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CASE REPORT

Combined asciminib and olverembatinib in blast-phase chronic myeloid leukemia

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Running title: Asciminib plus olverembatinib in BP-CML

Disclosures

No conflicts of interest to disclose.

Authors' contributions

Weiming Li conceptualized and designed the study. Fang Cheng and Weiming Li wrote, reviewed, and approved the manuscript.

Data-sharing statement

The data generated in this study are not publicly available due to information that could compromise patient privacy or consent.

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Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder typically managed with BCR::ABL1 tyrosine kinase inhibitors (TKIs). However, it can progress from chronic phase (CML-CP) to blast phase (CML BP), during which BCR::ABL1 kinase domain (KD) genetic variants (e.g., T315I, Y253H) and aberrant activation of cellular bypass signaling pathways contribute to multidrug resistance, complicating treatment and potentially causing death. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative option, but patients with advanced disease that cannot revert to a second chronic phase (CP2) have a heightened risk of relapse after transplantation.[1, 2] Combining TKIs with chemotherapy can improve efficacy, but increases treatment-related toxicity.[3] Therefore, it is essential to facilitate an efficient and rapid reversion from CML-BP to CML-CP.

Asciminib, an allosteric STAMP (specifically targeting the ABL myristoyl pocket) inhibitor, can overcome ATP-competitive TKI resistance by binding to the myristoyl pocket. Olverembatinib, a third-generation (3G) TKI developed and approved in China, is indicated for patients with CML-CP and accelerated-phase CML (CML-AP) harboring the *T315I* genetic variant and adults with CML-CP resistant or intolerant to other TKIs.[4-6] Co-administration of 3G TKIs and asciminib may elicit synergistic anticancer effects.[7, 8] This report introduces clinical data on the efficacy and safety of asciminib plus olverembatinib in patients with CML-BP.

Case 1

A 51-year-old male was diagnosed with CML-CP in January 2025 at primary

hospital, but with extramedullary infiltration of lymph nodes, so he was diagnosed as extramedullary blastic. He initially received imatinib (400 mg daily [qd]) and achieved hematologic remission. However, on March 2, 2025, he was identified a *T315I* genetic variant, and the LN metastases exhibited a mixed phenotype of lymphoid (T-cell) and myeloid blasts, leading to a treatment switch to olverembatinib (40 mg, every other day [qod]). Follow-up BM aspiration (on March 10) revealed: blast cells comprised 28% of the sample; compound mutations (*T315I*, *E255V*, and *E255K*) with *BCR::ABL1* fusion gene positivity of 68.32% (measured by quantitative real-time polymerase chain reaction), and no changes observed in LNs, indicating treatment failure. After extensive discussions, the patient declined chemotherapy. On March 16, 2025, we began closely monitoring peripheral blood (PB) smears daily for blast cell counts and LN size variations, while administering olverembatinib (40 mg, qod) plus asciminib (80 mg, twice daily [bid]). The plan was to transition to chemotherapy if this treatment regimen failed. During treatment, PB smear analyses demonstrated a gradual decrease in blast cell counts. A follow-up BM aspiration on March 27, 2025, revealed that blast cells had decreased to 3%, indicating a return to CML-CP. In addition, LN enlargement disappeared and the PET scans were negative. On April 4, 2025, we documented that the patient had achieved complete cytogenetic response (CCyR) with a *BCR::ABL1* International Scale (IS) level of 3.029%. By June 9, 2025, the disease remained controlled in CML-CP, and the patient had achieved a *BCR::ABL1*^{IS} level of 0.019%. On June 19, 2025, the patient underwent transplantation. The treatment timeline is outlined in Figure 1. During treatment, the

patient experienced grade 3 thrombocytopenia and neutropenia, which were managed with supportive transfusions and therapies, resulting in normalization of neutrophil and platelet counts after 7 days.

Case 2

A 37-year-old male presented with leukocytosis and was diagnosed with CML-CP in 2023. Initial treatment was with imatinib (400 mg, qd), however, this treatment failed after 6 months, with a *BCR::ABL1* ^{IS} of 97.82%. Treatment was switched to flumatinib (600 mg, qd), but severe hematologic toxicity (G3 anemia, G4 thrombocytopenia) prompted transition to dasatinib 50 mg qd in February 2024. In March, 2024, a follow-up BM aspiration revealed 21.5% blast cells. The treatment regimen was then changed to a generic version of ponatinib plus DCHG regimen from March 5 to 11, 2024. In September 2024, *BCR::ABL1* KD mutation testing identified a *T315I* genetic variant, with a *BCR::ABL1*^{IS} of 65.45% (karyotype:50, XY, +Y, +9, t(9, 22)(q34 q11.2)x2,+21,+22[18]/46, XY[2]), indicating treatment failure. In September 2024, the patient enrolled in a clinical trial examining the safety and efficacy of TGRX-678 in CML intolerant or resistant to prior TKI treatment (NCT05434312). TGRX-678 is an investigational STAMP inhibitor.[9] He received an initial daily dose of 240 mg, which was decreased to 120 mg because of treatment-related thrombocytopenia. After platelet recovery, he resumed treatment at daily doses of 240 mg. On December 5, 2024, a follow-up BM aspiration revealed 45% BM blast cells (karyotype: XY, +Y, +9, t(9 22)(q34;q11.2)x2, +21, +22[20]). In addition, testicular infiltration and the presence of a *T315I* genetic variant indicated

disease progression to CML-BP with acute myeloid features [10], leading to the patient's withdrawal from the trial. On December 14, 2024, treatment was changed to olverembatinib (30 mg, qod) plus BCL-2 inhibitor venetoclax, and hypomethylating agent azacitidine. However, due to hematologic AEs and financial constraints (he only received venetoclax for 20 days), treatment was shifted to olverembatinib monotherapy. In March 2025, a BM sample revealed 35% blast cells. In light of the failure of all current TKI treatments and the patient's concurrent severe pneumonia and myelosuppression, which precluded the use of high-dose chemotherapy. Due to concerns regarding treatment tolerance (previous grade 4 hematologic AEs), a combination regimen of olverembatinib (20 mg, qod) and asciminib (40 mg, qd) was initiated on March 12, 2025. Grade 4 neutropenia recurred during this treatment, however, the patient's condition improved after G-CSF therapy. On March 20, 2025, FCM analyses were performed using a BM aspirate. Approximately 4.5% of abnormal cells were detected. A follow-up BM aspiration on April 10, 2025, indicated 8.5% blast cells with a *BCR::ABL* ^{IS} of 96.24% (karyotype: 47，XY, +8, t(9;22)(q34;q11.2)[20]), the disease returned to CML-CP and remained stable (with 2% blast cells noted on May 8, 2025). Because of economic difficulties, the patient declined allo-HSCT and died on July 18, 2025. The treatment timeline is outlined in Figure 2.

European LeukemiaNet (ELN) guidelines recommend that patients in CML-BP undergo allo-HSCT as early as possible, ideally once they attain CP2.[10] Consequently, consensus guidelines advocate for intensive chemotherapy, with or without TKIs, as a

bridge to transplantation, often tailored according to mutation analysis. However, intensive chemotherapy is intolerable for some patients.

This study demonstrates, for the first time, the potential utility of combining asciminib and olverembatinib in patients with CML-BP. The findings indicate a rapid return to CML-CP with tolerable AEs, thus facilitating early allo-HSCT. In the first case, a patient with newly diagnosed CML-BP responded positively to combination therapy. In the second case, the patient had multidrug-resistant CML-BP with resistance to both olverembatinib and TGRX-678 monotherapy, yet rapidly reverted to CP2 after the addition of asciminib to olverembatinib. These observations suggest that dual inhibition targeting distinct BCR::ABL1 sites on may overcome resistance encountered with traditional ATP-competitive TKIs. In addition, allosteric ligands may synergistically enhance the antileukemic activity of TKIs.

Preclinical studies suggest that asciminib exhibits synergistic effects when combined with traditional TKIs.[7] Synergy mechanisms may include: ① conformational locking: asciminib stabilizes BCR::ABL1's inactive state, enhancing ponatinib binding to resistant mutants; ② overcoming compound mutations: asciminib + ponatinib eradicated T315I-containing IMP-R clones (e.g., T315I+H396R Y253H) in murine models;③ the combination inhibited expansion of resistant subpopulations. Eide[11] first reported the effectiveness of combining ponatinib and asciminib in patients with CML-CP harboring the *BCR::ABL1 T315I*/*E355G* variant. Ponatinib and asciminib exhibit a three-tiered synergistic mechanism (conformation-occupancy-signaling pathway) against *BCR::ABL1* compound

mutations. Critically, the binding pockets for ponatinib and asciminib do not overlap, allowing simultaneous saturation at clinically achievable concentrations. Concurrent targeting of two distinct sites elevated the mutation barrier and reduced the emergence of *in vitro* resistant clones by >100-fold. Furthermore, due to their divergent pharmacokinetic pathways, synergistic efficacy could be maintained at lower individual doses, potentially reducing toxicities. Similarly, Hall[12] documented clinical efficacy of the asciminib-bosutinib combination in overcoming TKI resistance in patients with CML-CP. Multiple clinical trials (e.g., NCT03578367, NCT02081378) are evaluating effects of asciminib plus TKIs among patients with newly diagnosed, previously treated with at least 1 other TKI, and relapsed CML-AP or -CP.[13, 14] The study demonstrated that asciminib combined with TKIs provided rapid efficacy in CML-CP/AP patients, but was less well-tolerated than asciminib monotherapy. In the subset of patients who may respond to this proposed combination therapy, a potential benefit that it offers is stronger efficacy (versus monotherapy) which may prevent TKI switching that might result in the development of treatment-resistant mutations. This case report presents the first empirical evidence supporting the feasibility of this combination treatment strategy in patients with CML-BP, establishing a rational foundation for its prospective evaluation in a clinical trial. Future larger studies are warranted to validate these findings and define potential mechanisms.

This study was performed in concordance with the ethical rules of China.

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Figure legands

Figure 1. Outline of treatment schedule for Case 1

Abbreviations: CCyR, complete cytogenetic response; FISH, fluorescence *in situ* hybridization; MMR, major molecular response; PET, positron emission tomography

Figure 2. Outline of treatment schedule for Case 2

Footnotes:

a. Prior to assessment on December 5, 2024, the patient appeared to initially respond to treatment. On October 10, 2024, we observed a *BCR::ABL* IS of 60.39%, peripheral blood (PB) blasts at 1%, bone marrow (BM) blasts at 0.5%, no mutation, and the following chromosome profile: 50, XY, +Y,+9,t(9 22)(q34 q11 .2)x2,+21,+22[19]/46,XY,(9;22)(q34; q11.2)[1]. Subsequent assessments on October 23, 2024, November 6, 2024, and November 20, 2024, showed PB blasts cells at 0%, 0%, and 0.5%, respectively.
b. The specific treatment regimen was administered at an external hospital, and some information is unclear as the efficacy during follow-up evaluations was undocumented. During this period, the patient developed pancytopenia (reduction in all three blood cell lineages), with the lowest recorded white blood cell count at 0.34×10□/L. Intermittent discontinuation and dose reduction of medications occurred throughout the treatment course.
c. Flow cytometric analysis (via CD45/side scatter [SSC] dot plot) gating analysis revealed that blast/precursor region cells accounted for approximately 4.5% of nucleated cells. Within the detection range, these cells positively expressed HLA-DR, CD13, CD33, CD34, CD117, and CD123, suggesting the presence of immunophenotypically abnormal cell.


Diagnosis: CML-CP (extramedullary blastic)
Imatinib; 200 mg (oral administration/po, twice a day/bid)
Post-treatment evaluation
March 2, 2025
• Lymph node metastasis, exhibiting a mixed phenotype of lymphoid (T-cell) and myeloid blasts
• Mutation: BCR::ABL1 T3151+
Reason for therapy change: Poor efficacy
2025.1
Olverembatinib; 40 mg (every other day/qod)
Post-treatment evaluation
March 10, 2025
• BCR::ABL1 IS: 68.32%
• Bone marrow (BM) blast cells: 28%
• Mutation: Compound (T315I, E255V, and E255K)
• FISH analysis: 99% (198/200)
Reason for therapy change: Poor efficacy
2025.3
Olverembatinib; 40 mg qod + Asciminib; 80 mg, bid
Post-treatment evaluation
March 27, 2025
• BM blast cells: 3%
• Lymph node enlargement had disappeared
• PET scans: negative
Post-treatment evaluation
April 4, 2025
• CCyR
• BCR::ABL1 IS: 3.029%
• Chromosome analysis: 46, XY,[20]
2025.4
Post-treatment evaluation
June 9, 2025
• MMR
• BCR::ABL1 IS: 0.019%
2025.6
Patient underwent transplantation on June 19, 2025
Post-treatment evaluation
July 21, 2025
• BM blast cells: 0.5%
• Peripheral blood (PB) blast cells: 0%
• Flow cytometric analysis (of 750,000 nucleated cells)
➢ CD34+/CD117+ myeloid blast cells: 0.09%
➢ CD34-/CD117+ myeloid blast cells: 0.57%
➢ No significant abnormalities were observed in both proportions/immunophenotypes
➢ BCR::ABL1 IS: 0%


Diagnosis: CML-CP
Imatinib; 200 mg (oral administration/po, twice a day/bid)
Post-treatment evaluation
June 20, 2023
BCR::ABL1 IS: 97.83%
Chromosome analysis: 46, XY, t(9;22)(q34;q11.2)[20]
Peripheral blood (PB) blast cells: 2%
Bone marrow (BM) blast cells: 4.5%
No mutations observed
Reason for therapy change: Poor efficacy
2023.2
Flumatinib; 600/400/200 mg (daily/qd, po, alternate use
Post-treatment evaluation
October 10, 2023
BCR::ABL1 IS: 61.96%
Chromosome analysis: 46, XY, t(9;22)(q34;q11.2)[[20]
PB blast cells: 0%
BM blast cells: 4.5%
Reason for therapy change: Adverse events (grade 3 anemia, grade 4 thrombocytopenia) and poor efficacy
2023.7
Dasatinib; 50 mg qd, po
Post-treatment evaluation
March 5, 2024
BM blast cells: 21.5%
March 13, 2024
Chromosome analysis: 46, XY, t(9;22)(q34;q11.2)[12]/47~50,idem,+Y, +9,t(9;22)(q34;q11.2),+21[cp8]
Reason for therapy change: Poor efficacy.
2024.2
Ponatinib; 45/15 mg qd; alternate use plus DCHG:
Decitabine; 10 mg, D1-5
Cytarabine; 25 mg, every 12 hours, D1-7
Homoharringtonine; 2 mg, D1-7
Granulocyte colony-stimulating factor
Post-treatment evaluation
March 13, 2024
BM blast cells: 0%
August 27, 2024
BCR::ABL1 IS: 65.45%
Mutation: BCR::ABL1 T3151+
Chromosome analysis: 50, XY, +Y,+9,t(9 22)(q34 q11.2)x2,+21,+22[18]/46,XY[2]
BM blast cells: 2.5%
Reason for therapy change: Severe hematological AEs and poor efficacy
2024.3
TGRX-678; 240/120 mg, alternate use
Post-treatment evaluation[a]
December 5, 2024
BCR::ABL1 IS: 122.44%
Mutation: BCR::ABL1 T3151+
Chromosome analysis: XY, +Y, +9, t(9 22)(q34;q11.2)x2, +21+22[20]
PB blast cells: 48%
BM blast cells: 45% (with testicular infiltration)
December 10, 2024
PB blast cells: 61%
Reason for therapy change: Adverse events (grade 3 anemia, grade 4 thrombocytopenia) and poor efficacy
2024.9
Olverembatinib; 30 mg (every other day/qod) + Venetoclax; 100-400 mg ramp up, 400 mg qd + Azacitidine; 75 mg/m2 qd, D1-7
Post-treatment evaluation[b]
January 1, 2025
BCR::ABL1 IS: 12.93%
February 29, 2025
BM blast cells: 35%
Reason for therapy change: Olverembatinib dose reduced because of intolerance
2024.12
Olverembatinib; 20 mg qod + Asciminib; 40 mg, qd
Post-treatment evaluation
March 20, 2025
PB blast cells: 15%[c]
April 10, 2025
BCR::ABL1 IS: 96.24%
Mutation: BCR::ABL1 T3151+
Chromosome analysis: 47, XY,+8, t(9;22)(q34;q11.2)[20]
PB blast cells: 7%
BM blast cells: 8.5%
Emergent adverse event: pleural effusion
2025.3
2025.7.18
Patient died