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CASE REPORT

# Asciminib and pulsed ATRA as post-remission therapy in T315I mutated PML-RARA-positive blast crisis of chronic myeloid leukemia

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**Abstract**

Promyelocytic blast crisis (BC) of CML is an extremely rare event, with only seven cases described as arising during therapy with TKIs. We present a 68-year-old male who developed promyelocytic blast crisis 12 months after CML diagnosis and start of Imatinib therapy, confirmed by the concomitant presence of the t(15;17) and t(9;22) translocations in the leukemic cells. Molecular remission for the *PML-RARA* clone was achieved with standard acute promyelocytic leukemia induction therapy with ATRA and idarubicin. However, *BCR-ABL* showed resistance to first-line Dasatinib and second-line Ponatinib, principally due to the presence of multiple mutations in ABL1 kinase domain, including T315I. Hematological and molecular response was achieved with Asciminib, a first-in-class STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor in combination with pulsed ATRA as post-remission strategy. Of the 7 cases of promyelocytic BC reported in the era of TKI therapy for CML, this is the first case effectively treated with Asciminib therapy.

**Keywords** CML · Blast crisis · Asciminib · T315I · PML-RARA

## Case report

The occurrence of blast crisis in chronic myeloid leukemia (CML) has been drastically reduced since the introduction of tyrosine kinase inhibitors (TKIs). Despite its rarity, blast crisis still represents a clinical challenge, with low remission rates and need of treatment intensification including allogeneic stem cell transplantation (Allo-SCT) [1]. PML-RARα positive blast crisis of Ph + CML has been rarely described over the past two decades, with only seven cases arising during TKI therapy [2–8].

Herein, we report a unique case of PML-RARα-positive blast crisis (BC) arising during imatinib therapy and successfully managed with all-trans retinoic acid (ATRA) and anthracyclines in combination with Asciminib, a first-in-class STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor after resistance to third-line Ponatinib therapy.

A 68-year-old male with a history of drug and alcohol abuse was diagnosed with CML, classified as low-risk according to the Sokal score in August 2022. Cytogenetics

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at diagnosis was done but was not evaluable. He started on imatinib 400 mg/day.

Monitoring of the *BCR-ABL1* transcript during imatinib therapy revealed 29% IS after 3 months indicating treatment failure according to ELN guidelines [9]. The patient admitted poor adherence to therapy and was unwilling to switch to a second-generation TKI. At 9 months, *BCR-ABL1* levels had decreased to 1.4% IS. Twelve months after starting imatinib, the patient developed thrombocytopenia (70 × 10^3/μL), that required temporary discontinuation of imatinib. However, subsequent blood counts revealed worsening thrombocytopenia (14 × $10^3$/ul) and evidence of leukocytosis (30 × $10^3$/ul).

A peripheral blood smear showed 50% of abnormal hypergranular promyelocytes with bi-lobed and folded nuclei strongly suggestive of acute promyelocytic leukemia (APL) (Fig. 1). Coagulation parameters showed typical APL-related disseminated intravascular coagulation (DIC) with hypofibrinogenemia.

A bone marrow (BM) study revealed 80% of abnormal promyelocytes blasts, confirmed by immunophenotype, this latter consistent with typical pattern of promyelocyte blasts (CD117/CD13/CD33/+; CD34/HLADR-). A diagnosis of APL blast crisis (BC) was confirmed by the detection of *PML-RARα* fusion transcript (BCR3) by RT-PCR. *BCR-ABL1* transcript at the time of disease progression was 51% IS.

Chromosome banding analysis revealed 46,XY, t(9;22)(q34;q11.2), t(15;17)(q24;q21) in 10 metaphases with no metaphases harboring normal karyotype. The concomitant presence in blast cells of *PML-RARα* and *BCR-ABL1* fusion transcripts was confirmed with interphase fluorescence in-situ hybridization (FISH). (Fig. 1) Mutational analysis by high throughput next-generation sequencing (NGS) using Illumina platform (MiSeq) showed M244V (VAF 3%) and F359I (VAF 12%) mutations in the ABL kinase domain. FLT3-ITS mutational screening was also performed and resulted negative. Interestingly, a retrospective Q-PCR analysis of *PML-RARα* transcript by quantitative PCR showed the presence of a subclone (1.4%) already in the samples analyzed for *BCR-ABL1* MRD during the chronic phase, one month before the diagnosis of BC (Fig. 2).

The patient started induction therapy for high-risk APL according to the AIDA2000 protocol, including ATRA and idarubicin, as elsewhere reported wihtout concomitant administration of TKIs [9]. However, he developed atrial fibrillation after the third dose of idarubicin and did not receive the expected fourth idarubicin dose. Sixty-days after induction, the patient showed incomplete hematologic recovery and bone marrow examination showed hypocellularity without blast infiltration. BM biopsy showed hypocellularity (< 10%) in absence of blasts. Quantitative molecular studies revealed the absence of *PML-RARα* transcript but the persistence of *BCR-ABL1* (37% IS).

Consolidation therapy for acute promyelocytic leukemia with arsenic trioxide (ATO) and ATRA was planned considering the cardiotoxicity occurred during anthracyclines therapy. However, the persistent bone marrow aplasia with transfusion-dependent anemia and thrombocytopenia, and the occurrence of clinical complications in the post-induction phase including pneumonia and gastric hemorrhage secondary to peptic ulcer, hampered the APL consolidation program.

Sixty days after induction the patient was started on pulsed ATRA (15 days on and 15 days off) and dasatinib 80 mg/day. After 2 months of therapy, *BCR-ABL1* transcript

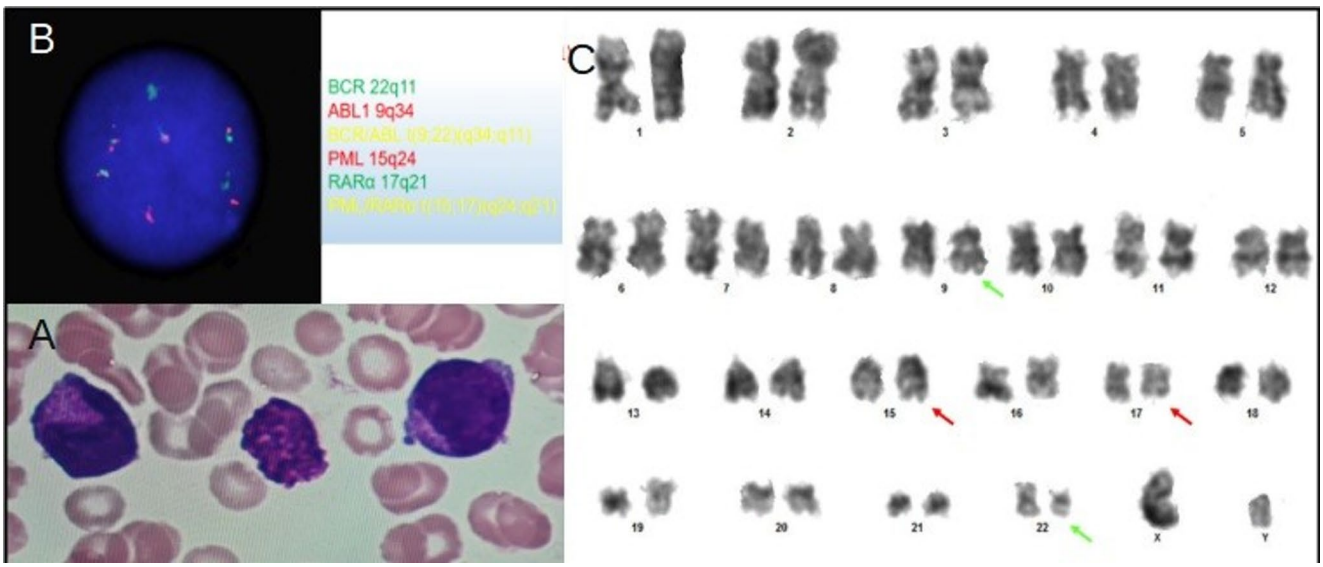


**Fig. 1** Morphology (A), FISH (B) and karyotype (C ) analysis of *PML-RARA*-positive CML BC

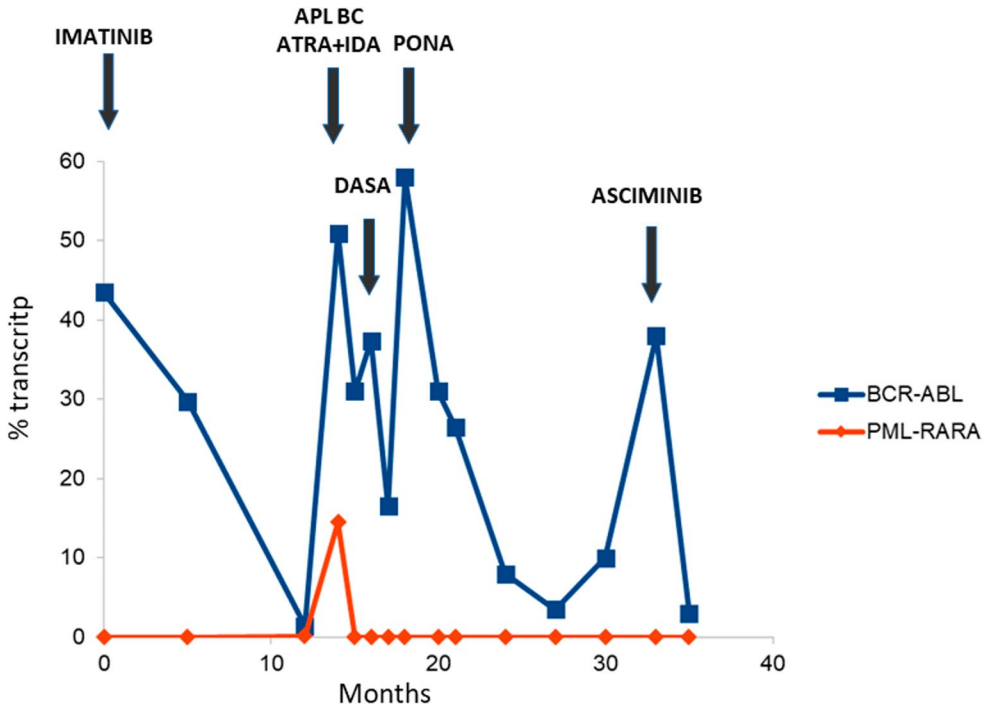


**Fig. 2** Kinetics of *PML-RARA* and *BCR-ABL* transcripts during the disease course. BC,blast crisis; DASA,Dasatinib; PONA,Ponatinib

level showed only a mild reduction (16.4% IS) and mutation analysis by NGS revealed the increased VAF for two mutations previously observed (M244V, VAF 15.2%; F359I, VAF 33.2%), and the occurrence of additional mutations such as E225K (VAF 1.3%), I418V (VAF 4%), and T315I (VAF 2.7%). NGS panel for myeloid genes did not reveal additional mutations. The presence of T315I mutation prompted a therapeutic switch to ponatinib at the starting dose of 30 mg QD and the search for an available donor for allogeneic transplant. However, significant cardiac, pulmonary and gastrointestinal comorbidities rendered the patient ineligible to the transplant procedure. After 6 months of therapy with Ponatinib and pulsed ATRA, the patient showed negative PML-RARα transcript and progressive decrease of BCR-ABL1 transcript (5% IS), with mild improvement of peripheral cytopenias. However, at 9 months from Ponatinib start, molecular biology showed increasing BCR-ABL transcipt up to 29% IS. NGS mutations disclosed increase in T315I VAF to 38%. In addition, the patient presented a new episode of atrial fibrillation, for which he underwent left atrial appendage closure (LAAC) procedure. In consideration of rise in BCR-ABL transcipt and cardiac complications the patients switched to Asciminib at the dose of 200 mg BID. After 5 months of Asciminib the patient showed reduction of BCR-ABL1 transcript to MR1 (3% IS) and significant improvement of peripheral cytopenias, reaching transfusion indipendence. The patient showed only grade 1 elevation of serum bilirubin.

At 20 months from diagnosis of PML-RARA blast-crisis the patients is in molecular CR for PML-RARA and MR1 (3%IS) for BCR-ABL transcipt and is still receiving high-dose asciminib and pulsed ATRA.

PML-RARα positive blast crisis arising during TKI therapy is an exceedingly rare event with only 7 cases reported in the literature up to date, the majority occurring under imatinib [2–8]. BC-CML exhibits clonal and molecular heterogeneity, often presenting additional chromosomal aberrations and mutations in the BCR-ABL1 kinase domain [10, 11]. Our case raises important issues in BC pathogenesis and therapeutic management. The availability of sequential biologic samples for BCR.ABL1 monitoring allowed the identification of *PML-RARα* transcript at the subclonal level already during the CP, when *BCR-ABL1* transcript was apparently trending down. This suggests that the PML-RARα subclone may have been present in earlier phases of the disease and expanded during imatinib therapy, possibly due to selective pressure exerted by TKI treatment itself on the clone harboring both BCR-ABL1 and PML-RARα translocations.

Notably, NGS did not reveal any additional myeloid mutations at the time of blast phase, highlighting the important role of PML-RARα in the pathogenesis of this type of myeloid BC [2–6]. BCR-ABL mutational events also retain a pivotal role in blast phase CML. Studies performed with NGS on the BCR-ABL1 transcript disclosed multiple events in the ABL kinase domain. These compound mutational events are rare in CP-CML, however their frequency significantly increases in advanced disease, with the T315I mutations being the most commonly detected during disease evolution [10]. Previous cases of promyelocytic BC during CML are reported in Table 1, the majority occurring

**Table 1** Review of the literature on PML-RARA-positive BP of CML

| Reference | Age/ Gender | CML therapy | Time to progression to BP | Sanz risk score | Cytogenetics | APL BP therapy | Allo-SCT | Outcome |
|---|---|---|---|---|---|---|---|---|
| Oku et al. [2] | 66/F | Imatinib | 16 months | Low risk | 46,XX, t(9;22)(q34;q11), t(15;17)(q22;q12) [20] | Idarubicin, Ara-C and ATRA | No | mCR for BCR-ABL and PML-RARA |
| Chung et al. [3] | 32/M | Imatinib | 6 months | High risk | 46, XY, t(9;22) (q34;q11.2), t(15;17)(q22;q21) | ATRA + imatinib | Not reported | mCR for PML-RARA and BCR-ABL |
| Hoehn et al. [4] | 72/F | Imatinib | 23 months | High risk | 46,XX, der(3)t(3;15)(q21;q15)t(15;17)(q24.1;q21.2), t(9;22)(q34;q11.2), der(15), t(3;15), del(17)(q21) | ATRA + ATO | No | mCR for PML-RARA, MRD + for BCR-ABL. Death after 2 months |
| Kim et al. [5] | 35/M | Dasatinib | 26 months | High risk | 46,XY, t(9;22)(q34;q11.2)(q24;q21) | Idarubicin, ATRA and dasatinib | It was consider | Marrow cellularity recovered, but did not reach CR |
| Wolanin et al. [6] | 40/M | Imatinib Dasatinib | 17 months | Low risk | 46 XY, t(9;22) (q34;q11.2) t(15; 17)(q22;q21) | ATRA + ATO and nilotinib | Not reported | mCR for PML-RARa; MMR for BCR-ABL |
| Parsi et al. [7] | 50/M | Bosutinib | 24 months | Intermediate risk | 46, XY, t(9;22) (q34;q11.2) t(15;17)(q24;q21) del (17) (q23) [24] | ATRA + ATO and gemtuzumab | Not reported | Complete remission with absent PML/RARα by FISH |
| Abiyev et al. [8] | 19/M | Imatinib | 12 months | Low risk | 46, XY, t(9;22) t(15;17) | ATRA + cytarabine + idarubicin dasatinib | Planned | mCR for PML-RARA and BCR-ABL |

CR, complete remission; mCR, molecular complete remission; ATRA, all-trans-retinoic acid; ATO, artrioxide; MRD, minimal residual disease; MMR, major molecular response; FISH, fluorescence in situ hybridization

under imatinib therapy. Our case is the first PML-RARa-positive blast crisis of CML to have obtained hematologic remission and molecular response to first-in-class TKI inihibitor Asciminib in the context T315I mutation showing clinical resistance to Ponatinib.

Asciminib is an allosteric inhibitor that binds to the myristoyl pocket of the BCR-ABL1 protein to induce a conformational change and lock the BCR-ABL protein in an inactive confirmation. Limited studies of asciminib in CML BP are available. In the phase 1 study, CABL001 × 2101 (NCT02081378), 20 CP and 5 AP CML patients with T315I mutation were included. Among all patients with the T315I mutation, 88% achieved a complete hematologic response by 12 months [11]. A MMR was achieved in 25% and 11% of those with CP CML and AP CML, respectively. In those with CP CML and the T315I mutation who were deemed to have resistance to ponatinib, 20% had a MMR at 12 weeks [11]. Our case showed rapid hematologic response to Asciminib with improvement of previous cytopenias, molecular response and only mild toxicity in a patients showing resistance to 3 lines of TKIs including Ponatinib.

PML-RARα-positive blast crisis in CML is rare, but analogous to *de novo* APL, treatment with standard APL regimens is of choice in these patients during induction. However, post –remission therapy with TKIs should be tailored based on BCR-ABL mutations. This case report shows in these context that asciminib is an effective treatment option for PML-RARA-positive blast crisis with T315I mutation recurring after Ponatinib therapy.

**Author contributions** R.M., L.C., S.P., wrote the manuscript; P.P.,S.C.,T.O., A.N., E.C,. performed and interpreted laboratory analysis; M.T.V, M.B., A.P., helped in data analysis and participated in data interpretation; L.F., E.O., A.R., G.P., A.B., A.C. helped in clinical management and data interpretation. All co-authors revised the manuscript.

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

## Declarations

**Disclosure** The authors have no relevant financial or non-financial interests to disclose.

**Ethics and consent to publish declarations** Informed consent was obtained from the patienta nd approval was obtained from the reference ethics committee of Santa Maria goretti Hospital (Latina). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

**Competing interests** Prof. Massimo Breccia, one of authors, serves as Editor-in-Chief of the journal.

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