Case Report/Series

Tyrosine kinase inhibitor resistance in pediatric chronic myeloid leukemia: a case report

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ABSTRACT

Pediatric chronic myeloid leukemia (CML) is a hematopoietic malignancy, treated by tyrosine kinase inhibitor (TKI). Previously, imatinib resistance in CML was treated with nilotinib as a second line. However, in Indonesia, where the options of TKIs are limited, no case has been reported. We describe TKI-resistance of a pediatric CML case in Dharmais Cancer Hospital, Jakarta. A 17-year-old boy presented with loss of complete hematologic response after 4 years of imatinib treatment. Diagnosis of relapsed CML with blast crisis was confirmed, and nilotinib was given accordingly. He achieved hematological and optimal response after 2 weeks and 3 months of treatment, respectively. However, in the 12-month evaluation, he failed to achieve major molecular response and acquired the second resistance to TKI. Since imatinib resistance marks the poor prognosis, initial optimal response of nilotinib treatment remains inconclusive to predict the final outcome.

KEYWORDS children, chronic myeloid leukemia, tyrosine kinase inhibitor

Chronic myeloid leukemia (CML) is a chronic clonal myeloproliferative neoplasm characterized by myeloid cell overproduction. It occurs as a result of a genetic translocation between chromosomes 9 and 22, creating a new chromosome called the Philadelphia chromosome with a karyotype of t(9;22) and abnormal fusion of BCR-ABL oncogene.[1] This gene code is used for chimeric BCR-ABL protein activating ABL tyrosine kinase activity. As the hallmark of CML,[2] the tyrosine kinase controls cell cycle, speeds up cell division, and inhibits cell apoptosis.[3] Furthermore, it causes DNA repair inhibition and makes cells more prone to develop a malignancy.[4] Consequently, identifying and targeting this protein become the main focus of CML treatment.

Currently, there are five tyrosine kinase inhibitors (TKIs) approved by the United States Food and Drug Administration (US FDA) for CML with positive BCR-ABL therapy, namely, imatinib, nilotinib, dasatinib, bosutinib, and ponatinib.[5] Imatinib is the first approved for pediatric CML since 2001.[6] Despite its wide use, imatinib resistance developed in 20–25% of cases and thus prompted to switch to second-line TKIs, such as nilotinib.[7] Nilotinib has been reported

to be effective in achieving both early and major molecular responses (MMRs).[8] However, its failure as second-line therapy is rarely found, particularly in Indonesia, where a small incidence of CML is still of concern. Other challenges of nilotinib treatment are the cost burden of serial quantitative BCR-ABL ratio measurement and the availability of the drug. The only available TKIs in Indonesia are imatinib and nilotinib, leaving a lack of therapeutic options for CML. Here, we report the case of imatinib resistance who failed to nilotinib after 1 year of treatment. The optimal response in the initial evaluation was insufficient to predict the outcome of nilotinib treatment.

CASE PRESENTATION

A 17-year-old male patient was referred to Dharmais Cancer Hospital for further evaluation because of pallor and abdominal enlargement. He had a history of CML with positive BCR-ABL and been in imatinib medication for the last 4 years. On physical examination, his conjunctiva was anemic. There was a palpable lymph node sized 2 × 2 × 1 cm in the region of his left neck. The liver was palpable at 4 cm below the right costal margin and spleen at Schuffner I. The extremities showed multiple skin-colored nodules, which were firm and fixed on palpation. The skin biopsy confirmed these as leukemia cutis. Blood examination showed leukocyte count 86.37 × 10^3/l (normal range: 4–10 × 10^3/l), hemoglobin (Hb) 10.0 (normal range: 12–15) g/dl, and platelet count 294 × 10^3/l (normal range: 150–400 × 10^3/l). Bone marrow aspiration confirmed the diagnosis of CML blast crisis (CML-BC) with a BCR-ABL ratio of 69.37% international scale (IS) and 27% blast cells (Figure 1).

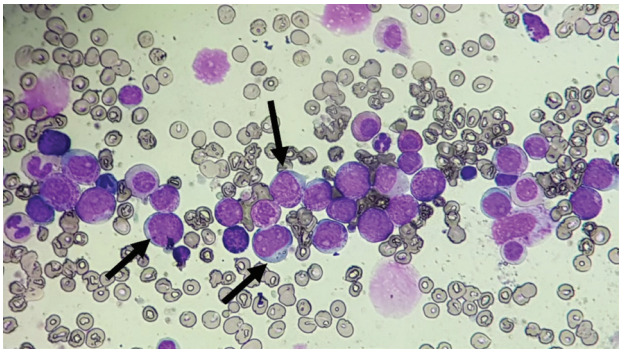

Figure 1. Bone marrow staining showing a hypercellularity with suppressed erythropoiesis, an increased granulopoiesis activity, shift to the left, and a decreased thrombopoietic activity. Black arrow indicates myeloblast cells (40× magnification)

Subsequently, nilotinib 200 mg twice daily (b.i.d) was administered. After 2 weeks, he was checked again for blood examination, which showed a reduction in Hb (8.6 g/dl), leukocyte (3.58 × 10^3/µl), and platelet count (39 × 10^3/µl). Blast cells also reduced to 7%. Consequently, nilotinib was adjusted to 150 mg four times a day. After 2 months of treatment, neither the liver nor the spleen was palpable. Lymphadenopathy and leukemia cutis had been improved along with better hematologic parameters (Hb 10.0 g/dl, leukocyte 14.70 × 10^3/µl, and platelet 176 × 10^3/µl). Following this, BCR-ABL/ABL ratio successfully declined to 7.91% IS in the 3rd month and to 1.39% IS in concordance with stable Hb (14.7 g/dl) and leukocyte (4.36 × 10^3/µl) but low platelet count (89 × 10^3/µl) in the 6th month. However, in the 12-month evaluation, the patient was admitted with petechiae over the lower extremities. His platelet and leukocyte count declined to 58 ×10^3/µl and 3.47 × 10^3/µl, respectively. The patient, therefore, underwent another bone marrow aspiration. The blast percentage in the bone marrow was 34%, with the BCR-ABL ratio at 22.70% IS, confirming the failure to achieve MMR. After 6 months, the patient reached the blast crisis phase and eventually passed away.

DISCUSSION

CML is rare among adolescents, accounting for 9% in children aged 15–19 years.[9] It has a triphasic clinical course and an initial indolent chronic phase, accelerated phase, and a terminal blast crisis. The chronic phase is marked with fewer than 10% of blast cells in the blood and bone marrow. Meanwhile, accelerated phase and blast crisis are indicated by 10–19% and ≥30% blast cells in the blood and/or bone marrow, respectively.[10] In our case, the patient was diagnosed with blast crisis after detecting 27% of blast cells in the bone marrow.

Imatinib resistance was defined as a lack of complete hematologic response in CML chronic phase (CML-CP) patients or failure to return to the chronic phase for CML accelerated phase or CML-BC patients undergoing imatinib therapy. It is divided into primary (lack of response from the initial evaluation) and secondary resistance (loss of initial response in subsequent evaluation).[7] The latter occurred in our patient who developed resistance after 4 years

of treatment. It was even shorter than the result from a recent trial indicating that 80–90% of patients maintained a cytogenetic response for 6 years.[11]

The outcome of imatinib treatment in CML is relatively inconsistent. In pediatric cases, Millot et al[12] showed that 63% of children treated with imatinib achieved BCR-ABL1 transcript levels ≤10% in the 3rd month and correlated with better progression-free survival and higher MMR. In contrast, our study failed to achieve MMR despite the optimal initial response. The failure of achieving a hematological response is even highly observed in CML-BC despite using the recommended dose.[13] In our case, the loss of hematologic response and failure of MMR (BCR-ABL ratio of 69.37% IS) eventually prompted a second-line therapy, for example, nilotinib.

Based on the promising results of the phase 3 trial, nilotinib was approved for the treatment of newly diagnosed CML-CP and imatinib-resistant or imatinib-intolerant CML in chronic or accelerated phase.[14] In our case, nilotinib served as second-line therapy for imatinib-resistant CML. Nilotinib inhibits BCR-ABL1 by binding to an inactive, aspartate-phenylalanine-glycine motif exchange positions (DFG-out), part of the ABL1 kinase domain, thus preventing the enzyme from active conformation and blocking the tyrosine phosphorylation of proteins involved in BCR-ABL1-mediated signal transduction.

Nilotinib has been acknowledged to be superior to imatinib. Its high affinity for the binding site creates greater specificity in CML. In preclinical models, nilotinib was 30 times more potent than imatinib in imatinib-sensitive CML cell lines.[15] Furthermore, a study by Hughes et al[16] found that compared with nilotinib 300 mg b.i.d and imatinib 600 mg b.i.d, nilotinib 400 mg b.i.d successfully achieved MMR in a larger number of patients.

Although nilotinib was considered to be effective in several studies, some cases also developed side effects. The common nilotinib-associated negative effects are thrombocytopenia (9%), neutropenia (17%), anemia (4%), headache (37%), nausea (50%), diarrhea (45%), rash and pruritus (40%), fatigue (31–39%), and hepatic and pancreatic toxicity (5–17%).[17] In our case, hematological suppression occurred within 2 weeks after administering nilotinib and was well treated by modifying the dose to 150 mg b.i.d.

Our patient tolerated nilotinib well in the starting dose of 200 mg b.i.d. The adjusting dose (150 mg b.i.d) was based on prescribing information published by the US FDA.[18] This adjusted dose significantly suppressed the percentage of BCR-ABL in our patient within 3 and 6 months of the administration, indicating that it as an optimal dose for our case. The optimal response (BCR-ABL1 ≤10%), alongside other factors that were present at the time of initiation of second-line TKI therapy, such as hematological response, has value in predicting response and survival outcomes.[12] The recent guideline from the European LeukemiaNet recommends evaluating the baseline and 3rd, 6th, and 12th months of the treatment.[19] The responses are categorized into optimal, warning, and failure based on either molecular or cytogenetic responses.[19] It can be seen in our case that the result of the two initial evaluations (3rd- and 6th-months BCR-ABL ratios of 7.91% and 1.39%, respectively) provided an optimal response.

The optimal molecular response is important as it correlates with good long-term prognosis and a reduced progression probability to accelerated or blast phase as well as increased overall survival.[13] Jain et al[20] highlighted that regardless of the type of TKIs, the 5-year outcomes after achieving an optimal molecular response, including event-free survival and overall survival were 84% and 93%, respectively. Similarly, 95–98% of patients with an early optimal response in the 3rd month had 3-year event-free survival.[21] This remarkable finding was highlighted in Thailand's report, which pointed out that achieving response in the 3rd month was associated with a higher possibility of achieving MMR (p<0.001) and maintained the MMR within 24 months of treatment.[22] In contrast, the initial optimal responses in our case were incapable of predicting the overall outcome therapy as failure to treatment (BCR-ABL ratio at 22.70%) was detected in the 12th-month evaluation.

The progressivity of the CML led to the failure of second-line nilotinib treatment. Although many studies have reported the success story of nilotinib in inducing free remission in CML-CP,[15,23] only one case report has highlighted the failure of nilotinib.[24] Cannella et al[24] reported a patient that lost complete cytogenetic response after 13 months of treatment and continued the third-line therapy with dasatinib. Administering another TKIs for the multiple-resistant CML (failure of and/or intolerance to two TKIs) has been suggested by the European LeukemiaNet.[19]

However, a similar approach was unable to perform in our institution because of the unavailability of other TKIs, leaving an escalation of nilotinib dose as an alternative option.

In this case, optimal response in the early evaluation was not directly proportional to the overall outcome of nilotinib treatment in CML. Therefore, serial measurement of BCR-ABL, along with careful monitoring of hematological side effects, should be performed. The loss of hematological response and failure to molecular response after treatment with first-line and second-line TKIs suggested the diagnosis of TKIs resistance and prompted a dose escalation of the current TKI in the limited facility and resource setting.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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