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CASE REPORT

Molecular response with asciminib 20 mg QD in a patient intolerant to multiple TKIs

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Abstract

This case highlights a young CML patient who achieved a major molecular response (MMR) after just four months with a subtherapeutic dose of asciminib. The patient could not tolerate full-dose asciminib, or the full dose of two previous tyrosine kinase inhibitors (TKI) due to myelotoxicity, but blood counts recovered rapidly upon TKI suspension and reduced dosing enabled sustained treatment. This is the second reported case of the use of 20 mg QD asciminib, four times below the recommended dose, and the first to demonstrate efficacy at this dose. The study emphasizes asciminib's potential for overcoming treatment challenges associated with multi-resistant/intolerant CML patients.

Keywords Asciminib · Tyrosine kinase inhibitors (TKIs) · Cytopenia · Subtherapeutic dosing

Six tyrosine kinase inhibitors (TKI) are currently available in Europe for the treatment of chronic myeloid leukemia (CML) patients in the chronic phase. TKIs are generally well-tolerated drugs, although anemia, neutropenia, and thrombocytopenia typically occur in the first trimester. Most adverse effects are dose-dependent and resolve after dose reduction or TKI interruption [1, 2].

Prolonged pancytopenia related to TKI treatment is rare but can lead to suboptimal responses due to continued low doses or interruptions [3, 4]. Switching TKIs may be necessary, although cross-intolerance is common, thus myelotoxicity poses a significant treatment challenge. Consistent with its unique mechanism of action, asciminib may offer a further treatment option for multi-resistant or multi-intolerant patients [5, 6], including for patients with the T315I mutation [7, 8].

Here, we present the case of a CML patient intolerant to three TKIs who achieved a major molecular response (MMR) on a subtherapeutic dose of asciminib in just four months.

The 37-year-old female patient was diagnosed with low-risk chronic-phase CML in February 2019 after routine blood work revealed leukocytosis ($142 \times 10^3/\mu L$). At diagnosis, she had normal hemoglobin and platelet counts, splenomegaly (15 cm), and 70% *BCR::ABL1/ABL1*^{IS} (e14a2). The karyotype showed no additional chromosomal abnormalities.

The patient initiated treatment with nilotinib 300 mg BID, achieving complete hematologic response within 2 months. By the fourth month, the *BCR::ABL1/ABL1*^{IS} was 4.6%, but she developed bicytopenia (Hgb 7 g/dL, platelets 48,000/μL, both grade 3 according to the CTCAE v5.0), requiring TKI interruption. After 5 weeks, her blood counts recovered and nilotinib restarted at 300 mg QD (Fig. 1).

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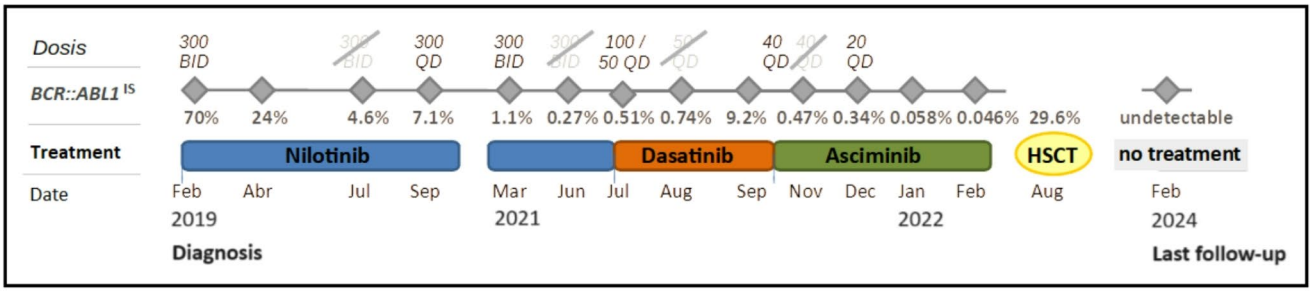

Fig. 1 Timeline of the patient's clinical trajectory from diagnosis, in February 2019, to last follow-up, in April 2024. The TKI lines and doses received are indicated, as are the *BCR::ABL1*/*ABL1*^{IS} levels (silver diamonds)

After 12 months, her *BCR::ABL1*/*ABL1*^{IS} was 1.1%. The dose was increased to 300 mg BID, resulting in the recurrence of grade 1 cytopenias in all three blood cell lines. The decision was made to switch TKIs due to her inability to tolerate the full dose. No *ABL1* kinase domain mutations were detected.

At 15 months post-diagnosis she began dasatinib 100 mg QD, reduced to 50 mg QD within a few days because of severe headaches. After 2 months, her *BCR::ABL1*/*ABL1*^{IS} was 0.74%, but she again developed pancytopenia (neutrophils 630/µL, grade 3; Hgb 10.5 g/dL, grade 1; platelets 96,800/µL, grade 1). Dasatinib was interrupted and the blood counts recovered.

After 18 months of TKI treatment, the patient's transcripts were at 9.18%. Since the patient had not achieved a MMR and experienced difficulty tolerating full treatment doses of dasatinib, asciminib was requested to mitigate cross-reactions with TKIs.

Asciminib was initiated at half the recommended dose (40 mg QD). Despite good initial tolerance, and 0.47% *BCR::ABL1*/*ABL1*^{IS}, pancytopenia reappeared after 3 months (although less severe than previous occurrences: neutrophils 900/µL, grade 3; Hgb 11 g/dL, grade 1; platelets 100,000/µL, grade 1). Asciminib was reduced to 20 mg QD and after just four months of treatment, the patient achieved a MMR (0.056%, Fig. 1).

A bone marrow aspirate carried out in February 2022 led to the detection of 11% blasts and the appearance of monosomy of chromosome 7 (45,XX,-7[9]/46,XX, t(9;22)(q34;q11)[1]/46,XX[10]). This indicated the clonal evolution of a leukemic Ph-negative clone despite the effectiveness of low-dose asciminib.

Retrospective NGS of a diagnostic sample using the SOPHiA Myeloid Tumor panel revealed a pathogenic variant in *ASXL1* with low variant allele frequency (VAF 8.6%; p.Gly646Trpfs*12). NGS analysis with a sample from February 2022 revealed expansion of the *ASXL1*-mutated clone (VAF 34%) and the acquisition of a pathogenic variant in *PTPN11* (p. Phe285Leu, 27.3%), as well as deletion of the *RUNX1* gene on chromosome 21 and monosomy of chromosome 7, according to copy number analysis with the same panel.

In May 2022, although asymptomatic, a bone marrow aspirate revealed 20% blasts. Karyotype showed the persistence of the monosomy 7 clone and the emergence of a tetrasomic clone (45,XX,-7[11]/92,XXXX[9]). Acute myeloid leukemia (AML) in a Ph-negative clone was confirmed.

Asciminib was discontinued and the patient received standard induction chemotherapy (anthracycline + cytarabine, 7 + 3) followed by a haploidentical hematopoietic stem cell transplant in August 2022. Pre-transplant the patient had 0.8% blasts, 29.58% *BCR::ABL1*/*ABL1*^{IS}, and the karyotype had normalized (46,XX, t(9;22)[10]/46,XX[10]).

The patient is currently not receiving any treatment. At last follow-up, nearly two years post-transplant (April 2024), the patient was in complete remission from her AML, with sustained complete donor chimerism, undetectable *BCR::ABL1*, and a normal karyotype.

This case presents the case of a young patient who failed to achieve MMR on nilotinib and dasatinib in the first and second lines due to intolerance. Unable to receive the full dose of nilotinib, dasatinib, or asciminib, she did reach MMR on just 20 mg QD asciminib, four times below the recommended dose (40 mg BID).

The ASECMBL trial for patients with intolerance or lack of efficacy after at least 2 prior TKI lines found thrombopenia and neutropenia to be among the most frequent adverse events of grade 3 or higher, reported in 22.4% and 18.6% of patients treated with asciminib 40 mg BID [6, 7]. However, these cytopenias were managed with dose reduction allowing patients to achieve an MMR.

A dose of 20 mg QD asciminib has only been previously reported once in the scientific literature for CML treatment. A dose of 10 mg BID was received by one patient in the Phase 1 dose-escalation study, although the molecular response of the patient was not described [8]. This makes our patient the second reported in the literature to receive 20 mg QD and the only CML patient, to the best of our knowledge to obtain an MMR with this dose.

Despite asciminib's novel mechanism of action compared to the ATP-competitive TKIs nilotinib and dasatinib, our patient showed cross-intolerance to asciminib at full dose due to myelotoxicity. A real-life retrospective study of 77 CML patients treated with asciminib following therapeutic failure to second-generation TKIs reported that patients who experienced cytopenias on previous TKIs were at a higher risk of hematological cross-intolerance with asciminib [9], with the risk of cross-toxicity calculated as 43% for thrombopenia, 22% for anemia and 21% for neutropenia [10]. Our patient's myelotoxicity was caused by TKI treatment, as her blood counts promptly recovered upon TKI suspension.

Our case demonstrates that asciminib may be a viable treatment option for CML patients who fail to reach a molecular response after multiple TKI lines. However, further studies are needed to clarify the long-term efficacy of subtherapeutic doses.

Author contributions ASD and MTGC were critical in the diagnosis and treatment of CML; VVB, CRM, AVV, AMC, LGP, MTO, MMP carried out treatment of AML, transplant and post-transplant follow-up; CBS and RS performed molecular studies; JFLR carried out cytometry; MTGC supervised the study; RS, LNB, ABB, ASD and MTGC wrote the manuscript; all authors have read and agreed to the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval Our institution does not require ethical approval for reporting individual cases or case series. This case was reported according to the CARE guidelines.

Patient consent Verbal informed consent was obtained from the patient for their anonymized information to be published in this case report.

Competing interests The authors declare no competing interests.

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