Case Series

Asciminib-a magic bullet for chronic myeloid leukemia with T315I mutation: a case series

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ABSTRACT

Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm typically characterized by the presence of the Philadelphia chromosome. The advent of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of most CML patients. However, resistance to TKIs poses a significant challenge, leading to poor treatment outcomes and prognosis in some patients. Fortunately, the introduction of asciminib, a novel allosteric BCR-ABL1 inhibitor, has provided a ray of hope. We present three cases in this report that highlight the remarkable efficacy of asciminib seen in our patients. All of these patients initially responded positively to conventional TKIs but developed a T315I mutation in the BCR-ABL fusion protein during their chemotherapy, rendering conventional TKIs ineffective and resulting in loss of response. Asciminib led to the achievement of a major molecular response in all of our patients.

Keywords: CML, Asciminib, TKIs

INTRODUCTION

Chronic myeloid leukemia (CML) is classified as a myeloproliferative neoplasm and is invariably associated with an abnormal chromosome 22 known as the Philadelphia chromosome (t(9;22)(q34;q11)). This chromosomal abnormality results in the formation of a unique gene product called BCR-ABL1, which is a constitutively active tyrosine kinase. The dysregulated activity of this tyrosine kinase is implicated in the development of CML and has become a primary target for the treatment of this disorder.

The central role of the BCR-ABL1 tyrosine kinase in the pathogenesis of CML has been established through the therapeutic efficacy of small molecule inhibitors targeting the ABL1 tyrosine kinase, which effectively reduce cellular proliferation of BCR-ABL1 expressing cells.[2]

TKIs have become the standard therapy for most CML patients. While they have a high rate of long-term disease control, these agents do not have curative potential for the majority of CML patients. The failure of TKIs to achieve a cure in CML is believed to be due to inherent resistance, particularly in a subset of leukemia stem cells that exhibit resistance to these treatments.[3,4]

Resistance to treatment can be categorized as primary or secondary. Primary resistance occurs when a tyrosine kinase inhibitor fails to achieve the desired response, which can happen in up to 25 percent of patients with chronic phase CML treated with imatinib. Secondary resistance refers to relapse following an initial response to a tyrosine kinase inhibitor. The occurrence of secondary resistance has been estimated to be approximately 8 percent at two years for patients in the chronic phase treated with imatinib.[5-8]

The primary cause of resistance to TKIs is the emergence of leukemic clones carrying specific point mutations in the BCR/ABL gene, including E255K, Y253F/H (P-loop), H396R (activation loop), or the T315I (gatekeeper) mutation. The T315I mutation, also known as the "gatekeeper" mutation, confers resistance to all available

TKIs except for Ponatinib, a multi-target kinase inhibitor, and asciminib, a novel allosteric BCR-ABL1 inhibitor.[9]

CASE SERIES

Case 1

We present the case of a male patient who presented with fever, fatigue, and abdominal pain. The patient had a previous diagnosis of CML-chronic phase (CML-CP) made 11 years prior, but could not provide baseline clinical and laboratory data. In 2018, suspecting a loss of complete hematologic response (CHR) likely due to non-compliance with imatinib treatment, we conducted investigations to assess the patient's condition.

The BCR-ABL1/ABL1 ratio was found to be very high (85.88384 IS%) with the detection of the p210 transcript. Cytogenetic analysis revealed a double Philadelphia chromosome [46,XY,t(9;22)(q34;q11.2)[12]/47,XY,t(9;22)(q34;q11.2) ,+der(22)t(9;22)[8]], and a tyrosine kinase domain (TKD) mutation (M388L) sensitive to nilotinib was also detected. The patient was initiated on nilotinib (400 mg twice daily) but failed to achieve response milestones at 3 months, 6 months, and 1 year (BCR-ABL1/ABL1 ratio 43.381% IS).

A repeat TKD mutation analysis revealed the presence of the T315I mutation with a variant allele frequency of 48.6%. This indicated that the patient had developed a mutation conferring resistance to all first and second generation TKIs, except ponatinib.

Due to limited availability and cost constraints of ponatinib in India, the patient was counseled about ponatinib and allogeneic hematopoietic stem cell transplant (HSCT). Additionally, asciminib, a recently FDA-approved drug for refractory CML, was discussed as a potential treatment option. However, asciminib also faced availability limitations similar to ponatinib. After significant effort, the patient was able to access these drugs on a compassionate basis and was initiated on asciminib (200 mg twice a day).

The patient's BCR-ABL assay results throughout the course of Asciminib therapy are shown in Table 1. The results showed a significant reduction in the P210(b3a2,b2a2) major transcript levels over the duration of therapy, indicating a positive response to asciminib treatment. The therapy was well-tolerated, with no observed metabolic, cardiac, gastrointestinal, or musculoskeletal side effects.

The promising results observed with asciminib therapy encouraged us to continue the patient on this treatment regimen. The patient is currently asymptomatic and expresses the desire to continue asciminib therapy, deferring allogeneic HSCT for the time being.

Table 1: Patient's BCR-ABL assay results through course of therapy.

Duration of asciminib therapy	P210(b3a2,b2a2) major transcript (%)
0 months	11.2
3 months	0.12740
6 months	0.0459
9 months	0.0435
12 months	0.0663

Case 2

In 2016, a young male patient in his twenties presented with symptoms of diarrhea, vomiting, and an abdominal mass on left side. Lab investigations led to a diagnosis of CML based on characteristic CBC, peripheral smear, and genetic abnormalities (BCR-ABL1/ABL1 IS% ratio: 15.72%). Immediate initiation of Imatinib therapy at a dosage of 400 mg/day resulted in an initial positive response, with improvements in symptoms and normalization of hematological parameters (BCR-ABL1/ABL1 IS% ratio: 6.02% at 3 months and 0.3% at 12 months). However, patient was infrequent with follow-up assessments and did not provide BCR-ABL1/ABL1 assays as advised during treatment.

Five years later, patient returned to facility with weakness and weight loss. Relapse of CML was suspected, and a bone marrow aspiration confirmed the presence of CML in chronic phase (CML-CP). Imatinib resistance was suspected, but no TKD mutation was observed on next generation sequencing (NGS). Imatinib was switched to dasatinib at a daily dosage of 140 mg. Within one month of starting dasatinib therapy, patient achieved complete hematological response (CHR). However, this response was not sustained, and patient lost CHR after 2 months.

To investigate underlying cause of treatment resistance, another TKD mutation analysis was performed using NGS, revealing the presence of the T315I mutation. The patient was counseled on available treatment options, including bone marrow transplant and drugs such as ponatinib and asciminib (not readily available in India). After significant efforts, asciminib was arranged, and the patient was initiated on asciminib therapy at a dosage of 200 mg twice daily. The patient's BCR-ABL1/ABL1 ratio results throughout the course of asciminib therapy are displayed in Table 2. Patient showed promising response to asciminib and achieved a sustained state of CHR.

Table 2: Patient's BCR-ABL assay results through the course of therapy.

Duration of asciminib therapy	P210(b3a2,b2a2) major transcript (%)
0 months	35.510
3 months	6.193
6 months	0.883
9 months	0.00

Asciminib therapy was well-tolerated, with no major side effects observed. The patient remains asymptomatic and expresses the desire to continue asciminib therapy rather than opting for hematopoietic stem cell transplantation (HSCT) at present.

Case 3

We present the case of a 35-year-old male patient who presented with fever and upper abdominal pain. Initial blood analysis revealed leukocytosis with left shift, and splenomegaly was observed during physical examination. Further examination through bone marrow analysis confirmed the diagnosis of CML in the chronic phase (CP), with a high BCR-ABL1/ABL-1 ratio (29.74% IS ratio). The patient's ELTS score was 1.8702, placing him in the intermediate-risk category.

The patient was initially started on a daily dose of 100 mg of dasatinib. However, after two weeks of treatment, no significant improvement was observed, and the patient experienced grade 4 myelosuppression (platelet count <10,000/mm^3), suggesting possible intolerance to dasatinib. Due to this intolerance, the treatment strategy was modified, and the patient was prescribed imatinib at a daily dose of 400 mg.

The patient continued Imatinib therapy, and subsequent monitoring of treatment response was conducted. However, a follow-up BCR-ABL1/ABL-1 ratio performed 2 months later still showed a high value (27.39% IS Ratio). As a result, the dose of Imatinib was escalated to 600 mg, but the persistently high BCR-ABL1/ABL-1 ratio necessitated further investigation. NGS was performed to identify a TKD mutation, which revealed the presence of a T315I mutation.

Although ponatinib and asciminib were not readily available in India, efforts were made to arrange asciminib on a compassionate basis for the patient. Asciminib was prescribed at a dosage of 200 mg twice daily. Remarkable improvement was observed in the patient over the following months, as shown in Table 3, and minimal side effects were noted. The positive outcome encouraged the continuation of the patient on the same therapy.

Table 3: Patient's BCR-ABL assay results through the course of therapy.

Duration of asciminib therapy	P210(b3a2,b2a2) major transcript (%)
0 months	31.240
3 months	9.276
6 months	1.140
9 months	0.02

DISCUSSION

In recent years, there have been significant advancements in the treatment of CML. The primary treatment approach for CML still involves the use of TKIs such as imatinib, nilotinib, dasatinib, bosutinib, and ponatinib.

TKIs exert their anti-tumor effects through various mechanisms, including inhibiting tumor cell repair, blocking cell division, inducing and maintaining apoptosis (cell death), and inhibiting the formation of new blood vessels to the tumor. The treatment goals in CML include achieving hematological response (normalization of blood counts), cytogenetic response (elimination or reduction of abnormal cells), and major molecular response (reduction in the level of the BCR-ABL1 gene, the hallmark of CML).[11]

Imatinib is typically the first-line TKI prescribed for CML patients due to its effectiveness. It has shown positive outcomes, with a proportion of patients achieving major molecular response ranging from 18% to 58% after one year of therapy, and complete cytogenetic response rates ranging from 49% to 77%.[12] In our case series, patients 1 and 2 were initially started on imatinib.

However, some patients may develop resistance to imatinib, which is defined as the failure to achieve desired responses within specific timeframes. The resistance rate to imatinib in the first five years of treatment is approximately 15-20%.[13] Resistance can be primary, caused by BCR-ABL1-independent mechanisms, or secondary, arising after an initial response due to BCR-ABL1-dependent mechanisms. Mutations in the TKD of the BCR-ABL1 gene account for a significant proportion of imatinib resistance (40% to 50%).[14] In our case series, the T315I mutation, which confers resistance to imatinib and all second-generation TKIs, was observed in all three patients.

While some mutations may respond to increased doses of imatinib, most mutations do not, necessitating a switch to a second- or third-generation TKI. Dose escalation of imatinib was attempted in patient 3 until the T315I mutation was detected, but it was not successful. Patients 1 and 2 were switched to second-generation TKIs, which have shown greater efficacy in improving major molecular response in cases of imatinib resistance compared to increasing the dose of imatinib itself. However, the development of the T315I mutation in these patients eventually led to a lack of sustained response.[15]

The T315I mutation remains a challenge as it confers resistance to imatinib and all second-generation TKIs except ponatinib. Asciminib, a selective allosteric inhibitor of BCR-ABL1, offers a promising therapeutic approach for patients with refractory CML, including those with the T315I mutation. Preclinical studies have demonstrated that asciminib effectively inhibits BCR-ABL1 and overcomes TKI resistance, including the T315I mutation.[16]

Clinical trials evaluating the efficacy of asciminib in CML patients with the T315I mutation have shown

promising results. In the ASCEMBL study, which included patients with resistant or intolerant CML, asciminib demonstrated significant cytogenetic and molecular responses with manageable side effects.[17]

In our case series, all patients were initiated on asciminib therapy at a dose of 200 mg twice daily. Subsequent assessments showed normalization of peripheral blood counts and improvement in the burden of BCR-ABL1 without significant side effects. These findings indicate a favorable response to asciminib treatment and highlight its potential as an effective therapeutic strategy for CML patients with the T315I mutation.

The unique mechanism of action of asciminib, targeting the myristoyl-binding site of BCR-ABL1, sets it apart from traditional TKIs and may contribute to its efficacy in overcoming resistance. Its ability to inhibit multiple isoforms of BCR-ABL1 makes it a promising therapeutic option for patients with refractory disease, including those with the T315I mutation.[18]

Despite the encouraging results seen in your case series and in clinical trials, further studies are needed to establish the long-term safety, efficacy, and optimal dosing of asciminib in the treatment of refractory CML. Ongoing research and clinical trials will provide more insights into the use of asciminib and its role in managing CML patients with the T315I mutation.

CONCLUSION

Absolutely, the introduction of asciminib has indeed brought about a significant breakthrough in the treatment of CML, particularly for patients facing resistance to TKIs. The promising results seen in clinical trials and real-world evidence highlight the potential of asciminib as a valuable therapeutic option for patients with limited treatment options, especially those with the T315I mutation.

However, to fully understand the long-term safety, optimal dosing regimens, and overall effectiveness of asciminib in refractory CML, further investigations and research are necessary. Ongoing studies will provide valuable insights into its role in improving patient outcomes and advancing personalized treatment approaches.

By integrating asciminib into clinical practice and refining treatment strategies, healthcare professionals can enhance patient outcomes and provide better care for those with refractory CML. Continued research and real-world evidence will be crucial in establishing the full potential and optimal utilization of asciminib as a treatment option for this patient population.

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