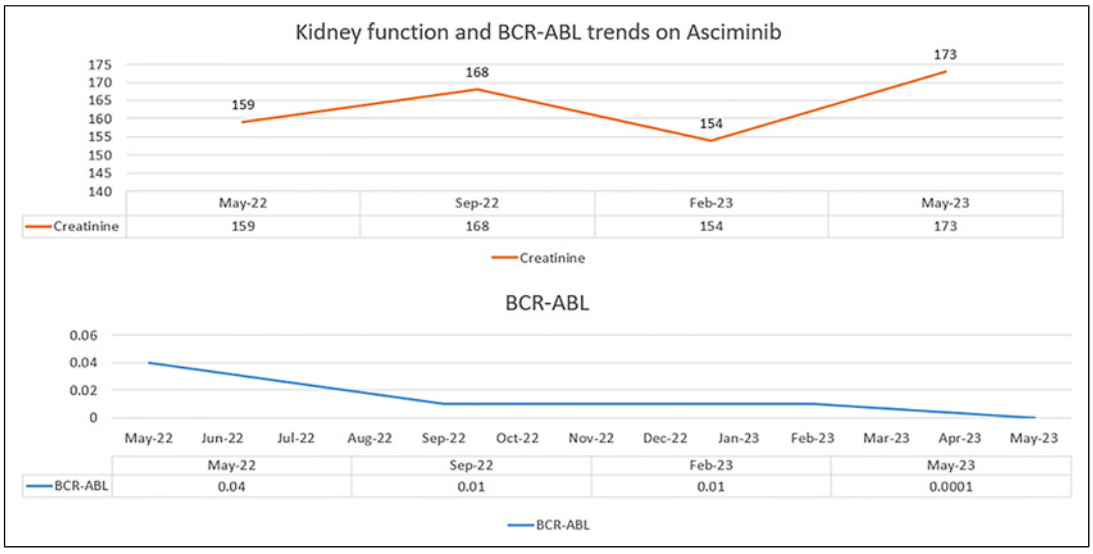

Fig. 1. Kidney function and BCR-ABL results while receiving asciminib.

decision was made to switch the patient to asciminib as a 2nd line. Over 1 year of follow-up, the patient not only maintained a deep molecular response but also exhibited stable kidney function, and the issue of fluid retention was successfully resolved.

In conclusion, based on the available limited data, this case report suggests that asciminib can be considered a safe and effective option for patients with CML who also have severe renal impairment. Nevertheless, additional research is needed to validate this observation.

Statement of Ethics

The case was approved by Hamad Medical Corporation Medical Research Center (MRC-04-23-605), and the patient signed written informed consent for the publication of any potentially identifiable images or data included in this article.

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest to declare.

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Author Contributions

Conception and design of the study, revising the manuscript for intellectual content, and approval of the version of the manuscript to be published: Dr. A. Alshurafa and Dr. M. Yasin. Acquisition of data and drafting the manuscript: Dr. A. Alshurafa and Dr. Afshan.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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