Efficacy of Dasatinib in a CML Patient in Blast Crisis with F317L Mutation: A Case Report and Literature Review

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ABSTRACT: The introduction of tyrosine kinase inhibitors (TKIs) in the treatment of chronic myeloid leukemia (CML) has significantly increased survival rate and quality of life for patients with CML. Despite the high efficacy of imatinib, not all patients benefit from this treatment. Resistance to imatinib can develop from a number of mechanisms. One of the main reasons for treatment failure is a mutation in the *BCR-ABL* gene, which leads to therapy resistance and clonal evolution. Clearly, new treatment approaches are required for patients who are resistant to imatinib. However, mutated clones are usually susceptible to second-generation TKIs, such as nilotinib and dasatinib. The choice of the therapy depends on the type of mutation. A large trial program showed that dasatinib is effective in patients previously exposed to imatinib. However, for a minority of patients who experience treatment failure with TKI or progress to advanced-phase disease, allogeneic stem cell transplantation (allo-SCT) remains the therapeutic option. In spite of the high curative potential of allo-SCT, its high relapse rate still requires a feasible strategy of posttransplant treatment and prophylaxis. We report a case of a CML patient with primary resistance to first-line TKI therapy. The patient developed an undifferentiated blast crisis. Before dasatinib therapy, the patient was found to have an F317L mutation. He was successfully treated with dasatinib followed by allo-SCT. In the posttransplant period, preemptive dasatinib treatment was used to prevent disease relapse.

KEYWORDS: CML, TKI, dasatinib, *BCR-ABL* mutations, F317L mutation, allo-SCT

SUPPLEMENT: Tyrosine Kinases in Cancer

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Background

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm characterized by uncontrolled growth of bone marrow myeloid progenitor cells. CML is defined by the presence of reciprocal translocation t(9;22), (q34;q11), which determines the formation of the *BCR-ABL* fusion gene with constitutively active tyrosine kinase.[1,2] With the development of tyrosine kinase inhibitors (TKIs) that specifically target *BCR-ABL* activity, the treatment of CML patients has modified rapidly.[3] Imatinib therapy resulted in significantly better patient outcome, response rates, and overall survival compared with previous standards.[4–6] Despite this advance, not all patients benefit from imatinib because of resistance and intolerance. Approximately one-third of imatinib-treated patients discontinue therapy because of an inadequate response or toxicity.[3,7] There is a whole range of possible reasons for lack of effect from imatinib. The most significant mechanisms of imatinib resistance involve point mutations in the ABL kinase domain, leading to structural changes in this domain and overexpression of *BCR-ABL*.[8–10] In addition, imatinib resistance in some patients may be mediated through loss of kinase target dependence[11] or clonal evolution and amplification of chimeric genes.[9] *BCR-ABL*-independent mechanisms, such as poor intestinal absorption, drug interactions, and wrong drug administration, have also been implicated.[9,12]

There are currently more than 90 known *BCR-ABL* gene mutations that are able to cause TKI resistance.[13] They are rarely found in newly diagnosed patients, but their incidence increases in the first year of imatinib therapy, reaching 30%–90% in cases of secondary resistance.[14] It has frequently been shown that the incidence of mutations is different in various phases of CML, ranging from 25% to 30% of early chronic-phase (CML-CP) patients to 70%–80% of blast crisis (CML-BC) patients. In addition, *BCR-ABL* mutations are more commonly detected in cases with acquired resistance than in cases with primary resistance.[14–16]

Introduction of second-generation TKIs such as nilotinib and dasatinib did not solve the problem completely. However, the spectrum of mutations that can cause resistance to second-generation TKIs is considerably less than that for

imatinib.[15,17] It should be noted that a *BCR-ABL* mutated cell clone resistant to treatment with one of the drugs may be sensitive to the other one.[14]

Only the T315I mutation causes complete failure of treatment with first- and second-generation TKIs. Recently, third-generation TKIs have been developed to overcome the inhibitory effect of this mutation.[18] The Food and Drug Administration approved this drug in 2012, but clinical application is limited due to toxicity and extremely high price. Thus, the inclusion of other treatment modalities such as allogeneic stem cell transplantation (allo-SCT) is required in patients.[19–21]

Although after the introduction of TKIs, the role of allo-SCT therapy for CML patients has significantly decreased, it is still currently a curative treatment option for CML-BC patients.[22] Resistance to TKI treatment and detection of mutations, especially T315I mutation, are common indications for allo-SCT. Moreover, experts recommend continuing TKI treatment after allo-SCT as consolidation therapy.[22] Also, TKIs have shown promising effects in patients with relapse after transplantation.[23–25]

Case Presentation

A 23-year-old male was diagnosed with CML-CP (low Sokal score, 0.6) in April 2009. Written informed consent was obtained from the patient in accordance with the Declaration of Helsinki and the ethical guidelines of our institution. Routine laboratory tests revealed leukocytosis (30/nL) and thrombocytopenia (40/nL). Cytogenetic and molecular genetic analyses developed the presence of a translocation t(9;22)(q34;q11) (Fig. 1) and chimeric *BCR-ABL* mRNA transcripts. From May to June 2009, the patient received cytotoxic therapy with hydroxyurea. From June 2009, he was treated with imatinib (400 mg daily). Four weeks later, complete hematologic response (CHR) was achieved. Two months later, complete cytogenetic response (CCyR) was achieved.

In December 2009, six months after initiation of imatinib therapy, routine laboratory investigations revealed leukocytosis (20.3/nL) with 65% of blast cells on peripheral smear and 81% of blast cells in bone marrow. Immunophenotyping and cytochemistry analysis corresponded to undifferentiated, mixed-phenotype blast crisis. Using cytogenetic analysis, translocation t(9;22)(q34;q11) without additional chromosomal abnormalities was found in 90% of mitosis, and normal karyotype was determined in 10% of metaphases. Using Sanger sequencing for mutational analysis of *BCR-ABL*, mutation F317L was detected. From December 2009 to January 2010, the patient was treated with dasatinib (140 mg daily) and hydroxyurea (2–3 g daily). From January 2010, the patient received daily 140 mg of dasatinib as monotherapy. After this treatment, the patient again reached a CHR.

Subsequently, the patient was scheduled for allo-SCT. According to EBMT criteria for CML, the patient was at low risk.[26] In April 2010, 12 months after initial diagnosis, match-related allo-SCT was performed. Because of the young age of the patient, absence of comorbidity, good performance status, and CHR before allo-SCT, myeloablative conditioning was chosen. The myeloablative conditioning regimen consisted of busulfan (16 mg/kg), cyclophosphamide (120 mg/kg body weight), and antithymocyte globulin (ATGAM; Pfizer). For prophylaxis of graft-versus-host disease (GvHD), the patient received tacrolimus and methotrexate. The count of

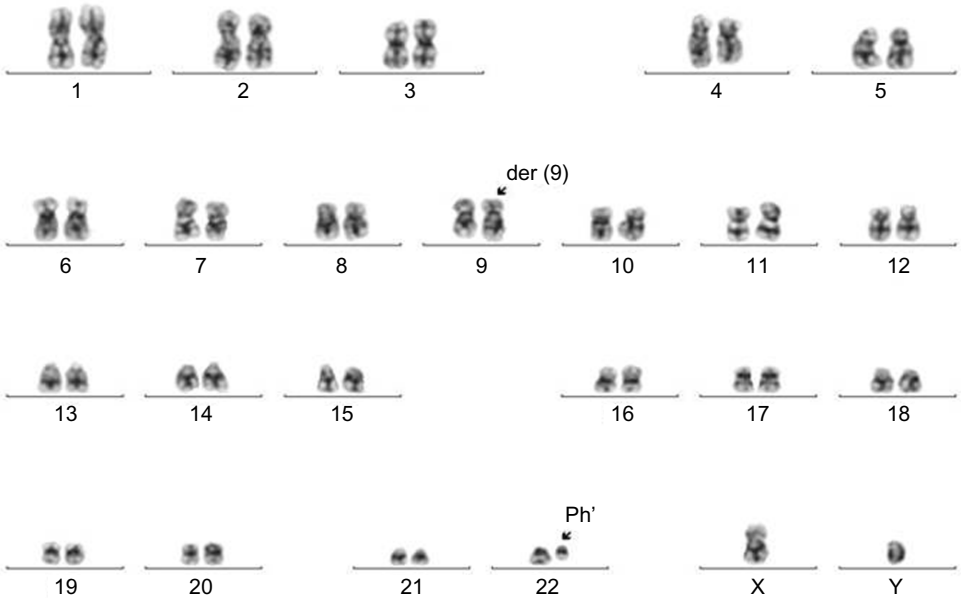

Figure 1. The translocation t(9;22)(q34;q11) in bone marrow at diagnosis. Karyotype abnormality was revealed by cytogenetic analysis using standard G-banding technique: 46,XY,t(9;22)(q34;q11). The t(9;22)(q34;q11) was found in 20 metaphases at diagnosis. Two marker chromosomes are indicated by arrow: der9q and Ph'. Der indicates derivate, Ph' indicates Philadelphia chromosome, 22q-.

CD34+cells in the graft was 12.2 × 10^6/kg body weight. On day 17 after allo-SCT, platelet and neutrophil engraftment were obtained. No signs of acute GvHD were seen.

At day +129 after allo-SCT, repeated *BCR-ABL* monitoring showed an increased level of chimeric genes in the bone marrow. Withdrawal of immunosuppression and immunoadoptive therapy (donor lymphocytes infusion [DLI]) in combination with dasatinib (140 mg daily) was begun. Reduction of immunosuppressive therapy instigated the appearance of chronic GvHD with the involvement of skin and mucosa. Thus, the patient received tacrolimus (0.25 mg daily). When the DLI was stopped, the therapy with dasatinib (100 mg daily) was continued. At day +158 after allo-SCT, HCR, CCyR, and deep molecular response (MR4.5) were determined. From October 2011 to date, repeated cytogenetic and molecular genetic analyses demonstrated normal female donor karyotype (Fig. 2), complete donor chimerism, and no detected disease at the molecular level. The monitoring of the patient's response to therapy is demonstrated in Figure 3. Currently, the patient is alive with a follow-up of five years after allo-SCT in clinical, hematological, and cytogenetic remission, with complete molecular response and complete donor chimerism. He receives dasatinib as a prophylactic treatment (100 mg daily).

Discussion

The most common mechanisms for resistance in CML patients receiving imatinib are mutations in the kinase domain of the *BCR-ABL* gene.[12] Some mutations have been confirmed to have clinical resistance to second generation of TKIs, and these are associated with poor outcome.[12,13,15,27–29] Here, we present a CML patient who experienced disease progression after six months of therapy with imatinib. In CML-BC, mutation F317L was found. The F317L mutation results in an amino acid substitution at position 317 in BCR-ABL, from a phenylalanine (F) to a leucine (L). Frequency of *BCR-ABL* F317L mutation in *BCR-ABL1*-mutated CML is 5.7%. Presence of point mutations in *BCR-ABL* has been implicated as a mechanism for the development of imatinib resistance.[14] In preclinical studies, F317L-mutated cell lines demonstrated decreased sensitivity to dasatinib and bosutinib, but comparatively little reduced sensitivity to nilotinib, compared with CML cell lines wild type for mutations.[14] Moreover, some authors consider that F317L mutation can occur more often after dasatinib therapy and lead to resistance.[30] Although F317L mutation confers reduced sensitivity to dasatinib, there are some previous reports of efficacy of dasatinib in CML patients with F317L mutation.[31,32] National Comprehensive Cancer Network considers that nilotinib treatment rather than dasatinib could be recommended for imatinib-resistant CML patients with F317L mutation.[14,33] On the contrary, Faber et al have found that the lack of dasatinib efficacy in patients with F317L is not absolute; some other biological factors could modify the treatment outcome.[31] In our case, the patient with mixed CML-BC was resistant to imatinib therapy and responded well to dasatinib. CHR and CCyR were achieved four weeks after introduction of the therapy.

Since the patient was diagnosed with CML-BC, he was primarily considered a candidate for allo-SCT in order to achieve

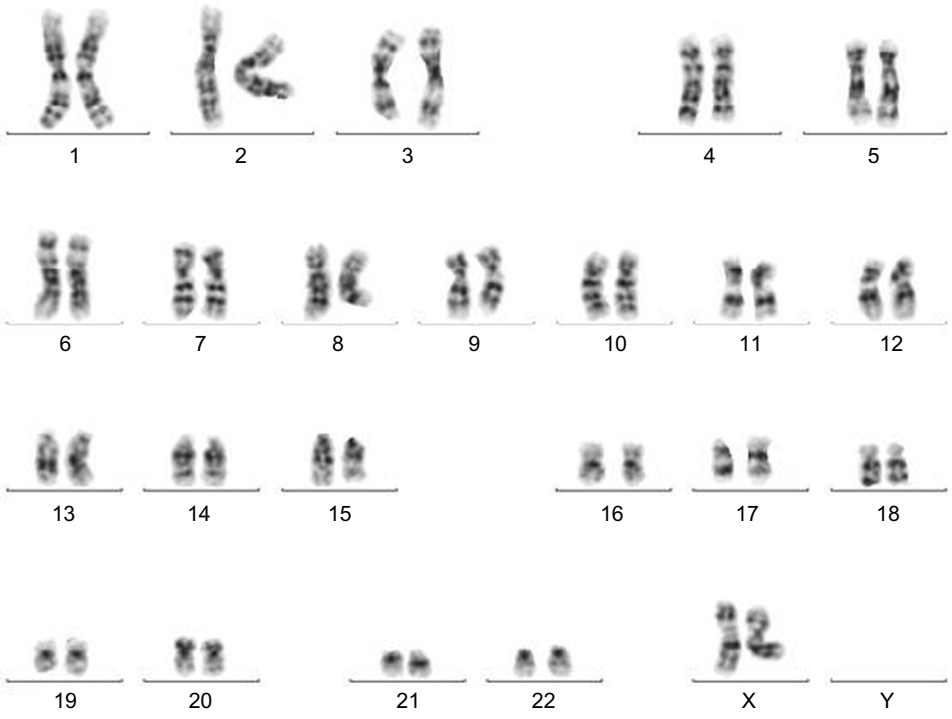

Figure 2. Normal female karyotype after allo-SCT. Normal female donor karyotype was found in bone marrow cells after allo-SCT: 46,XX.

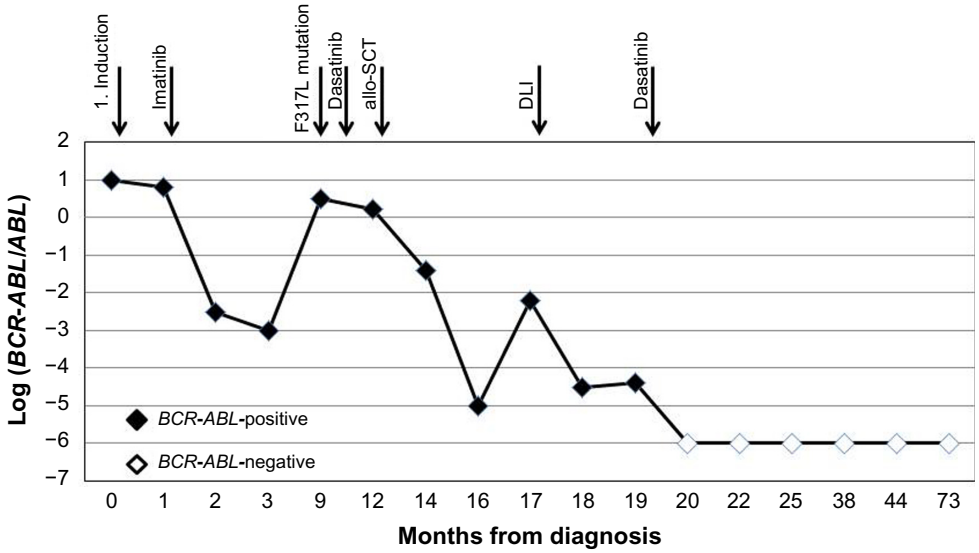

Figure 3. The monitoring of the patient's response to therapy. Responses of the patient to therapy with imatinib, dasatinib, and allo-SCT were estimated by *BCR-ABL* transcript levels. *BCR-ABL* were monitored using quantitative polymerase chain reaction either in the bone marrow or peripheral blood and expressed as the logarithmic ratio of *BCR-ABL* to the control gene *ABL* gene.

a CR. Currently, allo-SCT is recommended for eligible patients in advanced-phase CML and in instances of failure of and/or intolerance to TKI treatment.[22] In view of the curative potential of allo-SCT, transplantation could become the preferred second-line option after failure of first-line TKI therapy for suitable patients with a donor.[22] This therapy also enabled effective monitoring of minimal residual disease and hematopoietic chimerism after allo-SCT. The monitoring of treatment response in CML patients using both cytogenetic tests and *BCR-ABL* transcript levels is essential in the management of CML. Level of *BCR-ABL* transcript is the important prognostic factor that defines individual treatment.[34] In our patient, increasing of *BCR-ABL* gene in bone marrow was detected at day +100 after allo-SCT. Given the high risk of relapse, withdrawal of immunosuppressive therapy and DLI were used.

Treatment with DLI is a well-established therapeutic approach for CML patients who relapse after allo-SCT. Responses achieved after DLI are frequently durable, offering a potential cure for the majority of patients.[35,36] After effective therapy with DLI, CHR and CCyR were detected. Then, the patient received therapy with dasatinib (100 mg daily).

There is limited published data available on the efficacy of TKIs both before and after allo-SCT. It has been shown that this combination is superior to TKI treatment alone and can improve outcome.[37] Therefore, early allo-SCT after short-term TKI therapy should be the treatment of choice for CML-BC. Improved outcomes from the combination treatment may be because pretreatment with TKIs reduced the leukemia burden before allo-SCT, and more importantly, the individualized TKI-based intervention strategy based on TKIs and modified DLI posttransplant reduced the risk of relapse.[37] Our data indicate that allo-SCT in combination with TKI is a better option for CML-BC patients. In addition, we confirmed that preemptive treatment with dasatinib (100 mg daily) is capable of preventing disease relapse after allo-SCT.

We conclude that F317L mutation is an informative prognostic biomarker. Despite conflicting data on the sensitivity of F317L mutation to the dasatinib,[14,30–32] we have shown efficacy of dasatinib in combination with allo-SCT in CML-BC patients. Evidence indicating the resistance of mutation to dasatinib is mainly based on *in vitro* studies. The outcome of patients is related to complex factors. Future clinical studies are needed to assess the sensitivity of specific *BCR-ABL* mutations to TKI therapy.

Author Contributions

Conceived and designed the experiments: KL, YV, MP, EM. Analyzed the data: EM, YV, MP, KL. Wrote the first draft of the manuscript: EM, KL. Contributing to the writing the manuscript: EM, YV, MP, KL. Agree with manuscript results and conclusions: EM, YV, MP, KL, BA. Jointly developed the structure and arguments for the paper: EM, YV, MP, KL, BA. Made critical revision and approved final version: EM, YV, MP, KL, BA. All authors reviewed and approved of the final manuscript.

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