The third-time chronic myeloid leukemia in lymphoblastic crisis with ABL1 kinase mutation induced by decitabine, dexamethason combined with nilotinib and dasatinib

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ABSTRACT

Blast crisis (BC) is the major remaining challenge in the management of chronic myeloid leukemia (CML). The prognosis of the BC patient who carries ABL kinase mutation is very poor. One patient, with lymphoid CML-BC third time, was detected with *T315A/F359I/M244V* compound mutation by direct sequencing after treatment with tyrosine kinase inhibitions three years. The patient was treated with decitabine, dexamethasone, in combination with nilotinib and dasatinib. Then this patient received a complete hematologic response and cytogenetic response after two cycles of treatment.

Key words: chronic myeloid leukemia, *T315A*, *F359I*, *M244VA*, lymphoid blast crisis, decitabine

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In June 2009, a 45-year-old female was hospitalized after two weeks of dizziness and weakness. Blood test showed white blood cell (WBC) count of $200.0 \times 10^9/L$, and the hemoglobin (Hb) level and platelet count were in normal scope. Chronic myeloid leukemia – crisis phase (CML-CP) was diagnosed on bone marrow examination, Ph chromosome and the BCR-ABL fusion gene. She was given 400 mg Imatinib Mesylate (IM) daily, and she achieved complete hematologic response (CHR) and cytogenetic response (CCyR) after three months. In June 2012, there was a significant increase in the number of the WBC of this patient. The bone marrow smear revealed lymphoid blast crisis of CML, she was treated with nilotinib 400 mg twice daily for three months and obtained CHR. In July 2013, she was diagnosed with CML-BC for the second time, although with the maintenance therapy of nilotinib. *F359I* mutation was detected in ABL kinase domain, the treatment was changed to dasatinib 140 mg daily. After five months, she achieved CHR once again.

On 24th March 2014, the patient came to our hospital with fever and weakness, which she had been suffering from since past one week. The blood examination showed Hb level of 78 g/L, WBC count of $3.41 \times 10^9/L$ and platelet count of $66 \times 10^9/L$. The bone marrow smear revealed 90.4% primitive and immature lymphocytes. And the flow cytometry (FCM) analysis showed that 74.5% of the nucleated cells were malignant lymphoid blasts, expressing human leukocyte antigen-DR (HLA-DR), CD13, CD38, CD19, CD33, CD10, CD34. The BCR-ABL (P210) fusion gene had a quantitative result of 149.0%. The BCR-ABL fusion gene kinase domain mutation analysis showed *T315A*, *F359I*, *M244V* mutations. Lymphoid blast crisis of CML was definitely diagnosed.

The patient suffered high fever with a body temperature of 39°C and with a saturation of pulse oxygen less than 95%. Chest CT showed severe pneumonia. Considering the patient's intolerance of combined chemotherapy, and the mutation *T315A*,

which is resistant to dasatinib and *F359I* that is less sensitive to nilotinib,^[1] we tried to treat the patient with decitabine (DAC) and dexamethasone, combining it with nilotinib and dasatinib (DAC 20 mg/m² over 1 h daily on day 1 to 5, dexamethasone 10 mg daily on day 1 to 10, nilotinib 400 mg and dasatinib 70 mg orally daily). Then the patient was administered CHR with bone marrow smear, which detected no primitive and immature lymphocytes. The blood test identified Hb level of 70 g/L, WBC count of $4.70 \times 10^9/L$ and platelet count of $37 \times 10^9/L$.

On 10th April 2014, the patient was given a consolidation treatment. As a result, only 2.0% immature cells were discovered in the bone marrow smear. Minimal residual disease (MRD) was 2.3×10^{-4} (malignant clone expressed CD45dim, CD34+, CD19+, CD10+, CD20-/dim, CD13, CD3+/dim) by flow cytometry. Although the *T315A/F359I/M244V* mutations were still positive, the quantity of BCR-ABL (P210) fusion gene was 8.98%, and the bone marrow cell chromosome was 46, XX [20].

DISCUSSION

Under the tyrosine kinase inhibitions (TKIs) therapy, there are still a number of patients with CML who progress to BC. How this leukemia transforms from a relatively indolent CP to an aggressive BC is still unclear.^[2] Once BC happens, the management depends on the type of leukemia (myeloid or lymphoid) and if they successfully achieve CR or not.^[3] Allogeneic stem cell transplantation (Allo-HSCT) may be the only curative therapy for the patients,^[4] but as influenced by a donor source and recipient status, it is successful in only a minority of CML-BC patients.^[5]

This patient was diagnosed with CP and was given IM 400. Three years later, she progressed to BC with compound BCR-ABL1 kinase domain mutations of *T315A*, *F359I*, *M244V* by direct sequencing. The mutation *T315A* is resistant to dasatinib, *F359I* is less sensitive to nilotinib, and *M244V* is sensitive both to dasatinib and nilotinib.^[1] There was no standard therapy for these patients with BCR-ABL1 kinase domain mutations. Since this patient still progressed to BC during being treated by dasatinib and nilotinib orderly, it was suggested that the mechanisms of resistance or BC were more than ABL1 kinase domain mutation. So, we had to seek the novel therapy for her.

In CML, DNA hypermethylation was in concert with disease progression.^[6] DAC, as one of hypomethylating agents, is a cytosine analog causing DNA methyltransferase (DNMT) inhibition. Beside its single-agent efficiency in CML, including imatinib-resistant cases, it has been studied in various combination treatment regimens.^[7]

Schenekburger *et al* found DAC could trigger differentiation, senescence, and autophagy in CML K-562 and MEG-01 cell lines at clinically relevant concentration, respectively.^[8] Prolonged treatment of DAC could induce mitochondrial-dependent apoptosis in CML cells. The combinatory treatment of relatively resistant CML with DAC and either cisplatin or etoposide increased apoptosis synergistically.^[8]

DAC was also able to decrease telomere length, to reduce telomerase activity and to decrease human telomerase reverse transcriptase (hTERT) expression through decreased binding of c-myc to the hTERT promoter.^[9] Then, it induces senescence in CML cell lines.

In Kantarjian's report,^[10] 130 patients with CML were treated with high dose of DAC. DAC was given at 100 mg/m² over 6 hours every 12 hours for 5 days to the first 13 patients, 75 mg/m² to the subsequent 33 patients, and 50 mg/m² to the remaining 84 patients. Of the 64 patients in BC, 6 patients (9%) achieved CHR and 5 patients (8%) achieved CCyR. The high dose of DAC appeared to have significant anti-CML activity.

Since this patient had experienced her third BC and her case was complicated due to her suffering from pneumonia, we did not choose a high dose DAC to avoid serious myelosuppression. As nilotinib and dasatinib can be targeted at *T315A* and *F359I* respectively, and the mutation of *M244V* is sensitive to both TKIs, we combined these two TKIs with DAC and dexamethasone. The patient achieved CHR and CCR after two cycles of therapy.

We infer that DAC combined with correspondingly sensitive TKIs for these patients who progress into CML-BC with ABL kinase mutations may have clinical activity. This warrants further clinical exploration.

Conflict of Interest

None declared.

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