**BCR-ABL** Mutation-Guided Therapy for CML Blast Crisis: A Case Report

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**Supplementary Issue: Tyrosine Kinases in Cancer**

**ABSTRACT:** The management of patients with chronic myeloid leukemia (CML) in advanced phases is challenging and requires the consideration of different treatment approaches, including targeted therapy with tyrosine kinase inhibitors, cytotoxic chemotherapy, and allogeneic stem cell transplantation. Here, we present the case of a patient with CML in mixed phenotype blast phase illustrating the integration of these strategies and demonstrating the need for close monitoring of treatment response in order to individually adjust treatment regimens.

**KEYWORDS:** BCR-ABL, CML, mutation, ponatinib, TKI, transplantation

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**Background**

The advent of BCR-ABL–targeted therapy with the tyrosine kinase inhibitor (TKI) imatinib marked a turning point in the therapy of chronic myeloid leukemia (CML). Imatinib establishes long-term remissions in most patients and TKI therapy has become standard of care in patients with CML in chronic phase (CML-CP). However, a substantial proportion of patients experience primary or secondary disease resistance to imatinib.¹ Additionally, adverse effects such as myelosuppression, diarrhea, nausea, skin rashes, and edema lead to treatment discontinuation in approximately 10% of patients.² Point mutations in the kinase domain of **BCR-ABL** are the most frequent reason for resistance to imatinib, with more than 90 mutations known to confer varying degrees of resistance.³ Recently, new generation TKIs have been developed, which exhibit different resistance and adverse effect profiles. These include second-generation TKIs nilotinib,⁴ dasatinib,⁵ bosutinib,⁶ and third-generation TKI ponatinib.⁷ Common side-effects vary between agents and include pleural effusions, hyperglycemia, and pancreatitis.⁸ Importantly, recent data indicate a significant cardiovascular risk because of arterial occlusions and thrombotic events to be associated with some TKIs, particularly nilotinib and ponatinib.⁹

Notably, patients in accelerated and blast phase CML often do not achieve a complete molecular remission with TKI monotherapy and responses are usually short-lived.¹⁰,¹¹ Thus, the inclusion of other treatment modalities such as conventional chemotherapy, allogeneic stem cell transplantation, and non-TKI targeted therapy is required in affected patients.¹²

Given the diversity of treatment options, the management of patients with CML has become complex and depends on individual clinical and molecular cues.

Here, we present the case of a patient with CML blast crisis who was diagnosed with several **BCR-ABL** mutations. Therapeutic management included induction chemotherapy, sequential and **BCR-ABL** mutation-guided TKI therapy, and allogeneic stem cell transplantation, thus illustrating major current treatment options for patients with advanced phase CML. The patient has given his written consent for publication of information contained in this case report.

**Case Description**

In July 2013, a 54-year-old male patient presented with superficial venous thrombosis of the lower leg. His medical history included hepatic steatosis and prostate carcinoma three years prior, which had successfully been treated with brachytherapy. The patient also reported exposure to nuclear radiation while working as a physicist in the past. He did not have any siblings.

Routine laboratory tests revealed hyperleukocytosis (75 × 10⁹/L with 45% blast cells, 5.4% promyelocytes, 4.8% metamyelocytes, and 15.2% myelocytes). Administration of...
hydroxyurea for cytoreduction was started and the patient was transferred to our institution. Here, initial workup showed 45% blasts on peripheral smear and immunophenotyping showed expression of both lymphatic (CD10, CD19, and CD79a with notable absence of cytoplasmic CD22), myeloid (CD13, CD15, and CD33), and progenitor (CD34, TdT, and CD117) markers. Cytogenetic and molecular analyses of the bone marrow confirmed the presence of a translocation t(9;22)(q34;q11.2) and chimeric BCR-ABL mRNA transcripts (Fig. 1), thus establishing the diagnosis of CML in mixed phenotype blast crisis according to the revised criteria of the European Group for the Immunological Classification of Leukemias. Subsequently, the patient received induction therapy with cytarabine (100 mg/m², days 1–7) and daunorubicin (60 mg/m², days 3–5) and a search for a suitable stem cell donor was initiated. During induction, the patient had to be treated for tumor lysis syndrome and fever of unknown origin, both of which resolved under standard supportive care. The patient achieved a complete hematologic response, but bone marrow examination on day 14 showed persistent minimal residual disease, with 3% of mononuclear bone marrow cells bearing the leukemia-associated immune phenotype. After reconstitution of hematopoiesis, BCR-ABL inhibition was started with imatinib 400 mg once daily 27 days after induction therapy.

Four weeks after initiation of TKI therapy, the BCR-ABL transcript level remained significantly elevated and imatinib was switched to second-generation TKI nilotinib at a dosage reduced to 200 mg twice daily because of neutropenia.

One month after nilotinib was started a considerable elevation of BCR-ABL transcripts was detected, indicating treatment failure. cDNA Sanger sequencing of the BCR-ABL PCR product was performed on an Applied Biosystems sequencer using standard methods. The resulting chromatogram was analyzed with the Sequencher software (Gene Codes Corporation), revealing point mutations Y235H, E255K, and T315I. Reinduction therapy according to the Mito-FLAG protocol, revealing point mutations Y235H, E255K, and T315I. Reinduction therapy according to the Mito-FLAG protocol, reverting to second-generation TKI nilotinib at a dosage reduced to 200 mg twice daily due to neutropenia.

In the meantime, an unrelated 10/10-HLA-matched bone marrow donor had been found, enabling subsequent allogeneic stem cell transplantation six months after initial diagnosis in what was found to be complete cytogenetic and molecular remission. Ponatinib was stopped prior to conditioning therapy. Myeloablative conditioning consisted of cyclophosphamide (60 mg/kg bodyweight, days −6 and −5) and total body irradiation (10 Gy total, days −4, −3, and −2). For prophylaxis of graft-versus-host disease (GVHD), the patient received antithymocyte globulin (10 mg/kg body weight, days −6, −5, and −4), cyclosporine A (target trough serum level 200 µg/L), and methotrexate (15 mg/m², day 1 and 10 mg/m², days 3, 6, and 11). During months 1 and 2 after transplantation, the patient had to be treated for neutropenic sepsis, grade 4 mucositis, and CMV-viremia. He also suffered from acute GVHD of the skin grade 3, which largely resolved after a course of systemic steroids with low-grade GVHD of the skin persisting. Following reconstitution of hematopoiesis, ponatinib was reinitiated on post-transplant day 123. Six months after transplantation, the BCR-ABL chimeric gene was again detected by RT-PCR in the bone marrow, prompting tapering of immunosuppression in light of largely resolved GVHD. Consequently, BCR-ABL levels dropped. Currently, the patient is alive with a follow-up of 10 months after allogeneic transplantation. Repeated BCR-ABL monitoring with correspondingly tailored therapy is scheduled for the future.

Discussion

Management of patients with CML has undergone significant changes since the introduction of BCR-ABL inhibition by TKIs. Currently, first-generation TKI imatinib and second-generation TKIs nilotinib and dasatinib are approved for first-line treatment of patients with CML-CP. Additionally, second-generation TKI bosutinib and third-generation TKI ponatinib have been approved for second-line treatment of patients with CML-CP after failure of first-line therapy. The individual choice for a TKI depends on patient comorbidities, drug availability, and cost. While TKI therapy is highly effective in patients with CML-CP, therapy for patients with biologically more aggressive disease in advanced phases, particularly for those in blast phase, requires additional strategies. Here, we illustrate several therapeutic options in a patient with CML in mixed phenotype blast phase.

Initially, the patient presented with hyperleukocytosis. In light of the delay until definite diagnosis by molecular and cytogenetic tests, cytoreduction with hydroxyurea was initiated. Given that the patient was diagnosed with CML in blast phase, he was primarily considered a candidate for allogeneic stem cell transplantation and high-intensity induction chemotherapy was administered in order to achieve a deep remission before transplantation. Although the role of allogeneic transplantation in CML therapy has decreased significantly after the introduction of TKIs, it still represents the only treatment option establishing long-term remissions in patients with CML in blast phase. Transplantation should also be discussed in patients with CML in accelerated phase depending on individual risk factors and treatment response.

Close monitoring of treatment response using either cytogenetic analyses or, preferably, molecular tests for BCR-ABL are essential in managing patients with CML, as the response to treatment is the most important prognostic factor...
and should guide individual treatment. Usually, monitoring should take place every three months. However, in patients at higher risk monthly monitoring might be necessary. Constantly elevated BCR-ABL transcript levels one month after initiation of BCR-ABL inhibition prompted us to switch TKI therapy from imatinib to nilotinib. Notably, one month after initiation of nilotinib, BCR-ABL levels rose again despite blood counts at first remain normal, prompting us to search for specific disease resistances. Sequencing of BCR-ABL revealed three mutations, Y253H, E255K, and T315I, all of which confer resistance to both imatinib and nilotinib. Importantly, sequencing of BCR-ABL in patients with blast phase should be considered already at diagnosis, given that several studies revealed a high prevalence of BCR-ABL mutations in this population. In this case, it is unknown whether BCR-ABL mutations were present already at diagnosis or whether they developed under TKI-treatment. Earlier detection of specific mutations might have prompted immediate new-generation TKI therapy.

In order to achieve another deep remission, reinduction therapy was chosen as subsequent therapy in preparation for allogeneic transplantation. While second-generation TKIs dasatinib and bosutinib show activity in Y253H- and E255K-mutated CML, only third-generation TKI ponatinib is active against T315I. Thus, ponatinib was administered for bridging to transplantation. Ponatinib shows impressive anti-leukemic activity against all known single BCR-ABL mutations, but an increased risk of vascular occlusive events after prolonged exposition currently limits its use to patients with a T315I mutation. Despite its side effect profile, we chose to continue ponatinib at full dosage (45 mg/day) after transplantation because of molecular relapse. Recently, protein synthesis inhibitor Omacetaxine has been FDA-approved for use after failure or intolerance of two TKIs and could represent an alternative option in patients with T315I-mutation and ineligibility for transplantation.

Regarding allogeneic transplantation, current guidelines recommend myeloablative conditioning for patients in CML blast phase, as performed in this case. To date, there are no definitive data on the strategy of TKI administration after transplantation, although expert consensus favors continued BCR-ABL inhibition as consolidation therapy. Indeed, TKIs have shown promising effects in patients with relapse after transplantation, including those with CNS relapse. Care needs to be taken not to mistake TKI side effects for transplantation-associated complications, such as GVHD.

The case presented here illustrates that close monitoring is required even in patients undergoing transplantation in deep remission. In addition to the treatment modalities discussed above therapy options for patients with relapse after transplantation include withdrawal of immunosuppressive therapy as well as administration of donor lymphocyte infusions (DLI). In light of persistent mild GVHD, the use of DLIs in this patient was reserved for potential relapses after tapering of immunosuppression.

In summary, we report on a patient with CML in mixed phenotype blast phase, who was treated with induction chemotherapy, sequential TKI inhibition, and allogeneic stem cell transplantation. This case illustrates major challenges in treating patients with advanced-phase CML and highlights...
the need for individual tailoring of therapies in accordance with thorough monitoring of treatment response. Future studies will need to further establish the role of TKI therapy after transplantation and the value of other treatment approaches, such as non-TKI-mediated targeted therapy, in high-risk patients.

Author Contributions
Conceived and designed the experiments: BNO. Analyzed the data: BNO, HN, CDB, TB, RA. Wrote the first draft of the manuscript: BNO, TB. Contributed to the writing of the manuscript: BNO, HN, CDB, TB, RA. Agree with manuscript results and conclusions: BNO, HN, CDB, TB, RA. Jointly developed the structure and arguments for the paper: BNO, HN, CDB, TB, RA. Made critical revisions and approved final version: BNO, HN, CDB, TB, RA. All authors reviewed and approved of the final manuscript.

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